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Davis, S. orcid.org/0000-0002-6609-4287, Goodacre, S. orcid.org/0000-0003-0803-8444, Pandor, A. orcid.org/0000-0003-2552-5260 et al. (4 more authors) (2019) Decision-analysis modelling of the effects of thromboprophylaxis for people with lower limb immobilisation for injury. British Journal of Haematology, 186 (1). pp. 166-168. ISSN 0007-1048

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Online appendix

Model structure

A decision analytic model was developed to estimate lifetime QALYs for a cohort of people having lower limb immobilisation due to injury. The model was developed in collaboration with an expert clinical group (see acknowledgements) who provided guidance on the selection of model outcomes based on clinical importance, and assessed the appropriateness of data sources and model assumptions. A six-month decision tree model (see Fig 1) was used to estimate for each strategy; the number of patients receiving thromboprophylaxis, the impact of thromboprophylaxis on VTE outcomes (PEs and DVTs), and the incidence of major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants. Major bleeds were divided into fatal bleeds, non-fatal ICHs and other major bleeds, with the latter being assumed to resolve within the six-month timeframe of the decision tree. 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. Patients having major bleeds during either prophylaxis or VTE treatment are assumed to stop their anticoagulant medication at the time of the bleed. The six-month time frame was considered sufficient to capture the period of immobilisation (6 weeks), the period of treatment following VTE during immobilisation (3 months) and a one-month period for recovery from major bleeds that are not intracranial. As it is difficult to distinguish PTS and CTEPH from acute symptoms during the first three months after VTE, diagnosis of these chronic complications is assumed not to occur until the end of the decision-tree phase of the model. The decision tree allows for the possibility that patients not having anticoagulation may have a major bleed during the period of lower limb immobilisation based on the risk of bleeding in the general population. The likelihood of VTE and the likelihood of bleeding during treatment for VTE is assumed to be independent of whether the patient had major bleeding during lower limb immobilisation, and independent of patient characteristics.

A Markov model (see Fig 2) 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 PTS following VTE and the risk of 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 survival between these groups. There is also a post ICH state to capture ongoing morbidity following ICHs. Further adverse outcomes (PTS, CTEPH) are not modelled following ICH as lifetime QALYs are assumed to be predominantly determined by

morbidity related to ICH. Recurrent VTEs are not allowed within the Markov model as these were not expected to differ according to whether patients received thromboprophylaxis following their lower limb injury. The Markov model has one 6-month cycle to extrapolate the outcomes of the decision tree up to 1 year, followed by annual cycles thereafter. All-cause mortality during the first year is applied at 6 months. Thereafter, the health state occupancy is half-cycle corrected such that all transitions between states, including mortality, is assumed to occur mid-cycle.

Patient population

The target population is patients having lower limb immobilisation following injury. The model estimates outcomes for a cohort of identical patients based on the average characteristics (age 46 and 51.5% male) of patients enrolled in the POT-CAST trial (van Adrichem *et al,* 2017). This study was selected as the source of baseline characteristics as it is a recent, large RCT conducted exclusively in Europe (the Netherlands) and the inclusion and exclusion criteria were similar to our population of interest.

Prophylaxis and treatment of VTE

In the base-case analysis, thromboprophylaxis was assumed to be subcutaneous LMWH, at a dose consistent with that recommended for daily thromboprophylaxis after hip or knee replacement. Prophylaxis was modelled to last for the duration of lower limb immobilisation which was assumed to be 42 days based on clinical expert advice. We assumed that the lowest cost preparation would be used, which we identified to be dalteparin (5000 units every 24 hours in pre-filled syringes for subcutaneous injection, marketed by Ennogen Healthcare Ltd and J M McGill Ltd) based on the NHS Drug Tariff (Joint Formulary Committee, 2018). Anticoagulant treatment for subsequent VTEs was assumed to be either phased anticoagulation (LMWH followed by warfarin) or direct oral anticoagulants (DOACs) with a 60:40 split based on registry data (Cohen *et al,* 2017).

The effectiveness of LMWH was derived from a systematic review of thromboprophylaxis in lower limb immobilisation. The number of major bleeding events identified in this review was low leading to an imprecise estimate of the relative risk for this adverse event (Pandor *et al,* in press). Instead of using this imprecise estimate, we applied the increased risk estimated from a pooled analysis of bleeding risks across all VTE prophylaxis studies taken from a systematic review conducted to inform national guidance on VTE prophylaxis in England (National Clinical Guideline Centre – Acute and Chronic Conditions (UK), 2010). The relative risk of bleeding on VTE prophylaxis was applied to the risk of major bleeding in patients without anticoagulation, determined from a large primary care database

with 16.4 million person years of follow-up (Hippisley-Cox and Coupland 2014). The clinical parameters incorporated in the model are summarised in Table 1.

Epidemiological parameters

The risk of VTE in patients not receiving thromboprophylaxis and the proportion of those VTE events that were PE, symptomatic DVT or asymptomatic DVT were informed by simple pooling of events across the comparator arms of the studies included in the review on the clinical effectiveness of thromboprophylaxis in lower limb injury (Pandor *et al,* in press). This also informed the split between proximal and distal DVTs. The proportion of major bleeds during thromboprophylaxis that are fatal and the split of non-fatal bleeds into ICH and other non-fatal bleeds was based on published estimates (Button *et al,* 2011; Fang *et al,* 2007; Hippisley-Cox and Coupland 2014). The absolute risk of bleeding during anticoagulant treatment, and the proportion of bleeds that are fatal, non-fatal ICH and other major bleeds was based on registry studies in patients having treatment for VTE (Kooiman *et al,* 2015; Nieto *et al,* 2010). The probability of PE being fatal and the cumulative risk of PTS were also based on registry studies (Hach-Wunderle *et al,* 2013; Maestre *et al,* 2010). A study which examined the relationship between PTS and adequate anticoagulation following DVT was used to adjust the risk of PTS in patients with asymptomatic proximal DVT, which is assumed to remain undiagnosed and untreated (van Dongen *et al,* 2005). The 2-year risk of CTEPH in patients surviving 3-6 months after PE was taken from a systematic review (Ende-Verhaar *et al,* 2017). Based on a prospective study with 10 year follow-up, we assumed that no new case of CTEPH would be diagnosed more than 2 years after PE (Pengo *et al,* 2004). The proportion of patients having medical or surgical management of CTEPH and the long-term survival in each group was taken from a registry study (Delcroix *et al,* 2016). An increased risk of mortality was applied in the first 6 years following haemorrhagic stroke based on estimates from a retrospective study (Fogelholm *et al,* 2005). Patients not having CTEPH, ICH, fatal PEs or fatal bleeds were assumed to have mortality risks equivalent to the general population (Office of National Statistics, 2017)

QALYs

In order to estimate QALYs it is necessary to quantify an individual's health utility, which is a measure of health-related quality of life (HRQoL) on a scale of zero to one. A systematic search was conducted to identify utility data specific to the population having lower limb immobilisation but this only identified a single study (Domeij-Arverud *et al,* 2016). To supplement this we examined a published systematic review of long-term HRQoL data in patients having VTE, (Lubberts *et al,* 2016) models submitted to inform NICE Technology Appraisals (Bayer Schering Pharma 2008; Bristol-Myers Squibb Pharmacetuicals Ltd and Pfizer Ltd, 2011; Bristol-Myers Squibb Pharmacetuicals Ltd and Pfizer Ltd,

2014; Copley *et al*, 2012; Edwards *et al*, 2015; Edwards *et al,* 2014; Greenhalgh *et al*, 2014; Harnan *et al*, 2012; Holmes *et al*, 2008; Riemsma *et al*, 2011; Stevenson *et al*, 2009) and Clinical Guidelines on the prevention and treatment of VTE, (National Clinical Guideline Centre – Acute and Chronic Conditions [UK] 2010, National Guideline Centre, 2017) and selected models already known to the authors (Goodacre *et al,* 2006; Goodacre *et al*, 2017; Simpson *et al,* 2009). From these sources, we selected utility data based on relevance to the health states in the model and the population having lower limb immobilisation. In order to maintain consistency with NICE's reference case, priority was given to utilities measured using the EQ-5D.

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 on HRQoL and a disutility was applied during VTE treatment to reflect patients' preferences to avoid long-term treatment with warfarin. During the Markov model phase (i.e beyond 6 months), patients without long-term sequelae or ongoing symptoms (PTS, CTEPH, ICH or PE) 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.

Patients having ICH were assumed to have reduced HRQoL life-long with separate utility values applied before and after 6 months. DVT without PTS was assumed not to result in any HRQoL decrement beyond 6 months, but patients having PTS, CTEPH or PE without CTEPH were assumed to have some ongoing HRQoL decrement. Patients having successful surgical treatment of CTEPH were assumed to have the same HRQoL as those with PE without CTEPH after 1 year. Utility data applied in the model are summarised in Table 2.

We assigned probability distributions to reflect the uncertainty around each parameter input and used Monte-Carlo simulation to propagate this uncertainty through the model. We estimated the mean and 95% credible interval for QALYs gained based on 10,000 sets of parameter samples.

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Table 1 Clinical parameters

Parameter description	Mean value	95% CI [a]	Source	Notes
CLINICAL PARAMETERS				
Probabilities of VTE in patients having lower limb immobilisation without thromboprophylaxis			Systematic review of thromboprophylaxis effectiveness (Pandor *et al,* in press)	Average proportion across 12 RCTs
- 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 (Pandor *et al,* in press)	Average proportion across 6 RCTs
Proportion of symptomatic DVTs that are distal	50%	26.5% to 73.4%	Systematic review of thromboprophylaxis effectiveness (Pandor *et al,* in press)	Based on single RCT that focused exclusively on symptomatic DVTs

Effectiveness of prophylaxis – Odds ratio (OR) for VTE	0.52	0.37 to 0.71	Systematic review of decision tools for identifying patients at risk of VTE (Pandor *et al,* in press)	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 patient years	1.86 to 1.92	Hippisley-Cox and Coupland (2014)	Age-standardised incidence across whole QBleed cohort: 1.34 per 1000 for GI bleed, 0.55 per 1000 for ICH
Bleed risk for prophylaxis versus none – HR	1.64	0.98 to 2.75	Pooled analysis of bleed risks across all VTE prophylaxis studies in NICE CG92 (National Clinical Guideline Centre – Acute and Chronic Conditions [UK] 2010)	Data presented in CG92 re-analysed 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%	17% to 25%	Case fatality rate of ICH bleeds taken from Fang *et al* (2007) Case fatality rate of GI bleeds taken from Button *et al* (2011)	Average fatality across GI and ICH bleeds with case fatality rates of 10% (95%CI 9.7% to 10.4%) case and 49% (95%CI 37% to 60%) respectively

			Proportion of bleeds that are GI and ICH based on Hippisley-Cox and Coupland (2014)	
Proportion of non-fatal major bleeds during lower limb immobilisation that are ICH (with and without prophylaxis)	19%	15.4% to 22.2%	Fang *et al* (2007), Button *et al* (2011) and Hippisley-Cox and Coupland (2014)	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 (* 2015)	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%	21% to 28%	Nieto *et al (*2010)	Based on case fatality rates for major bleeds within the RIETE registry (Nieto *et al,* 2010)
Proportion of non-fatal major bleeds during VTE treatment that are ICH	9%	6.5% to 11.9%	Nieto *et al (*2010)	Based on proportion of major non-fatal bleeds within RIETE registry that were ICH (Nieto *et al,* 2010)
All-cause (non VTE related) mortality	Varies by age	NA	Office of National Statistics (ONS) Lifetables, (ONS 2017)	Risk applied each year is based on current age and is not adjusted to account for contribution of VTE to population mortality.

Standardised mortality ratio (SMR) for patients surviving ICH compared with general population – year 1 after ICH - years 2 to 6 after ICH	 - 4.5 - 2.2	Ranges for SMRs not stated so have assumed ±20% on the logged scale	Fogelholm *et al* (2005)	Assumed no increased mortality risk after 6 years.
Probability of PE being fatal	2.9%	2.5% to 3.3%	Maestre *et al* (2010)	Data from RIETE registry. Case fatality rate of clinically overt PE in outpatients.
Cumulative risk of PTS for treated symptomatic DVT at 3 years - proximal - distal	 - 32.4% - 15.6%	 - 22.1% to 43.6% - 7.9% to 25.3%	Hach-Wunderle *et al (*2013) (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* (2005) Zero risk assumed from year 4 onwards

Cumulative risk of PTS for untreated asymptomatic DVT at 3 years - proximal - distal	 - 56.5% - 15.6%	 - 29.0% to 79.8% - Fixed relative to symptomatic	Hach-Wunderle *et al* (2013) and van Dongen *et al* (2005)	For proximal DVT the data for symptomatic DVT were uplifted using the OR from van Dongen *et al* (2005) 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 in distal DVT.
Risk of CTEPH per annum applied in the first 2 years after PE	1.6%	1.0% to 2.2%	Ende-Verhaar *et al (*2017)	3.2% (95%CI 2.0 %–4.4%) at 2 years based on incidence in those surviving the initial treatment period of 3-6 months Assumed no risk beyond 2 years based on Pengo *et al* (2004)
Proportion of CTEPH treated surgically	59.5%	55.8% to 63.2%	Delcroix *et al (*2016)	

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 (*2016) but curves taken from Goodacre *et al* (2017)	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
Mortality for CTEPH - Surgically treated	Lognormal 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 (*2016) but curves taken from Goodacre *et al* (2017)	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

CI, confidence interval; CG, clinical guideline; CTEPH, chronic thromboembolic pulmonary hypertension; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ED, emergency department; GI, gastrointestinal; GP, general practitioner; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; HR, hazard ratio; HRG, healthcare resource group; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; NHS, national health service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; ONS, Office for National Statistics; OR, odds ratio; OXVASC, Oxford Vascular Study; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RCT, randomised controlled trial; RIETE, The

Computerized Registry of Patients with Venous Thromboembolism; SMR, standardised mortality ratio; TULIPA, Thrombosis and Pulmonary Embolism in Out-Patients; SD, standard deviation; SE, standard error; VKA, vitamin K antagonist; VTE, venous thromboembolism;

[a] except where stated otherwise e.g. SD or SE

Table 2 Utility values applied in the decision tree and Markov phases of the model

Description of health state	Utility value	Range	Source	Notes
Absolute utility values applied during the 6 month decision tree model				
Well / asymptomatic DVT without prophylaxis	0.879	0.878 to 0.882	Ara and Brazier (2011)	Population mean utility values based on person (average for male and females) with starting age of 46
Symptomatic proximal or distal DVT	0.848	0.846 to 0.850	Cohen *et al* (2014) (using additional detail reported in TA354 (Edwards *et al,* 2015) company submission Table B78)	5% reduction relative to well patients based on comparison of average utility over 6 months for DVT (0.819) versus utility at 6 months (0.850) for patients with DVT
non-fatal PE	0.80	0.780 to 0.825	Cohen *et al* (2014) (using additional detail reported in TA354 (Edwards *et al,* 2015) company submission Table B78)	9% reduction relative to well patients based on comparison of average utility over 6 months (0.775) for PE versus utility at 6 months (0.850) for patients with DVT

non-fatal ICH	0.66	0.616 to 0.701	Luengo-Fernandez *et al,* (2013)	Absolute decrement of 0.22 measured at 1 month
non-fatal non-ICH bleed	0.69	0.652 to 0.688	Cohen *et al* (2014)	Assumed same disutility 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* (2014) Non-fatal non-ICH bleed bleeds assumed to last 28 days
Prophylaxis – absolute decrement applied to utility values of well / asymptomatic DVT	0.007	0.000 to 0.050	Marchetti *et al,* (2001)	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,* (2001)	Patients willing to trade average of 4 days per year to avoid treatment with warfarin
Fatal PE / fatal bleed	0	NA	Assumption	
Utility values applied as multipliers to age-based general population utility values in the Markov model				

PE survivor without CTEPH and PE survivor more than 1 year after surgery for CTEPH	0.95	0.927 to 0.978	Cohen *et al* (2014)	5% reduction relative to well patients based on comparison of at 6 months for PE (0.81) versus utility at 6 months (0.85) for patients with DVT
Any DVT without PTS	1	NA	Assumption	Supported by Lubberts *et al,* (2016) systematic review finding no significant HRQoL decrement in 9 long-term studies based on SF-36 outcomes
non-fatal ICH	0.89	0.810 to 0.955	Luengo-Fernandez *et al* (2013)	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,* (2013)	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,* (2008)	Multiplier calculated based on comparison of utility for CTEPH (0.56) versus utility for NYHA class I (0.89)
Dead	0		Assumption	

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