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Economic evaluation of strategies for restarting anticoagulation therapy with warfarin based on Venous Thromboembolism (VTE) risk after an index unprovoked VTE event

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Essentials

- Correct length of treatment after an index unprovoked Venous Thromboembolism (VTE) is unknown.
- Cost-utility analysis assessed at what predicted VTE risk it is worthwhile to restart therapy.
- Results imply restarting therapy if a patient's 1 year VTE risk is ≥17.5% may be cost-effective.
- However, sensitivity analyses indicate large parameter uncertainty in base case results.

Summary

Background: Following at least three months of anticoagulation therapy after a first unprovoked Venous Thromboembolism (VTE), there is uncertainty about the duration of therapy. Further anticoagulation therapy reduces the risk of having a potentially fatal recurrent VTE but at the expense of a higher risk of bleeding which can also be fatal.

Objective: An economic evaluation sought to estimate the long-term cost-effectiveness of using a decision rule for restarting anticoagulation therapy versus no extension of therapy in patients based on their risk of a further unprovoked VTE.

Methods: A Markov patient-level simulation model was developed which adopted a lifetime time horizon with monthly time cycles and was from a UK National Health Service (NHS) /Personal Social Services (PSS) perspective.

Results: Base case model results suggest that treating patients with a predicted one year VTE risk of 17.5% or higher may be cost-effective if decision makers are willing to pay up to £20,000 per Quality Adjusted Life Year (QALY) gained. However probabilistic sensitivity analysis show the model was highly sensitive to overall parameter uncertainty and warrants caution in selecting the optimal decision rule on cost-effectiveness grounds. Univariate sensitivity analyses indicate variables such as anticoagulation therapy disutility and mortality risks were very influential for driving model results.

Conclusion: This represents the first economic model to consider the use of a decision rule for restarting therapy for unprovoked VTE patients. Better data are required to predict long-term bleeding risks on therapy in this patient group.

Introduction

Venous Thromboembolism (VTE) is the development of a clot in the veins. The number of deaths from VTE in the UK each year is five times greater than deaths from breast cancer, AIDS, and road traffic incidents combined [1] and the cost of managing VTE was estimated at around £640 million to the UK National Health Service (NHS)[2]. While there are several risk factors that can provoke an initial VTE event (such as hormone intake, surgery, trauma, pregnancy and prolonged immobility), patients can suffer an initial VTE event without any known trigger (unprovoked).[3-5] Patients with an unprovoked VTE have a much higher risk of VTE recurrence than patients whose index VTE event has an identifiable cause.[6] The UK National Institute of Health and Care Excellence (NICE)[7] and the American College of Chest Physicians (ACCP) [8] recommend at least 3 months anticoagulation therapy following a first unprovoked VTE event; after three months of anticoagulation therapy following a first unprovoked VTE event, there is clinical equipoise on whether to extend anticoagulation therapy.[9-11] Extending anticoagulation therapy reduces the risk of having a possible recurrent VTE fatality; but treatment increases the risk of bleeding which can be fatal. Balancing the benefit and harm of further treatment requires the identification of risk of recurrent VTE and an optimal threshold of VTE risk above which recommending anticoagulation therapy is beneficial.

A previously developed prognostic model estimated an individual patient's risk of a further unprovoked VTE without treatment.[12] A

decision rule was developed using this prognostic model to stratify patients treatment strategies based on a threshold of VTE recurrence risk (e.g. 5% VTE recurrence risk at 1 year post therapy). This study aims to evaluate the cost-effectiveness of a decision rule for restarting therapy in patients after a first unprovoked VTE. The prognostic model uses data from D-Dimer testing 30 days after cessation of anticoagulation, however this test is not currently part of routine practice. A systematic review did not uncover any economic evaluations using a decision rule in this patient group.[12]

Methods

Model population

The patient population comprised adult individuals having already completed at least three months of anticoagulation therapy in response to their first unprovoked VTE. An initial VTE was defined as unprovoked where there was no history in the previous three months of any of the following risk factors: major surgery, lower limb trauma, use of combined oral contraceptive pill or hormone replacement therapy, pregnancy, significant immobility, or cancer.

Patients entered the model having already had their D-Dimer level measured thirty days after stopping at least three months of anticoagulation therapy. Individual patients were generated from patient data (Recurrent VTE Collaborative database)[13] previously used to develop the prognostic model. Each patient had characteristics created by randomly sampling the patient-level data by means of a uniform distribution. Patient characteristics

comprised age [mean: 61.7 years; standard deviation: 15.2], gender [61.8% Male], type of index VTE event (Distal Deep Vein Thrombosis (DVT)[9.2%], proximal DVT [58.5%], and Pulmonary Embolism (PE)[32.3%]) and post-anticoagulation D-Dimer level [mean: 667.3µg/L; standard deviation: 751.3]. The individual's risk of a recurrent VTE within 12 months was then determined by inputting their newly created characteristics into the prognostic model risk equation (Appendix Table I).[12] The risk distribution of the simulated patients is given in Appendix Table II.

Model pathways and clinical events

The economic model compared a strategy of no therapy (usual care) with a number of decision rule strategies, where therapy was restarted if the predicted annual risk of VTE recurrence was equal to or greater than the given threshold risk (Appendix Fig I). For pragmatic reasons, the arbitrary but clinically relevant thresholds were explored in the analyses:1%, 3%, 5%, 7.5% 10%, 12.5%, 15%, 17.5%, 20%, 22.5%, 25% and a treat-all strategy was also included as a comparator. These specified VTE risks were used as different decision rule comparators (example patient predicted risks are given in Appendix Table III). No patients initially resumed anticoagulation therapy in the no decision rule comparator. The decision rule was applied at the starting point of the model only. Once the decision rule was applied, all the patients encountered the same potential

pathways in all strategies (Fig I), with their characteristics determining the probabilities of clinical events, costs and utilities.

In one month, an individual had the probability of experiencing one clinical event: death from other causes, recurrent VTE (non-fatal distal or proximal DVT, fatal or non-fatal PE), fatal or non-fatal major bleeds (intracranial bleed, gastrointestinal bleed, and other major bleeds). A recurrent VTE carried a risk of Post-Thrombotic Syndrome (PTS).

Other cause mortality was dependent on the current age and gender of the patient and was taken from UK life tables.[14] Recurrent VTE risk depended on a patient's characteristics, time spent in the model, previous history of a recurrent VTE event taking place in the model, and treatment status. A recurrent VTE could be a PE, distal DVT, or proximal DVT. The recurrent VTE type was assumed to be affected by an individual's initial VTE site. Once a patient suffered a recurrent VTE, they were put on anticoagulation therapy for life with therapy cessation only occurring with a later major bleeding event. VTE events were assumed to incur a one-off quality of life reduction, with a proportion of surviving patients assumed to suffer from severe PTS for life.

The risk factors for a major bleed in the model were treatment status and an individual's' age if on treatment. Major bleeds were split into "gastrointestinal bleeds", "intracranial bleeds" and "other major bleeds." All major bleeding events had short-term costs and quality of life decrements. In addition, an intracranial bleed was

assumed to be associated with ongoing costs and a permanent quality of life decrement along with a sustained increased lifetime risk of other cause mortality. For the “other major bleeds” category, it was agreed by clinical consensus that this heterogenous category of bleeds should have the same costs and quality of life decrement as a gastrointestinal bleed, for model simplification purposes.

Any major bleeding event led to discontinuation of anticoagulation therapy. A recurrent VTE in a later cycle was assumed to restart therapy. It was assumed that there was no effect of anticoagulation therapy on VTE recurrence risk by thirty days post cessation of therapy.

Model type

A Markov patient-level simulation was developed in TreeAge 2014 (TreeAge software, Williamstown, MA, USA) to estimate the cost-effectiveness of using a decision rule for restarting anticoagulation therapy versus no anticoagulation therapy (usual care) in patients with a first unprovoked VTE event. A Markov model was deemed appropriate as it can represent a clinical situation where patients move between health states over a long period of time. A patient-level simulation allows individual patients, each with a set of varying characteristics created from patient level data, to be assigned a risk of VTE recurrence. Patient characteristics and clinical events which affect subsequent risks were remembered in the model with tracker variables. The model was run with a large number of simulated patients (50,000) to account for inter-patient variability.

A time cycle of one month was selected to represent an assumption that this reflects a period in which a single clinical event might occur. Costs, utilities and probabilities were transformed into monthly equivalents as per the time cycle length. A half cycle correction was applied to costs and effects. The base-case cost-utility analysis was undertaken from a UK National Health Service (NHS)/ Personal Social Services (PSS) perspective and considered a lifetime horizon.

Clinical Parameters

Parameter estimates and their sources are listed in Table ~~I~~Table I. The base case scenario used warfarin as the anticoagulation therapy. The risk of a patient's first recurrent VTE off therapy was calculated using the prognostic model for up to three years post D-Dimer measurement (30 days after initial therapy cessation). Weak calibration statistics of the prognostic model after three years prompted the use of an annual constant risk for the first recurrent VTE event off therapy thereafter. [15] Annual risk of a further VTE event after a VTE recurrence was an average of values for patients with normal and elevated D-Dimer levels, on and off therapy respectively in the PREVENT trial.[16]

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Resource use and costs

Costs of therapy and clinical events were included in the model (Table ~~I~~Table I). The cost of a D-Dimer test was incurred by the decision rule strategies as the D-Dimer information was needed to

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enact the decision rules. All costs were updated to 2012/2013 prices using the Hospital and Community Health Services (HCHS) Index.[17]

Quality of life

Quality of life (utility) values were assumed to be age related as they enter the model using EuroQol–5 Dimensions (EQ-5D) UK normative values.[18] As patients aged in the model, their utility score changed to reflect their updated quality of life for their age. Utility values for clinical events and being on warfarin therapy (Table II~~Table II~~) were multiplied by the age-specific utility to derive quality of life reductions for patients experiencing a clinical event and/or on warfarin therapy.

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Assessment of cost-effectiveness

The sequential incremental analysis was designed to calculate the cost per quality-adjusted life year (QALY) gained for applying a decision rule versus the next most effective option, applying the rules of dominance and extended dominance. Cost-effectiveness was assessed in relation to the National Institute for Health and Care Excellence (NICE) lower threshold of £20,000 per QALY, where a value of £20,000/QALY is judged to be cost-effective.[19] Strategies were compared by increasing effectiveness and incremental cost-effectiveness ratios (ICERs) were calculated from the difference in costs and effects between a decision rule strategy and the next best alternative. A strategy is said to be dominated if they were more expensive and less effective than a comparator. All costs and outcomes were discounted at the recommended 3.5%.[20]

Deterministic Sensitivity Analysis

To test the robustness of base-case results, a number of deterministic sensitivity analyses were run to determine the impact of changing key parameters on results.

- The model time horizon was restricted to 3 years corresponding to the length of time the VTE prognostic model is used.[12]
- The utility of warfarin therapy was reduced from 0.997 to 0.950 to assess how greater disutility associated with anticoagulant treatment affects results.
- The probability of death from a PE was increased to 30% due to uncertainty amongst clinical experts on the true value.
- The model entry was restricted to patients aged 60 and above, where risk of bleeding on therapy is higher.
- Sub-group analyses were undertaken for index PE patients and index DVT patients, as the sub-group of PE patients were at higher risk of recurrence and mortality.
- Sub-group analyses were undertaken for male and female patients respectively
- The lag time in days for d-dimer was adjusted from 30 days to 20 and 40 days respectively which changed the risk profile of the patients.

Probabilistic Sensitivity Analysis

Where available, data were input into the model as distributions to assess parameter uncertainty in the form of a probabilistic sensitivity analysis (PSA). The model was rerun with 10,000 simulations for each trial of 1,000 simulated patients and the results expressed as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

Results

Base Case Results

Under base-case assumptions, restarting warfarin therapy for patients with a predicted annual VTE recurrence risk of 25% gave the lowest cost per QALY of £1,983 (Table III~~Table III~~). However, resuming anticoagulation therapy for patients with a predicted annual VTE recurrence risk of 17.5% yielded the highest number of QALYs while also being considered cost-effective with an ICER of £14,980/QALY gained.

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Probabilistic Sensitivity Analysis Results

The PSA results demonstrate there is considerable uncertainty around the base case results. The cost-effectiveness planes (Appendix Fig II-VIII) show the large uncertainty in the QALY differences for all strategies. The majority of the cost-QALY difference values indicate all strategies to be more costly than treating no-one, but many of the points were in the north-west quadrant, where a strategy is more expensive and less effective compared to treat no-one (dominated).

The CEACs, which compared the most cost-effective base case option (17.5%) against several strategies (10%,12.5%,15%, 20%, 22.5%, 25%), show that treating those with a one year VTE risk of 17.5% has a 44.8-73.3% probability of being cost-effective at a willingness to pay threshold of £20,000 per QALY gained (Appendix Fig IX-XV). The results highlight substantial parameter uncertainty even if the calculated ICER point estimates for the base-case results appear to be cost-effective.

Deterministic sensitivity analysis results

Deterministic sensitivity scenario results are shown in Table IV~~Table IV~~. These illustrate that some variables were pivotal in changing the direction of model results. Assuming a greater disutility of being on warfarin therapy permits the 22.5% and 25% threshold decision rule to be cost-effective.

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Increasing the risk of death from PE had improved the cost-effectiveness of the lower risk decision rule strategies compared with no therapy, with the 12.5% decision rule strategy yielding an ICER of £11,129/QALY gained. The age profile of patients made a difference to results. Allowing for a patient population to be aged 60 and above only (higher bleeding risk on anticoagulation) revealed the 22.5% threshold option and above to be a cost-effective option, with all other options not cost-effective. Likewise, model results were sensitive to a patient's index VTE event type. All decision rule strategies of 10% and above were cost effective when the patients' index event was a PE reflecting the high risk nature of such index

events. In contrast, the 25% threshold was the only cost effective options when the patients' index event was a DVT.

Adjusting the lag time had little effect on the cost-effectiveness of the results except for the 15% decision rule; this was now cost-effective when the lag time was increased from 20 to 40 days. Having a male-only cohort meant the lowest threshold to be cost-effective is the 12.5% while a female-only cohort restricted the lowest threshold to be cost-effective to 15%.

Discussion

Principal findings

The economic evaluation assessed the cost-effectiveness of utilising a decision rule for the resumption of anticoagulation therapy in patients with a first unprovoked VTE. The base-case results indicate that treating patients with a predicted one year VTE risk of 17.5% and above with warfarin could be cost-effective compared to the next most effective option. These VTE risk cut-off points for treatment were much higher than what is considered acceptable in the literature.[21]

However, PSA results suggest great caution must be applied when considering the base case results. Above 25% of the iterations showed less QALYs in the restarting anticoagulation decision rule strategies compared to the not restarting anticoagulation therapy strategy ("treat no-one"); the 17.5% decision rule was the optimal

option in less than half the iterations when compared to the higher VTE risk thresholds in the CEACs.

Quality of life on treatment and mortality risk were important determinants in the cost-effectiveness results. Incorporating a greater disutility on warfarin therapy changes the results with only the 22.5% and 25% VTE risk threshold options remaining cost-effective. Meanwhile, a small change in the proportion of PEs that result in death makes restarting anticoagulation therapy at 12.5% even more cost-effective.

Focusing on different subcategories of patients also changes the base-case results. Sensitivity analyses suggest that all index PE patients with a predicted VTE recurrence risk of 10% and above should be treated with lifelong anticoagulation therapy, likely because these patients were assumed to have a higher risk of a recurrent VTE that would be a PE. Conversely, for index DVT patients, the only restart anticoagulation option favoured on cost-effectiveness grounds is a one year recurrent VTE risk of 25% or higher. The impact of higher bleeding risks from anticoagulation therapy in the older patient population aged sixty and above was not offset by the reduced risk of recurrent VTE at the lower risk thresholds strategies.

Strengths and weaknesses of the analysis

This is the first economic evaluation to consider using a decision rule to weigh up the advantages and disadvantages of resuming

anticoagulation treatment in unprovoked VTE patients. A key strength of the analysis is the use of an individual patient simulation which allows a personalised risk prediction for hypothetical patients with characteristics drawn from real patient data. This was preferable to the more common cohort model with a homogenous set of characteristics as the model results were more representative of a realistic patient population. The modelling method lessened the need for a multitude of separate health states as the Markovian lack of memory assumption encountered in cohort models was overcome by tracker variables.

Several simplifying assumptions were needed. The prognostic model used to calculate individual risk predictions was applied at 30 days post cessation of anticoagulation therapy which is not clinically ideal as some patients will have recurrence in these thirty days. This was due to D-dimer measurements being included within the prognostic model as an important predictor improving model discrimination, and so stratification of patients into high and low risk groups (as in the decision rule examined here).[12] D-dimer measurements were only available post cessation of therapy in the original dataset, however there is much interest and potential benefit in the use of D-dimer measurements on therapy as a predictor.[22] Indeed this would allow immediate treatment decisions to be made before cessation of therapy, potentially negating the small number of possible recurrent events in the 30 day window from cessation of therapy to use of the decision rule evaluated here. The model does not include pulmonary hypertension which could be considered a

further limitation and its inclusion may lower the risk threshold for treatment.

In the absence of data, constant VTE recurrence risks were used beyond three years, after a subsequent VTE and on treatment. In practice, recurrent VTE risk is likely to vary by patient characteristics. Additionally, the use of the prognostic model for the economic analysis implicitly assumes that the risk prediction tool is perfectly accurate. However, there will be a degree of error between predictions and reality. For example, the prognostic model was derived from patient level trial data and there is an inherent selectivity of patients in trials (e.g. fewer co-morbidities).In addition, the course of action on the resumption and cessation of anticoagulation after a major bleeding event may differ between patients. In truth, some patients may continue with their anticoagulation therapy after a major bleed while others who subsequently go on to suffer a VTE may not restart anticoagulation due to their high bleeding risk.

Only considering a health care perspective was considered in this model, in line with UK national guidance, where threshold values of cost-effectiveness are available (£20,000-£30,000 per QALY).[19] Cost-effectiveness may differ when using the societal perspective, but it would be difficult to determine in what direction. Whilst patient-incurred costs would be higher with prolonged treatment with lifelong anticoagulation due to visits for INR tests, productivity losses may be higher in where there is a higher risk of clinical events

such as DVT, PE and bleeds, or if anticoagulation is required due to a further thrombotic event.

Future research

The sensitivity analyses have shown the large uncertainty underlying many of the parameters and their effect on results. Thus, there is a need for robust long-term data on the risk of recurrent VTE in unprovoked index VTE patients. The decision rule aims to balance the risks of recurrence and bleeding, and as such accurate bleeding risk data is required for the unprovoked population. It is likely that similar to the risk of VTE recurrence, the bleeding risk of individuals is highly heterogeneous, and as such a prognostic model similar to that used for predicting patients VTE recurrence risk could be invaluable in improving the accuracy of the economic evaluation results. Lastly, future research should aim to incorporate on therapy predictors such as D-dimer in prognostic models to provide more timely risk predictions useful for clinical practice.

Author Contributions

SJ is the guarantor. JE, DM, DF and SJ wrote the study protocol. MM contributed to the development of the economic model, undertook cost-effectiveness analyses, and drafted the first manuscript under the supervision of SJ. DF provided clinical input. SJ, JE, DM, and DF contributed to the planning/methodological development and writing of the manuscript. All authors read, provided feedback and approved the final manuscript.

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1 Table I- Model Parameters

Parameter (distribution type)	Estimate (distribution parameters)	Source
Clinical Parameters	-	-
Annual risk of recurrent VTE off therapy (fixed)	Prognostic model equation (see Appendix Table I)	[12]
Short term 6 month risk of recurrent VTE on anticoagulation therapy (beta)	2.1% (α=27, β=1239)	[23]
Long-term annual risk of VTE recurrence beyond 6 months on therapy (beta)	1.3% (α=1, β=78)	[24]
Long-term annual risk of VTE recurrence beyond 3 years off therapy(beta)	5.0% (α=5, β=95)	[15]
Annual risk of further VTE off therapy after previous recurrent VTE (beta) Off therapy On therapy	 12.0% (α=11, β=81) 5.0% (α=5, β=95)	[16]
Probability a recurrent VTE is a PE by index event (beta) Index event DVT Index event PE	 0.15 (α=15, β=88) 0.52 (α=30, β=28)	[13]
Probability of death from PE in the first month (beta)	0.2 (α=2, β=8)	Clinical consensus
Proportion of recurrent VTEs resulting in severe PTS (beta)	1.1% (α=4, β=345)	[25]
Annual risk of major bleed by age group (beta) Not on therapy On therapy <65 65-74 75+	 0.45%(α=25,β=5593) 2.43% (α=23, β= 929) 3.25% (α=86, β=2554) 4.37% (α=106, β=2324)	 [26] [27]
Split of major bleeds by bleed type (dirichlet) Gastrointestinal bleed Intracranial bleed Other major bleed	 36.5% 17.9% 45.6% (α_1;α_2;α_3) = (499;245;622)	[28]
Risk of death from major bleed (first month) (beta) Gastrointestinal bleed Intracranial bleed Other major bleed	 18.4% (α=92, β=407) 32.2% (α=79, β=166) 10.5% (α=65, β=557)	[28]
Standardised mortality ratio for after an intracranial bleed (Lognormal)[1]	2.2 (95% CI 2.0-2.4)	[29]
Unit costs	-	-

Pulmonary Embolism (fixed)	£1,519	[30]
Distal Deep Vein Thrombosis (fixed)	£732	[30]
Proximal Deep Vein Thrombosis (fixed)	£732	[30]
12 months warfarin monitoring (fixed)	£337	[31]
Warfarin (4mg per day, 12 months) (fixed)	£22	[32]
Gastrointestinal bleed (fixed)	£1,092	[30]
Other major bleed (fixed)	£1,092	Assumed same as GI Bleed
Intracranial bleed: acute cost (gamma)	£8,350 (α=31.0, β=269.4)[2]	[33]
Intracranial bleed: annual cost (fixed)	£1,300	[33]
D-Dimer test	£26	[34]

[1.] A 95% confidence interval is assumed to be ±0.2 of the mean.
[2.] α is the shape parameter and β is the scale parameter
VTE= Venous Thromboembolism, PTS=Post Thrombotic Syndrome, PE= Pulmonary Embolism

Table II- Utility Values for Health States

Health state/ clinical event	Median Utility value (Inter-Quartile Range)	Beta distribution	Duration of Disutility	Source
DVT	0.84 (0.64-0.98)	α=2.0, β=0.6	1 month	[35]
PE	0.63 (0.36-0.86)	α=1.2, β=0.8	1 month	[35]
Non-fatal intracranial bleed	0.33 (0.14-0.53)	α=1.2, β=2.1	Permanent	[35]
GI Bleed	0.65 (0.49-0.86)	α=1.2, β=0.8	2 weeks	[35]
Other Bleeds	0.65 (0.49-0.86)	α=1.2, β=0.8	2 weeks	Assumed same as GI Bleeds
Severe PTS	0.82 (0.66-0.97)	α=3.0, β=0.9	Permanent	[35]
Warfarin	0.997 (0.953-1.0)[1]	α=16.4, β=0.3	Treatment length	[36]

[1.] 10th and 90th percentile reported instead of Inter-Quartile Range (IQR)
GI Bleed= Gastrointestinal Bleed, DVT= Deep Vein Thrombosis, PTS=Post Thrombotic Syndrome

Table III - Cost-effectiveness of using each decision rule sorted by increasing effectiveness (Lifetime time horizon)

Strategy	Mean cost (£)	Mean QALYs	ICER (Cost/QALY) (£)
Treat all	5882	10.4134	Dominated
Decision rule: 1%	5791	10.4223	Dominated
Decision rule: 3%	5468	10.4522	Dominated
Decision rule: 5%	5006	10.4897	Dominated
Treat No one	3284	10.5160	-
Decision rule: 7.5%	4411	10.5309	Dominated
Decision rule: 25%	3324	10.5361	1983
Decision rule: 22.5%	3347	10.5404	5360
Decision rule: 20%	3385	10.5427	Extended domination
Decision rule: 17.5%	3443	10.5468	14980
Decision rule: 15%	3541	10.5511	22708
Decision rule: 10%	3962	10.5534	Dominated
Decision rule: 12.5%	3703	10.5542	53178

ICER= Incremental Cost-Effectiveness Ratio, QALY= Quality-Adjusted Life Year, VTE= Venous Thromboembolism

Decision rule strategies based on whether to restart warfarin therapy according to a patient's predicted 1 year risk of a VTE recurrence. Strategies are compared with the next best non-dominated option.

Table IV- Sensitivity Analysis Scenarios

Strategy	Mean cost (£)	Mean QALYs	ICER (Cost/QALY) (£)	Strategy	Mean cost (£)	Mean QALYs	ICER (Cost/QALY) (£)
3 year time horizon				**Male only patients**			
Treat No-one	385	2.2066	-	Treat No-one	3520	10.6271	-
Decision Rule: 25%	395	2.2085	5108	Decision Rule: 25%	3580	10.6666	1509
Decision Rule: 22.5%	402	2.2090	14520	Decision Rule: 22.5%	3613	10.6764	3378
Decision Rule: 17.5%	430	2.2097	40182	Decision Rule: 17.5%	3743	10.7019	5085
Decision Rule: 12.5%	510	2.2107	82797	Decision Rule: 12.5%	4109	10.7352	10975
				Decision Rule: 10%	4455	10.7471	29022
Higher risk of death from PE				**Female only patients**			
Treat No-one	3163	10.3430	-	Treat No-one	2842	9.8863	-
Decision Rule: 25%	3208	10.3725	1507	Decision Rule: 25%	2856	9.8906	3217
Decision Rule: 22.5%	3234	10.3802	3447	Decision Rule: 20%	2881	9.8963	4403
Decision Rule: 17.5%	3332	10.3958	6250	Decision Rule: 17.5%	2906	9.9001	6746
Decision Rule: 15%	3434	10.4088	7882	Decision Rule: 15%	2948	9.9058	7272
Decision Rule: 12.5%	3602	10.4238	11129	Decision Rule: 10%	3182	9.9144	27337
Decision Rule: 10%	3868	10.4327	29850	Decision Rule: 7.5%	3510	9.9176	102125
All patients aged ≥60 years				**Lag d-dimer time of 20 days**			
Treat No-one	2412	8.3657	-	Treat No-one	3376	10.4989	-
Decision Rule: 25%	2443	8.3771	2767	Decision Rule: 25%	3427	10.5245	1994
Decision Rule: 22.5%	2462	8.3783	15460	Decision Rule: 17.5%	3575	10.5370	11842
Decision Rule: 20%	2487	8.3794	22315	Decision Rule: 15%	3690	10.5423	21728
Decision Rule: 17.5%	2531	8.3805	42386	Decision Rule: 12.5%	3883	10.5459	53213
Decision Rule: 15%	2601	8.3807	253213				
All patients with index PE event				**Lag d-dimer time of 40 days**			
No treat	3309	10.1416	-	Treat No-one	3227	10.5295	-
Decision Rule: 25%	3356	10.1842	1105	Decision Rule: 25%	3261	10.5459	2073
Decision Rule: 22.5%	3384	10.1975	2094	Decision Rule: 22.5%	3280	10.5492	5701
Decision Rule: 20%	3429	10.2102	3561	Decision Rule: 20%	3314	10.5519	12669
Decision Rule: 17.5%	3499	10.2229	5479	Decision Rule: 15%	3447	10.5594	17634
Decision Rule: 15%	3614	10.2403	6634	Decision Rule: 12.5%	3589	10.5619	58581
Decision Rule: 12.5%	3799	10.2639	7836				
Decision Rule: 10%	4089	10.2868	12633				
Decision Rule: 7.5%	4589	10.3000	38079				
All patients with index DVT event				**Higher warfarin disutility**			
Treat No-one	3165	10.7310		Treat No-one	3284	10.3319	
Decision Rule: 25%	3197	10.7361	6277	Decision Rule: 25%	3324	10.3451	3008
Decision Rule: 22.5%	3213	10.7365	50891	Decision Rule: 22.5%	3347	10.3466	16217

ICER= Incremental Cost-Effectiveness Ratio, QALY= Quality-Adjusted Life Year, PE= Pulmonary Embolism, DVT= Deep Vein Thrombosis

Decision rule strategies based on whether to restart warfarin therapy according to a patient's predicted 1 year risk of a VTE recurrence. Dominated strategies (more costly and less effective) are excluded from the table.