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

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Declared competing interests of authors: Steve Goodacre is chairperson of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme Clinical Evaluation and Trials Board and a member of the HTA Funding Boards Policy Group. Tim Nokes received personal fees from Bayer Pharmaceuticals (Bayer AG, Leverkusen, Germany), personal fees from the Bristol-Myers Squibb Company (New York City, NY, USA)–Pfizer Inc. (New York City, NY, USA) Alliance and personal fees from Daiichi Sankyo Company Ltd (Tokyo, Japan) outside the submitted work. Kerstin de Wit reports grants from Bayer Pharmaceuticals outside the submitted work.

Published December 2019
DOI: 10.3310/hta23630

Scientific summary

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Health Technology Assessment 2019; Vol. 23: No. 63
DOI: 10.3310/hta23630

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

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

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 15/187/06. The contractual start date was in April 2017. The draft report began editorial review in April 2018 and was accepted for publication in August 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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