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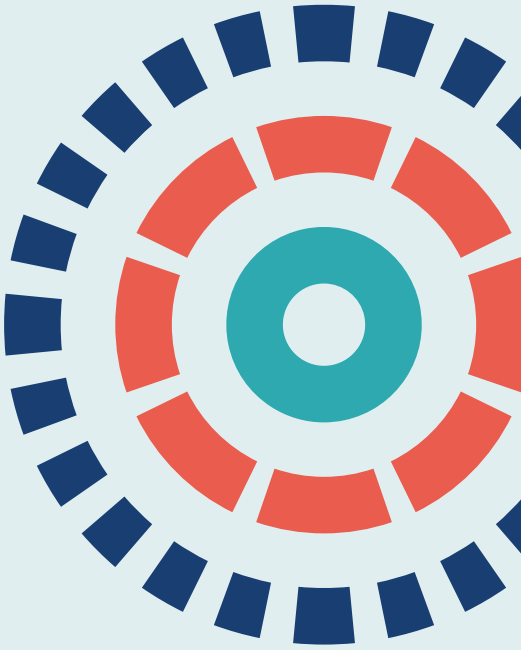

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This report

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Abstract

Different strategies for pharmacological thromboprophylaxis for lower-limb immobilisation after injury: systematic review and economic evaluation

Abdullah Pandor,[1] Daniel Horner,[2] Sarah Davis,[1] Steve Goodacre,[1]* John W Stevens,[1] Mark Clowes,[1] Beverley J Hunt,[3] Tim Nokes,[4] Jonathan Keenan[4] and Kerstin de Wit[5]

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Background: Thromboprophylaxis can reduce the risk of venous thromboembolism (VTE) during lower-limb immobilisation, but it is unclear whether or not this translates into meaningful health benefit, justifies the risk of bleeding or is cost-effective. Risk assessment models (RAMs) could select higher-risk individuals for thromboprophylaxis.

Objectives: To determine the clinical effectiveness and cost-effectiveness of different strategies for providing thromboprophylaxis to people with lower-limb immobilisation caused by injury and to identify priorities for future research.

Data sources: Ten electronic databases and research registers (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Review of Effects, the Cochrane Central Register of Controlled Trials, Health Technology Assessment database, NHS Economic Evaluation Database, Science Citation Index Expanded, ClinicalTrials.gov and the International Clinical Trials Registry Platform) were searched from inception to May 2017, and this was supplemented by hand-searching reference lists and contacting experts in the field.

Review methods: Systematic reviews were undertaken to determine the effectiveness of pharmacological thromboprophylaxis in lower-limb immobilisation and to identify any study of risk factors or RAMs for VTE in lower-limb immobilisation. Study quality was assessed using appropriate tools. A network meta-analysis was undertaken for each outcome in the effectiveness review and the results of risk-prediction studies were presented descriptively. A modified Delphi survey was undertaken to identify risk predictors supported by expert consensus. Decision-analytic modelling was used to estimate the incremental cost per quality-adjusted life-year (QALY) gained of different thromboprophylaxis strategies from the perspectives of the NHS and Personal Social Services.

Results: Data from 6857 participants across 13 trials were included in the meta-analysis. Thromboprophylaxis with low-molecular-weight heparin reduced the risk of any VTE [odds ratio (OR) 0.52, 95% credible interval (CrI) 0.37 to 0.71], clinically detected deep-vein thrombosis (DVT) (OR 0.40, 95% CrI 0.12 to 0.99) and pulmonary embolism (PE) (OR 0.17, 95% CrI 0.01 to 0.88). Thromboprophylaxis with fondaparinux (Arixtra®, Aspen Pharma Trading Ltd, Dublin, Ireland) reduced the risk of any VTE (OR 0.13, 95% CrI 0.05 to 0.30) and clinically detected DVT (OR 0.10, 95% CrI 0.01 to 0.94), but the effect on PE was inconclusive (OR 0.47,

95% CrI 0.01 to 9.54). Estimates of the risk of major bleeding with thromboprophylaxis were inconclusive owing to the small numbers of events. Fifteen studies of risk factors were identified, but only age (ORs 1.05 to 3.48), and injury type were consistently associated with VTE. Six studies of RAMs were identified, but only two reported prognostic accuracy data for VTE, based on small numbers of patients. Expert consensus was achieved for 13 risk predictors in lower-limb immobilisation due to injury. Modelling showed that thromboprophylaxis for all is effective (0.015 QALY gain, 95% CrI 0.004 to 0.029 QALYs) with a cost-effectiveness of £13,524 per QALY, compared with thromboprophylaxis for none. If risk-based strategies are included, it is potentially more cost-effective to limit thromboprophylaxis to patients with a Leiden thrombosis risk in plaster (cast) [L-TRiP(cast)] score of ≥ 9 (£20,000 per QALY threshold) or ≥ 8 (£30,000 per QALY threshold). An optimal threshold on the L-TRiP(cast) receiver operating characteristic curve would have sensitivity of 84–89% and specificity of 46–55%.

Limitations: Estimates of RAM prognostic accuracy are based on weak evidence. People at risk of bleeding were excluded from trials and, by implication, from modelling.

Conclusions: Thromboprophylaxis for lower-limb immobilisation due to injury is clinically effective and cost-effective compared with no thromboprophylaxis. Risk-based thromboprophylaxis is potentially optimal but the prognostic accuracy of existing RAMs is uncertain.

Future work: Research is required to determine whether or not an appropriate RAM can accurately select higher-risk patients for thromboprophylaxis.

Study registration: This study is registered as PROSPERO CRD42017058688.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Chronic thromboembolic pulmonary hypertension Persistent increased blood pressure in the arteries supplying the lungs, which is caused by pulmonary embolism and results in long-term shortness of breath and fatigue.

Cost-effectiveness acceptability curve A way of illustrating cost-effectiveness results by plotting the probability that the intervention is cost-effective (*y*-axis) against the maximum that society is willing to pay for an improvement in health (*x*-axis).

Cost-effectiveness plane A way of illustrating cost-effectiveness results by plotting the mean incremental cost and effectiveness on a four-quadrant graph. Interventions that are more costly and more effective fall in the north-east quadrant.

Deep-vein thrombosis A blood clot that develops within a deep vein in the body, usually in the leg.

Incremental cost-effectiveness ratio The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

L-TRiP(cast)–N A strategy of giving thromboprophyalxis to patients with a L-TRiP(cast) score of N or above.

Post-thrombotic syndrome Pain, swelling, itching, skin discolouration and leg ulcers occurring after a deep-vein thrombosis, caused by damage to the valves in the leg veins that prevent backflow of blood.

Predictor Throughout this report, 'predictor' is used to refer to any clinical, laboratory or demographic characteristic. The term 'predictor' encompasses other similar terms, such as prognostic factor, covariate and variable.

Prophylaxis A measure taken to prevent a disease.

Pulmonary embolism A blood clot that breaks off from the deep veins and travels around the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from deep-vein thrombosis are caused by pulmonary embolism.

Quality-adjusted life-year A measure of the benefit of health care that combines the impact of both the expected length of life and quality of life.

Risk assessment models In this report, defined as a combination of at least two predictors within a statistical model that is used to predict an individual's risk of outcome, for example venous thromboembolism. Other terms also related to risk assessment models may include prognostic model, prediction models, clinical decision rules and clinical prediction guides. The term 'risk assessment model' is used in this report to encompass all of these terms; therefore, all are considered to refer to the same thing.

Thromboprophylaxis A measure taken to reduce the risk of thrombosis.

Vein thrombosis A condition in which a blood clot (thrombus) forms in a vein.

Venous thromboembolism The blocking of a blood vessel by a blood clot dislodged from its site of origin. It includes both deep-vein thrombosis and pulmonary embolism.

List of abbreviations

AF	atrial fibrillation
AUC	area under the curve
BMI	body mass index
CaVenT	catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep-vein thrombosis
CEAC	cost-effectiveness acceptability curve
CG	clinical guideline
CI	confidence interval
CrI	credible interval
CRNMB	clinically relevant non-major bleeding
CTEPH	chronic thromboembolic pulmonary hypertension
DOAC	direct oral anticoagulant
DVT	deep-vein thrombosis
DVTQoL	Deep Venous Thrombosis Quality of Life
ED	emergency department
NHS EED	NHS Economic Evaluation Database
EQ-5D	EuroQoL-5 Dimensions
EVPI	expected value of perfect information
GEMNet	Guidelines in Emergency Medicine Network
GI	gastrointestinal
GP	general practitioner
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
HUI-3	Health Utilities Index – 3
ICER	incremental cost-effectiveness ratio
ICH	intracranial haemorrhage
INMB	incremental net monetary benefit
INR	international normalised ratio
LMWH	low-molecular-weight heparin
L-TRiP(cast)	Leiden thrombosis risk in plaster (cast)
MCS	mental component summary
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
OXVASC	Oxford Vascular Study
PAH	pulmonary arterial hypertension
PCS	physical component summary
PE	pulmonary embolism
POT-CAST	Prevention of Thrombosis after Lower Leg Plaster Cast
PPI	patient and public involvement
PREFER-VTE	Prevention of thromboembolic events – European registry in venous thromboembolism
PSA	probabilistic sensitivity analysis
PTS	post-thrombotic syndrome
QALY	quality-adjusted life-year
RAM	risk assessment model
RCEM	Royal College of Emergency Medicine
RCT	randomised controlled trial
RIETE	Computerized Registry of Patients with Venous Thromboembolism
RoB	Cochrane Risk of Bias tool

ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
ROC	receiver operating characteristic
RR	relative risk
SD	standard deviation
SF-6D	Short-Form questionnaire-6 Dimensions
SF-12	Short-Form questionnaire-12 items
SF-36	Short-Form questionnaire-36 items
SMD	standardised mean difference
STA	single technology appraisal
TA	technology appraisal
TTO	time trade-off
VKA	vitamin K antagonist
VTE	venous thromboembolism

Plain English summary

People who have their leg immobilised in a plaster cast or brace following an injury are at risk of developing a blood clot. Sometimes the clot can break up and lodge in the lungs, which can make the person seriously ill. Drugs that thin the blood (anticoagulants) can reduce the risk of blood clots, but they carry a small risk of serious bleeding. This study analysed all published trials of anticoagulants for people with leg immobilisation and found that, without treatment, there was a 1–2% risk of a serious blood clot. This risk was roughly halved by using anticoagulant treatment. These estimates were used in a simulation model of patient treatment and it was found that the benefit of anticoagulants in reducing blood clots (in terms of length and quality of life) outweighed the risks of bleeding.

Next, all published studies of risk assessment tools were analysed. Risk assessment tools can be used to predict who is most likely to get a blood clot. There were only a few studies and they had significant weaknesses. The risk assessment tools in the simulation model were evaluated and it was found that the most cost-effective approach was to use a risk assessment tool to select approximately half of the patients for treatment (those at higher risk), while not treating those at lower risk. Treating only the higher-risk patients would be a cost-effective use of NHS resources, compared with treating nobody. Treating everybody, compared with just treating higher-risk patients, would improve outcomes for some patients but would not be a cost-effective use of NHS resources.

This study suggests that anticoagulant drugs are an effective and potentially cost-effective way of preventing blood clots in people with leg immobilisation due to injury. Research is needed to determine whether or not risk assessment tools can accurately predict who needs anticoagulant drugs and who does not.

Scientific summary

Background

People with lower-limb immobilisation following an injury are at risk of venous thromboembolism (VTE), including symptomatic and asymptomatic deep-vein thrombosis (DVT) and pulmonary embolism (PE). Preventative treatment with anticoagulant drugs (thromboprophylaxis) has the potential to reduce the risk of VTE, but it is not clear if this translates into a meaningful health benefit for patients, justifies the risk of treatment-related bleeding or is cost-effective. Risk assessment models (RAMs) could improve the ratio of benefit to risk and benefit to cost, but the evidence to support RAMs for lower-limb immobilisation has not been robustly evaluated.

Objectives

The aims were to determine the clinical effectiveness and cost-effectiveness of different strategies for providing thromboprophylaxis to people with lower-limb immobilisation due to injury and to identify priorities for future research. Specifically:

- To undertake systematic reviews and, if appropriate, a meta-analysis to (1) estimate the effectiveness of thromboprophylaxis for preventing VTE outcomes, (2) identify individual risk factors associated with VTE risk and (3) identify RAMs that predict the risk of VTE and to estimate the accuracy of these models.
- To undertake a modified Delphi survey of expert opinion regarding risk factors and RAMs for VTE in lower-limb immobilisation, augmenting the limited data anticipated from reviews 2 and 3 above.
- To develop an economic model to estimate the clinical effectiveness of different strategies for providing thromboprophylaxis [in terms of adverse outcomes avoided or incurred by treatment, and quality-adjusted life-years (QALYs)], the cost-effectiveness of different strategies (in terms of the incremental cost per QALY gained by each strategy compared with the next most effective strategy on the efficiency frontier) and the expected value of information provided by further primary research.

Methods

Systematic reviews were undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A range of bibliographic sources was searched, comprising MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Review of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment database, NHS Economic Evaluation Database, Science Citation Index Expanded, ClinicalTrials.gov and the International Clinical Trials Registry Platform, from inception to April/May 2017. Searches were supplemented by hand-searching reference lists, undertaking citation searches, contacting key experts and carrying out systematic keyword searches of the internet.

For the effectiveness review, controlled trials were selected that reported VTE or bleeding outcomes in people requiring temporary lower-limb immobilisation following an injury who received pharmacological thromboprophylaxis or control/no treatment. For the risk-prediction reviews, any study that reported and analysed risk factors or RAMs for VTE outcomes in a cohort of people requiring temporary lower-limb immobilisation following an injury was selected. Methodological quality was assessed using a revised Cochrane Risk of Bias tool for randomised trials for the effectiveness review, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for the risk factor prediction review and a generic list of important methodological features for the review of RAMs.

A network meta-analysis (NMA) was undertaken for each outcome in the effectiveness review. A fixed-effects model was used to estimate the effects of different thromboprophylaxis regimes relative to control in the available studies and a random-effects model was used to allow for heterogeneity in the effects of interventions between studies. The results of risk-prediction studies were presented descriptively.

A modified Delphi survey of experts in haematology, emergency medicine and orthopaedics was undertaken to identify risk factors for VTE in lower-limb immobilisation that expert consensus suggested could be incorporated in a RAM. This involved two rounds of elicitation of expert opinion via an online survey, followed by a facilitated round-table discussion.

A de novo decision-analytic model was created to simulate the management of a cohort of people with lower-limb immobilisation due to injury in accordance with strategies including thromboprophylaxis for all, thromboprophylaxis for none and risk-based thromboprophylaxis using a RAM. Costs were estimated from the perspective of the UK NHS and Personal Social Services. A decision tree was used to model rates of prophylaxis, VTE events and major bleeds in the first 6 months. A Markov model with a lifetime horizon was used to extrapolate costs and QALY losses associated with chronic complications following VTE or bleeding events. The model was populated with data from the effectiveness and risk-prediction reviews and additional model inputs were sourced from the published literature. Costs and QALYs were discounted to their net 2018 value at 3.5%. Probabilistic sensitivity analysis, deterministic sensitivity analysis and expected value-of-information analysis were used to explore and quantify decision uncertainty.

Results

Effectiveness of thromboprophylaxis

Data from 6857 participants across 13 randomised controlled trials (RCTs) were included: 11 comparing low-molecular-weight heparin (LMWH) with no thromboprophylaxis, one comparing fondaparinux (Arixtra®, Aspen Pharma Trading Ltd, Dublin, Ireland) or LMWH with no thromboprophylaxis and one comparing fondaparinux with LMWH. A risk of bias was present in all studies, with 10 raising some concerns and three rated as being at a high risk of bias, principally attributable to outcome assessment in three open-label studies. LMWH and fondaparinux were analysed as separate nodes in the NMA and each was compared with control treatment, which included aspirin, placebo and no treatment.

The rate of any VTE in the control group ranged from 1.8% to 40.4% (median 12.2%). LMWH [odds ratio (OR) 0.52, 95% credible interval (CrI) 0.37 to 0.71] and fondaparinux (OR 0.13, 95% CrI 0.05 to 0.30) both reduced the risk of any VTE compared with no thromboprophylaxis. Clinically detected (symptomatic) DVTs were reported in 11 out of 13 trials, with control event rates ranging from 0.0% to 5.5% (median 0.7%). LMWH (OR 0.40, 95% CrI 0.12 to 0.99) and fondaparinux (OR 0.10, 95% CrI 0.01 to 0.94) both reduced the risk of clinically detected DVT compared with control. The rate of PE in the control group was 0.0% in eight trials and ranged from 0.7% to 2.1% in the other four trials. LMWH (OR 0.17, 95% CrI 0.01 to 0.88) reduced the risk of PE compared with control, whereas results were inconclusive for fondaparinux (OR 0.47, 95% CrI 0.01 to 9.54). Only four major bleeding events were reported across the studies; therefore, estimates of the risk of bleeding with thromboprophylaxis were inconclusive. In all analyses, evidence of heterogeneity suggested that the true effects may vary according to study characteristics, but network metaregressions showed no reliable evidence of effect modification from key covariates.

Individual risk predictors for venous thromboembolism

Fifteen studies were included (five RCTs, three prospective observational cohort or cross-sectional studies, one case–control study and six retrospective cohort studies), reporting data from 80,678 participants. Overall, studies were rated as being at a moderate or serious risk of bias. The only factors consistently identified as being associated with the risk of VTE were age (ORs ranging from 1.05 to 3.48), and injury type (severe traumatic injuries and fractures associated with VTE).

Other potential risk factors were not examined or showed inconsistent associations with VTE across the studies or no association with VTE.

Risk assessment models

Six studies were included (three prospective observational cohort studies, two case–control studies and one unclear design), reporting data from 16,893 participants. Overall, the risk of bias was rated as being high or unclear for the criteria assessed. Validation data were very limited, with only two studies reporting estimates of sensitivity and specificity. Receiving operating characteristic (ROC) analysis for the Leiden thrombosis risk in plaster (cast) [L-TRiP(cast)] score showed sensitivity of 92.6% and specificity of 39.7% using a threshold score of ≥ 8.

Expert consensus

Consensus was achieved for 13 risk predictors in lower-limb immobilisation due to injury: age, body mass index (BMI), thrombophilia, pregnancy/puerperium, active cancer, surgery in the preceding 3 months, prior VTE, exogenous oestrogen/hormone therapy, lower-limb paralysis, superficial thrombophlebitis, Achilles tendon rupture, rigid immobilisation and an above-knee cast.

Decision-analytic modelling

The decision-analytic modelling suggested that the combined risk of non-fatal intracranial bleeding or death from VTE or bleeding after lower-limb immobilisation due to injury was around 1 in 4000, regardless of thromboprophylaxis use. The effectiveness of thromboprophylaxis was therefore mainly determined by the relative effects of non-fatal VTE and non-intracranial major bleeding. Thromboprophylaxis compared with no thromboprophylaxis produced a mean QALY gain of 0.015 per patient (95% CrI 0.004 to 0.029) in the probabilistic sensitivity analysis, suggesting that the overall benefits outweigh the risks. The mean incremental cost was £203 (95% CrI £172 to £245) and the incremental cost-effectiveness ratio (ICER), based on the mean costs and QALYs, was £13,524, with a 76% probability of thromboprophylaxis being cost-effective compared with no treatment at the £20,000 per QALY threshold.

If risk-based strategies for providing thromboprophylaxis are included in the analysis, the optimal strategy would be to use the L-TRiP(cast) score with a threshold of ≥ 9 (sensitivity 80.8%, specificity 60.8%) if £20,000 per QALY is used and with a threshold of ≥ 8 (sensitivity 92.6%, specificity 39.7%) if £30,000 per QALY is used. Analyses to determine the optimal balance of sensitivity and specificity using the L-TRiP(cast) ROC curve showed that, at £20,000 per QALY, the incremental net monetary benefit is maximised for a sensitivity of 84% and a specificity of 55%, whereas, at £30,000 per QALY, the incremental net monetary benefit is maximised for a sensitivity of 89% and a specificity of 46%.

The expected value of perfect information (EVPI) was £4.12 per patient treated; therefore, over 5 years, assuming that 70,000 patients have lower-limb immobilisation every year across the English NHS, the overall discounted population EVPI is £1.3M. The most important parameters for decision uncertainty are the utility value for post-thrombotic syndrome, the efficacy of thromboprophylaxis in reducing VTE, the probability of post-thrombotic syndrome for patients with distal DVT and the utility decrement associated with taking thromboprophylaxis. Sensitivity analysis showed that a strategy of treating all patients would be most cost-effective if the prognostic accuracy of the RAM were lower (i.e. assuming a lower area under the ROC curve).

Sensitivity analyses suggested that using a direct oral anticoagulant (DOAC) for thromboprophylaxis, assuming equivalent effectiveness to LMWH, shifted the optimal strategy from L-TRiP(cast)-9 to L-TRiP(cast)-8 at the £20,000 per QALY threshold and to treat all at the £30,000 per QALY threshold. Using fondaparinux resulted in L-TRiP(cast)-8 being the optimal strategy at both the £20,000 per QALY and £30,000 per QALY thresholds.

Discussion

Thromboprophylaxis with LMWH approximately halves the risk of any VTE in people with temporary lower-limb immobilisation following an injury and has similar effects on other VTE outcomes. Fondaparinux appears to have a greater effect based on evidence from two trials. The effect of thromboprophylaxis on major bleeding is uncertain as a result of the very low event rate.

The only risk factors for VTE consistently identified in studies of lower-limb immobilisation are age, BMI and type of injury. A number of RAMs have been developed for predicting VTE risk in this patient group, but validation has been very limited and so estimates of prognostic accuracy are very uncertain. Expert consensus identified 13 potential predictors for VTE that are also commonly incorporated in RAMs, but other variables included in the RAMs were not supported by expert consensus.

The evidence for thromboprophylaxis with LMWH is reasonably strong but is limited by heterogeneity between studies and exclusion of patients known to be at risk of VTE or bleeding. The evidence base for risk prediction, using either individual predictors or a RAM, is weak and based on studies with significant methodological limitations and relatively small numbers of participants with lower-limb immobilisation.

Decision-analytic modelling showed that the combined risk of death (from VTE or bleeding) and non-fatal intracranial bleeding would be very low, regardless of the approach used, but the QALYs gained by using thromboprophylaxis to prevent VTE and their sequelae outweighed the QALYs associated with bleeding and administering thromboprophylaxis.

Thromboprophylaxis for all patients is probably cost-effective compared with thromboprophylaxis for none, with an ICER of £13,524, which is lower than the National Institute for Health and Care Excellence (NICE) threshold of £20,000 per QALY, and a 76% probability of being cost-effective at the £20,000 per QALY threshold. If risk-based thromboprophylaxis is considered alongside thromboprophylaxis for all and thromboprophylaxis for none, then providing thromboprophylaxis on the basis of a L-TRiP(cast) score of ≥ 8 is the optimal strategy if the threshold for willingness to pay is £20,000 per QALY, and providing thromboprophylaxis on the basis of a L-TRiP(cast) score of ≥ 9 is the optimal strategy if the threshold for willingness to pay is £30,000 per QALY. Assuming that a RAM has a ROC curve similar to L-TRiP(cast), the optimal balance of sensitivity and specificity for a RAM appears to be 84–89% and 46–55%, respectively.

The decision-analytic modelling was able to draw on reasonably robust effectiveness data for thromboprophylaxis and data sources for other parameters that have been used in previous models of VTE management. The main limitation of the model related to the weakness of estimates of RAM sensitivity and specificity. This uncertainty could not be addressed in a probabilistic sensitivity analysis, but a deterministic sensitivity analysis suggested that RAM prognostic accuracy is a potentially important determinant of cost-effectiveness.

There are also important limitations relating to the generalisability of findings to other drugs. The estimates of effectiveness of thromboprophylaxis were based on trials of LMWH and, to a lesser extent, fondaparinux, both of which are administered by injection. The patient representatives suggested that this was a significant barrier to use and that thromboprophylaxis with a DOAC would be preferable. However, we found no relevant trials of these agents, so modelling used potentially favourable assumptions that DOACs are as effective as LMWH but can be delivered at lower cost to determine their cost-effectiveness.

Trials of thromboprophylaxis excluded important patient groups, particularly those at an increased risk of bleeding. It was assumed that the modelling population had a risk of bleeding similar to that of the general population and so these findings should not be applied to those at a higher risk. The trials were also limited to people with full immobilisation rather than including those with removable splints or splints that allowed some movement. Therefore, these findings should not be applied to this wider group, for whom the benefits of thromboprophylaxis are unknown.

Conclusions

Thromboprophylaxis for lower-limb immobilisation due to injury appears to be clinically effective and cost-effective. Risk-based thromboprophylaxis using a RAM with 84–89% sensitivity and 46–55% specificity for predicting VTE is a potentially optimal strategy that would cost £6M and gain 891 QALYs per year across the English NHS compared with no thromboprophylaxis. Compared with this, providing thromboprophylaxis for all would cost an additional £8.2M per year and gain an additional 160 QALYs.

Future work

Research is required to determine whether or not an appropriate RAM can accurately select higher-risk patients for thromboprophylaxis. However, given the evidence of effectiveness for thromboprophylaxis, this probably needs to be an implementation study rather than the scientifically ideal design of a prognostic accuracy study of untreated patients. Research is also required to determine the effectiveness of DOACs in lower-limb immobilisation and the effectiveness of thromboprophylaxis for incomplete (removable or flexible) immobilisation. Efficient designs are likely to be required to deliver the large numbers of participants required to estimate key outcomes with acceptable precision.

The patient and public representatives identified substantial potential for shared decision-making in risk assessment and delivery of thromboprophylaxis for lower-limb immobilisation, but this requires clear communication of the potential risks and benefits. Research is required to develop methods of and tools for communicating the risks and benefits to patients and involving patients in decision-making.

Study registration

This study is registered as PROSPERO CRD42017058688.

Funding

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Chapter 1 Background

Description of the health problem

Venous thromboembolism (VTE) is a condition in which a blood clot (a thrombus) forms in a vein. It predominantly occurs in the large veins of the legs and causes a deep-vein thrombosis (DVT). When part or all of the thrombus dislodges from its site of origin, it can travel to the lungs and disrupt or block the blood flow in a pulmonary artery, causing a pulmonary embolism (PE).[1] VTE encompasses a range of clinical presentations. Thrombosis in the venous circulation may be asymptomatic (no clinical symptoms), whether a DVT or a PE, or symptomatic (clinically apparent e.g. DVT may cause leg pain or swelling, whereas PE may lead to sudden death or cause symptoms such as breathlessness or chest pain).[2]

If patients survive the acute episode of VTE, they may go on to develop long-term problems. Post-thrombotic syndrome (PTS) can occur if DVT causes damage to the valves in the leg veins that prevent backflow of blood, resulting in pain, swelling, itching, discolouration of the skin and, in some cases, an ulcer on the leg. Chronic thromboembolic pulmonary hypertension (CTEPH) can occur if a PE blocks blood flow to the lungs and increases the blood pressure in the arteries supplying the lungs, resulting in chronic shortness of breath and fatigue.

Despite modern advances in care, both asymptomatic and symptomatic VTE are still associated with significant morbidity and mortality.[3,4] In the past decade, VTE has resulted in more deaths than prostate cancer, breast cancer, road traffic accidents and acquired immune deficiency syndrome combined.[5] It is the second most common cause of vascular death after heart attack.[6] In 2005, the total cost (comprising direct and indirect costs) to the UK for the management of VTE was estimated at approximately £640M.[6]

Temporary immobilisation of lower-limb injury is an important cause of potentially preventable VTE. In this context, injury is defined as physical trauma caused by an external force (e.g. a fall or a direct blow), abnormal movement (e.g. twisting or overstretching) or normal movement applied to a weakened limb structure (e.g. rupture of an inflamed tendon). Immobilisation is defined as involving a temporary splint, cast or boot that prevents movement in the knee and/or ankle joint. It is temporary insofar as it is applied after the injury and then removed when the injury has healed. For the purposes of this report, removable splints that are used only at times of activity during healing and hinged splints or bandages that allow joint movement while they are in place are not included.

Case reports, observational cohort studies and randomised controlled trials (RCTs) suggest that patients with lower-limb immobilisation due to injury have a significant risk of VTE, morbidity and death.[7–16] A typical type one emergency department (ED) is likely to see, immobilise and discharge around 360 patients per year with lower-limb injury, with an overall subsequent VTE rate approaching 2%.[16–18] There are currently 194 type one EDs in the English NHS that generate a relevant annual patient population of just under 70,000 patients. The exclusion of type two EDs, minor injury units and walk-in centres, probably renders this an underestimate of the population. The incidence of VTE in ambulatory trauma patients with lower-limb immobilisation is ≈11%. However, this rate can vary from 2% to 30%, depending on the type of injury and the immobilisation used.[19] Although the majority of these events will be asymptomatic distal DVT, there is a small risk of clot propagation, potentially leading to fatal PE[19] in 20–30% of patients receiving no prophylaxis,[14] reducing to 0.3–2.0% in those with prophylaxis.[20]

Description of the technology under assessment

Thromboprophylaxis, both mechanical [e.g. antiembolism stockings or VTE compression devices (not the subject of this report, as plaster cast immobilisation precludes the application of devices to support the calf muscle pump and/or stimulate blood flow in the leg)] and pharmacological, has been the routine standard of care after lower-limb immobilisation. The main goal of administering thromboprophylaxis is to prevent PE and DVT and their sequelae. Pharmacological thromboprophylaxis in patients with lower-limb immobilisation due to injury has been principally studied using subcutaneous low-molecular-weight heparin (LMWH). Several different agents are available [e.g. dalteparin (Fragmin®, Pfizer Inc., New York City, NY, USA), enoxaparin (Clexane®, Sanofi Genzyme, Cambridge, MA, USA) and tinzaparin (Innohep®, Leo Pharma A/S, Copenhagen, Denmark)][21] and equivalent doses are used for hospital inpatients, extended spectrum groups (e.g. post-operative orthopaedic cases) and pregnant patients. LMWH is well tolerated in these groups and has clear acceptability to staff and patients, given its widespread utilisation across the NHS. LMWH has some limitations. As an injection-only agent, it causes a degree of pain and discomfort, which are poorly tolerated by some. It also requires administration; therefore, patients unhappy to self-inject, or elderly patients, often require expensive and time-consuming additional district nursing support to facilitate home medication. Finally, there are associated complications with LMWH, principally bleeding and, rarely, heparin-induced thrombocytopenia.

Aspirin use has also been studied in this patient group, albeit with limited evidence of efficacy.[22,23] The attractions and benefits of aspirin include familiarity and availability, cost and a clearly understood side-effect profile. Despite this, the National Institute for Health and Care Excellence (NICE) guidelines on VTE (clinical guideline number 92[24] and NICE guideline number 89[1]) do not consider aspirin or other antiplatelet agents to be appropriate for VTE prophylaxis. In addition, aspirin is not indicated as a treatment for VTE prophylaxis in lower-limb immobilisation.[21,25,26]

Fondaparinux (Arixtra®, Aspen Pharma Trading Ltd, Dublin, Ireland) is a synthetic pentasaccharide antithrombotic that inactivates factor X (Xa) and results in a strong inhibition of thrombin generation and clot formation without affecting thrombin or platelets. It is administered subcutaneously and has similar limitations to LMWH. However, it is not widely used in the UK for VTE prophylaxis.

Finally, direct oral anticoagulant (DOAC) medications [e.g. apixaban (Eliquis®, Bristol-Myers Squibb Company, New York City, NY, USA), dabigatran etexilate (Pradaxa®, Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) and rivaroxaban (Xarelto®, Bayer AG, Leverkusen, Germany)] are of increasing interest to clinicians and offer an option for thromboprophylaxis. DOACs present an attractive option based on applicable evidence from extrapolated orthopaedic surgical thromboprophylaxis trials, in addition to their inherent acceptability and practicality.[27–29] Oral anticoagulant prophylaxis regimens can be taken orally once or twice daily, have no additional specific contraindications to LMWH, are convenient and reliable, and appear acceptable to staff and patients. However, they are currently more expensive and are associated with more limited clinical experience than heparin products; furthermore, the management of bleeding complications may be challenging, given the lack of an agent to reverse DOACs' anticoagulant effect.[30]

Preventative treatment with anticoagulant drugs (thromboprophylaxis) could reduce the risk of VTE, but these drugs carry risks of adverse events, in particular an increased risk of intracranial or gastrointestinal (GI) bleeding. Thromboprophylaxis can be justified only if the benefits of reducing VTE outweigh the risks of bleeding and other side effects. Furthermore, the considerable expense of providing thromboprophylaxis to all patients with lower-limb immobilisation can be justified only if this treatment delivers meaningful improvements in health at an acceptable cost. The risk to benefit and cost to benefit ratios of thromboprophylaxis could be improved if patients were selected for treatment on the basis of risk factors for VTE, but this requires accurate and usable risk assessment methods.

A number of risk assessment models (RAMs) have been developed to select patients with lower-limb cast immobilisation due to injury for thromboprophylaxis.[17,31–33] These models aim to target high-risk patients who stand to gain maximal health benefit on treatment and avoid treatment in low-risk groups. However, the methodology for deriving and validating these RAMs is often poorly described, limited in validity or based on expert consensus only.[17,31–33]

In general, risk prediction tools use clinical information from a patient's history and examination to identify those with an increased risk of VTE who could be selected for thromboprophylaxis. Existing risk prediction rules use either a flow chart or a checklist to guide the user through risk assessment and lead him or her to a decision regarding thromboprophylaxis. Tools may take the form of rules that simply categorise patients by whether or not they need thromboprophylaxis, or scores that estimate the risk of VTE but leave the decision to provide thromboprophylaxis in the hands of the user. The tools may be paper based or electronic. The latter can potentially facilitate more complex risk assessment based on weighting of risk factors, if appropriate data are available to support such weighting.

Current service provision

Extended spectrum thromboprophylaxis for outpatients immobilised in plaster following lower-limb injury continues to generate international debate. There is substantial variation in both the use of thromboprophylaxis and the use of RAMs. Although VTE events are potentially preventable with prophylaxis, international guidance offers conflicting advice, from no intervention, to pragmatic shared decision-making, all the way to routine chemical thromboprophylaxis.[17,34,35]

In many European countries, thromboprophylaxis is routine,[35] whereas, in North America, recent guidelines interpret the literature as too weak to justify intervention, and actively discourage thromboprophylaxis.[34] Current UK guidance from NICE recommends that clinicians consider pharmacological VTE prophylaxis with LMWH or fondaparinux for people with lower-limb immobilisation whose risk of VTE outweighs their risk of bleeding, but does not provide guidance on how these risks can be determined.[24] This may foster clinical uncertainty and has led to a UK position of variable practice, using variable drug regimens throughout the NHS, with limited understanding of the safety, efficacy or cost-effectiveness of local protocols. Since 2015, there has been a move towards using the DOACs for this indication, despite the lack of applicable research or licence, based on convenience and cost implications. Personal correspondence from the Royal College of Emergency Medicine (RCEM) Clinical Studies Group suggests that DOAC drugs are currently being used for this indication in at least four NHS trusts (Catherine Roberts, Lancashire Teaching Hospitals, 2018, personal communication).

In the UK, risk assessment strategies in current use include the Plymouth VTE risk assessment tool (derived by expert consensus),[31] the Guidelines in Emergency Medicine Network (GEMNet) guidance (produced in 2012 for RCEM, following a rapid review of the applicable literature and expert consensus)[17] and several expert-derived pathways supported by the British Orthopaedic Association Standards for Trauma.[33] However, uptake of these RAMs seems to be poor as a result of equipoise/uncertainty, and many centres utilising these tools have pragmatically amended them without published supporting evidence.

Chapter 2 Research questions

Rationale for the study

Venous thromboembolism is a documented global health burden.[4,5] Preventative treatment with anticoagulant drugs (thromboprophylaxis) has the potential to reduce the risk of symptomatic or asymptomatic VTE in patients with lower-limb immobilisation due to injury; however, it is not clear whether or not this translates into meaningful health benefit for patients, justifies the risk of treatment-related adverse events (in particular, an increased risk of intracranial or GI bleeding) or is cost-effective. Risk assessment strategies could improve the ratios of benefit to risk and benefit to cost, but the evidence to support VTE RAMs for lower-limb immobilisation has not been robustly evaluated.

International guidelines have made clear recommendations for research in this area. Previous NICE clinical guidelines (CG92)[24] made a specific recommendation of research into the clinical effectiveness and cost-effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower-limb plaster casts, which this research proposal was designed to address. The 2012 American College of Chest Physicians guidance contains a grade 2C recommendation (i.e. weak recommendation, low- or very-low-quality evidence) on the topic and highlights the extensive list of exclusion criteria from previous research.[34] In addition, the RCEM guidelines[17] and several additional review papers published in specialist journals have called for further research to address the equipoise.[13,36]

Primary research could reduce uncertainty around decision-making, but carries substantial risks of failure. A large pragmatic trial could estimate the benefits and harms of thromboprophylaxis and determine whether or not it is effective, but the low rates of symptomatic VTE events and bleeding events mean that a very large sample would be required. Furthermore, it may not be ethical to randomise patients to no treatment if convincing evidence of the effectiveness of thromboprophylaxis already exists. It is also not clear whether or not a risk-based approach might be better than thromboprophylaxis for all, and, if it is, what RAM should be used. A cohort study could be used to derive or validate a RAM but it is not clear whether or not participants in such a study should receive thromboprophylaxis or how a RAM should weigh the relative benefits of optimising sensitivity and specificity when there is inevitably a trade-off between these parameters.

In these circumstances, an evidence synthesis project, involving systematic review, meta-analysis, elicitation of expert consensus, decision-analytic modelling and value-of-information analysis, provides a relatively quick and inexpensive way of drawing together all of the existing evidence in a rational and explicit manner, exploring the trade-off between treatment harms and benefits, and between sensitivity and specificity in risk assessment, estimating the cost-effectiveness of different strategies and the cost-effectiveness of different options for future primary research.

Overall aims and objectives of assessment

The overall aim was to determine the clinical effectiveness and cost-effectiveness of different strategies for providing thromboprophylaxis to people with lower-limb immobilisation due to injury and identify priorities for future research. More specifically, the objectives were as follows:

1. To undertake systematic reviews and meta-analysis (when appropriate) to (1) assess the effectiveness of pharmacological thromboprophylaxis for preventing any VTE, clinically detected (symptomatic) DVT, clinically relevant (symptomatic, proximal or extensive) DVT, PE and asymptomatic DVT in people with lower-limb immobilisation due to injury; (2) identify individual risk factors associated with VTE risk in

patients with temporary lower-limb immobilisation due to injury; and (3) identify RAMs that predict the risk of VTE in people with lower-limb immobilisation due to injury and estimate the accuracy of these models.

2. To undertake a modified Delphi survey of expert opinion to augment reviews 2 and 3 above, on the assumption that the available evidence will be very limited and expert opinion will be required to identify risk factors and RAMs for VTE in lower-limb immobilisation due to injury.
3. To develop an economic model to estimate the (i) clinical effectiveness of thromboprophylaxis, in terms of overall adverse outcomes avoided or incurred by treatment and quality-adjusted life-years (QALYs); (ii) cost-effectiveness of different strategies for providing thromboprophylaxis (including thromboprophylaxis for all, thromboprophylaxis for none and risk-based strategies), in terms of the incremental cost per QALY gained by each strategy compared with the next most effective strategy on the efficiency frontier; and (iii) expected value of information provided by further primary research and to determine the optimal direction of future research.

Chapter 3 Assessment of clinical effectiveness

A series of systematic reviews of the literature and (network) meta-analysis (when appropriate) were undertaken to (1) assess the effectiveness of pharmacological thromboprophylaxis for preventing VTE, (2) identify individual risk factors associated with VTE risk and (3) identify RAMs for the prediction of VTE risk in people with temporary lower-limb immobilisation due to injury.

All reviews of the evidence were undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[37] and were registered on the PROSPERO international prospective register of systematic reviews (CRD42017058688).[38] The full protocol is available on the project web page [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/1518706/#/ (accessed 3 December 2018)].

Review of pharmacological thromboprophylaxis for preventing venous thromboembolism

Objective

The objective was to assess the effectiveness of pharmacological thromboprophylaxis for preventing any VTE, clinically detected (symptomatic) DVT, clinically relevant (symptomatic, proximal or extensive) DVT, PE and asymptomatic DVT in patients with temporary lower-limb immobilisation due to injury. In this study, proximal DVT is defined as disease at or above the level of the popliteal trifurcation. Distal DVT is defined as disease below the popliteal trifurcation, confined to the calf veins (e.g. peroneal, posterior, anterior tibial and muscular veins).

Methods of reviewing effectiveness

Identification of studies

Studies were identified by searching the following electronic databases and research registers:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, MEDLINE and Versions(R) (OvidSP), 1946 to April 2017.
- EMBASE (OvidSP), 1974 to April 2017.
- Cochrane Database of Systematic Reviews (Wiley Online Library), 1996 to April 2017.
- Database of Abstracts of Review of Effects (Wiley Online Library), 1995 to March 2015.
- Cochrane Central Register of Controlled Trials (Wiley Online Library), 1898 to April 2017.
- Health Technology Assessment (HTA) database (Wiley Online Library), 1995 to April 2017.
- NHS Economic Evaluation Database NHS EED (Wiley Online Library), 1995 to March 2015.
- Science Citation Index Expanded (Web of Science), 1900 to April 2017.
- ClinicalTrials.gov (US National Institutes of Health), 2000 to April 2017.
- International Clinical Trials Registry Platform (World Health Organization), 1990 to April 2017.

The search strategy used free text and thesaurus terms and combined synonyms relating to the condition (i.e. VTE in people with lower-limb immobilisation) with synonyms relating to the interventions (e.g. LMWH, aspirin and oral anticoagulants). No language restrictions were used. However, as the search strategy of the current review updated the search strategy of an existing review on LMWH,[15] searches were limited by date from 2013 (the last search date from the earlier review) to April 2017 for this intervention. For the other interventions, the search strategy was amended to include terms for aspirin and oral anticoagulants and searched from inception to April 2017. Further details of the search strategy can be found in *Appendix 1*. Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews), performing a citation search of relevant articles, contacting key experts in the field and

undertaking systematic keyword searches of the internet using the Google search engine (Google Inc., Mountain View, CA, USA).

All identified citations from the electronic searches and other resources were imported into and managed using EndNote bibliographic software version X8 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA].

Inclusion and exclusion criteria

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer (AP) and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to VTE) were excluded. Second, all abstracts and full-text articles were examined independently by two reviewers (AP and DH). When necessary, non-English-language studies were translated using Google Translate (Google Inc., Mountain View, CA, USA) to facilitate study selection and subsequent data extraction. Any disagreements in the selection process were resolved through discussion or, if necessary, arbitration by a third reviewer (SG), and articles were included by consensus.

Studies were considered eligible for inclusion if they met the following criteria: (1) study design – RCTs and controlled clinical trials; (2) population – adults (aged > 16 years) requiring temporary immobilisation (e.g. leg cast or brace in an ambulatory setting) for an isolated lower-limb injury; (3) interventions – chemical thromboprophylaxis with LMWH (e.g. dalteparin, enoxaparin, tinzaparin), fondaparinux or oral anticoagulants (e.g. apixaban, dabigatran etexilate, rivaroxaban); (4) comparators – these included placebo, no treatment, aspirin or alternative treatment (although the original protocol considered aspirin to be an option for VTE prophylaxis, NICE guidelines on venous thromboembolism (CG92)[24] do not consider aspirin or other antiplatelet agents to be appropriate for VTE prophylaxis; in addition, aspirin is not indicated as a treatment for VTE prophylaxis in lower-limb immobilisation);[21,25,26] and (5) outcomes – these included symptomatic or asymptomatic DVT, PE, major bleeding or mortality. Exclusion criteria for selection included studies that had not been designed as experimental studies (e.g. cohort studies and case–control studies), studies that had involved hospital inpatient care or any patient requiring hospital admission of > 5 days and studies in which patients received mechanical thromboprophylaxis or underwent ambulant orthopaedic surgery (e.g. arthroscopy, arthroscopic surgery).

Data abstraction and quality assessment strategy

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (AP) into a standardised data extraction form and independently checked for accuracy by a second reviewer (DH). Any discrepancies were resolved through discussion or, if necessary, arbitration by a third reviewer (SG), and articles were included by consensus. If required, authors of primary studies were contacted to obtain additional data, clarify uncertainties and/or confirm data that had been extracted. When multiple publications of the same study were identified, data were extracted and reported as a single study.

The methodological quality of each included study was evaluated using a revised Cochrane Risk of Bias tool for randomised trials (RoB 2.0).[39] The original tool[40] was updated because of questionable inter-rater agreement, subjectivity in assigning risk-of-bias judgements and bias judgements assigned at the trial level.[41–44] In general, RoB 2.0 redefined the potential for bias to five domains: (1) bias arising from the randomisation process, (2) bias as a result of deviations from intended interventions, (3) bias as a result of missing outcome data, (4) bias in the measurement of the outcome and (5) bias in the selection of the reported result. To limit subjectivity in assigning bias judgements, the RoB 2.0 tool provides detailed guidance and contains decision algorithms. An overall judgement of bias was assigned as 'low risk' if all domains were judged as being at a low risk of bias, a judgement of bias was assigned as 'high risk' if at least one domain was judged to be at a high risk of bias (or if the study had some concerns for multiple domains in a way that substantially lowers confidence in the result) and as 'some concerns' if some concerns of bias were noted in at least one domain.[39] The methodological quality of each included study was independently evaluated by two reviewers (AP and DH). Any discrepancies were resolved through discussion or, if necessary, the involvement of a third reviewer (SG). Blinding of the quality assessor to author, institution or journal was not considered necessary.

Methods of data synthesis and analysis

The extracted data and quality assessment variables were presented for each included study, both in structured tables and as a narrative description. For each outcome of interest, a network meta-analysis (NMA) was performed to allow a simultaneous comparison between interventions using all available studies. The data were the number of events out of the number of patients randomised to each intervention, which were assumed to arise from an underlying binomial distribution. The probabilities of an event for each intervention were modelled using a logistic model to estimate odds ratios (ORs). The control intervention was defined as placebo, no treatment or aspirin, and the reference intervention defined in the NMA was the control intervention. Aspirin was grouped with placebo and no treatment on the basis that aspirin is not indicated as a treatment for VTE prophylaxis in lower-limb immobilisation[21,25] and NICE guidelines on VTE (CG92[24] and NG89[1]) do not consider aspirin or other antiplatelet agents to be appropriate for VTE prophylaxis. It was planned to analyse different types of thromboprophylaxis drugs as separate interventions (i.e. LMWH, DOACs and fondaparinux) in the NMA on the basis of having different mechanisms of action and, therefore, potentially different effects.

The analysis was implemented using a Markov chain Monte Carlo simulation using WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).[45] A fixed-effect model was used to estimate the effects of LMWH and fondaparinux relative to control in the available studies, namely a conditional inference. In addition, a random-effects model was used to allow for heterogeneity in the effects of interventions between studies and to estimate whether or not the interventions can have an effect in future studies. The random-effects model was the primary analysis. The baseline log odds in each study were given normally distributed prior distributions with mean 0 and variance 1000, namely N(0, 1000). The log-odds ratios for LMWH and fondaparinux versus control were given normally distributed prior distributions with a mean of 0 and variance of 1000, namely N(0, 1000). The between-study standard deviation (SD) was given a half-normal prior distribution with a mean of 0 and precision of 1.82, namely HN(0, 0.5495); this prior distribution was chosen to have, a priori, 95% of the study-specific odds ratios lie within a factor of 5 from the median odds ratio for each comparison. Convergence of the Markov chains to their stationary distributions was assessed using the Gelman–Rubin convergence statistic.[46] For all outcomes other than major bleeding, convergence occurred within 30,000 iterations of the Markov chain and within 100,000 samples for major bleeding; a burn-in of 100,000 iterations was used in all analyses. There was some evidence of high autocorrelation between successive iterations of the Markov chain; parameters were estimated after retaining every 10th sample of the Markov chain to limit the number of unnecessary runs of the decision model that are informed by the results of the NMA. Results were presented using ORs, 95% credible intervals (CrIs) and the 95% predictive intervals[47] for the OR in a randomly chosen study relative to the control, and the probability of each intervention being the best.[48]

It was planned to assess the following potential treatment effect modifiers in a series of meta-regressions: (1) population characteristics (e.g. proportion who were male, baseline risk of VTE), (2) type of injury (i.e. fractures, Achilles tendon rupture, other soft-tissue injury), (3) treatment of injury (surgical vs. conservative, above- vs. below-knee immobilisation), (4) thromboprophylactic agent used and (5) duration of thromboprophylaxis.

Results

Quantity and quality of research available

The literature searches identified 1105 citations. Of these, 13 studies (all RCTs) met the inclusion criteria.[23,49–60] A flow chart describing the process of identifying relevant literature can be found in *Figure 1*. A total of 23 full-text articles were excluded as they did not meet all of the prespecified inclusion criteria. The majority of the articles were excluded primarily on the basis of inappropriate study design (i.e. non-randomised controlled trial or controlled clinical trial), wrong target population (i.e. not isolated lower-limb injury requiring temporary immobilisation) or unsuitable publication type (i.e. reviews, commentaries, editorials or multiple publications of the same study). A full list of excluded studies with reasons for exclusion is presented in *Appendix 2*.

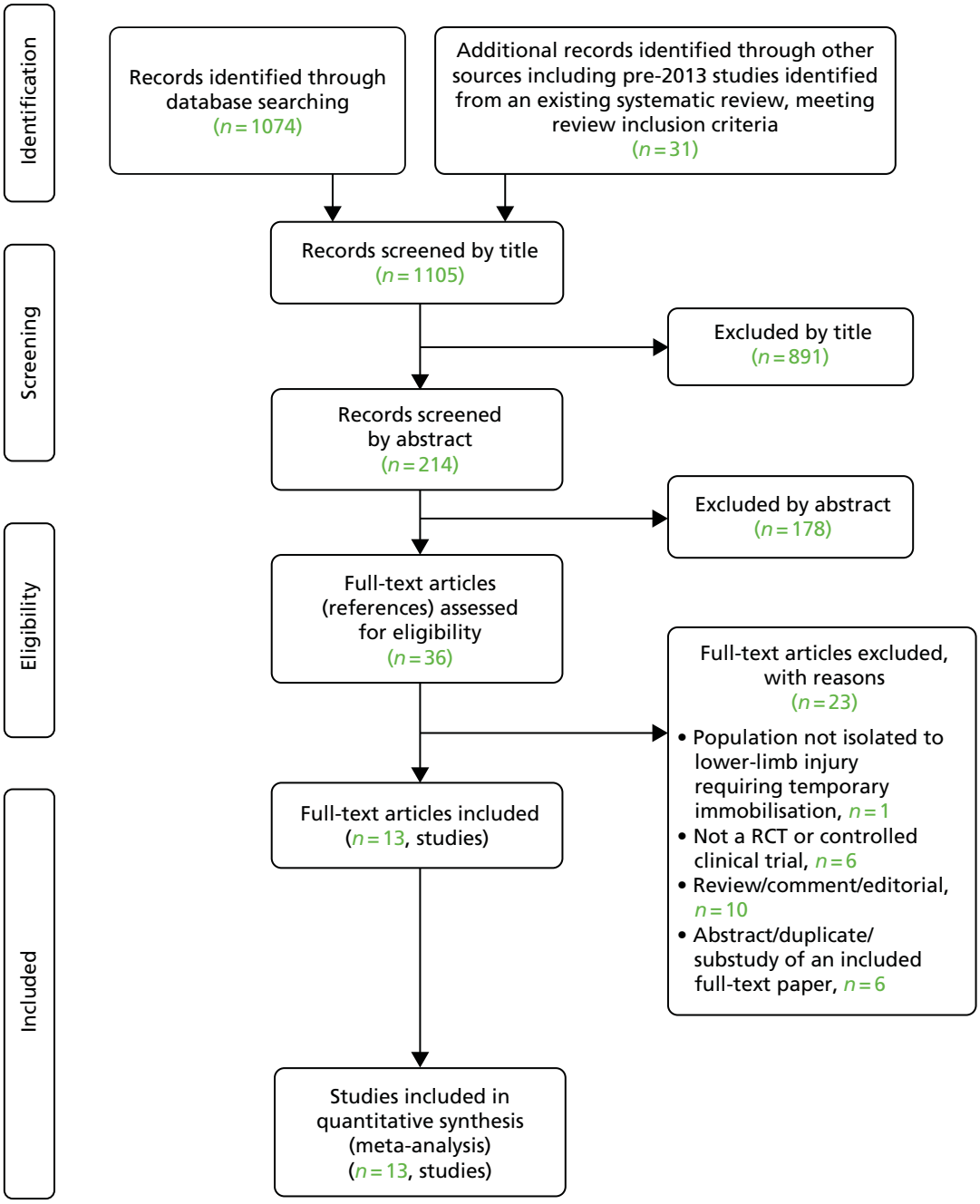

FIGURE 1 Study flow chart (adapted):[37] review of pharmacological thromboprophylaxis for preventing VTE. © 2009 Moher *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Description of included studies (design and participant characteristics)

The design and participant characteristics of the 13 included studies[23,49–60] that evaluated the effectiveness of pharmacological thromboprophylaxis for preventing VTE in ambulatory trauma patients with temporary lower-limb immobilisation are summarised in *Table 1*.

All studies were published between 1993 and 2017. In total, 6857 patients were included and randomised across 10 countries (i.e. Canada,[50,58] China,[60] Denmark,[51,56] France,[57] Germany,[23,52,53,57] Italy,[57] the Netherlands,[49,57,59] Russia,[57] Spain[57] and Sweden[54,55]) to receive either intervention or control treatment. LMWH injections were the primary intervention, using variable agents (i.e. certoparin,[52] dalteparin,[50,54,55,58] nadroparin,[49,53,57,59] reviparin[23,56] and tinzaparin[51]) and dosing regimes (e.g. administered once daily without

TABLE 1 Summary of design and participant characteristics: review of pharmacological thromboprophylaxis for preventing VTE

Authors, year	Country (sites)	Design	Population	Exclusion criteria (main)	Time between injury and recruitment/immobilisation duration (mean)	Prophylaxis before randomisation	Intervention	Comparator	Outcome measure (primary)
Goel *et al.*, 2009[50]	Canada (NR)	RCT, DB[a]	• Adults (aged 18–75 years; mean age, 41 years; male: 62%) • Fractures below knee • Surgically treated • Outpatients • *n* = 305	History of VTE, foot fractures, contraindications to surgery, anticoagulant medication, platelet counts of < 100, elevated serum creatinine of > 200 µmol/l	• Within 48 hours • Immobilisation duration: 14 days[b]	No	LMWH (dalteparin: 5000 IU/day for 14 days, administered by s.c. injection; compliance: > 95%)	Matching placebo for 14 days (compliance with injections: > 95%)	Incidence of DVT determined by bilateral venography at end of treatment
Jørgensen *et al.*, 2002[51]	Denmark (three centres)	RCT, OL[a]	• Adults (aged > 18 years; mean age 48 years; male: 57%) • Fracture or soft-tissue injury • Conservative treatment or surgically treated • Outpatients • *n* = 300	Pregnancy, allergy to heparin or contrast media, renal or liver impairment, uncontrolled hypertension, bleeding disorders, recent GI bleeding, inability to perform self-injection	• NR • Immobilisation duration: 5.5 weeks	No	LMWH (tinzaparin: 3500 IU/day for duration of cast immobilisation, administered by s.c. injection; compliance: NR)	No treatment	Incidence of DVT determined by unilateral venography after plaster cast removal
Kock *et al.*, 1995[52]	Germany (NR)	RCT, OL	• Adults (aged 18–75 years; mean age 34 years; male: 61%) • Fracture or soft-tissue injury • Conservative treatment • Outpatients • *n* = 428	Previous DVT, pregnancy, clotting disorders or anticoagulant medication, bleeding, chronic venous insufficiency, contraindication to heparin, surgical treatment	• NR • Immobilisation duration: 17 days[b]	No	LMWH [certoparin (Mono-Embolex®, Novartis International AG, Basel, Switzerland): 3000 IU/day for duration of cast immobilisation, administered by s.c. injection; compliance: NR]	No treatment	Incidence of DVT determined by duplex sonography and confirmed by phlebography after plaster cast removal
Kujath *et al.*, 1993[53]	Germany (one hospital)	RCT, OL	• Patients aged > 16 years (mean age 34 years; male: 58%) • Fracture or soft-tissue injury • Conservative treatment • Outpatients • *n* = 306	Known thrombopathy, oral anticoagulation, recent brain or GI bleeding, acute pancreatitis, inflammatory heart disease	• NR • Immobilisation duration: 15.7 days[b]	No	LMWH [nadroparin (Fraxiparine®, Sanofi SA, Paris, France): 2850 IU/day for duration of cast immobilisation, administered by s.c. injection; compliance: NR]	No treatment	Incidence of DVT determined by compression ultrasonography and phlebography (positive findings only) after plaster cast removal
Lapidus *et al.*, 2007[55]	Sweden (one centre)	RCT, DB[a]	• Adults (aged 18–75 years; mean age 40 years; male: 79%) • Soft-tissue injury (Achilles tendon rupture) • Surgically treated • Outpatients • *n* = 105	Anticoagulant medication, contrast media allergy, kidney disorder, VTE in preceding 3 months, surgery in preceding month, malignancy, bleeding disorder, pregnancy, high-dose aspirin or platelet inhibitors	• Within 72 hours of injury • Immobilisation duration: 43 days[b]	No	LMWH (dalteparin: 5000 IU/day for 6 weeks, administered by s.c. injection; compliance: NR)	Matching placebo for 6 weeks (compliance with injections: NR)	Incidence of DVT determined by unilateral duplex sonography and confirmed by phlebography

continued

TABLE 1 Summary of design and participant characteristics: review of pharmacological thromboprophylaxis for preventing VTE (*continued*)

Authors, year	Country (sites)	Design	Population	Exclusion criteria (main)	Time between injury and recruitment/immobilisation duration (mean)	Prophylaxis before randomisation	Intervention	Comparator	Outcome measure (primary)
Lapidus *et al.*, 2007[54]	Sweden (one centre)	RCT, DB[a]	• Adults (aged 18–75 years; mean age 48 years; male: 46%) • Fracture of the ankle • Surgically treated • Outpatients • *n* = 272	Anticoagulant medication, allergy to contrast media, renal disorders (including transplant), VTE in preceding 3 months, surgery in preceding month, malignancy, bleeding disorder, pregnancy, high-dose aspirin or platelet inhibitors, multitrauma	• Within 72 hours of injury • Immobilisation duration: 44 days[b]	Yes, all patients received 1 week of initial treatment with dalteparin (5000 IU/day) before randomisation	LMWH (dalteparin: 5000 IU/day for 5 weeks, administered by s.c. injection; compliance: 94.6%)	Matching placebo for 5 weeks (compliance with injections: 94.6%)	Incidence of DVT confirmed by unilateral phlebography after cast removal or compression ultrasonography if the phlebography failed
Lassen *et al.*, 2002[56]	Denmark (six hospitals)	RCT, DB[a]	• Adults (aged > 18 years; median age 47 years; male: 52%) • Fracture or rupture of the Achilles tendon • Conservative treatment or surgically treated • Outpatient (in most cases) • *n* = 440	Current VTE, hypertension, cerebral aneurysm, CVA in preceding 3 weeks, active GI ulcer, bleeding disorder, previous heparin use, contraindication to heparin or contrast allergy, venography, kidney disorder, MI in the preceding 3 months, multiple myeloma, pregnancy, body weight of < 35 kg, history of drug or alcohol abuse	• Within 4 days of injury • Immobilisation duration: 44 days[b]	Yes, approximately one-third of participants in each group received other LMWH for up to 4 days before randomisation	LMWH [reviparin (Clivarin®, Abbott Laboratories, Lake Bluff, IL, USA): 1750 IU/day for the duration of cast immobilisation, administered by s.c. injection; compliance: approximately 100%]	Matching placebo for the duration of cast immobilisation (compliance with injections: approximately 100%)	Incidence of DVT determined by unilateral venography after plaster cast removal (or earlier if clinical symptoms of thrombosis suspected)
Selby *et al.*, 2015[58]	Canada (13 hospitals)	RCT, DB[a]	• Patients aged > 16 years (mean age 49 years; male: 52%) • Fractures • Surgically treated • Outpatients • *n* = 265	Major trauma, other anticoagulant use, allergy to LMWH, pregnancy, active cancer, previous VTE, hypercoagulable state, active bleeding or bleeding disorder, intracranial bleeding in preceding 4 weeks, vascular injury needing repair	• Within 72 hours of injury • Immobilisation duration: 43 days[b]	No	LMWH (dalteparin: 5000 IU/day for 14 days, administered by s.c. injection; compliance: 90%)	Matching placebo for 14 days (compliance with injections: 92%)	Symptomatic VTE within 3 months after surgery or asymptomatic proximal DVT determined by bilateral Doppler ultrasonography at end of treatment
van Adrichem *et al.*, 2017[59]	The Netherlands (eight hospitals)	RCT, OL[a]	• Adults (aged > 18 years; mean age 46 years; male: 49.9%) • Fracture or soft-tissue injury • Conservative treatment or surgically treated • Outpatients • *n* = 1519	History of VTE, contraindications to LMWH therapy, pregnancy, current use of anticoagulant therapy for other indications (use of antiplatelet drugs was allowed)	• NR • Immobilisation duration: 4.9 weeks[b]	No	LMWH [nadroparin: 2850 IU/day or dalteparin (2500 IU/day for < 100 kg or 5000 IU/day for > 100 kg) for the duration of cast immobilisation, administered by s.c. injection; compliance: 87%]	No treatment	Incidence of symptomatic VTE within 3 months after the procedure. DVT determined by abnormal compression ultrasonography

Authors, year	Country (sites)	Design	Population	Exclusion criteria (main)	Time between injury and recruitment/immobilisation duration (mean)	Prophylaxis before randomisation	Intervention	Comparator	Outcome measure (primary)
Zheng *et al.*, 2016[60]	China (three hospitals)	RCT, DB[a]	• Adults (aged > 18 years; mean age 47.8 years; male: 62.3%) • Fracture of the ankle or foot • Surgically treated • Outpatients • *n* = 814	Multiple fractures; history of VTE; a tibial, fibular, femoral or hip fracture that required operative treatment or had casts or splints; history of thromboembolic event; anticoagulation; active cancer; or known hypercoagulability and pilon fractures	• Mean 3.3 days • Immobilisation duration: NR	No	LMWH (NR but given once daily for 14 days, administered by s.c. injection; compliance: NR)	Matching placebo for 14 days (compliance with injections: NR)	Incidence of VTE. DVT determined by bilateral Doppler ultrasonography
Gehling *et al.*, 1998[23]	Germany (one hospital)	RCT	• Patients aged > 16 years (mean age 36 years; male: 49%) • Fracture or soft-tissue injury • Management approach unclear (but majority appear to have been surgically treated) • Outpatients • *n* = 287	Patients aged < 40 years without lower-limb injury and risk factors, contraindication to LMWH or aspirin anticoagulation, thrombocytopenia, pregnancy, kidney damage, apoplectic insult, haemorrhagic diathesis, gastric ulcer, hypertension, acute thrombosis	• NR • Immobilisation duration: NR	NR	LMWH (reviparin: 1750 IU/day, administered by s.c. injection; compliance: NR)	Aspirin (1000 mg/day, administered orally; compliance: NR)	Incidence of DVT determined by duplex sonography (all) or phlebography (if thrombosis suspected)
Bruntink *et al.*, 2017[49] (three-arm study)	The Netherlands (seven hospitals)	RCT, SB[a]	• Adults (aged > 18 years; mean age 47 years; male: 42%) • Fracture of the ankle or foot • Conservative treatment • Outpatients • *n* = 467	History of VTE, hypersensitivity to nadroparin or fondaparinux, anticoagulation, hypercoagulability, bleeding tendency/disorder (including previous or active bleeding from the digestive tract), pregnancy or lactation, 'active' malignancy, severe hepatic or renal impairment, retinopathy, haemorrhagic stroke, major surgery in the preceding 2 months, severe hypertension	• Within 72 hours of injury • Immobilisation duration: 39.5 days[b]	No	LMWH (nadroparin: 2850 IU/day for the duration of cast immobilisation, administered by s.c. injection; compliance: approximately 100%)	1. Fondaparinux (2.5 mg/day for the duration of cast immobilisation, administered by s.c. injection; compliance: approximately 100%) 2. No treatment	Incidence of DVT determined by duplex sonography after the removal of the cast (or earlier if thrombosis was suspected)

continued

TABLE 1 Summary of design and participant characteristics: review of pharmacological thromboprophylaxis for preventing VTE (*continued*)

Authors, year	Country (sites)	Design	Population	Exclusion criteria (main)	Time between injury and recruitment/immobilisation duration (mean)	Prophylaxis before randomisation	Intervention	Comparator	Outcome measure (primary)
Samama *et al.*, 2013[57]	France, Russia, the Netherlands, Spain, Germany and Italy (93 centres)	RCT, OL[a]	• Adults (aged > 18 years; mean age 46 years; male: 46.6%) • Fracture or soft-tissue injury • Conservative treatment • Outpatients • *n* = 1349	Antithrombotic therapy; bleeding tendency/ disorder; peptic ulcer disease; haemorrhagic stroke, brain, spinal or ophthalmological surgery (in the preceding 12 months); severe head injury in the preceding 3 months; uncontrolled arterial hypertension; severe hepatic impairment; body weight of < 50 kg; contraindication to anticoagulant therapy; pregnancy/lactation or not using a reliable contraceptive method	• Within 72 hours of injury • Immobilisation duration: 33.7 days[b]	No	LMWH (nadroparin: 2850 IU/day for the duration of cast immobilisation, administered by s.c. injection; compliance: NR)	Fondaparinux (2.5 mg/day for the duration of cast immobilisation, administered by s.c. injection; compliance: NR)	Incidence of VTE. Compression ultrasonography and/or venography performed for suspected DVT after cast removal

CVA, cerebrovascular accident; DB, double blind; MI, myocardial infarction; NR, not reported; OL, open label; SB, single blind; s.c, subcutaneous.
a Blinded outcome assessment.
b Means were calculated from the reported group means of intervention and comparator arms.

dose adjustment for bodyweight), but two studies used fondaparinux.[49,57] One study used aspirin as a control group treatment,[23] with others using placebo injections or nothing dependent on design.[50–56,58–60] In general, most studies excluded patients at highest risk of VTE, namely those with active cancer,[49,54,55,58,60] previous VTE[49,50,52–56,58–60] or first-degree family history of VTE.[59,60]

Five identified studies used open-label methodology with subjective screening outcomes (duplex sonography or phlebography on cast removal).[51–53,57,59] Six studies used double blinding within the design.[50,54–56,58,60] The single largest study had symptomatic VTE only as an identified primary outcome, confirmed with imaging.[59] Although all studies included adult patients with an isolated lower-limb injury requiring temporary immobilisation, there was wide variation in terms of injury type. Five studies focused on patients with fractures,[49,50,54,58,60] one focused on Achilles tendon ruptures[55] and the remaining seven studies included patients with mixed pathology.[23,51–53,56,57,59] Depending on the type of injury, the management of lower-limb injury included conservative treatment,[49,52,53,57] surgical management[50,54,55,58,60] or both.[51,56,59] In eight studies,[49,50,54–58,60] patients were recruited within 4 days of injury, whereas, in the remaining studies,[23,51–53,59] the time to recruitment was not stated. The duration of immobilisation ranged from 14 days[50] to 44 days.[54,56] In two studies, all[54] or some (approximately one-third)[56] patients first received prophylaxis prior to randomisation; these studies were included, as any final impact on outcome would be likely to take the form of a reduction in VTE outcome events. In addition, the results of these trials remain relevant to the study question in the light of current regimes, suggesting that prophylaxis continue for the duration of immobilisation (usually 4–6 weeks). The sample sizes of the included studies ranged from 105[55] to 1519[59] patients, with the mean age of participants ranging from 34 years[52,53] to 49 years.[58] The number of male participants ranged from 42%[58] to 79%.[55]

Quality characteristics

The overall methodological quality of the 13 included studies is summarised in *Figure 2* and *Table 2*. Overall, risk of bias was present in all studies. Ten studies raised some concerns of bias.[49–51,54–60] The potential sources of bias most frequently identified included concerns about the randomisation process (allocation concealment was not reported in nine studies),[23,50–56,60] blinding (open-label design)[23,49,51–53,57,59] and analyses intentions (only one study provided sufficient information on the selection of the reported result).[59] A high risk of bias was noted in three studies.[23,52,53] High risk of bias was principally attributable to outcome assessment; in three open-label studies,[23,52,53] outcome assessment was performed on all patients with routine screening compression ultrasonography and phlebography for confirmation of positive findings. Finally, all of the included studies were conducted outside the UK, making generalisability of the findings to the UK setting uncertain.

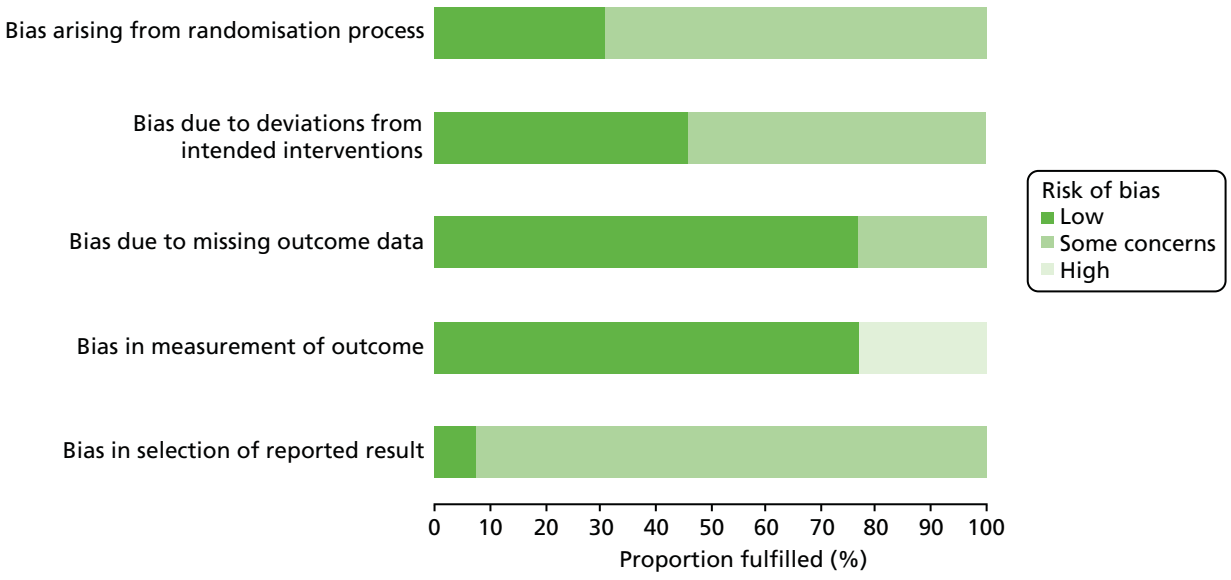

FIGURE 2 Risk-of-bias assessment graph:[39] review authors' judgements about each methodological quality item across all included studies – review of pharmacological thromboprophylaxis for preventing VTE.

TABLE 2 Risk-of-bias assessment summary:[39] review authors' judgements about each methodological quality item for each included study – review of pharmacological thromboprophylaxis for preventing VTE

Study authors, year	Area of potential bias					Overall[a]
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	
Goel *et al.*, 2009[50]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Jørgensen *et al.*, 2002[51]	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Kock *et al.*, 1995[52]	Some concerns	Some concerns	Low	High	Some concerns	High
Kujath *et al.*, 1993[53]	Some concerns	Some concerns	Some concerns	High	Some concerns	High
Lapidus *et al.*, 2007[55]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Lapidus *et al.*, 2007[54]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Lassen *et al.*, 2002[56]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Selby *et al.*, 2015[58]	Low	Low	Low	Low	Some concerns	Some concerns
van Adrichem *et al.*, 2017[59]	Low	Some concerns	Low	Low	Low	Some concerns
Zheng *et al.*, 2016[60]	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Gehling *et al.*, 1998[23]	Some concerns	Some concerns	Some concerns	High	Some concerns	High
Bruntink *et al.*, 2017[49]	Low	Some concerns	Low	Low	Some concerns	Some concerns
Samama *et al.*, 2013[57]	Low	Some concerns	Low	Low	Some concerns	Some concerns

Note
Overall, risk-of-bias judgement (equal to the most severe level of bias found in any domain) was as follows: (1) being at a low risk of bias – the study is judged to be at a low risk of bias for all domains for this result; (2) some concerns – the study is judged to have some concerns of bias in at least one domain for this result; and (3) being at a high risk of bias – the study is judged to be at a high risk of bias in at least one domain for this result or have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Quantitative data synthesis

Details of the results of the primary studies are provided in *Appendix 3*. All 13 studies reported outcomes for any VTE, PE and major bleeding. The rate of any VTE in the control group ranged from 1.8% to 40.4% with a median of 12.2%. The rate of PE in the control group was zero in eight studies and ranged from 0.7% to 2.1% in the other four. There was only one bleeding event across all the control groups. Clinically relevant (proximal or symptomatic) DVTs were reported in 10 out of 13 studies, with control event rates ranging from 0.0% to 6.4% (median 1.5%). Clinically detected (symptomatic) DVTs were reported in all 13 studies, with control event rates ranging from 0.0% to 5.5% (median 0.7%). Any proximal or distal asymptomatic DVTs were reported in 10 out of 13 studies, with control event rates ranging from 1.6% to 25.7% (median 6.9%). Asymptomatic proximal DVTs were reported in 8 out of 13 studies, with control event rates ranging from 0.0% to 6.4% (median 0.7%). Asymptomatic distal DVTs were reported in 8 out of 13 studies, with control event rates ranging from 0.8% to 16.0% (median 3.0%).

A NMA was undertaken to compare the effectiveness of two alternative forms of thromboprophylaxis (i.e. LMWH or fondaparinux) with no thromboprophylaxis (i.e. aspirin, placebo or no treatment). *Figure 3* presents the network of evidence. All 13 studies were included in the analysis and provided information on at least one of the outcomes being analysed. Eleven of the studies compared LMWH thromboprophylaxis with no thromboprophylaxis, one three-arm study compared LMWH with fondaparinux with no thromboprophylaxis, and one study compared LMWH with fondaparinux. A summary of the key results of fixed-effect and random-effects NMA are provided in *Table 3*.

Clinically detected deep-vein thrombosis (symptomatic)

Data were available from all 13 studies.[23,49–60] The risk of clinically detected DVT (symptomatic) was lower in adult outpatients with lower-limb immobilisation who received LMWH (OR 0.40, 95% CrI 0.12 to 0.99) and fondaparinux (OR 0.10, 95% CrI 0.01 to 0.94) than those in the control group. Fondaparinux is likely to be the most effective treatment (probability of being the most effective = 0.91). However, the heterogeneity in treatment effects between studies suggests that the true effects may vary depending on study characteristics (between-study SD 0.55, 95% CrI 0.03 to 1.59).

Asymptomatic deep-vein thrombosis (proximal segment)

Data were available from eight studies.[23,50–52,55,57,58,60] The risk of asymptomatic DVT (proximal segment) was lower in adult outpatients with lower-limb immobilisation who received LMWH (OR 0.21, 95% CrI 0.04 to 0.82) than those in adults in the control group. A similar effect was found for fondaparinux, although the results were inconclusive (OR 0.28, 95% CrI 0.02 to 3.42). The heterogeneity in treatment effects between studies suggests that the true effects may vary depending on study characteristics (between-study SD 0.42, 95% CrI 0.02 to 1.44).

Asymptomatic deep-vein thrombosis (distal)

Data were available from eight studies.[23,50–52,56–58,60] The risk of asymptomatic DVT (distal) was lower in adult outpatients with lower-limb immobilisation who received fondaparinux (OR 0.11, 95% CrI 0.03 to 0.35) than in those in the control group; fondaparinux is likely to be the most effective treatment (probability of being the most effective = 1.00). There was insufficient evidence of an effect of LMWH (OR 0.69, 95% CrI 0.43 to 1.12) compared with control, although the effect favoured treatment with LMWH. There was evidence of mild to moderate heterogeneity between studies, suggesting that the true effects may vary depending on study characteristics (between-study SD 0.20, 95% CrI 0.01 to 0.83).

Asymptomatic deep-vein thrombosis (all)

Data were available from 10 studies.[23,49–52,54,56–58,60] The risk of asymptomatic DVT (all) was lower in adult outpatients with lower-limb immobilisation who received LMWH (OR 0.57, 95% CrI 0.39 to 0.82) and fondaparinux (OR 0.14, 95% CrI 0.05 to 0.31) than in those in the control group. Fondaparinux is likely to be the most effective treatment (probability of being the most effective = 1.00). There was evidence of mild to moderate heterogeneity in treatment effects between studies, suggesting that the true effects may vary depending on study characteristics (between-study SD 0.17, 95% CrI 0.01 to 0.70).

Pulmonary embolism

Data were available from all 13 studies.[23,49–60] The risk of PE was lower in adult outpatients with lower-limb immobilisation who received LMWH (OR 0.17, 95% CrI 0.01 to 0.88) than in those in the control group. A reduction in risk was also found for fondaparinux, although the results were inconclusive (OR 0.47, 95% CrI 0.01 to 9.54). The heterogeneity in treatment effects between studies suggests that the true effects may vary depending on study characteristics (between-study SD 0.81, 95% CrI 0.05 to 2.04).

Major bleeding

Data were available from all 13 studies,[23,49–60] but, with only four events across all the studies, estimates of the effects of LMWH (OR 1.45, 95% CrI 0.08 to 32.17) and fondaparinux on the risk of major bleeding were inconclusive. Control had the highest probability of being the best treatment (probability of being the best = 0.59). The between-study SD was 0.50 (95% CrI 0.02 to 1.64).

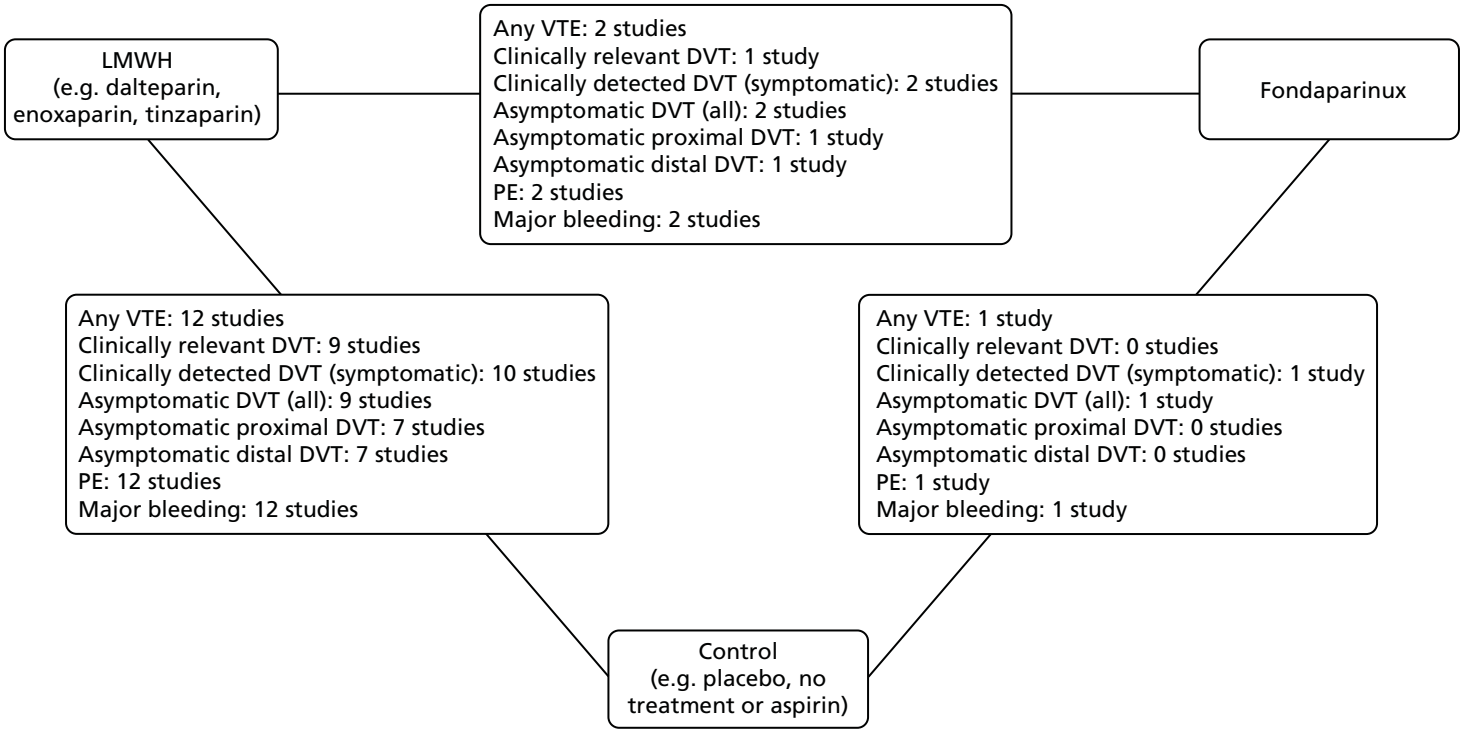

FIGURE 3 Network diagram of different pharmacological thromboprophylaxis interventions vs. no thromboprophylaxis for preventing VTE. The nodes are the interventions. The numbers against each outcome represent the number of times that each pair of interventions has been compared. There was one multiarm study comparing LMWH vs. fondaparinux vs. control. Diagrams for specific outcomes depend on the number of studies that provide data and the number of non-zero event studies; not all outcomes involve feedback loops.

TABLE 3 Results of fixed-effect and random-effects NMAs of different pharmacological thromboprophylaxis interventions vs. no thromboprophylaxis

Treatment	NMA, OR (95% CrI)			Probability of being best
	Fixed effect	Random effects	OR (95% PrI)	
Clinically detected DVT (symptomatic)				
LMWH	0.45 (0.22 to 0.89)	0.40 (0.12 to 0.99)	0.41 (0.05 to 2.31)	0.09
Fondaparinux	0.11 (0.01 to 0.60)	0.10 (0.01 to 0.94)	0.10 (0.00 to 1.46)	0.91
None	–	–	–	0.00
Asymptomatic DVT (proximal segment)				
LMWH	0.22 (0.05 to 0.71)	0.21 (0.04 to 0.82)	0.21 (0.02 to 1.34)	0.63
Fondaparinux	0.29 (0.03 to 2.35)	0.28 (0.02 to 3.42)	0.28 (0.01 to 4.49)	0.36
None	–	–	–	0.01
Asymptomatic DVT (distal)				
LMWH	0.69 (0.47 to 1.01)	0.69 (0.43 to 1.12)	0.69 (0.29 to 1.62)	0.00
Fondaparinux	0.11 (0.04 to 0.27)	0.11 (0.03 to 0.35)	0.11 (0.03 to 0.42)	1.00
None	–	–	–	0.00
Asymptomatic DVT (all)				
LMWH	0.57 (0.42 to 0.77)	0.57 (0.39 to 0.82)	0.57 (0.28 to 1.12)	0.00
Fondaparinux	0.14 (0.07 to 0.27)	0.14 (0.05 to 0.31)	0.14 (0.05 to 0.38)	1.00
None	–	–	–	0.00
PE				
LMWH	0.30 (0.07 to 0.96)	0.17 (0.01 to 0.88)	0.18 (0.00 to 1.79)	0.74
Fondaparinux	0.64 (0.05 to 7.26)	0.47 (0.01 to 9.54)	0.48 (0.01 to 17.53)	0.25
None	–	–	–	0.01
Major bleeding				
LMWH	1.60 (0.14 to 25.67)	1.45 (0.08 to 32.17)	1.46 (0.06 to 42.87)	0.37
Fondaparinux	14,380 (0.48 to 9.9×10^{14})	8422 (0.32 to 1.3×10^{14})	8421 (0.29 to 1.3×10^{14})	0.03
None	–	–	–	0.59
Clinically relevant DVT[a]				
LMWH	0.43 (0.22 to 0.79)	0.40 (0.16 to 0.85)	0.40 (0.07 to 1.76)	0.22
Fondaparinux	0.25 (0.07 to 0.82)	0.23 (0.03 to 1.36)	0.23 (0.02 to 2.11)	0.77
None	–	–	–	0.01
Any VTE				
LMWH	0.53 (0.41 to 0.67)	0.52 (0.37 to 0.71)	0.52 (0.23 to 1.12)	0.00
Fondaparinux	0.14 (0.07 to 0.25)	0.13 (0.05 to 0.30)	0.13 (0.04 to 0.39)	1.00
None	–	–	–	0.00

PrI, predictive interval.
a Clinically relevant DVT was defined as the cumulative figure of any symptomatic or asymptomatic proximal DVT.

Clinically relevant deep-vein thrombosis

Data were available from 10 studies.[23,50–52,55,57,58,60] The risk of clinically relevant DVT was lower in adult outpatients with lower-limb immobilisation who received LMWH (OR 0.40, 95% CrI 0.16 to 0.85) than in those in the control group. The risk was also lower in patients treated with fondaparinux, although the results were inconclusive (OR 0.23, 95% CrI 0.03 to 1.36). The heterogeneity in treatment effects between studies suggests that the true effects may vary depending on study characteristics (between-study SD 0.45, 95% CrI 0.02 to 1.39).

Any venous thromboembolism

Data were available from all 13 studies.[23,49–60] The risk of any VTE was lower in adult outpatients with lower-limb immobilisation who received LMWH (OR 0.52, 95% CrI 0.37 to 0.71) and fondaparinux (OR 0.13, 95% CrI 0.05 to 0.30) than in those not receiving thromboprophylaxis. Fondaparinux is likely to be the most effective treatment (probability of being the most effective = 1.00). There was mild to moderate heterogeneity in treatment effects between studies. Although the results suggest that the true effects may vary depending on study characteristics, the predictive distribution still favoured fondaparinux relative to control (between-study SD 0.23, 95% CrI 0.01 to 0.75).

There were few reported adverse effects in the treated patients. Minor bleeding event rates varied from 0.0% to 10.5% in the LMWH intervention groups, 0.0% to 1.5% in the fondaparinux intervention groups and 0.0% to 6.8% in the control groups. In the largest RCT to date,[59] the most common adverse event (of infection) occurred at a similar rate in the intervention and control groups (1.6% vs. 2.0%, respectively). When assessed in the trials, compliance appeared good, with only a single open-label study[49] recording pain on injection, which was seen in 1.4% of participants in the intervention group. In studies monitoring for the incidence of heparin-induced thrombocytopaenia, no cases were found.[58] No deaths in any study were deemed attributable to either VTE or the use of an intervention.

The results of the network meta-regressions are detailed in *Appendix 4*. A network meta-regression of population characteristics (e.g. proportion of males, baseline risk of VTE), type of injury (i.e. fractures, Achilles tendon rupture, other soft-tissue injury), treatment of injury (surgical vs. conservative, above- vs. below-knee immobilisation) and the duration of thromboprophylaxis was undertaken for each available outcome. This showed that no covariate improved model fitted and, therefore, explained the variation in treatment effects.

The effect of the type of thromboprophylactic agent used (i.e. dalteparin, tinzaparin, certoparin, nadroparin, reviparin) was assessed using a separate NMA. This suggested that there were differences in the effects of the type of thromboprophylactic agent used, including between the different types of LMWH, with certoparin having the highest probability of having the greatest effect on any VTE. However, this finding was based on the effect of certoparin being used in one study,[52] so it is not possible to draw any reliable conclusions.

Summary of key findings

- Thromboprophylaxis with LMWH approximately halves the risk of any VTE. The effects on different types of VTE are variable and uncertain (in accordance with random error), but all are consistent with a halving of risk.
- Thromboprophylaxis with fondaparinux appears to have a greater effect on the risk of VTE and a greater probability than LMWH of being the more clinically effective, but estimates for fondaparinux are based on only two trials.
- Major bleeding is very uncommon; therefore, the effect of thromboprophylaxis on major bleeding in this group is uncertain.
- Meta-regression did not identify any reliable evidence of effect modification by key covariates.

Review of individual risk factors associated with venous thromboembolic risk

Objectives

To identify individual, patient identifiable risk factors associated with VTE risk in patients with temporary lower-limb immobilisation due to injury.

Methods of reviewing effectiveness

Identification of studies

Studies were identified by searching the following electronic databases and research registers:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, MEDLINE and Versions(R) (via OvidSP), 1946 to May 2017.
- EMBASE (via OvidSP), 1974 to May 2017.
- Cochrane Database of Systematic Reviews (via Wiley Online Library), 1996 to May 2017.
- Database of Abstracts of Review of Effects (via Wiley Online Library), 1995 to March 2015.
- Cochrane Central Register of Controlled Trials (via Wiley Online Library), 1898 to May 2017.
- HTA database (via Wiley Online Library), 1995 to May 2017.
- NHS EED (via Wiley Online Library), 1995 to March 2015.
- Science Citation Index Expanded (via Web of Science), 1900 to May 2017.
- ClinicalTrials.gov (via US National Institutes of Health), 2000 to May 2017.
- International Clinical Trials Registry Platform (via World Health Organization), 1990 to May 2017.

The search strategy used free-text and thesaurus terms and combined synonyms relating to the condition (i.e. VTE in people with lower-limb immobilisation) with risk factor assessment or risk prediction modelling terms (used in the searches of MEDLINE, The Cochrane Library and EMBASE only). No language or date restrictions were used on any database. Further details on the search strategy can be found in *Appendix 5*. Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews), performing a citation search of relevant articles, contacting key experts in the field and undertaking systematic keyword searches of the internet using the Google search engine.

All identified citations from the electronic searches and other resources were imported into and managed using EndNote bibliographic software.

Inclusion and exclusion criteria

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer (AP) and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to VTE) were excluded. Second, all abstracts and full-text articles were then examined independently by two reviewers (AP and DH). When necessary, non-English-language studies were translated using Google Translate to facilitate study selection and subsequent data extraction. Any disagreements in the selection process were resolved through discussion or, if necessary, arbitration by a third reviewer (SG), and articles were included by consensus.

Studies were considered eligible for inclusion if they met the following criteria: (1) any study design that included a measurement of VTE patient outcome, (2) a study population of adults (aged > 16 years) requiring temporary immobilisation (e.g. leg cast or brace in an ambulatory setting) for an isolated lower-limb injury, (3) any studies that reported and analysed data on individual risk factors associated with DVT or PE. Exclusion criteria for the selection included studies that involved hospital inpatient care or any patient requiring hospital admission for > 5 days, or studies that involved patients undergoing ambulant orthopaedic surgery (e.g. arthroscopy, arthroscopic surgery).

Data abstraction and quality assessment strategy

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (AP) into a standardised data extraction form and independently checked for accuracy by a second reviewer (DH). Any discrepancies were resolved through discussion to achieve agreement. When differences were unresolved, the opinion of a third reviewer (SG) was sought. When multiple publications of the same study were identified, data were extracted and reported as a single study.

The methodological quality of each included study was assessed using the Risk Of Bias In Non-randomized Studies – of Interventions tool (ROBINS-I) [formerly called A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI)].[61] The tool is based on the original Cochrane Risk of Bias tool for randomised studies[40] and also builds on related tools, such as the quality assessment of diagnostic accuracy studies (QUADAS-2).[62]

The ROBINS-I[61] tool provides a detailed framework for assessment and judgement of risk-of-bias domains that may arise in three phases: (1) at pre-intervention, bias arising from confounding and selection of participants into the study; (2) at intervention, bias in measurement of interventions; and (3) at post-intervention, bias due to deviations from intended interventions, missing data, measurement of outcomes and selection of reported results. Each domain is rated as being at low, moderate, serious or critical risk of bias. A low risk of bias indicates that the study is comparable to a well-performed randomised trial in the domain being evaluated. A moderate risk of bias indicates that the study is sound for a non-randomised study but is not comparable to a well-performed randomised trial. A serious risk of bias indicates the presence of important problems in the domain and a critical risk of bias indicates that the study is too problematic to provide any useful evidence on the intervention effects. If insufficient information is provided to determine the risk of bias of a certain domain, the domain is marked as having no information. In general, the overall risk of bias of each study was determined to be equal to that of the most severe level of bias found in any domain.

All studies were analysed using ROBINS-I,[61] regardless of whether or not the original study design included randomisation to other exposures, thus ensuring that risk of bias was assessed specifically for the comparisons of interest to this review. It is important to note that the quality assessment reflects how well a specific result evaluated the association of interest to this review, regardless of the objectives of the original study.

Methods of data synthesis and analysis

Venous thromboembolism was considered to comprise any subsequent recorded diagnosis of DVT or PE, or death attributable to either pathology. No attempt was made to distinguish between anatomical location, thrombus burden or clinical sequelae of VTE for this project, in accordance with the definitions of hospital-acquired thrombosis produced by NHS England.[63] Individual risk factors highlighted through regression, OR analysis or parametric testing as significantly associated with an increased or decreased likelihood of subsequent VTE were extracted. In particular, each paper was scrutinised for evidence of individual risk factors, especially those highlighted within current risk stratification tools,[17,31–33] and their predictive performance was recorded, when available. Other risk factors demonstrating an association with VTE in the context of individual studies were also reported. A meta-analysis was not possible owing to significant levels of heterogeneity between studies, variable reporting items and the high risk of attributable bias. Descriptive statistics and thematic analysis were used to synthesise risk factors acting in a reproducible fashion across studies. Thematic analysis took an inductive/semantic form, using familiarisation and coding directed by data content. Consistent risk factor themes were then highlighted in ordinal fashion. All analyses were conducted using Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

Quantity and quality of research available

The literature searches identified 4771 citations. Of these, 15 studies[9,11,23,50,52,53,60,64–71] met the inclusion criteria. *Figure 4* presents a flow chart describing the process of identifying relevant literature. Sixty full-text articles were excluded as they did not meet all the prespecified inclusion criteria. The majority of the articles were excluded primarily on the basis of an inappropriate target population (not isolated lower-limb injury requiring temporary immobilisation), no data or analysis of risk factors associated with VTE, or an unsuitable publication type (i.e. reviews, commentaries, editorials or abstracts of excluded/included full-text papers). More specifically, two potentially relevant papers[72,73] were excluded as they included a specific elective surgical population who were not considered to meet the inclusion criterion of lower-limb injury. A potentially relevant prospective observational cohort study[74] was excluded, based on the authors'

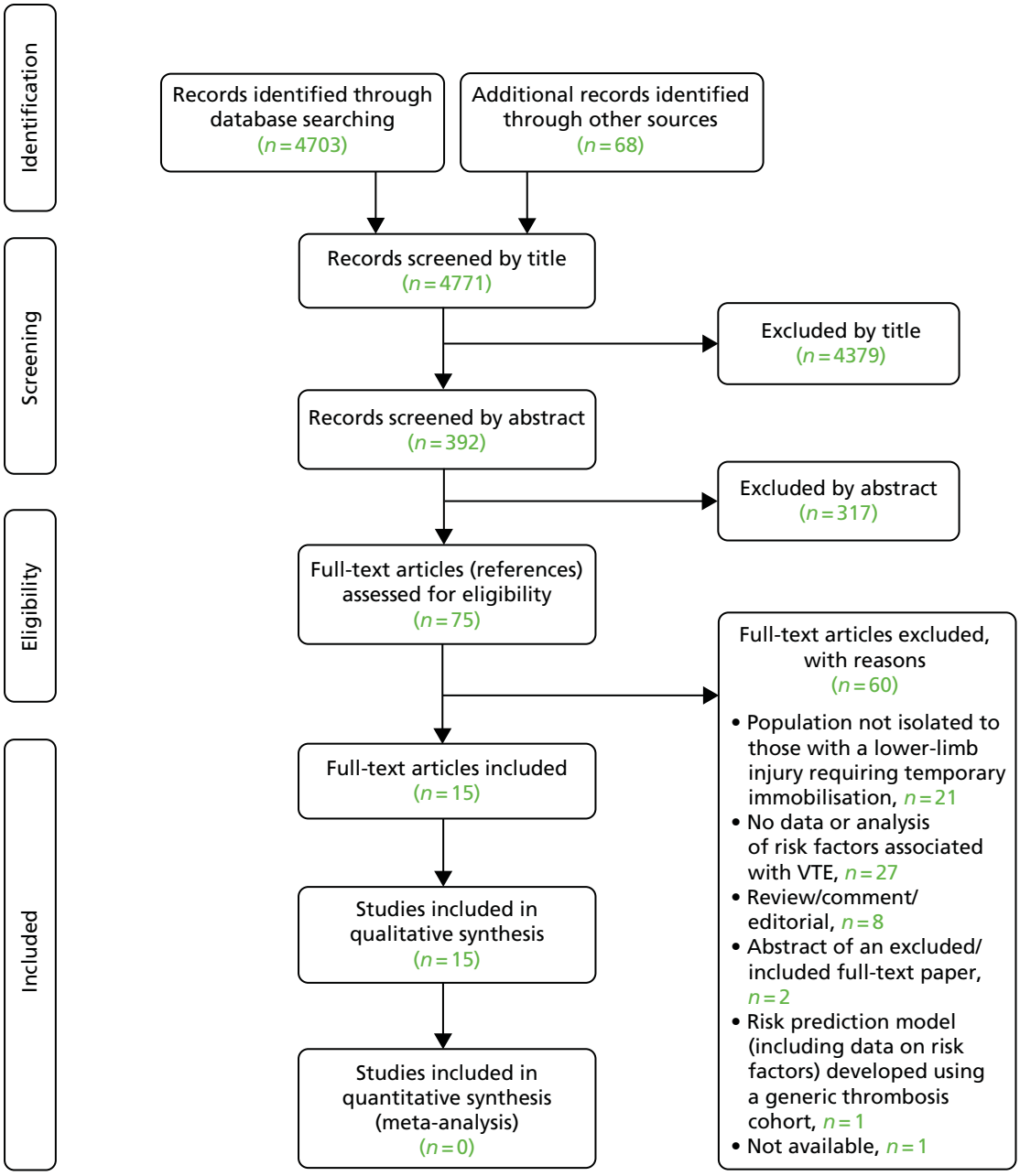

FIGURE 4 Study flow chart (adapted):[37] review of individual risk factors associated with VTE risk. © 2009 Moher *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

conclusion of a low event rate precluding any subsequent analysis for predictors of VTE. Finally, a case–control study[32] specifically seeking to derive a decision rule for the cohort of interest was excluded, based on the creation of this rule from a generic thrombosis cohort rather than a subgroup of patients with temporary lower-limb immobilisation. A full list of excluded studies with reasons for exclusion is presented in *Appendix 6*.

Description of included studies (design and patient characteristics)

The design and patient characteristics of the 15 included studies[9,11,23,50,52,53,60,64–71] that provided data on individual patient identifiable risk factors associated with VTE risk in ambulatory trauma patients with temporary immobilisation following lower-limb injury is summarised in *Table 4*.

All studies were published between 1993 and 2017 (five were RCTs with conservative arms,[23,50,52,53,60] three were prospective observational cohort or cross-sectional studies,[65,67,69] one was a case–control study[70] and six were retrospective cohort studies)[9,11,64,66,68,71] and conducted in 10 countries (Australia,[11,64,65] Canada,[9,50] China,[60] Denmark,[71] France,[69] Germany,[23,52,53] Iran,[67] the Netherlands,[70] the UK[66] and the USA).[68] Most of the studies (n = 11) were entirely outpatient based,[11,23,50,52,53,60,64–67,69] whereas the remaining studies[9,68,70,71] included patients with a short-duration inpatient stay to facilitate day-case surgery. In total, data were collated on 80,678 patients with a subsequent reported outcome of VTE positive or negative following temporary lower-limb immobilisation. The incidence of VTE across the studies with interpretable outcome data (79,202 patients) ranged from 0.22%[66] to 23.5%[9] (median 4.8%), mean age ranged from 33.8 years[52] to 52.6 years[71] and the proportion of male patients ranged from 45.8%[65] to 86.1%,[9] with a median across those studies with reported data of 56.3%.

The duration of follow-up varied between studies. Ten studies reported follow-up over a period of at least 3 months[9,50,60,64–66,68–71] and one study followed up patients for up to 14 days.[67] Although four studies failed to record the duration of follow-up,[11,23,52,53] two of these appeared to report follow-up only for the duration of the plaster cast, which averaged at 15.7 days[53] and 17 days.[52] Eight studies collected data on risk factors prospectively via physician assessment or questionnaire,[23,50,52,53,60,65,69,70] whereas six studies collected these data through clinical records, electronic patient notes or registries.[9,11,64,66,68,71] One study did not report the methodology for this aspect of data collection.[67] Analysis and methodology of VTE diagnosis subsequent to immobilisation varied markedly across studies and included prospective screening in all patients following plaster cast removal (seven studies),[23,50,52,53,60,65,67] adjudicated diagnostic evaluation in those with symptoms (two studies)[69,70] and retrospective identification of VTE through the interrogation of clinical records/health databases (six studies).[9,11,64,66,68,71] A single study[66] looked only at the subsequent diagnosis of PE as an outcome, with reduced prevalence as expected. The association of individual risk factors with subsequent VTE was highlighted through regression analyses (nine studies),[11,50,60,64,66,68–71] non-parametric tests (two studies)[9,65] and descriptive statistics (four studies).[23,52,53,67]

Quality characteristics

The overall methodological quality of the 15 included studies is summarised in *Figure 5* and *Table 5*.

All studies were deemed to be at overall moderate (seven studies)[23,50,52,53,60,68,71] or serious (eight studies)[9,11,64–67,69,70] risk of bias, using the ROBINS-I[61] framework for assessment and judgement. Studies scoring a serious risk of bias did so predominantly on the selection of participants into the study, perhaps highlighting the issue with retrospective observational work into VTE outcomes; patients deemed to be at high risk in these cohorts are often treated with thromboprophylaxis (as highlighted in *Table 4*), or managed in a different manner from other patients. If this is not highlighted within a prospective analysis plan, a false low event rate is seen and risk is marginalised.

TABLE 4 Summary of design and patient characteristics: review of individual risk factors associated with VTE risk

Study authors, year; country	Design, setting	Inclusion criteria (main)	Patients, sex, age (years)	Incidence of VTE	Prophylaxis	Duration of follow-up	Risk factor ascertainment	Outcome ascertainment	Statistical analysis
Gehling *et al.*, 1998; Germany[23]	• Design: prospective open-label RCT • Setting: outpatient	Age > 16 years with lower-limb injury requiring immobilisation with plaster or bandages (and at least one risk factor for VTE)	• *n* = 287 • 50.5% male • Mean age: 36.3 years[a]	• LMWH group: 6.3% • Aspirin group: 4.8%	NR	NR	Physician assessment (prospective)	Clinical assessment, screening sonography and confirmation phlebography	NR (appears descriptive)
Goel *et al.*, 2009; Canada[50]	• Design: prospective double-blind RCT • Setting: outpatient	Adults aged 18–75 years with unilateral displaced fractures below the knee requiring operative intervention	• *n* = 238 • 62% male • Mean age: 40.5 years[a]	LMWH group: 8.7% Control group: 12.6%	No prophylaxis prior to randomisation	Minimum of 3 months following surgery or until the fracture had united	Physician assessment (prospective)	Clinical assessment and bilateral lower-leg venography for all patients	Univariate and multivariate logistic regression
Kock *et al.*, 1995; Germany[52]	• Design: prospective open-label RCT • Setting: outpatient	Adults aged 18–65 years undergoing conservative treatment for below-knee injury with cylinder or below-knee cast	• *n* = 339 • 61% male • Mean age: 33.8 years[a]	LMWH group: 0.0% Control group: 4.3%	No prophylaxis prior to randomisation	NR (however, duration of casting: LMWH group, 15.2 days; control group, 18.8 days)	Physician assessment (prospective)	Clinical assessment, screening sonography and confirmation phlebography	NR (appears descriptive)
Kujath *et al.*, 1993; Germany[53]	• Design: prospective open-label RCT • Setting: outpatient	Aged > 16 years undergoing conservative treatment for lower-limb injury with below-knee plaster applied for > 7 days	• *n* = 253 • 58% male • Mean age: 34.3 years[a]	LMWH group: 4.8% Control group: 16.5%	No prophylaxis prior to randomisation	NR (however, duration of casting: LMWH group, 15.6 days; control group, 15.8 days)	Physician assessment (prospective)	Compression ultrasonography by two examiners and confirmation phlebography	NR (appears descriptive)
Zheng *et al.*, 2016; China[60]	• Design: prospective double-blind RCT • Setting: outpatient	Adults aged > 18 years with any fracture of the lower limb requiring operative treatment	• *n* = 814 • 62.3% male • Mean age: 47.8 years	LMWH group: 1.5% Control group: 3.2%	No prophylaxis prior to randomisation	3 months	Physician assessment (prospective)	Blinded bilateral Doppler compression ultrasonography	Logistic regression
Riou *et al.*, 2007; France[69]	• Design: prospective cohort study • Setting: outpatient	Aged > 18 years with isolated lower-limb injury (below the knee) managed conservatively (immobilisation duration of > 7 days)	• *n* = 2761 • 51% male • Mean age: 40 years	6.4%	Antithrombotic prophylaxis was given to 61% of patients	3 months	Physician assessment (prospective)	Adjudication committee	Logistic regression with propensity score analysis
Hanslow *et al.*, 2006; Australia[64]	• Design: retrospective cohort study • Setting: outpatient	Patients who had an operative intervention to the foot or ankle	• *n* = 602 • 52% male • Mean age: 42.9 years	5.3%	Antithrombotic prophylaxis was given to 31% of patients	4.4 months	Collected from clinical records (retrospectively)	Case note search, including hospital reattendance and diagnostic imaging	Logistic regression
Jameson *et al.*, 2014; UK[66]	• Design: retrospective cohort study • Setting: outpatient	Patients with isolated unilateral closed ankle fracture, managed conservatively	• *n* = 14,777 • 47% male • Mean age: 46.4 years	0.22% (PE only)	No data recorded	3 months	NR, assumed to be collected from clinical records (retrospective)	Inpatient mortality or coded diagnosis of PE within 90 days of injury	Logistic regression

continued

TABLE 4 Summary of design and patient characteristics: review of individual risk factors associated with VTE risk (*continued*)

Study authors, year; country	Design, setting	Inclusion criteria (main)	Patients, sex, age (years)	Incidence of VTE	Prophylaxis	Duration of follow-up	Risk factor ascertainment	Outcome ascertainment	Statistical analysis
Makhdom *et al.*, 2013; Canada[9]	• Design: retrospective cohort study • Setting: outpatient until surgery, short day-case stay thereafter	All patients undergoing Achilles tendon repair	• *n* = 115 • 86.1% male • Mean age: 41 years	23.5%	No peri- or post-operative prophylaxis	3 months	Collected from electronic medical record system (retrospectively)	Case note search, including hospital reattendance and diagnostic imaging	Non-parametric testing using Fisher's exact test
Meek and Tong, 2012; Australia[11]	• Design: retrospective cohort study • Setting: outpatient	Aged > 18 years with acute lower-limb injury requiring temporary immobilisation (ED discharge within 24 hours of presentation)	• *n* = 1231 • 56.3% male • Mean age: 37 years	2.9%	No prophylaxis (excluded if received at any dose)	NR	Electronic notes screened for eligibility by one investigator (retrospective)	Case note search, including hospital reattendance and diagnostic imaging	Logistic regression
Patel *et al.*, 2012; USA[68]	• Design: retrospective cohort study • Setting: mostly outpatient, some with short inpatient stays (of < 3 days)	All patients who had Achilles tendon rupture	• *n* = 1172 • Sex: NR • Mean age: 45 years	0.77%	Nil routine, assumed to be none provided	3 months	Collected from electronic medical record system (retrospective)	Case note search, including hospital reattendance and diagnostic imaging	Logistic regression
Wahlsten *et al.*, 2015; Denmark[71]	• Design: retrospective cohort study • Setting: inpatient or outpatient	Aged > 18 years undergoing an operative procedure for a fracture of the foot, ankle, tibia or patella	• *n* = 57,619 • 51.4% male • Mean age: 52.6 years[a]	1.0%	Routine perioperative prophylaxis with nil post operative prophylaxis	180 days	Collected from five different cross-linked registries (retrospective)	Case note search, including hospital reattendance and diagnostic imaging	Multivariate Cox regression
van Adrichem *et al.*, 2014; the Netherlands[70]	• Design: case–control study • Setting: mostly outpatient, some with short inpatient stays (of < 3 days)	• Aged 18–70 years with a first VTE identified at an anticoagulation clinic (cases) • Control group identified by random dialling method (matched for sex and age)	• *n* = 10,567[b] • Sex: NR • Mean age: NR	NR	No data recorded	3 months	Participant completed questionnaire (prospective collection)	Case note search, including hospital reattendance and diagnostic imaging	Logistic regression
Ho and Omari, 2017; Australia[65]	• Design: cross-sectional study • Setting: outpatient	Aged > 18 years with fracture to foot/ankle with conservative management	• *n* = 72 • 45.8% male • Mean age: NR (median: 38 years)	11.0%	Nil routine, assumed to be none provided	6 months	Questionnaire (unclear if physician or patient completed)	Prospective compression ultrasonography	Parametric and non-parametric testing with bootstrapping
Manafi Rasi *et al.*, 2013; Iran[67]	• Design: cross-sectional study • Setting: outpatient	Aged > 15 years with stable foot/ankle fracture or grade 3 sprain (non-surgical treatment)	• *n* = 95 • 77.9% male • Mean age: 38 years	3.0%	NR	7–14 days	NR	Compression ultrasonography by two independent examiners	NR (appears descriptive)

NR, not reported.
a Data calculated based on mean of means.
b Sample included 4418 cases and 6149 controls (of these, only 227 cases and 76 controls had lower-extremity injuries).

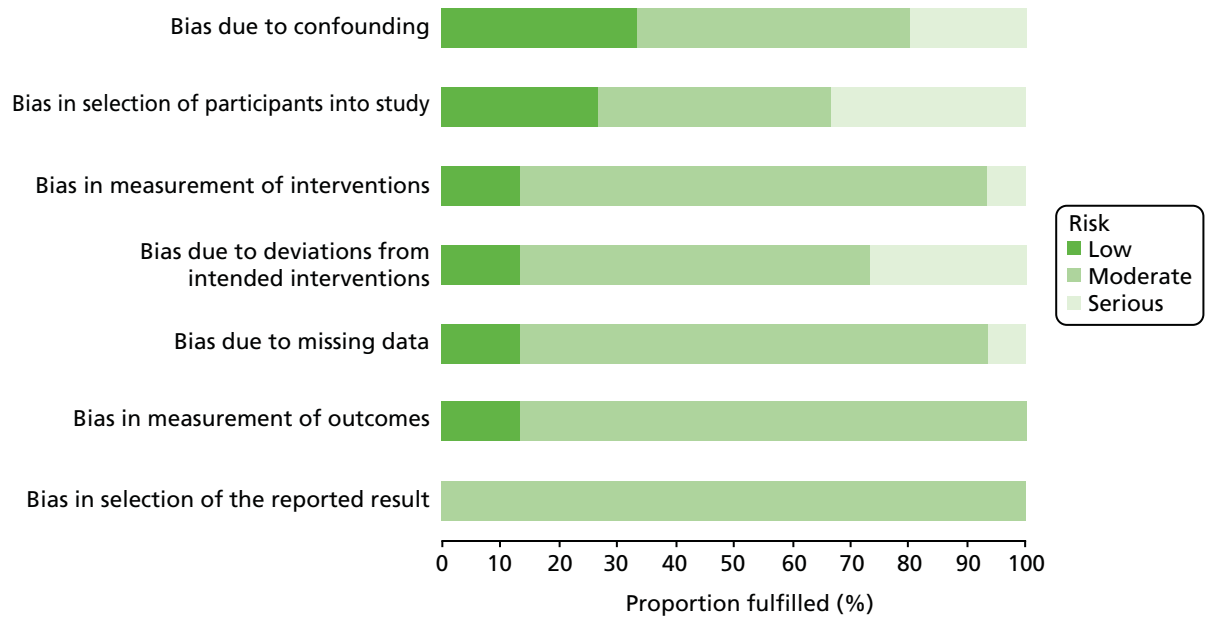

FIGURE 5 ROBINS-I[61] risk-of-bias assessment graph: review authors' judgements about each methodological quality item across all included studies – review of individual risk factors associated with VTE risk.

Narrative data synthesis

Age was the most consistent individual risk prediction factor, highlighted across 11 studies.[9,11,50,52,53,60,65,68–71] ORs reported for age varied from 1.05[60] to 3.48,[11] with limited estimates of precision. Meta-analysis was not undertaken owing to limitations in the data reported and concerns about the heterogeneous nature of the study populations. Injury type was the second most highlighted risk factor across six studies,[11,50,52,53,69,70] all using multivariate logistic regression to suggest that severe traumatic injuries and fractures (when compared with soft-tissue injuries) were independently associated with VTE. Body mass index (BMI) was the third most consistent individual risk highlighted, noted as independently predictive of VTE across four studies,[53,60,70,71] with ORs ranging from 1.201[60] to 17.2.[70] Other risk factors were highlighted in fewer than four studies. Despite being present within several currently used risk stratification tools, pregnancy, recent hospital admission and preceding immobility prior to injury failed to demonstrate an independent association with VTE in any of the selected studies. Individual risk factors currently used within risk stratification tools and their association with VTE across all studies are shown in *Table 6*.

Other potential risk factors associated with subsequent development of VTE after lower-limb immobilisation included recent air travel (one study),[64] coagulopathy and peripheral arterial disease (one study).[71] A single paper[67] looked at the cumulative incidence of risk factors per patient and reported the presence of three or more factors to be significantly associated with the development of VTE. Methodology of reporting individual variables to have no association with subsequent VTE was inconsistent and heterogeneous. Six studies reported no association between sex and VTE in this cohort,[11,50,52,65,66,70] five studies reported no association between exogenous oestrogen use and VTE[9,50,52,53,65] and six studies reported no association between smoking and subsequent VTE.[9,50,52,65,69,71] Several papers produced conflicting results; six studies reported no association between raised BMI and subsequent risk of VTE[9,50,52,65,68,69] and one study reported no association of VTE with increasing age.[66] These other identified risk factors and all negative associations are reported in *Table 7*.

TABLE 5 ROBINS-I[48] risk-of-bias assessment summary: review authors' judgements about each methodological quality item for each included study – review of individual risk factors associated with VTE risk

Study authors, year	Cause/area of bias							Overall[a]
	Confounding	Selection of participants into the study	Classification/ measurement of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	
Gehling *et al.*, 1998[23]	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Goel *et al.*, 2009[50]	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Kock *et al.*, 1995[52]	Low	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Kujath *et al.*, 1993[53]	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Zheng *et al.*, 2016[60]	Low	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Riou *et al.*, 2007[69]	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Hanslow *et al.*, 2006[64]	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Jameson *et al.*, 2014[66]	Moderate	Serious	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Makhdom *et al.*, 2013[9]	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Meek and Tong, 2012[11]	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Patel *et al.*, 2012[68]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Wahlsten *et al.*, 2015[71]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
van Adrichem *et al.*, 2014[70]	Moderate	Serious	Serious	Serious	Moderate	Moderate	Moderate	Serious
Ho and Omari, 2017[65]	Serious	Serious	Moderate	Moderate	Serious	Moderate	Moderate	Serious
Manafi Rasi *et al.*, 2013[67]	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Serious

a Overall risk-of-bias judgement (equal to the most severe level of bias found in any domain) was: (1) low risk of bias – the study is comparable to a well-performed randomised trial; (2) moderate risk of bias – the study is sound for a non-randomised study but not comparable to a rigorous randomised trial; (3) serious risk of bias – the study has some important problems; or (4) critical risk of bias – the study is too problematic to provide any useful evidence on the effects of intervention.

TABLE 6 Individual risk factors and their reported strength of association with developing VTE

	Risk factors associated with developing VTE														
	Permanent (present before episode of lower-limb immobilisation)												Transient (during injured period)		
Study authors, year	Age	BMI	Active cancer	Pregnancy	Smoking	Varicosities	Prior or family history of VTE	Significant comorbidity	Known thrombophilia	Exogenous oestrogen therapy	Recent hospital admission or surgery	Preceding immobility	Injury type	Immobilisation type	Weight-bearing status
Using an end point of asymptomatic VTE, detected by routine screening															
Gehling *et al.*, 1998[23]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Goel *et al.*, 2009[50]	PSAR[a]	NSAR[a]	NSAR[a]	N/A	NSAR[a]	N/A	N/A	NSAR[a]	NSAR[a]	NSAR[a]	N/A	N/A	PSAR[a]	N/A	N/A
Kock *et al.*, 1995[52]	PSAR[b]	NSAR[b]	N/A	N/A	NSAR[b]	NSAR[b]	N/A	N/A	N/A	NSAR[b]	N/A	N/A	PSAR[b]	PSAR[b]	N/A
Kujath *et al.*, 1993[53]	PSAR[c]	PSAR[c]	N/A	N/A	N/A	PSAR[c]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[c]	N/A	N/A
Zheng *et al.*, 2016[60]	PSAR[d]	PSAR[d]	N/A	N/A	N/A	N/A	N/A	NSAR[d]	N/A	N/A	N/A	N/A	N/A	NSAR[d]	N/A
Ho and Omari, 2017[65]	PSAR[e]	NSAR[e]	N/A	N/A	NSAR[e]	N/A	NSAR[e]	N/A	N/A	NSAR[e]	N/A	N/A	N/A	NSAR[e]	NSAR[e]
Manafi Rasi *et al.*, 2013[67]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Using an end point of symptomatic VTE, detected by clinical follow-up and targeted investigation															
Riou *et al.*, 2007[69]	PSAR[f]	NSAR[f]	N/A	N/A	NSAR[f]	NSAR[f]	NSAR[f]	NSAR[f]	N/A	NSAR[f]	N/A	N/A	PSAR[f]	PSAR[f]	PSAR[f]
Hanslow *et al.*, 2006[64]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[g]	PSAR[g]	N/A	N/A	N/A	N/A	N/A	PSAR[g]	PSAR[g]
Jameson *et al.*, 2014[66]	NSAR[h]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[h]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Makhdom *et al.*, 2013[9]	PSAR[i]	NSAR[i]	N/A	N/A	NSAR[i]	N/A	N/A	NSAR[i]	N/A	NSAR[i]	N/A	N/A	N/A	N/A	N/A
Meek and Tong, 2012[11]	PSAR[j]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[j]	NSAR[j]	N/A
Patel *et al.*, 2012[68]	PSAR[k]	NSAR[k]	N/A	N/A	N/A	N/A	NSAR[k]	NSAR[k]	N/A	N/A	N/A	N/A	N/A	N/A	N/A

continued

TABLE 6 Individual risk factors and their reported strength of association with developing VTE (*continued*)

	Risk factors associated with developing VTE														
	Permanent (present before episode of lower-limb immobilisation)												Transient (during injured period)		
Study authors, year	Age	BMI	Active cancer	Pregnancy	Smoking	Varicosities	Prior or family history of VTE	Significant comorbidity	Known thrombophilia	Exogenous oestrogen therapy	Recent hospital admission or surgery	Preceding immobility	Injury type	Immobilisation type	Weight-bearing status
Wahlsten *et al.*, 2015[71]	PSAR[l]	PSAR[l]	PSAR[l]	N/A	NSAR[l]	N/A	PSAR[l]	N/A	N/A	PSAR[l]	N/A	N/A	N/A	N/A	N/A
van Adrichem *et al.*, 2014[70]	PSAR[m]	PSAR[m]	N/A	N/A	N/A	N/A	N/A	N/A	PSAR[m]	PSAR[m]	N/A	N/A	PSAR[m]	N/A	N/A

CI, confidence interval; HR, hazard ratio; N/A, no attempt to report or analyse in the published manuscript; NSAR, no significant association reported; PSAR, positive significant association reported.

a Multivariate logistic regression: $p = 0.001$ for age, $p = 0.009$ for injury type; otherwise reported as showing no association for the relevant prespecified variables.

b Descriptive statistics: comparison of percentages only, with Fisher's exact test. It is notable that no patients in the LMWH group had a VTE event.

c Descriptive statistics: comparison of percentages only.

d Binary logistic regression analysis: noting OR 1.050 (95% CI 1.014 to 1.088; $p = 0.007$) for advancing age and OR 1.201 (95% CI 1.034 to 1.395; $p = 0.016$) for high BMI, with no evidence of association between comorbidity, immobilisation type or sex and outcome of VTE detected.

e Direct comparison of percentages using Fisher's exact test, or continuous variables using independent *t*-test. $p = 0.011$ for age, other identified risk factors all failing to reach predefined significance level. It is notable that the size of the analysed group was 35 patients only.

f Logistic regression technique described, suggesting the following associations: OR 3.14 (95% CI 2.27 to 4.33) for age > 50 years, OR 2.70 (95% CI 1.66 to 4.38) for rigid immobilisation, OR 4.11 (95% CI 1.72 to 9.86) for non-weight-bearing and OR 1.88 (95% CI 1.34 to 2.62) for severe injury.

g Descriptive statistics, with *p*-values presented for direct comparisons without mention of a statistical test. Significant comorbidity, prior VTE and weight-bearing status were noted to be associated with VTE development ($p = 0.04$, 0.02 and 0.003). Logistic regression also performed, highlighting plaster immobilisation as an independent predictor of risk (no OR presented).

h Logistic regression analysis using univariate and multivariable analysis. OR 11.97 (95% CI 5.14 to 27.87; $p < 0.001$) reported for a Charlson score of ≥ 1. No significant association of age with subsequent PE on univariate or multivariate analysis.

i Fisher's exact test used to compare categorical variable. Higher proportional rate of VTE for patients aged > 40 years ($p = 0.0026$). No significant association seen regarding VTE and categorised BMI, comorbidity and exogenous oestrogen use.

j Multivariable logistic regression: OR 3.48 (95% CI 1.11 to 10.89) for age and OR 0.16 (95% CI 0.03 to 0.80) for soft-tissue injury compared with Achilles repair. No association seen between VTE development and sex, immobilisation type or length of stay.

k Categorical variables assessed using Fisher's exact test; age > 40 years deemed to be associated with higher risk ($p = 0.016$). No association with BMI, comorbidity or prior VTE and no presentation of significant ORs on further multivariable analysis.

l Multivariable cox regression: HR 1.13 for age, HR 4.15 for exogenous oestrogens, HR 6.27 (95% CI 4.18 to 9.40) for prior VTE, HR 1.65 (95% CI 1.12 to 2.42) for active cancer and HR 2.68 (95% CI 1.66 to 4.33) for increased BMI.

m Adjusted ORs reported following binary logistic regression: OR 12.7 (95% CI 6.6 to 24.6) for traumatic indication (vs. non-traumatic), OR 18.2 (95% CI 6.2 to 53.4) for oral contraceptive use, OR 17.2 (95% CI 5.4 to 55.2) for obesity and OR 23.0 (95% CI 11.5 to 44.6) for known thrombophilia.

TABLE 7 Other identified individual risk factors and their association with developing VTE

Study authors, year	Other risk factors shown to be associated with VTE	Risk factors shown to have no association with VTE	Other key findings/author conclusions
Gehling *et al.*, 1998[23]	NR	Unable to demonstrate association between cumulative risk factors and thrombosis	Non-relevant
Goel *et al.*, 2009[50]	NR	• Sex • Comorbidities • BMI	Given the overall number of fractures, it is difficult to define a specific type as increasing the risk for DVT, but those fractures of the tibial plateau did display a tendency towards higher rates of DVT in the study
Kock *et al.*, 1995[52]	NR	• Sex • Exogenous oestrogen • BMI	Treatment procedures involving less immobilisation should be used whenever possible
Kujath *et al.*, 1993[53]	NR	• Smoking • Prior VTE • Exogenous oestrogen	The patients who did not develop a thrombosis had an average of 1.24 risk factors, whereas the patients with thrombosis had an average of 1.96 risk factors. The patients who suffered a thrombosis despite prophylaxis had 2.7 risk factors
Zheng *et al.*, 2016[60]	NR	NR	The study was not statistically powered to properly cull out any additional potential risk factors that might affect VTE incidence in this population
Riou *et al.*, 2007[69]	Non-weight-bearing status (OR 4.11, 95% CI 1.72 to 9.86)	No association seen on multivariate regression with: • VTE development and cancer • Exogenous oestrogen and comorbidity	Owing to a very low incidence of certain variables (e.g. cancer, severe diseases and hormonal treatment), the power of the study was not sufficient to identify their roles as potential risk factors. Because the incidence of obesity was not high in the study population, the results may not apply to morbidly obese patients
Hanslow *et al.*, 2006[64]	• Air travel (multivariate logistic regression) • History of rheumatoid arthritis (multivariate logistic regression)	Tourniquet use and mode of anaesthesia for those undergoing operative intervention	The incidence of thromboembolic disease after foot and ankle surgery could be higher than that previously reported, particularly if a patient has certain risk factors
Jameson *et al.*, 2014[66]	Charlson score of ≥ 1 gives OR 11.97 (95% CI 5.14 to 27.87; $p < 0.001$)	• Age • Sex	Comorbidities elevate the risk of PE and these data can be utilised by clinicians when considering whether or not to prescribe LMWH for VTE prophylaxis with the attendant risks of the therapy itself borne in mind

continued

TABLE 7 Other identified individual risk factors and their association with developing VTE (*continued*)

Study authors, year	Other risk factors shown to be associated with VTE	Risk factors shown to have no association with VTE	Other key findings/author conclusions
Makhdom *et al.*, 2013[9]	NR	• Smoking • BMI • Exogenous oestrogen use • Steroid use	Patient education is necessary regarding anticipated complications, and early mobilisation should be advocated, especially for patients aged > 40 years
Meek and Tong, 2012[11]	Achilles tendon rupture (descriptive)	• Sex • Soft-tissue injury • Method of immobilisation • ED length of stay • Surgical intervention	Increasing age and a diagnosis of Achilles tendon rupture appeared to increase the risk of VTE
Patel *et al.*, 2012[68]	NR	• Age • Comorbidity • Previous VTE • BMI • Operative intervention	Congestive heart failure, history of DVT or PE, and obesity might be risk factors, but perhaps the study did not have an adequate number of patients to show this difference
Wahlsten *et al.*, 2015[71]	• Coagulopathy (HR 2.47, 95% CI 1.1 to 5.7) • Peripheral arterial disease (HR 2.34, 95% CI 1.2 to 4.6) • Non-steroidal anti-inflammatory drugs use (HR 1.3, 95% CI 1.1 to 1.6)	• Smoking • Statin therapy and use of ACE inhibitor medications appeared to convey a protective effect, with HRs of 0.8 and 0.6, respectively	Patients with risk factors, especially previous DVT or PE, use of oral contraceptives and mobid obesity, have an increased risk of DVT/PE that exceeds the risk of DVT/PE in healthy patients undergoing total hip or knee replacement
van Adrichem *et al.*, 2014[70]	The presence of two or more acquired or genetic risk factors in patients with below-knee cast immobilisation produced an OR of 43.4 (95% CI 13.4 to 141.0)	Sex	Patients with below-knee cast immobilisation have a substantially increased risk of venous thrombosis, namely a 56-fold increased risk, compared with patients with no cast, corresponding to an estimated incidence of 1% in the first 3 months after cast application
Ho and Omari, 2017[65]	Subsequent presentation with symptoms suggestive of DVT ($p = 0.006$)	• Sex • BMI • Type of injury • Type of immobilisation • Weight-bearing status • Smoking • Exogenous oestrogen use • Family history of VTE	This pilot study unveiled limitations and logistical issues to be addressed in the future. Notably, the limitations include the small number of patients and the low adherence to attending ultrasonography assessment
Manafi Rasi *et al.*, 2013[67]	Cumulative number of risk factors: presence of ≥ 3 risk factors reported as being significantly associated with VTE development ($p = 0.01$)	NR	The incidence of DVT significantly increased in the presence of ≥ 3 risk factors ($p = 0.01$)

ACE, angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio; NR, not reported or analysed.

Summary of key findings

- Increasing age and injury severity were the most consistent risk factors associated with the development of VTE in patients with lower-limb injury and temporary immobilisation.
- Many clinical features considered to be risk factors for VTE were not examined or associated with VTE in the studies.
- All studies included in the review were deemed to be at moderate or serious risk of bias.
- The evidence base for tailored risk prediction in people with lower-limb immobilisation due to injury is very weak.

Review of risk assessment models for predicting venous thromboembolic risk

Objective

The objective was to identify RAMs that predict the risk of VTE in ambulatory trauma patients with temporary immobilisation following lower-limb injury.

Methods of reviewing effectiveness

Identification of studies

Studies were identified by searching the following electronic databases and research registers:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, MEDLINE and Versions(R) (via OvidSP), 1946 to May 2017.
- EMBASE (via OvidSP), 1974 to May 2017.
- Cochrane Database of Systematic Reviews (via Wiley Online Library), 1996 to May 2017.
- Database of Abstracts of Review of Effects (via Wiley Online Library), 1995 to March 2015.
- Cochrane Central Register of Controlled Trials (via Wiley Online Library), 1898 to May 2017.
- HTA database (via Wiley Online Library), 1995 to May 2017.
- NHS EED (via Wiley Online Library), 1995 to March 2015.
- Science Citation Index Expanded (via Web of Science), 1900 to May 2017.
- ClinicalTrials.gov (via US National Institutes of Health), 2000 to May 2017.
- International Clinical Trials Registry Platform (via Word Health Organization), 1990 to May 2017.

The search strategy used free text and thesaurus terms and combined synonyms relating to the condition (i.e. VTE in people with lower-limb immobilisation) with risk factor assessment or risk prediction modelling terms (used in the searches of MEDLINE, The Cochrane Library and EMBASE only). No language or date restrictions were used on any database. Further details on the search strategy can be found in *Appendix 5*. Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews), performing a citation search of relevant articles, contacting key experts in the field and undertaking systematic keyword searches of the World Wide Web using the Google search engine.

All identified citations from the electronic searches and other resources were imported into and managed using EndNote bibliographic software.

Inclusion and exclusion criteria

The inclusion of potentially relevant articles was undertaken using a two-step process. First, all titles were examined for inclusion by one reviewer (AP) and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to VTE) were excluded. Second, all abstracts and full-text articles were then examined independently by two reviewers (AP and DH). When necessary, non-English-language studies were translated using Google Translate to facilitate study selection and subsequent data extraction.

Any disagreements in the selection process were resolved through discussion or, if necessary, arbitration by a third reviewer (SG), and articles were included by consensus.

Studies were considered eligible for inclusion if they met the following criteria: (1) any study design that included a measurement of VTE patient outcome, (2) studies that recruited adults (aged > 16 years) who required temporary immobilisation (e.g. leg cast or brace in an ambulatory setting) for an isolated lower-limb injury and (3) any studies that reported any validation, or estimates of utility and performance of VTE risk assessment models for people with lower-limb cast immobilisation.

Data abstraction and quality assessment strategy

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (AP) into a standardised data extraction form and independently checked for accuracy by a second reviewer (DH). Any discrepancies were resolved through discussion or, if necessary, arbitration by a third reviewer (SG) and included by consensus. When multiple publications of the same study were identified, data were extracted and reported as a single study.

There are no validated (or widely agreed on) tools for the assessment of prognosis research studies and there is little empirical evidence to support the importance of particular study features affecting the reliability of findings, including the avoidance of bias.[75] For this review, a generic list of important methodological features recommended by Altman[76] and Moons *et al.*[77] for prediction modelling studies was deemed to be the most appropriate (i.e. useful) to assess the internal validity of the included studies. In general, five domains were considered important for assessing biases sufficiently large to distort the findings of prognosis research. These included (1) participant selection, (2) predictor assessment, (3) outcome assessment, (4) sample size and missing data and (5) statistical analysis. An overall judgement of bias was assigned as 'low risk' if all domains were judged as low risk, as 'high risk' if at least one domain was judged to be at high risk and as 'unclear risk' if an unclear risk of bias was noted in at least one domain and it was 'low risk' for all other domains. The methodological quality of each included study was independently evaluated by two reviewers (AP and DH). Any discrepancies were resolved through discussion or, if necessary, through the involvement of a third reviewer (SG). Blinding of the quality assessor to author, institution or journal was not considered necessary.

Methods of data synthesis and analysis

Venous thromboembolism was considered to comprise any subsequent recorded diagnosis of DVT, PE or death attributable to either pathology. No attempt was made to distinguish between anatomical location, thrombus burden or clinical sequelae of VTE for this project, in accordance with the definitions of hospital-acquired thrombosis produced by NHS England.[63] A narrative review of all identified scoring systems was performed, to compare design characteristics with thresholds for prophylaxis. Estimates of sensitivity, specificity, predictive values or likelihood ratios were directly extracted from validation studies or retrospectively calculated using available baseline data when applicable. All analyses were conducted using Microsoft Excel 2010.

Results

Quantity and quality of research available

The literature searches identified 4771 citations. In total, only six studies[32,78–82] met the inclusion criteria. Of these, one paper[32] focused on prediction model development with external validation in independent data. The remaining papers focused on external model validation without model updating.[78–82] A flow chart describing the process of identifying relevant literature is given in *Figure 6*. A total of 69 full-text articles were excluded as they did not meet all of the prespecified inclusion criteria. The majority of the articles were excluded on the basis of inappropriate target population (i.e. not isolated lower-limb injury requiring temporary immobilisation), having no relevant RAMs or outcome evaluations and being an unsuitable publication type (i.e. reviews, commentaries, editorial or abstracts of included full-text papers). A full list of excluded studies with reasons for exclusion is presented in *Appendix 7*.

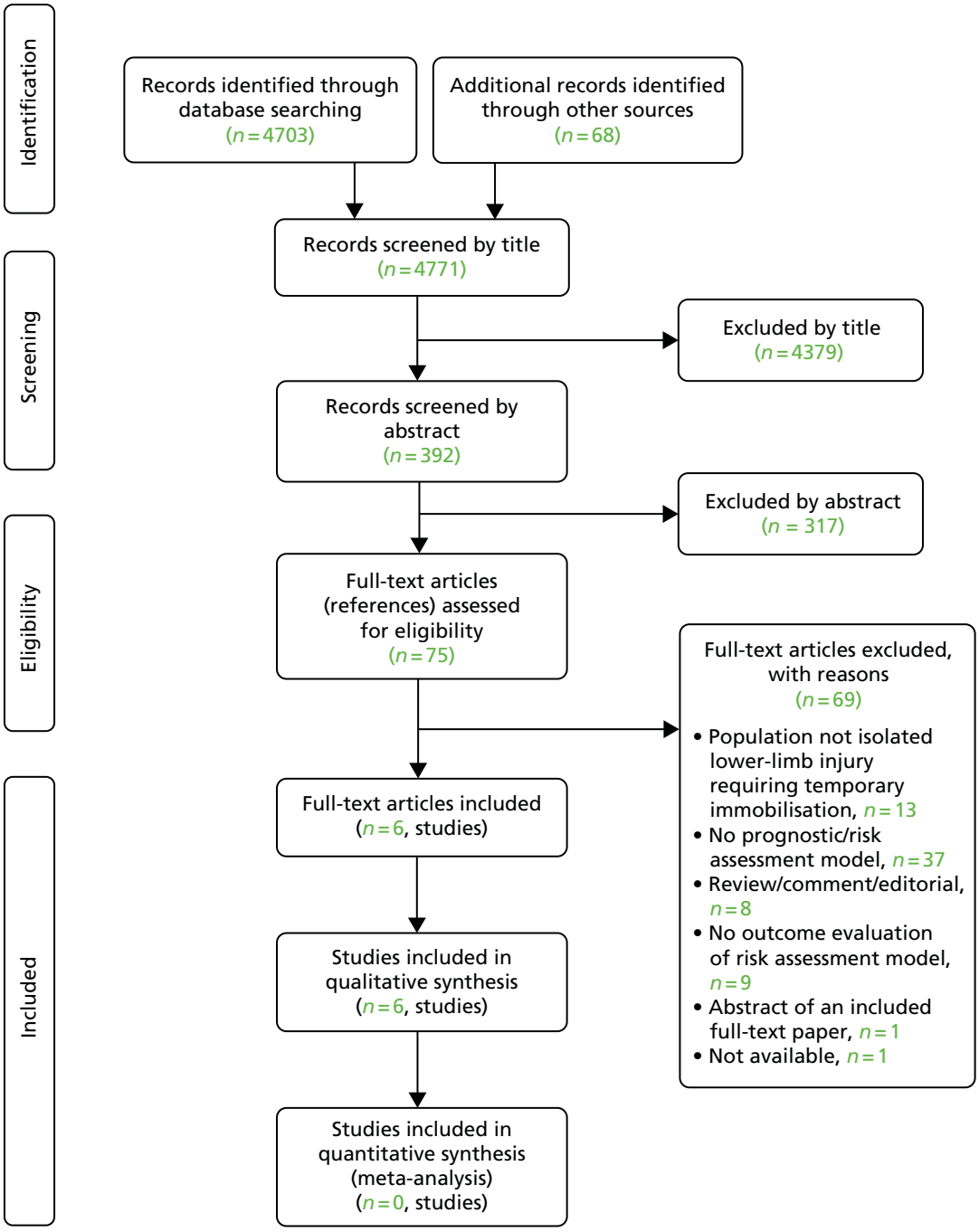

FIGURE 6 Study flow chart (adapted):[37] review of RAMs that predict the risk of VTE. © 2009 Moher *et al.* This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Description of included studies (design and patient characteristics)

Study characteristics are described in *Table 8*. Two case–control studies[32,82] and four observational studies[78–81] that described the evaluation of seven RAMs were found. A single study[32] presented data on derivation and validation; this study used a generic thrombosis database (including all acute thrombosis patients seen in an outpatient clinic matched with partner controls) to derive a new rule, rather than a relevant cohort of patients with temporary lower-limb immobilisation. All other papers looked to provide measures of external validation or implementation metrics regarding previously derived scores, with no description of the initial derivation methodology.

TABLE 8 Summary of key characteristics of RAM studies that predict the risk of VTE

Authors, year	Study objective/type	Source of data	Recruitment method	Study dates	Setting, country	Eligibility criteria	Study population
Nemeth *et al.*, 2015[32]	• Develop and validate a clinical prediction score for VTE after cast immobilisation of the lower leg • Prediction model development with external validation in independent data	Case–control study	Consecutive recruitment	1 March 1999 to 31 August 2004	Six clinics, the Netherlands	Patients aged 18–70 years with a first DVT, PE or both. Control group consisted of partners of participating patients or individuals identified via random digit dialling (controls were frequency matched to cases with respect to sex and age). Information on thromboprophylaxis use during plaster cast immobilisation was missing	• Derivation: $n = 10,564$[a] • Validation 1: $n = 1307$[a] • Validation 2: $n = 4205$[a]
Watson *et al.*, 2016[82]	• Evaluate the performance of VTE RAMs for lower-limb cast immobilisation • External model validation without model updating	Case–control study	Consecutive recruitment	1 November 2010 to 31 May 2011	Single centre (fracture clinic), Wales	Patients aged 19–75 years with lower-limb casts who developed symptomatic VTE (confirmed by Doppler ultrasonography, CT pulmonary angiography or a pulmonary V/Q scan within 5 months of application of cast). Control group consisted of patients (case matched to age, sex and injury) who were treated with casts during the same date range, but did not develop symptomatic VTE. Routine thromboprophylaxis was not used	Validation: $n = 42$
Saragas *et al.*, 2017[81]	• Evaluate a thrombosis risk assessment form on incidence of VTE in an external population • External model validation without updating	Prospective cohort study without control	Consecutive recruitment	March 2014 to April 2015	NR, South Africa	All patients aged > 18 years who underwent foot and ankle surgery requiring the combination of below-knee immobilisation in a cast and non-weight bearing for ≥ 4 weeks. Patients who were already on anticoagulants or had previously had a DVT were excluded	Validation: $n = 142$

Outcome to be predicted	Candidate predictors	Sample size (events)	Missing data	Model development	Model performance	Model evaluation	Results (key comparisons)
• Accuracy in diagnosing VTE (DVT or PE was confirmed by Doppler ultrasonography, a V/Q scan, angiography or a spiral CT scan) after cast immobilisation of the lower extremity • Outcome assessment blinding NR	• 54 candidate predictors (mix of environmental risk factors, genetic risk factors and biomarkers) • Predictor assessment at presentation to clinic	• 4446 patients with first VTE (plaster cast subpopulation, $n = 194$ cases) • The number of events per variable (candidate predictor): 82.3 (4446/54)	Multiple imputation was used to complete missing predictor values	Modelling method: logistic regression Predictor selection: full model (32 predictors), forward selection procedure, and if $p \leq 0.25$ in the univariate analysis of all participants or a well-established association with VTE Restricted model (11 predictors) and clinical model (14 environmental predictors) also developed. Based on the regression coefficients in the clinical logistic regression model, L-TRiP(cast) score developed for plaster cast patients Shrinkage of predictor weight or regression coefficient: NR	• Discrimination: an AUC (c-statistic) was calculated by means of a ROC curve analysis, based on the predictions from the multiple logistic regression models • Calibration: NR • Classification measures: the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated	Internal validation: test set for derivation and two separate validation data sets	Comparison of sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios
• Accuracy of each RAM in assessing a patient's VTE risk after cast immobilisation of the lower extremity • Outcome assessment blinding NR	• Validation: 2 models (Roberts *et al.*[17] and Keenan *et al.*[31]). Completion of a risk assessment form on demographics, patient history and clinical examination • Predictor assessment in retrospect (i.e. retrospective review of individual patient hospital and GP notes)	21 symptomatic VTE cases	NR	Modelling method: NA Predictor selection: Roberts *et al.*[17] 11 predictor variables (environmental factors with a well-established association with the occurrence of VTE in the literature); Keenan *et al.*[31] 14 predictor variables (no details provided) Shrinkage of predictor weight or regression coefficient: NA	Discrimination, calibration, classification measures: NR	No recalibration; no adjustment or update	Comparison of sensitivity, specificity and positive and negative predictive values
• Development of a clinically evident DVT, as confirmed by compression ultrasonography or a V/Q lung scan in the case of PE • Outcome assessment blinding NR	• Validation: 1 model. Completion of a risk assessment form on demographics, patient history and clinical examination • Predictor assessment before surgery	Three DVT cases (2.1%)	NR	Modelling method: NA Predictor selection: 36 risk factors (no details provided on how these were selected/derived) Shrinkage of predictor weight or regression coefficient: NA	Discrimination, calibration, classification measures: NR	No recalibration; no adjustment or update	Incidence of VTE following prophylactic anticoagulation for 4–6 weeks, namely until non-weight bearing or cast removal, whichever came first (non-comparative study)

continued

TABLE 8 Summary of key characteristics of RAM studies that predict the risk of VTE (*continued*)

Authors, year	Study objective/type	Source of data	Recruitment method	Study dates	Setting, country	Eligibility criteria	Study population
Haque *et al.*, 2016[80]	• Evaluate a risk scoring system on incidence of VTE in an external population • External model validation without updating	Prospective cohort study without control	Consecutive recruitment	NR	Single centre, UK	Patients aged ≥ 18 years with isolated foot and ankle fractures who were treated non-operatively and immobilised in a plaster cast (weight bearing as well as non-weight bearing) and managed as outpatients. Patients were excluded if they had a known bleeding disorder, renal disorder, multiple injury/polytrauma, complex pilon fracture or if they had a known allergy to LMWH (minimum of 6 months following injury)	Validation: *n* = 150
Giannadakis *et al.*, 2000[79]	• Evaluate risk of thrombosis using a checklist on incidence of DVT in an external population • External model validation without updating	Prospective cohort study without control	NR	March 1994 to March 1996	Single centre, Germany	Selected patients (aged > 16 years) with minor lower-limb injuries and at low risk of DVT, who required cast immobilising and did not receive medical thromboprophylaxis, were included. Patients who required medical thromboprophylaxis were excluded	Validation: *n* = 178
Eingartner *et al.*, 1995[78]	• Evaluate risk of thrombosis using a patient questionnaire and a scoring system on incidence of thrombosis in an external population • External model validation without updating	NR	NR	July 1993 to February 1994	Single centre, Germany	Outpatients with an immobilising cast of a lower-limb after an injury	Validation: *n* = 305

AUC, area under the curve; CT, computerised tomography; CTPA, computerised tomography pulmonary angiography; GP, general practitioner; L-TRIP(cast), Leiden Thrombosis Risk in Plaster(cast); NA, not applicable; NR, not reported; ROC, receiver operating characteristic; V/Q, ventilation/perfusion.

a Derivation: cases, *n* = 4446 with first VTE; control, *n* = 6118 (plaster cast subpopulation: cases, *n* = 194; control, *n* = 36); validation 1 – the THE-VTE study[83] (a two-centre population-based case–control study from the Netherlands and UK, study dates, March 2003 to December 2008) *n* = 784 with first VTE, control, *n* = 523 (plaster cast subpopulation: cases, *n* = 32; control, *n* = 7); the Milan study[84] (a single-centre population-based case–control study from Italy, study dates December 1993 to December 2010) *n* = 2117 with first VTE, control, *n* = 2088 (plaster cast subpopulation: cases, *n* = 143; control, *n* = 8).

Outcome to be predicted	Candidate predictors	Sample size (events)	Missing data	Model development	Model performance	Model evaluation	Results (key comparisons)
• Risk of VTEs (hospital records searched for radiological reports of ultrasonography and CTPA for symptomatic VTEs during the period of plaster cast immobilisation) • Outcome assessment blinding NR	• Validation: 1 model. Patient-completed questionnaire on demographics, patient history and clinical examination • Predictor assessment at presentation to fracture clinic	Three symptomatic VTE (two distal DVT's and one PE) cases (2.0%)	NR	Modelling method: NA Predictor selection: 14 predictor variables (consensus selection of predictors from NICE guidelines[24] and GEMNet,[17] which focuses on patients managed as outpatients, with an arbitrary cut-off point) Shrinkage of predictor weight or regression coefficient: NA	Discrimination, calibration, classification measures: NR	No recalibration; no adjustment or update	Incidence of VTE in those considered to be at high risk, namely with a score of ≥ 3 (non-comparative study)
• Risk of DVT (a clinical examination and a colour-coded duplex sonography were performed after the removal of the cast for detection of DVT of the lower limb. A phlebography was performed when thrombosis was suspected) • Outcome assessment blinding NR	• Validation: 1 model. Completion of a risk assessment form on demographics, patient history and clinical examination • Predictor assessment at presentation to trauma clinic	Two DVT cases (1.1%)	NR	Modelling method: NA Predictor selection: 12 predictor variables (no details provided on how these were selected/derived) Shrinkage of predictor weight or regression coefficient: NA	Discrimination, calibration, classification measures: NR	No recalibration; no adjustment or update	Incidence of thrombosis in low-risk patients who received no thromboprophylaxis, namely no risk factors (non-comparative study)
• Risk of thrombosis • Outcome assessment blinding NR	• Validation: 1 model. Patient-completed questionnaire on demographics, patient history and clinical examination • Predictor assessment at presentation to clinic	No VTE events	NR	Modelling method: NA Predictor selection: nine predictor variables (no details provided on how these were selected/derived) Shrinkage of predictor weight or regression coefficient: NA	Discrimination, calibration, classification measures: NR	No recalibration; no adjustment or update	Incidence of thrombosis (non-comparative study)

The seven identified RAMs varied in design, structure, output and threshold for prophylaxis. Several scores were dichotomous, with others providing ordinal measure of risk. Design characteristics and threshold levels for each RAM are presented for comparison in *Table 9*. The majority of RAMs focused solely on the estimate of thromboembolic risk; a single method featured characteristics designed to balance the risk of bleeding with thromboprophylaxis.[17] The individual predictors and their weighting varied markedly between RAMs. Variables (and their definitions) for each RAM are presented for comparison in *Table 10*.

Quality characteristics

The overall methodological quality of the six included studies is summarised in *Figure 7* and *Table 11*. The majority of studies were deemed to be at high risk of bias,[32,78,79,81,82] based primarily on participant selection; all reviewed studies attempted validation of proposed decision rules in heterogeneous cohorts, with pragmatic observational follow-up only. Outcomes were also non-standardised and varied by site in terms of description and inclusion.

Both case–control studies[32,82] had specific and notable limitations in methodology. The larger study, by Nemeth *et al.*,[32] used three distinct generic thrombosis data sets to derive and validate the proposed RAM. As such, the tool is derived from a group of patients with unprovoked or hospital-acquired VTE and has limited potential generalisability to the cohort of interest in this study. The authors looked at a subgroup of patients with temporary lower-limb immobilisation within the study data, finding only a small proportion in whom to attempt validation (230 patients, 2% of the original derivation data set). The smaller study, by Watson *et al.*,[82] derived case–control data using an equal measure of appropriate patients with thrombosis following cast immobilisation, alongside a separate cohort of those without. As such, the prevalence of thrombosis within this study cohort was 50%. This is 20 times the estimated prevalence within the literature and, therefore, renders their estimates of predictive value at high risk of error.

Narrative data synthesis

The study by Nemeth *et al.*[32] derived and validated a clinical risk score for plaster cast patients: the Leiden thrombosis risk in plaster (cast) [L-TRiP(cast)] score. In this study,[32] data from a large population-based case–control study of approximately 10,000 patients (4446 consecutive patients with a first episode of venous thrombosis and 6118 controls) were used in developing the model (included in patients with

TABLE 9 Summary of design characteristics and threshold levels of identified RAMs

Risk assessment model	Acronym/ descriptor	Derivation	Design	Incorporation of bleeding risk?	Number of variables	Threshold (suggested cut-off point)	Attempted validation?
Roberts *et al.*[17]	The GEMNet guideline	EC	Dichotomous	Yes	11	N/A	Yes
Keenan *et al.*[31]	The Plymouth Rule	EC	Ordinal	No	14	> 2	Yes
Nemeth *et al.*[32]	The L-TRiP(cast) score	Regression	Ordinal	No	14	> 8	Yes
Saragas *et al.*[81]	The modified Caprini score	EC	Ordinal	No	36	> 1	No
Eingartner *et al.*[78]	N/A	EC	Ordinal	No	9	> 1	No
Haque *et al.*[80]	N/A	EC	Ordinal	No	14	> 2	No
Giannadakis *et al.*[79]	N/A	EC	Dichotomous	No	12	N/A	No

EC, expert consensus; GEMNet, Guidelines in Emergency Medicine Network; L-TRIP(cast), Leiden Thrombosis Risk in Plaster (cast); N/A, not applicable.

TABLE 10 Summary of predictor variables included in studies of RAMs that predict the risk of VTE

Variable	Study authors, year						
	Nemeth *et al.*, 2015[32] L-TRiP(cast)	Watson *et al.*, 2016[82] Keenan *et al.*, 2009[31]	Roberts *et al.*, 2013[17]	Saragas *et al.*, 2017[81]	Haque *et al.*, 2016[80]	Giannadakis *et al.*, 2000[79]	Eingartner *et al.*, 1995[78]
Brief details of RAMs	VTE risk scoring model for thromboprophylaxis in patients after cast immobilisation of the lower extremity (14 clinical predictor variables)	VTE risk scoring model for thromboprophylaxis in patients after lower-limb cast/boot immobilisation [14 clinical predictor variables (patient completed)]	VTE risk assessment for thromboprophylaxis in ambulatory trauma patients requiring temporary lower-limb plaster cast immobilisation after acute severe injury (11 clinical predictor variables)	Thrombosis risk factor assessment in foot and ankle surgery patients requiring below-knee cast immobilisation and non-weight bearing for ≥ 4 weeks (36 predictor variables)	VTE risk scoring model for thromboprophylaxis in patients requiring lower-limb immobilisation [14 clinical predictor variables (patient completed)]	Checklist for pharmacological thromboprophylaxis for outpatients who required cast immobilisation after lower-limb injury (12 clinical predictor variables)	VTE risk scoring system for thromboprophylaxis in patient with lower-limb immobilisation [9 clinical predictor variables (patient completed)]
Predictor variables included in RAMs							
Age	Yes (≥ 35 and < 55 years; ≥ 55 years)	Yes (≥ 60 years)	Yes (> 60 years)	Yes (≥ 41 years)	Yes (≥ 60 years)	Yes (> 40 years)	Yes (> 60 years)
Sex	Yes (male sex)	–	–	–	–	–	–
Overweight/obese	Yes (BMI of ≥ 25 kg/m^2 and < 35 kg/m^2; ≥ 35 kg/m^2)	Yes (very overweight, BMI of ≥ 30 kg/m^2)	Yes (BMI of ≥ 30 kg/m^2)	Yes (BMI of > 25 kg/m^2)	Yes (BMI of ≥ 30 kg/m^2)	Yes (Broca Index of > 20%)	Yes (overweight, > 100 kg)
Cancer	Yes (within previous 5 years)	Yes (active)	Yes (active)	Yes (malignancy present or previous)	Yes (active or cancer treatment including tamoxifen and raloxifen)	Yes (malignancies)	Yes (ongoing malignancy)
Pregnancy or puerperium	Yes	Yes	Yes	Yes (including history of unexplained stillborn infant, recurrent spontaneous abortion, premature birth with toxaemia or growth-restricted infant)	Yes	–	–
Smoking	–	–	Yes (active)	–	–	Yes (> 20 cigarettes per day)	Yes (active)
Varicosities	Yes (superficial vein thrombosis)	Yes (varicose veins)	Yes (extensive varicosities)	Yes (varicose veins, large)	Yes (varicose veins)	Yes (varicose veins)	Yes (varicose veins even after varicose vein surgery)
Prior or family history of VTE	Yes [family history (first-degree relative)]	Yes [family history (brother, sister, father, mother) or personal history of DVT/PE]	Yes (personal history or first-degree relative)	Yes (personal history of DVT/PE, family history of thrombosis)	Yes [personal or family history (brother, sister, father, mother, child) of blood clot in leg or lung]	Yes (personal history of previous thrombosis/PE, family history of thrombosis/PE)	Yes (personal history of previous DVT/PE)

continued

TABLE 10 Summary of predictor variables included in studies of RAMs that predict the risk of VTE (*continued*)

Variable	Study authors, year						
	Nemeth *et al.*, 2015[32] L-TRiP(cast)	Watson *et al.*, 2016[82] Keenan *et al.*, 2009[31]	Roberts *et al.*, 2013[17]	Saragas *et al.*, 2017[81]	Haque *et al.*, 2016[80]	Giannadakis *et al.*, 2000[79]	Eingartner *et al.*, 1995[78]
Significant comorbidity	Yes (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	Yes (heart disease, lung disease, bowel disease, hormone disease or other long-term medical condition requiring treatment)	Yes (any serious medical comorbidity including cardiac failure, COPD, chronic renal failure or inflammatory bowel disease)	Yes (history of inflammatory bowel disease, acute MI, CHF for < 1 month, COPD, stroke with lower-extremity weakness for < 1 month)	Yes (active heart, lung, bowel or joint disease)	Yes (diabetes mellitus, CHD)	Yes (history of cardiovascular disease, including arterial hypertension)
Known thrombophilia	–	–	Yes	Yes (positive factor V Leiden, positive prothrombin G20210 A, other congenital or acquired thrombophilia)	Yes (thrombophilia associated with increased risk of blood clots)		
Exogenous oestrogen therapy	Yes (oral contraceptives)	Yes (oral contraceptive pill or HRT)	Yes [hormone therapy (combined oral contraceptive pill/HRT/ tamoxifen)]	Yes (oral contraceptives or HRT)	Yes (on HRT or taking oestrogen-containing contraceptive)	Yes (contraception use)	Yes (oral contraceptives)
Hospital admission or surgery	Yes (hospital admission or surgery within the previous 3 months)	Yes (abdominal surgery in previous 6 weeks)	Yes (any recent hospital admission/major surgery)	Yes (minor surgery planned, major surgery < 1 month previously, major surgery > 45 minutes previously, arthroscopic surgery, elective major lower-extremity arthroplasty)	Yes (hospital admission within the previous 6 weeks, including lower-limb surgery)	–	Yes (lower-limb, pelvic or lower-abdominal surgery over the previous 6 months)
Preceding immobility	Yes (bedridden within previous 3 months)	Yes (unable to walk before accident/injury)	–	Yes [medical patient currently at bed rest, patient confined to bed (> 72 hours)]	–	–	–
Injury type	–	Yes (Achilles tendon rupture)	–	Yes [hip, pelvis or leg fracture of < 1 month, acute spinal-cord injury (paralysis) of < 1 month]	Yes (Achilles tendon rupture)	Yes (soft-tissue injury of higher than grade 1)	–

Variable	Study authors, year						
	Nemeth *et al.*, 2015[32] L-TRiP(cast)	Watson *et al.*, 2016[82] Keenan *et al.*, 2009[31]	Roberts *et al.*, 2013[17]	Saragas *et al.*, 2017[81]	Haque *et al.*, 2016[80]	Giannadakis *et al.*, 2000[79]	Eingartner *et al.*, 1995[78]
Immobilisation type	Yes (plaster cast: complete leg, circular knee cast – ankle free, foot, lower leg)	–	–	Yes (immobilising plaster cast for < 1 month)	Yes (plaster cast extending above the knee)	Yes (thigh bandage)	–
Pneumonia	Yes	–	–	Yes (serious lung disease including pneumonia < 1 month)	–	–	–
Travel	–	–	–	–	Yes [continuous travel of ≥ 3 hours (road, rail or air travel) in the previous 4 weeks or needing to travel while wearing plaster cast]	–	–
Swollen legs	–	–	–	Yes (current)	–	–	–
Sepsis	–	–	–	Yes (occurred < 1 month previously)	–	–	–
Central venous access	–	–	–	Yes	–	–	–
Antiphospholipid antibodies	–	–	–	Yes (positive lupus anticoagulant, elevated anticardiolipin antibodies)	–	–	–
Multiple trauma	–	–	–	Yes (multiple trauma occurring < 1 month previously)	–	–	–

CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; MI, myocardial infarction.

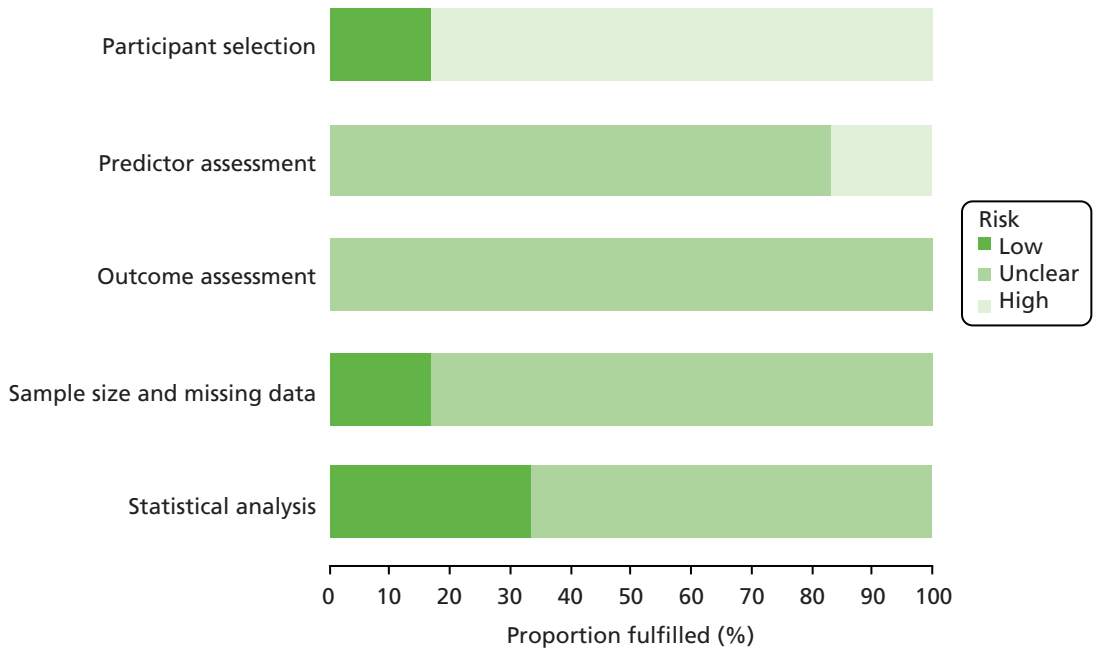

FIGURE 7 Risk-of-bias assessment graph:[76,77] review authors' judgements about each methodological quality item across all included studies in the review of RAMs that predict the risk of VTE.

TABLE 11 Risk-of-bias assessment summary:[76,77] review authors' judgements about each methodological quality item for each included study in the review of RAMs that predict the risk of VTE

Study author, year	Participant selection	Predictor assessment	Outcome assessment	Sample size and missing data	Statistical analysis	Overall[a]
Nemeth *et al.*, 2015[32]	High	Unclear	Unclear	Low	Low	High
Watson *et al.*, 2016[82]	High	High	Unclear	Unclear	Low	High
Saragas *et al.*, 2017[81]	High	Unclear	Unclear	Unclear	Unclear	High
Haque *et al.*, 2016[80]	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Giannadakis *et al.*, 2000[79]	High	Unclear	Unclear	Unclear	Unclear	High
Eingartner *et al.*, 1995[78]	High	Unclear	Unclear	Unclear	Unclear	High

a Overall risk-of-bias judgement (equal to the most severe level of bias found in any domain) was judged as: (1) low risk of bias – the study is judged to be at low risk of bias for all domains for this result, (2) high risk of bias – the study is judged to be at high risk of bias in at least one domain for this result, (3) unclear – the study is judged to have unclear risk of bias in at least one domain for this result.

disease and many other confounding factors). After minimising the variables in an attempt to produce a clinical (14 environmental predictor variables) and pragmatic rule (11 predictor variables), the authors validated this rule in two subsequent VTE case–control data sets.

Watson *et al.*[82] assessed the diagnostic accuracy of five RAMs (only two of these, the GEMNet model[17] and the Plymouth model,[31] were specific to patients with lower-limb trauma and cast immobilisation) in a case–control study of 42 patients with lower-limb immobilisation following injury (21 cases and 21 controls). The reported sensitivity and specificity of the GEMNet model (85.7% and 47.6%, respectively) did not seem to be compatible with the numbers of cases and controls, so contact was made with the authors for clarification. They identified an error in the sensitivity, which should have been reported as 4.76%, and provided the raw numbers for both RAMs, which were used to calculate all diagnostic parameters and confidence intervals (CIs).

Prognostic accuracy measures for the three scores evaluated in these two studies are presented in *Table 12*. Sensitivity ranged from 57.1% to 92.6% across the RAMs and specificity ranged from 4.76% to 60.8%. The L-TRiP(cast) data are displayed in this table using thresholds denoting optimal performance and to allow direct comparison with other validated scores. The estimates of positive and negative predictive value for the L-TRiP(cast) score were modelled using an appropriately low prevalence of VTE, whereas the estimates for the GEMNet and Plymouth models used the artificial 50% prevalence from the case–control study. This explains the relatively high positive predictive values and the relatively low negative predictive values for these scores.

The area under the curve (AUC) for the L-TRiP(cast) score ranged from 0.77 (95% CI 0.66 to 0.87) in the derivation cohort to 0.77 (95% CI 0.58 to 0.96) and 0.95 (95% CI 0.91 to 0.99) in the two subsequent validation cohorts.

In addition to these rules, four additional models were identified (Saragas *et al.*,[81] Haque *et al.*,[80] Giannadakis *et al.*[79] and Eingartner *et al.*[78]). No measures of external validation of these RAMs were found. All were found as single-centre small-scale implementation studies, revealing no further additional information on performance, utility or reliability.

Summary of key findings

- A number of RAMs have been developed using a variety of methods and based on a variety of predictor variables.
- External validation studies have weak designs and limited generalisability, so estimates of prognostic accuracy are very uncertain.
- The limited data available suggest that the L-TRiP(cast) score with a cut-off point of 8 can achieve reasonable sensitivity for predicting VTE without an excessive loss of specificity.

Identifying key variables to assess thromboembolic risk: a Delphi consensus exercise

Objectives

The systematic reviews revealed a lack of evidence relating to individual risk predictors and RAMs for VTE in lower-limb immobilisation due to trauma. Therefore, expert consensus methods were used to identify potential risk factors for VTE and expert consensus was sought on which were considered to be the most useful predictors. The aim was to bring together topic experts from haematology, orthopaedics and emergency medicine and achieve consensus through serial rounds and facilitated discussion. The results of this Delphi exercise would then be compared with current risk prediction models and consensus opinion on clinical engagement, utility and acceptability to patients would be gauged. Delphi methodology has been previously described[85–87] and used throughout health services research for similar indications.[88,89]

Methods

Delphi methodology

A three-round Delphi study was conducted between August 2017 and April 2018 using a panel of international topic experts, identified from the published literature and national clinical research network (injuries and emergency theme).

Expertise was ascribed using two criteria: (1) evidence of experience in relevant guideline or risk assessment tool design and (2) routine clinical experience with the relevant patient cohort and topic of interest. These criteria were selected to allow disclosure of unpublished methodology deriving existing rules, confer practicality of any rule and to ensure broad dissemination and uptake of consensus findings. Experts were identified through national bodies, relevant literature and local thrombosis committee groups.

TABLE 12 Diagnostic performance of the L-TRiP(cast), GEMNet and Plymouth RAMs

Author	RAM	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Likelihood ratio positive (95% CI)	Likelihood ratio negative (95% CI)	Percentage receiving thromboprophylaxis (95% CI)
Roberts *et al.*[17]	GEMNet	85.7 (62.6 to 96.2)	4.76 (0.2 to 25.9)	47.4 (31.3 to 64.0)	25.0 (1.3 to 78.1)	0.90 (0.73 to 1.10)	3.00 (0.16 to 55.31)	90.5 (76.5 to 96.9)
Keenan *et al.*[31]	Plymouth	57.1 (33.4 to 77.4)	52.4 (30.3 to 73.6)	54.5 (32.7 to 74.9)	55.0 (32.0 to 76.2)	1.20 (0.67 to 2.15)	0.81 (0.46 to 1.46)	52.4 (36.6 to 67.7)
Nemeth *et al.*[32]	L-TRiP(cast) with a cut-off point of ≥ 8	92.6	39.7	3.8	99.5	1.5	0.2	87.8
	L-TRiP(cast) with a cut-off point of ≥ 9	80.8	60.8	5.0	99.2	2.1	0.3	74.7

Note
None of the studies reported measures of precision and we were unable to calculate a 95% CI for any of the L-TRiP(cast) parameters.

National bodies included The British Orthopaedic Association, The Royal College of Emergency Medicine and The Clinical Research Network Injuries and Emergencies Specialty group. Additional national or international societies were not approached for independent representation owing to time constraints and workload. All individuals approached agreed to participate and provided written informed consent. Experts were entirely independent of the core review team ($n = 11$), local colleagues independent of the review work ($n = 3$) and members of the core review team ($n = 6$).

The open first round of the classical Delphi approach was replaced with a systematic literature review to identify possible VTE predictors, as previously described. Round 1 of the Delphi study was then delivered via a web-based platform using SmartSurvey Ltd (Tewkesbury, UK)[90] through a subscribed account. All potential individual predictor variables identified through the previous systematic review of existing decision rules and the wider literature on risk prediction in the relevant cohort were presented to participants as potential candidate predictors. Participants were then asked to rate the strength of the VTE prediction risk for each variable using a four-point Likert scale, with the option to record uncertainty. Their replies were collated into quantitative and qualitative output for each individual question. An opportunity to identify new relevant predictor variables was provided and participants were encouraged to identify missing themes.

New candidate variables were proposed, and those failing to achieve consensus in round 1 of the Delphi exercise were carried forward to a second round. Participants were presented with these variables together with a summary of the panel results from round 1, when applicable. Participants were asked to complete the same Likert scale as before, with the advantage of having additional insight into comments and quantitative results revealed by the rest of the group.

At the end of round 2 of the Delphi exercise, all variables were carried forward to a facilitated round-table discussion where consensus results and comments were provided to all participants. Data were collated and analysed to calculate frequencies, mean and range of scores.

Data synthesis and analysis

Criteria for inclusion in the decision rule were defined by a variable identified as a moderate or strong predictor by consensus between two, three or more respondents. Variables identified as uncertain or not or weakly predicting VTE risk by consensus between two, three or more respondents were likewise excluded from the exercise. Quantitative data from rounds 1 and 2 were presented to participants as bar charts with percentages. All analyses were conducted using Microsoft Excel 2010.

Results

Expert engagement

Twenty participants were identified to participate in the study. All (100%) completed round 1; 19 participants (95.0%) completed round 2. Ten participants (50.0%) contributed to the final facilitated round-table discussion. A list of participants and the clinical scope of the Delphi panel is provided in *Appendix 8*.

Systematic review and identification of candidate predictors

Trial flow results from the relevant systematic reviews prior to the Delphi exercise have been previously described (see *Review of individual risk factors associated with venous thromboembolic risk* and *Review of risk assessment models for predicting venous thromboembolic risk*). Thirty-five individual candidate predictors were identified and included for dissemination in round 1. Predictors were subdivided into risks related to injury/immobilisation and generic thrombosis risks. Initial proposed candidate predictors are shown in *Table 13*, which also shows the results of subsequent Delphi rounds.

TABLE 13 Summary of results from rounds 1 and 2 of the Delphi consensus exercise

Consensus as predictor	Consensus as non-predictor	No consensus	Additional suggested variables
Delphi consensus exercise: round 1 results			
Thrombophilia	Smoker	Age	Non-weight-bearing status
Prior VTE	Hepatitis	Intravenous drug use	Partial weight-bearing status
Surgery in the preceding 3 months	Dehydration	Hospital admission in the preceding 3 months	Significant soft-tissue injury
BMI of > 30 kg/m^2	Sex	Pneumonia	Baseline D-dimer level
Above-knee plaster cast	Antipsychotic drug use	Exogenous oestrogen/ hormone therapy	
Pregnant/puerperium	Extensive varicosities	Preceding immobility	
Active cancer	Non-type O blood	Superficial thrombophlebitis	
	Aircast® boot (DJO, LLC, Dallas, TX, USA)	Ankle fracture/dislocation[a]	
	Complete ligament rupture (non-Achilles tendon)	Family history of VTE (first-degree relative)	
	Red cell distribution width	Significant injury in the preceding 3 months	
	Factor 8 activity	Significant medical comorbidity	
	Factor 11 activity	Lower-limb paralysis	
	von Willebrand factor antigen levels	Achilles tendon rupture	
		Comminuted injury	
		Rigid immobilisation in plaster	
Delphi consensus exercise: round 2 results			
Age	Hospital admission within the preceding 3 months	Intravenous drug use	
Exogenous oestrogen/ hormone therapy	Baseline D-dimer level	Significant injury in the preceding 3 months	
Lower-limb paralysis	Pneumonia	Significant medical comorbidity	
Superficial thrombophlebitis	Partial weight-bearing status	Preceding immobility	
Achilles tendon rupture	Significant soft-tissue injury	Comminuted injury	
Rigid immobilisation in plaster		Non-weight-bearing status	
		Family history of VTE (first-degree relative)	

a Further to discussion at the end of round 1, this variable was removed based on agreement that this degree of severity would usually merit inpatient admission and prescription of routine thromboprophylaxis.

Round 1 results

Seven variables were identified as predictive of VTE risk by consensus criteria during round 1. Thirteen variables were identified as *not* predictive of VTE by consensus criteria and excluded from the exercise. No consensus was achieved on 15 variables; 14 predictors were carried forward to the second round, with moderated peer feedback and tabular display. A single variable was excluded from the exercise after collated comments, group discussion and feedback regarding the lack of primary suitability for inclusion. Four new variables were suggested during the round 1 exercise and these were also carried forward. All candidate predictors and their round 1 results are presented in *Table 13*.

Round 2 results

In the second round, consensus was achieved on six further variables as predictive of VTE risk. Five variables were identified on reflection as *not* predictive of VTE risk by consensus criteria and these were excluded from the exercise. No consensus remained for 7 of the 17 variables carried forward from round 1. No further risk predictors were suggested by participants during round 2. Candidate variables taken forward and their round 2 results are presented in *Table 13*.

Variables failing to achieve consensus

Of the seven variables failing to achieve consensus, two failed because of a dichotomous split with clear unresolvable disagreement by experts (intravenous drug use and comminuted fracture). The other five variables appeared to be categorised as weakly to moderately predictive by all, but fell short of agreed criteria for inclusion. Further rounds were deemed unlikely to generate further consensus at this stage and the trial team proposed a move to the facilitated round-table discussion to achieve consensus.

Facilitated round-table discussion

There was general round-table agreement about all variables for which consensus had been achieved by the Delphi exercise. A specific point was made by the group regarding the inclusion of several variables depicting the degree of immobilisation of the calf pump, and whether or not this should become a single ordinal variable. A single variable (active intravenous drug use) on which the group did not reach consensus was discussed in further detail, with the majority of the round table proposing that the variable be refined or this entire cohort of patients be excluded based on safety concerns. Several discussion points followed regarding the need for strict inclusion criteria when applying any decision rule, with particular regard to the type of immobilisation in this group. The final agreed variables considered to be predictors of VTE risk via the Delphi expert consensus were eight generic VTE risk predictors (i.e. thrombophilia, pregnancy/puerperium, active cancer, surgery in the preceding 3 months, prior VTE, exogenous oestrogen/hormone therapy, lower-limb paralysis and superficial thrombophlebitis), two patient demographics (i.e. age and BMI) and three variables specific to lower-limb immobilisation or injury (i.e. Achilles tendon rupture, rigid immobilisation and above-knee cast).

Table 14 compares the expert consensus variables to those included in the RAMs. Most of the expert consensus variables were included in one or more of the RAMs but the RAMs also included many variables that were not supported by expert consensus.

Originally, it was planned to use the expert consensus methods to refine existing RAMs or construct up to five new RAMs from the selected risk factors, and then produce a consensus estimate of sensitivity and specificity for each RAM that would allow the exploration of the trade-off between sensitivity and specificity in decision-analytic modelling. It was decided not to proceed with this for the following reasons:

- The difficulty of achieving consensus on individual risk factors (which was felt to be unsurprising given the limited available evidence) suggested that it would not be possible to achieve the necessary consensus on the content and structure required to refine an existing RAM or construct a new RAM.
- The receiver operating characteristic (ROC) analysis of the L-TRiP(cast) score published by Nemeth *et al.*[32] (identified in the systematic review of RAMs) provided an estimate of the trade-off between sensitivity and specificity that could be used in decision-analytic modelling, and would be more credible and usable than expert-derived estimates of sensitivity and specificity for expert-derived RAMs.

TABLE 14 Summary of predictor variables included in studies of RAMs, with comparison with the Delphi consensus exercise

	RAM							
Variable	**L-TRiP(cast)[32]**	**Plymouth[31]**	**GEMNet[17]**	**Saragas *et al.*[81]**	**Haque *et al.*[80]**	**Giannadakis *et al.*[79]**	**Eingartner *et al.*[78]**	**Delphi**
Predictor variables included in risk assessment models								
Age	Yes (≥ 35 and ≥ 55 years)	Yes (≥ 60 years)	Yes (> 60 years)	Yes (≥ 41 years)	Yes (≥ 60 years)	Yes (> 40 years)	Yes (> 60 years)	Yes (> 60 years)
Sex	Yes (male sex)	–	–	–	–	–	–	No
Overweight/obese	Yes (BMI of ≥ 25 kg/m^2 and ≥ 35 kg/m^2)	Yes (BMI of ≥ 30 kg/m^2)	Yes (BMI of ≥ 30 kg/m^2)	Yes (BMI of > 25 kg/m^2)	Yes (BMI of ≥ 30 kg/m^2)	Yes (Broca Index of > 20%)	Yes (overweight, > 100 kg)	Yes (BMI of > 30 kg/m^2)
Cancer	Yes (within previous 5 years)	Yes (active)	Yes (active)	Yes (malignancy present or previous)	Yes (active or cancer treatment)	Yes (malignancies)	Yes (ongoing malignancy)	Yes (active)
Pregnancy or puerperium	Yes	Yes	Yes	Yes	Yes	–	–	Yes
Smoking	–	–	Yes (active)	–	–	Yes (> 20 cigarettes per day)	Yes (active)	No
Varicosities	–	Yes (varicose veins)	Yes (extensive varicosities)	Yes (varicose veins, large)	Yes (varicose veins)	Yes (varicose veins)	Yes (varicose veins even after surgery)	No
Superficial thrombophlebitis	Yes (superficial vein thrombosis)	–	–	–	–	–	–	Yes
Prior or family history of VTE	Yes [family history (first-degree relative)]	Yes [family history (brother, sister, father, mother) or personal history of DVT/PE]	Yes (personal history or first-degree relative)	Yes (personal history of DVT/PE, family history of thrombosis)	Yes [personal or family history (brother, sister, father, mother, child) of blood clot in leg or lung]	Yes (personal history of previous thrombosis/PE, family history of thrombosis/PE)	Yes (personal history of previous DVT/PE)	Yes (prior VTE only)
Significant comorbidity	Yes (rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis)	Yes (heart disease, lung disease, bowel disease, hormone disease or other long-term medical condition requiring treatment)	Yes (any serious medical comorbidity, including cardiac failure, COPD, chronic renal failure or inflammatory bowel disease)	Yes [history of inflammatory bowel disease, acute MI, CHF (diagnosed < 1 month previously), COPD, stroke with lower-extremity weakness < 1 month]	Yes (active heart, lung, bowel or joint disease)	Yes (diabetes mellitus, CHD)	Yes (history of cardiovascular disease, including arterial hypertension)	No
Known thrombophilia	–	–	Yes	Yes (positive factor V Leiden, positive prothrombin G20210 A, other congenital or acquired thrombophilia)	Yes (thrombophilia associated with increased risk of blood clots)	–	–	Yes

	RAM							
Variable	L-TRiP(cast)[32]	Plymouth[31]	GEMNet[17]	Saragas *et al.*[81]	Haque *et al.*[80]	Giannadakis *et al.*[79]	Eingartner *et al.*[78]	Delphi
Exogenous oestrogen therapy	Yes (oral contraceptives)	Yes (oral contraceptive pill or HRT)	Yes [hormone therapy (combined oral contraceptive pill/HRT/ tamoxifen)]	Yes (oral contraceptives or HRT)	Yes (on HRT or taking oestrogen-containing contraceptive)	Yes (contraception use)	Yes (oral contraceptives)	Yes (exogenous oestrogen or hormone therapy)
Hospital admission or surgery	Yes (hospital admission or surgery within the previous 3 months)	Yes (abdominal surgery in last 6 weeks)	Yes (any recent hospital admission/major surgery)	Yes [minor surgery planned, major surgery (occurring < 1 month previously), major surgery (occurring > 45 minutes previously) arthroscopic surgery, elective major lower-extremity arthroplasty]	Yes (hospital admission within the previous 6 weeks, including lower-limb surgery)	–	Yes (lower limb, pelvic or lower-abdominal surgery over the previous 6 months)	Yes (surgery in the preceding 3 months only)
Preceding immobility	Yes (bedridden within previous 3 months)	Yes (unable to walk before accident/injury)	–	Yes [medical patient currently at bed rest, patient confined to bed (> 72 hours)]	–	–	–	No
Injury type	–	Yes (Achilles tendon rupture)	–	Yes [hip, pelvis or leg fracture (occurring < 1 month previously), acute spinal-cord injury (paralysis) < 1 month]	Yes (Achilles tendon rupture)	Yes (soft-tissue injury of higher than grade 1)	–	Yes (Achilles tendon rupture)
Immobilisation type	Yes (plaster cast: complete leg, circular knee cast – ankle free, foot, lower leg)	–	–	Yes (immobilising plaster cast acquired < 1 month previously)	Yes (plaster cast extending above the knee)	Yes (thigh bandage)	–	Yes (rigid immobilisation and/or above-knee plaster cast)
Pneumonia	Yes	–	–	Yes (serious lung disease including pneumonia, diagnosed < 1 month previously)	–	–	–	No
Travel	–	–	–	–	Yes [continuous travel of ≥ 3 hours (road, rail or air travel) in the previous 4 weeks or needing to travel while wearing plaster cast]	–	–	No
Swollen legs	–	–	–	Yes (current)	–	–	–	No

continued

TABLE 14 Summary of predictor variables included in studies of RAMs, with comparison with the Delphi consensus exercise (*continued*)

	RAM							
Variable	L-TRiP(cast)[32]	Plymouth[31]	GEMNet[17]	Saragas *et al.*[81]	Haque *et al.*[80]	Giannadakis *et al.*[79]	Eingartner *et al.*[78]	Delphi
Sepsis	–	–	–	Yes (occurring < 1 month previously)	–	–	–	No
Central venous access	–	–	–	Yes	–	–	–	No
Antiphospholipid antibodies	–	–	–	Yes (positive lupus anticoagulant, elevated anticardiolipin antibodies)	–	–	–	No
Multiple trauma	–	–	–	Yes (multiple trauma occurring < 1 month previously)	–	–	–	No

CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; MI, myocardial infarction.

Summary of key findings

- Expert consensus on 13 variables most likely to predict VTE risk for outpatients with lower-limb injury and temporary immobilisation has been established: eight generic VTE risk predictors (i.e. thrombophilia, pregnancy/puerperium, active cancer, surgery in the preceding 3 months, prior VTE, exogenous oestrogen/hormone therapy, lower-limb paralysis and superficial thrombophlebitis), two patient demographics (i.e. age and BMI) and three variables specific to lower-limb immobilisation or injury (i.e. Achilles tendon rupture, rigid immobilisation and above-knee cast).
- It was not possible to achieve expert consensus on the following seven variables: intravenous drug use, significant injury in the preceding 3 months, significant medical comorbidity, preceding immobility, comminuted injury, non-weight-bearing status and family history of VTE.
- Injury- and plaster-associated risk was proposed as a single ordinal variable based primarily on the degree of calf pump immobilisation.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic review was undertaken to identify any existing studies on the cost-effectiveness of thromboprophylaxis for lower-limb immobilisation due to injury.

Methods of reviewing cost-effectiveness

Identification of studies

Studies were identified by searching the following electronic databases and research registers:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, MEDLINE and Versions(R) (via OvidSP), 1946 to October 2017.
- EMBASE (via OvidSP), 1974 to October 2017.
- Cochrane Database of Systematic Reviews (via Wiley Online Library), 1996 to October 2017.
- Database of Abstracts of Review of Effects (via Wiley Online Library), 1995 to March 2015.
- HTA database (via Wiley Online), 1995 to October 2017.
- NHS EED (via Wiley Online Library), 1995 to March 2015.

For the MEDLINE and EMBASE searches, the aim was to maximise the specificity of the search in these databases that do not target economic evaluations. In these searches, the keyword strategies developed in the review of clinical effectiveness (see *Chapter 3*, *Objective*), which combined terms related to VTE with terms related to lower-limb immobilisation, were used with sensitive economic evaluation, quality of life and cost search filters[91–93] aimed at restricting search results to economic and cost-related studies. For the searches of HTA and NHS EED, terms for lower-limb immobilisation were not included, in order to maximise sensitivity and find all economic evaluations relating to VTE. All resources were searched initially from inception to October 2017 (or, in the case of discontinued sources such as NHS EED, the date at which coverage ceased). Further details on the search strategy can be found in *Appendix 9*.

All identified citations from the electronic searches and other resources were imported into and managed using EndNote bibliographic software.

Inclusion and exclusion criteria

The inclusion of potentially relevant articles was undertaken using a two-step process by a single reviewer. During the screening stage, all titles were examined for inclusion by the health economist and any citations that clearly did not meet the inclusion criteria (e.g. non-human, unrelated to VTE) were excluded. During the screening stage, abstracts were also examined if the paper could not be excluded based on the title alone. During the eligibility stage, all full-text articles that could not be excluded based on title and abstract were examined.

Studies were selected for inclusion on the basis of pre-determined inclusion and exclusion criteria. The population, interventions and comparators were defined as per the clinical effectiveness review of pharmacological thromboprophylaxis for preventing VTE (see *Chapter 3, Inclusion and exclusion criteria*). In addition, the study population was restricted to patients treated in the UK NHS because estimates of resource use and costs may not be transferable between different health-care settings. Criteria for the study design and outcomes were specified to identify studies meeting the NICE reference case.[94] In terms of study design, the review was restricted to cost-effectiveness studies, thereby excluding cost-minimisation studies. In terms of outcomes, the review was restricted to studies that measured benefits using QALYs because the QALY has been defined by NICE as the reference case measure for benefit for UK cost-effectiveness

studies[94] and the NICE methods guide[94] provides guidance on the range of cost-per-QALY values that can be considered to represent good value for money within the UK NHS. Studies reporting alternative outcomes, such as cost per VTE avoided, were therefore excluded. Cost-consequence studies and other studies that reported data on costs, resource use or utility values in relevant populations were excluded from the cost-effectiveness review but were examined for relevant data that might inform the modelled estimates of cost-effectiveness (described in *Independent economic assessment methods*).

Results of cost-effectiveness review

The literature searches identified 1299 citations. Of these, no relevant published cost-effectiveness studies were identified. A flow chart describing the process of identifying relevant literature can be found in *Figure 8*. A total of three full-text articles were excluded as they did not meet all the prespecified inclusion criteria.[95–97] The articles were excluded for the following reasons: inappropriate study design (not a cost-effectiveness analysis)[96] and wrong target population (not isolated lower-limb injury requiring temporary immobilisation).[95,97] A full list of excluded studies with reasons for exclusion is presented in *Appendix 10*. One study was identified that examined the costs of providing thromboprophylaxis following lower-limb injuries but benefits were not assessed. This study was retained as a potential source of cost inputs for the analysis described in *Independent economic assessment methods*.

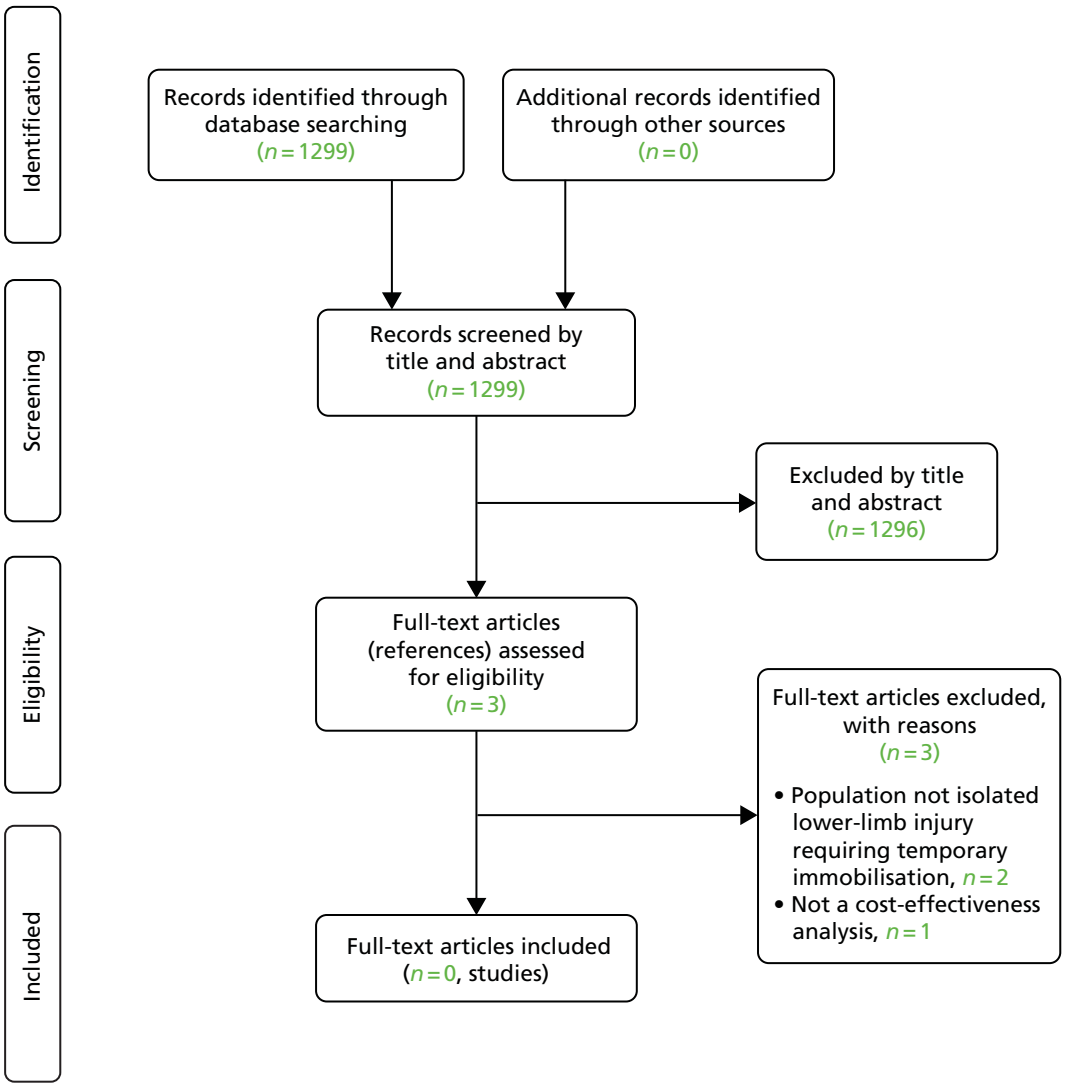

FIGURE 8 Study flow chart (adapted):[37] cost-effectiveness review of pharmacological thromboprophylaxis for preventing VTE in patients having lower-limb immobilisation due to injury.

Given the lack of published analyses in directly relevant populations, it was decided to retain papers describing cost-effectiveness analyses in related populations for the purpose of identifying suitable model inputs. Based on clinical advice, only those studies examining the cost-effectiveness of thromboprophylaxis in patients having elective knee surgery were retained, as these patients are more likely to be generally fit and well prior to surgery, do not have long periods of hospitalisation, will have some degree of reduced mobility in the lower limb during their recovery from surgery and the impact of surgery may mimic, to some extent, the trauma of lower-limb injury. Although two papers[98,99] were identified that reported the cost-effectiveness for thromboprophylaxis in patients having elective knee surgery, both corresponded to the same study, namely main analysis[99] and subgroup analysis[98] of patients aged > 75 years or with moderate renal impairment. Given that the parameter sources of interest did not vary between these two citations, only the paper reporting the main analysis was retained.[99] The parameters identified from this paper are described in the next section.

Independent economic assessment methods

Given the lack of published analyses examining the cost-effectiveness of thromboprophylaxis in patients having lower-limb immobilisation due to injury (see *Systematic review of existing cost-effectiveness evidence*), a de novo economic evaluation was conducted using decision-analytic modelling.

Decision problem

The aim of the decision-analytic model was to estimate the incremental cost-effectiveness of different strategies for thromboprophylaxis in patients with lower-limb injury requiring immobilisation. The thromboprophylaxis strategies examined were based on treating all patients or treating patients in accordance with the application of the RAMs identified in the review of RAMs described in *Chapter 3*, *Review of risk assessment models for predicting venous thromboembolic risk*. Based on the estimates of sensitivity and specificity identified in the review, it was decided to examine the L-TRiP(cast) tool, published by Nemeth *et al.*,[32] using cut-off scores ranging from 6 to 10. The Plymouth tool, published by Keenan *et al.*,[31] and the GEMNet tool, published by Roberts *et al.*,[17] were not included in the economic analysis. The only available estimates of the sensitivity and specificity for these RAMs, from an evaluation by Watson *et al.*,[82] suggested that both of these tools would be outperformed by the L-TRiP(cast) tool. The comparator considered in the economic analysis was no thromboprophylaxis. The base-case economic analysis assumes that prophylaxis consists of LMWH being given for the duration of lower-limb immobilisation (e.g. duration of casting or splinting).

Context

The model estimates lifetime costs and QALYs for the different thromboprophylaxis strategies and the comparator of no thromboprophylaxis under a NHS and Personal Social Services perspective. Future costs and benefits are discounted from their net present value at a rate of 3.5% per annum in accordance with the NICE *Guide to the Methods of Technology Appraisal*.[94] Costs are reported in Great British pounds, based on 2017 prices. To achieve this, historical prices used as model inputs were inflated using the hospital and community health services pay and prices index.[100]

Conceptual model

The clinical events that are expected to be affected by whether or not thromboprophylaxis is given to patients with lower-limb immobilisation due to injury are as follows:

- bleeding events during the period of prophylaxis, including fatal bleeds, non-fatal intracranial bleeds, other major bleeds and clinically relevant non-major bleeds
- VTE events, which includes distal and proximal DVT, both of which may be either symptomatic or asymptomatic, and PE, which may be either fatal or non-fatal
- bleeding events during the treatment of symptomatic VTE with anticoagulants
- long-term complications of VTE, such as PTS and CTEPH
- long-term complications of bleeds, such as disability following non-fatal intracranial bleeds.

It should be noted that, within the modelling framework, symptomatic DVTs include any DVTs causing symptoms that result in the patient seeking medical care and any DVTs categorised as asymptomatic would include those with minor symptoms that are not sufficient for the patient to seek medical care. In the context of lower-limb injury and immobilisation, some DVTs may be categorised as asymptomatic in this analysis despite symptoms being present if these symptoms are attributed to the injury and do not prompt the patient to seek medical care.

Model structure

The model structure consists of a decision tree followed by a Markov model. The decision tree captures outcomes related to prophylaxis and VTE events in the first 6 months. The Markov model is used to extrapolate the QALY losses from fatal events and the costs and QALY losses from long-term complications that develop or persist beyond 6 months. The model estimates outcomes for a cohort of identical patients with average characteristics.

The decision tree captures the impact of alternative strategies on thromboprophylaxis rates, the impact of thromboprophylaxis on VTE events (e.g. symptomatic/asymptomatic DVT and PE) and bleeding complications related to either the initial thromboprophylaxis or anticoagulants used in the management of VTE in symptomatic patients. Bleeding complications are split into fatal bleeds, non-fatal intracranial haemorrhage (ICH) and other (i.e. non-fatal non-intracranial) major bleeds. The decision tree captures the first 6 months after lower-limb injury as this is considered a sufficient time frame to capture both 6–8 weeks of thromboprophylaxis during lower-limb immobilisation and 3 months of anticoagulant treatment for any VTEs arising during lower-limb immobilisation. All costs and health effects related to major bleeds that are non-fatal and non-intracranial are assumed to resolve within the 6-month timeframe of the decision tree model. Any chronic complications of VTE are assumed not to be diagnosed until after the completion of VTE treatment as it is difficult to distinguish PTS and CTEPH from acute symptoms during the first 3 months after VTE. Therefore, PTS and CTEPH are assumed not to occur during the decision tree phase of the model. The decision tree structure is shown in *Figure 9*. The key model assumptions were as follows:

- Bleeding events during immobilisation are possible in both those having thromboprophylaxis and those having no thromboprophylaxis.
- Bleeds associated with thromboprophylaxis are assumed to occur before VTE associated with immobilisation and both are assumed to occur within 12 weeks of the start of lower-limb immobilisation.
- Patients who have major bleeding will stop thromboprophylaxis immediately, but the treatment effect of thromboprophylaxis is assumed to be the same as for those who completed treatment, as patients who bleed are assumed to be adequately anticoagulated.
- The risk of VTE is the same whether or not prophylaxis caused bleeding.
- All patients with symptomatic DVT receive accurate diagnosis and initiate treatment with anticoagulants (3 months of either DOACs or phased anticoagulation).
- Asymptomatic DVTs are not detected and are not treated.
- All PEs are symptomatic and lead to detection and treatment with anticoagulants in all cases.
- Patients treated for symptomatic DVT and PE have a bleed risk associated with treatment, which is assumed to occur during the 3-month treatment period (i.e. within 6 months of the start of lower-limb immobilisation).
- Chronic complications of VTE (e.g. CTEPH following PE and PTS following DVT) are assumed to be diagnosed at least 3 months after VTE and, therefore, occur after any bleeds associated with VTE treatment.
- Deaths caused by PE occur before any bleeding associated with the treatment of PE.
- Risk of bleeding during treatment of VTE is independent of whether or not the patient bled during prophylaxis.
- Risk of VTE, risk of bleeding and risk of PTS/CTEPH are not dependent on patient characteristics.

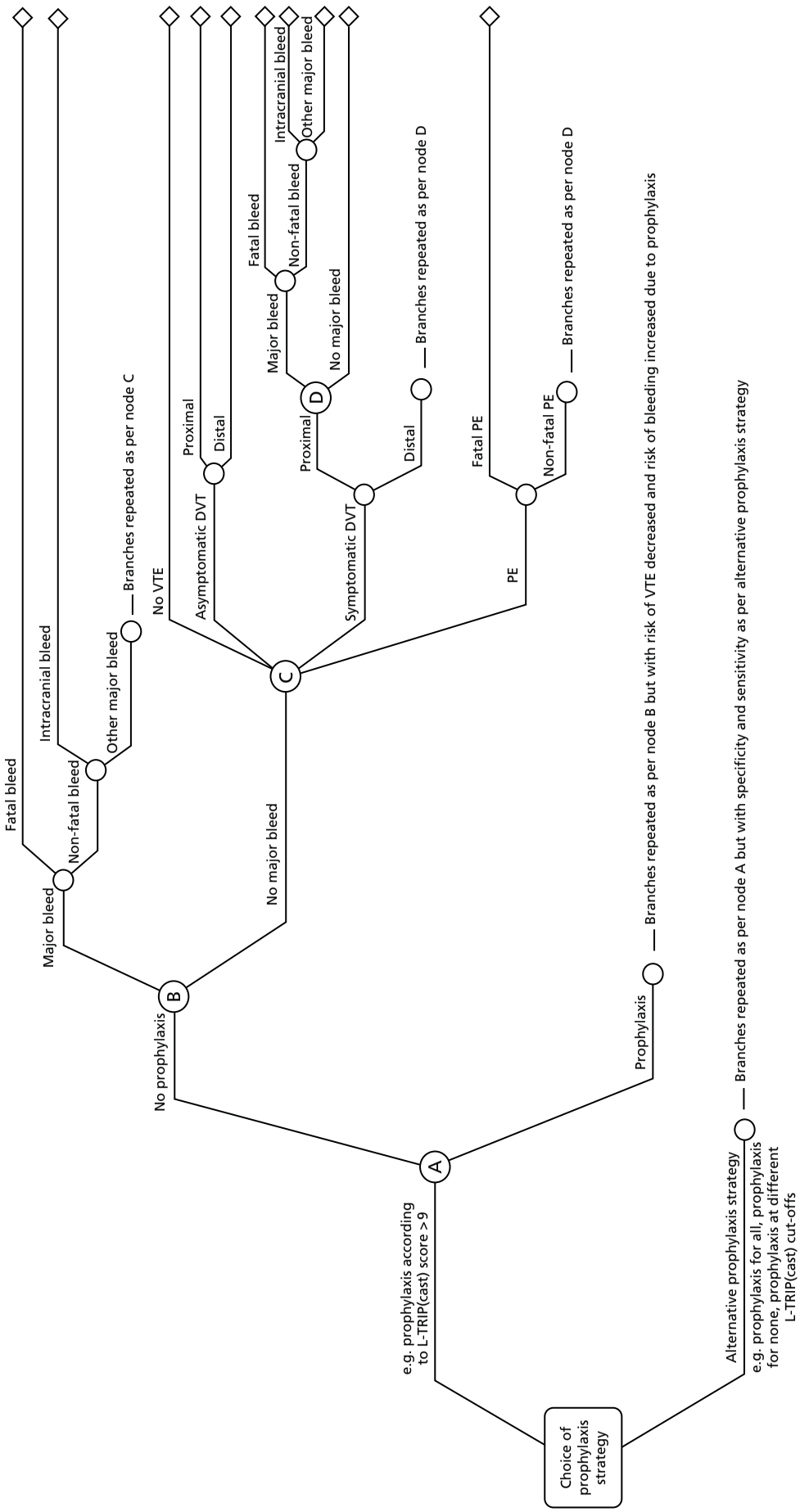

FIGURE 9 Decision tree structure.

A key structural assumption within the model is the use of a cohort modelling approach that assumes that all patients have identical characteristics based on the average characteristics of those having lower-limb immobilisation due to injury. Depending on the RAMs used, the likelihood of receiving prophylaxis may be dependent on patient characteristics, leading to the treated and untreated populations having different characteristics, which is not captured in a cohort model. Based on clinical advice, it was expected that age would be the only relevant patient characteristic that would predict different outcomes. A scenario analysis was conducted to explore whether or not patient heterogeneity would affect the conclusions by varying the age of the cohort. Based on this, it was concluded that the cohort-level modelling approach was adequate and would not introduce significant bias.

Clinically relevant non-major bleeding (CRNMB), which is any non-major bleeding that results in contact with a health-care professional, was not expected to be a significant driver of cost-effectiveness. It was therefore excluded from the base-case analysis, but the impact of this assumption was explored in a scenario analysis. As CRNMB has no long-term implications, it was not modelled using a separate branch in the decision tree. Instead, it was included in a scenario analysis by applying a simple one-off cost for consultation to a proportion of the population having thromboprophylaxis.

Outcomes related specifically to surgical site wounds, such as wound infection and wound breakdown, were excluded from the model as there is substantial uncertainty as to whether or not thromboprophylaxis influences wound healing. Furthermore, only a small proportion of the lower-limb immobilisation population would have surgical intervention or open fractures. This is supported by data from the largest RCT to date,[59] in which only 12% of participants across both arms had surgery and the rate of infections was similar across arms (12/719 for treatment vs. 14/716 for control).

The aim of the Markov model is to capture QALY losses due to fatal PEs or fatal bleeds and the costs and QALY losses associated with chronic complications following VTE events (e.g. PTS or CTEPH) or bleeds (e.g. disability following ICH). At 6 months, patients enter one of eight Markov states: (1) well, (2) dead, (3) post-ICH, (4) asymptomatic proximal DVT, (5) asymptomatic distal DVT, (6) symptomatic proximal DVT, (7) symptomatic distal DVT or (8) PE. The Markov model is then used to estimate the number of patients from the DVT and PE states who develop either PTS or CTEPH, respectively, and the long-term survival in each health state. Separate DVT states were required to capture differences in PTS risk depending on whether the DVT was proximal or distal and whether it was symptomatic and treated or was asymptomatic and, therefore, remained undiagnosed and untreated. The prevalence of PTS and CTEPH is captured by having separate health states for patients with these long-term complications. All patients with PTS are combined in a single health state, as costs, utilities and survival are not expected to be affected by whether or not PTS occurred following proximal or distal DVT. The PTS state is not split into different severity levels as the utility estimates are based on the average across severity levels and the costs are not expected to differ by severity. Separate Markov states were required for medically and surgically managed CTEPH as the type of management affects life expectancy, costs and utilities in patients with CTEPH. The health states are shown in *Figure 10*.

The Markov model has one 6-month cycle, to extrapolate the decision tree outcomes to the end of the first year, followed by annual cycles thereafter. All-cause mortality during the first year is assumed to occur at 6 months (i.e. between the end of the decision tree and the start of the Markov model) and then mid-way through each annual cycle thereafter. The CTEPH and post-ICH health states have state-specific mortality risks, whereas the other states experience general population mortality rates. Average costs and QALYs across each model cycle were calculated by applying a half-cycle correction.

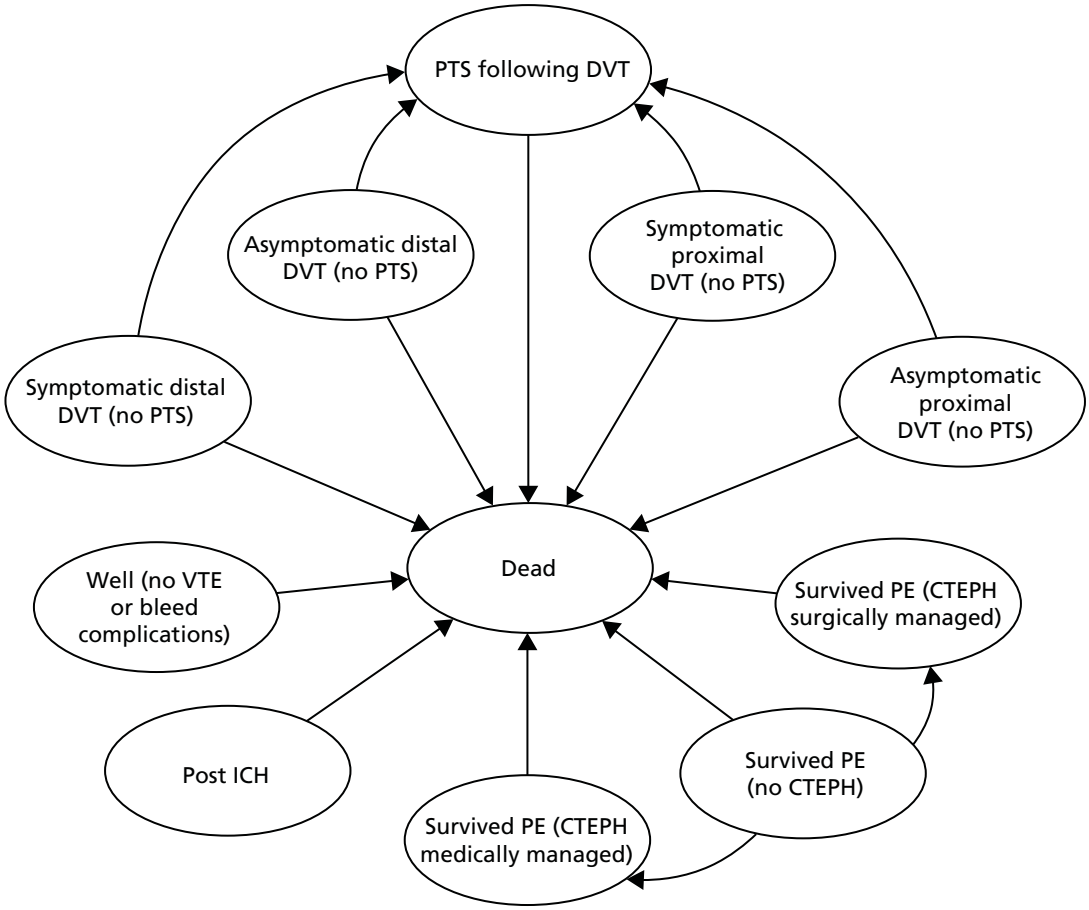

FIGURE 10 Markov model structure.

Assumptions related to the Markov phase of the model are as follows:

- All symptomatic DVTs are associated with a risk of PTS but the rate is allowed to differ depending on whether the DVT is distal or proximal and whether it is symptomatic and treated or asymptomatic and untreated.
- There is no risk of PTS for PE.
- CTEPH is possible only after PE.
- Further outcomes (i.e. VTE, CTEPH and PTS) are not modelled for those who experience ICH, as lifetime cost and QALYs will be determined predominantly by disability related to the ICH.
- All-cause mortality is applied to all Markov states with state-specific mortality rates possible for patients who have experienced ICH or who have CTEPH that is either medically or surgically managed.
- Recurrent VTE is not modelled as it is not likely to be related to the initial provoked VTE and, therefore, would occur equally regardless of whether or not thromboprophylaxis was given during immobilisation.

Data sources

Identification of data sources

A summary of the model parameters and data sources used to populate the model are provided in *Table 15*, with the exception of utility values, which are provided in *Treatment-related utility decrement*. The number of patients receiving thromboprophylaxis under the various treatment strategies is estimated by combining data on sensitivity and specificity, from the systematic review of RAMs (see *Chapter 3*, *Review of risk assessment models for predicting venous thromboembolic risk*), with data on the risk in untreated patients, from the review of RCTs comparing thromboprophylaxis with no thromboprophylaxis (see *Chapter 3*, *Review of pharmacological thromboprophylaxis for preventing venous thromboembolism*). Parameters relating to the

TABLE 15 Summary of clinical and cost parameters

Parameter description	Mean value	95% CI[a]	Source	Notes
Clinical parameters				
Sensitivity of decision tools			See *Chapter 3*, *Narrative data synthesis*	
L-TRiP(cast) score of				
≥ 6	98.4%	Assumed fixed		
≥ 7	95.3%	Assumed fixed		
≥ 8	92.6%	Assumed fixed		
≥ 9	80.8%	Assumed fixed		
≥ 10	65.1%	Assumed fixed		
Specificity of decision tools			See *Chapter 3*, *Narrative data synthesis*	
L-TRiP(cast) score of				
≥ 6	14.2%	Assumed fixed		
≥ 7	26.2%	Assumed fixed		
≥ 8	39.7%	Assumed fixed		
≥ 9	60.8%	Assumed fixed		
≥ 10	72.2%	Assumed fixed		
Probabilities of VTE in patients having lower-limb immobilisation without thromboprophylaxis			Systematic review of thromboprophylaxis effectiveness	Average proportion across 12 RCTs (see *Table 16*)
PE	0.4%	0.2% to 0.7%		
Symptomatic DVT	0.9%	0.5% to 1.3%		
Asymptomatic DVT	7.1%	6.0% to 8.1%		
Proportion of asymptomatic DVTs that are distal	83.9%	73.3% to 92.2%	Systematic review of thromboprophylaxis effectiveness	Average proportion across six RCTs (see *Table 16*)
Proportion of symptomatic DVTs that are distal	50%	26.5% to 73.4%	Systematic review of thromboprophylaxis effectiveness	Based on a single RCT that focused exclusively on symptomatic DVTs (see *Table 16*)

Parameter description	Mean value	95% CI[a]	Source	Notes
Effectiveness of prophylaxis: OR for VTE	0.52	0.37 to 0.71	Systematic review of decision tools for identifying patients at risk of VTE	OR for LMWH vs. placebo for all VTE based on random-effects Bayesian NMA
Risk of major bleed with no prophylaxis	1.89 per 1000 person-years	1.86 to 1.92 per 1000 patient years	Hippisley-Cox and Coupland[101]	Age-standardised incidence across whole cohort used to derive the QBleed[101] risk score: • 1.34 per 1000 person-years for GI bleed • 0.55 per 1000 person-years for ICH
Bleed risk for prophylaxis vs. no prophylaxis: HR	1.64	0.98 to 2.75	Pooled analysis of bleed risks across all VTE prophylaxis studies in NICE CG92[24]	Data presented in CG92 reanalysed on log-odds scale using random-effects Bayesian meta-analysis
Proportion of major bleeds during lower-limb immobilisation that are fatal (with and without prophylaxis)	21.0%	17.0% to 25.0%	• Case fatality rate of ICH bleeds taken from Fang *et al.*[102] • Case fatality rate of GI bleeds taken from Button *et al.*[103] • Proportion of bleeds that are GI and ICH are based on Hippisley-Cox and Coupland[101]	Average fatality across GI and ICH bleeds with case fatality rates of 10% (95% CI 9.7% to 10.4%) and 49% (95%CI 37% to 60%), respectively
Proportion of non-fatal major bleeds during lower-limb immobilisation that are ICH (with and without prophylaxis)	19.0%	15.4% to 22.2%	Fang *et al.*,[102] Button *et al.*[103] and Hippisley-Cox and Coupland[101]	Estimated based on incidence and case fatality rates for GI and ICH bleeds
Risk of bleeding during 3-month anticoagulant treatment for VTE	0.9%	0.2% to 2.0%	Kooiman *et al.*[104]	6-month incidence pooled across patients with HAS-BLED score of 0 or 1
Proportion of major bleeds during VTE treatment that are fatal	25.0%	21.0% to 28.0%	Nieto *et al.*[105]	Based on case fatality rates for major bleeds within RIETE (Nieto *et al.*)[105]
Proportion of non-fatal major bleeds during VTE treatment that are ICH	9.0%	6.5% to 11.9%	Nieto *et al.*[105]	Based on proportion of major non-fatal bleeds within RIETE that were ICH (Nieto *et al.*)[105]
All-cause (non-VTE-related) mortality	Varies by age	N/A	ONS lifetables[106]	Risk applied each year is based on current age and is not adjusted to account for contribution of VTE to population mortality

continued

TABLE 15 Summary of clinical and cost parameters (*continued*)

Parameter description	Mean value	95% CI[a]	Source	Notes
SMR for patients surviving ICH, compared with general population		Ranges for SMRs not stated so ± 20% on the logged scale is assumed	Fogelholm *et al.*[107]	Assumed no increased mortality risk after 6 years
Year 1 after ICH	4.5			
Years 2 to 6 after ICH	2.2			
Probability of PE being fatal	2.9%	2.5% to 3.3%	Maestre *et al.*[108]	• Data from RIETE • Case fatality rate of clinically overt PE in outpatients
Cumulative risk of PTS for treated symptomatic DVT at 3 years			Hach-Wunderle *et al.*[109] (TULIPA PLUS registry)	Cumulative incidence at 3 years based on the TULIPA PLUS registry. Distribution of risk across years 1 to 3 based on van Dongen *et al.*[110] Zero risk assumed from year 4 onwards
Proximal	32.4%	22.1% to 43.6%		
Distal	15.6%	7.9% to 25.3%		
Cumulative risk of PTS for untreated asymptomatic DVT at 3 years			Hach-Wunderle *et al.*[109] and van Dongen *et al.*[110]	• For proximal DVT, the data for symptomatic DVT were uplifted using the OR from van Dongen *et al.*[110] for the impact of inadequate anticoagulation on PTS risk: OR 2.71 (95% CI 1.44 to 5.1) • Assumed no increased risk for asymptomatic distal DVT
Proximal	56.5%	29.0% to 79.8%		
Distal	15.6%	Fixed relative to symptomatic		
Risk of CTEPH per annum applied in the first 2 years after PE	1.6%	1.0% to 2.2%	Ende-Verhaar *et al.*[111]	• 3.2% (95% CI 2.0% to 4.4%) at 2 years based on the incidence in those surviving the initial treatment period of 3–6 months • Assumed no risk beyond 2 years, based on Pengo *et al.*[112]

Parameter description	Mean value	95% CI[a]	Source	Notes
Proportion of CTEPH treated surgically	59.5%	55.8% to 63.2%	Delcroix *et al.*[113]	
Mortality for CTEPH				
Medically treated	Exponential survival curve with mean hazard of 0.1168	SE of mean hazard 0.0123	Original data from Delcroix *et al.*[113] but curves taken from Goodacre *et al.*[114]	• Medically treated patients have a death risk of 11% per annum (fixed over time) • If the death hazard falls below general population values, then general population values apply
Surgically treated	Log-normal survival curve with mean 5.081 and SD of 3.343	• SE of mean 0.574 • SE of SD 0.399	Original data from Delcroix *et al.*[113] but curves taken from Goodacre *et al.*[114]	• Surgically treated patients have a risk that declines over time (6% in year 1 declining to 1.5% at year 5, 1% at year 10 and 0.8% at year 15) • If the death hazard falls below general population values, then general population values apply
Cost parameters				
Application of RAM to patient	£8.83	Fixed	Curtis and Burns[100]	Cost for 5 minutes of hospital consultant time
Prophylaxis: 6 weeks of LMWH (dalteparin), including costs of initiating treatment and district nurse administration for 4% of patients	£224.64	£197 to £267	• Administration costs based on Menakaya *et al.*[115] • Drug costs based on Drug Tariff[21]	• Costs from Menakaya *et al.*[115] updated to current prices using inflation indices from Curtis and Burns[100] • Dalteparin is the lowest-cost formulation of LMWH based on 2018 Drug Tariff prices[21] • See *Table 18* for a more detailed costing breakdown
Treatment of symptomatic proximal DVT	£687.69	£660 to £715	NHS reference costs[116] Drug Tariff[21]	Clinical expert discussion regarding the likelihood of resource use, combined with NHS reference cost data[116] for health-care contacts and Drug Tariff[21] costs for treatments (see *Table 19* for a more detailed costing breakdown)

continued

TABLE 15 Summary of clinical and cost parameters (*continued*)

Parameter description	Mean value	95% CI[a]	Source	Notes
Treatment of symptomatic distal DVT	£559.62	£536 to £584	NHS reference costs[116] Drug Tariff[21]	Clinical expert discussion regarding the likelihood of resource use, combined with NHS reference cost data[116] for health-care contacts and Drug Tariff[21] costs for treatments (see *Table 19* for more detailed costing breakdown)
Treatment of non-fatal PE	£1788.44	£1995 to £2168	NHS reference costs[116] Drug Tariff[21]	Clinical expert discussion regarding the likelihood of resource use, combined with NHS reference cost data[116] for health-care contacts and Drug Tariff[21] costs for treatments (see *Table 19* for more detailed costing breakdown)
Fatal PE	£1498.14	£1430 to £1571	NHS reference costs[116]	As per non-fatal bleed, minus drug therapy for PE
Fatal bleed	£1802.48	£322 to £3283	Luengo-Fernandez *et al.*[117]	• Costs of fatal haemorrhagic stroke from OXVASC subgroup with atrial fibrillation • Updated to current prices using inflation indices[100]
Non-fatal, non-ICH bleed	£1197.88	£1118 to £1288	NHS reference costs 2015/16[116]	Weighted average of reference costs for GI bleed (HRG codes FZ38G – FZ38P)
Post non-fatal ICH: first 90 days	£21,255.00	£16,814 to £26,217	Luengo-Fernandez *et al.*[117]	Weighted average of costs for non-fatal haemorrhagic strokes Uplifted to current prices using inflation indices[100]
Post non-fatal ICH: post acute (beyond 90 days) costs per annum	£8013.00	£5300 to £11,271	Luengo-Fernandez *et al.*[117]	• Average costs across all stroke types (haemorrhagic not reported separately) • Includes GP and ED costs and long-term care cost • Updated to current prices using inflation indices[100]

Parameter description	Mean value	95% CI[a]	Source	Notes
PTS cost per annum: year 1 (mild/moderate/severe)	£308 in year 1	£294 to £323	NHS reference costs 2015/16[116]	One first and one follow-up vascular surgery outpatient appointment 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 2 (mild/moderate/severe)	£74 in each subsequent year	Fixed	Curtis and Burns[100]	Two GP surgery consultations with qualification costs including direct-care staff costs at £37 per appointment
CTEPH cost per annum				
Medically managed	£17,942 each year	Fixed	NICE CG92[24]	• Cost in CG92 was £1219 per 4 weeks in 2008/09 prices.[24] This was updated to 2016/17 prices using inflation indices[100] • Assume treatment is lifelong
Surgically managed	£9890 in year 1 and zero in year 2 onwards	£9471 to £10,370	NHS reference costs 2015/16[116]	• 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)

CG, clinical guideline; GI, gastrointestinal; GP, general practitioner; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly; HR, hazard ratio; HRG, Healthcare Resource Group; N/A, not applicable; ONS, Office for National Statistics; OXVASC, Oxford Vascular Study; RIETE, Computerized Registry of Patients with Venous Thromboembolism; SE, standard error; SMR, standardised mortality ratio; TULIPA PLUS, Thrombosis and Pulmonary Embolism in Out-Patients – plus; VKA, vitamin K antagonist.
a Except where stated otherwise (e.g. SD or SE).

relative risk (RR) of VTE events in patients receiving thromboprophylaxis compared with those not receiving thromboprophylaxis have been taken from the review of clinical effectiveness of thromboprophylaxis to prevent VTE in lower-limb immobilisation. For all other parameters, data were obtained by reviewing the data sources used in published cost-effectiveness analyses and other published sources. As no relevant models were identified that were specific to the population having lower-limb immobilisation, the search for parameter sources was broadened to models in related populations or indications. This search focused, first, on models used to inform NICE guidance on anticoagulants to prevent and treat VTE as the models used to inform any existing NICE guidance were considered highly likely to contain data relevant to the UK context and the NICE reference case, and have been critically scrutinised by independent academic groups. Second, the additional studies identified in the literature review for the related population of patients having elective knee surgery were used (as discussed in *Results of cost-effectiveness review*). Finally, ad hoc searches were conducted using the reference lists of recently published reviews to identify any relevant sources not identified during the review of published models and clinical experts were consulted to see if any key data sources known to them had been missed. This included any sources used in relevant models known to the authors. The published cost-effectiveness analyses identified as potential sources of model inputs are summarised in *Appendix 11*.

Characteristics of population having lower-limb immobilisation

The Prevention of Thrombosis after Lower Leg Plaster Cast (POT-CAST) trial by van Adrichem *et al.*[59] was selected as being representative of the population having lower-limb immobilisation due to injury who are at risk of thrombosis. This was selected as it is a recent, large RCT conducted exclusively in Europe (the Netherlands) and the inclusion and exclusion criteria were not too restrictive; patients with a prior history of VTE were excluded but those with cancer or family history of DVT were not excluded. The starting age in the model was set to be 46 years of age and 51.5% of the starting population were male.

Risk of venous thromboembolism and types of venous thromboembolism

The risk of VTE was based on data taken from the systematic review of clinical effectiveness for LMWH versus control (see *Chapter 3*, *Review of pharmacological thromboprophylaxis for preventing venous thromboembolism*). The rate of any form of VTE (i.e. PE, symptomatic DVT or asymptomatic DVT) was 8.39% across the 12 studies[23,49–56,58–60] reporting data for control (i.e. placebo, aspirin, no thromboprophylaxis). The risk of PE, including those that experienced PE with DVT, was 0.43%. Therefore, the risk of DVT without PE was 7.96%. Only nine studies[23,49–52,54,56,58,60] reported outcomes for both symptomatic and asymptomatic DVT. From these studies, it was estimated that 11.4% of DVT are symptomatic (16/140), giving an absolute incidence of 0.91% for symptomatic DVT and 7.05% for asymptomatic DVT in patients having lower-limb immobilisation without thromboprophylaxis. These are slightly higher than the raw figures (*Table 16*) as three studies[53,55,59] did not report outcome data for both symptomatic and asymptomatic DVT but did report data for all VTE and PE. These estimates effectively assume the same split of symptomatic and asymptomatic DVT for the three studies with missing data to achieve the total VTE rate observed across all 12 studies. For asymptomatic DVT, only six studies[23,50–52,58,60] reported outcomes for both distal and proximal asymptomatic DVT. From these six studies, it was estimated that 16% (9/56) of asymptomatic DVTs are proximal (and, therefore, 84% are distal). The data on the location of symptomatic DVTs (distal or proximal) were very sparse, with only 46 events reported across all trial arms and many studies not reporting the location. It was possible to extract data on the location of symptomatic DVTs for four studies[54,57–59] included in the review, covering a total of 34 events across all trials arms. The proportion of symptomatic DVTs that were proximal varied from 14% to 100% across these four studies, with a median estimate of 36%. The POT-CAST trial[59] was the only one of these four studies that focused exclusively on symptomatic VTE. The other three studies[54,57,58] screened patients for asymptomatic DVTs as well as recording the number of DVTs that were symptomatic. There is a risk that the process of screening patients for asymptomatic DVTs may lead to patients attributing symptoms to screening-detected DVTs that may otherwise not have been sufficiently symptomatic to result in the patient presenting with symptoms in routine care. For this reason, it was decided to use the POT-CAST trial[59] as the single source of estimates for the proportion of symptomatic DVTs that are proximal, as no routine screening was used in this trial to detect asymptomatic DVTs. As this single study provided a low number of events, it was decided to pool the data across trial arms. This resulted

TABLE 16 Data from the systematic review on clinical effectiveness used to inform VTE event rates

Event type	*n* with event	*N* at risk	Rate based on studies (%)	Number of studies	Data applied in model (%)
Any VTE	196	2336	8.39	12[23,49–56,58–60]	8.39
PE risk	10	2336	0.43	12[23,49–56,58–60]	0.43
DVT without PE[a]	186	2336	7.96	12[23,49–56,58–60]	
Asymptomatic DVT	124	1466	8.58	9[23,49–52,54,56,58,60]	7.05[b]
Symptomatic DVT	16	1466	1.11	9[23,49–52,54,56,58,60]	0.91[b]
Asymptomatic proximal DVT	9	1055	0.85	6[23,50–52,58,60]	1.13[c]
Asymptomatic distal DVT	47	1055	4.45	6[23,50–52,58,60]	5.59[c]
Symptomatic proximal DVT	8	1435	0.56	1[59]	0.45[d]
Symptomatic distal DVT	8	1435	0.56	1[59]	0.45[d]

a Based on the difference between the two rows above.
b Estimated using the total rate of DVT without PE from 12 studies and proportion that are symptomatic from six studies.
c Estimated using the total that are asymptomatic from nine studies and proportion that are proximal from six studies.
d Estimated from the total that are symptomatic from nine studies and proportion that are symptomatic from the POT-CAST trial[59] (50%) that focused exclusively on symptomatic VTE events.

in 50% of the 16 symptomatic DVTs being proximal. Given that these data were based on a single study and a small number of events, two extreme scenarios were examined, assuming that either 0% or 100% of symptomatic DVTs are proximal, to see if the overall conclusions were sensitive to uncertainty around this parameter.

All-cause mortality

It was not considered necessary to model males and females separately as the risks of VTE during lower-limb immobilisation were not expected to vary according to sex. However, life-expectancy is dependent on sex and, consequently, any QALY gains from deaths prevented would be dependent on sex. For this reason, a weighted mortality risk was applied, based on the proportion of males (51.5%) in the POT-CAST trial,[59] using data on the risk of death for males and females by age obtained from lifetables. The weighting across males and females was allowed to vary over the course of the model to allow for the fact that lower mortality risks in females leads to a slight increase in the proportion of people alive who are female over time.

Case fatality rate for pulmonary embolism

None of the studies included in the review of clinical effectiveness reported any fatal PEs. Given that 14 PEs were reported within the 13 studies[23,49–60] included in the review, this suggests that the rate of fatality due to PE is < 7% in the population having lower-limb immobilisation due to injury. The research team looked for alternative data sources on the case fatality rate of PE. Data were identified from the Computerized Registry of Patients with Venous Thromboembolism (RIETE) (an extensive data registry of consecutive patients with VTE), which found that the rate of all-cause mortality at 30 days had fallen over time from 6.6% in 2001–05 to 4.9% in 2010–13 (reported by Jiménez *et al.*[118]). However, some of this mortality may not be related to PE. When looking at only PE-related mortality, the rate at 30 days was 1.8%. Another analysis of RIETE, by Maestre *et al.*,[108] found that rates of fatal PE at 90 days were lower for outpatients than inpatients. They found that of 7591 outpatients with clinically overt PE, 219 (2.9%) had fatal PE at 90 days; this was lower than the 4.1% (119/2870) rate with clinically overt PE having a fatal PE in the inpatient population. Given that patients having lower-limb immobilisation due to injury would generally be managed as outpatients, this suggests that a lower risk may be seen in this population.

The Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR) cohort study (reported by Pollack *et al.*[119]), which recruited patients with PE from EDs in the USA, reported a 30-day all-cause mortality rate of 5.4% for patients with confirmed PE, but the rate of mortality was only 1.1% when restricted to PE-related in-hospital mortality. These data seem reasonably consistent with the 30-day data from RIETE.

It was decided to apply the case fatality rate for outpatients from the RIETE study (2.9%) in the model, as patients having lower-limb immobilisation would be managed as outpatients and there was a slight increase from 30 days to 90 days, which is captured in the analysis by Maestre *et al.*[108] but not in the other two analyses, which were limited to 30 days.

Combining the incidence and case fatality rate for PE, it is estimated that one fatal PE per 8097 patients having lower-limb immobilisation without thromboprophylaxis would be expected, which is consistent with there being no fatal PEs observed in the studies included in the systematic review for treatment effectiveness.

Effectiveness of thromboprophylaxis on prevention of venous thromboembolism during lower-limb immobilisation

We applied the OR for LMWH versus control for the outcome of any VTE estimated from the NMA to all forms of VTE within the model. Although the NMA provides estimates of clinical effect that are specific to different types of VTE (i.e. symptomatic DVT, asymptomatic DVT and PE) the estimates for these specific VTE types are more uncertain as they are based on fewer events. The pooled effect for the OR (0.52, 95% CrI 0.37 to 0.71) was converted to a RR and applied to the baseline risk within the model.

For the sensitivity analyses examining thromboprophylaxis using alternative drug classes, it was assumed that DOACs would have the same effectiveness as LMWH, as no studies examining the effectiveness of DOACs in this population were included in the systematic review. For the analysis assuming that fondaparinux is used, the OR for fondaparinux versus control from the NMA was applied (0.13, 95% CrI 0.05 to 0.30). In both cases, the same adverse effects profile for LMWH, DOACs and fondaparinux were implicitly assumed, as the only adverse event included in the model was bleeding and it was assumed that all prophylaxis had the same impact on bleeding rates.

Risk of bleeding during lower-limb immobilisation

There is a risk of major bleeding within the general population regardless of whether or not they receive treatment with anticoagulants. A cohort study (reported by Hippisley-Cox and Coupland[101]), conducted in a large primary care population using data from 4.4 million patients with 16.4 million person-years of follow-up, estimated an age-standardised incidence rate of 1.34 (95% CI 1.32 to 1.36) per 1000 person-years for upper GI bleeding and 0.55 (95% CI 0.54 to 0.56) per 1000 person-years for intracranial bleeds for patients not taking anticoagulants. Given that the study cohort was patients aged 21–99 years registered with a general practice and that the only relevant exclusion criteria appears to be existing anticoagulated patients, this study was considered to be reflective of the risk of GI bleeds and ICH in the general population at risk of lower-limb injury who are not currently taking anticoagulants. The baseline characteristics of patients not taking anticoagulants in the study by Hippisley-Cox and Coupland[101] were compared with the characteristics of those in the comparator arm of the POT-CAST trial[59] (*Table 17*). Although Hippisley-Cox and Coupland[101] did not present a mean age, a weighted mean age was calculated using the distribution across age bands and the mid-point ages for each band: this was found to be 40 years (with a range of 36–45 years when using the lower and upper limits of the age bands), which is lower than the mean age of 46 years from the POT-CAST trial.[59] The proportion of non-smokers was slightly lower in the POT-CAST trial and the proportion of patients with previous cancer was slightly higher.

TABLE 17 Comparison of baseline characteristics reported by both QBleed (reported by Hippisley-Cox and Coupland[101]) and the POT-CAST trial (reported by van Adrichem *et al.*[59])

Characteristic	QBleed (no anticoagulation)[101]	POT-CAST[59]
Male (%)	48.9	51.5
Age (years), mean (SD)	NR[a]	46 (16)
Age group (years) (%)		
21–24	54.6	NR
45–64	29.0	NR
65–74	8.5	NR
75–84	5.4	NR
≥ 85	2.5	NR
BMI (kg/m^2), mean (SD)	26 (4.8)	26 (4.4)
Smoking status (%)		
Non-smoker	55.9	46.5
Former smoker	18.7	26.8
Current smoker	21.7	26.8
Previous cancer (%)	2.7	4.3

NR, not reported.
a The mean age of 40 years was estimated using the mid-point ages for each age band and age 85 years for the '≥ 80 years' band (range of mean 36–45 years, using upper and lower limits of age bands).

To see if the rates of major bleeding in the RCTs included in the clinical effectiveness review were similar, data on the rates of major bleeding (see *Appendix 3*) were combined with data on the number of person-years people were at risk of bleeding within each study. It was assumed that the period at risk was the period of cast immobilisation, unless the study explicitly reported a longer duration of follow-up. The number of person-years at risk could be estimated for only 11 of the 13 studies.[23,49–56,59,60] One study used an active control group,[57] whereas another did not explicitly report the duration of follow-up.[23] There was only one episode of major bleeding across 447 person-years, giving an incidence of major bleeding of two per 1000 person-years. This appears to be relatively consistent with the estimates for ICH and GI bleeds combined from the cohort reported by Hippisley-Cox and Coupland.[101] Therefore, it was decided to use the age-standardised estimates from the cohort reported by Hippisley-Cox and Coupland[101] within the model.

Thromboprophylaxis would be expected to increase the risk of a major bleed but the very small number of major bleeding events in the systematic review meant that the estimate of the risk of major bleeding due to thromboprophylaxis in people with lower-limb immobilisation was very uncertain (OR 1.45, 95% CrI 0.08 to 32.17). Although the baseline risk of bleeding will vary between patient groups, there is no strong reason to believe that the relative effect of thromboprophylaxis will vary. Therefore, data from the NICE clinical guideline (CG) on reducing the risk of VTE (NICE CG92)[24] was used, which pooled all indications into a single meta-analysis.[24] These data were reanalysed to use a random-effects approach. In this meta-analysis, the median OR was found to be 1.643 (95% CrI 0.90 to 2.53). The OR was converted to a RR and applied to the baseline risk within the model.

The significance of major bleeding depends primarily on whether or not it is fatal; for non-fatal bleeds, the significance depends on whether or not it is intracranial, as ICH has the potential to result in long-term disability. Fang *et al.*[102] examined death and disability following bleeds associated with warfarin (Coumadin®, Bristol-Myers Squibb Company, New York City, NY, USA). These data were used to estimate the proportion of major bleeding episodes that were fatal. Fang *et al.*[102] found that 48.6% of patients having ICH died within 30 days, whereas only 5.1% of patients having non-intracranial bleeds died within 30 days.[102] Although it is acknowledged that bleeds associated with warfarin use may be more likely to result in fatalities than bleeds in patients not having anticoagulation,[120] it seemed reasonable to apply the case fatality rates from bleeds associated with warfarin use in the model as these would be directly applicable to the additional cases of bleeding associated with thromboprophylaxis. Any overestimation of mortality in those having bleeds not related to anticoagulant use would be similar across arms and, therefore, would affect estimates of absolute QALYs for each thromboprophylaxis strategy but not the incremental QALY gains when comparing thromboprophylaxis strategies.

The case fatality rate for non-intracranial bleeds reported by Fang *et al.*[102] was lower than the case fatality rates observed for GI bleeds by Rockall *et al.*[121] and Button *et al.*,[103] but this may be because GI bleeds have a greater mortality risk than other non-ICHs. Although Button *et al.*[103] found that the case fatality rate had fallen over time, the case fatality rate of 10% estimated by Button *et al.*[103] appears to be consistent with a 2015 report[122] from the National Confidential Enquiry into Patient Outcome and Death, based on data collected in 2013. As the data from QBleed[101] related only to the incidence of ICH and GI bleeds, the 10% risk of mortality from Button *et al.*[103] was used instead of the 5% for extracranial bleeds from Fang *et al.*[102]

In addition to the risk of ICH being fatal at the time of the bleed itself, there is an increased risk of death in patients having ICH compared with population norms. Fogelholm *et al.*[107] found that patients with primary ICH who survived to 28 days had a standardised mortality rate that was 4.5-fold higher in the first year and 2.2-fold higher in years 2–6 than that of age- and sex-matched controls. These figures were applied as RRs to the all-cause mortality rates to increase the risk of mortality in those patients who survived ICH. Although Fogelholm *et al.*[107] reported a 10% reduction in mortality compared with general population norms in years 7–16, no increased or decreased risk beyond 6 years was assumed as there was doubt over the clinical plausibility of a reduced risk of death following ICH.

Risk of bleeding during anticoagulation treatment of venous thromboembolism

Several sources of data on bleeding risks during treatment of VTE were identified. These included the RIETE[105] and Prevention of thromboembolic events – European registry in venous thromboembolism (PREFER-VTE)[123] studies and a systematic review of RCTs and cohort studies by Carrier *et al.*[124] In the review by Carrier *et al.*,[124] 56 of the 69 studies included were RCTs, which the authors say are not generalisable to all patients with VTE because those with additional comorbid conditions are often excluded from clinical trials. Carrier *et al.*[124] reported a rate of major bleeding for any VTE of 1.6% (95% CI 1.3% to 2.0%) at 3 months and a rate of fatal bleeding of 0.2% (95% CI 0.1% to 0.3%). The case fatality rate for bleeding following any VTE was 11.3%. RIETE reports a rate of major bleeding of 2.24% (95% CI 2.05% to 2.42%) at 3 months and a rate of fatal major bleeding of 0.55% (95% CI 0.46% to 0.65%) giving a case fatality rate equivalent to 24.7%.[105] This higher case fatality rate may be because of a higher rate of comorbidities in an unselected cohort. In the PREFER-VTE cohort, the rate of major bleeds was 1.5% at 12 months but the rate of fatal bleeds was not reported.[123] In addition, the timing of the bleeds was not reported so it is unclear what the rate of bleeding would have been during the treatment period. The data from PREFER-VTE were considered to be more applicable to current UK practice than the data from RIETE as PREFER-VTE included only European sites, included UK patients and recruited patients after the introduction of DOACs. However, it was noted that only 56.7% of patients in the PREFER-VTE cohort had a low risk of bleeding at baseline [a HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly) score of 0 or 1].[123] As thromboprophylaxis for lower-limb

injury is likely to be limited to those with a low risk of bleeding, the research team looked for alternative data sources. A study by Kooiman *et al.*[104] estimated the incidence of major bleeding at 6 months for patients having treatment for VTE stratified by HAS-BLED score. The combined incidence for patients with a HAS-BLED score of 0 or 1 was 0.9% (3/335). Kooiman *et al.*[104] did not report risks separately for PE and DVT but Cohen *et al.*[123] reported that, in PREFER-VTE, the rates of major bleeds were not significantly different after PE and DVT, so the same rate of 0.9% has been applied to both DVT and PE. This seems reasonable given that the same treatment is assumed in both groups.

Owing to the greater detail reported by RIETE, the breakdown of major bleeding events into fatal events, non-fatal ICH and other non-fatal major bleeds was based on the event rates from RIETE.[105] The analysis of RIETE also found that symptomatic PE was not a significant predictor of whether a fatal bleed occurred and the site of DVT was not a significant predictor unless the DVT was distal when the OR was 0.39 (95% CI 0.16 to 0.95). This lower rate may be as a result of less aggressive anticoagulation therapy or another confounding factor not accounted for in the analysis. It was decided to apply the same rates of fatal bleeding in all patients treated for VTE regardless of the VTE event type.

Clinically relevant non-major bleeding during prophylaxis

Clinically relevant non-major bleeding was not included in the base-case analysis as it has a low impact on quality of life and would be likely to incur a relatively small cost compared with major bleeding. However, to test whether or not the model was sensitive to this structural assumption, the cost of one ED attendance was applied to those experiencing CRNMB. To estimate the rate of CRNMB, the ratio of CRNMB to major bleeding (2.05) from Cohen *et al.*[123] (PREFER-VTE) was applied to the rate of major bleeding for those having prophylaxis to estimate the proportion of patients having CRNMB during prophylaxis. Owing to the low rate of bleeding during prophylaxis, the cost of CRNMB was only £0.19 for each patient receiving prophylaxis. Therefore, the exclusion of this cost from the base-case analysis is not expected to have significantly biased the base-case results.

Risk of chronic thromboembolic pulmonary hypertension

The incidence of CTEPH following PE was based on a systematic review by Ende-Verhaar *et al.*,[111] which reported an overall incidence of CTEPH of 2.3% (95% CI 1.5% to 3.1%). The review[111] also reported the incidence separately for all patients with PE (0.56%, 95% CI 0.13% to 0.98%) and for those who survived the initial 3- to 6-month treatment period for PE (3.2%, 95% CI 2.0% to 4.4%). The follow-up period in the studies included in the review varied from 3 months to 8 years, with most reporting follow-up of ≈2 years. One study, by Pengo *et al.*,[112] which followed patients prospectively for 10 years, found that no cases occurred beyond 2 years, despite a median follow-up of 94 months. It is therefore assumed in the model that all cases are diagnosed between 6 months and 2 years after PE. The rate of CTEPH for those surviving the initial 3- to 6-month treatment period (3.2%) was considered to be the most relevant estimate for the model as no diagnoses of CTEPH are assumed until patients complete their anticoagulant treatment, and deaths during VTE and during anticoagulation are already accounted for in the decision tree part of the model.

Mortality risks in patients with CTEPH were based on data from an international prospective registry reported by Delcroix *et al.*[113] A recent HTA report by Goodacre *et al.*[114] used data from this registry to estimate survival curves for patients having medical or surgical management of CTEPH. The same survival curves were used in this model to estimate the hazard of death over time for patients diagnosed with CTEPH. The proportion having surgical management in the registry was 60% and this was applied in the model. Given that deaths related to PE occurring within 6 months of PE are already accounted for in the model, all-cause mortality has been applied to those with PE in the first year regardless of whether or not CTEPH occurs and the rate of mortality for those with CTEPH is applied from year 2 onwards. To ensure that the risk of death in the CTEPH group was not artificially low compared with the risk of death in the general population, general population mortality risks were applied whenever these were higher than the risk in the CTEPH population, based on the survival curves.

Risk of post-thrombotic syndromes

A review of epidemiological studies by Galanaud *et al.*[125] describes how the incidence of PTS is dependent on the scoring system used to diagnose PTS, the location and extent of the DVT (e.g. proximal vs. distal), and the duration of time since DVT. Galanaud *et al.*[125] also discuss how pre-existing chronic venous insufficiency and the symptomatic versus asymptomatic nature of the DVT may also affect the risk of PTS.

The risk of PTS in patients with symptomatic DVT in the model was estimated from a prospective registry [Thrombosis and Pulmonary Embolism in Out-Patients – plus (TULIPA-PLUS)], reported by Hach-Wunderle *et al.*[109] This source was chosen as the study design excluded patients with previous DVT or signs of PTS prior to the index DVT. The incidence is reported separately for proximal and distal DVT and is stratified into mild, moderate and severe PTS using a validated scoring system (Villalta scale), which is the scale preferred by the International Society on Thrombosis and Haemostasis.[126] The prevalence of symptomatic PTS at 3 years was 24.4% for all DVTs, 32.4% for proximal DVT and 15.6% for distal DVT, with 70% being mild, 24% being moderate and 6% being severe (average across both proximal and distal).[109]

One applicability issue related to this study was that patients received anticoagulation for a whole year, which is longer than the period of anticoagulation assumed in the model. Therefore, the rates of PTS may be underestimated if longer anticoagulation is protective of PTS. However, as it was not known if longer anticoagulation was protective, and the risk of PTS in this study may reasonably be lower than other estimates as a result of careful exclusion of PTS symptoms at the time of the index DVT, it was decided that it was reasonable to apply the incidence from Hach-Wunderle *et al.*[109] in the model given that the incidence was in the range generally reported (20–50%).[125]

There are only limited data on the incidence of PTS in patients with asymptomatic DVT because these patients are less likely to be followed up for a PTS diagnosis as their DVT is less likely to be diagnosed outside a research setting. However, a study by Persson *et al.*[127] examining PTS incidence in 83 patients operated on for Achilles tendon rupture, which prospectively identified DVT using colour duplex scanning 3 and 6 weeks after surgery and assessed PTS (assessors were blinded to DVT diagnosis) 5 years post operatively, reported a low rate of a PTS diagnosis (Villalta score of ≥ 5) of 8% (3/38) in the DVT group and 4% (2/45) in the no-DVT group. All of the diagnosed cases had a Villalta score of < 15 and were therefore of mild to moderate severity. However, it should be noted that most of those patients with asymptomatic DVT diagnosed post operatively received warfarin for 3 months and were advised to wear compression stockings for 1 year. As a result, the rate of PTS in asymptomatic, undiagnosed and, therefore, untreated DVT is unknown but is likely to be at least 8%. Furthermore, only three of the 38 DVTs were proximal, making it difficult to estimate the rate of PTS in patients with asymptomatic proximal DVTs from this study.[127]

A study by Schindler and Dalziel[128] in a related population (those having total hip or knee arthroplasty) found that four of 34 (11%) with asymptomatic distal DVT and three of eight (32.5%) with asymptomatic proximal DVT developed PTS 15 to 24 months after surgery. In the knee arthroplasty subgroup (which is considered to be more clinically relevant to those having lower-limb immobilisation), 28 patients had distal DVT with one of these having clot propagation leading to proximal DVT. Four of these 28 patients (14.3%) with DVT developed PTS, with one of these being the patient who had clot propagation. However, PTS was also diagnosed in 5.3% of those patients without DVT. In this study,[128] all those with proximal DVT were treated with anticoagulants (i.e. 3 months of warfarin), whereas those with distal DVT received 3 months of aspirin. Therefore, the rate of PTS in untreated asymptomatic DVT following hip and knee surgery remains unknown.

van Dongen *et al.*[110] studied the relationship between inadequate anticoagulation with vitamin K antagonist (VKA) and the risk of PTS with symptomatic proximal DVT and found that patients who spend $> 50\%$ of their time beneath the international normalised ratio (INR) level of 2.0 are at a higher risk for PTS (OR 2.71,

95% CI 1.44 to 5.10). Based on this, one would expect a higher risk of PTS in patients with asymptomatic proximal DVT that is untreated than in those with treated asymptomatic proximal DVT. Although van Dongen *et al.*[110] did not include untreated patients in their study, they reported a fourfold increase (OR 3.69, 95% CI 1.29 to 10.53) for those patients spending > 90% of their time outside the target INR range, which suggests that the risks may be higher still in those patients not offered any anticoagulation.

The rate of PTS in patients with asymptomatic proximal DVTs reported by Schindler *et al.*[128] (32.5%) was similar to that reported in symptomatic proximal DVT by Hach-Wunderle *et al.*[109] (32.4%). This suggests that the risk of PTS is similar regardless of whether or not the proximal DVT is symptomatic, provided that it is treated with anticoagulants. However, given that patients who are asymptomatic in the model will not receive any anticoagulant treatment as they are not being proactively screened for asymptomatic DVT, a higher rate for asymptomatic proximal DVT was applied using the OR reported by van Dongen *et al.*[110] for good versus poor anticoagulation (OR 2.71 for those patients spending > 50% of their time outside the target INR). This gave a rate of PTS of 56.5% for untreated asymptomatic proximal DVT. It is recognised that the rate of PTS may be higher still for those receiving no anticoagulation at all, as discussed in the previous paragraph, but this may be partially offset by asymptomatic DVTs being less extensive and, therefore, less likely to cause PTS.

The rate of PTS in asymptomatic untreated distal DVT was set as equal to that for treated symptomatic distal DVT, namely 15.6% as reported by Hach-Wunderle *et al.*[109] Inflating this risk further by applying the OR from van Dongen *et al.*[110] did not seem appropriate, given that this would give a risk of 33.4% and the clinical experts believed that the rate for untreated distal DVT should be lower than for treated proximal DVT. Furthermore, it is noted that the rate from Hach-Wunderle *et al.*[109] of 15.6% is nearly twice the rate reported for treated asymptomatic distal DVT by Persson *et al.*,[127] which would support not inflating the rate further.

The timing of PTS within the model has been based on data reported by van Dongen *et al.*,[110] who reported the incidence of PTS at 0.5, 1, 2 and 4 years (*Figure 11*). The shape of the curve for incidence over time was compared with that reported by Prandoni *et al.*[129] and was found to be similar, although the magnitude better matched the upper 95% CI of the estimates of incidence reported by Prandoni *et al.*[129] The hazards based on the incidence reported by van Dongen *et al.*[110] were scaled to match the rate reported at 3 years by Hach-Wunderle *et al.*[109] for symptomatic proximal and distal DVT. As van Dongen *et al.*[110] reported no further incidence beyond 4 years, no new incidence of PTS from 4 years was assumed. The prevalence of PTS over time incorporated within the model is shown in *Figure 12*.

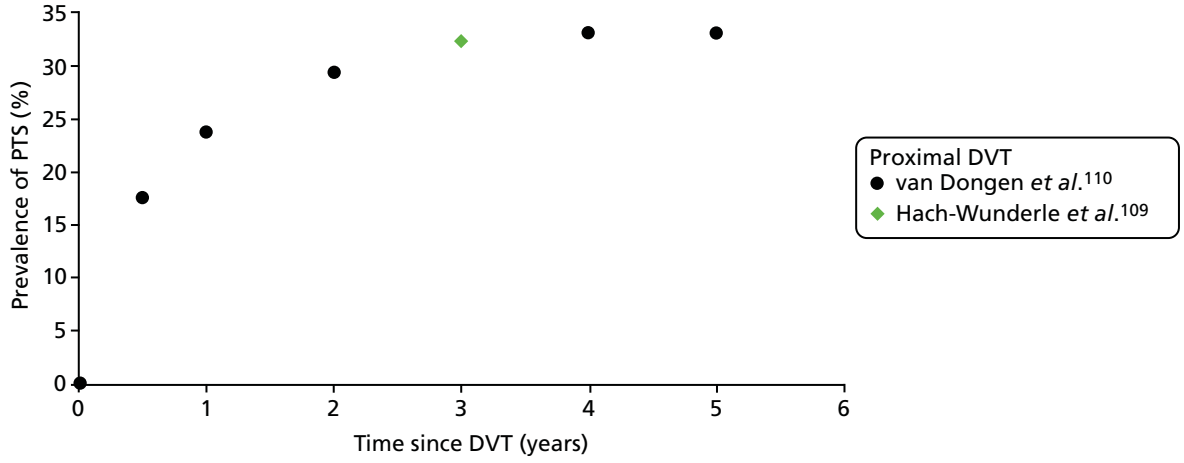

FIGURE 11 Prevalence of PTS in years following proximal DVT from studies.

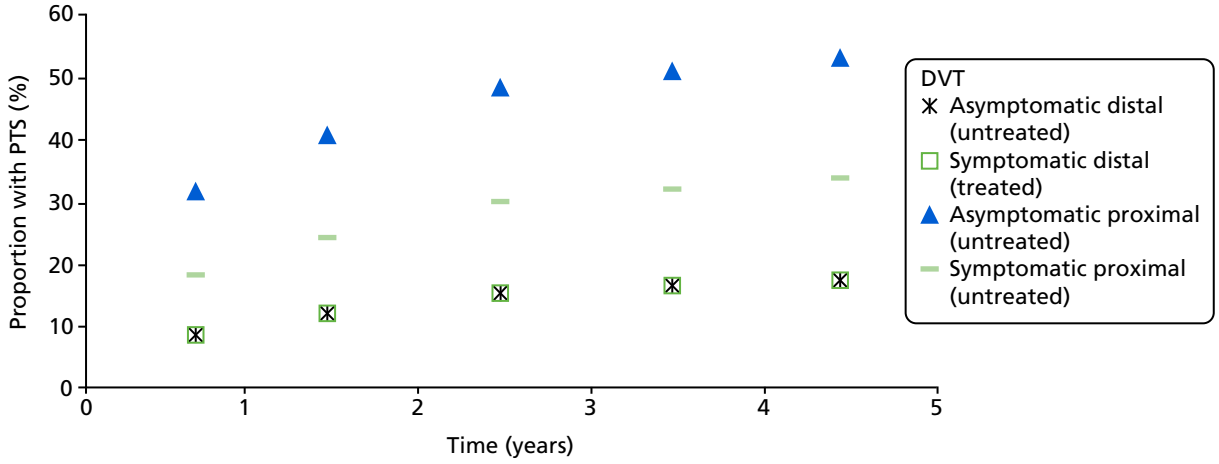

FIGURE 12 Prevalence of PTS in the model for treated symptomatic and untreated asymptomatic DVTs.

Costs of prophylaxis

For thromboprophylaxis during lower-limb immobilisation, it was assumed that patients receive 6 weeks of treatment using LMWH at the dose recommended for long-term treatment after hip or knee replacement. In the base-case analysis, it was assumed that the lowest-cost formulation of LMWH would be used (dalteparin), but the impact of treatment with either fondaparinux or dabigatran was explored in sensitivity analyses as these represented the highest- and lowest-cost alternatives to LMWH. The dosages and drug costs are summarised in *Table 18*.

Menakaya *et al.*[115] estimated the costs of outpatient VTE prophylaxis for patients having lower-limb injuries based on 388 patients receiving prophylaxis who were recruited from 7048 patients attending a fracture clinic in England. The total cost for an average of 46 days of anticoagulant treatment was £107.54 for the self-administration of LMWH, with £46 of this being the drug cost (the authors assumed £1 per day). Therefore, the total cost of administration was £61.54. This covered clinical time for counselling and taking blood samples (including a 5-day platelet count), pharmacy dispensing and initial administration. For patients requiring district nurse administration (£23 per home visit), the average cost of administration across the treatment course was £1096.54 but this was required in only 4% of cases, giving an average cost of £102.94 across the cohort. Adjusting the number of doses from 46 to 42, which affects only the district nurse administration costs, and updating this from 2011/12 to 2016/17 prices (Curtis and Burns[100]), gives a total administration cost of £105.13. The total cost for the 6-week course of dalteparin, including administration costs, was £223.70.

For the sensitivity analysis on fondaparinux, the same administration costs as those required for LMWH were assumed. Patients initiating treatment with a DOAC were assumed to require one nurse-led telephone consultation at 10 days. The range tested in sensitivity analysis for the whole course of treatment was £84.23 for dabigatran to £355.66 for fondaparinux.

When assessing the cost-effectiveness of using RAMs to determine thromboprophylaxis, it is necessary to include the cost of the time spent by the clinician to determine the individual's risk score. It was assumed that this would require 5 minutes of time by a hospital consultant, which was estimated to be £8.83 based on an hourly cost of £106.[100] This was applied to all patients in the RAM-based thromboprophylaxis strategies but to none of the patients in the treat-all and treat-none strategies.

TABLE 18 Drug costs for pharmacological prophylaxis of VTE in patients having lower-limb immobilisation

Drug	Dosing and delivery[21]	Product and cost[21]	Cost per day (£)	Cost per course (assuming 42 days treatment) (£)	Administration cost per course (£)	Total cost per course (£)
Dalteparin	5000 units every 24 hours by subcutaneous injection for 4–6 weeks	Dalteparin sodium 5000 units/0.2 ml solution for injection: £28.23 for 10 pre-filled syringes	2.82	118.57	105.13	223.70
Exonaparin	40 mg every 24 hours by subcutaneous injection for 4–6 weeks	Enoxaparin sodium 40 mg/0.4 ml: £30.27 for 10 pre-filled syringes	3.03	127.13	105.13	232.26
Tinzaparin	4500 units every 24 hours by subcutaneous injection for 4–6 weeks	Tinzaparin sodium 4500 units/0.45 ml solution for injection: £35.63 for 10 pre-filled syringes	3.56	149.65	105.13	254.78
Fondaparinux	2.5 mg every 24 hours by subcutaneous injection for 4–6 weeks	• Arixtra 2.5 mg/0.5 ml solution for injection: £62.79 for 10 pre-filled syringes • Fondaparinux 2.5 mg/0.5 ml solution for injection: £59.65 for 10 pre-filled syringes [Dr Reddy's Laboratories (UK) Ltd, Beverley, UK]	5.97 (assuming that the lowest-cost formulation was prescribed)	250.53	105.13	355.66
Apixaban	2.5 mg orally twice daily	Eliquis 2.5 mg tablets	1.90	79.80	12.83	92.63
Dabigatran	220 mg orally daily	Pradaxa 110 mg capsules: £51.00 for 60 capsules (same cost per capsule for 10)	1.70	71.40	12.83	84.23
Rivaroxaban	10 mg orally daily	Xarelto 10 mg tablets: £54.00 for 30 tablets (same cost per tablet for 10)	1.80	75.60	12.83	88.43

Cost of treatment

Patients who have lower-limb immobilisation may later present with symptomatic DVT or PE, requiring diagnosis and treatment. The costs of VTE have been estimated for three broad categories of costs: health-care contacts, diagnostic costs and drug treatment costs. It was assumed that all patients presenting with symptomatic VTE would require an ED assessment, but that a proportion would present first to a general practitioner (GP) before attending an ED, and that only a proportion of those attending an ED would require admission. It was assumed that those patients requiring admission would also be likely to require ambulance transfer to the ED. The proportion of patients attending GPs prior to ED attendance and the proportion requiring admission (*Table 19*) were based on clinical expert opinion. Discussions with clinical experts were informed by the assumptions used in the model described in the 2017 draft update to the NICE guideline on managing VTE[130] and the assumptions used in relevant NICE single technology appraisals (STAs).[131–139]

Diagnostic tests that occur during the ED episode of care, such as electrocardiography monitoring and chest radiography, are not costed separately. However, scans occurring later as outpatient activity were costed separately as these diagnostic tests are 'unbundled' within the NHS reference cost data.[116] Assumptions regarding the use of diagnostic tests to assess patients with suspected DVT and PE were based on clinical expert opinion. The main costs not covered within the ED episode of care are assumed to be leg vein ultrasonography for patients with a suspected DVT and computerised tomography pulmonary angiography (CTPA) or ventilation/perfusion scans for patients with a suspected PE. A minority of patients (20%) with suspected PE are also assumed to require echocardiography. The diagnostic tests are summarised in *Table 19*. It was assumed that all patients presenting with PE or symptomatic DVT (proximal or distal) would be treated with anticoagulants.

Treatment for VTE was assumed to consist of 3 months of either a VKA (warfarin) or a DOAC. Patients being treated with a VKA would also require initial anticoagulation with LMWH until adequate oral anticoagulation is established. The proportion receiving DOACs versus VKA was informed by data from the PREFER-VTE study,[123] which found that 40% of patients in countries where DOACs had been launched were receiving a DOAC as their initial treatment following DVT. The split between drugs in the LMWH class was informed by assumptions used in a previous appraisal.[140] The costs of administering treatment with LMWH are based on the costs estimated by Menakaya *et al.*[115] for initiating prophylaxis using LMWH but with a reduction in district nurse administration based on the shorter duration of treatment (7 vs. 42 days). Patients receiving VKA are assumed to require nine visits to an anticoagulation service in 3 months to monitor their INR. Patients initiating treatment with a DOAC are assumed to require one nurse-led telephone consultation at 10 days. All patients are assumed to require a consultant-led face-to-face visit at 3 months to assess the need for ongoing treatment. The overall cost, including monitoring, when averaged across the treatment strategies was £290.24 (*Table 20*).

The total cost for non-fatal PE was estimated to be £1788, which includes health-care contacts, diagnostic costs and 3 months of drug treatment for VTE. Fatal PE was assumed to incur the same costs for health-care contacts and diagnostics, but without the cost of VTE treatment, giving a cost of £1498. Symptomatic proximal and distal DVTs had a total cost of £688 and £560, respectively, with the higher cost of proximal DVTs driven by a greater likelihood of admission.

Cost of bleeding complications

A paper by Luengo-Fernandez *et al.*[117] on the acute and long-term costs of care after stroke in patients with atrial fibrillation (AF) was identified as a source of costs in those having ICH from the NICE appraisal of edoxaban tosylate (Lixiana®; Daiichi Sankyo UK Ltd, Gerrards Cross, UK) for the treatment and secondary prevention of DVT and/or PE.[140] The paper[117] provides estimates of acute (up to 90-day) and long-term costs (average annual costs up to 5 years post stroke) using data from the Oxford Vascular Study (OXVASC), which was a prospective study of 91,000 UK patients registered with general practices in Oxfordshire. The paper by Luengo-Fernandez *et al.*[117] reports costs for the subset of patients who experienced a stroke during the study and who had a history of AF prior to that index stroke (n = 153). The mean age of patients in this subset was 80 years, with 26% of patients having previous stroke and 20% of patients having pre-morbid warfarin use.

TABLE 19 Resource use and costs for patients presenting with PE and symptomatic DVT

Resource item	Proportion using resource (%)			Unit cost per patient using this resource (£)	Description
	Non-fatal PE	Symptomatic proximal DVT	Symptomatic distal DVT		
Health-care contacts/admission					
GP visit	20	50	50	37	Curtis and Burns,[100] GP cost per surgery consultation with qualification costs, including direct care staff costs
Ambulance transfer to ED	60	10	0	236	NHS Schedule of Reference Costs 2015–16.[116] 'See and treat and convey', code ASS02
ED visit leading to admission	60	10	0	228	NHS Schedule of Reference Costs 2015–16.[116] VB05Z type 01 admitted (category 2 investigation with category 3 treatment)
ED visit without admission	40	90	100	196	NHS Schedule of Reference Costs 2015–16.[116] VB05Z type 01 non-admitted (category 2 investigation with category 3 treatment)
Short stay admission for PE	60	0	0	1498	NHS Schedule of Reference Costs 2015–16.[116] Weighted average cost of non-elective inpatient (short and long stay with excess bed-days) for 'pulmonary embolus with interventions', codes DZ09 J to DZ09 N and DZ09P and DZ09Q
Short stay admission for DVT	0	10	0	1012	NHS Schedule of Reference Costs 2015–16.[116] 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 YQ51 A to YQ51E
Critical care unit stay	10	0	0	1012	NHS Schedule of Reference Costs 2015–16.[116] Weighted average cost of adult critical care, 0 to 6 or more organs supported, codes XC01Z to XC01Z
Subtotal for health-care contacts (£)	1365	342	214		

continued

TABLE 19 Resource use and costs for patients presenting with PE and symptomatic DVT (*continued*)

Resource item	Proportion using resource (%)			Unit cost per patient using this resource (£)	Description
	Non-fatal PE	Symptomatic proximal DVT	Symptomatic distal DVT		
Diagnostic costs					
Risk assessment tool (Wells score)	Included in an ED episode of care so not costed separately				
D-dimer	Included in an ED episode of care so not costed separately				
ECG	Included in an ED episode of care so not costed separately				
Chest radiography					
Proximal leg vein ultrasonography	0	100	100	55	RD40Z, outpatient ultrasound scan (duration of < 20 minutes), without contrast, cost £55 [RD47Z may be more relevant for the diagnosis of distal DVTs, but cost is similar (£58)][116]
CTPA	90	0	0	102	RD21A, outpatient computerised tomography scan of one area, with post contrast only, patients aged ≥ 19 years[116]
V/Q SPECT	5	0	0	261	RN08A, outpatient SPECT, patients aged ≥ 19 years[116]
V/Q planar	5	0	0	274	RN18A, outpatient lung ventilation or perfusion scan, patients aged ≥ 19 years[116]
Echocardiography	20	0	0	72	RD51A, outpatient simple echocardiography[116]
Subtotal for unbundled diagnostics (£)	133	55	55		
Subtotal for drug treatment (£)	290	290	290		See *Table 20*
Total (£)	1788[a]	688	560		

CC, complication or comorbidity; ECG, electrocardiography; SPECT, single-photon emission computed tomography; V/Q, ventilation/perfusion.
a Fatal PEs are assumed to incur diagnostic and inpatient costs but not VTE treatment costs (i.e. total cost of £1498).

TABLE 20 Drug costs for treating DVT and PE

Drug	Dosing and delivery	Product and cost	Cost (£)		Percentage using treatment
			Drug, per course	Monitoring/ administration	
Apixaban	Initially, 10 mg twice daily for 7 days, orally, followed by 5 mg twice daily, orally, for the remainder of the 3-month (91-day) treatment period	Apixaban, 5 mg: £53.20 for 56 tablets (cost per tablet is the same for the 28-tablet pack size)	186.20	50.00[a]	20% (half of the 40% using DOACs)
Rivaroxaban	Initially, 15 mg twice daily for 21 days, to be taken orally with food. This is followed by 20 mg once daily, to be taken orally with food for the remainder of the 3-month (91-day) treatment period	Rivaroxaban, 20 mg: £50.40 for 28 tablets (cost per tablet is the same for 15 mg tablets and larger and smaller pack sizes)	201.60	50.00[a]	20% (half of the 40% using DOACs)
Enoxaparin	1.5 mg/kg every 24 hours by subcutaneous injection until adequate oral anticoagulation established (7 days) (i.e. 120 mg of enoxaparin if assuming weight of 80 kg)	• Clexane Forte, 120 mg/0.8 ml solution: £87.93 for 10 pre-filled syringes, prescription-only medicine • Assumed for other drugs	61.55	70.26[b]	30% (45% of heparin use)
Dalteparin	15,000 units (assuming body weight of 80 kg) once daily until adequate oral anticoagulation established (7 days)	Dalteparin sodium, 15,000 units/ 0.6 ml solution: £42.34 for five pre-filled syringes	59.28	70.26[b]	18% (35% of heparin use)
Tinzaparin	175 units/kg once daily until adequate oral anticoagulation established (7 days) (i.e. 14,000 units if assuming body weight of 80 kg)	Innohep, 14,000 units/0.7 ml solution: £83.30 for 10 pre-filled syringes	58.31	70.26[b]	6% (20% of heparin use)
Warfarin	5 mg twice daily orally for 3 months (91 days)	Warfarin sodium, 5 mg (various suppliers): £0.70 for 28 tablets	4.55	186.27[c]	60%
Average across those using DOACs and those using LMWH/VKA			116.35	173.89	Total: £290.24

HRG, Healthcare Resource Group.

a Based on one nurse-led telephone follow-up (WF01C) at 10 days and one consultant-led follow-up (WF01A) at 3 months to assess the need for ongoing treatment.[116]

b Based on the costs estimated by Menakaya *et al.*,[115] with the number of district nurse administrations reduced to reflect the shorter duration of treatment (7 days vs. 6 weeks).

c Based on HRG costs for nine face-to-face visits at a non-consultant-led anticoagulation service over 3 months (WF01B for first attendance and WF01A for follow-up) plus a consultant-led follow-up at 3 months to assess the need for ongoing treatment.[116]

Note

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

The costs were reported separately on the basis of disability level and whether the type of stroke was ischaemic, haemorrhagic or not known. Only 17 of the 191 strokes experienced by the 153 patients were haemorrhagic. The mean acute cost of fatal haemorrhagic strokes was £1592 (SD £1886; *n* = 8). This mean cost was substantially lower than the average for all haemorrhagic strokes, which was £10,683 (SD £12,885; *n* = 17). Given that these estimates were based on a small number of patients, the estimates for all stroke types were also considered. The cost of fatal strokes across all types was also lower, at £2680 (SD £2661; *n* = 40), than the average for all strokes (mean £10,413, SD £15,105; *n* = 191), suggesting that fatal strokes do incur a lower acute cost than non-fatal strokes. The cost of fatal haemorrhagic strokes was used in the base-case analysis for fatal intracranial bleeds. The cost was updated from 2008/9 prices to 2016/17 prices (using Curtis and Burns[100]), giving an acute cost of £1802 over 3 months.

The paper by Luengo-Fernandez *et al.*[117] also provided relevant data on the cost of non-fatal ICHs. The cost of a non-fatal haemorrhagic stroke was estimated to range from £3401 to £24,234, depending on the level of disability following the stroke. A weighted average cost for non-fatal haemorrhagic strokes of £18,764 was calculated across the non-disabling, moderately disabling and totally disabling haemorrhagic strokes. However, it was noted that these estimates were based on only nine non-fatal haemorrhagic strokes. The equivalent average across all non-fatal strokes was £12,461. The higher cost for haemorrhagic non-fatal strokes appeared reasonable given that haemorrhagic strokes appeared to result in higher than average costs across all categories except fatal strokes. This is supported by data presented by Fernando *et al.*,[141] which show that patients with haemorrhagic stroke who are admitted to an intensive care unit (ICU) incur higher costs than matched patients (matched for age, sex and comorbidity) admitted to an ICU for other (non-ICH) reasons. Furthermore, ICHs associated with oral anticoagulant use were also found to be significantly more costly than those not associated with oral anticoagulant use.[141] The weighted average cost for non-fatal haemorrhagic stroke from Luengo-Fernandez *et al.*[117] was used in the base-case analysis for the acute cost of non-fatal ICH. This cost was updated from 2008/9 prices to 2016/17 prices (using Curtis and Burns[100]), giving non-fatal ICH a cost of £21,245 over 3 months.

It was noted that this cost for non-fatal ICH is significantly higher than the weighted average cost of stroke based on NHS reference costs for non-elective long- and short-stay inpatients (including excess bed-days), which was £3290 [average of reference costs[116] for Healthcare Resource Group (HRG) codes AA35A to AA35F]. However, the average NHS reference cost is similar to the cost reported by Luengo-Fernandez *et al.*[117] for non-disabling stroke costs. This may reflect the fact that rehabilitation costs are reported separately in NHS reference costs and these costs are between £332 and £402 per day for admitted rehabilitation. These rehabilitation costs would have been included in the hospitalisation costs reported by Luengo-Fernandez *et al.*[117] and would be much higher for moderately and totally disabling strokes, which may explain the higher costs in these groups than the NHS reference cost for admitted care in stroke patients, which excludes rehabilitation.

The model also required post-acute costs (post 90 days) for patients having non-fatal ICH. Luengo-Fernandez *et al.*[117] estimated the post-acute costs per annum relative to the year before stroke (baseline). The total post-acute costs were found to be non-significantly higher versus baseline costs at £804 (95% CI –£832 to £2440). However, the GP and emergency care components were significantly higher at £98 (95% CI £27 to £169) and £99 (95% CI £56 to £141), respectively. In addition, the paper separately reported long-term residential care costs for patients not previously admitted to residential care. They reported that 18% of strokes resulted in a new admission to long-term care (i.e. warden housing, residential care or nursing home care), with an average annual cost of £6880 across all patients surviving the acute period (90 days). Post-acute and long-term costs were not reported separately by stroke type (haemorrhagic vs. other) by Luengo-Fernandez *et al.*[117] The total costs of GP, emergency care and long-term care were averaged across all stroke types and uplifted to current prices (using inflation indices from Curtis and Burns[100]) to give a total cost per year for non-fatal ICH patients of £8013 in the post-acute (beyond 90 days) period. This was applied in the Markov phase of the model to patients in the non-fatal ICH health state. It was also applied pro rata to patients having non-fatal ICH more than 90 days before the end of the decision tree model.

The cost of non-fatal extracranial bleeds was estimated using average inpatient costs for GI bleeds, based on the approach taken in the NICE Technology Appraisal (TA) 354.[140] A weighted average was taken across bleeds requiring single, multiple or no intervention and across short- and long-stay non-elective inpatients (including excess bed-days). This gave an average cost of £1198 based on 2015/16 reference costs (HRG codes FZ38G to FZ38P).[116]

Cost of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension

Several reviews of studies relating to PTS were examined to identify any cost papers cited.[125,142–145] None of the cost papers identified were specific to the UK NHS. Three examined costs from a US perspective (Caprini *et al.*,[146] MacDougall *et al.*[147] and Olin *et al.*[148]), one examined costs from a Brazilian perspective (Ramacciotti *et al.*[149]), one examined costs from a Swedish perspective (Bergqvist *et al.*[150]) and one examined costs from a Canadian perspective (Guanella *et al.*[151]). Although the paper by Bergqvist *et al.*[150] was from a European country, the data related to patients diagnosed between 1970 and 1985.

Several of the NICE STAs identified in *Appendix 11* cited cost assumptions from Goodacre *et al.*[152] One cited the US study by Caprini *et al.*[146] and another cited costs from a 2001 abstract by Cohen *et al.*[153]

It was assumed in the model that management of PTS would involve one first and one follow-up vascular surgery outpatient appointment in the first year after diagnosis and two follow-up GP appointments every year thereafter. This was based on clinical expert advice regarding current management of PTS in the UK and is consistent with the assumptions made by Goodacre *et al.*,[152] which have been applied in several previous NICE STAs.[131,132,140,154]

A review by Grosse *et al.*[143] on the costs attributable to VTE in the USA identified one paper[155] on the cost burden of CTEPH. Kirson *et al.*[155] compared costs for patients with CTEPH with those for controls (matched for age, sex, employee status and geographical region) in a cohort of privately insured US patients. They found that costs per month were US$2368 ($p < 0.0001$) higher in patients with CTEPH than in matched controls, but they also found higher rates of comorbidities, suggesting that some of the differences may not be directly attributable to CTEPH. Grosse *et al.*[143] commented that CTEPH patients are far more likely to have chronic heart failure or chronic pulmonary disease, and no risk-adjusted treatment cost estimates were identified in their review.

The cost of CTEPH was based on the approach taken in technology appraisal (TA) number 354 (i.e. TA354)[140] in which pulmonary endarterectomy costs were applied based on reference costs for complex thoracic procedures. Updating this estimate by using current reference costs[116] gave a cost of £7898. The Evidence Review Group's preferred assumption for TA354[140] was to use the cost of drugs from CG92,[24] which estimated a cost of £1219 per 4 weeks, giving a cost of £17,942 per annum when uplifted to 2016/17 prices (using inflation indices from Curtis and Burns[100]). Data from Delcroix *et al.*[113] were used to estimate the proportion having surgical management and the proportion receiving medical management. The fact that some surgical patients receive bridging therapy, as reported by Delcroix *et al.*,[113] was taken into account by allowing them 4.6 months of medical therapy based on the average time to surgery for these patients. This increased the costs in the first year for patients having surgical management to £9890. It was assumed that no further costs are incurred in year 2 and beyond for those having surgical management.

Summary of methods used to identify studies reporting utility values relevant to the model

The searches for the systematic review of published cost-effectiveness studies included a filter to identify health-related quality of life (HRQoL) data. While sifting these studies, one study[156] reporting HRQoL data in patients with lower-limb immobilisation was identified; this study by Arverud *et al.*,[156] reported EuroQol-5 Dimensions (EQ-5D)[157] scores in patients who had an Achilles tendon rupture. The study reported mean EQ-5D scores at 1 year for patients who did and patients who did not experience DVT following surgical repair and immobilisation. The average EQ-5D score was lower in patients with DVT but the difference was

not statistically significant ($p = 0.6$). A second study[158] identified in the search reported the validation of a disease-specific HRQoL measure, Deep Venous Thrombosis Quality of Life (DVTQoL), in patients with DVT but this study reported only the correlation between the EQ-5D and the domains of the DVTQoL; utility values based on EQ-5D scores could not be extracted. No other studies reporting preference-based measures of utility in patients with lower-limb immobilisation were identified from the searches conducted for the economic review.

One published study by Wolowacz *et al.*[99] was identified from the literature review that examined the cost-effectiveness of thromboprophylaxis for a similar, but not directly relevant, population (elective knee replacement) as described in *Results of cost-effectiveness review*. This was supplemented by searches of the NICE website to identify models developed to inform NICE TAs and CGs, as these models would be expected to have a relevant setting and methodological approach and would not always be identified through database searches. The cost-effectiveness analyses identified are summarised in *Appendix 11*.

In addition, ad hoc searches for systematic reviews of utilities for relevant model states (e.g. PTS) were conducted using the Google Scholar search engine (Google Inc., Mountain View, CA, USA). This identified a published systematic review of HRQoL studies for VTE and related complications by Lubberts *et al.*[159] This review focused on studies with a minimum follow-up of 1 year in order to capture the long-term impact of complications such as PTS and CTEPH. Only two of the studies included by Lubberts *et al.*[159] reported a generic preference-based utility measure (EQ-5D). One of the two studies reporting EQ-5D was conducted in patients with subclavian DVT and is therefore less applicable to this population. The other study, by Haig *et al.*,[160] reported EQ-5D scores for patients with and without PTS following DVT.

In addition, the systematic review by Lubberts *et al.*[159] reports outcomes for 15 studies that used either the Short Form questionnaire-36 items (SF-36)[161] or the Short Form questionnaire-12 items (SF-12). Data from these studies were meta-analysed to assess the difference in HRQoL between patients and members of the general population matched by country, age and sex. Lubberts *et al.*[159] report the meta-analysed decrement in SF-36/SF-12 mental component summary (MCS) and physical component summary (PCS) scores compared with general population norms (matched by country, age and sex) using the standardised mean difference (SMD) as a common currency across studies. These meta-analyses by Lubberts *et al.*[159] do not provide a preference-based utility measure that can be used directly in the model, but their outcomes are summarised below as they provide evidence as to whether or not each VTE-related outcome has an important impact on long-term HRQoL based on more than a single study. They are therefore useful in interpreting the utility estimates from individual studies identified from existing cost-effectiveness models.

Although Lubberts *et al.*[159] included only studies reporting outcomes more than 1 year after VTE, they also listed nine studies[158,162–169] that were excluded for reporting outcomes at shorter follow-up points. Of these, one study by Hogg *et al.*[163] reported useful data (see *Appendix 12*); the remaining eight studies did not report utility values for relevant health states.[158,162,164–169]

One additional HRQoL study[170] was identified from ad hoc searches; Roberts *et al.*[170] examined the predictors of HRQoL for patients following DVT using the SF-36. This is also discussed below as it provides useful additional information on PTS as a determinant of HRQoL.

The sources of utility data identified from both the published models listed in *Appendix 11* and the systematic review by Lubberts *et al.*[159] are summarised in *Appendix 12*.

Utility values in pulmonary embolism

Lubberts *et al.*[159] report that PE is associated with a significant reduction in SF-36 PCS score (SMD –0.30, 95% CI –0.45 to –0.14) but not SF-36 MCS score (SMD 0.14, 95% CI –0.01 to 0.30), relative to general population norms at time periods of > 1 year based on an analysis of two studies.[171,172] This suggests that PE has an important long-term impact on patients. Three studies[173–175] reported EQ-5D outcomes for patients with PE, although two of these studies[173,174] were published only in abstract form and the other

study[175] used Danish rather than UK population norms. One study used an alternative generic preference-based measure, the Short Form questionnaire-6 Dimensions (SF-6D).[163] In addition, two studies[176,177] reported utility values for PE measured directly using either standard gamble or time trade-off (TTO). Data from the study abstract by Cohen *et al.*[173] were reported in additional detail in the company submission for TA354[140,178] (*Figure 13*).

The data from Cohen *et al.*[153] were selected for use in the model because these were measured using the EQ-5D, were sourced from a large registry database (PREFER-VTE) including patients recruited in the UK and the paper included estimates of the change in utility over time (see *Figure 13*). The data reported by Cohen *et al.*[173] demonstrated that utility values varied depending on the time since PE, with utility values appearing to stabilise at between 3 and 6 months. The average utility in patients with PE during the 6 months following PE was calculated using the data from Cohen *et al.*[173] This was compared with the utility value at 6 months in patients with DVT (who do not have a long-term utility decrement according to the review Lubberts *et al.*[159]) to calculate the utility multiplier for PE, which was then applied to the age appropriate utility for patients without PE. A linear change in utility between the points measured was assumed, giving an average utility of 0.775 over the 6 months after PE, which is a 9% decrement relative to utility at 6 months post DVT. Given that there was some evidence of a reduction in HRQoL for patients with PE found by Lubberts *et al.*[159] at 1 year, it was decided to use the 6-month utility decrement for PE relative to DVT, when no long-term reduction was found, to estimate the long-term utility reduction for patients following PE. This gave a 5% reduction in utility beyond 6 months for a patient surviving PE beyond 6 months. Tavoly *et al.*[175] reported mean EQ-5D values of 0.8 in patients post PE versus 0.86 in age- and sex-matched general population controls, suggesting a 7% reduction in utility despite a median time since diagnosis of 3.8 years. This supports the assumption that there are some ongoing post-PE symptoms beyond 6 months.

Utility values in deep-vein thrombosis

The data sources for utility values in DVT were similar to those identified for PE, except that the study by Tavoly *et al.*[175] was not relevant because it examined only patients with PE. However, a similar study by Utne *et al.*[179] examining DVT outcomes from the same hospital registry was identified instead. One additional study by Arverud *et al.*[156] examining DVT versus no DVT after lower-limb immobilisation due to injury was also identified. This study found that DVT identified by screening (colour duplex sonography) 2 weeks post operatively was a non-statistically significant predictor of worse EQ-5D scores (0.918 vs. 0.906; $p = 0.604$). This may be expected given that the DVTs were detected by screening and, therefore, may have been asymptomatic. Utne *et al.*[179] found that EQ-5D score was statistically significantly lower for patients with DVT compared with age- and sex-matched buddy controls. However, these patients were recruited any time after DVT, and a significant proportion had PTS, so the reduction compared with controls may have been partly due to PTS symptoms, which are likely to be persistent beyond 6 months.

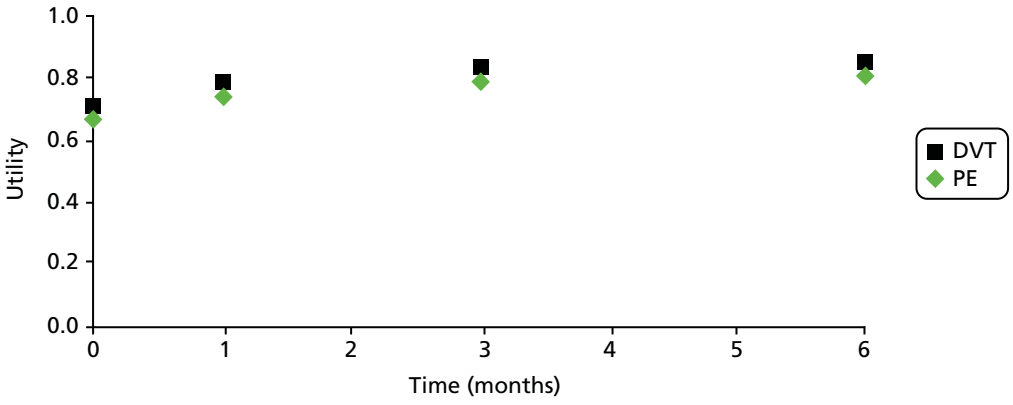

FIGURE 13 Data from Cohen *et al.*,[173] as reported in the company submission for TA354.[140,178]

In the first 6 months of the model, the data from Cohen *et al.*[173] were used to estimate the average utility, which was compared with the utility at 6 months. This gave a utility decrement of 4%, on average, during the first 6 months after DVT. Beyond 6 months, no utility decrement for patients without PTS was assumed, as the systematic review by Lubberts *et al.*[159] reported that there was no statistically significant difference in SF-36 PCS and MCS scores for DVT at time periods of > 1 year based on an analysis of nine studies.[172,180–187] Utne *et al.*[179] did not find a statistically significant difference in the odds of having impaired HRQoL, measured by EQ-5D, depending on whether the DVT was proximal or distal. In the absence of any other data on the difference in HRQoL impact of proximal versus distal DVT, the same utility loss was assumed during the first 6 months for symptomatic proximal DVT and symptomatic distal DVT.

Utility values in post-thrombotic syndrome

Lubberts *et al.*[159] reported that patients with PTS had significantly lower MCS and PCS scores than matched population norms (SMD for MCS score –0.27, 95% CI –0.43 to –0.11; SMD for PCS score –0.89, 95% CI –1.21 to –0.57), based on an analysis of seven studies.[180–182,184–186,188] Five studies reported utility values for patients with PTS,[160,177,189–191] with two studies[160,189] reporting EQ-5D scores and three studies[177,190,191] using direct measures of utility such as standard gamble or TTO. The data reported by Haig *et al.*[160] and Enden *et al.*[189] were the 2-year and 5-year follow-up points from the catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (CaVenT) study that compared catheter-directed thrombolysis (with 24 months of compression stockings) against standard treatment (6 months of anticoagulant and 24 months of compression stockings) for patients with high proximal DVT. The CaVenT study[189] found no difference in EQ-5D scores between treatment arms at 6 months, 2 years or 5 years, but did find a statistically significant difference in HRQoL between those with PTS ($n = 92$) and those without PTS ($n = 97$) at 24 months and 5 years. At 6 months, the mean EQ-5D scores were lower for those with PTS but the difference was not statistically significant ($p = 0.062$).

The decrement measured at 2 years in the CaVenT study[189] was applied to all patients with PTS in the Markov phase of the model. It was decided not to model a change in HRQoL for patients with PTS over time as some HRQoL decrement is likely to be present from the time of diagnosis of PTS (i.e. 6 months after DVT) and the HRQoL impact of PTS appears to remain apparent at 5 years. Therefore, a 10% decrement was applied based on the 24-month data from Enden *et al.*[189]

Supportive evidence is provided in the study by Roberts *et al.*,[170] which reported that patients without PTS recovered their SF-36 PCS scores from below population norms by 6 months, whereas those with mild or moderate/severe PTS did not experience a similar recovery. This study[170] also reported that the location of DVT (i.e. proximal or distal) was not an independent predictor of HRQoL, with only sex, comorbidities and PTS being significant predictors in the multivariate analysis.

As the CaVenT study[189] reported the average utility decrement across all PTS, without stratifying by PTS severity, this value was applied in the model for all patients with PTS. This may overestimate the utility decrement if patients in the CaVenT study had more severe PTS than would be seen in the modelled population and severity was a predictor of utility decrement. However, in the study by Roberts *et al.*,[170] the coefficients for mild versus no PTS and for moderate/severe versus no PTS were similar in the regressions for SF-36 PCS and MCS scores, suggesting that both mild and moderate/severe PTS had similar implications for HRQoL. Furthermore, the review by Lubberts *et al.*[159] shows that the 5-year estimates from the CaVenT study reported by Haig *et al.*[160] are fairly consistent with the average across the 10 studies[160,180–182,184–186,188,192,193] that reported outcomes for the disease-specific measure of HRQoL Venous Insufficiency Epidemiological and Economic Study – Quality of life (VEINES-QoL). A sensitivity analysis was conducted to see if halving the utility decrement for PTS had a significant impact on the model results. A sensitivity analysis was also conducted using the data from Lenert and Soetikno[190] and estimating a weighted average utility across severe and mild/moderate PTS using the data from Hach-Wunderle *et al.*[109] to estimate the proportion of PTS that is severe (6%). This gave an average utility decrement of 2% rather than the 10% assumed in the base-case analysis.

Utility values in chronic thromboembolic pulmonary hypertension

Only one study included in the review by Lubberts *et al.*[159] reported outcomes for CTEPH, and this reported statistically significantly lower MCS (SMD –0.31, 95% CI –0.54 to –0.08) and PCS scores (SMD –1.72, 95% CI –1.95 to –1.48) than matched population norms. Six studies were identified as providing information on preference-based measures of HRQoL in patients with CTEPH. Three of these studies reported data based on the EQ-5D,[194–196] a fourth reported data from an alternative generic preference-based measure, the SF-6D[197] and a fifth reported data from a condition-specific preference-based measure, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[198] Finally, one study reported values based on a standard gamble.[199] Only one of the papers reported values specifically for patients with CTEPH[195] but this paper was restricted to those with resistant/recurrent or inoperable CTEPH (i.e. those in whom pulmonary endarterectomy had failed or was not possible). The paper by Ara and Brazier[194] reported data for 'other heart problems' (i.e. not heart attack/angina). The study by Keogh *et al.*[197] only included patients with idiopathic pulmonary arterial hypertension (PAH) or PAH related to connective tissue disease. Two studies, by Olschewski *et al.*[196] and Meads *et al.*,[198] included patients with CTEPH and other forms of PAH but Meads *et al.*[198] reported utility outcomes separately for those with CTEPH. Meads *et al.*[198] also reported a statistically significant difference in utility between CTEPH and those with PAH associated with connective tissue disorder. There was some inconsistency in the estimates provided by Ghofrani *et al.*[195] and Meads *et al.*,[198] with higher baseline scores in the population with inoperable/recurrent resistant CTEPH (0.66 for placebo arm) in Ghofrani *et al.*[195] than in the CTEPH subgroup reported by Meads *et al.*[198] (0.56). This may be because patients accepted into trials have slightly better general health than those receiving treatment in general practice. It was decided to use the data from Meads *et al.*[198] in the model; this was calculated based on the difference between the average utility for patients with CTEPH (0.56) and the average utility for those with New York Heart Association (NYHA) class 1 (0.89), who would be expected to have minimal HRQoL impact. This gave a multiplier of 0.63 or, equivalently, a 37% decrement relative to patients who are well. The decrement was applied for a patient's lifetime for those who were medically managed but only applied for the first year for those being surgically managed, who had the decrement for PE applied thereafter.

Utility values following intracranial haemorrhage

Of the 10 studies[177,190,194,200–206] reporting utility values for stroke patients, six studies [194,200–204] measured utility using the EQ-5D. Another four studies[177,190,205,206] reported utility values using a direct standard gamble or TTO measure, but these were disregarded as generic measures of HRQoL are preferred by NICE.[94] The values based on the EQ-5D ranged from 0.31 (as reported by Pickard *et al.*)[203] to 0.70 (as reported by Lunde *et al.*).[202] Luengo-Fernandez *et al.*[201] reported that the decrement ranged from 0.22 at 1 month to 0.09 at 5 years. Studies that reported multiple time points found that the absolute utility value increased and the decrement versus controls decreased over time. The study with the longest follow-up[201] found that utility values were relatively stable from 6 months to 5 years post stroke. The data from the 5-year follow-up of the OXVASC study[201] were chosen for application in the model as this was the largest sample of stroke patients, the population was selected from the UK, the duration of follow-up allowed time since stroke to be accounted for, and a comparison was made against general population norms. A decrement of 0.22 was assumed in the decision tree part of the model where time since stroke was < 6 months and a decrement of 0.09 was assumed in the long-term part of the model.

Utility values for major non-intracranial haemorrhage bleeds

For major non-ICH bleeds, no studies were identified that measured utility using the EQ-5D or another generic preference-based measure. Two studies[176,206] reported values using the standard gamble and a third used TTO.[177] Two of the studies that recruited at least some patients with VTE reported a utility value of 0.65,[176,177] whereas the study in patients with AF reported a much higher value of 0.841.[206] The study by Locadia *et al.*[177] (median 0.65, interquartile range 0.49 to 0.86) was considered to be the most relevant as it used TTO, which is the same method used to generate utility vales for the EQ-5D, and it explicitly included patients with experience of major bleeding episodes during VKA treatment in addition to some patients with VTE. However, using the data from Locadia *et al.*[177] directly would have resulted in a lower utility value for non-ICH bleeds than for ICH, which would not have had face validity. As the study by

Locadia *et al.*[177] showed similar valuations for the PE and GI bleed health states, and these states were ranked as equivalent, it was decided to use the data for PE from Cohen *et al.*[173] in the model as the longer-term data provided by Cohen *et al.*[173] allows the utility multiplier to be calculated relative to a patient who has recovered from VTE (i.e. relative to a patient 6 months after a DVT). The utility multiplier was, therefore, estimated to be 0.80 (0.68/0.84). As major non-ICH bleeds are not expected to lead to long-term disability, the utility multiplier for major bleeding was applied for 28 days.

Treatment-related utility decrement

Given that thromboprophylaxis involves giving patients treatment even though they may not go on to experience a VTE event without treatment, it is important to include in the model the possibility that treatment itself is associated with harm.

Several sources of data were identified for the decrement associated with prophylaxis and treatment of VTE. Six studies reported the utility decrement for warfarin or other VKAs. Four of these studies[177,205–207] used a direct measure of utility (e.g. TTO or standard gamble) and two of these studies[173,208] measured utility using the EQ-5D. The study by Monz *et al.*[208] examined HRQoL in a subset of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which was a randomised comparison of dabigatran and warfarin in patients with AF. Therefore, it was unable to measure the utility impact of warfarin alone. However, it did report that there was no statistically significant difference in HRQoL based on treatment type (DOAC vs. warfarin) and the utility scores observed were similar to age-comparable population norms. Cohen *et al.*[173] reported EQ-5D data by treatment type (heparin only, heparin/VKA, DOAC) from the PREFER-VTE registry. However, it was not clear whether or not patients receiving heparin alone in the PREFER-VTE registry would have different characteristics from those receiving other forms of treatment for VTE, in which case the difference in utility between heparin and other VTE treatments may have been confounded by patient characteristics and their influence on clinicians' choice of anticoagulant.

Only two studies[173,207] provided data on the disutility associated with heparin. Given the potential bias described above for Cohen *et al.*,[173] it was decided to use the data provided by Marchetti *et al.*;[207] in this study, a TTO exercise was used in 48 patients attending an anticoagulation clinic who had experience of LMWH. The trade-off was based on clinical vignettes for hypothetical patients receiving LMWH. The average number of days they were willing to trade was 2.7 days over a 1-year time frame. Therefore, a mean decrement of 0.007 was applied during thromboprophylaxis.

Four studies provided directly elicited measures of utility for warfarin therapy. Two were in patients with AF.[205,206] Marchetti *et al.*[207] was the only study conducted exclusively in patients with a history of VTE. Half of the patients recruited by Marchetti *et al.*[207] had previous experience of receiving warfarin. All of the patients in the study reported by Locadia *et al.*[177] had been treated previously with a VKA, but not all had previous VTE. The utility decrement for VKA versus no VKA was 4% for Locadia *et al.*[177] (0.92 vs. 0.96) based on median estimates of utility for both states, whereas it was 1% for Marchetti *et al.*[207] based on a willingness to trade 4 of 365 days of full health to avoid warfarin. The estimate from Marchetti *et al.*[207] is similar to the estimates from Gage *et al.*[205] in patients with AF, whereas the estimate from Locadia *et al.*[177] is close to the estimate from Robinson *et al.*[206] It was decided to use the data from Marchetti *et al.*[207] to provide an estimate consistent with the methodology used to estimate the utility decrement for LMWH.

In the sensitivity values exploring the use of DOACs as prophylaxis, no utility decrement has been assumed, as DOACs are taken orally and do not require frequent blood tests to monitor INR levels. In the sensitivity analysis exploring the use of fondaparinux as prophylaxis, the same utility decrement as for LMWH was assumed as both treatments are given by subcutaneous injection.

The utility values applied in the model are summarised in *Tables 21* and *22*.

TABLE 21 Utility values included in the decision tree model

Health state value	Absolute utility value	Range	Source	Notes
Well/asymptomatic DVT without prophylaxis	0.879	0.878 to 0.882	Ara and Brazier[194]	Population mean utility values based on person (average for male and females) with starting age of 46 years
Symptomatic proximal or distal DVT	0.848	0.846 to 0.850	Cohen *et al.*[173] (using additional detail reported in TA354,[140] Daiichi Sankyo company submission, table B78[178])	5% reduction relative to well patients based on comparison of average utility over 6 months for DVT (0.819) vs. utility at 6 months (0.850) for patients with DVT
Non-fatal PE	0.80	0.780 to 0.825	Cohen *et al.*[173] (using additional detail reported in TA354,[140] Daiichi Sankyo company submission, table B78[178])	9% reduction relative to well patients based on comparison of average utility over 6 months (0.775) for PE vs. utility at 6 months (0.850) for patients with DVT
Non-fatal ICH	0.66	0.616 to 0.701	Luengo-Fernandez 2013[201]	Absolute decrement of 0.22 measured at 1 month
Non-fatal non-ICH bleed	0.69	0.652 to 0.688	Cohen *et al.*[173]	• Assumed same utility decrement for PE and GI bleeds at 1 month • 21% reduction based on utility for PE at 1 month (0.67) versus utility for DVT at 6 months (0.85) from Cohen *et al.*[173]
Prophylaxis: absolute decrement applied to utility values of well/ asymptomatic DVT	0.007	0.000 to 0.050	Marchetti *et al.*[207]	Patients willing to trade average of 2.7 days per year to avoid treatment with LMWH
Treatment: absolute decrement applied to utility values for non-fatal PE or symptomatic DVT	0.011	0.000 to 0.081	Marchetti *et al.*[207]	Patients willing to trade average of 4 days per year to avoid treatment with warfarin
Fatal PE	0	NA	Assumption	

Timing and duration of utility decrements applied in the decision tree

To calculate the QALYs gained by patients having different paths through the decision tree, it is necessary to make some assumptions regarding the timing of events, as these are not explicitly modelled in a decision tree. The following assumptions were made when estimating QALYs in the decision tree:

- Baseline utilities using general population utility values for the starting age are applied to those not having treatment and not having any clinical events (e.g. VTE, bleeds).
- Bleeds during lower-limb immobilisation are assumed to occur halfway through the immobilisation period, which is assumed to last 8 weeks (56 days), namely bleeds occur at 28 days.
- VTEs occurring during lower-limb immobilisation are assumed to be diagnosed at the end of immobilisation (i.e. at 56 days) and utility decrements for PE and DVT are applied from diagnosis until the end of the decision tree period.
- Bleeds occurring during treatment for VTE are assumed to occur at 13, 32 and 12 days post diagnosis of VTE for fatal, ICH and other major bleeds, respectively (based on data from RIETE, reported by Nieto *et al.*[105]).

- Disutilities for ICH are applied lifelong, but separate disutilties are applied in decision tree and Markov phases of the model (i.e. before and after 6 months post lower-limb immobilisation).
- Disutility of GI bleeding is assumed to last a maximum of 28 days.
- Disutility of prophylaxis applies for the duration of prophylaxis (6 weeks) and is therefore less in those stopping early because of major bleeding.
- Disutility of treatment for VTE applies for the duration of treatment (3 months) and is therefore less in those stopping early because of major bleeding.

The following assumptions were made when estimating QALYs in the Markov model:

- Utility values for patents without any long-term sequelae (e.g. ICH, CTEPH, PTS) are taken from general population values and decrease as patients age in the model.
- All other utility values are applied as multipliers, such that the absolute utility value decreases for all patients as a result of ageing.
- Utility decrements continue in the Markov model for the remainder of a patient's lifetime for PE but not for DVT, for which patients are assumed to return to general population utility values at 6 months.
- Patients with CTEPH who are treated medically have a lifelong utility decrement, whereas those treated surgically return after 1 year to the same utility as those surviving PE without CTEPH.
- Patients with PTS have the same utility decrement from diagnosis to death.
- Patients with ICH have the same utility decrement from 6 months (i.e. the start of Markov model) to death.

TABLE 22 Utility multipliers applied in the Markov model to the absolute utility value for well patients

Health state(s)	Utility multiplier relative to well	Range	Source	Notes
PE survivor without CTEPH and PE survivor > 1 year after surgery for CTEPH	0.95	0.927 to 0.978	Cohen *et al.*[173]	5% reduction relative to well patients based on comparison of average utility at 6 months for patients with PE (0.81) vs. utility at 6 months (0.85) for patients with DVT
Any DVT without PTS	1	N/A	Assumption	Supported by Lubberts *et al.*'s[159] systematic review finding no significant HRQoL decrement in nine long-term studies based on SF-36 outcomes
Non-fatal ICH	0.89	0.810 to 0.955	Luengo-Fernandez *et al.*[201]	Multiplier calculated based on absolute decrement of 0.09 at 5 years (utility values stable from 6 months to 5 years) relative to absolute utility for well state of 0.88 from general population values
PTS	0.90	0.855 to 0.944	Enden *et al.*[189]	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	0.63	0.579 to 0.690	Meads *et al.*[198]	Multiplier calculated based on comparison of utility for CTEPH (0.56) vs. utility for NYHA class I (0.89)
Dead	0		Assumption	

N/A, not applicable; NYHA, New York Heart Association.

Methods used to quantify decision uncertainty

A probabilistic sensitivity analysis (PSA) was used to estimate the impact of parameter uncertainty on the estimates of costs and QALYs. For each input parameter, a probability distribution was assigned that reflected the degree of uncertainty surrounding the mid-point parameter estimate and we sampled from the distribution 10,000 times. This number of runs was deemed sufficient because it ensured that the coefficient of variation was < 2% for both incremental costs and incremental QALYs. In general, utility values, which must be < 1, and probabilities, which are bounded by 0 and 1, were sampled from beta distributions, and costs, which must be > £0, were sampled from gamma distributions. Uncertainty surrounding the ORs for efficacy (all VTE events) and adverse events (major bleeds) were captured using the convergence diagnostics and output analysis (CODA) samples from the NMA. When parameters were calculated from regression equations, multivariate normal sampling was used to incorporate the covariance between the regression parameters. The estimates of sensitivity and specificity were fixed within the PSA as the uncertainty around these parameters was not reported by Nemeth *et al.*[32] *Table 39* in *Appendix 13* presents the distributions for each parameter included in the PSA. For each of the 10,000 sets of parameter inputs, the costs and QALYs of each thromboprophylaxis strategy were re-estimated.

The 10,000 PSA estimates of costs and QALYs were used to estimate the mean costs and QALYs for each thromboprophylaxis strategy. From this, the incremental net monetary benefit (INMB) was estimated when using a willingness-to-pay threshold of £20,000 or £30,000 per QALY, which is the range of thresholds used by NICE when assessing value for money in the context of the UK NHS.[94] The strategy with the maximum INMB at a given threshold is considered to have the optimal cost-effectiveness. The INMB was used to calculate the optimal thromboprophylaxis strategy at both of these thresholds and the proportion of times, within the 10,000 PSA samples, that each strategy is optimal across a range of thresholds was estimated in order to generate the cost-effectiveness acceptability curve (CEAC).

The global expected value of perfect information (EVPI) was estimated, which tells a decision-maker the value of reducing all current decision uncertainty associated with the parameters included in the PSA. This was estimated across all the complete set of possible thromboprophylaxis strategies. The parameter EVPI analysis was also used to assess the importance of each individual parameter in generating uncertainty around the optimal strategy. The Sheffield Accelerated Value of Information (SAVI) tool was used to calculate parameter EVPI.[209]

It should be noted that a PSA and an EVPI analysis can capture only uncertainty related to parameters included in the PSA and will not capture any uncertainty associated with structural assumptions or the choice of data inputs used to estimate parameter uncertainty. These uncertainties are quantified instead using deterministic sensitivity analyses, in which a range of alternative parameter inputs and assumptions are explored within the model to see whether or not the conclusions are robust under these changes.

Results of the de novo economic evaluation

Clinical outcomes predicted by the model

The symptomatic adverse clinical outcomes predicted by the model at 6 months (based on mid-point parameter values) are summarised in *Figures 14* and *15*. As patients may have more than one adverse outcome during the 6-month time period of the decision tree model, patients are summarised on the basis of the worst outcome experienced, such that those recorded as having non-fatal PE or symptomatic DVT are those who did not also have fatal bleed, fatal PE or ICH. In *Figure 14* it can be seen that prophylaxis for all is the strategy that minimises the total number of symptomatic adverse outcomes at 6 months. The numbers of the most serious adverse clinical outcomes (e.g. fatal bleeds, fatal PEs or ICHs) are similar across the prophylaxis strategies and the differences are too small to see based on *Figure 14*. *Figure 15* focuses solely on these serious adverse clinical outcomes and shows that giving prophylaxis based on a L-TRiP(cast) score of ≥ 9 minimises the total number of these outcomes, although the rate is very low (≈1 in 4000) and shows little variation between strategies.

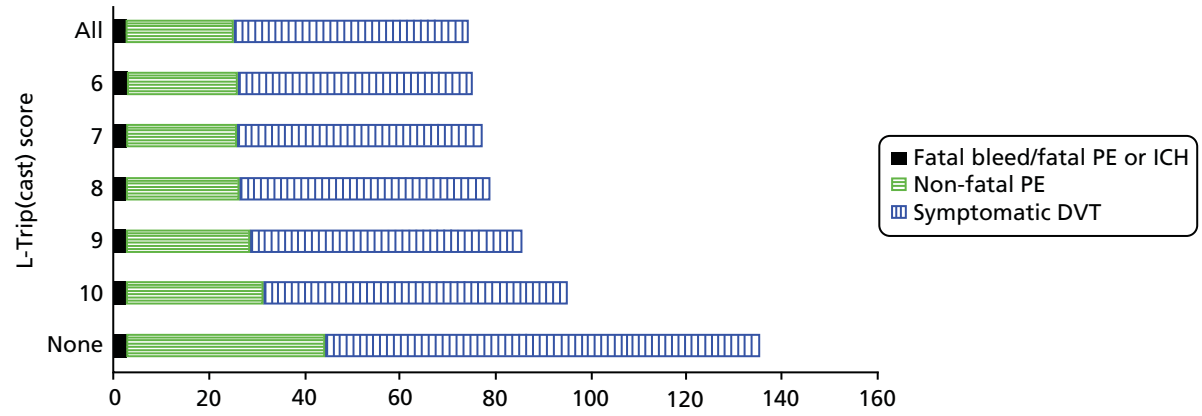

FIGURE 14 Symptomatic clinical outcomes predicted at 6 months for 10,000 patients having lower-limb immobilisation due to injury.

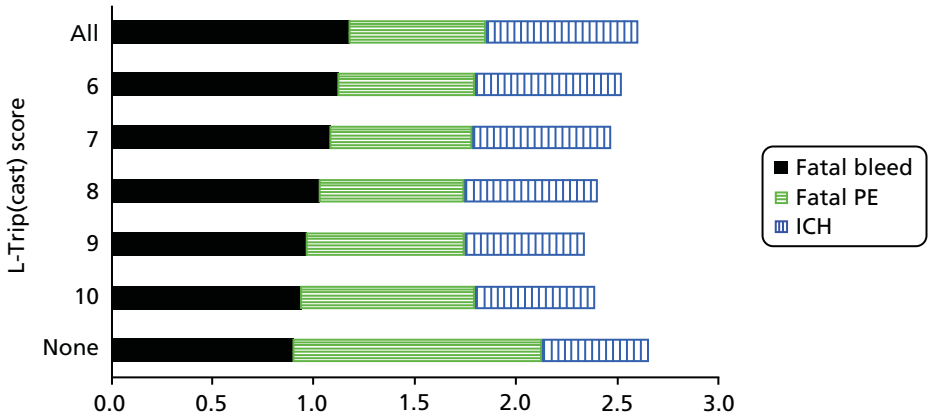

FIGURE 15 Serious adverse clinical outcomes predicted at 6 months for 10,000 patients having lower-limb immobilisation due to injury.

It should be noted that major bleeds that are non-fatal and not ICHs are assumed to resolve within 6 months and are, therefore, not included in *Figure 14*. The number of major bleeding outcomes is summarised in *Figure 16*, which shows that the total number of major bleeds, including fatal and non-fatal ICHs, increased from 4.03 per 10,000 having lower-limb immobilisation when no prophylaxis is given to 5.38 per 10,000 when prophylaxis is given to all. Giving prophylaxis to all patients with lower-limb immobilisation, therefore, results in fewer than two additional cases of major bleeding per 10,000 patients receiving prophylaxis. The increase in major bleeding is smaller than would be expected based solely on the RR of 1.64 for bleeding with prophylaxis versus bleeding without prophylaxis, because prophylaxis prevents VTE, thereby lowering the rate of bleeding experienced during VTE treatment.

The adverse clinical outcomes predicted by the model at 5 years (based on mid-point parameter values) are summarised in *Figure 17*. Only those outcomes resulting in long-term morbidity are included; therefore, patients who experience DVTs without any subsequent PTS are not included in the adverse clinical outcomes shown. It can be seen that the number of people surviving to 5 years is fairly similar across all the thromboprophylaxis strategies. The strategy of thromboprophylaxis for all results in the smallest number of people surviving with CTEPH, PTS or ongoing morbidity due to previous ICH or PE. The numbers surviving with either ongoing morbidity due to ICH or CTEPH following PE are relatively small, at ≈1 per 10,000 patients for each outcome.

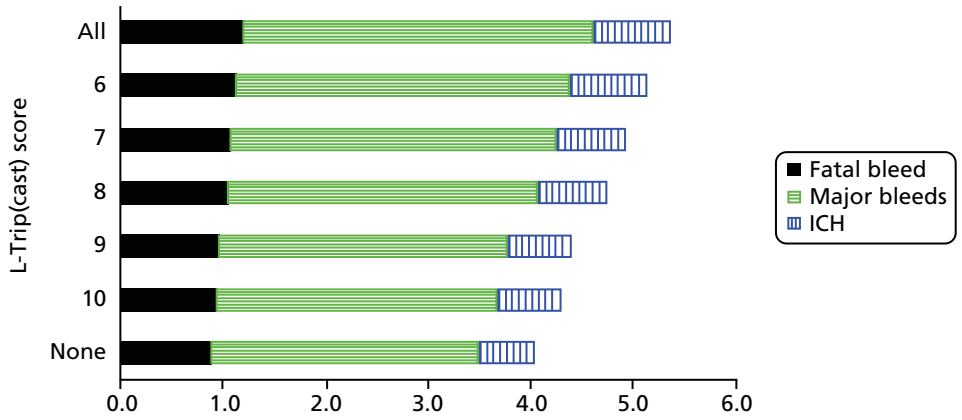

FIGURE 16 Major bleeding predicted at 6 months for 10,000 patients having lower-limb immobilisation due to injury.

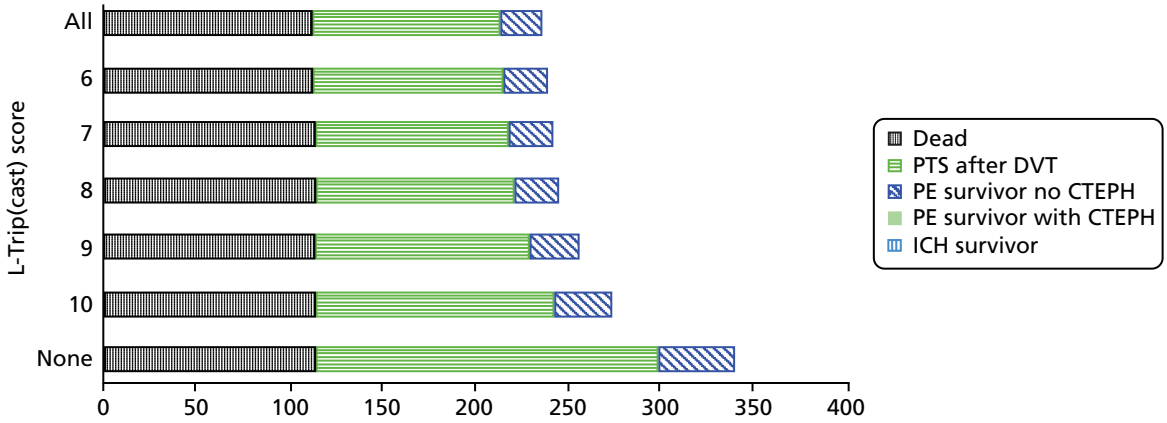

FIGURE 17 Adverse clinical outcomes predicted at 5 years for 10,000 patients having lower-limb immobilisation due to injury.

Cost-effectiveness of thromboprophylaxis for all compared with thromboprophylaxis for none

Figure 18 shows the estimates of incremental costs and QALYs for the comparison of thromboprophylaxis for all with thromboprophylaxis for none for 10,000 PSA samples. The mean incremental costs and QALYs from the 10,000 PSA samples are shown as an × on the cost-effectiveness plane. The mean QALY gain is 0.015, but it can be seen that there is a wide spread of incremental QALY estimates, with 95% of the incremental QALYs falling in the range of 0.004 to 0.029 but with some PSA samples (0.53%) having a negative QALY gain. The mean incremental cost is £203 with 95% of the PSA estimates falling in the range £172–245. The incremental cost-effectiveness ratio (ICER) for thromboprophylaxis for all compared with thromboprophylaxis for none based on the mean costs and QALYs is £13,524. Therefore, if a decision-maker is willing to pay £20,000 per QALY, it would be cost-effective to give thromboprophylaxis to all patients with lower-limb immobilisation due to injury if this was the only alternative to giving thromboprophylaxis to none. However, it can be seen that a significant proportion of the PSA estimates fall above the £20,000 per QALY threshold; therefore, there is a 24% probability that thromboprophylaxis for all is not cost-effective.

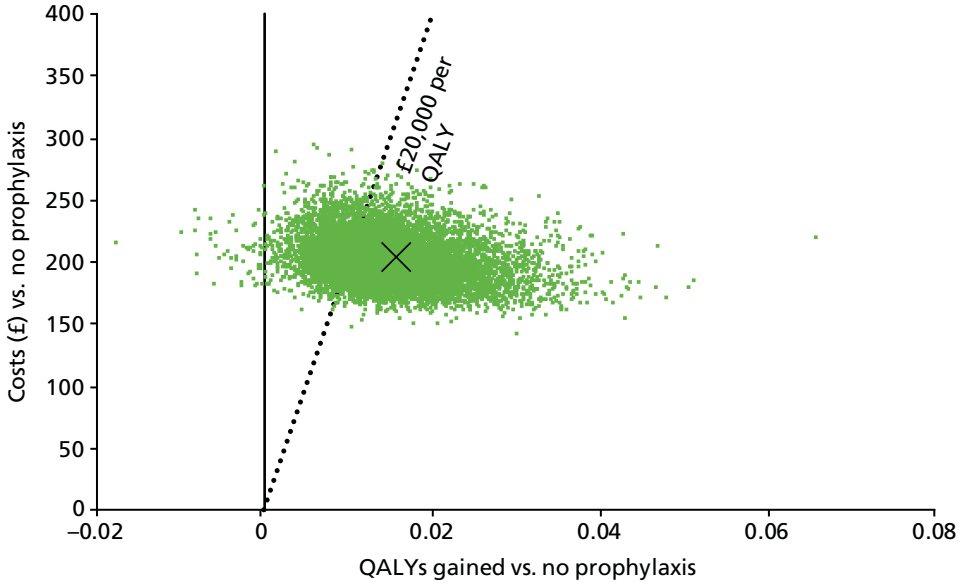

FIGURE 18 Cost-effectiveness plane for the comparison of thromboprophylaxis for all vs. thromboprophylaxis for none.

Cost-effectiveness of using a risk assessment model to determine thromboprophylaxis

The results of all of the thromboprophylaxis strategies considered in the model (based on the mean outputs of the PSA for 10,000 samples) are summarised in *Table 23* and *Figure 19*. It can be seen in *Figure 19* that, generally, the QALYs increase as the proportion receiving prophylaxis increases across the decision tools, with the QALY gains becoming more marginal as the proportion receiving prophylaxis increases. Furthermore, it can be seen in *Figure 19* that L-TRiP(cast)-7 is extendedly dominated, as the ICER to move from L-TRiP(cast)-8 to L-TRiP(cast)-6 would be lower than the ICER to move from L-TRiP(cast)-8 to L-TRiP(cast)-7, but more QALYs are gained by L-TRiP(cast)-6. However, it should be noted that the point for L-TRiP(cast)-7 is close to falling on the cost-effectiveness frontier [i.e. on the line between L-TRiP(cast)-8 and L-TRiP(cast)-6]. The incremental analysis for the remaining non-dominated strategies is shown in *Table 24*. The optimal strategy would be L-TRiP(cast)-9 if the decision-maker values QALYs at £20,000 and L-TRiP(cast)-8 if the decision-maker values QALYs at £30,000.

Optimal balance of sensitivity and specificity for a risk assessment model

From the base-case results, it can be seen that as we move from higher to lower thresholds of the L-TRiP(cast) score, the QALYs gained increase as the sensitivity of the risk assessment tool increases but the cost increases as the specificity decreases. The ROC curve for the L-TRiP(cast) score provided by Nemeth *et al.*[32] allows us to explore where the optimal balance of sensitivity and specificity lies when assuming that it lies somewhere on the ROC curve provided by L-TRiP(cast). To do this, a linear regression on the logit scale was fitted to the points on the ROC plane from L-TRiP(cast)-6 to L-TRiP(cast)-10 (intercept = –1.5256, gradient = 0.8098, R^2 = 0.9926). The sensitivity and specificity values were then varied between the L-TRiP(cast)-9 and L-TRiP(cast)-8 points of the curve to maximise the INMB using the deterministic model that uses mid-point parameter estimates. It was identified that, when valuing a QALY at £20,000, the INMB is maximised for a sensitivity of 84% and a specificity of 55%, resulting in 48% of patients being treated. When valuing a QALY at £30,000, the INMB is maximised for a sensitivity of 89% and a specificity of 46%, resulting in 57% of patients being treated. Therefore, even when using an optimised balance between sensitivity and specificity on the ROC curve predicted by the data from Nemeth *et al.*,[32] between 43% and 52% of patients would not receive thromboprophylaxis. The incremental costs and QALYs for these optimal points are shown in *Figure 20*. It can be seen from this that the optimal points on the ROC curve are actually extendedly dominated by the points for LTRiP(cast)-9 and LTRiP(cast)-8. This is because the ROC curve predicted by the linear regression on the logit scale passes below the data points for LTRiP(cast) scores of 9 and 8.

TABLE 23 Base-case results (mean from 10,000 PSA samples) in order of the percentage receiving prophylaxis

Prophylaxis strategy	% receiving prophylaxis	Sensitivity	Specificity	Absolute costs (£)	Absolute QALYs	Cost vs. no prophylaxis (£)	QALYs vs. no prophylaxis	ICER vs. prophylaxis for none (£)	INMB vs. prophylaxis for none, at £20,000 per QALY (£)[a]	INMB vs. prophylaxis for none, at £30,000 per QALY (£)[a]
Prophylaxis for none	0	0	1	65.37	16.6198	N/A	N/A	N/A	N/A	N/A
L-TRiP(cast)-10	31	0.651	0.722	128.11	16.6301	62.73	0.0103	6085	143.44	246.53
L-TRiP(cast)-9	43	0.808	0.608	150.96	16.6326	85.58	0.0127	6724	**168.96**	296.23
L-TRiP(cast)-8	63	0.926	0.397	194.41	16.6342	129.04	0.0144	8984	158.24	**301.88**
L-TRiP(cast)-7	76	0.953	0.262	222.55	16.6345	157.17	0.0146	10,755	135.10	281.23
L-TRiP(cast)-6	87	0.984	0.142	247.51	16.6348	182.14	0.0150	12,183	116.87	266.38
Prophylaxis for all	100	1	0	268.35	16.6348	202.98	0.0150	13,524	97.20	247.29

N/A, not applicable.

a INMB at £20,000 per QALY and INMB at £30,000 per QALY are the INMBs when valuing a QALY at £20,000 and £30,000 per QALY, respectively.

Note

Bold text indicates the optimal strategy.

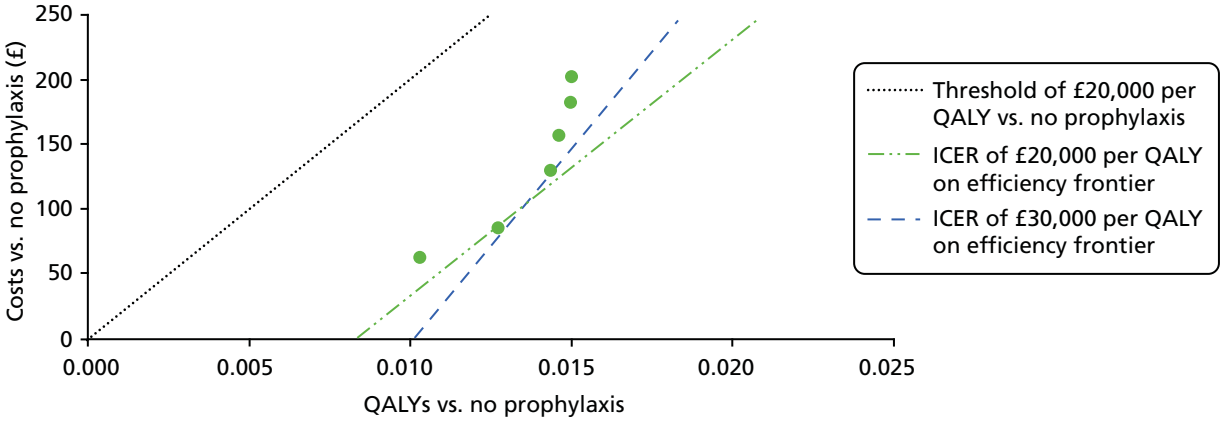

FIGURE 19 Base-case results on CE plane (mean from 10,000 PSA samples).

TABLE 24 Incremental analysis for interventions sitting on the cost-effectiveness frontier[a]

	Absolute costs (£)	Absolute QALYs	Cost vs. previous row (£)	QALY vs. previous row	ICER vs. previous row (£)
No prophylaxis	65.37	16.6198	N/A	N/A	N/A
L-TRiP(cast)-10	128.11	16.6301	62.73	0.01031	6085
L-TRiP(cast)-9	150.96	16.6326	22.85	0.00242	9448
L-TRiP(cast)-8	194.41	16.6342	43.46	0.00164	26,550
L-TRiP(cast)-6	247.51	16.6348	53.09	0.00059	90,554
Prophylaxis for all	268.35	16.6348	20.84	0.00006	357,026

N/A, not applicable.
a L-TRiP(cast)-7 does not fall on the cost-effectiveness frontier as it is extendedly dominated.

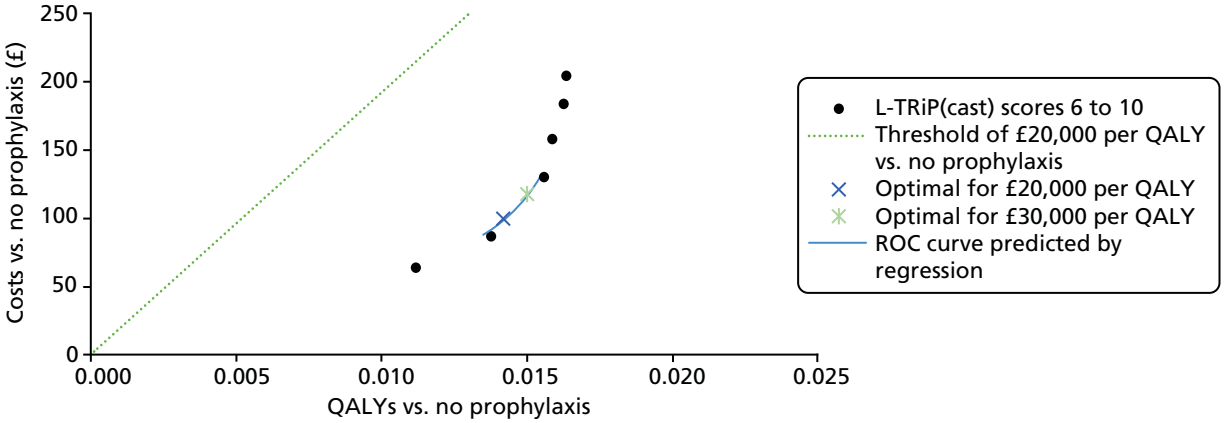

FIGURE 20 Cost-effectiveness plane showing optimal points on the ROC curve when valuing a QALY at either £20,000 or £30,000 (generated using mid-point parameter values).

Uncertainty surrounding base-case results

Figure 21 shows the cost-effectiveness plane for L-TRiP(cast)-9 (the optimal strategy when valuing QALYs at £20,000) versus no prophylaxis. It can be seen that there is considerable uncertainty in the size of the QALY gain but there is a low chance of the optimal strategy resulting in QALY losses, compared with no prophylaxis, with 95% of the incremental QALYs falling in the range of 0.005 to 0.024. In terms of costs savings, 95% of the incremental costs fell in the range of £69 to £107, suggesting that the optimal strategy is unlikely to result in cost savings compared with no prophylaxis. This is expected, as prophylaxis results in definite costs to those receiving it but the benefits of preventing VTE are small and uncertain when averaged over the whole population receiving prophylaxis. Similar distributions of incremental costs and QALYs were seen for the other L-TRiP(cast) cut-off scores, with all predicting additional costs and additional QALYs and a mean ICER of < £20,000 relative to a strategy of no prophylaxis.

Figure 22 is the CEAC, which shows the probability that each strategy is optimal when varying the amount that the decision-maker is willing to pay for a QALY. It can be seen that L-TRiP(cast)-9 has the highest probability (66.8%) of being optimal when valuing a QALY at £20,000, which is consistent with the results in

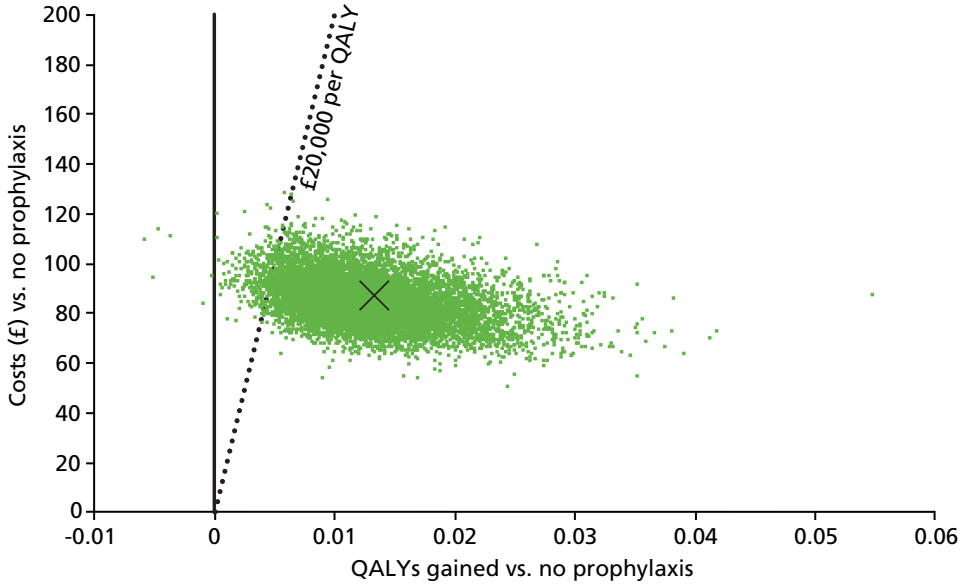

FIGURE 21 Cost-effectiveness plane for L-TRiP(cast)-9 showing incremental costs and QALYs relative to no prophylaxis.

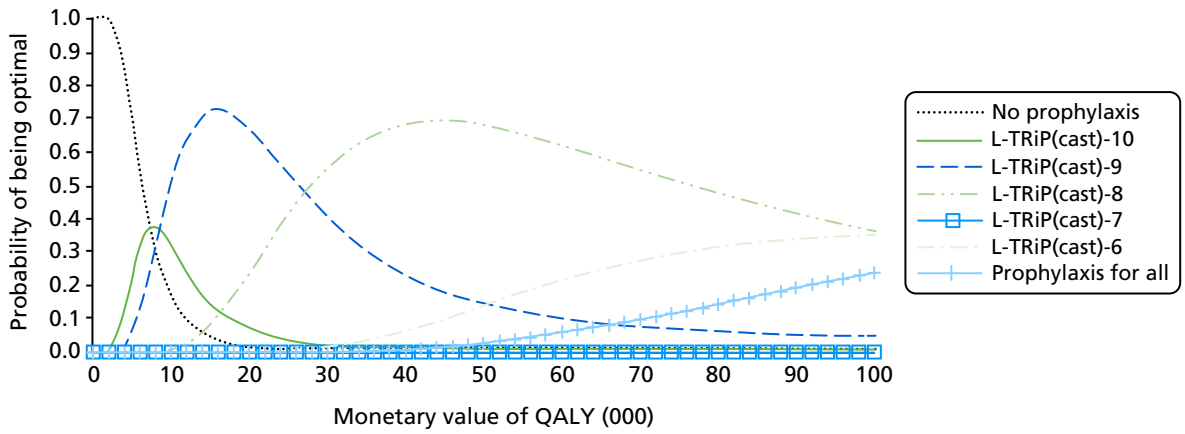

FIGURE 22 Cost-effectiveness acceptability curve.

Table 24. L-TRiP(cast)-8 has a slightly higher probability of being optimal when valuing a QALY at £30,000, but there is also a high probability of L-TRiP(cast)-9 remaining optimal. This makes sense given that the ICER for L-TRiP(cast)-8 versus L-TRiP(cast)-9 is only just under £30,000 per QALY. It can also be seen that L-TRiP(cast)-7 always has a low probability of being optimal regardless of what the decision-maker is willing to pay and that the decision-maker would need to be willing to pay more than £100,000 per QALY before prophylaxis for all is the optimal strategy. This is interesting because if the risk-stratifying decision tools had not been included in the analysis, then prophylaxis for all would have been cost-effective compared with prophylaxis for none. This demonstrates the potential value of using decision tools to target prophylaxis in a cost-effective manner instead of focusing on evaluating all or nothing prophylaxis options.

To demonstrate the impact of different strategies on a health service, L-TRiP(cast)-9 can be compared with a strategy of using prophylaxis for all across the English NHS. In *Chapter 1*, *Description of the health problem*, it was estimated that 70,000 people per year across the English NHS experience temporary lower-limb immobilisation due to injury as an outpatient. Using the mean outputs from the PSA, it is found that prophylaxis for all would result in an additional 0.0023 QALYs per person, but for an additional cost of £117.40 per person when compared with L-TRiP(cast)-9. Applied to the 70,000 annual population for the English NHS, the cost saving that could be achieved by giving prophylaxis to only those with a L-TRiP(cast) score of ≥ 9 would be £8.2M pounds and the QALYs lost would be 160. Conversely, if the impact of giving prophylaxis to patients at a L-TRiP(cast) score of 9 compared with treatment for none is considered, it is found that the additional cost to the NHS is £6.0M, with QALY gains of 891 for a population of 70,000 patients having lower-limb immobilisation. One-tenth of this additional cost to the NHS is the upfront cost of performing risk assessment in all patients with lower-limb immobilisation following injury to identify those requiring prophylaxis.

Value to the decision maker of reducing uncertainty in the estimates of cost-effectiveness

The global EVPI was estimated, which tells a decision-maker the value of reducing all current decision uncertainty associated with the PSA parameters. It was found that the overall EVPI was £4.12 per patient treated, suggesting that although treating patients at the L-TRiP(cast)-9 cut-off score would be expected to achieve an INMB of £168.96 per patient compared with no prophylaxis, based on current information, only 2.4% more INMB could be achieved with perfect information. This suggests that the value of reducing the decision uncertainty further is low on a per-patient basis. However, if the EVPI is estimated over 5 years, assuming that 70,000 patients have lower-limb immobilisation due to injury every year, then the overall discounted population EVPI is £1.3M.

Parameter EVPI analysis was also used to assess the importance of each individual parameter in generating uncertainty around the optimal strategy. Based on this, the most important parameters for decision uncertainty were the utility value for PTS, the efficacy of thromboprophylaxis in reducing VTE, the probability of PTS for patients with distal DVT and the utility decrement associated with taking prophylaxis. This suggests that the main factors driving uncertainty in the model are the efficacy and disutility of receiving prophylaxis, and the long-term complications of PTS. The incidence of PTS in patients with distal DVT is particularly important probably because asymptomatic DVT is more common than symptomatic DVT and the majority of asymptomatic DVTs are expected to be distal in this population. However, the magnitude of the overall EVPI suggests that a large-scale RCT comparing thromboprophylaxis with no thromboprophylaxis would be unlikely to be cost-effective.

It should be noted that EVPI analysis can capture only uncertainty related to parameters included in the PSA and will not capture any uncertainty associated with structural assumptions or the choice of data inputs used to estimate parameter uncertainty. These uncertainties are quantified instead using deterministic sensitivity analyses.

Important factors driving the cost-effectiveness estimates identified during model validation were:

- incidence, long-term costs and utility decrement for PTS
- baseline risks of VTE and the proportion of DVTs that are distal
- costs and efficacy of prophylaxis and prophylaxis-related disutility.

These have been explored in deterministic sensitivity analyses by examining changes in the outputs of the deterministic model (the values produced when assuming mid-point parameter inputs) when changing one or more selected parameter inputs.

Scenario analyses and threshold analyses

The results of the individual scenario analyses are summarised in *Table 25* by reporting the optimal thromboprophylaxis strategy when valuing a QALY at £20,000 and £30,000 for each scenario.

Whether or not the age of the cohort being offered prophylaxis would alter the conclusions was examined, as it is likely that those receiving prophylaxis under the various decision tools would be older than the mean age of the whole group who have lower-limb immobilisation due to injury. It was found that increasing the mean starting age of the whole cohort to 70 years increased the ICERs but L-TRiP(cast)-9 remained optimal at £20,000 and L-TRiP(cast)-8 remained optimal at £30,000 with an ICER of £29,555 versus L-TRiP(cast)-9. This suggests that the decision to use a cohort approach based on average age is unlikely to have over- or underestimated prophylaxis benefits sufficiently to alter the key conclusions regarding the optimal strategy.

A threshold analysis was conducted to see how much the mid-point estimates of efficacy for LMWH in preventing VTE would need to change to alter the optimal prophylaxis strategies. It was found that a decrease in the hazard ratio (HR) (improvement in efficacy) from 0.54 to 0.44 would make L-TRiP(cast)-8 the optimal strategy at both £20,000 and £30,000 per QALY, whereas an increase in the HR (decrease in efficacy) to 0.60 would make L-TRiP(cast)-9 optimal at both £20,000 and £30,000 per QALY. An increase in the HR to 0.76 would be required for L-TRiP(cast)-9 to no longer be optimal at £20,000 per QALY. An increase in the HR to 0.84 would be required for treatment for none to be the optimal strategy at £20,000 per QALY.

It was examined whether or not the conclusions would differ if all patients were assumed to receive either fondaparinux or DOACs instead of LMWH for prophylaxis. For this, no difference in adverse event rates was assumed across the different prophylaxis options. Costs were assumed to vary in each case as per the costing analysis in *Table 18*. For DOACs, equivalent efficacy to LMWH was assumed and no utility decrement for DOACs was assumed because they are taken orally. For fondaparinux, the efficacy estimates from the NMA for fondaparinux versus control (OR 0.1, 95% predictive interval 0.05 to 0.3, from the random effects analysis) were used and the same utility decrement as applied for LMWH was assumed because both drugs are given by subcutaneous injection. Using DOACs shifted the optimal strategy when valuing a QALY at £20,000 from L-TRiP(cast)-9 to L-TRiP(cast)-8 and shifted the optimal strategy when valuing a QALY at £30,000 to treat all. Using fondaparinux resulted in the ICER for L-TRiP(cast)-8 versus L-TRiP(cast)-9 falling under £20,000 per QALY but L-TRiP(cast)-8 remained optimal when valuing a QALY at £30,000. It should be noted that these two scenarios are fairly crude and do not fully explore differences between the different drug classes in terms of adverse events. Furthermore, in the case of DOACs the analysis is based on an assumption of equivalent efficacy. The intention here was to explore whether or not the optimal cut-off point for providing thromboprophylaxis would differ when using a different drug class, rather than determining the optimal drug class to use for thromboprophylaxis.

In addition to a lack of precision in the estimates of utility decrement associated with PTS, there were differences in the estimates provided by different papers. The data from Lenert and Soetikno[190] were used, which had lower decrements for PTS and showed that the optimal strategy when willing to pay £20,000 per QALY became L-TRiP(cast)-10, with L-TRiP(cast)-9 having an ICER of just under £30,000 in this scenario. This suggests that there is considerable decision uncertainty associated with the choice of utility data for PTS.

TABLE 25 Deterministic sensitivity analyses

Scenario description	Base-case parameter value	Alternative parameter value	Optimal strategy when valuing a QALY at £20,000	Optimal strategy when valuing a QALY at £30,000
Base case	N/A	N/A	L-TRiP(cast)-9	L-TRiP(cast)-8
High starting age	46 years	70 years	L-TRiP(cast)-9	L-TRiP(cast)-8
Low starting age	46 years	20 years	L-TRiP(cast)-9	L-TRiP(cast)-8
DOACS used for prophylaxis	LMWH with cost of £223.70 and utility decrement of 0.007 and an OR for preventing VTE of 0.52	DOACs with cost of £84.23 and no utility decrement and an OR for preventing VTE of 0.52	L-TRiP(cast)-8	Prophylaxis for all
Fondaparinux used for prophylaxis	LMWH with cost of £223.70 and utility decrement of 0.007, and an OR for preventing VTE of 0.52	Fondaparinux with cost of £355.66 and utility decrement of 0.007 and an OR for preventing VTE of 0.13	L-TRiP(cast)-8	L-TRiP(cast)-8
Double utility decrement for LMWH	Utility decrement of 0.007	Utility decrement of 0.015	L-TRiP(cast)-9	L-TRiP(cast)-8
Cost of patients with CRNMB attending ED	£0 (costs of CRNMB excluded in base-case analysis)	£196 per patient having CRNMB	L-TRiP(cast)-9	L-TRiP(cast)-8
Discounting	3.5% costs and 3.5% QALYs	1.5% costs and 1.5% QALYs	L-TRiP(cast)-8	L-TRiP(cast)-8
Discounting	3.5% costs and 3.5% QALYs	3.5% cost and 1.5% QALYs	L-TRiP(cast)-8	L-TRiP(cast)-8
Utility decrement of PTS based on data from Lenert and Soetikno[190]	10% utility decrement for PTS vs. no PTS	2% utility decrement for PTS vs. no PTS	L-TRiP(cast)-10	L-TRiP(cast)-9
Costs of PTS based on US estimates by Caprini *et al.*[146]	• Year 1: £308 • Year 2: £74	• Year 1: £1022 • Year 2: £423	L-TRiP(cast)-9	L-TRiP(cast)-8
Time to complete risk assessment scoring tool	5 minutes of consultant time	20 minutes of consultant time	L-TRiP(cast)-9	L-TRiP(cast)-8
Risk of PTS in patients with asymptomatic distal DVT	15.6% at 3 years	None	L-TRiP(cast)-9	L-TRiP(cast)-9
Risk of PTS in patients with asymptomatic proximal DVT	56.4% at 3 years (inflated vs. symptomatic as untreated)	Same as symptomatic proximal DVT: 32.4% at 3 years	L-TRiP(cast)-9	L-TRiP(cast)-8
Higher risk of bleeding without prophylaxis	0.03% in 8 weeks	Five times base-case value, namely 0.15% in 8 weeks	L-TRiP(cast)-9	L-TRiP(cast)-8
Higher risk of bleeding without prophylaxis	0.03% in 8 weeks	10 times base-case value, namely 0.29% in 8 weeks	L-TRiP(cast)-9	L-TRiP(cast)-9

Scenario description	Base-case parameter value	Alternative parameter value	Optimal strategy when valuing a QALY at £20,000	Optimal strategy when valuing a QALY at £30,000
Proportion of symptomatic DVTs that are distal	50% distal	0% distal (all proximal)	L-TRiP(cast)-9	L-TRiP(cast)-8
Proportion of symptomatic DVTs that are distal	50% distal	100% distal (none proximal)	L-TRiP(cast)-9	L-TRiP(cast)-8
Proportion of asymptomatic DVTs that are distal	84% distal	0% distal (all proximal)	L-TRiP(cast)-8	L-TRiP(cast)-8
Proportion of asymptomatic DVTs that are distal	84% distal	100% distal (none proximal)	L-TRiP(cast)-9	L-TRiP(cast)-9
Increased VTE baseline risk	8.39% total VTE with 1.34% symptomatic DVT or PE	Three times baseline, namely 25% total VTE with 4.01% symptomatic DVT or PE	L-TRiP(cast)-6	Prophylaxis for all
Decreased VTE baseline risk	8.39% total VTE with 1.34% symptomatic DVT or PE	One-third of baseline, namely 2.8% total VTE risk with 0.45% symptomatic DVT or PE	Prophylaxis for none	L-TRiP(cast)-10

N/A, not applicable.

An assumption was made regarding the resource use associated with management of PTS based on clinical expert advice. A costing study from the USA[146] reported higher costs, possibly related to more aggressive management of PTS. Whether or not using these higher cost estimates changed the conclusions was tested; it was found that the optimal strategies did not change, suggesting that the costs of managing PTS are not an important source of decision uncertainty.

It should also be noted that the PSA does not incorporate any uncertainty related to the estimates of sensitivity and specificity. Therefore, a scenario analysis was conducted in which, for each strategy, the specificity was fixed and the sensitivity was reduced so that it fell half-way between the observed value and the line on the ROC curve, which represents a tool that is no better than random selection. The alternative points are shown in *Figure 23*. The approximate AUC for the alternative points is 0.62, which is in the lower range of the CI for the AUC for the L-TRiP(cast) score is the plaster cast subgroup of the derivation cohort (AUC mean 0.76, 95% CI 0.66 to 0.86).[32] A similar AUC was achieved when L-TRiP(cast) score was validated in a subgroup of patients having plaster cast in the THE-VTE study (0.77, 95% CI 0.58 to 0.96) but a much better AUC was achieved when it was validated in the Milan study (0.95, 95% CI 0.91 to 0.99).[32] It can be seen in *Figure 24* that, in this scenario assuming a lower AUC, the ICER for moving from each L-TRiP(cast) cut-off score to the next is fairly constant, such that the gains in QALYs when increasing the numbers treated are fairly proportional to the gains in cost across all L-TRiP(cast) cut-off scores. In this scenario, treatment for all is the optimal strategy when valuing a QALY at either £20,000 or £30,000. This tells us that the shape of the ROC curve is important in determining whether or not risk assessment tools can be used to target treatments more cost-effectively. If the tool used is less efficient at identifying the patients at risk, as indicated by a lower AUC, then a strategy of treating all patients would be most cost-effective. It was examined how much the sensitivity and specificity values could change before the RAM based thromboprophylaxis became

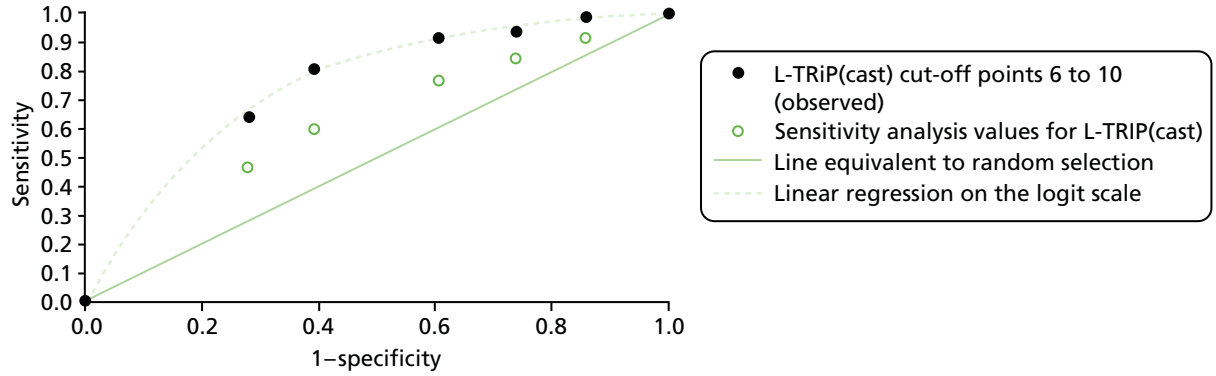

FIGURE 23 The ROC curve for the observed sensitivity and specificity values for L-TRiP(cast)-6 to L-TRiP(cast)-10 and the alternative values used in the sensitivity analysis.

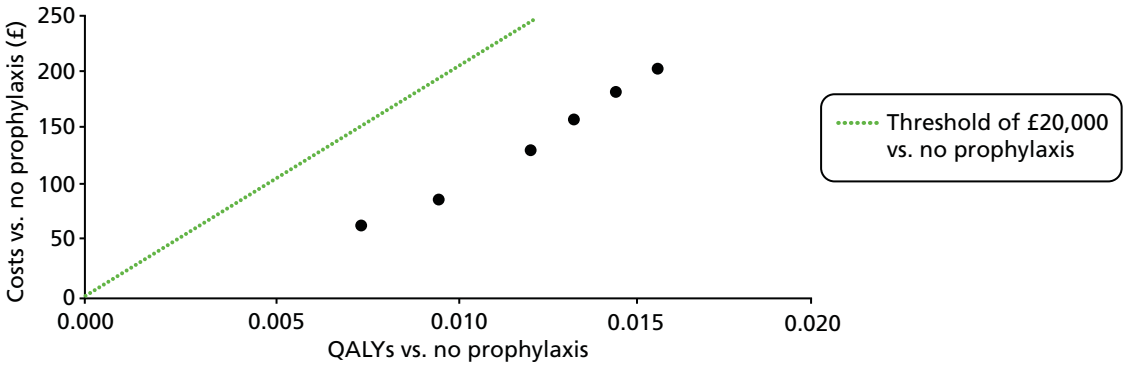

FIGURE 24 Cost-effectiveness plane when assuming that L-TRiP(cast) performs less well than observed by Nemeth *et al.*[32] (AUC of 0.62 instead).

extendedly dominated by treatment for all (i.e. when the ICER vs. no treatment was the same for both). It was found that for a specificity of 55%, the sensitivity would need to fall to 49% before thromboprophylaxis using a RAM became extendedly dominated by thromboprophylaxis for all. However, the absolute QALY gains would be 42% lower than the optimal point on the ROC curve and the costs would be only 16% lower.

Given that the use of a decision tool would result in clinical time being spent for every patient who has lower-limb immobilisation, it was important to evaluate whether or not the assumption regarding the time taken for risk assessment was associated with significant decision uncertainty. The time taken was changed from 5 minutes to 20 minutes and it was found that this had an impact on the ICER only for L-TRiP(cast)-10 versus no prophylaxis; as this remained < £20,000, L-TRiP(cast)-9 remained optimal.

Whether or not the exclusion of costs related to CRNMB had an important impact on the model conclusions was examined and it was found that the optimal strategies did not change when assuming that all patients with CRNMB attended ED for assessment.

It was initially planned to have a zero rate of PTS in patients with asymptomatic distal DVT based on clinical expectations that the rate of PTS would be low in this group. Given that we had identified that PTS following distal DVT was an important driver of uncertainty in the model, a scenario analysis was conducted with a zero rate of PTS for asymptomatic distal DVT. Under this assumption, L-TRiP(cast)-9 was still the optimal strategy when willing to pay £20,000 per QALY but L-TRiP(cast)-8 had an ICER of > £50,000 compared with L-TRiP(cast)-9. In addition, under this scenario, prophylaxis for all had an ICER of £26,962 versus prophylaxis for none. This is because the marginal gains of preventing VTE are smaller when PTS risk is limited to the minority with proximal DVTs or symptomatic distal DVTs.

There was some uncertainty regarding the rate of PTS in asymptomatic proximal DVT that remains undetected and untreated, as most of the studies that identified asymptomatic proximal DVT treated patients. It was examined whether or not the conclusions varied if assuming the same rate of PTS as observed in symptomatic proximal DVT but it was found that the optimal strategies were unchanged.

The estimates of the proportion of symptomatic DVTs that are proximal were based on 16 DVTs reported in a single study.[59] To determine if this factor was an important driver of cost-effectiveness, the proportion was varied from 0% to 100%; it was found that this had no impact on the optimal strategy when valuing a QALY at either £20,000 or £30,000.

Similarly, as the estimates of the proportion of asymptomatic DVTs that are distal was based on a small number of events, an extreme analysis was conducted to see if varying the proportion from 0% to 100% had a large impact on the conclusions. It was found that, when assuming that all asymptomatic DVTs are distal, the optimal strategy was L-TRiP(cast)-9 when valuing a QALY at either £20,000 or £30,000. Conversely, when assuming that all asymptomatic DVTs are proximal, the optimal strategy was L-TRiP(cast)-8 when using a willing-to-pay threshold of either £20,000 or £30,000 per QALY.

Given that the major risk of adverse effects to patients is the risk of a bleed following prophylaxis, a threshold analysis was conducted to see how much higher the bleed risk in the general population would need to be to change the optimal strategy. It was found that L-TRiP(cast)-9 was optimal at £20,000 per QALY until the bleed risk reached 30 times that assumed in the base-case analysis. However, a sixfold increase in bleed risk in the population was required to make L-TRiP(cast)-8 have an ICER of > £30,000 per QALY. Furthermore, when the bleed risk is 15-fold higher than assumed in the base-case analysis, the treat-all strategy is no longer cost-effective relative to the treat-none strategy at a threshold of £20,000 per QALY.

The risk of VTE without prophylaxis was increased and decreased threefold; it was found that this had a significant impact on the optimal strategy, with a threefold increase resulting in treating all being the optimal strategy when valuing a QALY at £30,000, and a threefold decrease resulting in treat none being optimal when valuing a QALY at £20,000. For a strategy of treat all to result in fewer QALYs gained than

lost, namely for there to be a net harm to patients, the VTE risk would need to be < 9% of its base-case value, suggesting that baseline risks would need to be substantially lower than thought before prophylaxis would be at risk of doing more harm than good to a patient's health. However, at this level of risk, none of the prophylaxis strategies would be cost-effective.

Summary of key findings

- The benefits of thromboprophylaxis in terms of reducing VTE outweigh the harms in terms of increased bleeding risk in the modelled population.
- Thromboprophylaxis for all has an ICER of £13,524 compared with thromboprophylaxis for none.
- When considering whether or not the cost-effectiveness of thromboprophylaxis can be improved by using a RAM to target thromboprophylaxis, the optimal strategy would be to use the L-TRiP(cast) score with a threshold score of 9 if the £20,000-per-QALY threshold is used and with a threshold score of 8 if the £30,000-per-QALY threshold is used.
- An optimal RAM would be expected to operate with a sensitivity of 84–89% and specificity of 46–55%, assuming the ROC curve for the L-TRiP(cast) score reflects the typical trade-off between sensitivity and specificity in risk assessment.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness reviews

Pharmacological thromboprophylaxis for preventing venous thromboembolism

In the meta-analysis, it was found that thromboprophylaxis with LMWH reduced any VTE (OR 0.52, 95% CrI 0.37 to 0.71), clinically detected DVT (OR 0.40, 95% CrI 0.12 to 0.99) and PE (OR 0.17, 95% CrI 0.01 to 0.88) compared with no thromboprophylaxis. The effect of LMWH thromboprophylaxis varied between different VTE outcomes but all estimates were consistent with an approximate halving of risk. The number of deaths and bleeding events were too small to draw reliable conclusions. Thromboprophylaxis with fondaparinux also reduced any VTE (OR 0.13, 95% CrI 0.05 to 0.30) and clinically detected DVT (OR 0.10, 95% CrI 0.01 to 0.94) compared with no thromboprophylaxis, but the effect on PE was inconclusive (OR 0.47, 95% CrI 0.01 to 9.54). Event rates for symptomatic DVT and PE were generally low across the studies, so an approximate halving of risk may result in a small absolute risk reduction. Network meta-regression did not identify evidence of effect modification associated with population characteristics, type of injury, type of immobilisation or duration of treatment. There was evidence of difference in the effect of different types of LMWH used, with certoparin having the highest probability of the greatest effect on any VTE, but this was based on findings from one study.[52]

Individual risk factors associated with venous thromboembolism risk

In the systematic review, it was found that only older age was consistently associated with increased risk of VTE across the included studies. Four studies[53,60,70,71] showed that higher BMI was associated with increased risk and six studies[11,50,52,53,69,70] show associations between injury type and risk of VTE. All studies were deemed to be at moderate[23,50,52,53,60,68,71] or serious[9,11,64–67,69,70] risk of bias overall following structured quality assessment. The use of individual risk factors to predict VTE risk in people with lower-limb immobilisation due to injury is, therefore, based on limited and weak evidence.

Risk assessment models for prediction of venous thromboembolism risk

The systematic review identified a number of RAMs but only two studies[32,82] (both case–control design) provided estimates of sensitivity and specificity for three of the RAMs. The L-TRiP(cast) score[32] using a threshold score of 8 (sensitivity 92.6%, specificity 39.7%) or 9 (sensitivity 80.8%, specificity 60.8%) may have appropriate accuracy for use in practice but these estimates are subject to considerable uncertainty.

Expert consensus study

The Delphi study resulted in agreement that the following were potentially useful predictors of VTE in lower-limb immobilisation due to injury: age, BMI of > 30 kg/m^2, active cancer, pregnancy/puerperium, thrombophilia, prior VTE, surgery in the previous 3 months, exogenous oestrogen, lower-limb paralysis, superficial thrombophlebitis, Achilles tendon rupture, above-knee plaster cast and rigid immobilisation in a cast (as opposed to removable immobilisation). Most of the predictors agreed by the experts were not supported by evidence in the systematic review. Therefore, it appears that experts are willing to draw on evidence from other patient groups, pathophysiological knowledge and their clinical experience to identify predictors of VTE.

Most of the agreed predictors were included in one or more of the RAMs, presumably reflecting the role of clinical expertise in developing most of the RAMs. However, the expert group were unable to reach consensus on many potential predictors, including many variables that were included in one or more RAMs. The differences between RAMs are likely to reflect differences in expert opinion, which may, in turn, reflect the lack of available evidence for VTE predictors in lower-limb immobilisation due to injury.

Economic evaluation

Decision-analytic modelling compared thromboprophylaxis for all people with lower-limb immobilisation due to injury with thromboprophylaxis for none and risk-based approaches [i.e. the L-TRIP(cast) score was used to select higher-risk patients for thromboprophylaxis]. Effectiveness analysis suggested that the rate of serious adverse outcomes (ICH or death from VTE or bleeding) would be very low regardless of the approach used (around 1 in 4000). Rates of symptomatic DVT and non-fatal PE would be higher (around 22 to 41 per 10,000 and 49 to 91 per 10,000, respectively) and varied across the strategies. The total number of major bleeds, including fatal and non-fatal ICHs, ranged from 4.03 per 10,000 with no thromboprophylaxis (reflecting baseline population rates and bleeding as a result of treatment of subsequent VTE) to 5.38 per 10,000 when thromboprophylaxis is given to all. The higher rates of VTE events compared with bleeding events meant that overall quality-adjusted life expectancy increased in accordance with the proportion of the population receiving thromboprophylaxis with each strategy. It therefore appears that the benefits of thromboprophylaxis in terms of reducing VTE outweigh the harms in terms of increased bleeding risk in the modelled population.

Cost-effectiveness analysis comparing thromboprophylaxis for all with thromboprophylaxis for none showed that thromboprophylaxis for all gained a mean of 0.0147 QALYs at a mean cost of £204 per patient, with an ICER of £13,524. This suggests that, if no acceptable RAM is available, then thromboprophylaxis for all would be cost-effective according to NICE thresholds, but there was some uncertainty in this estimate, with a 24% probability that thromboprophylaxis for all is not cost-effective at the £20,000-per-QALY threshold.

Cost-effectiveness analysis comparing thromboprophylaxis for all, thromboprophylaxis according to varying thresholds of the L-TRiP(cast) score and thromboprophylaxis for none showed that the optimal strategy would use the L-TRiP(cast) score with a threshold of 9 if the £20,000-per-QALY threshold is used and with a threshold of 8 if the £30,000-per-QALY threshold is used. Analyses to determine the optimal trade-off between sensitivity and specificity suggested that INMB is maximised when sensitivity is 84% and specificity is 55% when the £20,000-per-QALY threshold is used, or when sensitivity is 89% and specificity is 46% when the £30,000-per-QALY threshold is used. An optimal RAM would therefore be expected to operate with a sensitivity of 84–89% and a specificity of 46–55%, assuming that the ROC curve of the L-TRiP(cast) score is typical of RAMs.

The EVPI analysis suggested that the most important parameters for decision uncertainty were the utility value for PTS, the effectiveness of thromboprophylaxis in reducing VTE, the probability of PTS for patients with distal DVT and the utility decrement associated with taking thromboprophylaxis. The value of reducing the decision uncertainty further was low on a per-patient basis. However, the uncertainty surrounding estimates of RAM accuracy in the PSA could not be appropriately reflected. As noted in the review of RAMs, these estimates are based on very weak and limited data, and are therefore likely to be subject to substantial uncertainty.

Strengths and limitations of the assessment

Clinical effectiveness review

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The meta-analysis synthesised data from 6857 participants in 13 randomised trials that were judged to have a low risk of bias or some concerns only for most quality criteria. This represents a large, methodological robust data set across a variety of settings that allows us to draw generalisable conclusions. Reasonably precise estimates of the effect of thromboprophylaxis compared with control could be produced for most outcomes. Statistical power was more limited for uncommon outcomes, such as PE, but even here it was possible to generate an estimate that suggested a statistically significant effect. It was also possible to undertake a NMA to compare across three alternatives: (1) LMWH, (2) fondaparinux and (3) no thromboprophylaxis.

A recent Cochrane meta-analysis by Zee *et al.*[18] reported data from eight trials,[49,51–56,59] including 3680 participants, that compared thromboprophylaxis with no treatment or placebo. They found that LMWH was associated with a significantly reduced risk of any DVT (OR 0.45, 95% CI 0.33 to 0.61) and symptomatic VTE (OR 0.40, 95% CI 0.21 to 0.76) but not PE (OR 0.50, 95% CI 0.17 to 1.47). Zee *et al.*[18] excluded four trials that were included in this analysis (Goel *et al.*,[50] Selby *et al.*,[58] Gehling *et al.*[23] and Samama *et al.*[57]), and one additional trial was published after their updated meta-analysis (Zheng *et al.*[60]). Two of the trials were excluded because they focused on operatively treated fractures rather than immobilisation (Goel *et al.*[50] and Selby *et al.*[58]), one because the comparator was aspirin (Gehling *et al.*[23]) and one because the intervention was fondaparinux rather than LMWH (Samama *et al.*[57]). The inclusion of these trials has ensured that this analysis is more comprehensive and provides more precise estimates of effectiveness, but at the expense of greater heterogeneity.

This analysis was inevitably limited by the primary data. The variety of settings and patient groups may be a strength in terms of increasing generalisability; there was evidence of heterogeneity of effect for many of the outcomes, suggesting that effects may differ between populations. Three trials[23,52,53] were judged as having a high risk of bias on the basis of outcome ascertainment being potentially subject to bias in an open-label trial. One trial that administered aspirin to the control group was included on the basis that NICE guidelines on VTE[1,24] do not consider aspirin or other antiplatelet agents to be appropriate for VTE prophylaxis and aspirin is not indicated as a treatment for VTE prophylaxis in lower-limb immobilisation.[21,25,26] If aspirin has a significant prophylactic effect, then this trial may underestimate the effect of thromboprophylaxis.

The primary studies had a number of selection criteria that limit the ability to apply the findings to certain populations. Patients at a high risk of VTE (such as those with active cancer, thrombophilia, previous VTE or pregnancy/puerperium) and those with an increased risk of bleeding were often excluded. The studies generally included patients with rigid immobilisation rather than those with a degree of movement or a removable cast or splint, so the findings may be applicable only to those with full immobilisation.

The analysis included a substantial number of participants but the event rates for some outcomes were very low. As a consequence, it was not possible to produce reliable estimates of the effect of thromboprophylaxis on major bleeding or death. The low rate of bleeding provides some reassurance that thromboprophylaxis is not causing a clinically important rate of serious adverse outcome in this population but this may not be applicable to patients at a higher risk of bleeding.

Individual risk factors associated with venous thromboembolism risk

This is the first systematic review conducted to look directly at individual risk factors increasing the risk of VTE in patients with lower-limb injury immobilised in plaster, discharged to an outpatient setting. This is an important distinction, as the population of interest differs markedly from generic thrombosis data sets; patients with lower-limb injury tend to be younger, more active and devoid of comorbidity than those presenting with unprovoked or cancer-associated thrombosis. Previous work has attempted to address a similar issue in patients undergoing elective foot and ankle surgery.[72,73,81] We consider this to be a different population because of the absence of acute blunt trauma causing local vessel/endothelial injury, expert postoperative immobilisation and often bespoke immobilisation regimes.

The review was undertaken in accordance with guidelines published by the Centre for Reviews and Dissemination[75] and the protocol was registered with the PROSPERO register.[38] Clinical experts were involved throughout as checkers and to assess the validity and applicability of research during the project. Descriptive statistics were reported to provide plain insight into the limited evidence base applicable to the subject matter and the scientific concerns regarding validity of the data.

The review was limited by a lack of studies specifically examining risk prediction in lower-limb immobilisation due to injury. Therefore, studies, such as RCTs, that were designed for another purpose but reported risk predictors in their analyses were included. The studies of risk prediction were a combination of prospective cohorts and retrospective health database registries. Both have significant limitations. Retrospective studies

of health database registries may have large numbers but may be limited by poor data quality and failure to accurately ascertain outcomes. Prospective cohorts may have better-quality data but lack statistical power because of smaller numbers. The included studies demonstrated high levels of heterogeneity, so a meta-analysis could not be undertaken.

Several studies included patients receiving operative intervention and short inpatient stays. Following the introduction of NICE guidance on thromboprophylaxis to reduce the risk of hospital-acquired thrombosis, it is reasonable to assume that, in a modern health-care environment, all these patients would receive some form of routine thromboprophylaxis.[24] For this reason, inclusion of these patients could lead to false reassurance regarding low incidence of VTE. However, patients with a short inpatient stay (< 5 days) were considered to fit within the scope of interest; these patients often remain temporarily immobilised for a period of 4–8 weeks in total, and debate persists about the role of thromboprophylaxis that is similar to debate around patients discharged directly from the ED.

All the studies within the review were classed as being at moderate or severe risk of bias. Therefore, any conclusions regarding the influence of risk factors on the subsequent development of VTE drawn are based on weak evidence and have the potential to be inaccurate.

Risk assessment models for prediction of venous thromboembolism risk

This review had strengths of following recognised guidance, prospective registration, a clear protocol and drawing on appropriate clinical and reviewing expertise. It was anticipated that the data would not allow meta-analysis; therefore, descriptive analyses only were planned.

A previous review by Watson *et al.*[82] identified two of the RAMS included in this review (Keenan *et al.*[31] and Roberts *et al.*[17]), along with three generic RAMs that could be applied to people with lower-limb immobilisation due to injury.[210–212] Watson *et al.*'s[82] review then undertook primary analysis of these two RAMs to estimate sensitivity and specificity for predicting VTE. This review included these data and a number of other studies[32,78–81] but only the study of Nemeth *et al.*[32] provided estimates of sensitivity and specificity.

The review is, therefore, limited by the paucity of data. Furthermore, case–control designs are known to be associated with a risk of bias,[213] so sensitivity and specificity may have been overestimated. The study by Watson *et al.*[82] was relatively small (21 cases and 21 controls), so estimates of sensitivity and specificity are imprecise. The study by Nemeth *et al.*[32] involved validation using two data sets but each only contained a small number of patients with lower-limb immobilisation (32 cases, 7 controls, and 143 cases, 8 controls, respectively).

Expert consensus study

The Delphi study involved a wide range of experts from emergency medicine, orthopaedics and haematology, and used recognised techniques to attempt to achieve consensus without supressing divergent views. There were acceptable levels of participation and the experts seemed to understand and engage with the process.

Expert consensus is considered to represent weak evidence and is usually sought only when (as in the case of VTE risk prediction in lower-limb immobilisation) other forms of evidence are weak or absent. It is hoped that experts will draw on weak evidence appropriately and combine it with clinical experience and pathophysiological understanding. However, experts may be subject to a number of cognitive biases that may influence their judgement. For example, the availability heuristic may lead experts to place undue emphasis on a risk predictor if they have seen a case in which a patient with that characteristic developed VTE after lower-limb immobilisation.

The Delphi process achieved consensus on 13 predictors but failed to achieve consensus on many more. This is perhaps unsurprising in the light of the limited evidence base relevant to the population of interest.

It could be argued that achieving consensus on 13 predictors reflects undue certainty in the light of the limited evidence to support these judgements.

Economic evaluation

A key strength of the de novo economic analysis is that it is able to synthesise the evidence on both benefits and harms to assess the overall impact of different thromboprophylaxis strategies in people having lower-limb immobilisation. Therefore, it was possible to explore the trade-off between preventing VTE and the adverse effects associated with prophylaxis, including the direct impact of subcutaneous injections of anticoagulants on patient quality of life. The estimates of clinical effectiveness were based on the systematic review and meta-analysis and the decision uncertainty associated with the uncertainty in the estimates of clinical effectiveness was captured in the model. The availability of the ROC curve for the L-TRiP(cast) score allowed us to explore what the optimal sensitivity and specificity might be for a tool to identify patients needing thromboprophylaxis when assuming that any future tool would have similar characteristics to L-TRiP(cast).

The main limitation of the economic analysis was that it was not possible to incorporate the uncertainty in the sensitivity and specificity estimates for the RAMs within the PSA as these were not reported. A scenario analysis was conducted, which suggested that the cost-effectiveness of using a RAM to guide thromboprophylaxis is dependent on the performance characteristics of the RAM, but it was not possible to quantify the decision uncertainty associated with the RAMs currently available.

Another potential limitation of the economic analysis is that a cohort modelling approach was used, which estimates outcomes based on average patient characteristics and, therefore, does not allow for heterogeneity in patient outcomes on the basis of patient characteristics. However, whether or not variation in outcomes on the basis of age would significantly alter the conclusions of the model was explored; it was found that the optimal thromboprophylaxis strategy was not sensitive to variations in age.

The estimate of the incidence of major bleeds during thromboprophylaxis was based solely on the incidence of GI bleeds and ICHs; therefore, this may have underestimated the impact on costs and QALYs of major bleeds at other sites. In addition, CRNMBs were excluded from the model. However, the sensitivity analyses suggest that neither of these factors is likely to have significantly biased the results, as incorporating costs for CRNMBs and increasing the risk of bleeding during thromboprophylaxis fivefold did not alter the main conclusions.

Another potential limitation is that many of the data sources quantifying the impact of VTE on patients, such as the incidence and quality-of-life impact of post-thrombotic syndrome following DVT, were not specific to patients having lower-limb immobilisation. Therefore, the benefits of thromboprophylaxis in this population may have been overestimated if the risks of complications following DVT are lower in patients having lower-limb immobilisation than in other groups at risk of VTE.

Uncertainties

The main uncertainty identified in the analysis related to the prognostic accuracy of RAMs. The estimates were based on very weak data but suggested that L-TRiP(cast) score, using a threshold score of 8 or 9, would be an optimal strategy. However, this conclusion holds only if the prognostic accuracy of L-TRiP(cast) is confirmed. More precise and accurate estimates of the prognostic accuracy of RAMs are required but this may be difficult to achieve if higher-risk patients receive thromboprophylaxis as standard care.

Most of the effectiveness data for thromboprophylaxis relate to LMWH, with a smaller number relating to fondaparinux. LMWH is administered by injection, thereby incurring additional costs and inconvenience for patients. DOACs are taken orally and, therefore, do not incur these additional costs and inconvenience. However, no studies evaluating the effectiveness of DOACs as thromboprophylaxis for lower-limb

immobilisation were found. DOACs have been used for thromboprophylaxis in other conditions and have been shown to be generally as safe and effective as LMWH.[214–216] On this basis, a secondary economic analysis was undertaken, assuming that DOACs were as effective as LMWH and could be delivered at lower cost and with less inconvenience. This suggested that at the £30,000-per-QALY threshold, DOACs would be cost-effective in a thromboprophylaxis-for-all strategy, even compared with an optimal RAM. The obvious uncertainty affecting this conclusion is whether or not it can be assumed that DOACs are at least as effective and safe as LMWH.

The value-of-information analysis showed that the most important parameters for decision uncertainty were the utility value for PTS, the effectiveness of thromboprophylaxis in reducing VTE, the probability of PTS for patients with distal DVT and the utility decrement associated with taking prophylaxis. The importance of uncertainty around PTS is consistent with the observation from the modelling that the benefit of thromboprophylaxis lies in avoiding long-term complications rather than avoiding short-term adverse outcomes. The utility decrement associated with taking prophylaxis is relevant to the potential role of DOACs discussed in the paragraph above, because most of the decreased utility is assumed to be as a result of the need to administer LMWH by injection.

The primary studies for the review of effectiveness, and, by implication, the economic model, excluded a number of important patient groups. Patients at a high risk of VTE, because of active cancer, previous VTE, pregnancy/puerperium or thrombophilia, were excluded but, as they have a higher risk of VTE, these patients are even more likely to benefit from thromboprophylaxis. Patients with an increased risk of bleeding were also excluded; these represent a more difficult group with regard to guiding recommendations. The model assumed a low risk of bleeding so, clearly, the findings of modelling analysis cannot be applied to this group. It may be possible to develop the model to provide estimates of overall effectiveness if bleeding risk is higher, but increased bleeding risk is often associated with conditions that also increase the risk of VTE. It is, therefore, unlikely that general recommendations can be made for those with an increased risk of bleeding and decisions will have to be made on an individual case-by-case basis.

The primary studies for the review of effectiveness were also generally limited to patients with full, rigid immobilisation and did not include those with more limited immobilisation, such as splints that allow a degree of movement and removable splints or casts. There are pathophysiological reasons for expecting the VTE risk to be lower for these patients and the benefit of thromboprophylaxis to be consequently lower or even negligible. However, current evidence is insufficient to determine whether or not this is the case and what, if any, role there may be for thromboprophylaxis.

Patient and public involvement

The patient and public involvement (PPI) representatives were involved in a number of elements of the study and met regularly with the project team to discuss the interpretation and implications of the emerging findings. The PPI representatives identified the following issues at these meetings:

- The risks and benefits of thromboprophylaxis need to be explained to patients in clear and comprehensible terms so that they can participate in decision-making. It would be helpful to provide this information in written form, along with information about the symptoms of VTE and what to do if they have concerns.
- It was considered acceptable to provide thromboprophylaxis in accordance with the patient's risk of VTE. It may be acceptable for patients to be involved in assessing their risk of VTE but this should be done in consultation with a health professional.
- If a risk-based approach was used and a patient was assessed as not requiring thromboprophylaxis on the basis of lack of cost-effectiveness when the risk is low, then they should be informed of the possible benefit of thromboprophylaxis in case they wish to arrange their own treatment.

- Use of LMWH for thromboprophylaxis has clear disadvantages related to the inconvenience and discomfort of injections. Oral treatment would be much more acceptable but the risks of DOACs need to be explained to patients, specifically the lack of a means of reversing DOACs in the event of bleeding. The lack of research into the use of DOACs as thromboprophylaxis for lower-limb immobilisation was also a concern.
- If the risk of adverse outcome is low (i.e. < 1 in 100), then patients may not think the benefit of thromboprophylaxis is worth the inconvenience and discomfort of LMWH.
- An implementation study of risk-based thromboprophylaxis, potentially involving comparison of different approaches, would be acceptable provided it was justified on the basis of current practice being variable and the need to identify best practice.

Assessment of factors relevant to the NHS and other parties

Current NICE guidance[1] recommends that clinicians consider pharmacological VTE prophylaxis with LMWH or fondaparinux for people with lower-limb immobilisation whose risk of VTE outweighs their risk of bleeding. This analysis suggests that the risk of VTE outweighs the risk of bleeding for any patient who does not have risk factors for bleeding. The review for the NICE guidance[1] did not identify any relevant economic evidence and only considered the unit costs for different agents (LMWH and fondaparinux). This economic analysis showed that thromboprophylaxis with LMWH is cost-effective compared with no thromboprophylaxis and a risk-based strategy is potentially optimal, when valuing a QALY at £20,000 to £30,000. The NICE guidance[1] also recommends that clinicians assess all patients to identify the risk of VTE and bleeding, but does not identify or recommend any specific RAM for lower-limb immobilisation. This analysis suggests that the L-TRiP(cast) score with a threshold score of 8 or 9 could have appropriate prognostic accuracy for cost-effective risk stratification in lower-limb immobilisation but the available estimates of prognostic accuracy are very uncertain.

Chapter 6 Conclusions

Implications for service provision

The meta-analysis of effectiveness suggested that thromboprophylaxis in lower-limb immobilisation due to injury approximately halves the risk of any VTE and is associated with reductions in the risks of symptomatic DVT and PE. However, the evidence is limited to LMWH and fondaparinux, so it is unclear whether or not the findings can be extrapolated to DOACs. This in an important consideration as the absolute risks of clinically relevant VTE are low and patients may not be willing to submit to the inconvenience of parenteral treatment to reduce a relatively small risk.

The economic analysis suggested that thromboprophylaxis is effective and cost-effective compared with no thromboprophylaxis, so it would be reasonable to offer thromboprophylaxis to patients undergoing lower-limb immobilisation due to injury. This is based on the potential for thromboprophylaxis to reduce the risk of DVT and PE, with their long-term sequelae, rather than any meaningful reduction in the risk of mortality. The economic analysis also suggested that risk-based thromboprophylaxis using a RAM with a sensitivity of 84–89% and specificity of 46–55% is, potentially, the most cost-effective approach. This is similar to the prognostic accuracy of the L-TRiP(cast) score using a threshold score of 8 or 9, although estimates of sensitivity and specificity are very uncertain.

The cost-effectiveness of using an appropriate RAM is based on (1) reducing the number of people requiring thromboprophylaxis (and thus costs) compared with thromboprophylaxis for all, with only a small reduction in effectiveness and (2) increasing the number of VTE events prevented (and this effectiveness) compared with no thromboprophylaxis, with only a small increase in costs. Assuming universal acceptance by patients, a risk-based strategy, as outlined in the previous paragraph, would cost the English NHS £6M per year and gain 891 QALYs compared with no thromboprophylaxis. Compared with this, providing thromboprophylaxis for all would cost an additional £8.2M per year and gain an additional 160 QALYs. These estimates are not intended to be precise figures, as strategies are unlikely to be implemented perfectly and patients may decline treatment, but they provide an indication of the potential implications of different strategies for service provision.

The PPI representatives highlighted the importance of patient involvement in decision-making and the need for clear and comprehensible information to be provided. This has important implications for service provision. To participate in shared decision-making, patients need to understand that the risk of clinically important VTE is relatively low but that it can be reduced by thromboprophylaxis. The effectiveness of thromboprophylaxis relies on the benefits of reducing DVT and PE (and their sequelae), outweighing a small increase in the risk of bleeding, but VTE events may still occur despite thromboprophylaxis. The risks of death from VTE or bleeding after immobilisation due to injury are very small regardless of the treatment strategy, and thromboprophylaxis is unlikely to have any significant impact on the risk of death.

Suggested research priorities

This analysis suggested that risk-based thromboprophylaxis using a RAM with sensitivity of 84–89% and specificity of 46–55% would be the most cost-effective strategy. However, the current evidence base for RAMs is very limited and estimates of sensitivity and specificity are subject to substantial uncertainty. Improving the evidence base for RAMs is therefore a key priority.

Ideally, a large prognostic cohort study of people experiencing lower-limb immobilisation due to injury would be undertaken to estimate the prognostic accuracy of existing RAMs for VTE and possibly derive a new RAM. However, the evidence of effectiveness and cost-effectiveness provided by this analysis suggests that thromboprophylaxis should be offered to patients in this cohort, or at least those considered as being at a higher risk. Administration of thromboprophylaxis would be expected to reduce the risk of VTE and thus lead to underestimation of the prognostic accuracy of RAMs. Furthermore, the VTE events that were prevented by thromboprophylaxis would be precisely those that we would want a RAM to predict.

A large cohort study could still provide useful information if it is used to evaluate implementation rather than accuracy. It could determine the proportion of the cohort receiving thromboprophylaxis with different RAMs or different thresholds for treatment. It could be used to determine whether or not the low rate of bleeding events is confirmed in practice and, if risk-based thromboprophylaxis were provided, it could be used to determine whether or not the low rate of VTE events is confirmed in low-risk patients who do not receive treatment.

Direct oral anticoagulants could provide the benefits of thromboprophylaxis without the costs, inconvenience and discomfort of injections, which the PPI representatives identified as a potential barrier to patient acceptance. However, all the evidence of effectiveness in this review related to LMWH or fondaparinux. Ideally, an appropriately powered RCT comparing thromboprophylaxis of DOACs with LMWH would provide evidence of equivalent effectiveness, but such a trial may be prohibitively expensive, especially if it were felt that evidence of effectiveness of DOAC for other indications could be reasonably extrapolated to lower-limb immobilisation.

The most important parameters for decision uncertainty in the value-of-information analysis were related to the efficacy and disutility of receiving prophylaxis, and the long-term complications of PTS, so estimating these parameters should be a priority for future research. The disutility of receiving LMWH injections or oral DOACs could be investigated as part of a cohort study or trial of different types of thromboprophylaxis. The uncertainty around the long-terms effects of PTS mainly relate to subclinical DVT rather than clinically detected and treated DVT, so research to reduce uncertainty around the incidence and disutility of PTS would need to involve long-term follow-up or a retrospective observational study of people following lower-limb immobilisation due to injury.

It is currently unclear whether or not people with limited lower-limb immobilisation (such as splints that allow some movement or removable splints or casts) carry similar risks of VTE to those with full immobilisation. A cohort study of this population, perhaps undertaken alongside a cohort study evaluating risk-based thromboprophylaxis, could determine the risk of VTE and identify risk predictors.

All of these research suggestions would require large numbers of participants to generate meaningful results. There are plenty of eligible participants presenting to the NHS but an efficient research design would be required, using standardised collection of predictor variables and routine data sources for outcomes, to ensure that any study was not prohibitively expensive.

Finally, the PPI representatives identified the need for patients to receive clear and comprehensible communication of the risks and benefits of thromboprophylaxis, including written materials. Research is required to develop information for patients and ways of communicating benefits and risks.

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Abdullah Pandor (Senior Research Fellow) co-ordinated the review and was responsible for the design of the study, acquisition of data, analysis and interpretation of data (for the systematic review), and drafting and revision of the final report.

Daniel Horner (Professor at the Royal College of Emergency Medicine and Substantive NHS Consultant Emergency Physician) was responsible for the conception and design of the study, acquisition of data, analysis and interpretation of data (for the systematic reviews and health economic evaluations), and drafting and revision of the final report.

Sarah Davis (Senior Lecturer) was responsible for the design of the study, acquisition of data, analysis and interpretation of data and model construction (for the health economic evaluations), and drafting and revision of the final report.

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John W Stevens (Reader in Decision Science) was responsible for the design of the study, statistical analyses, interpretation of data, and drafting and revision of the final report.

Mark Clowes (Information Specialist) was responsible for developing and undertaking the electronic literature searches.

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Tim Nokes (Consultant Haematologist) was responsible for the design of the study, interpretation of data (for the systematic reviews and health economic evaluations), and drafting and revision of the final report.

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Kerstin de Wit (Assistant Professor and Thrombosis Physician) was responsible for the design of the study, interpretation of data (for the systematic reviews and health economic evaluations), and drafting and revision of the final report.

Publications

Horner D, Pandor A, Goodacre S, Clowes M, Hunt BJ. Individual risk factors predictive of venous thromboembolism in patients with temporary lower limb immobilisation due to injury: a systematic review. *J Thromb Haemost* 2019;**17**:329–44.

Davis S, Goodacre S, Pandor A, Horner D, Stevens JW, de Wit K, Hunt BJ. Decision-analysis modelling of the effects of thromboprophylaxis for people with lower limb immobilisation for injury. *Br J Haematol* 2019;**186**:130–95.

Horner D, Stevens J, Pandor A, Nokes T, Keenan J, de Wit K, Goodacre S. Pharmacological thromboprophylaxis to prevent venous thromboembolism in patients with temporary lower limb immobilisation after injury: a systematic review and network meta-analysis [published online ahead of print October 26 2019]. *J Thromb Haemost* 2019.

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Data-sharing statement

Most of the data used in this study are already publicly available. Requests for access to other data should be addressed to the corresponding author for consideration.

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Appendix 1 Literature search strategies for the review of pharmacological thromboprophylaxis for preventing venous thromboembolism

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Platform or provider used: Ovid SP.

Date range searched: 1946 to April 2017.

Date searched: April 2017.

Search strategy

1. thrombosis/ or exp venous thrombosis/
2. Venous Thromboembolism/ or Thromboembolism/
3. exp Pulmonary Embolism/
4. (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab,kw.
5. ((vein* or ven*) adj7 thromb*).ti,ab,kw.
6. (PE or DVT or VTE).ti,ab,kw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Immobilization/
9. exp Mobility Limitation/
10. Splints/
11. Braces/
12. exp Casts, Surgical/
13. immobili*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. brace*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. splint*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. plaster*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. cast.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. (leg* or tibia* or fibula* or ankle*).mp. and (fracture*.hw. or su.fs.) and co.fs.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp Heparin, Low-Molecular-Weight/

21. (heparin* or LMWH or nadroparin* or fraxiparin* or enoxaparin or Clexane or klexane or lovenox or dalteparin or Fragmin or ardeparin or normiflo or tinzaparin or logiparin or Innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or bemiparin or bioparin or Alphaparin or Troparin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22. (antixarin or ardeparin* or bemiparin* or Zibor or cy 222 or embolex or monoembolex or Mono-embolex or parnaparin* or "rd 11885" or tedelparin or Kabi-2165 or Kabi 2165).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
23. (emt-966 or emt-967 or pk-10169 or pk10169).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
24. (cy-216 or cy216 or seleparin* or tedegliparin or seleparin* or tedegliparin* or tedelparin or Boxol or Liquemine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25. fr-860.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26. (wy90493 or wy-90493).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27. (kb-101 or kb101 or lomoparan or orgaran).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
28. (parnaparin or fluxum or lohepa or lowhepa or "op 2123" or parvoparin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
29. (AVE5026 or M118 or RO-14).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
30. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. (Rivaroxaban or xarelto or Apixaban or eliquis or Edoxaban or lixiana or Dabigatran or pradaxa or prazaxa or Praxibind or idaricuzimab).mp.
32. (novel oral anticoagulant* or novel oral anti-coagulant* or (new adj3 (anticoagulant* or anti-coagulant*))).mp.
33. (direct oral anticoagulant* or direct oral anti-coagulant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
34. (NOAC* or DOAC*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
35. exp Aspirin/
36. (acetylsalicylic acid* or aspirin).mp.
37. 31 or 32 or 33 or 34 or 35 or 36
38. 7 and 19 and 30
39. limit 38 to yr="2013 -Current"
40. 7 and 19 and 37
41. 39 or 40

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Review of Effects, Health Technology Assessment Database and NHS Economic Evaluation Database

Platform or provider used: Wiley Online Library.

Date range searched: 1898 to April 2017.

Date searched: April 2017.

Search strategy

#1 MeSH descriptor: [Thrombosis] explode all trees
#2 MeSH descriptor: [Venous Thrombosis] explode all trees
#3 MeSH descriptor: [Thromboembolism] explode all trees
#4 MeSH descriptor: [Venous Thromboembolism] explode all trees
#5 MeSH descriptor: [Pulmonary Embolism] explode all trees
#6 (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw (Word variations have been searched)
#7 ((vein* or ven*) near/7 thromb*):ti,ab,kw
#8 (PE or DVT or VTE):ti,ab,kw
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Immobilization] explode all trees
#11 MeSH descriptor: [Mobility Limitation] explode all trees
#12 MeSH descriptor: [Splints] explode all trees
#13 MeSH descriptor: [Braces] explode all trees
#14 MeSH descriptor: [Casts, Surgical] explode all trees
#15 (immobili* or brace* or splint* or plaster* or cast):ti,ab,kw
#16 ((leg* or tibia* or fibula* or ankle*) and (fracture* or surg*) and complication*):ti,ab,kw
#17 #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees
#19 (heparin* or LMWH or nadroparin* or fraxiparin* or enoxaparin or Clexane or klexane or lovenox or dalteparin or Fragmin or ardeparin or normiflo or tinzaparin or logiparin or Innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or bemiparin or bioparin or Alphaparin or Troparin):ti,ab,kw
#20 (antixarin or ardeparin* or bemiparin* or Zibor or cy 222 or embolex or monoembolex or Mono-embolex or parnaparin* or "rd 11885" or tedelparin or Kabi-2165 or Kabi 2165):ti,ab,kw
#21 (emt-966 or emt-967 or pk-10169 or pk10169):ti,ab,kw
#22 fr-860:ti,ab,kw
#23 (wy90493 or wy-90493 or kb-101 or kb101 or lomoparan or orgaran or parnaparin or fluxum or lohepa or lowhepa or "op 2123" or parvoparin or AVE5026 or M118 or RO-14):ti,ab,kw
#24 #18 or #19 or #20 or #21 or #22 or #23
#25 #9 and #17 and #24 Publication Year from 2013 to 2017
#26 MeSH descriptor: [Anticoagulants] explode all trees
#27 (Rivaroxaban or xarelto or Apixaban or eliquis or Edoxaban or lixiana or Dabigatran or pradaxa or prazaxa or praxibind or idaricuzimab):ti,ab,kw
#28 (novel oral anticoagulant* or novel oral anti-coagulant* or (new near/3 (anticoagulant* or anti-coagulant*))):ti,ab,kw
#29 (direct oral anticoagulant* or direct oral anti-coagulant*):ti,ab,kw
#30 (NOAC* or DOAC*):ti,ab,kw
#31 MeSH descriptor: [Aspirin] explode all trees
#32 (acetylsalicylic acid* or aspirin):ti,ab,kw

#33 #26 or #27 or #28 or #29 or #30 or #31 or #32
#34 #9 and #17 and #33
#35 #25 or #34

EMBASE

Platform or provider used: Ovid SP.

Date range searched: 1974 to April 2017.

Date searched: April 2017.

Search strategy

1. thrombosis/ or exp vein thrombosis/ or deep vein thrombosis/
2. Venous Thromboembolism/ or Thromboembolism/
3. exp lung embolism/
4. (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab,kw.
5. ((vein* or ven*) adj7 thromb*).ti,ab,kw.
6. (PE or DVT or VTE).ti,ab,kw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Immobilization/
9. exp Mobility Limitation/
10. Splints/
11. Braces/
12. exp Casts, Surgical/
13. immobili*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
14. brace*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
15. splint*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
16. plaster*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
17. cast.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
18. (leg* or tibia* or fibula* or ankle*).mp. and (fracture*.hw. or su.fs.) and co.fs.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
20. exp Heparin, Low-Molecular-Weight/
21. (heparin* or LMWH or nadroparin* or fraxiparin* or enoxaparin or Clexane or klexane or lovenox or dalteparin or Fragmin or ardeparin or normiflo or tinzaparin or logiparin or Innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or bemiparin or bioparin or Alphaparin or Troparin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
22. (antixarin or ardeparin* or bemiparin* or Zibor or cy 222 or embolex or monoembolex or Mono-embolex or parnaparin* or "rd 11885" or tedelparin or Kabi-2165 or Kabi 2165).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
23. (emt-966 or emt-967 or pk-10169 or pk10169).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

24. (cy-216 or cy216 or seleparin* or tedegliparin or seleparin* or tedegliparin* or tedelparin or Boxol or Liquemine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
25. fr-860.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
26. (wy90493 or wy-90493).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
27. (kb-101 or kb101 or lomoparan or orgaran).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
28. (parnaparin or fluxum or lohepa or lowhepa or "op 2123" or parvoparin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
29. (AVE5026 or M118 or RO-14).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
30. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. (Rivaroxaban or xarelto or Apixaban or eliquis or Edoxaban or lixiana or Dabigatran or pradaxa or prazaxa or Praxibind or idaricuzimab).mp.
32. (novel oral anticoagulant* or novel oral anti-coagulant* or (new adj3 (anticoagulant* or anti-coagulant*))).mp.
33. (direct oral anticoagulant* or direct oral anti-coagulant*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
34. (NOAC* or DOAC*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
35. acetylsalicylic acid/
36. (acetylsalicylic acid* or aspirin).mp.
37. 31 or 32 or 33 or 34 or 35 or 36
38. 7 and 19 and 30
39. limit 38 to yr="2013 -Current"
40. 7 and 19 and 37
41. 39 or 40

Appendix 2 Excluded studies: review of pharmacological thromboprophylaxis for preventing venous thromboembolism

TABLE 26 Excluded studies with rationale: review of pharmacological thromboprophylaxis for preventing VTE

Number	Authors, year	Reason for exclusion
1	Blackwell *et al.*,[218] 2017	Not a randomised or controlled clinical trial
2	Braithwaite *et al.*,[22] 2016	Not a randomised or controlled clinical trial
3	Calder *et al.*,[219] 2016	Systematic review
4	Chapelle *et al.*,[220] 2014	Systematic review
5	Doggrell *et al.*,[221] 2003	Review (non-systematic)
6	Ettema *et al.*,[36] 2008	Systematic review
7	Griffiths *et al.*,[222] 2012	Not a randomised or controlled clinical trial
8	Haque and Davies,[223] 2015	Not a randomised or controlled clinical trial
9	Hickey *et al.*,[224] 2016	Systematic review
10	Kaye *et al.*,[225] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
11	Kock *et al.*,[226] 1993	Duplicate of included full-text study: Kock *et al.*[52]
12	Little,[227] 2016	Commentary
13	López-Reyes *et al.*,[217] 2015	Not a randomised or controlled clinical trial (letter to the editor)
14	Mangwani *et al.*,[228] 2015	Systematic review
15	Menakaya *et al.*,[229] 2013	Not a randomised or controlled clinical trial
16	Metz *et al.*,[230] 2009	Systematic review
17	Ramos *et al.*,[231] 2008	Systematic review
18	Samama *et al.*,[232] 2014	Duplicate of an included full-text study: Samama *et al.*,[57] 2013
19	Samama *et al.*,[233] 2013 (abstract)	Abstract of an included full-text study: Samama *et al.*,[57] 2013
20	Samama *et al.*,[234] 2013	Subgroup results of an included full-text study: Samama *et al.*,[57] 2013
21	Spannagel and Kujath,[235] 1993	Duplicate of included full text study: Kujath *et al.*,[53] 1993
22	Testroote *et al.*,[15] 2014	Systematic review
23	Walenga *et al.*,[236] 2014	Substudy of an included full-text study (Lassen *et al.*,[56] 2002) – focus on biomarker evaluation

Appendix 3 Summary of trials included in the base-case network meta-analysis of pharmacological thromboprophylaxis for preventing venous thromboembolism

TABLE 27 Summary of outcomes: any VTE and clinically relevant DVT

		Any VTE						Clinically relevant DVT (i.e. symptomatic or proximal/extensive)					
		LMWH		Fondaparinux		Control		LMWH		Fondaparinux		Control	
Authors, year	Comparison	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[a] *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[b] *n* (%)
Goel *et al.*,[50] 2009	LMWH vs. placebo	11	127 (8.7)	–	–	14	111 (12.6)	0	127 (0.0)	–	–	0	111 (0.0)
Jørgensen *et al.*,[51] 2002	LMWH vs. no treatment	10	99 (10.1)	–	–	18	106 (17.0)	0	99 (0.0)	–	–	1	106 (0.9)
Kock *et al.*,[52] 1995	LMWH vs. no treatment	0	176 (0)	–	–	7	163 (4.3)	0	176 (0.0)	–	–	5	163 (3.1)
Kujath *et al.*,[53] 1993	LMWH vs. no treatment	6	126 (4.8)	–	–	21	127 (16.5)	–	–	–	–	–	–
Lapidus *et al.*,[55] 2007	LMWH vs. placebo	18	49 (36.7)	–	–	19	47 (40.4)	1	49 (2.0)	–	–	3	47 (6.4)
Lapidus *et al.*,[54] 2007	LMWH vs. placebo	24	117 (20.5)	–	–	34	109 (31.2)	2	117 (1.7)	–	–	6	109 (5.5)
Lassen *et al.*,[56] 2002	LMWH vs. placebo	17	183 (9.3)	–	–	35	188 (18.6)	–	–	–	–	–	–
Selby *et al.*,[58] 2015	LMWH vs. placebo	4	130 (3.1)	–	–	4	128 (3.1)	2	130 (1.5)	–	–	2	128 (1.6)
van Adrichem *et al.*,[59] 2017	LMWH vs. no treatment	10	719 (1.4)	–	–	13	716 (1.8)	7	719 (1.0)	–	–	9	716 (1.3)
Zheng *et al.*,[60] 2016	LMWH vs. placebo	6	411 (1.5)	–	–	13	403 (3.2)	1	411 (0.2)	–	–	6	403 (1.5)
Gehling *et al.*,[23] 1998	LMWH vs. aspirin	9	143 (6.3)	–	–	7	144 (4.9)	2	143 (1.4)	–	–	1	144 (0.7)
Bruntink *et al.*,[49] 2017	LMWH vs. fondaparinux vs. no treatment	2	92 (2.2)	1	92 (1.1)	11	94 (11.7)	–	–	–	–	–	–
Samama *et al.*,[57] 2013	LMWH vs. fondaparinux	49	622 (7.9)	14	621 (2.3)	–	–	10	622 (1.6)	6	621 (1.0)	–	–

a Median incidence in control group, 12.2%.
b Median incidence in control group, 1.5%.

TABLE 28 Summary of outcomes: clinically detected DVT and asymptomatic DVT (all)

		Clinically detected DVT (i.e. symptomatic)						Asymptomatic DVT (all)					
		LMWH		Fondaparinux		Control		LMWH		Fondaparinux		Control	
Authors, year	Comparison	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[a] *n* (%)	Events, *n*	Total,[b] *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[b] *n* (%)
Goel *et al.*,[50] 2009	LMWH vs. placebo	0	127 (0.0)	–	–	0	111 (0.0)	11	127 (8.7)	–	–	14	111 (12.6)
Jørgensen *et al.*,[51] 2002	LMWH vs. no treatment	0	99 (0.0)	–	–	0	106 (0.0)	10	99 (10.1)	–	–	18	106 (17.0)
Kock *et al.*,[52] 1995	LMWH vs. no treatment	0	176 (0.0)	–	–	4	163 (2.5)	0	176 (0.0)	–	–	3	163 (1.8)
Kujath *et al.*,[53] 1993	LMWH vs. no treatment	–	–	–	–	–	–	–	–	–	–	–	–
Lapidus *et al.*,[55] 2007	LMWH vs. placebo	–	–	–	–	–	–	–	–	–	–	–	–
Lapidus *et al.*,[54] 2007	LMWH vs. placebo	2	117 (1.7)	–	–	6	109 (5.5)	22	117 (18.8)	–	–	28	109 (25.7)
Lassen *et al.*,[56] 2002	LMWH vs. placebo	0	183 (0.0)	–	–	4	188 (2.1)	17	183 (9.3)	–	–	31	188 (16.5)
Selby *et al.*,[58] 2015	LMWH vs. placebo	1	130 (0.8)	–	–	1	128 (0.8)	3	130 (2.3)	–		2	128 (1.6)
van Adrichem *et al.*,[59] 2017	LMWH vs. no treatment	7	719 (1.0)	–	–	9	716 (1.3)	–	–	–	–	–	–
Zheng *et al.*,[60] 2016	LMWH vs. placebo	0	411 (0.0)	–	–	0	403 (0.0)	6	411 (1.5)	–	–	13	403 (3.2)
Gehling *et al.*,[23] 1998	LMWH vs. aspirin	2	143 (1.4)	–	–	1	144 (0.7)	7	143 (4.9)	–	–	6	144 (4.2)
Bruntink *et al.*,[49] 2017	LMWH vs. fondaparinux vs. no treatment	0	92 (0.0)	0	92 (0.0)	0	94 (0.0)	2	92 (2.2)	1	92 (1.1)	9	94 (9.6)
Samama *et al.*,[57] 2013	LMWH vs. fondaparinux	7	622 (1.1)	2	621 (0.3)	–	–	42	622 (6.8)	11	621 (1.8)	–	–

a Median incidence in control group, 0.7%.
b Median incidence in control group, 6.9%.

TABLE 29 Summary of outcomes: asymptomatic proximal and distal DVT

		Asymptomatic DVT (proximal)						Asymptomatic DVT (distal)					
		LMWH		Fondaparinux		Control		LMWH		Fondaparinux		Control	
Authors, year	Comparison	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[a] *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[b] *n* (%)
Goel *et al.*,[50] 2009	LMWH vs. placebo	0	127 (0.0)	–	–	0	111 (0.0)	11	127 (8.7)	–	–	14	111 (12.6)
Jørgensen *et al.*,[51] 2002	LMWH vs. no treatment	0	99 (0.0)	–	–	1	106 (0.9)	10	99 (10.1)	–	–	17	106 (16.0)
Kock *et al.*,[52] 1995	LMWH vs. no treatment	0	176 (0.0)	–	–	1	163 (0.6)	0	176 (0.0)	–	–	2	163 (1.2)
Kujath *et al.*,[53] 1993	LMWH vs. no treatment	–	–	–	–	–	–	–	–	–	–	–	–
Lapidus *et al.*,[55] 2007	LMWH vs. placebo	1	49 (2.0)	–	–	3	47 (6.4)	–	–	–	–	–	–
Lapidus *et al.*,[54] 2007	LMWH vs. placebo	–	–	–	–	–	–	–	–	–	–	–	–
Lassen *et al.*,[56] 2002	LMWH vs. placebo	–	–	–	–	–		14	183 (7.7)	–	–	21	188 (11.2)
Selby *et al.*,[58] 2015	LMWH vs. placebo	1	130 (0.8)	–	–	1	128 (0.8)	2	130 (1.5)	–	–	1	128 (0.8)
van Adrichem *et al.*,[59] 2017	LMWH vs. no treatment	–	–	–	–	–	–	–	–	–	–	–	–
Zheng *et al.*,[60] 2016	LMWH vs. placebo	1	411 (0.2)	–	–	6	403 (1.5)	5	411 (1.2)	–	–	7	403 (1.7)
Gehling *et al.*,[23] 1998	LMWH vs. aspirin	0	143 (0.0)	–	–	0	144 (0.0)	7	143 (4.9)	–	–	6	144 (4.2)
Bruntink *et al.*,[49] 2017	LMWH vs. fondaparinux vs. no treatment	–	–	–	–	–	–	–	–	–	–	–	–
Samama *et al.*,[57] 2013	LMWH vs. fondaparinux	3	585 (0.5)	4	582 (0.7)	–	–	39	585 (6.7)	7	582 (1.2)	–	–

a Median incidence in control group, 0.7%.
b Median incidence in control group, 3.0%.

TABLE 30 Summary of outcomes: PE and major bleeding

		PE						Major bleeding					
		LMWH		Fondaparinux		Control		LMWH		Fondaparinux		Control	
Authors, year	Comparison	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[a] *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total, *n* (%)	Events, *n*	Total,[b] *n* (%)
Goel *et al.*,[50] 2009	LMWH vs. placebo	0	127 (0.0)	–	–	0	111 (0.0)	0	127 (0.0)	–	–	0	111 (0.0)
Jørgensen *et al.*,[51] 2002	LMWH vs. no treatment	0	99 (0.0)	–	–	0	106 (0.0)	0	99 (0.0)	–	–	0	106 (0.0)
Kock *et al.*,[52] 1995	LMWH vs. no treatment	0	176 (0.0)	–	–	0	163 (0.0)	0	176 (0.0)	–	–	0	163 (0.0)
Kujath *et al.*,[53] 1993	LMWH vs. no treatment	0	126 (0.0)	–	–	0	127 (0.0)	0	126 (0.0)	–	–	0	127 (0.0)
Lapidus *et al.*,[55] 2007	LMWH vs. placebo	0	49 (0.0)	–	–	0	47 (0.0)	0	49 (0.0)	–	–	0	47 (0.0)
Lapidus *et al.*,[54] 2007	LMWH vs. placebo	0	117 (0.0)	–	–	0	109 (0.0)	0	117 (0.0)	–	–	0	109 (0.0)
Lassen *et al.*,[56] 2002	LMWH vs. placebo	0	183 (0.0)	–	–	2	188 (1.1)	2	217 (0.9)	–	–	1	221 (0.5)
Selby *et al.*,[58] 2015	LMWH vs. placebo	0	130 (0.0)	–	–	1	128 (0.8)	0	134 (0.0)	–	–	0	131 (0.0)
van Adrichem *et al.*,[59] 2017	LMWH vs. no treatment	4	719 (0.6)	–	–	5	716 (0.7)	0	719 (0.0)	–	–	0	716 (0.0)
Zheng *et al.*,[60] 2016	LMWH vs. placebo	0	411 (0.0)	–	–	0	403 (0.0)	0	411 (0.0)	–	–	0	403 (0.0)
Gehling *et al.*,[23] 1998	LMWH vs. aspirin	0	143 (0.0)	–	–	0	144 (0.0)	0	143 (0.0)	–	–	0	144 (0.0)
Bruntink *et al.*,[49] 2017	LMWH vs. fondaparinux vs. no treatment	0	92 (0.0)	0	92 (0.0)	2	94 (2.1)	0	92 (0.0)	0	92 (0.0)	0	94 (0.0)
Samama *et al.*,[57] 2013	LMWH vs. fondaparinux	0	622 (0.0)	2	621 (0.3)	–	–	0	670 (0.0)	1	674 (0.1)	–	–

a Median incidence in control group, 0%.
b Median incidence in control group, 0%.

Appendix 4 Details of the network meta-regressions

The following potential treatment effect modifiers were assessed: (1) population characteristics (i.e. proportion that were male, baseline risk of VTE), (2) type of injury (i.e. fractures, Achilles tendon rupture, other soft-tissue injury), (3) treatment of injury (surgical vs. conservative, above- vs. below-knee immobilisation), (4) thromboprophylactic agent used and (5) duration of thromboprophylaxis.

For each outcome of interest, except for major bleeding, a network meta-regression of the potential treatment effect modifiers 1–3 and 5 was performed separately for each covariate using an approach similar to that described in *Chapter 3*, *Methods of data synthesis and analysis*. The analyses were performed by centring the covariates at their mean values of the reference treatment (i.e. placebo, no treatment and aspirin) to improve mixing of the Markov chain Monte Carlo chains. In each model, the regression parameter was given a normally distributed prior distribution with mean 0 and variance 1000, that is N(0, 1000). Only Lassen *et al.*[56] and Samama *et al.*[57] provided information about major bleeding. Consequently, a meta-regression of major bleeding was not performed.

The analysis of the effect of the baseline risk of VTE was performed with respect to the true baseline rather than the sample estimate of the baseline in order to avoid regression to the mean. Simultaneously assessing the effect of three types of injury would have involved a model with two covariates to estimate in relatively sparse data sets; in practice, only the effect of fractures versus other types of injury was assessed. The effect of the management of the injury using a surgical or conservative approach, and the method of immobilisation (i.e. whether above or below the knee), were assessed separately. Several studies (i.e. Kujath *et al.*,[53] Samama *et al.*,[57] Selby *et al.*,[58] van Adrichem *et al.*[59] and Zheng *et al.*[60]) provided insufficient information to allow a classification of whether the immobilisation was above or below the knee; these studies were excluded from the meta-regression.

In a network meta-regression, three assumptions can be made about the interaction between a covariate and each treatment effect: (1) independent – treatment-specific interaction terms for each pair of treatments, (2) exchangeable – treatment-specific but related interaction terms and (3) identical interaction effects for all treatments. Given the relative sparseness of the data, the analysis was performed by only assuming identical interaction terms for all treatments.

The effect of the type of thromboprophylactic agent used (i.e. dalteparin, tinzaparin, certoparin nadroparin, reviparin) was assessed using a separate NMA. Van Adrichem *et al.*[59] allowed nadroparin or dalteparin to be used in accordance with the preference of each hospital and no further information was provided as to what was actually used. No information was available on the LMWH used in Zheng *et al.*[60] Therefore, Van Adrichem *et al.*[59] and Zheng *et al.*[60] were excluded from the analysis.

The unadjusted and covariate-adjusted models were compared using the deviance information criterion. Models fitted to a particular data set that have lower deviance information criterion values provide the best predictions. However, differences in deviance information criterion values of < 5 are generally not important and the simpler model is generally preferred, irrespective of the estimated effect of individual parameters. In addition, deviation information criterion values can only be compared for models applied to the same data sets. Consequently, it is not possible to compare unadjusted and adjusted models with respect to the effect of immobilisation above or below the knee, or the type of thromboprophylactic agent used, because the analyses make use of data from different studies.

It was not possible to use data from all the studies in all the analyses. Gehling *et al.*[23] and Goel *et al.*[50] had no asymptomatic DVT proximal events and, consequently, provided no information with which to estimate treatment effects or the effects of potential treatment effect modifiers. Jørgensen *et al.*,[51] Goel *et al.*,[50] Bruntink *et al.*[49] and Zheng *et al.*[60] had no clinically detected DVT events and, consequently, provided no information with which to estimate treatment effects or the effects of potential treatment effect modifiers.

Goel *et al.*[50] had no clinically relevant DVT events and, consequently, provided no information with which to estimate treatment effects or the effects of potential treatment effect modifiers. Only Lassen *et al.*,[56] Samama *et al.*,[57] Selby *et al.*,[58] Bruntink *et al.*[49] and van Adrichem *et al.*[59] had PEs; all other studies provided no information with which to estimate treatment effects or the effects of potential treatment effect modifiers.

Table 31 shows the results of the network meta-regression for all potential effect modifiers except thromboprophylactic agent used. Results according to the proportion of patients with immobilisation below the knee should be treated with caution as the model is fitted to a subset of the data and it is not possible to compare the fit of this model with that of the unadjusted model. The adjusted deviance information criterion suggested that no covariate improved the model fits.

TABLE 31 Network metaregression for all potential effect modifiers except thromboprophylactic agent used

Covariate	No treatment[a]	Adjusted DIC	Regression parameter coefficient (95% CI)
Any VTE (unadjusted DIC = 157.6)			
Proportion male	56	159.1	0.007 (–0.029 to 0.043)
Baseline VTE (%; logit)	0.10 (–2.214)	159.5	–0.024 (–0.358 to 0.299)
Type of injury: proportion fractures	68	158.9	0.003 (–0.007 to 0.015)
Treatment of injury: proportion surgery	63	153.6	0.009 (0.002 to 0.018)
Treatment of injury: proportion below knee	91	N/A	–0.001 (–0.043 to 0.041)
Duration of thromboprophylaxis (days)	28	159.2	0.005 (–0.021 to 0.033)
Asymptomatic DVT (all) (unadjusted DIC = 113.9)			
Proportion male	54	115.8	–0.005 (–0.064 to 0.053)
Baseline VTE (%; logit)	0.12 (–2.039)	172.1	–0.003 (–0.452 to 0.445)
Type of injury: proportion fractures	85	114.6	0.015 (–0.011 to 0.050)
Treatment of injury: proportion surgery	71	112.1	0.012 (–0.000 to 0.026)
Treatment of injury: proportion below knee	90	N/A	–0.005 (–0.045 to 0.034)
Duration of thromboprophylaxis (days)	27	115.6	–0.005 (–0.035 to 0.025)
Asymptomatic DVT (distal) (unadjusted DIC = 84.4)			
Proportion male	56	85.6	–0.040 (–0.153 to 0.059)
Baseline VTE (%; logit)	0.10 (–2.249)	128.8	–0.172 (–0.879 to 0.510)
Type of injury: proportion fractures	81	84.7	0.022 (–0.011 to 0.070)
Treatment of injury: proportion surgery	77	85.1	0.013 (–0.009 to 0.044)
Treatment of injury: proportion below knee	85	N/A	–0.003 (–0.057 to 0.050)
Duration of thromboprophylaxis (days)	23	86.2	–0.005 (–0.045 to 0.038)
Asymptomatic DVT (proximal) (unadjusted DIC = 44.8)			
Proportion male	60	46.6	–0.018 (–0.205 to 0.148)
Baseline VTE (%; logit)	0.11 (–2.141)	89.3	–0.060 (–1.467 to 1.123)
Type of injury: proportion fractures	69	46.5	0.003 (–0.032 to 0.045)
Treatment of injury: proportion surgery	84	43.9	0.900 (0.045 to 2.650)
Treatment of injury: proportion below knee	87	N/A	1.289 (–0.128 to 4.068)
Duration of thromboprophylaxis (days)	23	46.5	–0.007 (–0.146 to 0.111)

TABLE 31 Network metaregression for all potential effect modifiers except thromboprophylactic agent used (*continued*)

Covariate	No treatment[a]	Adjusted DIC	Regression parameter coefficient (95% CI)
Clinically detected (DVT) (unadjusted DIC = 64.4)			
Proportion male	53	63.8	–0.209 (–0.685 to 0.056)
Baseline VTE (%; logit)	0.10 (–2.229)	127.0	–0.514 (–1.505 to 0.303)
Type of injury: proportion fractures	85	62.6	0.080 (0.003 to 0.267)
Treatment of injury: proportion surgery	65	64.9	0.007 (–0.017 to 0.041)
Treatment of injury: proportion below knee	90	N/A	1.247 (0.101 to 4.133)
Duration of thromboprophylaxis (days)	28	65.5	–0.018 (–0.119 to 0.076)
Clinically relevant (DVT) (unadjusted DIC = 80.9)			
Proportion male	58	81.0	–0.062 (–0.176 to 0.029)
Baseline VTE (%; logit)	0.10 (–2.229)	137.3	–0.267 (–0.983 to 0.377)
Type of injury: proportion fractures	75	81.1	0.017 (–0.008 to 0.052)
Treatment of injury: proportion surgery	77	82.1	0.002 (–0.017 to 0.027)
Treatment of injury: proportion below knee	88	N/A	2.056 (0.128 to 7.393)
Duration of thromboprophylaxis (days)	27	82.2	0.010 (–0.063 to 0.082)
PE (unadjusted DIC = 38.2)			
Proportion male	56	37.7	0.308 (–0.269 to 1.062)
Baseline VTE (%; logit)	0.09 (–2.277)	104.2	–15.190 (–36.670 to –3.094)
Type of injury: proportion fractures	74	38.3	–0.058 (–0.309 to 0.191)
Treatment of injury: proportion surgery	63	38.8	–0.057 (–0.263 to 0.028)
Treatment of injury: proportion below knee	91	N/A	0.060 (–0.212 to 0.488)
Duration of thromboprophylaxis (days)	28	38.9	0.060 (–0.212 to 0.488)

DIC, deviance information criterion; N/A, not applicable – analysis based on a subset of studies.
a Value used to centre the meta-regression.

Table 32 shows the results according to the type of thromboprophylactic agent used. These findings should be treated with caution as the model is fitted to a subset of the data and it is not possible to compare the fit of this model with the original model. In the case of an asymptomatic DVT (distal) outcome, the study by Samama *et al.*[57] is not connected; consequently, it is not possible to estimate the effects of nadroparin or fondaparinux on an asymptomatic DVT (distal) outcome. In the case of an asymptomatic DVT (proximal segment) outcome, the study by Samama *et al.*[57] is not connected and the Gehling *et al.*[23] study had no events; consequently, it is not possible to estimate the effects of nadroparin, reviparin or fondaparinux on an asymptomatic DVT (proximal segment) outcome. In the case of a clinically detected (symptomatic) outcome, Jørgensen *et al.*[51] and Bruntink *et al.*[49] had no events and provide no information about relative treatment effect; in addition, the study by Samama *et al.*[57] is connected in the network only via the nadroparin and fondaparinux arms of the study by Bruntink *et al.*[49] Consequently, it is not possible to estimate the effect of nadroparin, tinzaparin or fondaparinux on a clinically detected (symptomatic) outcome. In the case of a clinically relevant DVT outcome, the study by Samama *et al.*[57] is not connected; consequently, it is not possible to estimate the effects of nadroparin or fondaparinux on a clinically relevant DVT outcome.

TABLE 32 Random-effects NMA of different pharmacological thromboprophylaxis interventions vs. no thromboprophylaxis

	OR (95% CrI)	OR (95% PrI)	Probability of being the best
Clinically detected DVT (symptomatic)			
Dalteparin	0.38 (0.05 to 2.60)	0.38 (0.03 to 5.28)	0.01
Tinzaparin	NE	NE	NE
Certoparin	7.2×10^{-10} (3.6×10^{-31} to 0.09)	7.0×10^{-10} (3.5×10^{-31} to 0.11)	0.98
Nadroparin	NE	NE	NE
Reviparin	0.35 (0.03 to 2.71)	0.35 (0.02 to 4.99)	0.01
Fondaparinux	NE	NE	NE
None	–	–	0.00
Asymptomatic DVT (proximal segment)			
Dalteparin	0.43 (0.04 to 3.26)	0.42 (0.03 to 5.23)	0.00
Tinzaparin	6.4×10^{-10} (1.0×10^{-29} to 0.66)	6.1×10^{-10} (1.0×10^{-29} to 0.69)	0.51
Certoparin	5.8×10^{-10} (1.5×10^{-32} to 0.59)	5.8×10^{-10} (1.5×10^{-32} to 0.65)	0.49
Nadroparin	NE	NE	NE
Reviparin	NE	NE	NE
Fondaparinux	NE	NE	NE
None	–	–	0.01
Asymptomatic DVT (distal)			
Dalteparin	0.79 (0.25 to 3.13)	0.79 (0.15 to 5.36)	0.00
Tinzaparin	0.58 (0.13 to 2.48)	0.58 (0.08 to 3.96)	0.01
Certoparin	1.4×10^{-10} (2.5×10^{-30} to 0.20)	1.5×10^{-10} (2.6×10^{-30} to 0.22)	0.99
Nadroparin	NE	NE	NE
Reviparin	0.81 (0.29 to 2.41)	0.80 (0.16 to 4.40)	0.00
Fondaparinux	NE	NE	NE
None	–	–	0.00
Asymptomatic DVT (all)			
Dalteparin	0.72 (0.35 to 1.59)	0.72 (0.23 to 2.54)	0.00
Tinzaparin	0.54 (0.16 to 1.84)	0.54 (0.11 to 2.54)	0.00
Certoparin	3.5×10^{-10} (4.7×10^{-31} to 0.13)	3.5×10^{-10} (4.6×10^{-31} to 0.13)	0.96
Nadroparin	0.23 (0.04 to 1.06)	0.23 (0.03 to 1.31)	0.00
Reviparin	0.66 (0.29 to 1.70)	0.66 (0.20 to 2.63)	0.00
Fondaparinux	0.06 (0.01 to 0.33)	0.06 (0.01 to 0.40)	0.04
None	–	–	0.00

TABLE 32 Random-effects NMA of different pharmacological thromboprophylaxis interventions vs. no thromboprophylaxis (*continued*)

	OR (95% CrI)	OR (95% PrI)	Probability of being the best
PE			
Deltaparin	4.2×10^{-10} (9.0×10^{-31} to 0.43)	4.2×10^{-10} (9.3×10^{-31} to 0.47)	0.27
Tinzaparin	NE	NE	NE
Certoparin	NE	NE	NE
Nadroparin	2.8×10^{-13} (8.8×10^{-28} to 1.6×10^{-3})	2.7×10^{-13} (8.7×10^{-28} to 1.9×10^{-3})	0.48
Reviparin	6.5×10^{-10} (1.6×10^{-27} to 0.26)	6.4×10^{-10} (1.4×10^{-27} to 0.28)	0.25
Fondaparinux	1.6×10^{-6} (5.9×10^{-15} to 62)	1.6×10^{-6} (5.3×10^{-15} to 0.70)	0.00
None	–	–	0.01
Major bleeding			
Deltaparin	NE	NE	NE
Tinzaparin	NE	NE	NE
Certoparin	NE	NE	NE
Nadroparin	NE	NE	NE
Reviparin	NE	NE	NE
Fondaparinux	NE	NE	NE
None	–	–	NE
Clinically relevant DVT			
Deltaparin	0.40 (0.10 to 1.46)	0.40 (0.06 to 2.52)	0.00
Tinzaparin	3.4×10^{-10} (7.5×10^{-32} to 0.67)	3.3×10^{-10} (7.0×10^{-32} to 0.70)	0.46
Certoparin	1.3×10^{-11} (1.9×10^{-31} to 0.05)	1.3×10^{-11} (1.8×10^{-31} to 0.06)	0.54
Nadroparin	NE	NE	NE
Reviparin	2.35 (0.14 to 92.18)	2.35 (0.11 to 112.10)	0.00
Fondaparinux	0.23 (0.03 to 1.36)	0.23 (0.02 to 2.11)	0.00
None	–	–	0.01
Any VTE			
Dalteparin	0.69 (0.40 to 1.23)	0.68 (0.27 to 1.83)	0.00
Tinzaparin	0.54 (0.17 to 1.61)	0.54 (0.13 to 2.95)	0.00
Certoparin	8.5×10^{-12} (9.9×10^{-29} to 0.02)	8.6×10^{-12} (9.8×10^{-29} to 0.02)	0.99
Nadroparin	0.22 (0.08 to 0.54)	0.22 (0.06 to 0.69)	0.00
Reviparin	0.63 (0.31 to 1.42)	0.62 (0.23 to 1.97)	0.00
Fondaparinux	0.06 (0.02 to 0.19)	0.06 (0.01 to 0.24)	0.01
None	–	–	0.00

NE, not estimable; PrI, predictive interval.

There was evidence to suggest that there were differences in the effects based on the type of thromboprophylactic agent used, including between the different types of LMWH, with certoparin having the highest probability of the greatest effect on any VTE. However, this is based on the effect of certoparin being used in one study (Kock *et al.*),[52] so it is not possible to draw any reliable conclusions.

The meta-regression used in this assessment was a between-study comparison and lacked information with which to estimate parameters compared with a within-study comparison using patient data. In addition, comparisons between treatments involving zero events within a study provide no information about the relative treatment effect or the relationship between a potential treatment effect modifier and treatment effect. The between-study meta-regression has the potential to suffer from an ecological fallacy, such that the estimate of the relationship between a potential treatment effect modifier and treatment effect in a between-study comparison may be qualitatively different from the relationship between the treatment effect modifier and treatment effect within studies. Potential treatment effect modifiers were assessed separately, whereas they could be affecting treatment effect simultaneously; there is insufficient information with which to estimate potential treatment effect modifiers simultaneously. An adjusted model that is indistinguishable from an unadjusted model may reflect a lack of evidence rather than a lack of a relationship between potential treatment effect modifier and treatment. Estimates of the regression parameter should be interpreted with caution when they indicate evidence of a relationship between a potential treatment effect modifier and treatment but the adjusted model is indistinguishable from the unadjusted model.

There was insufficient evidence to suggest that any of the potential treatment effect modifiers defined in the protocol affected the treatment effect.

There was evidence to suggest that there were differences in the effects based on the type of thromboprophylactic agent used, including between the different types of LMWH.

Appendix 5 Literature search strategies for the review of individual risk factors associated with venous thromboembolism risk and risk assessment models for prediction of venous thromboembolism

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Platform or provider used: Ovid SP.

Date range searched: 1946 to May 2017.

Date searched: May 2017.

Search strategy

1. thrombosis/ or exp venous thrombosis/
2. Venous Thromboembolism/ or Thromboembolism/
3. exp Pulmonary Embolism/
4. (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab,kw.
5. ((vein* or ven*) adj7 thromb*).ti,ab,kw.
6. (PE or DVT or VTE).ti,ab,kw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Immobilization/
9. exp Mobility Limitation/
10. Splints/
11. Braces/
12. exp Casts, Surgical/
13. immobili*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. brace*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. splint*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. plaster*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. cast.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. (leg* or tibia* or fibula* or ankle*).mp. and (fracture*.hw. or su.fs.) and co.fs.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 7 and 19
21. predict:.mp. or scor:.tw. or observ:.mp.

22. (validation or validate).tw.
23. predict:.tw. or validat:.mp. or develop.tw.
24. 21 or 22 or 23
25. (risk assess* or risk predict* or risk stratif*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26. exp *Risk/ or exp Models, Statistical/ or exp Risk Assessment/ or *Postoperative Complications/ or risk model*.mp. or *Risk Factors/
27. 24 or 25 or 26
28. (Risk model* or prognostic model* or prediction model* or predictive model* or risk assessment model* or prediction score* or algorithm* or matrix or matrices or assessment tool* or prediction rule* or decision rule* or risk score*).mp.
29. 27 or 28
30. 20 and 29

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Review of Effects, Health Technology Assessment Database and NHS Economic Evaluation Database

Platform or provider used: Wiley Online Library.

Date range searched: 1898 to May 2017.

Date searched: May 2017.

Search strategy

#1 MeSH descriptor: [Thrombosis] explode all trees
#2 MeSH descriptor: [Venous Thrombosis] explode all trees
#3 MeSH descriptor: [Venous Thromboembolism] explode all trees
#4 MeSH descriptor: [Pulmonary Embolism] explode all trees
#5 (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw
#6 ((vein* or ven*) and thromb*):ti,ab,kw
#7 (PE or DVT or VTE):ti,ab,kw
#8 MeSH descriptor: [Immobilization] explode all trees
#9 MeSH descriptor: [Mobility Limitation] explode all trees
#10 MeSH descriptor: [Splints] explode all trees
#11 MeSH descriptor: [Braces] explode all trees
#12 MeSH descriptor: [Casts, Surgical] explode all trees
#13 immobili* or brace* or splint* or plaster* or cast*:ti,ab,kw (Word variations have been searched)
#14 ((leg* or tibia* or ankle* or fibula*) and (fracture* or surg*) and complicat*):ti,ab,kw
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14
#17 #15 and #16
#18 MeSH descriptor: [Risk] explode all trees
#19 MeSH descriptor: [Models, Statistical] explode all trees
#20 MeSH descriptor: [Risk Assessment] explode all trees
#21 MeSH descriptor: [Postoperative Complications] explode all trees
#22 MeSH descriptor: [Risk Factors] explode all trees
#23 (risk and (assess* or predict* or model* or stratif*)):ti,ab,kw

#24 (predict* or scor* or observ* or validat* or develop* or Risk model* or prognostic model* or prediction model* or predictive model* or risk assessment model* or prediction score* or algorithm* or matrix or matrices or assessment tool* or prediction rule* or decision rule* or risk score*):ti,ab,kw
#25 #18 or #19 or #20 or #21 or #22 or #23 or #24
#26 #17 and #25

EMBASE

Platform or provider used: Ovid SP.

Date range searched: 1974 to May 2017.

Date searched: May 2017.

Search strategy

1. thrombosis prevention/ or exp thrombosis/ or exp deep vein thrombosis/ or exp vein thrombosis/ or leg thrombosis/ or lower extremity deep vein thrombosis/
2. exp thromboembolism/ or exp venous thromboembolism/
3. exp lung embolism/
4. (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab,kw.
5. ((vein* or ven*) adj7 thromb*).ti,ab,kw.
6. (PE or DVT or VTE).ti,ab,kw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Immobilization/
9. exp Mobility Limitation/
10. exp splint/
11. exp brace/
12. exp plaster cast/
13. immobili*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
14. brace*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
15. splint*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
16. plaster*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
17. cast.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
18. (leg* or tibia* or fibula* or ankle*).mp. and (fracture*.hw. or su.fs.) and co.fs.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 7 and 19
21. predict:.mp. or scor:.tw. or observ:.mp.
22. (validation or validate).tw.
23. predict:.tw. or validat:.mp. or develop.tw.
24. 21 or 22 or 23
25. (risk assess* or risk predict* or risk stratif*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

26. (Risk model* or prognostic model* or prediction model* or predictive model* or risk assessment model* or prediction score* or algorithm* or matrix or matrices or assessment tool* or prediction rule* or decision rule* or risk score*).mp.
27. statistical model/
28. exp *risk factor/
29. exp *postoperative complication/
30. exp *risk/
31. exp risk assessment/
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 24 or 32
34. 20 and 33

Appendix 6 Excluded studies: review of individual risk factors associated with venous thromboembolism risk

TABLE 33 Excluded studies with rationale: review of individual risk factors associated with VTE risk

Authors, year	Reason for exclusion
Ajwani *et al.*,[237] 2016	No data or analysis of risk factors associated with VTE
Batra *et al.*,[238] 2006	No data or analysis of risk factors associated with VTE
Bertoletti *et al.*,[239] 2011	No data or analysis of risk factors associated with VTE
Caprini,[240] 2011	Narrative review
Caprini *et al.*,[210] 2001	Population: not isolated lower-limb injury requiring temporary immobilisation
Cirlincione *et al.*,[241] 2001	Narrative review
Decramer *et al.*,[242] 2008	No data or analysis of risk factors associated with VTE
Department of Health and Social Care,[211] 2010	No data or analysis of risk factors associated with VTE
Douna,[243] 2008	Commentary
Dyall *et al.*,[244] 2012 (abstract)	No data or analysis of risk factors associated with VTE
Eingartner *et al.*,[78] 1995	No data or analysis of risk factors associated with VTE
Engbers *et al.*,[245] 2013	No data or analysis of risk factors associated with VTE
Fall *et al.*,[246] 2014	No data or analysis of risk factors associated with VTE
Felcher *et al.*,[247] 2009	Population: not isolated lower-limb injury requiring temporary immobilisation
Fleischer *et al.*,[248] 2015	No data or analysis of risk factors associated with VTE
Gearhart *et al.*,[249] 2000	Population: not isolated lower-limb injury requiring temporary immobilisation
Giannadakis *et al.*,[79] 2000	No data or analysis of risk factors associated with VTE
Haque *et al.*,[80] 2016	No data or analysis of risk factors associated with VTE
Healy *et al.*,[250] 2010	No data or analysis of risk factors associated with VTE
Jiang *et al.*,[251] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
Kocialkowski *et al.*,[252] 2016	No data or analysis of risk factors associated with VTE
Lawall *et al.*,[253] 2011	Population: not isolated lower-limb injury requiring temporary immobilisation
Lim *et al.*,[254] 2016	Population: not isolated lower-limb injury requiring temporary immobilisation
Mangwani *et al.*,[228] 2015	Systematic review
Micheli,[255] 1975	No data or analysis of risk factors associated with VTE
Mizel *et al.*,[73] 1998	Population: not isolated lower-limb injury requiring temporary immobilisation (elective surgical population)
Nemeth *et al.*,[32] 2015	RAM (including data on risk factors) developed using a generic thrombosis cohort rather than a subgroup of patients with temporary lower-limb immobilisation. However, based on regression coefficients in a clinical logistic regression model, a RAM was developed for individuals with a plaster cast of the lower extremity
Nemeth *et al.*,[256] 2013 (abstract)	Abstract of an excluded full-text study: Nemeth *et al.*[32]

continued

TABLE 33 Excluded studies with rationale: review of individual risk factors associated with VTE risk (*continued*)

Authors, year	Reason for exclusion
Nesheiwat and Sergi,[257] 1996	No data or analysis of risk factors associated with VTE
Nilsson-Helander *et al.*,[12] 2009	No data or analysis of risk factors associated with VTE
Nokes,[31] 2010	No data or analysis of risk factors associated with VTE
Nygaard *et al.*,[212] 2009	Population: not isolated lower-limb injury requiring temporary immobilisation
Park *et al.*,[258] 2016	Population: not isolated lower-limb injury requiring temporary immobilisation
Park *et al.*,[259] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
Parsonage,[260] 2009	Narrative review
Persson and Wredmark,[261] 1979	No data or analysis of risk factors associated with VTE
Randelli *et al.*,[262] 2013	No data or analysis of risk factors associated with VTE
Roberts *et al.*,[17] 2013	No data or analysis of risk factors associated with VTE
Rogers *et al.*,[263] 2012	Population: not isolated lower-limb injury requiring temporary immobilisation
Samama,[264] 2000	Population: not isolated lower-limb injury requiring temporary immobilisation
Saragas *et al.*,[81] 2017	No data or analysis of risk factors associated with VTE
Saragas *et al.*,[72] 2014	Population: not isolated lower-limb injury requiring temporary immobilisation (elective surgical population)
Selby *et al.*,[58] 2015	No data or analysis of risk factors associated with VTE (authors reported that a low event rate precluded any subsequent analysis of predictors for VTE)
Simon *et al.*,[265] 1982	Population: not isolated lower-limb injury requiring temporary immobilisation
Slaybaugh *et al.*,[266] 2003	Review
Solis and Saxby,[267] 2002	Population: not isolated lower-limb injury requiring temporary immobilisation (elective surgical population)
Spannagel and Kujath,[235] 1993	No data or analysis of risk factors associated with VTE
Spencer *et al.*,[268] 2009	Population: not isolated lower-limb injury requiring temporary immobilisation (elective surgical population)
Spyropoulos,[269] 2009	Population: not isolated lower-limb injury requiring temporary immobilisation (elective surgical population)
Spyropoulos *et al.*,[270] 2009	Population: not isolated lower-limb injury requiring temporary immobilisation (elective surgical population)
Stockport NHS Trust Foundation,[33] 2013	No data or analysis of risk factors associated with VTE
Tan *et al.*,[271] 2016	Systematic review
Testroote *et al.*,[15] 2014	Systematic review
Toure,[272] 2014	Population: not isolated lower-limb injury requiring temporary immobilisation
True and Williamson,[273] 2014	No data or analysis of risk factors associated with VTE
van Adrichem *et al.*,[274] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
van Adrichem *et al.*,[275] 2013 (abstract)	Abstract of included full-text study: van Adrichem *et al.*[70]
Vollans *et al.*,[276] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
Wang *et al.*,[277] 2015	Not available
Watson *et al.*,[82] 2016	No data or analysis of risk factors associated with VTE

Appendix 7 Excluded studies: review of risk assessment models for prediction of venous thromboembolism risk

TABLE 34 Excluded studies with rationale: review of RAMs for prediction of VTE risk

Authors, year	Reason for exclusion
Ajwani *et al.*,[237] 2016	No outcome evaluation of RAM
Batra *et al.*,[238] 2006	No prognostic model/RAM
Bertoletti *et al.*,[239] 2011	No prognostic model/RAM (letter to the editor)
Caprini,[240] 2011	Narrative review
Caprini *et al.*,[210] 2001	Generic RAM (no outcome evaluation)
Cirlincione *et al.*,[241] 2001	Narrative review
Decramer *et al.*,[242] 2008	No prognostic model/RAM
Department of Health and Social Care,[211] 2010	Generic RAM (no outcome evaluation)
Douna,[243] 2008	Commentary
Dyall *et al.*,[244] 2012 (abstract)	No prognostic model/RAM
Engbers *et al.*,[245] 2013	No prognostic model/RAM
Fall *et al.*,[246] 2014	No prognostic model/RAM
Felcher *et al.*,[247] 2009	Population: not isolated lower-limb injury requiring temporary immobilisation
Fleischer *et al.*,[248] 2015	No outcome evaluation of RAM
Gearhart *et al.*,[249] 2000	Population: not isolated lower-limb injury requiring temporary immobilisation
Gehling *et al.*,[23] 1998	No prognostic model/RAM
Goel *et al.*,[50] 2009	No prognostic model/RAM
Hanslow *et al.*,[64] 2006	No prognostic model/RAM
Healy *et al.*,[250] 2010	No prognostic model/RAM (letter to the editor)
Ho and Omari,[65] 2017	No prognostic model/RAM
Jameson *et al.*,[66] 2014	No prognostic model/RAM
Jiang *et al.*,[251] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
Kocialkowski *et al.*,[252] 2016	No outcome evaluation of RAM
Kock *et al.*,[52] 1995	No prognostic model/RAM
Kujath *et al.*,[53] 1993	No prognostic model/RAM
Lawall *et al.*,[253] 2011	Population: not isolated lower-limb injury requiring temporary immobilisation
Lim *et al.*,[254] 2016	Population: not isolated lower-limb injury requiring temporary immobilisation
Makhdom *et al.*,[9] 2013	No prognostic model/RAM
Manafi Rasi *et al.*,[67] 2013	No prognostic model/RAM
Mangwani *et al.*,[228] 2015	Systematic review
Meek and Tong,[11] 2012	No prognostic model/RAM

continued

TABLE 34 Excluded studies with rationale: review of RAMs for prediction of VTE risk (*continued*)

Authors, year	Reason for exclusion
Micheli,[255] 1975	No prognostic model/RAM
Mizel *et al.*,[73] 1998	No prognostic model/RAM
Nemeth *et al.*,[256] 2013 (abstract)	Abstract of an included full-text study: Nemeth *et al.*[32]
Nesheiwat and Sergi,[257] 1996	No prognostic model/RAM
Nilsson-Helander *et al.*,[12] 2009	No prognostic model/RAM
Nokes,[31] 2010	No outcome evaluation of RAM
Nygaard *et al.*,[212] 2009	Generic RAM (no outcome evaluation)
Park *et al.*,[258] 2016	Population: not isolated lower-limb injury requiring temporary immobilisation
Park *et al.*,[259] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
Parsonage,[260] 2009	Narrative review
Patel *et al.*,[68] 2012	No prognostic model/RAM
Persson and Wredmark,[261] 1979	No prognostic model/RAM
Randelli *et al.*,[262] 2013	No prognostic model/RAM
Riou *et al.*,[69] 2007	No prognostic model/RAM
Roberts *et al.*,[17] 2013	No outcome evaluation of RAM
Rogers *et al.*,[263] 2012	Population: not isolated lower-limb injury requiring temporary immobilisation
Samama,[264] 2000	Population: not isolated lower-limb injury requiring temporary immobilisation
Saragas *et al.*,[72] 2014	No prognostic model/RAM
Selby *et al.*,[58] 2015	No prognostic model/RAM
Simon *et al.*,[265] 1982	Population: not isolated lower-limb injury requiring temporary immobilisation
Slaybaugh *et al.*,[266] 2003	Review
Solis and Saxby,[267] 2002	No prognostic model/RAM
Spannagel and Kujath,[235] 1993	No prognostic model/RAM
Spencer *et al.*,[268] 2009	No prognostic model/RAM
Spyropoulos,[269] 2009	No prognostic model/RAM
Spyropoulos *et al.*,[270] 2009	No prognostic model/RAM
Stockport NHS Trust Foundation,[33] 2013	No outcome evaluation of RAM
Tan *et al.*,[271] 2016	Systematic review
Testroote *et al.*,[15] 2014	Systematic review
Toure,[272] 2014	Population: not isolated lower-limb injury requiring temporary immobilisation
True and Williamson,[273] 2014	No prognostic model/RAM
van Adrichem *et al.*,[70] 2014	No prognostic model/RAM
van Adrichem *et al.*,[274] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
van Adrichem *et al.*,[275] 2013 (abstract)	No prognostic model/RAM
Vollans *et al.*,[276] 2015	Population: not isolated lower-limb injury requiring temporary immobilisation
Wahlsten *et al.*,[71] 2015	No prognostic model/RAM
Wang *et al.*,[277] 2015	Not available
Zheng *et al.*,[60] 2016	No prognostic model/RAM

Appendix 8 Delphi panel

TABLE 35 List of Delphi participants and clinical scope of practice

Participant number	Initials	Specialty	Title/scope of practice
1	MC	Orthopaedic surgery	Professor
2	VL	Orthopaedic surgery	Advanced nurse practitioner
3	XG	Orthopaedic surgery	Consultant
4	JK	Orthopaedic surgery	Consultant
5	DJ	Orthopaedic surgery	Consultant
6	RS	Orthopaedic surgery	Consultant
7	SG	Emergency medicine	Professor
8	DH	Emergency medicine	Professor
9	RB	Emergency medicine	Professor
10	GJ	Emergency medicine	Consultant
11	JC	Emergency medicine	Consultant
12	CR	Emergency medicine	Consultant
13	JS	Emergency medicine	Professor
14	JT	Thrombosis and haemostasis	Consultant
15	BH	Thrombosis and haemostasis	Professor
16	KdW	Thrombosis and haemostasis	Assistant professor
17	TN	Thrombosis and haemostasis	Consultant
18	HW	Thrombosis and haemostasis	Consultant
19	RT-D	Thrombosis and haemostasis	Consultant
20	RM	Thrombosis and haemostasis	Consultant

Appendix 9 Literature search strategies for review of economic studies

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Platform or provider used: Ovid SP.

Date range searched: 1946 to October 2017.

Date searched: October 2017.

Search strategy

1. thrombosis/ or exp venous thrombosis/
2. Venous Thromboembolism/ or Thromboembolism/
3. exp Pulmonary Embolism/
4. (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab,kw.
5. ((vein* or ven*) adj7 thromb*).ti,ab,kw.
6. (PE or DVT or VTE).ti,ab,kw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Immobilization/
9. exp Mobility Limitation/
10. Splints/
11. Braces/
12. exp Casts, Surgical/
13. immobili*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. brace*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. splint*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. plaster*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. cast.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. (leg* or tibia* or fibula* or ankle*).mp. and (fracture*.hw. or su.fs.) and co.fs.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp "costs and cost analysis"/ or costs.tw. or cost effective:.tw.
21. (cost: or cost benefit analys: or health care costs).mp.
22. Economics/
23. exp "costs and cost analysis"/
24. Economics, Dental/
25. exp economics, hospital/

26. Economics, Medical/
27. Economics, Nursing/
28. Economics, Pharmaceutical/
29. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic $).ti,ab.
30. (expenditure$ not energy).ti,ab.
31. value for money.ti,ab.
32. budget$.ti,ab.
33. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. ((energy or oxygen) adj cost).ti,ab.
35. (metabolic adj cost).ti,ab.
36. ((energy or oxygen) adj expenditure).ti,ab.
37. 34 or 35 or 36
38. 33 not 37
39. letter.pt.
40. editorial.pt.
41. historical article.pt.
42. or/39-41
43. 38 not 42
44. exp animals/ not humans/
45. 43 not 44
46. bmj.jn.
47. "cochrane database of systematic reviews".jn.
48. health technology assessment winchester england.jn.
49. or/46-48
50. 45 not 49
51. "Value of Life"/
52. Quality of Life/
53. quality of life.ti,kf.
54. ((instrument or instruments) adj3 quality of life).ab.
55. Quality-Adjusted Life Years/
56. quality adjusted life.ti,ab,kf.
57. (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.
58. disability adjusted life.ti,ab,kf.
59. daly*.ti,ab,kf.
60. (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.
61. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.
62. (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.
63. (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.
64. (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.
65. (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.
66. (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.
67. (hye or hyes).ti,ab,kf.
68. (health* adj2 year* adj2 equivalent*).ti,ab,kf.
69. (pqol or qls).ti,ab,kf.

70. (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.
71. nottingham health profile*.ti,ab,kf.
72. sickness impact profile.ti,ab,kf.
73. exp health status indicators/
74. (health adj3 (utilit* or status)).ti,ab,kf.
75. (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.
76. (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.
77. disutilit*.ti,ab,kf.
78. rosser.ti,ab,kf.
79. willingness to pay.ti,ab,kf.
80. standard gamble*.ti,ab,kf.
81. (time trade off or time tradeoff).ti,ab,kf.
82. tto.ti,ab,kf.
83. (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.
84. duke health profile.ti,ab,kf.
85. functional status questionnaire.ti,ab,kf.
86. dartmouth coop functional health assessment*.ti,ab,kf.
87. (hui or hui1 or hui2 or hui3).ti,ab,kf.
88. or/51-87
89. 20 or 21 or 50 or 88
90. 7 and 19 and 89

EMBASE

Platform or provider used: Ovid SP.

Date range searched: 1974 to October 2017.

Date searched: October 2017.

Search strategy

1. thrombosis prevention/ or exp thrombosis/ or exp deep vein thrombosis/ or exp vein thrombosis/ or leg thrombosis/ or lower extremity deep vein thrombosis/
2. exp thromboembolism/ or exp venous thromboembolism/
3. exp lung embolism/
4. (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab,kw.
5. ((vein* or ven*) adj7 thromb*).ti,ab,kw.
6. (PE or DVT or VTE).ti,ab,kw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Immobilization/
9. exp Mobility Limitation/
10. exp splint/
11. exp brace/
12. exp plaster cast/
13. immobili*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

14. brace*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
15. splint*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
16. plaster*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
17. cast.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
18. (leg* or tibia* or fibula* or ankle*).mp. and (fracture*.hw. or su.fs.) and co.fs.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 7 and 19
21. cost effectiveness analysis.sh. or randomized.tw. or economic.tw.
22. (cost or costs).tw.
23. Economics/
24. Cost/
25. exp Health Economics/
26. Budget/
27. budget*.ti,ab,kw.
28. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.
29. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
30. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.
31. (value adj2 (money or monetary)).ti,ab,kw.
32. Statistical Model/
33. economic model*.ab,kw.
34. Probability/
35. markov.ti,ab,kw.
36. monte carlo method/
37. monte carlo.ti,ab,kw.
38. Decision Theory/
39. Decision Tree/
40. (decision* adj2 (tree* or analy* or model*)).ti,ab,kw.
41. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 21 or 22 or 41
43. 20 and 42
44. socioeconomics/
45. exp Quality of Life/
46. quality of life.ti,kw.
47. ((instrument or instruments) adj3 quality of life).ab.
48. Quality-Adjusted Life Year/
49. quality adjusted life.ti,ab,kw.
50. (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.
51. disability adjusted life.ti,ab,kw.
52. daly*.ti,ab,kw.
53. (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.
54. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.

55. (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.
56. (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.
57. (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.
58. (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.
59. (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.
60. (hye or hyes).ti,ab,kw.
61. (health* adj2 year* adj2 equivalent*).ti,ab,kw.
62. (pqol or qls).ti,ab,kw.
63. (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.
64. nottingham health profile*.ti,ab,kw.
65. nottingham health profile/
66. sickness impact profile.ti,ab,kw.
67. sickness impact profile/
68. health status indicator/
69. (health adj3 (utilit* or status)).ti,ab,kw.
70. (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.
71. (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.
72. disutilit*.ti,ab,kw.
73. rosser.ti,ab,kw.
74. willingness to pay.ti,ab,kw.
75. standard gamble*.ti,ab,kw.
76. (time trade off or time tradeoff).ti,ab,kw.
77. tto.ti,ab,kw.
78. (hui or hui1 or hui2 or hui3).ti,ab,kw.
79. (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.
80. duke health profile.ti,ab,kw.
81. functional status questionnaire.ti,ab,kw.
82. dartmouth coop functional health assessment*.ti,ab,kw.
83. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82
84. 21 or 22 or 41 or 83
85. 20 and 84

NHS Economic Evaluation Database, Health Technology Assessment Database

Platform or provider used: The Cochrane Library.

Date range searched: inception to 2015.

Date searched: October 2017.

Search strategy

ID Search
#1 MeSH descriptor: [Thrombosis] explode all trees
#2 MeSH descriptor: [Venous Thrombosis] explode all trees
#3 MeSH descriptor: [Venous Thromboembolism] explode all trees
#4 MeSH descriptor: [Pulmonary Embolism] explode all trees
#5 (thromboprophyla* or thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):ti,ab,kw
#6 ((vein* or ven*) and thromb*):ti,ab,kw
#7 (PE or DVT or VTE):ti,ab,kw
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

Appendix 10 Excluded studies: review of cost-effectiveness evidence

TABLE 36 Reasons for exclusion at full text

Authors, year	Reason for exclusion
Brasel *et al.*,[95] 1997	Population: patients hospitalised for ≥ 5 days
Lu *et al.*,[96] 2009	Design: not a cost-effectiveness analysis
Velmahos *et al.*,[97] 2000	Population: trauma population but not specific to lower-limb injury

Appendix 11 Supplementary table

TABLE 37 List of existing models used to identify relevant parameters

Model identifier	Population	Interventions and comparators	How found
TA354[140]	People with DVT and/or PE (treatment and secondary prevention)	• Edoxaban tosylate • LMWH/VKA • Rivaroxaban • Dabigatran	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA341[133]	People with DVT and/or PE (treatment and secondary prevention)	• Apixaban • LMWH/VKA • Rivaroxaban • LMWH/dabigatran	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA327[132]	People with DVT and/or PE (treatment and secondary prevention) (Subpopulation with cancer also considered but not considered relevant here)	• Dabigatran etexilate • LMWH/VKA • Rivaroxaban	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA261[154]	People with a confirmed symptomatic DVT	• Rivaroxaban • LMWH/VKA	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA245[135]	People having elective hip or knee replacement surgery	• Apixaban	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA287[131]	People with an acute symptomatic PE	• Rivaroxaban • LMWH/VKA	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA157[134]	People having elective hip or knee replacement surgery	• Dabagitran etexilate • LMWH • Fondaparinux	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
TA170[136]	People having elective hip or knee replacement surgery	• Rivaroxaban • LMWH • Dabigatran etexilate	Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
NICE CG92[24]	This guideline examined many populations but the group having elective knee surgery is the most relevant (note: the NG89 is more likely to include up-to-date sources)		Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
NG89[130]	People having elective hip or knee replacement surgery		Search of NICE website for models that informed NICE guidance on VTE prevention or treatment
Goodacre *et al.*,[114] 2017 (draft, not final)	Women with suspected PE during pregnancy	Alternative diagnostic pathways	Known to authors
Simpson *et al.*,[278] 2009	People with VTE	Thrombophilia testing strategies	Known to authors
Goodacre *et al.*,[152] 2006	People with suspected DVT	Alternative diagnostic pathways	Known to authors
Wolowacz *et al.*,[99] 2009	People having total knee and hip replacement surgery	Dabigatran etexilate	Published study for related population identified during economic review

Appendix 12 Sources of utility data

TABLE 38 Studies reporting utility data relevant to the de novo model for thromboprophylaxis in lower-limb immobilisation

Authors, year	Participants	HRQoL tool and valuation method	Health state(s) valued	Utility estimate, mean (SD)[a]	Cited by
Ara and Brazier,[194] 2011	General population sample with utilities reported according to whether or not responders were affected by particular conditions (stroke and other heart conditions reported here)	EQ-5D UK tariff	• Stroke ($n = 360$) • Stroke with no other conditions ($n = 102$) • No stroke • CTEPH (other heart conditions) • No CTEPH	• 0.541 (95% CI 0.488 to 0.593) • 0.672 (95% CI 0.649 to 0.694) • 0.828 (95% CI 0.804 to 0.851) • 0.672 (95% CI 0.649 to 0.694) • 0.802 (95% CI 0.771 to 0.831)	Goodacre *et al.*[114]
Cohen *et al.*,[173] 2014 (abstract)	2790 patients with VTE taking anticoagulants (1640 with DVT and 1150 with PE at baseline; 443 with DVT and 280 with PE at 6 months)	EQ-5D-5L	• Heparin • Heparin/VKA • DOACs • All DVT • All PE	• 0.66 baseline • 0.75 6 months • 0.70 baseline • 0.84 6 months • 0.73 baseline • 0.87 6 months • 0.71 baseline • 0.85 6 months • 0.67 baseline • 0.81 6 months	• NG89[130] • TA354[140] ERG report cites more detailed values from company submission table B 78[178]
Arverud *et al.*,[156] 2016	111 patients 1 year after surgery and immobilisation for Achilles tendon injury	EQ-5D (valuation set not stated)	• No DVT after lower-limb immobilisation • DVT after lower-limb immobilisation	• 0.918 (0.1) • 0.906 (0.1)	Searches conducted for the systematic review of published cost-effectiveness studies (see *Chapter 4*, *Systematic review of existing cost-effectiveness evidence*)
Enden *et al.*,[189] 2013 (same study as Haig *et al.*[160])	189 with proximal DVT	EQ-5D	• PTS vs. no PTS at 24 months • PTS vs. no PTS at 6 months	• Decrement of 0.09 (95% CI 0.03 to 0.15) • Decrement of 0.02 (95% CI –0.08 to 0.28)	TA354[140]
Gage *et al.*,[205] 1996	70 patients aged ≥ 50 years with AF (community dwelling), half of whom were taking warfarin	TTO and standard gamble	• Mild stroke • Moderate stroke • Major stroke • Warfarin • Aspirin	• 0.76 • 0.39 • 0.11 • 0.987 • 0.998	• TA341[133] • TA245[135,137] • Simpson *et al.*[278]

Authors, year	Participants	HRQoL tool and valuation method	Health state(s) valued	Utility estimate, mean (SD)[a]	Cited by
Ghofrani *et al.*,[195] 2013	259 people with CTEPH (inoperable or persistent post surgically)	EQ-5D (valuation set not stated)	• Placebo at baseline • Drug therapy at baseline • Placebo, change at 16 weeks • Drug, change at 16 weeks • Difference	• 0.66 (0.25) • 0.64 (0.24) • –0.08 (0.34) • 0.06 (0.28) • 0.13 (0.06 to 0.21); $p < 0.001$	TA341[133]
Haig *et al.*,[160] 2016	176 patients with DVT (mid-thigh level or higher)	EQ-5D	• DVT • DVT with PTS	• 0.88 (0.16) • 0.71 (0.28) • $p < 0.001$	Data as reported by Lubberts *et al.*[159]
Hogg *et al.*,[176] 2013	215 thrombosis clinic patients with a history of VTE (at any time, i.e. 56% of patients were diagnosed > 12 months previously)	Standard gamble for vignettes, not patient's own health state	• DVT • PE • Minor ICH • GI bleed • Major ICH	Mean (IQR) • 0.81 (0.55 to 0.94) • 0.75 (0.45 to 0.91) • 0.75 (0.55 to 0.92) • 0.65 (0.15 to 0.86) • 0.15 (0.00 to 0.65)	• TA341[133] • TA354[140] • TA327[132]
Hogg *et al.*,[163] 2014	44 patients with previous experience of VTE (PE or proximal DVT) within 12 months of diagnosis	SF-6D (standard gamble also reported)	• PE • DVT	Median (IQR) • 0.68 (0.62 to 0.84) • 0.64 (0.58 to 0.69)	Lubberts *et al.*'s[159] systematic review
Ingelgard *et al.*,[279] 2002	121 outpatients with DVT	EQ-5D (tariff not reported)	Patients with PE or DVT treated with warfarin	0.08 decrement for both	TA245[135] Wolowacz *et al.*[99]
Keogh *et al.*,[197] 2006	177 patients with PAH (idiopathic or related to connective tissue disease, i.e. not CTEPH)	SF-6D UK valuation set	• WHO functional class 1 • Class 2 • Class 3 • Class 4	• 0.73 (0.09) • 0.67 (0.10) • 0.60 (0.10) • 0.52 (0.09)	TA327[132] (company compared class 1 mean with HSE data to calculate decrement of 0.1)

continued

TABLE 38 Studies reporting utility data relevant to the de novo model for thromboprophylaxis in lower-limb immobilisation (*continued*)

Authors, year	Participants	HRQoL tool and valuation method	Health state(s) valued	Utility estimate, mean (SD)[a]	Cited by
Lenert and Soetikno,[190] 1997	30 healthy volunteers (all female) and 30 physicians (not selected by specialty)	Standard gamble	• Mild PTS • Severe PTS • Stroke	• 0.98 (0.04) • 0.93 (0.07) • Median 0.60 (95% CI 0.02 to 1.00)	• TA157[134] • TA170[136] • TA245[135] • TA261[154] • TA287[131] • TA327[132] • TA341[133] • TA354[140] • Wolowacz *et al.*[99]
Lindgren *et al.*,[200] 2007	60 patients with mild to moderate hypertension, of whom 18 experienced a stroke event during the study	EQ-5D UK tariff	Stroke over 1 year	Decrement of 0.145 (0.145) (95% CI 0.059 to 0.249)	TA327[132]
Locadia *et al.*,[177] 2004	Patients with VTE on VKA ($n = 53$), a bleeding episode during VKA therapy ($n = 23$) or PTS treated with VKA ($n = 48$)	TTO for clinical vignettes	Median (IQR) • No VKA • Own current health • VKA treatment • PTS • DVT • Muscular bleeding • GI bleeding • PE • Non-fatal haemorrhagic stroke	Median (IQR) • 0.96 (0.82 to 1.00) • 0.95 (0.81 to 1.00) • 0.92 (0.77 to 0.98) • 0.82 (0.66 to 0.97) • 0.84 (0.64 to 0.98) • 0.76 (0.59 to 0.95) • 0.65 (0.49 to 0.86) • 0.63 (0.36 to 0.86) • 0.33 (0.14 to 0.53)	• NG89[130] (GI bleeding and stroke) • TA341[133] (stroke, PE, DVT, GI) • TA327[132] (ERG cited) • Goodacre *et al.*[114] (PE and bleed) • TA261[154] (DVT, PE, non-ICH, ICH) • TA287[131] • TA287 (as for TA261[154]) • TA354[140] (PTS)
Luengo-Fernandez *et al.*,[201] 2013	1188 stroke and TIA patients (748 stroke patients)	EQ-5D UK TTO tariff	• Stroke at 1 month • Stroke vs. matched controls at 1 month • Stroke at 6 months stable from 6 months to 5 years • Stroke vs. matched controls at 5 years	• 0.64 • –0.22 (95% CI –0.26 to –0.18) • 0.70 • –0.09 (95% CI –0.13 to –0.05)	Follow-up of OXVASC cohort reported by Rivero-Arias *et al.*[204]

Authors, year	Participants	HRQoL tool and valuation method	Health state(s) valued	Utility estimate, mean (SD)[a]	Cited by
Lunde,[202] 2013	345 stroke patients (6 months post stroke)	EQ-5D UK TTO valuation set	Post stroke	0.70 (0.30) (also reports values for independent yes/no)	• NG89[130] (stroke) • TA354[140] • 0.713 with 11% decrement
Marchetti *et al.*,[207] 2001	48 patients attending an anticoagulation clinic with experience of heparin and half with experience of VKA	Direct TTO using clinical vignettes	• Warfarin treatment • Heparin treatment	• 0.989 (0.016) • 0.92 to 1.00 • 0.993 (0.024) • 0.94 to 1.00	• NG89[130] • TA354,[140] TA261,[154] TA287,[131] TA327[132]
Meads *et al.*,[198] 2008	308 patients with CTEPH	CAMPHOR QoL, which was valued by 249 members of the UK general population using TTO	CTEPH	0.56 (0.29) (ERG in TA327[132] calculated disutility relative to age-matched general population as 0.22 = 0.78–0.56)	• TA327[132] • TA261[154] and TA287[131] • TA354[140] • NG89[130]
Monz *et al.*,[208] 2013	1435 patients having dabigatran or warfarin during RE-LY study (AF patients)	EQ-5D UK TTO tariff	VKA treated DOAC treated	No statistically significant difference in HRQoL substudy as a whole	TA327[132]
Olschewski *et al.*,[196] 2002	203 patients with primary PAH and CTEPH ($n = 57$) (NYHA class III or IV)	EQ-5D index	• Iloprost (Ventavis;® Bayer Plc, Reading, UK) treated • Placebo controls	Improved from 0.49 ± 0.28 to 0.58 ± 0.27 in drug treatment group	Reference list of Keogh *et al.*[197]
O'Meara *et al.*,[191] 1994	36 patients > 50 years, of which 20 had no history of DVT	Standard gamble	• Mild postphlebitic syndrome • Severe postphlebitic syndrome • CNS bleeding	• 0.995 (95% CI 0.990 to 1.00) • 0.982 (95% CI 0.962 to 1.00) • 0.290 (95% CI 0.127 to 0.453)	• CG92[24] • Goodacre *et al.*[152] • Simpson *et al.*[278] • TA287[131]
Pickard *et al.*,[203] 2004	124 patients hospitalised following ischaemic stroke	EQ-5D with UK TTO tariff (HUI3 also reported)	Ischaemic stroke at • Baseline • 1 month • 3 months • 6 months	 • 0.31 (0.38) • 0.55 (0.36) • 0.61 (0.30) • 0.62 (0.34)	• TA287[131] • TA341[133]

continued

TABLE 38 Studies reporting utility data relevant to the de novo model for thromboprophylaxis in lower-limb immobilisation (*continued*)

Authors, year	Participants	HRQoL tool and valuation method	Health state(s) valued	Utility estimate, mean (SD)[a]	Cited by
Rivero-Arias *et al.*,[204] 2010	1293 stroke and TIA patients (subset of the OXVASC data set)	EQ-5D UK TTO tariff	Stroke and TIA (average over 2 years) Stroke data points ($n = 1359$)	• 0.713 (0.287) • 0.67 (0.30)	• TA287[131] • TA261[154]
Robinson *et al.*,[206] 2001 (data from abstract)	57 patients with AF	Standard gamble	• Warfarin (GP monitored) • Warfarin (hospital monitored) • Major bleed • Mild stroke • Severe stroke	• 0.948 • 0.941 • 0.841 • 0.641 • 0.189	• Wolowacz *et al.*[99] • TA157[134] • TA245[135,137] • TA327[132]
Shafazand *et al.*,[199] 2004	53 patients with pulmonary hypertension (not specifically CTEPH)	Standard gamble	All participants' current health	0.71 (95% CI 0.64 to 0.78)	TA327[132]
Sullivan *et al.*,[174] 2011	2299 patients with VTE taking secondary prophylaxis	EQ-5D UK valuation set	• Recurrent DVT • Recurrent PE • CRNMB	• –0.17 • –0.06 • –0.03 (Relative to baseline)	• TA354[140] • NG89[130]
Tavoly *et al.*,[175] 2016	213 patients with PE (median 3.8 years since diagnosis)	EQ-5D with Danish tariff	• PE • No PE (population norms) • No PE (age- and sex-matched controls)	• 0.80 (0.22) • 0.86 (NR) • $p < 0.005$ • 0.82 (0.16)	TA327[132] (cites 2013 abstract but data here from full paper)
Utne *et al.*,[179] 2016	254 patients with DVT during previous 1 to 10 years	EQ-5D with Danish tariff	• DVT • No DVT (age- and sex-matched controls)	• 0.79 (0.20) • 0.91 (0.12)	Review by Ghanima *et al.*[280]

CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; CNS, central nervous system; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; ERG, Evidence Review Group; HSE, Health Survey for England; HUI-3, Health Utilities Index – 3; IQR, interquartile range; NR, not reported; NYHA, New York Heart Association; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; TIA, transient ischaemic attack; WHO, World Health Organization.

a Unless otherwise stated.

Appendix 13 Parameter sampling

TABLE 39 Parameter sampling inputs

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
Probability of PE in those having lower-limb immobilisation	0.4%	95% CI 0.2% to 0.7%	Beta(10, 2326)	Rates across placebo arms of 12 studies included in the systematic review of clinical effectiveness (see *Table 16*)
Probability of DVT in those having lower-limb immobilisation not having PE	8.0%	95% CI 6.9% to 9.1%	Beta(186, 2140)	Rates across placebo arms of 12 studies included in the systematic review of clinical effectiveness (see *Table 16*)
Proportion of DVT that is symptomatic	11.4%	95% CI 6.7% to 17.2%	Beta(16, 124)	Rates across placebo arms of 9 studies included in the systematic review of clinical effectiveness (see *Table 16*)
Proportion of asymptomatic DVTs that are distal	83.9%	95% CI 73.3% to 92.2%	Beta(47, 9)	Rates across placebo arms of 6 studies included in the systematic review of clinical effectiveness (see *Table 16*)
Proportion of symptomatic DVTs that are distal	50%	95% CI 26.5% to 73.4%	Beta(8, 8)	Rates across placebo arms of a single study (see *Table 16*)
Effectiveness of prophylaxis: OR for VTE	0.52	95% CI 0.37 to 0.71	Not applicable	Systematic review of decision tools for identifying patients at risk of VTE. CODA samples from NMA used directly to characterise uncertainty around OR (see *Methods used to quantify decision uncertainty*)
Risk of major GI bleed with no prophylaxis (per 1000 person-years)	1.34	95% CI 1.32 to 1.36	Norm(1.34, 0.010)	Hippisley-Cox *et al.*[101]
Risk of ICH with no prophylaxis (per 1000 person-years)	0.55	95% CI 0.54 to 0.56	Norm(0.56, 0.005)	Hippisley-Cox *et al.*[101]
Bleed risk for prophylaxis vs. none: OR (OR is converted to RR using baseline risks for no prophylaxis)	1.64	95% CI 0.90 to 2.53	Not applicable	Pooled analysis of bleed risks across all VTE prophylaxis studies in NICE CG92 re-analysed on log-odds scale using random-effects Bayesian meta-analysis. CODA samples used directly to characterise uncertainty around OR
Case fatality rate for GI bleeds	10.0%	95% CI 9.7% to 10.4%	Beta(2452, 21,969)	Case fatality rate of GI bleeds taken from Button *et al.*[103]
Case fatality rate for ICH	49.0%	95% CI 37% to 60%	Beta(35, 37)	Case fatality rate of ICH bleeds taken from Fang *et al.*[102]
Risk of bleeding during 3-month anticoagulant treatment for VTE	0.9%	95% CI 0.2% to 2.0%	Beta(3, 352)	Kooiman *et al.*[104]
Proportion of major bleeds during VTE treatment that are fatal	25.0%	95% CI 21% to 28%	Beta(135, 411)	Nieto *et al.*[105]
Proportion of non-fatal major bleeds during VTE treatment that are ICH	9.0%	95% CI 6.5% to 11.9%	Beta(37, 374)	Nieto *et al.*[105]

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
SMR for patients surviving ICH compared with general population				
Year 1 after ICH	4.5	95% CI 3.7 to 5.5	Log(SMR) = norm(1.5, 0.1)	Fogelholm *et al.*[107]
Years 2–6 after ICH	2.2	95% CI 1.8 to 2.7	Log(SMR) = norm(0.8, 0.1)	CIs around SMR not reported, so have assumed ± 20% on the log scale
Probability of PE being fatal	2.9%	95% CI 2.5% to 3.3%	Beta(219, 7372)	Maestre *et al.*[108]
Cumulative risk of PTS for treated symptomatic DVT at 3 years				
Proximal	32.4%	95% CI 22.1% to 43.6%	Beta(23, 48)	Hach-Wunderle *et al.*[109]
Distal	15.6%	95% CI 7.9% to 25.3%	Beta(10, 54)	
OR for PTS in asymptomatic untreated proximal DVT vs. treated proximal DVT	2.71	95% CI 1.44 to 5.1	Log(OR) = norm(0.99, 0.32)	van Dongen *et al.*[110]
Incidence of CTEPH at 2 years (converted to annual risk of 1.6%)	3.2%	95% CI 2.0% to 4.4%	Beta(32, 967)	Ende-Verhaar *et al.*,[111] based on incidence in those surviving the initial treatment period of 3–6 months
Proportion of CTEPH patients treated surgically	59.5%	95% CI 55.8% to 63.2%	Beta(404, 275)	Delcroix *et al.*[113]
Proportion of those patients with CTEPH who are surgically treated who also received bridging medical care	30.0%	95% CI 24.6% to 33.5%	Beta(117, 287)	Delcroix *et al.*[113]
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.*[113] but curves taken from Goodacre *et al.*[114]
Mean and SD for log-normal 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.*[113] but curves taken from Goodacre *et al.*[114] Variance–covariance matrix Mean log: Mean 0.017708, SD –0.05572 SD log: Mean –0.05572, SD 0.230935
Ambulance transfer to ED	£236	IQR £211–256, $n = 11$	Gamma(551, 0.43)	• NHS reference costs[116] • HRG code AS02 'See and treat and convey'

continued

TABLE 39 Parameter sampling inputs (*continued*)

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
ED visit leading to admission	£228	IQR £184–261, *n* = 139	Gamma(2210, 0.10)	• NHS reference costs[116] • HRG code: Type 01, leading to admission, VB05Z Emergency Medicine, Category 2 Investigation with Category 3 Treatment
ED visit not leading to admission	£196	IQR £165–220, *n* = 138	Gamma(3203, 0.06)	• NHS reference costs[116] • HRG code: Type 01, not leading to admission, VB05Z Emergency Medicine, Category 2 Investigation with Category 3 Treatment
DVT admission: weighted average of following HRG costs				
YQ51A	£4632	IQR £2394–5794, *n* = 122	Gamma(42.4, 109)	• NHS reference costs[116] • Non-elective inpatient costs for HRG codes covering DVT, with CC scores ranging from 0 to 12+
YQ51B	£2943	IQR £1595–3629, *n* = 130	Gamma(30.0, 98.3)	
YQ51C	£2406	IQR £1559–2773, *n* = 136	Gamma(41.5, 57.9)	
YQ51D	£1731	IQR £1267–1903, *n* = 141	Gamma(48.5, 35.7)	
YQ51E	£1453	IQR £1041–1574, *n* = 134	Gamma(35.7, 40.6)	
PE admission: weighted average of following HRG costs				
DZ09J	£5903	IQR £3012–7602, *n* = 129	Gamma(45, 129)	• NHS reference costs[116] • Non-elective inpatient costs for HRG codes covering PE with and without interventions, with CC scores from 0 to 12+
DZ09K	£3440	IQR £2116–4204, *n* = 137	Gamma(41, 84)	
DZ09L	£3795	IQR £2369–4741, *n* = 136	Gamma(48, 79)	
DZ09M	£2851	IQR £1997–3291, *n* = 142	Gamma(65, 44)	
DZ09N	£2276	IQR £1751–2507, *n* = 143	Gamma(92, 25)	
DZ09P	£1837	IQR £1473–2077, *n* = 144	Gamma(73, 25)	
DZ09Q	£1550	IQR £1270–1724, *n* = 141	Gamma(76, 20)	

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
Critical care: weighted average of HRG costs for codes				
XC01Z	£2588	$n = 1$	Fixed	• NHS reference costs[116] • HRG codes for Adult Critical Care for 0 to 6 organs supported
XC02Z	£1682	IQR £1478–2014, $n = 6$	Gamma(107, 15.7)	
XC03Z	£1705	IQR £1419–1944, $n = 11$	Gamma(211, 8.1)	
XC04Z	£1581	IQR £1423–1781, $n = 17$	Gamma(605, 2.6)	
XC05Z	£1195	IQR £1133–1381, $n = 21$	Gamma(884, 1.4)	
XC06Z	£820	IQR £481–1001, $n = 23$	Gamma(104, 7.9)	
XC07Z	£521	IQR £188–868, $n = 15$	Gamma(16.0, 32.5)	
Proximal leg vein ultrasonography	£55	IQR £41–61, $n = 149$	Gamma(2135, 0.03)	• NHS reference costs[116] • RD40Z Outpatient Ultrasound Scan with duration of < 20 minutes, without contrast
CTPA	£102	IQR £71–135, $n = 137$	Gamma(635, 0.16)	• NHS reference costs[116] • RD21 A, Outpatient Computerised Tomography Scan of one area, with post contrast only, ≥ 19 years
V/Q SPECT	£261	IQR £118–337, $n = 78$	Gamma(202, 1.29)	• NHS reference costs[116] • RN08 A, Outpatient Single Photon Emission Computed Tomography (SPECT), ≥ 19 years
V/Q planar	£274	IQR £153–270, $n = 106$	Gamma(1045, 0.26)	• NHS reference costs[116] • RN18 A, Outpatient Lung Ventilation or Perfusion Scan, ≥ 19 years
Echocardiography	£72	IQR £38–94, $n = 47$	Gamma(146, 0.50)	• NHS reference costs[116] • RD51 A, Outpatient Simple Echocardiogram, ≥ 19 years
Proportion receiving LMWH who need district nurse administration	4%	95% CI 1.3% to 7.8%	Beta(5, 123)	Menakaya *et al.*[229]
Fatal bleed	£1592	SD 1886, $n = 8$	Gamma(5.70, 279)	Luengo-Fernandez *et al.*[117] (cost before inflation)
Acute costs for non-fatal ICH (first 90 days) – weighted average of				
Non-disabling non-fatal stroke	£9903	SD 4510, $n = 5$	Gamma(24, 411)	Luengo-Fernandez *et al.*[117] (cost before inflation)
Moderately disabling non-fatal stroke	£25,442	SD 9635, $n = 3$	Gamma(21, 1216)	
Totally disabling non-fatal stroke	£43,036	SD N/A, $n = 1$	Fixed	

continued

TABLE 39 Parameter sampling inputs (*continued*)

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
Residential costs for non-fatal ICH (first 90 days)	£6880	SD £15,600, *n* = 136	Gamma(26, 260)	Luengo-Fernandez *et al.*[117] (cost before inflation)
GP costs for non-fatal ICH (first 90 days)	£98	95% CI £27 to £169	Norm(98, 36)	Luengo-Fernandez *et al.*[117] (cost before inflation)
Emergency care costs for non-fatal ICH (first 90 days)	£99	95% CI £56 to £141	Norm (99, 22)	Luengo-Fernandez *et al.*[117] (cost before inflation)
Non-fatal non-ICH bleed (weighted average of HRG costs)				
FZ38G	£5369	IQR £3097–6235, *n* = 134	Gamma(63, 85)	• NHS reference costs 2015/2016[116] • HRG codes for GI bleed without interventions, with single interventions and with multiple interventions
FZ38H	£3172	IQR £2054–3876, *n* = 131	Gamma(35, 90)	
FZ38J	£3667	IQR £2100–4636, *n* = 135	Gamma(32, 115)	
FZ38K	£2630	IQR £1793–3153, *n* = 134	Gamma(39, 67)	
FZ38L	£2084	IQR £1655–£2332, *n* = 135	Gamma(72, 29)	
FZ38M	£2531	IQR £1646–3061, *n* = 136	Gamma(38, 66)	
FZ38N	£1882	IQR £1496–2051, *n* = 140	Gamma(94, 20)	
FZ38P	£1406	IQR £1161–1542, *n* = 142	Gamma(78, 18)	
Anticoagulant service				
Face-to-face follow-up, consultant led	£37	IQR £21–41, *n* = 58	Norm(37, 3.7) with minimum of zero	• NHS reference costs 2015/2016[116] • Service code 324 – WF01A non-admitted
Face-to-face follow-up, non-consultant led	£16	IQR £9–16, *n* = 46	Norm(16, 1.6) with minimum of zero	• NHS reference costs 2015/2016[116] • Service code 324 – WF01A non-admitted
First face-to-face attendance, non-consultant led	£22	IQR £8–17, *n* = 40	Norm(22, 2.2) with minimum of zero	• NHS reference costs 2015/2016[116] • Service code 324 – WF01B non-admitted
Non-face-to-face follow-up, non-consultant led	£13	IQR £5–7, *n* = 10	Norm(13, 1.3) with minimum of zero	• NHS reference costs 2015/2016[116] • Service code 324 – WF01C non-admitted

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
Vascular surgery				
First appointment face to face, consultant led	£167	IQR £124–211, *n* = 112	Gamma(759, 0.22)	• NHS reference costs 2015/2016[116] • Service code 107 – WF01B non-admitted
Follow-up appointment face to face, consultant led	£140	IQR £100–165, *n* = 111	Gamma(942, 0.15)	• NHS reference costs 2015/2016[116] • Service code 107 – WF01A non-admitted
First appointment face to face, non-consultant led	£173	IQR £100–240, *n* = 48	Gamma(312, 1.39)	• NHS reference costs 2015/2016[116] • Service code 107 – WF01B non-admitted
Follow-up appointment face to face, non-consultant led	£139	IQR £173–230, *n* = 55	Gamma(79, 1.76)	• NHS reference costs 2015/2016[116] • Service code 107 – WF01A non-admitted
Surgical management of CTEPH: average of following HRG costs				
DZ02H	£9871	IQR £7694–10,623, *n* = 35	Gamma(723, 13.7)	• NHS reference costs 2015/2016[116] • HRG codes for Complex Thoracic Procedures, ≤ 19 years, with CC score ranging from 0 to 6+
DZ02J	£7772	IQR £6437–9086, *n* = 40	Gamma(627, 12.4)	
DZ02K	£6702	IQR £5048–7597, *n* = 46	Gamma(579, 11.6)	
Utility decrement for stroke up to 6 months	–0.22	95% CI –0.26 to –0.18	Norm(–0.22, 0.02)	Luengo-Fernandez *et al.*[201]
Utility decrement for stroke from 6 months	–0.09	95% CI –0.13 to –0.05	Norm(–0.09, 0.02)	Luengo-Fernandez *et al.*[201]
Utility immediately after DVT	0.71	SD 0.26, *n* = 1640	Beta(3545, 1448)	Cohen *et al.*[173]
Utility immediately after PE	0.67	SD 0.24, *n* = 1150	Beta(1663, 819)	Cohen *et al.*[173]
Utility for DVT without PTS	0.86	95% CI 0.823 to 0.903	Beta(248, 40.3)	Enden *et al.*[189]
Utility decrement for PTS vs. no PTS after DVT	0.09	95% CI 0.03 to 0.15	Beta(7.78, 78.6)	Enden *et al.*[189]
Utility for CTEPH	0.56	SD 0.29, *n* = 308	Beta(505, 397)	Meads *et al.*[198]
Utility for NYHA class I	0.86	SD 0.17, *n* = 35	Beta(105, 12.9)	Meads *et al.*[198]
Utility for LMWH	0.993	SD 0.016	Beta(27.5, 0.205)	Marchetti *et al.*[207]

continued

TABLE 39 Parameter sampling inputs (*continued*)

Parameter description	Mid-point value	Uncertainty measure	Distribution	Source
Utility for warfarin	0.989	SD 0.024	Beta(17.6, 0.195)	Marchetti *et al.*[207]
Utility regression for age-related decrement: coefficients for				
Age	–0.0001728	SE 0.0003737	Multivariate normal	Ara and Brazier[194]
Age × age	–0.000034	SE 3.96×10^{-6}		Variance–covariance matrix
Constant	0.9584588	SE 0.0077431		

	Age	Age × age	Constant
Age	1.4×10^{-7}		
Age × age	-1.5×10^{-9}	1.6×10^{-11}	
Constant	-2.80×10^{-6}	2.8×10^{-8}	6×10^{-5}

CC, complications and comorbidities; CODA, convergence diagnostics and output analysis; CTPA, computerised tomography pulmonary angiography; IQR, interquartile range; N/A, not applicable; NYHA, New York Heart Association; SE, standard error; SMR, standardised mortality ratio; SPECT, single-photon emission computed tomography; V/Q, ventilation/perfusion.

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