

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

Monahan, Mark; Ensor, Joie; Moore, David; Fitzmaurice, David; Jowett, Sue

DOI:  
[10.1111/jth.13739](https://doi.org/10.1111/jth.13739)

License:  
None: All rights reserved

Document Version  
Peer reviewed version

Citation for published version (Harvard):  
Monahan, M, Ensor, J, Moore, D, Fitzmaurice, D & Jowett, S 2017, 'Economic evaluation of strategies for restarting anticoagulation therapy with warfarin based on Venous Thromboembolism (VTE) risk after an index unprovoked VTE event', *Journal of Thrombosis and Haemostasis*, vol. 15, no. 8, pp. 1591–1600.  
<https://doi.org/10.1111/jth.13739>

[Link to publication on Research at Birmingham portal](#)

## Publisher Rights Statement:

This is the peer reviewed version of the following article: Monahan M, Ensor J, Moore D, Fitzmaurice D, Jowett S. Economic evaluation of strategies for restarting anticoagulation therapy after a first event of unprovoked venous thromboembolism. *J Thromb Haemost* 2017; 15: 1591–600., which has been published in final form at <http://dx.doi.org/10.1111/jth.13739>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving

Eligibility for repository: Checked on 2/5/2017

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

Download date: 21. Jan. 2021

Economic evaluation of restarting OAC therapy

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

4 M Monahan<sup>1</sup>

5 J Ensor<sup>2</sup>

6 D Moore<sup>1</sup>

7 D Fitzmaurice<sup>1</sup>

8 S Jowett<sup>1#</sup>

9 <sup>1</sup>University of Birmingham, Birmingham, UK

10 <sup>2</sup> Keele University, Keele, UK

11 #Corresponding author: Sue Jowett, Senior Lecturer, Health

12 Economics Unit, Institute of Applied Health Research, Public Health

13 Building, University of Birmingham, Edgbaston, Birmingham, B15

14 2TT, UK.

15 Tel: 0121 414 7898, Fax: 0121 414 8969

16 Funding: NIHR Health Technology Assessment Programme

17 (10/94/02)

18 Key words: Deep Vein Thrombosis; Pulmonary Embolism; Cost-

19 Benefit Analysis; Medical Economics; Venous Thromboembolism

20 Word count: Abstract 242; Text 3278; Tables 4; Figures 1; Appendix

21 1; References 30

22

## Economic evaluation of restarting OAC therapy

### 1       **Essentials**

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

### 10 11       **Summary**

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

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

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

## Economic evaluation of restarting OAC therapy

- 1 Results: Base case model results suggest that treating patients with
- 2 a predicted one year VTE risk of 17.5% or higher may be cost-
- 3 effective if decision makers are willing to pay up to £20,000 per
- 4 Quality Adjusted Life Year (QALY) gained. However probabilistic
- 5 sensitivity analysis show the model was highly sensitive to overall
- 6 parameter uncertainty and warrants caution in selecting the optimal
- 7 decision rule on cost-effectiveness grounds. Univariate sensitivity
- 8 analyses indicate variables such as anticoagulation therapy disutility
- 9 and mortality risks were very influential for driving model results.
  
- 10 Conclusion: This represents the first economic model to consider the
- 11 use of a decision rule for restarting therapy for unprovoked VTE
- 12 patients. Better data are required to predict long-term bleeding risks
- 13 on therapy in this patient group.
  
- 14

## Economic evaluation of restarting OAC therapy

### 1 Introduction

2 Venous Thromboembolism (VTE) is the development of a clot in the  
3 veins. The number of deaths from VTE in the UK each year is five  
4 times greater than deaths from breast cancer, AIDS, and road traffic  
5 incidents combined [1] and the cost of managing VTE was estimated  
6 at around £640 million to the UK National Health Service (NHS)[2].

7 While there are several risk factors that can provoke an initial VTE  
8 event (such as hormone intake, surgery, trauma, pregnancy and  
9 prolonged immobility), patients can suffer an initial VTE event  
10 without any known trigger (unprovoked).[3-5] Patients with an  
11 unprovoked VTE have a much higher risk of VTE recurrence than  
12 patients whose index VTE event has an identifiable cause.[6] The UK  
13 National Institute of Health and Care Excellence (NICE)[7] and the  
14 American College of Chest Physicians (ACCP) [8] recommend at least  
15 3 months anticoagulation therapy following a first unprovoked VTE  
16 event; after three months of anticoagulation therapy following a  
17 first unprovoked VTE event, there is clinical equipoise on whether to  
18 extend anticoagulation therapy.[9-11] Extending anticoagulation  
19 therapy reduces the risk of having a possible recurrent VTE fatality;  
20 but treatment increases the risk of bleeding which can be fatal.  
21 Balancing the benefit and harm of further treatment requires the  
22 identification of risk of recurrent VTE and an optimal threshold of  
23 VTE risk above which recommending anticoagulation therapy is  
24 beneficial.

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

## Economic evaluation of restarting OAC therapy

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

## 10 Methods

### 11 *Model population*

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

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

## Economic evaluation of restarting OAC therapy

1 comprised age [mean: 61.7 years; standard deviation: 15.2], gender  
2 [61.8% Male], type of index VTE event (Distal Deep Vein Thrombosis  
3 (DVT)[9.2%], proximal DVT [58.5%], and Pulmonary Embolism  
4 (PE)[32.3%]) and post-anticoagulation D-Dimer level [mean:  
5 667.3 $\mu$ g/L; standard deviation: 751.3]. The individual's risk of a  
6 recurrent VTE within 12 months was then determined by inputting  
7 their newly created characteristics into the prognostic model risk  
8 equation (Appendix Table I).[12] The risk distribution of the  
9 simulated patients is given in Appendix Table II.

10

### 11 *Model pathways and clinical events*

12 The economic model compared a strategy of no therapy (usual care)  
13 with a number of decision rule strategies, where therapy was  
14 restarted if the predicted annual risk of VTE recurrence was equal to  
15 or greater than the given threshold risk (Appendix Fig I). For  
16 pragmatic reasons, the arbitrary but clinically relevant thresholds  
17 were explored in the analyses:1%, 3%, 5%, 7.5% 10%, 12.5%, 15%,  
18 17.5%, 20%, 22.5%, 25% and a treat-all strategy was also included as  
19 a comparator. These specified VTE risks were used as different  
20 decision rule comparators (example patient predicted risks are given  
21 in Appendix Table III). No patients initially resumed anticoagulation  
22 therapy in the no decision rule comparator. The decision rule was  
23 applied at the starting point of the model only. Once the decision  
24 rule was applied, all the patients encountered the same potential

## Economic evaluation of restarting OAC therapy

1 pathways in all strategies (Fig I), with their characteristics

2 determining the probabilities of clinical events, costs and utilities.

3 In one month, an individual had the probability of experiencing one

4 clinical event: death from other causes, recurrent VTE (non-fatal

5 distal or proximal DVT, fatal or non-fatal PE), fatal or non-fatal major

6 bleeds (intracranial bleed, gastrointestinal bleed, and other major

7 bleeds). A recurrent VTE carried a risk of Post-Thrombotic Syndrome

8 (PTS).

9 Other cause mortality was dependent on the current age and

10 gender of the patient and was taken from UK life tables.[14]

11 Recurrent VTE risk depended on a patient's characteristics, time

12 spent in the model, previous history of a recurrent VTE event taking

13 place in the model, and treatment status. A recurrent VTE could be a

14 PE, distal DVT, or proximal DVT. The recurrent VTE type was

15 assumed to be affected by an individual's initial VTE site. Once a

16 patient suffered a recurrent VTE, they were put on anticoagulation

17 therapy for life with therapy cessation only occurring with a later

18 major bleeding event. VTE events were assumed to incur a one-off

19 quality of life reduction, with a proportion of surviving patients

20 assumed to suffer from severe PTS for life.

21 The risk factors for a major bleed in the model were treatment

22 status and an individual's' age if on treatment. Major bleeds were

23 split into "gastrointestinal bleeds", "intracranial bleeds" and "other

24 major bleeds." All major bleeding events had short-term costs and

25 quality of life decrements. In addition, an intracranial bleed was



## Economic evaluation of restarting OAC therapy

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

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

### 12 *Model type*

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

## Economic evaluation of restarting OAC therapy

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

### 9 *Clinical Parameters*

10 Parameter estimates and their sources are listed in [Table 1](#).  
11 The base case scenario used warfarin as the anticoagulation  
12 therapy. The risk of a patient's first recurrent VTE off therapy was  
13 calculated using the prognostic model for up to three years post D-  
14 Dimer measurement (30 days after initial therapy cessation). Weak  
15 calibration statistics of the prognostic model after three years  
16 prompted the use of an annual constant risk for the first recurrent  
17 VTE event off therapy thereafter. [15] Annual risk of a further VTE  
18 event after a VTE recurrence was an average of values for patients  
19 with normal and elevated D-Dimer levels, on and off therapy  
20 respectively in the PREVENT trial.[16]

### 21 *Resource use and costs*

22 Costs of therapy and clinical events were included in the model  
23 ([Table 1](#)). The cost of a D-Dimer test was incurred by the  
24 decision rule strategies as the D-Dimer information was needed to

Formatted: Font: Not Bold

Formatted: Font: Not Bold

## Economic evaluation of restarting OAC therapy

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

### 3 *Quality of life*

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

### 12 *Assessment of cost-effectiveness*

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

Formatted: Font: Not Bold

## Economic evaluation of restarting OAC therapy

### 1 *Deterministic Sensitivity Analysis*

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

- 5 • The model time horizon was restricted to 3 years  
6 corresponding to the length of time the VTE prognostic  
7 model is used.[12]
- 8 • The utility of warfarin therapy was reduced from 0.997 to  
9 0.950 to assess how greater disutility associated with  
10 anticoagulant treatment affects results.
- 11 • The probability of death from a PE was increased to 30%  
12 due to uncertainty amongst clinical experts on the true  
13 value.
- 14 • The model entry was restricted to patients aged 60 and  
15 above, where risk of bleeding on therapy is higher.
- 16 • Sub-group analyses were undertaken for index PE patients  
17 and index DVT patients, as the sub-group of PE patients  
18 were at higher risk of recurrence and mortality.
- 19 • Sub-group analyses were undertaken for male and female  
20 patients respectively
- 21 • The lag time in days for d-dimer was adjusted from 30 days  
22 to 20 and 40 days respectively which changed the risk  
23 profile of the patients.

### 24 *Probabilistic Sensitivity Analysis*

## Economic evaluation of restarting OAC therapy

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

### 7 Results

#### 8 *Base Case Results*

9 Under base-case assumptions, restarting warfarin therapy for  
10 patients with a predicted annual VTE recurrence risk of 25% gave  
11 the lowest cost per QALY of £1,983 (Table III). However,  
12 resuming anticoagulation therapy for patients with a predicted  
13 annual VTE recurrence risk of 17.5% yielded the highest number of  
14 QALYs while also being considered cost-effective with an ICER of  
15 £14,980/QALY gained.

#### 16 *Probabilistic Sensitivity Analysis Results*

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

Formatted: Font: Not Bold

## Economic evaluation of restarting OAC therapy

1 The CEACs, which compared the most cost-effective base case  
2 option (17.5%) against several strategies (10%,12.5%,15%, 20%,  
3 22.5%, 25%), show that treating those with a one year VTE risk of  
4 17.5% has a 44.8-73.3% probability of being cost-effective at a  
5 willingness to pay threshold of £20,000 per QALY gained (Appendix  
6 Fig IX-XV). The results highlight substantial parameter uncertainty  
7 even if the calculated ICER point estimates for the base-case results  
8 appear to be cost-effective.

### 9 *Deterministic sensitivity analysis results*

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

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

Formatted: Font:

Formatted: Font: Not Bold

## Economic evaluation of restarting OAC therapy

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

3 Adjusting the lag time had little effect on the cost-effectiveness of  
4 the results except for the 15% decision rule; this was now cost-  
5 effective when the lag time was increased from 20 to 40 days.

6 Having a male-only cohort meant the lowest threshold to be cost-  
7 effective is the 12.5% while a female-only cohort restricted the  
8 lowest threshold to be cost-effective to 15%.

## 9 **Discussion**

### 10 *Principal findings*

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

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

## Economic evaluation of restarting OAC therapy

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

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

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

### 22 *Strengths and weaknesses of the analysis*

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



## Economic evaluation of restarting OAC therapy

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

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

## Economic evaluation of restarting OAC therapy

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

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

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

## Economic evaluation of restarting OAC therapy

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

### 3 *Future research*

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

### 17 **Author Contributions**

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

1 **Acknowledgements**

2 The authors would like to acknowledge Simon Stevens for his  
3 invaluable administrative support and excellent organisational skills,  
4 Pelham Barton for economic modelling guidance, Frits Rosendaal,  
5 Gregory YH Lip, Manuel Monreal, Maura Marcucci and Trevor Baglin  
6 for contributions to wider team meetings. This work formed part of  
7 a project funded by the National Institute for Health Research  
8 Health Technology Assessment (NIHR HTA) Programme (project  
9 number 10/94/02).

10 Disclaimer: This publication presents independent research  
11 commissioned by the National Institute for Health Research (NIHR).  
12 The views and opinions expressed by authors in this publication are  
13 those of the authors and do not necessarily reflect those of the NHS,  
14 the NIHR, MRC, CCF, NETSCC, the HTA programme or the  
15 Department of Health.

16 Competing interests: MM, SJ, JE, DM, and DF had financial support  
17 from the National Institute for Health Research Health Technology  
18 Assessment Programme (NIHR HTA, project number 10/94/02) for  
19 the submitted work.

20

21 **References**

- 22 1 Fitzmaurice DA, Murray E. Thromboprophylaxis for adults in  
23 hospital. *BMJ*. 2007; **334**: 1017-8.  
24 2 House of Commons Health Committee. The prevention of  
25 venous thromboembolism in hospitalised patients. *Second report of*  
26 *session*. 2004; **5**: 2007.

## Economic evaluation of restarting OAC therapy

- 1 3 White RH. The Epidemiology of Venous Thromboembolism.  
2 *Circulation*. 2003; **107**: I-4-I-8.  
3 10.1161/01.CIR.0000078468.11849.66.
- 4 4 Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for  
5 recurrent venous thrombosis. *Lancet*. 2010; **376**: 2032-9.
- 6 5 Baglin T, Luddington R, Brown K, Baglin C. Incidence of  
7 recurrent venous thromboembolism in relation to clinical and  
8 thrombophilic risk factors: prospective cohort study. *Lancet*. 2003;  
9 **362**: 523-6.
- 10 6 Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta  
11 M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term  
12 clinical course of acute deep venous thrombosis. *Ann Intern Med*.  
13 1996; **125**: 1-7.
- 14 7 Chong L-Y, Fenu E, Stansby G, Hodgkinson S, Group GD.  
15 Management of venous thromboembolic diseases and the role of  
16 thrombophilia testing: summary of NICE guidance. *BMJ*. 2012; **344**:  
17 e3979.
- 18 8 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D,  
19 Bounameaux H, Huisman M, King CS, Morris TA, Sood N.  
20 Antithrombotic therapy for VTE disease: CHEST guideline and expert  
21 panel report. *CHEST Journal*. 2016; **149**: 315-52.
- 22 9 Kearon C. Extended anticoagulation for unprovoked venous  
23 thromboembolism: a majority of patients should be treated. *J*  
24 *Thromb Thrombolysis*. 2011; **31**: 295-300.
- 25 10 Donadini MP, Ageno W. Which patients with unprovoked  
26 VTE should receive extended anticoagulation? The minority. *J*  
27 *Thromb Thrombolysis*. 2011; **31**: 301-5.
- 28 11 Hyers TM, Shetty HG, Campbell IA. What is the optimum  
29 duration of anticoagulation for the management of patients with  
30 idiopathic deep venous thrombosis and pulmonary embolism? *J R*  
31 *Coll Physicians Edinb*. 2010; **40**: 224-8.
- 32 12 Ensor J, Riley R, Jowett S, Monahan M, Snell K, Bayliss S,  
33 Moore D, Fitzmaurice D. Prediction of risk of recurrence of venous  
34 thromboembolism following treatment for a first unprovoked  
35 venous thromboembolism: systematic review, prognostic model and  
36 clinical decision rule, and economic evaluation. *Health Technol*  
37 *Assess*. 2016; **20**: 1.
- 38 13 Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M,  
39 Eichinger S, Palareti G, Poli D, Tait RC, Iorio A. Patient-level meta-  
40 analysis: effect of measurement timing, threshold, and patient age  
41 on ability of D-dimer testing to assess recurrence risk after  
42 unprovoked venous thromboembolism. *Ann Intern Med*. 2010; **153**:  
43 523-31.
- 44 14 Office for National Statistics. National Life Tables, England &  
45 Wales, 1980-82 to 2010-12. 2013.
- 46 15 Rodger MA, Scarvelis D, Kahn SR, Wells PS, Anderson DA,  
47 Chagnon I, Le Gal G, Gandara E, Solymoss S, Sabri E. Long-term risk  
48 of venous thrombosis after stopping anticoagulants for a first  
49 unprovoked event: A multi-national cohort. *Thrombosis research*.  
50 2016.

## Economic evaluation of restarting OAC therapy

- 1 16 Shrivastava S, Ridker P, Glynn R, Goldhaber S, Moll S,  
2 Bounameaux H, Bauer K, Kessler C, Cushman M. D-dimer, factor VIII  
3 coagulant activity, low-intensity warfarin and the risk of recurrent  
4 venous thromboembolism. *J Thromb Haemost.* 2006; **4**: 1208-14.
- 5 17 Curtis L. Unit costs of health and social care 2014. Personal  
6 Social Services Research Unit (PSSRU), University of Kent. 2014.
- 7 18 Kind P, Hardman G, Macran S. UK population norms for EQ-  
8 5D. York: Centre for Health Economics, University of York, 1999.
- 9 19 Appleby J, Devlin N, Parkin D. NICE's cost effectiveness  
10 threshold. *BMJ.* 2007; **335**: 358-9.
- 11 20 National Institute for Health and Care Excellence. Guide to  
12 the methods of technology appraisal. In: National Institute for  
13 Health and Care Excellence, ed. London: NICE, 2013.
- 14 21 Kearon C, Iorio A, Palareti G. Risk of recurrent venous  
15 thromboembolism after stopping treatment in cohort studies:  
16 recommendation for acceptable rates and standardized reporting. *J*  
17 *Thromb Haemost.* 2010; **8**: 2313-5. 10.1111/j.1538-  
18 7836.2010.03991.x.
- 19 22 Fattorini A, Crippa L, Vigano' D'Angelo S, Pattarini E,  
20 D'Angelo A. Risk of deep vein thrombosis recurrence: high negative  
21 predictive value of D-dimer performed during oral anticoagulation.  
22 *Thromb Haemost.* 2002; **88**: 162-3.
- 23 23 Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S,  
24 Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus  
25 Warfarin in the Treatment of Acute Venous Thromboembolism.  
26 *NEJM.* 2009; **361**: 2342-52. doi:10.1056/NEJMoa0906598.
- 27 24 Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR,  
28 Turpie AG, Green D, Ginsberg JS, Wells P. A comparison of three  
29 months of anticoagulation with extended anticoagulation for a first  
30 episode of idiopathic venous thromboembolism. *NEJM.* 1999; **340**:  
31 901-7.
- 32 25 Chitsike R, Rodger M, Kovacs M, Betancourt M, Wells P,  
33 Anderson D, Chagnon I, Le Gal G, Solymoss S, Crowther M. Risk of  
34 post-thrombotic syndrome after subtherapeutic warfarin  
35 anticoagulation for a first unprovoked deep vein thrombosis: results  
36 from the REVERSE study. *J Thromb Haemost.* 2012; **10**: 2039-44.
- 37 26 Castellucci LA, Le Gal G, Rodger MA, Carrier M. Major  
38 bleeding during secondary prevention of venous thromboembolism  
39 in patients who have completed anticoagulation: a systematic  
40 review and meta-analysis. *J Thromb Haemost.* 2014; **12**: 344-8.
- 41 27 Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey  
42 JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH. Risk of  
43 bleeding with 2 doses of dabigatran compared with warfarin in older  
44 and younger patients with atrial fibrillation an analysis of the  
45 randomized evaluation of long-term anticoagulant therapy (RE-LY)  
46 trial. *Circulation.* 2011; **123**: 2363-72.
- 47 28 Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R,  
48 Lobo JL, Monreal M, Investigators tR. Clinical Predictors for Fatal  
49 Pulmonary Embolism in 15 520 Patients With Venous  
50 Thromboembolism: Findings From the Registro Informatizado de la

## Economic evaluation of restarting OAC therapy

- 1 Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation*.  
2 2008; **117**: 1711-6. 10.1161/circulationaha.107.726232.
- 3 29 Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term  
4 survival after primary intracerebral haemorrhage: a retrospective  
5 population based study. *J Neurol Neurosurg Psychiatry*. 2005; **76**:  
6 1534-8.
- 7 30 Department of Health. NHS Reference Costs 2012-2013.  
8 2013.
- 9 31 NICE. Rivaroxaban for the Treatment of deep vein  
10 thrombosis and prevention of recurrent deep vein thrombosis and  
11 pulmonary embolism (NICE Technology Appraisal TA261). 2012.
- 12 32 Joint Formulary Committee. *British National Formulary 67th*  
13 *Ed*. London: BMJ Group and Pharmaceutical Press, 2014.
- 14 33 Luengo-Fernandez R, Gray AM, Rothwell PM. A population-  
15 based study of hospital care costs during 5 years after transient  
16 ischemic attack and stroke. *Stroke*. 2012; **43**: 3343-51.
- 17 34 National Clinical Guideline Centre. Appendix H: Cost-  
18 effectiveness analysis – Diagnosis of Pulmonary Embolism. *In*:  
19 *Venous thromboembolic diseases: the management of venous*  
20 *thromboembolic diseases and the role of thrombophilia testing*.  
21 London: National Clinical Guideline Centre, 2012, 533-70.
- 22 35 Locadia M, Bossuyt PMM, Stalmeier PFM, Sprangers MAG,  
23 van Dongen CJJ, Middeldorp S, Bank I, Meer Jvd, Hamulyák K, Prins  
24 MH. Treatment of venous thromboembolism with vitamin K  
25 antagonists: patients' health state valuations and treatment  
26 preferences. *Thromb Haemost*. 2004; **92**: 1336-41. 10.1160/TH04-  
27 02-0075.
- 28 36 Gage BF, Cardinali Ab FAU, Owens DK. The effect of stroke  
29 and stroke prophylaxis with aspirin or warfarin on quality of life.  
30 *Arch Intern Med*. 1996; **156**: 1829-36.
- 31

## Economic evaluation of restarting OAC therapy

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% ( $\alpha=27, \beta=1239$ )	[23]
Long-term annual risk of VTE recurrence beyond 6 months on therapy (beta)	1.3% ( $\alpha=1, \beta=78$ )	[24]
Long-term annual risk of VTE recurrence beyond 3 years off therapy(beta)	5.0% ( $\alpha=5, \beta=95$ )	[15]
Annual risk of further VTE off therapy after previous recurrent VTE (beta)		[16]
Off therapy	12.0% ( $\alpha=11, \beta=81$ )	
On therapy	5.0% ( $\alpha=5, \beta=95$ )	
Probability a recurrent VTE is a PE by index event (beta)		[13]
Index event DVT	0.15 ( $\alpha=15, \beta=88$ )	
Index event PE	0.52 ( $\alpha=30, \beta=28$ )	
Probability of death from PE in the first month (beta)	0.2 ( $\alpha=2, \beta=8$ )	Clinical consensus
Proportion of recurrent VTEs resulting in severe PTS (beta)	1.1% ( $\alpha=4, \beta=345$ )	[25]
Annual risk of major bleed by age group (beta)		[26]
Not on therapy	0.45% ( $\alpha=25, \beta=5593$ )	
On therapy		[27]
<65	2.43% ( $\alpha=23, \beta= 929$ )	
65-74	3.25% ( $\alpha=86, \beta=2554$ )	
75+	4.37% ( $\alpha=106, \beta=2324$ )	
Split of major bleeds by bleed type (dirichlet)		[28]
Gastrointestinal bleed	36.5%	
Intracranial bleed	17.9%	
Other major bleed	45.6%	
	$(\alpha_1; \alpha_2; \alpha_3) = (499; 245; 622)$	
Risk of death from major bleed (first month) (beta)		[28]
Gastrointestinal bleed	18.4% ( $\alpha=92, \beta=407$ )	
Intracranial bleed	32.2% ( $\alpha=79, \beta=166$ )	
Other major bleed	10.5% ( $\alpha=65, \beta=557$ )	
Standardised mortality ratio for after an intracranial bleed (Lognormal) <sup>1</sup>	2.2 (95% CI 2.0-2.4)	[29]
Unit costs	-	-



## Economic evaluation of restarting OAC therapy

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 ( $\alpha=31.0, \beta=269.4$ ) <sup>2</sup>	[33]
Intracranial bleed: annual cost (fixed)	£1,300	[33]
D-Dimer test	£26	[34]
<sup>1</sup> . A 95% confidence interval is assumed to be $\pm 0.2$ of the mean. <sup>2</sup> . $\alpha$ is the shape parameter and $\beta$ is the scale parameter VTE= Venous Thromboembolism, PTS=Post Thrombotic Syndrome, PE= Pulmonary Embolism		

1

2 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)	$\alpha=2.0,$ $\beta=0.6$	1 month	[35]
PE	0.63 (0.36-0.86)	$\alpha=1.2,$ $\beta=0.8$	1 month	[35]
Non-fatal intracranial bleed	0.33 (0.14-0.53)	$\alpha=1.2,$ $\beta=2.1$	Permanent	[35]
GI Bleed	0.65 (0.49-0.86)	$\alpha=1.2,$ $\beta=0.8$	2 weeks	[35]
Other Bleeds	0.65 (0.49-0.86)	$\alpha=1.2,$ $\beta=0.8$	2 weeks	Assumed same as GI Bleeds
Severe PTS	0.82 (0.66-0.97)	$\alpha=3.0,$ $\beta=0.9$	Permanent	[35]
Warfarin	0.997 (0.953-1.0) <sup>1</sup>	$\alpha=16.4,$ $\beta=0.3$	Treatment length	[36]
<sup>1</sup> . 10 <sup>th</sup> and 90 <sup>th</sup> percentile reported instead of Inter-Quartile Range (IQR) GI Bleed= Gastrointestinal Bleed, DVT= Deep Vein Thrombosis, PTS=Post Thrombotic Syndrome				

3

4

5

6

## Economic evaluation of restarting OAC therapy

- 1 Table III - Cost-effectiveness of using each decision rule sorted by increasing  
 2 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.

3

4

## Economic evaluation of restarting OAC therapy

Table IV- Sensitivity Analysis Scenarios

Strategy	Mean cost (£)	Mean QALYs	ICER (Cost/QALY) (£)	Strategy	Mean cost (£)	Mean QALYs	ICER (Cost/QALY) (£)
<b>3 year time horizon</b>				<b>Male only patients</b>			
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
<b>Higher risk of death from PE</b>				<b>Female only patients</b>			
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
<b>All patients aged ≥60 years</b>				<b>Lag d-dimer time of 20 days</b>			
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				
<b>All patients with index PE event</b>				<b>Lag d-dimer time of 40 days</b>			
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				
<b>All patients with index DVT event</b>				<b>Higher warfarin disutility</b>			
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.