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Decision-analysis modelling of the effects of thromboprophylaxis for people with lower limb immobilisation for injury

Running short title: Thromboprophylaxis for lower limb immobilisation following injury

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Pharmacological thromboprophylaxis reduces the risk of symptomatic venous thromboembolism (VTE) in people with lower limb immobilisation due to injury (Zee *et al,* 2017) but can increase the risk of bleeding. Clinicians therefore need to weigh the risks and benefits of thromboprophylaxis to determine the overall benefit of treatment. Decision-analytic modelling can inform this process by simulating patient management according to alternative strategies to determine the probability of different outcomes with each strategy. Outcomes can then be valued as quality-adjusted life years (QALYs) to determine which strategy is associated with the greatest quality-adjusted life expectancy.

We developed a decision-analytic model to compare the management of a cohort of patients with lower limb immobilisation following injury receiving pharmacological thromboprophylaxis to management without this treatment, in terms of 6-month and 5-year outcomes, and lifetime QALYs.

Full details of the methods and data sources are provided in the online appendix. Briefly, a six-month decision tree model was used to estimate for each strategy; the number of patients receiving thromboprophylaxis, the impact of thromboprophylaxis on VTE outcomes (pulmonary emboli (PE) and deep vein thrombosis (DVT)), and the incidence of major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants. Major bleeds were divided into fatal bleeds, non-fatal intracranial haemorrhage (ICH) and other major bleeds. PEs were divided into fatal and non-fatal events. DVTs were divided first into symptomatic and asymptomatic DVTs and then into proximal and distal DVTs. Symptomatic DVTs and non-fatal PEs are assumed to result in 3 months of anticoagulant treatment. A Markov model was then used to extrapolate life-time outcomes including overall survival and ongoing morbidity related to either bleeds or VTE. The health states included within the Markov model capture the risk of post-thrombotic syndrome (PTS) following VTE and the risk of chronic thromboembolic pulmonary hypertension (CTEPH) following PE. The risk of PTS is dependent on whether the DVT is symptomatic and treated or asymptomatic and untreated and also whether the DVT is proximal or distal. The CTEPH state is divided according to whether patients receive medical or surgical management to allow for differential costs and survival between these groups. There is also a post ICH state to capture ongoing morbidity following ICHs.

The effectiveness of thromboprophylaxis and the risk of VTE in patients not receiving thromboprophylaxis were estimated from a systematic review of thromboprophylaxis in lower limb immobilisation (Pandor *et al*, in press). The relative risk of bleeding was estimated from a systematic review of thromboprophylaxis across multiple conditions (National Clinical Guideline Centre – Acute and Chronic Conditions (UK), 2010) and applied to a baseline risk of bleeding from a large primary care database with 16.4 million person years of follow-up (Hippisley-Cox and Coupland 2014). The data

sources used to determine the probabilites of subsequent events in the decision tree and Markov models are described in the online appendix.

QALYs were estimated by applying estimates of health utility (a measure of health-related quality of life on a scale of zero to one) to life expectancy after each of the events in the model. During the decision tree phase, absolute utility values were applied based on the events occurring, with age dependent general population values applied to those not having any events. A disutility (i.e. a reduction in quality of life) was applied to patients receiving prophylaxis with LMWH to account for the impact of regular injections and a disutility was applied during VTE treatment to reflect patients' preferences to avoid long-term treatment. During the Markov model phase, patients without long-term sequelae or ongoing symptoms have general population levels of utility which vary with age and those with sequelae or ongoing symptoms have utility multipliers applied which reduce their utility by a fixed proportion relative to the general population level for their age. Details of utilities and life expectancy after each of the model states are provided in the online appendix.

Short and long-term clinical outcomes per 100,000 patients are presented in Table 1. The model predicts that the combined rate of serious acute adverse outcomes (ICH or death from VTE or bleeding) would be very low regardless of whether thromboprophylaxis is used (around 1 in 4000). The short-term benefits of thromboprophylaxis lie in reducing the rates of non-fatal PE (225 versus 415 per 100,000), symptomatic DVT (492 versus 907 per 100,000) and asymptomatic DVT (3820 versus 7052 per 100,000). These lead to longer term benefits in terms of reduced risks of PTS (1007 versus 1859 per 100,000) and CTEPH (6 versus 11 per 100,000), with an additional 4 patients in 100,000 surviving to 5 years compared with no thromboprophylaxis. Overall, thromboprophylaxis is estimated to result in 0.015 additional QALYs per patient (95% credible interval [CrI] 0.004 to 0.029).

Our findings suggest that thromboprophylaxis increases quality-adjusted life expectancy for people with lower limb immobilisation due to injury, but this is driven by the prevention of long-term complications, particularly the utility loss attributed to PTS and the prevention of PTS in patients with asymptomatic DVT, rather than the risk of short-term adverse outcomes. This may be at odds with the commonly perceived rationale for providing thromboprophylaxis. The effect of thromboprophylaxis upon PTS is based on a number of assumptions and extrapolations, rather than direct evidence, so further research is required to determine whether this potential benefit is realised in practice.

The estimates of adverse outcomes provided by our analysis can be used by clinicians to advise patients on the risks and benefits of thromboprophylaxis and support shared decision-making.

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Competing interests

S Goodacre is chair of the NIHR Health Technology Assessment Programme Clinical Evaluation and Trials Board and a member of the HTA Funding Boards Policy Group. K de Wit reports grants from Bayer, outside the submitted work. The remaining authors have no competing interests other than the grant support received by their respective institutions to deliver the study, as outlined in sources of funding below.

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Contributors

SD developed the decision analytic model and conducted the analysis. AP and DH conducted the systematic reviews that informed the modelling and JW undertook meta-analysis that informed the modelling. SG, DH, KW, and BH were members of the expert clinical group that informed development of the decision analytic model. All named authors contributed to management of the project and interpretation of the analysis. All named authors contributed to redrafting and approved the final draft of the paper. SG was Chief Investigator for this NIHR HTA project and is guarantor for the paper.

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Table 1: Predicted clinical outcomes per 100,000 patients with lower limb immobilisation due to injury

	Outcomes at 6 months per 100,000 patients							**Outcomes at 5 years per 100,000 patients**				
	Fatal PE	**Fatal bleed**	**Non-fatal ICH**	**Other major bleed[a]**	**Non-fatal PE**	**Symptomatic DVT**	**Asymptomatic DVT**	**PTS**	**PE survivor with CTEPH**	**PE survivor without CTEPH**	**ICH survivor**	**Dead (any cause)**
No prophylaxis	12	9	5	26	415	907	7052	1859	11	397	5	1133
Prophylaxis	7	12	8	35	225	492	3820	1007	6	215	7	1129

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

[a] Patients having other major bleeds could also have a DVT or non-fatal PE