National Institute for Health and Care Excellence

Final

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

[G] Economic modelling report for pharmacological treatment in people with confirmed deep vein thrombosis and/or pulmonary embolism

NICE guideline NG158

Economic modelling report underpinning recommendations 1.3.8, 1.3.9, 1.3.17, 1.3.18 and 1.4.8 in the guideline

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This report was developed by the NICE Guideline Updates Team

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Contents

List of abbreviations

ASA	acetylsalicylic acid
BNF	British National Formulary
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CKD	chronic kidney disease
COMMAND VTE	COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (registry)
CPRD	Clinical Practice Research Datalink
CrI	credible interval
CRNMB	clinically relevant non-major bleeding
CTEPH	chronic thromboembolic pulmonary embolism
CTPA	computed tomography pulmonary angiogram
DOAC	direct-acting oral anticoagulant
DVT	deep vein thrombosis
ECB	extracranial bleeding
ECG	electrocardiogram
GP	general practitioner
HR	hazard ratio
ICB	intracranial bleeding
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
INR	international normalised ratio
LMWH	low molecular weight heparin
NMB	net monetary benefit
NMA	network meta-analysis
MRI	magnetic resonance imaging

OR	odds ratio
PCA	Prescription Cost Analysis
PCC	prothrombin complex concentrate
PE	pulmonary embolism
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTS	post-thrombotic syndrome
QALY	quality-adjusted life years
RCT	randomised controlled trial
RIETE	Registro Informatizado de Enfermedad TromboEmbólica (Computerised Registry of Patients with Venous Thromboembolism)
VKA	vitamin k antagonists
VTE	venous thromboembolism
UFH	unfractionated heparin

Introduction

The *de novo* economic model described in this chapter was developed to address the following review questions:

- What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of deep vein thrombosis (DVT)?
- What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of pulmonary embolism (PE)?

The committee prioritised these questions for economic modelling because although a number of partially or directly applicable published economic evaluations were identified (see evidence review D), they do not include all relevant comparators in the decision space and had a number of limitations. In particular, most of the economic analyses were informed by individual trials comparing low-molecular weight heparin (LMWH) followed by a vitamin K antagonist (VKA) in the initial 6 months following a venous thromboembolism (VTE) and extrapolated to a longer time horizon.

For the clinical evidence review, we undertook network meta-analyses (NMAs) to assess the relative effectiveness of different pharmacological interventions for the initial treatment of VTE, extended therapy for VTE (including trials with up to 48 months of follow-up) and for the treatment of VTE in people with cancer. The results of the NMAs allowed us to compare a larger number of treatment options using a wider evidence base than in previously published economic evaluations. Further information about the NMAs that informed this economic model can be found in evidence review D.

Methods

Model overview

Population

Adults with a confirmed diagnosis of PE or DVT; a subgroup analysis was run for people with cancer.

Comparators

The model was divided into an initial treatment phase (first 3 to 6 months following a DVT or PE) and an extended therapy phase aimed at secondary prevention. The assumption about the duration of treatment in the model depended on whether the VTE was provoked or unprovoked.

In the base case, the model assumed that people remained on the same treatment in the initial and extended phases and compared the following 7 strategies:

1. LMWH/VKA
2. Unfractionated heparin/VKA
3. Fondaparinux/VKA
4. Apixaban
5. Rivaroxaban
6. Dabigatran
7. Edoxaban

The first 3 comparators in the model, the VKA was assumed to be warfarin as it is by far the most commonly used drug within the class. Warfarin takes time to achieve full anticoagulation so interim treatment (LMWH, unfractionated heparin or fondaparinux) is typically given to bridge the period until the target international normalised ratio (INR) is achieved. The model assumes these interim treatments are administered on average for 10 days, after which warfarin would be continued on its own. As per their labels, dabigatran and edoxaban were started after 5 days of parenteral anticoagulation, which was assumed to be subcutaneous LMWH in the model.

For extended therapy, additional comparators were identified for inclusion in the NMAs, giving rise to the potential to model a wider set of strategies if treatment switching was considered possible between the initial and extended phases. The sequencing analysis included the 7 comparators above for initial treatment and 10 comparators for extended therapy, yielding a total of 70 potential sequences. However, the committee noted that a number of these sequences were unlikely to be relevant to current clinical practice. In particular, the committee felt that a person would not normally switch from a direct-acting oral anticoagulant (DOAC) as initial treatment to warfarin as extended therapy unless there were specific clinical concerns. It was agreed in advance of running the model that the clinical plausibility of these treatment sequences would be taken into account by presenting incremental cost-effectiveness results both with and without these strategies. The 10 comparators of interest for extended therapy in the sequencing analysis included:

1. No treatment
2. VKA low (INR 1.5-2.0)
3. VKA standard (INR 2.0-3.0)
4. Aspirin
5. Apixaban (2.5 mg twice daily)
6. Apixaban (5 mg twice daily)
7. Dabigatran
8. Edoxaban
9. Rivaroxaban (10 mg)
10. Rivaroxaban (20 mg)

The committee advised that apixaban 5 mg twice daily is not licensed for prevention of VTE but felt this strategy was relevant to clinical practice and was aware of evidence from clinical trials that could inform the analysis.

For the cancer subgroup analysis, data were only available to estimate relative treatment effects from trials conducted in the initial phase following a VTE and so these were applied for the entire duration of treatment in the model. A total of 8 strategies were modelled in the cancer subgroup, including the 7 strategies listed in the base case above plus the addition of LMWH alone.

Type of evaluation, time horizon, perspective, discount rate

As per the NICE Reference Case, this evaluation is a cost–utility analysis (reporting health benefits in terms of QALYs), conducted from the perspective of the NHS/PSS. It adopts a lifetime horizon and uses a discount rate of 3.5% per annum for both costs and health benefits.

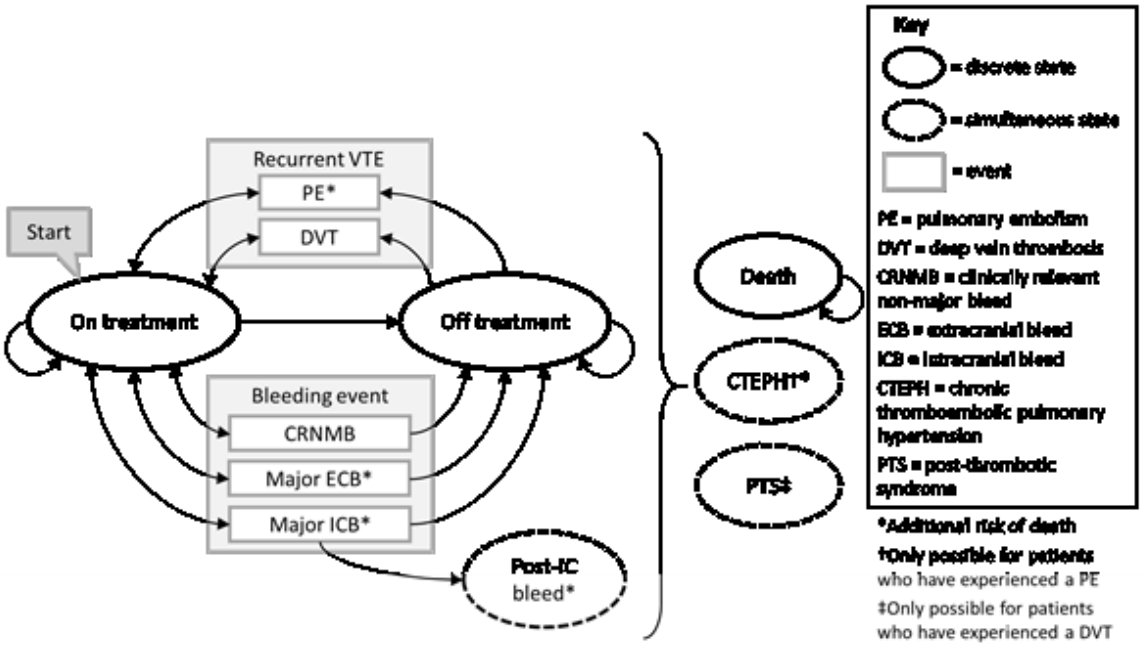
Model structure

A Markov model was used to represent key events associated with management of a DVT or PE including VTE recurrence, major bleeding events, clinically relevant non-major bleeding events (CRNMB) and downstream sequelae such as chronic thromboembolic pulmonary hypertension (CTEPH), post-thrombotic syndrome (PTS) and long-term disability associated with intracranial bleeds.

Separate cohorts were run for people who had experienced a DVT as the index event and people who had experienced a PE as the index event but in both cases the same model structure was used. The cohort starts in the “on treatment” state where individuals are at risk of both VTE recurrence and bleeding events. Individuals can transition to the “off treatment” state if their intended treatment course ends, they discontinue due to a bleeding event, or they discontinue for another reason (“spontaneous” discontinuation). While off treatment, people remain at risk of having a recurrent VTE (and the risk is higher than if they had continued treatment) but they are no longer at risk of bleeding events. People who have had a PE are at risk of developing CTEPH and people who have had a DVT are at risk of developing PTS. CTEPH and PTS are both modelled as simultaneous states, which track the proportion of people with these conditions over time while they are inhabiting one of the other discrete states in the model. A simultaneous state is also used to track the long-term impact of disability following a major intracranial bleed.

In the model, people can die at any point from background mortality. There is a one-off immediate risk of death associated with the following events: recurrent PE, major extracranial bleeding and major intracranial bleeding. There is also a long-term increased risk of death associated with CTEPH and with being in the post-intracranial bleed state.

Figure 1: Structure of the Markov model



The cohort is weighted to reflect the proportion of people who experience a provoked versus an unprovoked VTE and the model estimates the risk of recurrence separately for these populations. Unprovoked VTEs are associated with a higher risk of recurrence and are generally treated for longer. In the base case, committee consensus was that people with a provoked VTE would receive treatment for 3 months (this was assumed irrespective of the number of prior provoked events because it was not possible to track this at the individual level) and people with an unprovoked VTE would receive long-term treatment of an indefinite duration.

People who experience a recurrent VTE while off treatment are assumed to return to the same treatment that they received for the index event at the start of the model. People who experience a recurrent VTE while on treatment are assumed to switch to another treatment. For simplicity, this was modelled as a weighted average of the costs and effectiveness of all initial treatment comparators.

The model uses a 3-month cycle length. Observational data show that the probability of VTE recurrence and bleeding decrease over time before plateauing (Martinez 2014, Yamashita 2018), so the model uses a series of tunnel states to accommodate changing baseline event rates and to track the first 6 cycles since a VTE event. People who experience a recurrent VTE return to the first tunnel state.

Incorporating treatment effects

Results of the NMAs for the following outcomes were used to inform relative treatment effects in the economic model:

- VTE recurrence
- Major bleeding
- CRNMB

Relative effects from the initial treatment NMAs were applied for the first 6 months (2 cycles) following a VTE, after which point the relative effects from the extended therapy NMAs were applied. In the base case, relative effects were taken from the NMAs for treatment of VTE, which pooled all data in people who had experienced a DVT, PE or unspecified VTE as their index event (see evidence review D).

There were gaps in the estimates of relative treatment effects for several comparators that required the following additional assumptions:

- There was no extended therapy study for edoxaban; the point estimates for relative effects in the extended phase of treatment were assumed to be the same as the initial treatment phase for all 3 outcomes. However, we generally observed more uncertainty in the results for the extended therapy trials compared to the initial treatment trials. For the key outcomes VTE recurrence and major bleeding, uncertainty around the point estimate for edoxaban in the extended therapy phase was made equivalent to the average standard error observed in the extended therapy trials for the other 3 DOACs (apixaban, dabigatran and rivaroxaban).
- There were no studies that reported CRNMB for VKA low in the extended therapy phase; this was assumed to be equivalent to VKA standard.
- There were no studies reporting outcomes specifically in cancer patients for fondaparinux/VKA; relative effects were assumed to be the same as in the initial treatment phase for the overall population for all 3 outcomes.

Sensitivity analyses were run using relative treatment effects from the initial treatment NMAs that were conducted separately for people who had experienced a DVT and people who had experienced a PE as reported in RCTs. However, there were additional gaps in the evidence networks for the bleeding outcomes. Where data were not reported separately for DVT and PE, relative treatments effects from the pooled NMAs for treatment of VTE were used. For extended therapy, only relative effects from the pooled NMAs were used to inform all outcomes in the economic model as there were insufficient data to estimate bleeding outcomes separately for DVT and PE.

Table 1: Summary of availability of relative treatment effects from initial treatment NMAs to inform sensitivity analyses stratified by DVT and PE

Strategy	VTE recurrence		Major bleeding		CRNMB	
	DVT	PE	DVT	PE	DVT	PE
LMWH/VKA	✓	✓	✓	✓	✓	X
UFH/VKA	✓	✓	✓	✓	✓	X
Fondaparinux/VKA	✓	✓	✓	✓	✓	X
Apixaban	✓	✓	✓	✓	✓	X

Strategy	VTE recurrence		Major bleeding		CRNMB	
	DVT	PE	DVT	PE	DVT	PE
Dabigatran	✓	✓	X	X	X	X
Edoxaban	✓	✓	X	X	X	X
Rivaroxaban	✓	✓	✓	✓	✓	X

✓ = relative effects stratified by DVT or PE were available

X = relative effects from pooled NMAs for treatment of VTE were used

Baseline population and natural history

Baseline patient population

The characteristics of the cohort at the start of the model were based on a large observational study of 28,781 VTE patients extracted from the UK Clinical Practice Research Datalink (CPRD) and reported in Martinez 2014.

Table 2: Characteristics of the cohort at the start of the model

Characteristic	Mean (95% CI)	Source
Age (years)	65.5 (65.3 to 65.7)	Martinez 2014
Male	44.4% (43.8% to 44.9%)	Martinez 2014
DVTs that are provoked	40.5% (39.7% to 41.2%)	Martinez 2014
PEs that are provoked	43.6% (42.3% to 44.5%)	Martinez 2014

Baseline event rates

To estimate baseline event rates, the model uses LMWH/VKA as the reference regimen because most sources of data on the natural history and clinical course of VTEs were collected when LWMH/VKA was standard practice and before the availability of DOACs. The committee discussed the estimates of event rates reported in the various observational data sources summarised below and agreed they were consistent with their current clinical experience.

VTE recurrence

Separate estimates of the baseline risk of VTE recurrence were required to reflect the following phases of the model:

- Initial short-term period (first 3 months after a VTE) when everyone is on treatment
- Long-term risk of recurrence for people who are off treatment (after completing of a planned course of treatment for a provoked VTE or after discontinuing treatment after an unprovoked VTE or bleeding event)
- Long-term risk of recurrence for people who are on treatment.

Short-term risk of recurrence on treatment

The initial 3-month probability of recurrence while on the reference treatment (LMWH/VKA) was taken from the Martinez 2014 CPRD observational cohort study. Values were obtained by using Engauge Digitizer software (Version 10.7) to read data points off the cumulative incidence curves. The risk of recurrence was stratified by provoked versus unprovoked VTE. There was no evidence of a difference in the risk of recurrence depending on whether the index event was a DVT or a PE during this initial period.

Table 3: Short-term probability of VTE recurrence on treatment (LMWH/VKA)

	Mean (95% CI)	Source
Provoked VTE – 3 months	4.9% (4.3% to 5.5%)	Martinez 2014
Unprovoked VTE – 3 months	5.5% (5.0% to 6.0%)	Martinez 2014

Long-term risk of recurrence off treatment

Long-term (after the first 3 months) probability of recurrence while off treatment was derived from Prandoni 2007, which followed 1,626 consecutive patients who had discontinued anticoagulation and reported cumulative incidence of recurrence up to 10 years. Data were reported separately for provoked versus unprovoked VTE. The study also noted that recurrence was significantly associated with having a DVT as the index event and reported a hazard ratio of 1.44 versus having a PE as the index event. Using information about the proportion of people in the cohort who had an index DVT, we derived separate hazard ratios for the rate of recurrence in those who had an index DVT versus the overall rate of recurrence in the cohort and the rate of recurrence in those who had an index PE versus the overall rate of recurrence in the cohort.

Table 4: Long-term probability of VTE recurrence off treatment

	Mean (95% CI)	Source
Provoked VTE – 6 months[(a)]	4.2% (2.8% to 8.7%)	Prandoni 2007
Provoked VTE – 1 year[(a)]	6.6% (4.8% to 8.4%)	Prandoni 2007
Provoked VTE – 10 years[(a)]	22.5% (17.2% to 27.8%)	Prandoni 2007
Unprovoked VTE – 6 months[(a)]	10% (8% to 12%)	Prandoni 2007
Unprovoked VTE – 1 year[(a)]	15% (12.6% to 17.4%)	Prandoni 2007
Unprovoked VTE – 10 years[(a)]	52% (45.6% to 59.5%)	Prandoni 2007
HR recurrence for those with an index DVT vs an index PE	1.44 (1.03 to 2.03)	Prandoni 2007
Proportion of VTE index events that were DVTs	0.66 (0.64 to 0.68)	Prandoni 2007
HR recurrence for those with an index DVT vs recurrence in the overall cohort	1.12	Calculated[(b)]
HR recurrence for those with an index PE vs recurrence in the overall cohort	0.78	Calculated[(c)]

(a) Cumulative probability of recurrence

(b) $At\ mean\ values$: $\frac{r_{DVT}}{r_{Overall}} = \frac{r_{DVT}}{r_{PE}} * \frac{r_{PE}}{r_{Overall}} = 1.44 * \frac{\frac{r_{DVT}}{1.44}}{0.66*r_{DVT}+(1-0.66)*\frac{r_{DVT}}{1.44}} = 1.12$

(c) $At\ mean\ values$: $\frac{r_{PE}}{r_{Overall}} = \frac{r_{PE}}{r_{DVT}} * \frac{r_{DVT}}{r_{Overall}} = \frac{1}{1.44} * \frac{r_{DVT}}{0.66*r_{DVT}+(1-0.66)*\frac{r_{DVT}}{1.44}} = 0.78$

This allowed the model to estimate different baseline recurrence rates for people who had experienced a provoked DVT, an unprovoked DVT, a provoked PE and an unprovoked PE.

Long-term risk of recurrence on treatment

Long-term (after the first 3 months) risk of recurrence while on the reference treatment was estimated by applying a hazard ratio of 0.09 (95% CrI 0.05 to 0.17) for people on VKA to the rate of recurrence while off treatment. The hazard ratio was obtained from the comparison of VKA standard (INR 2.0-3.0) versus placebo in the extended therapy NMA. This approach was taken to ensure consistency of "on treatment" and "off treatment" probabilities for DVT versus PE and provoked versus unprovoked patients. In addition, it is difficult to identify observational data sources where we can be certain that all patients are on treatment and are compliant; using the hazard ratio from the NMA ensures there is consistency in estimating relative effects across comparators in the extended therapy phase.

Type of recurrent VTE

People whose index event was a PE are more likely to develop a recurrent PE than a person whose index event was a DVT. Estimates of these probabilities were obtained from the Prandoni 2007 cohort.

Table 5: Probabilities for the type of recurrent VTE depending on if the index event was a DVT or PE

	Mean (95% CI)	Source
Probability recurrent VTE is a PE if the index event was a DVT	24.4% (19.3% to 29.9%)	Prandoni 2007
Probability recurrent VTE is a PE if the index event was a PE	56.6% (47.7% to 65.2%)	Prandoni 2007

The committee felt that if the index VTE was provoked, the probability of the recurrent VTE being provoked would be the same as the index VTE, so we used the overall probability of a provoked VTE of 42.0% (95% CI 41.4% to 42.5%) from the Martinez 2014 CPRD observational cohort study. If the index VTE was unprovoked, then the assumption was that any recurrent VTE would also be unprovoked.

Cancer subgroup

Cancer patients who have had a VTE have been shown to have a higher risk of recurrence compared to people without cancer (Prandoni 2002). In the model, this elevated risk was implemented in the cancer subgroup analysis by applying a hazard ratio of 3.2 (95% CI 1.9 to 5.4) based on observational data from the Prandoni 2002 cohort study to the relevant baseline rate of VTE recurrence in the overall population.

Bleeding events

In the model, bleeding events can only occur in the "on treatment" state. Events are categorised as clinically relevant non-major bleeds (CRNMB) or major bleeds; major bleeds are further split into intracranial bleeds (ICB) or extracranial bleeds (ECB).

Major bleeding

The risk of bleeding is highest in the first 3 months of anticoagulation treatment (Klok 2014). Estimates for the short-term probability of major bleeding (first 3 months) on LMWH/VKA and the proportion of major bleeds that are intracranial were obtained from the RIETE study database, which is an international prospective registry of patients with VTE (Nieto 2010). Nieto 2010 did not report the risk of major bleeding beyond 3 months, so the long-term risk of major bleeding was estimated from the warfarin arm of the RE-MEDY trial (Schulman 2013), which compared dabigatran to warfarin as extended therapy for VTE. These data were used because the study had a relatively large sample size and more than 1 year of follow-up.

It was anticipated that the rate of major bleeding could have a big impact on outcomes in the cost-effectiveness model so an alternative source for estimating the baseline rate of major bleeding was explored in a sensitivity analysis. The COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND) registry is a multicentre retrospective cohort study that enrolled 3,027 consecutive patients with VTE in Japan and reported major bleeding events over a 5-year period (Yamashita 2018). Since there may be important differences in the characteristics of the Japanese and UK cohorts (such as treatment persistence), rather than using the absolute bleeding rates reported in the COMMAND registry, we calculated an odds ratio for long-term (3 years) to short-term (first 3 months) risk of bleeding and, as a sensitivity analysis, applied this to the short-term probability of major bleeding from the RIETE study. The COMMAND study also reported discontinuation rates at the same time points as major bleeding, so it was possible to adjust the major bleeding rate to take into account the proportion of patients who were still on treatment.

Table 6: Estimates for baseline risk of major bleeding on treatment (LMWH/VKA)

	Mean (95% CI)	Source
RIETE study		
Short-term probability (first 3 months)	2.24% (2.06% to 2.42%)	Nieto 2010
Proportion of major bleeds that are intracranial	13.0% (10.3% to 15.9%)	Nieto 2010
RE-MEDY study		
Long-term probability (473 days)	1.75% (1.14% to 2.50%)	Schulman 2013
COMMAND study (sensitivity analysis)		
Cumulative major bleeding		
3 months	2.9% (2.1% to 3.8%)	Yamashita 2018
3 years	7.2% (5.8% to 8.7%)	Yamashita 2018
OR major bleeding 3 yrs vs. 3 mos	2.60	Calculated
Cumulative discontinuation		
3 months	5.6% (4.4% to 6.9%)	Yamashita 2018
3 years	33.5% (30.9% to 36.1%)	Yamashita 2018
Cumulative major bleeding adjusted for discontinuation		
3 months	3.0%	Calculated
3 years	8.8%	Calculated
OR major bleeding 3 yrs vs. 3 mos	3.15	Calculated

CRNMB

In order to estimate the baseline risk of non-major bleeding, we also obtained the probability of a CRNMB of 10.2% (95% CI 8.7% to 11.8%) from the warfarin arm of the RE-MEDY trial (Schulman 2013). The risk of CRNMB is sparsely reported in the observational literature, which made it difficult to validate the probability of a CRNMB from the RE-MEDY trial. Therefore, rather than using the absolute probability of a CRNMB for warfarin as the baseline risk, we estimated a hazard ratio for CRNMB versus major bleeding and applied this in the model.

Cancer subgroup

In addition to having a higher risk of VTE recurrence, people with cancer also have a higher risk of major bleeding while on anticoagulation compared to people without cancer. This elevated risk was implemented using the same approach as for VTE recurrence, by applying a hazard ratio of 2.2 (95% CI 1.2 to 4.1) from the Prandoni 2002 cohort study to the baseline rate of major bleeding in the overall population.

Mortality

The limited duration of follow-up and the low number of deaths reported in RCTs was not sufficient to provide meaningful direct estimates of mortality to inform the economic model so the probability of death associated with various events was estimated from observational data sources. The probability of death from a PE was sourced from Bach 2016, a retrospective observational study in Germany that reported 30-day mortality. The probability of immediate death from a major intracranial or extracranial bleed was sourced from the RIETE study database (Nieto 2010).

The simultaneous states for CTEPH and post-intracranial bleed are both associated with a long-term increased risk of death. For CTEPH, the risk of death was dependent on the type of treatment, which included pulmonary endarterectomy, medical management or balloon pulmonary angioplasty (Delcroix 2016, Mizoguchi 2012). For the post-intracranial bleed state, standardised mortality ratios were obtained from a Danish registry that analysed long-term survival after various types of stroke (Bronnum-Hansen 2001).

Background mortality was implemented using national life tables for the general population in England (2015-2017).

Table 7: Estimates for death due to PE, major bleeding and CTEPH

	Mean (95% CI)	Source
Short-term probability of death from		
PE	10.7% (7.7% to 14.0%)	Bach 2016
Major intracranial bleed	47.9% (36.4% to 59.4%)	Nieto 2010
Major extracranial bleed	21.3% (17.7% to 25.1%)	Nieto 2010
Long-term probability of death from CTEPH		
Treated with pulmonary endarterectomy - 1 year	7.0% (5.0% to 10.0%)	Delcroix 2016
Treated with pulmonary endarterectomy - 3 years	11.0% (8.0% to 14.0%)	Delcroix 2016

	Mean (95% CI)	Source
Medically managed - 1 year	12.0% (9.0% to 17.0%)	Delcroix 2016
Medically managed - 3 years	30.0% (24.0% to 36.0%)	Delcroix 2016
Treated with balloon angioplasty - 1 year	2.9% (0.3% to 8.0%)	Delcroix 2016
Treated with balloon angioplasty - 3 years	7.4%	Calculated
Long-term probability of death from intracranial bleed		
Standardised mortality ratio – year 1	4.7% (4.3% to 5.2%)	Bronnum-Hansen 2001
Standardised mortality ratio – year 2-5	2.3% (2.2% to 2.5%)	Bronnum-Hansen 2001

CTEPH

The overall probability of CTEPH was taken from a meta-analysis of 16 studies (Ende-Verhaar 2017), from which it was possible to estimate separate probabilities of CTEPH following provoked versus unprovoked PEs. In order to implement CTEPH risk in the model, the probability of CTEPH per cycle was calculated for cycles 1 to 5 following a PE (equivalent to 1 year and 3 months). This is because the tunnel states in the model can only track time since a PE for this length of time. The committee agreed this assumption was reasonable because the literature suggests that the large majority of CTEPHs occur within 1 year of a PE (Pengo 2004).

Table 8: Estimates for the probability of CTEPH

	Mean (95% CI)	Source
Probability of CTEPH	2.3% (1.5% to 3.1%)	Ende-Varhaar 2017
OR CTEPH in unprovoked vs. provoked PE	4.1 (2.1 to 8.2)	Ende-Varhaar 2017
Proportion with unprovoked PE (all patients)	36.0% (33.3% to 38.8%)	Ende-Varhaar 2017
Proportion with unprovoked PE (patients who were alive after 6 months of treatment)	48.0% (46.2% to 49.8%)	Ende-Varhaar 2017
Proportion with unprovoked PE overall	44.5%	Calculated

PTS

The probability of moderate PTS and severe PTS was taken from Prandoni 1997, an Italian retrospective cohort assessing the long-term clinical course in 528 individuals with a DVT. As with CTEPH, this was implemented in the model by calculating a per-cycle probability for cycles 1-5 after DVT. Again, this assumption was deemed reasonable as the majority of PTS cases occur within 1 year of a DVT (Prandoni 1997).

Table 9: Estimates for the probability of PTS

	Mean (95% CI)	Source
Probability of severe PTS	5.3% (3.6% to 7.4%)	Prandoni 1997
Probability of mild/moderate PTS	17.2% (14.1% to 20.6%)	Prandoni 1997

Treatment discontinuation

The overall probabilities of treatment discontinuation were taken from Vora 2016, a meta-analysis of observational studies that reported persistence with anticoagulant therapy following a VTE at 3 months, 6 months and 1 year.

The probabilities of discontinuation due to a major intracranial bleed, major extracranial bleed and CRNMB bleed were estimated by the committee. The probabilities of "spontaneous discontinuation" were calculated by subtracting the probability of discontinuation due to bleeding events from the overall probability of discontinuation per cycle.

Table 10: Estimates for the probability of treatment discontinuation

	Mean (95% CI)	Source
Overall discontinuation (cumulative probability)		
At 3 months	17% (13% to 22%)	Vora 2016
At 6 months	38% (34% to 42%)	Vora 2016
At 1 year	69% (60% to 78%)	Vora 2016
Discontinuation due to specific events		
Major intracranial bleed	33.3% (6.5% to 69.0%)	Committee consensus
Major extracranial bleed	33.3% (6.5% to 69.0%)	Committee consensus
CRNMB	10.0% (2.5% to 21.7%)	Committee consensus

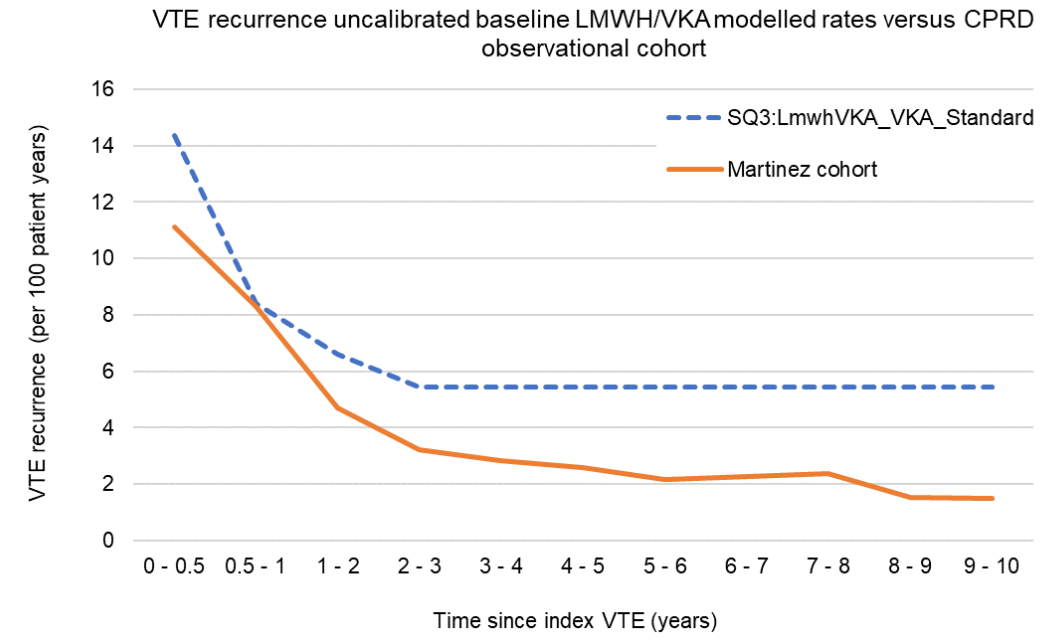
Model calibration

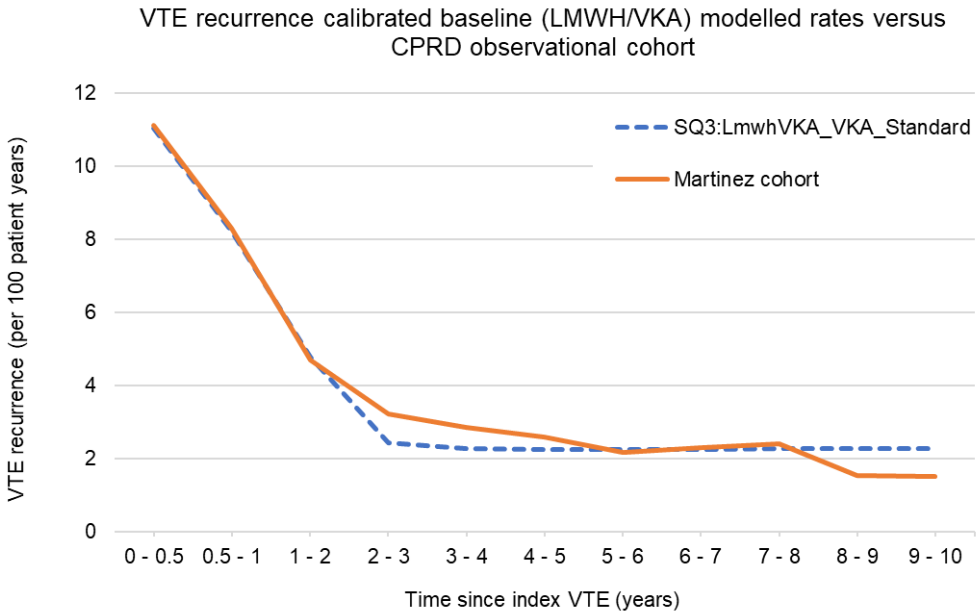
The baseline rates for VTE recurrence and mortality for the reference regimen (LMWH/VKA) that were generated by the model were compared to estimates from the Martinez 2014 CPRD observational cohort study. As there were some differences in the modelled estimates compared to the empirical data, calibration was undertaken to adjust the baseline modelled rates to fit the CPRD data as best as possible. We adopted this approach rather than using the Martinez 2014 observational data directly as the baseline rate in the model because that study did not allow us to stratify long-term recurrence rates by "on treatment" and "off treatment" status.

VTE recurrence

The modelled baseline recurrence of VTE for the reference regimen (LMWH/VKA) was producing higher estimates for the rate of VTE recurrence compared to the CPRD observational cohort, particularly for later time periods (beyond 3 years after the index VTE). There are at least 2 potential explanations for this. Firstly, in the model, patients who have a recurrent VTE return to the same higher baseline risk of recurrence as following the index VTE. The model does not distinguish between any potential changes in risk over time in relation to the number of VTEs that an individual has experienced. Secondly, unprovoked patients in the CPRD cohort may have been receiving anticoagulation for shorter periods than what has been assumed in the model (indefinite treatment) because it was noted that the modelled and empirical rates of VTE recurrence overlapped around 6 months to 1 year after the index event.

Figure 2: Uncalibrated and calibrated baseline VTE recurrence rates from the model in comparison to CPRD observational cohort data





For the purposes of calibration, the model parameters were set to assume a 6-month duration of treatment for provoked VTEs and to reflect the same proportion of patients with a DVT versus PE in the CPRD cohort (54% versus 46%). A fit statistic was calculated from the sum of squared differences between modelled and empirical recurrence rates at multiple time points over the 10-year period reported from the CPRD cohort and the Excel Solver tool was used to minimise the fit statistic by calculating calibration factors at 3 months, 6 months and 10 years. These calibration factors were then used to adjust the baseline probabilities of recurrence for the reference regimen (LMWH/VKA) in the model.

Table 11: Calibration factors for VTE recurrence

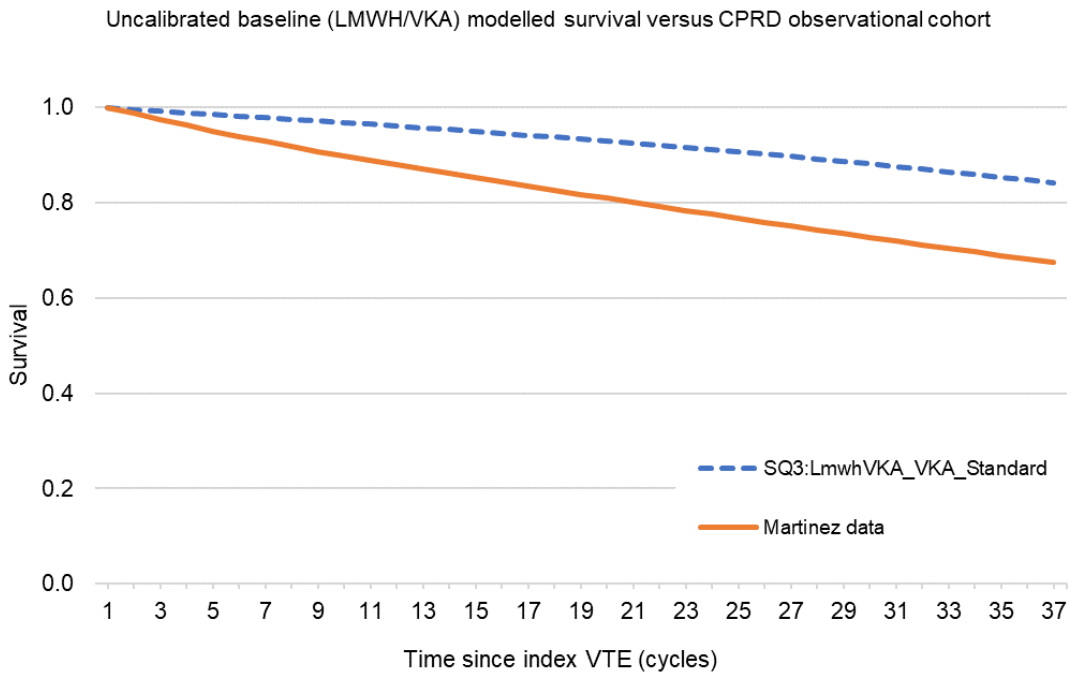
	Calibration factor
Short-term VTE recurrence – 3 months	0.9053
Long-term VTE recurrence – 6 months	0.3933
Long-term VTE recurrence – 1 year	0.7390
Long-term VTE recurrence – 10 years	0.5962

Mortality

A similar process was adopted to calibrate mortality using survival estimates from the CPRD observational cohort. However, because the modelled data is conditional on surviving the index VTE, we only calibrated long-term survival conditional on survival to 1 year. The modelled estimates of mortality were lower than the empirical data suggesting that the model may not be taking into account the effect of comorbidities or additional causes of death in the VTE population beyond PE, major bleeding events and CTEPH. A fit statistic was again calculated from the sum of squared differences between the modelled and empirical survival rates. The Excel Solver tool was used to minimise the fit statistic by calculating calibration factors at 2, 3, 5, and 10 years.

For the cancer subgroup analysis, mortality was calibrated using survival estimates for people with a VTE and a diagnosis of one of 4 common cancers (prostate, breast, lung and colorectal) reported in an analysis of the California Cancer Registry (Chew 2006). Calibration factors were used to adjust baseline probabilities for mortality at 1 and 2 years.

Figure 3: Uncalibrated and calibrated baseline survival from the model in comparison to CPRD observational cohort data



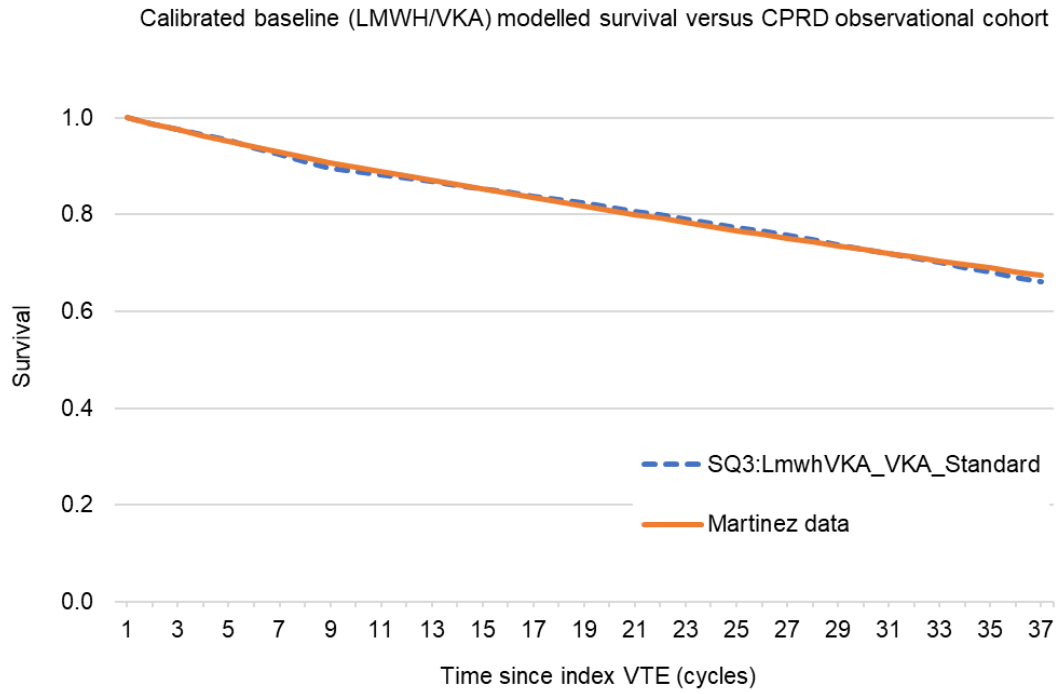


Table 12: Calibration factors for survival

	Calibration factor
Overall VTE population	
Survival - 2 years	3.744
Survival - 3 years	4.813
Survival - 5 years	2.237
Survival - 10 years	1.907
VTE population with cancer	
Survival – 1 year	65.581
Survival – 2 years	23.924

Calculating transition probabilities

The various sources of baseline events described above were used to calculate transition probabilities per 3-month cycle and applied in the economic model as summarised below. In order to do this, the probability of a given event in relation to the time period over which the event was reported in the literature was converted to a rate (formula 1) and then converted back to a probability per 3-month cycle (formula 2).

Formula 1: converting a probability to a rate

$$r = \frac{-\ln(1-P)}{t}$$

Where:

r = rate
P = probability of the event over time t
t = time period over which the probability occurred

Formula 2: converting a rate to a probability per 3-month cycle

$$p = 1 - e^{-rt}$$

Where:

p= probability per cycle
r = rate
t = cycle length (3 months)

Table 13: Sources used to inform baseline transition probabilities for VTE recurrence for each cycle

	Stratification	Source
Cycle 1	Provoked VTE on treatment	Martinez 2014
	Unprovoked VTE on treatment	
Cycle 2/3	Provoked DVT off treatment	Prandoni 2007 (6-month) for off treatment probabilities
	Provoked PE off treatment	
	Unprovoked DVT off treatment	

	Stratification	Source
	Unprovoked PE off treatment	For on treatment probabilities applied HR VKA standard vs. placebo from extended therapy NMA
	Provoked DVT on treatment	
	Provoked PE on treatment	
	Unprovoked DVT on treatment	
	Unprovoked PE on treatment	
Cycle 4/5	Provoked DVT off treatment	Prandoni 2007 (6-month to 1-year) for off treatment probabilities For on treatment probabilities applied HR VKA standard vs. placebo from extended therapy NMA
	Provoked PE off treatment	
	Unprovoked DVT off treatment	
	Unprovoked PE off treatment	
	Provoked DVT on treatment	
	Provoked PE on treatment	
	Unprovoked DVT on treatment	
	Unprovoked PE on treatment	
Cycle 6 onwards	Provoked DVT off treatment	Prandoni 2007 (1-year to 10-year) for off treatment probabilities For on treatment probabilities applied HR VKA standard vs. placebo from extended therapy NMA
	Provoked PE off treatment	
	Unprovoked DVT off treatment	
	Unprovoked PE off treatment	
	Provoked DVT on treatment	
	Provoked PE on treatment	
	Unprovoked DVT on treatment	
	Unprovoked PE on treatment	

Table 14: Baseline uncalibrated transition probabilities for VTE recurrence per 3-month cycle

		Treated[(a)]				Untreated		
		Cycles 1	Cycle 2/3	Cycle 4/5	Cycle 6+	Cycle 2/3	Cycle 4/5	Cycle 6+
General population								
DVT	Provoked	4.90%	0.23%	0.14%	0.06%	2.37%	1.41%	0.58%
	Unprovoked	5.50%	0.57%	0.31%	0.17%	5.71%	3.14%	1.76%
PE	Provoked	4.90%	0.16%	0.10%	0.04%	1.65%	0.98%	0.40%
	Unprovoked	5.50%	0.40%	0.22%	0.12%	4.00%	2.19%	1.22%
Cancer Population								
DVT	Provoked	14.85%	0.75%	0.44%	0.18%	7.38%	4.43%	1.83%
	Unprovoked	16.56%	1.82%	0.99%	0.55%	17.15%	9.70%	5.51%
PE	Provoked	14.85%	0.52%	0.31%	0.13%	5.18%	3.10%	1.28%
	Unprovoked	16.56%	1.27%	0.69%	0.38%	12.25%	6.84%	3.86%

(a) On reference regimen LMWH/VKA

Table 15: Baseline calibrated transition probabilities for VTE recurrence per 3-month cycle

		Treated[(a)]				Untreated		
		Cycles 1	Cycle 2/3	Cycle 4/5	Cycle 6+	Cycle 2/3	Cycle 4/5	Cycle 6+
General population								
DVT	Provoked	4.44%	0.10%	0.20%	0.03%	0.93%	1.84%	0.29%
	Unprovoked	4.98%	0.24%	0.47%	0.09%	2.21%	4.23%	0.78%
PE	Provoked	4.44%	0.07%	0.14%	0.02%	0.64%	1.28%	0.20%
	Unprovoked	4.98%	0.17%	0.33%	0.06%	1.54%	2.95%	0.54%
Cancer Population								
DVT	Provoked	13.51%	0.32%	0.64%	0.10%	2.93%	5.78%	0.93%
	Unprovoked	15.08%	0.77%	1.49%	0.27%	6.91%	12.90%	2.48%
PE	Provoked	13.51%	0.22%	0.45%	0.07%	2.04%	4.05%	0.65%
	Unprovoked	15.08%	0.54%	1.04%	0.19%	4.85%	9.15%	1.73%

(a) On reference regimen LMWH/VKA

Table 16: Sources used to inform transition probabilities for bleeding events for each cycle

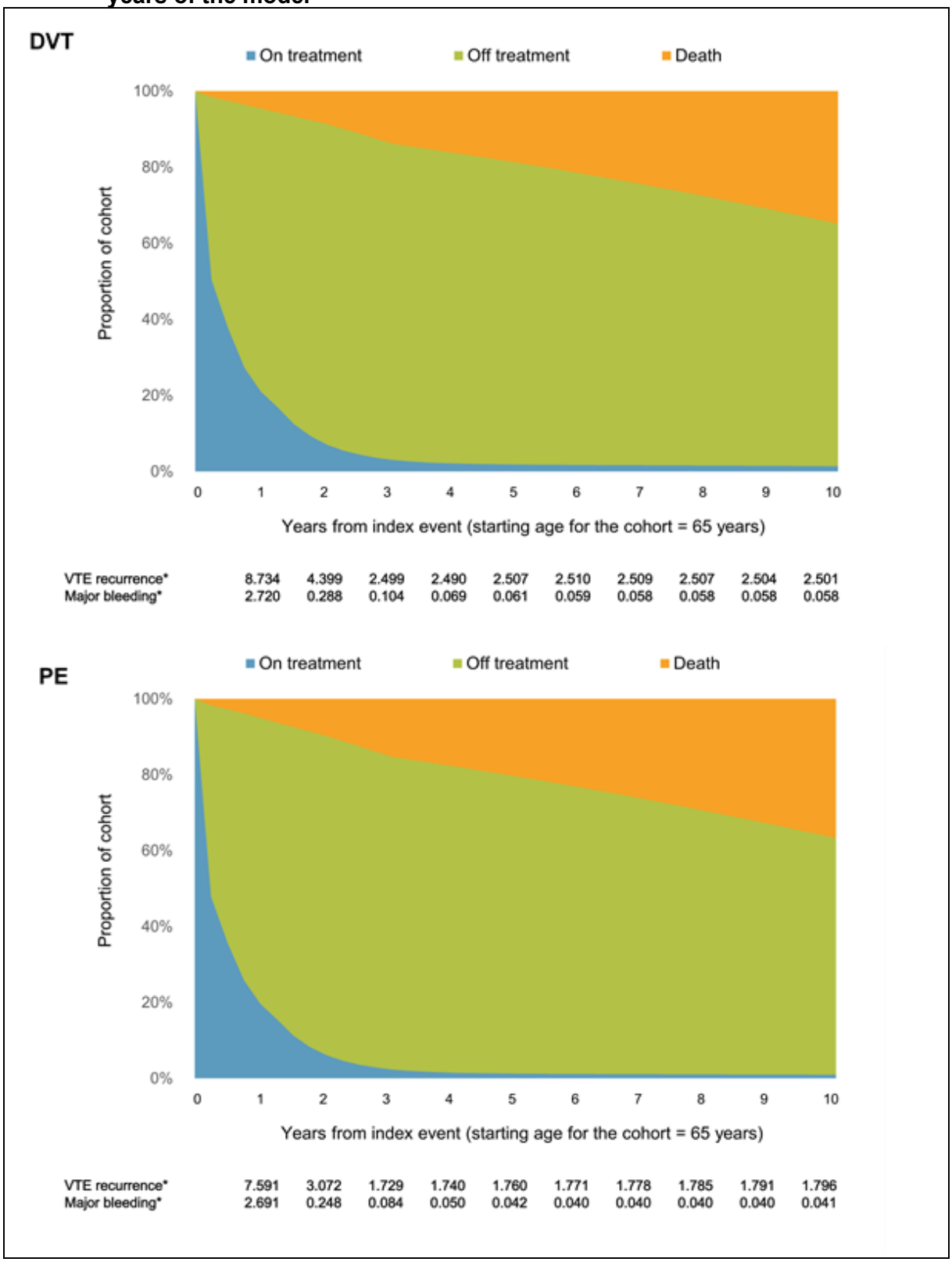
	Event	Source
Cycle 1	Major bleed	Nieto 2013
	CRNMB	Applied HR from Schulman 2013 vs. major bleed
Cycle 2 onwards	Major bleed	Schulman 2013
	CRNMB	Applied HR from Schulman 2013 vs. major bleed

Table 17: Baseline transition probabilities for bleeding events per 3-month cycle

	Overall population		Cancer population	
	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+
Major bleeding	2.24%	0.34%	4.86%	0.75%
CRNMB	12.83%	2.05%	26.08%	4.45%

To illustrate the effect of combining the baseline transition probabilities for recurrence, bleeding, treatment discontinuation, mortality and calibration on model dynamics, Figure 4 shows state membership (on treatment, off treatment and dead) for the first 10 years of the model alongside the number of VTE recurrences and major bleeds per 100 person-years for the reference treatment (LMWH/VKA) in the overall population for both DVT and PE.

Figure 4: Model dynamics on the reference treatment (LMWH/VKA) for the first 10 years of the model



**Per 100 person-years*

Treatment effects

Relative treatment effects from the NMAs (see evidence review D, appendix H) were estimated as either hazard ratios or odds ratios relative to LMWH/VKA as the reference regimen for the initial treatment phase and cancer subgroup and relative to VKA standard as the reference regimen for the extended therapy phase. The tables below report the mean and 95% credible intervals based on CODA outputs containing 10,000 iterations for each outcome generated in WinBUGS.

Table 18: Relative treatment effects versus LMWH/VKA from the initial treatment NMAs (hazard ratios)

Treatment	VTE (pooled) Mean (95% CrI)	DVT Mean (95% CrI)	PE Mean (95% CrI)
VTE recurrence			
UFH/VKA	1.326 (1.043 to 1.670)	1.457 (1.029 to 2.019)	1.746 (0.556 to 4.271)
Fondaparinux/VKA	0.987 (0.713 to 1.333)	0.990 (0.635 to 1.492)	1.326 (0.393 to 3.383)
Rivaroxaban	0.897 (0.663 to 1.187)	0.698 (0.444 to 1.050)	1.143 (0.746 to 1.678)
Dabigatran	1.111 (0.753 to 1.579)	1.564 (0.728 to 3.017)	1.111 (0.370 to 1.864)
Apixaban	0.840 (0.588 to 1.160)	0.854 (0.544 to 1.269)	0.944 (0.489 to 0.489)
Edoxaban	0.833 (0.593 to 1.122)	0.979 (0.643 to 1.425)	0.628 (0.338 to 1.078)
Major bleeding			
UFH/VKA	1.321 (0.923 to 1.829)	1.824 (1.040 to 3.005)	2.032 (0.575 to 4.346)
Fondaparinux/VKA	1.119 (0.718 to 1.692)	1.136 (0.642 to 1.859)	1.796 (0.307 to 0.790)
Rivaroxaban	0.548 (0.364 to 0.796)	0.691 (0.329 to 1.286)	0.505 (0.490 to 1.172)
Dabigatran	0.777 (0.490 to 1.172)	Used pooled VTE NMA	Used pooled VTE NMA
Apixaban	0.318 (0.167 to 0.535)	0.530 (0.241 to 0.991)	0.150 (0.589 to 1.201)
Edoxaban	0.853 (0.589 to 1.201)	Used pooled VTE NMA	Used pooled VTE NMA
CRNMB			
UFH/VKA	1.012 (0.758 to 1.320)	0.792 (0.529 to 1.135)[a]	Used pooled VTE NMA
Fondaparinux/VKA	0.795 (0.589 to 1.056)	0.978 (0.670 to 1.400)[a]	Used pooled VTE NMA
Rivaroxaban	0.998 (0.857 to 1.154)	1.064 (0.806 to 1.371)[a]	Used pooled VTE NMA
Dabigatran	0.593 (0.460 to 0.756)	Used pooled VTE NMA	Used pooled VTE NMA
Apixaban	0.487 (0.387 to 0.602)	0.681 (0.256 to 1.427)[a]	Used pooled VTE NMA
Edoxaban	0.803 (0.683 to 0.935)	Used pooled VTE NMA	Used pooled VTE NMA

(a) Estimated as odds ratios

Table 19: Relative treatment effects versus VKA standard from the extended therapy NMAs (hazard ratios)

Treatment	VTE recurrence Mean (95% CrI)	Major bleeding Mean (95% CrI)	CRNMB Mean (95% CrI)
No treatment	11.601 (5.992 to 20.032)	N/A[a]	N/A[a]
VKA low	3.787 (1.836 to 6.843)	0.962 (0.332 to 2.209)	Used VKA standard
Aspirin	7.786 (3.702 to 14.230)	0.318 (0.039 to 1.191)	0.516 (0.152 to 1.319)[b]
Apixaban 2.5mg	2.121 (0.801 to 4.413)	0.112 (0.005 to 0.542)	0.267 (0.088 to 0.617)[b]
Apixaban 5 mg	2.193 (0.834 to 4.508)	0.060 (0.001 to 0.325)	0.381 (0.128 to 0.879)[b]

Treatment	VTE recurrence Mean (95% CrI)	Major bleeding Mean (95% CrI)	CRNMB Mean (95% CrI)
Dabigatran	1.372 (0.750 to 2.307)	0.578 (0.282 to 1.039)	0.540 (0.389 to 0.723)[b]
Rivaroxaban 10 mg	2.087 (0.778 to 4.536)	0.825 (0.051 to 3.729)	0.608 (0.166 to 1.627)[b]
Rivaroxaban 20 mg	2.496 (1.062 to 4.912)	1.089 (0.083 to 4.821)	0.858 (0.269 to 2.142)[b]
Edoxaban	0.833 (0.383 to 1.808)[c]	0.853 (0.109 to 6.688) [c]	Used initial treatment

(a) The model assumes bleeding events can only occur while on treatment
(b) Estimated as odds ratios
(c) Mean value from initial treatment NMA and assuming standard error of the other DOACs with extended therapy data

Table 20: Relative treatment effects compared to LMWH/VKA from the NMAs in people with cancer (hazard ratios)

Treatment	VTE recurrence Mean (95% CrI)	Major bleeding Mean (95% CrI)	CRNMB Mean (95% CrI)
UFH/VKA	1.225 (0.355 to 3.247)	1.111 (0.282 to 3.019)	0.474 (0.208 to 0.939)
Fondaparinux/VKA	Used initial treatment	Used initial treatment	Used initial treatment
Rivaroxaban	0.377 (0.180 to 0.700)	1.054 (0.444 to 2.100)	1.352 (0.782 to 2.175)
Dabigatran	0.912 (0.201 to 2.643)	1.639 (0.277 to 5.381)	1.936 (0.613 to 4.966)
Apixaban	0.721 (0.104 to 2.315)	0.625 (0.054 to 2.448)	0.611 (0.232 to 1.306)
Edoxaban	0.463 (0.259 to 0.771)	2.072 (0.929 to 4.063)	0.822 (0.474 to 1.324)
LMWH	0.601 (0.436 to 0.808)	0.953 (0.607 to 1.435)	0.538 (0.370 to 0.751)

Transition probabilities for the initial treatment period

The following tables summarise transition probabilities for the first 2 cycles following a VTE event after treatment effects from the NMAs were applied to baseline estimates of VTE recurrence (calibrated values), major bleeding and CRNMB.

Table 21: Transition probabilities for VTE recurrence (calibrated) in the initial treatment period

	Provoked DVT		Unprovoked DVT		Provoked PE		Unprovoked PE	
Treatment	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
LMWH/VKA	4.44%	0.08%	4.98%	0.19%	4.44%	0.06%	4.98%	0.19%
UFH/VKA	5.84%	0.11%	6.55%	0.26%	5.84%	0.07%	6.55%	0.18%
Fondaparinux/VKA	4.38%	0.08%	4.92%	0.19%	4.38%	0.05%	4.92%	0.13%
Rivaroxaban	3.99%	0.07%	4.48%	0.17%	3.99%	0.05%	4.48%	0.12%
Dabigatran	4.92%	0.09%	5.52%	0.21%	4.92%	0.06%	5.52%	0.15%
Apixaban	3.74%	0.07%	4.20%	0.16%	3.74%	0.05%	4.20%	0.11%
Edoxaban	3.71%	0.07%	4.16%	0.16%	3.71%	0.05%	4.16%	0.11%

Table 22: Transition probabilities for bleeding events in the initial treatment period

	Major bleeding		CRNMB	
Treatment	Cycle 1	Cycle 2	Cycle 1	Cycle 2
LMWH/VKA	2.24%	0.34%	12.83%	2.05%

Treatment	Major bleeding		CRNMB	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
UFH/VKA	2.95%	0.45%	12.98%	2.07%
Fondaparinux/VKA	2.50%	0.38%	10.35%	1.63%
Rivaroxaban	1.23%	0.19%	12.81%	2.04%
Dabigatran	1.74%	0.26%	7.82%	1.22%
Apixaban	0.72%	0.11%	6.47%	1.00%
Edoxaban	1.91%	0.29%	10.44%	1.65%

Transition probabilities for the extended therapy period

The following tables summarise transition probabilities per 3-month cycle for the extended therapy period (cycle 3 onwards after a VTE event).

Table 23: Transition probabilities for VTE recurrence (calibrated) in the extended therapy period

Treatment	Provoked DVT			Unprovoked DVT		
	Cycle 3	Cycle 4/5	Cycle 6+	Cycle 3	Cycle 4/5	Cycle 6+
VKA standard	0.08%	0.16%	0.03%	0.19%	0.37%	0.07%
No treatment	0.93%	1.84%	0.29%	2.21%	4.23%	0.78%
VKA low	0.30%	0.61%	0.10%	0.73%	1.40%	0.26%
Aspirin (ASA)	0.62%	1.24%	0.20%	1.49%	2.86%	0.53%
Rivaroxaban 10mg	0.17%	0.33%	0.05%	0.40%	0.77%	0.14%
Rivaroxaban 20mg	0.20%	0.40%	0.06%	0.48%	0.92%	0.17%
Apixaban 2.5mg	0.17%	0.34%	0.05%	0.41%	0.79%	0.14%
Apixaban 5 mg	0.18%	0.35%	0.06%	0.42%	0.81%	0.15%
Dabigatran	0.11%	0.22%	0.03%	0.26%	0.51%	0.09%
Edoxaban[(a)]	0.07%	0.13%	0.02%	0.16%	0.31%	0.06%
Treatment	**Provoked PE**			**Unprovoked PE**		
	Cycle 3	Cycle 4/5	Cycle 6+	Cycle 3	Cycle 4/5	Cycle 6+
VKA standard	0.06%	0.11%	0.02%	0.13%	0.26%	0.05%
No treatment	0.64%	1.28%	0.20%	1.54%	2.95%	0.54%
VKA low	0.21%	0.42%	0.07%	0.51%	0.97%	0.18%
Aspirin (ASA)	0.43%	0.86%	0.14%	1.04%	1.99%	0.37%
Rivaroxaban 10mg	0.12%	0.23%	0.04%	0.28%	0.54%	0.10%
Rivaroxaban 20mg	0.14%	0.28%	0.04%	0.33%	0.64%	0.12%
Apixaban 2.5mg	0.12%	0.24%	0.04%	0.28%	0.55%	0.10%
Apixaban 5 mg	0.12%	0.24%	0.04%	0.29%	0.57%	0.10%
Dabigatran	0.08%	0.15%	0.02%	0.18%	0.35%	0.06%
Edoxaban[(a)]	0.05%	0.09%	0.01%	0.11%	0.21%	0.04%

(a) No extended therapy trial, uses relative effect from initial treatment NMA

Table 24: Transition probabilities for bleeding in the extended therapy period

Treatment	Major Bleeding	CRNMB
VKA standard	0.34%	2.05%
No treatment	N/A[(a)]	N/A[(a)]
VKA low	0.33%	2.05%
Aspirin (ASA)	0.11%	1.26%
Rivaroxaban 10mg	0.28%	1.26%
Rivaroxaban 20mg	0.37%	1.76%
Apixaban 2.5mg	0.04%	0.56%
Apixaban 5mg	0.02%	0.79%
Dabigatran	0.20%	1.12%
Edoxaban[(b)]	0.29%	1.65%

(a) The model assumes bleeding events can only occur while on treatment
(b) No extended therapy trial, uses relative effect from initial treatment NMA

Transition probabilities for the cancer subgroup

The following tables summarise transition probabilities per 3-month cycle for VTE recurrence, major bleeding and CRNMB in the cancer subgroup.

Table 25: Transition probabilities for VTE recurrence (calibrated) in the cancer subgroup

	Provoked DVT				
Treatment	Cycle 1	Cycle 2	Cycle 3	Cycle 4/5	Cycle 6+
LMWH/VKA	13.51%	0.26%	0.26%	0.51%	0.08%
UFH/VKA	16.29%	0.31%	0.31%	0.63%	0.10%
Fondaparinux/VKA[(a)]	13.36%	0.25%	0.25%	0.51%	0.08%
Rivaroxaban	5.33%	0.10%	0.10%	0.19%	0.03%
Dabigatran	12.41%	0.23%	0.23%	0.47%	0.07%
Apixaban	9.94%	0.18%	0.18%	0.37%	0.06%
Edoxaban	6.50%	0.12%	0.12%	0.24%	0.04%
LMWH	8.35%	0.15%	0.15%	0.31%	0.05%
	Unprovoked DVT				
Treatment	Cycle 1	Cycle 2	Cycle 3	Cycle 4/5	Cycle 6+
LMWH/VKA	15.08%	0.62%	0.62%	1.18%	0.22%
UFH/VKA	18.14%	0.75%	0.75%	1.45%	0.27%
Fondaparinux/VKA[(a)]	14.90%	0.61%	0.61%	1.17%	0.21%
Rivaroxaban	5.98%	0.23%	0.23%	0.45%	0.08%
Dabigatran	13.85%	0.56%	0.56%	1.08%	0.20%
Apixaban	11.12%	0.44%	0.44%	0.86%	0.16%
Edoxaban	7.28%	0.29%	0.29%	0.55%	0.10%
LMWH	9.35%	0.37%	0.37%	0.71%	0.13%
	Provoked PE				
Treatment	Cycle 1	Cycle 2	Cycle 3	Cycle 4/5	Cycle 6+
LMWH/VKA	13.51%	0.18%	0.18%	0.36%	0.06%

Treatment	Provoked DVT				
	Cycle 1	Cycle 2	Cycle 3	Cycle 4/5	Cycle 6+
UFH/VKA	16.29%	0.22%	0.22%	0.44%	0.07%
Fondaparinux/VKA[(a)]	13.36%	0.18%	0.18%	0.35%	0.06%
Rivaroxaban	5.33%	0.07%	0.07%	0.13%	0.02%
Dabigatran	12.41%	0.16%	0.16%	0.32%	0.05%
Apixaban	9.94%	0.13%	0.13%	0.26%	0.04%
Edoxaban	6.50%	0.08%	0.08%	0.16%	0.03%
LMWH	8.35%	0.11%	0.11%	0.21%	0.03%
Treatment	**Unprovoked PE**				
	Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4/5**	**Cycle 6+**
LMWH/VKA	15.08%	0.43%	0.43%	0.82%	0.15%
UFH/VKA	18.14%	0.52%	0.52%	1.01%	0.18%
Fondaparinux/VKA[(a)]	14.90%	0.42%	0.42%	0.81%	0.15%
Rivaroxaban	5.98%	0.16%	0.16%	0.31%	0.06%
Dabigatran	13.85%	0.39%	0.39%	0.75%	0.14%
Apixaban	11.12%	0.31%	0.31%	0.59%	0.11%
Edoxaban	7.28%	0.20%	0.20%	0.38%	0.07%
LMWH	9.35%	0.26%	0.26%	0.50%	0.09%

(a) No data in people with cancer, uses relative effect from NMA for initial treatment of VTE

Table 26: Transition probabilities for bleeding in the cancer subgroup

Treatment	Major Bleeding		CRNMB	
	Cycle 1	Cycle 2+	Cycle 1	Cycle 2+
LMWH/VKA	4.86%	0.75%	26.08%	4.45%
UFH/VKA	5.38%	0.83%	13.34%	2.14%
Fondaparinux/VKA[(a)]	5.42%	0.84%	21.36%	3.56%
Rivaroxaban	5.11%	0.79%	33.54%	5.97%
Dabigatran	7.84%	1.22%	44.29%	8.44%
Apixaban	3.06%	0.47%	16.85%	2.74%
Edoxaban	9.80%	1.54%	21.99%	3.67%
LMWH	4.63%	0.71%	15.00%	2.42%

(a) No data in people with cancer, uses relative effect from NMA for initial treatment of VTE

Utilities

Health state utilities were estimated in the model by subtracting disutilities associated with different events from baseline age-adjusted utilities for the UK general population (Kind 1999). A summary of all disutility estimates used in the model can be found in Table 27.

DVT and PE recurrence

Disutilities associated with the occurrence of a DVT or PE were sourced from Cohen 2014. This study assessed health status using the EQ-5D in a prospective European observational cohort of people who were receiving anticoagulation for treatment of VTE. The actual utility values at baseline, 1 month, 3 and 6 months were sourced from the NICE Technology

Appraisal 354 as they were not reported in enough detail in the available publication. QALYs were calculated using the area-under-the-curve method, assuming that health status would return to pre-VTE values by 6 months.

Adverse events

Disutilities for major intracranial bleeds (ICB) and major extracranial bleeds (ECB) were taken from Locadia 2004, a study that valued complications of VTE treatment using time trade-off methodology. It was assumed that the immediate, short-term ICB-related disutility would last for 3 months followed by a smaller value for long-term disutility. The disutility associated with an ECB was assumed to last for 1 month. The disutility associated with CRNMB used in the model was also sourced from Locadia 2004 (muscular bleeding) and was assumed to last for 2 days.

The long-term disutility for an ICB was taken from Luengo-Fernandez 2013, which used the EQ-5D to assess health status in UK patients who had experienced a stroke and compared this data to that of a matched cohort from Health Survey for England. The estimate for long-term ICB disutility used in the base-case analysis reflects the value reported in Luengo-Fernandez 2013 for all kinds of stroke (predominantly ischaemic) because the estimate specific to haemorrhagic stroke was based on a relatively small subset of patients.

The disutility for CTEPH was sourced from Meads 2008, a study validating the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) utility index in English patients. For PTS, disutilities were sourced from Lenert 1997, which elicited preferences from volunteers and physicians using standard gamble methodology.

Cancer

Cancer-related disutility was implemented as a weighted average value for the four most common types of cancer (breast, prostate, lung and colorectal). Utility estimates that reflected advanced or metastatic stages of disease were chosen from the literature because this is when the incidence of VTEs is highest (Khorana 2010). Utilities for breast cancer were sourced from Lloyd 2006 and for non-small cell lung cancer from Nafees 2008. Both studies elicited preferences from 100 members of UK general public using standard gamble. Utilities for prostate cancer were extracted from Torvinen 2013 and for colorectal cancer from Farkkila 2013. Both of these studies estimated utilities based on EQ-5D responses collected in patients.

Table 27: Disutility estimates used in the model

Health state or event	Value per cycle	Source
Recurrent DVT	-0.015	Cohen 2014
Recurrent PE	-0.018	Cohen 2014
Intracranial bleed short-term - Cycle 1	-0.155	Locadia 2004
Intracranial bleed long-term - Cycle 2 onwards	-0.045	Luengo-Fernandez 2013
Extracranial bleed	-0.025	Locadia 2004
CRNMB	-0.0002	Locadia 2004
CTEPH	-0.059	Meads 2008
Moderate PTS	-0.005	Lenert 1997

Health state or event	Value per cycle	Source
Severe PTS	-0.018	Lenert 1997
Cancer (weighted average)	-0.021	Nafees 2008, Lloyd 2006, Farkkila 2013, Torvinen 2013

Costs

Seven main categories of costs were considered in the model:

1. **Drug costs** – acquisition costs and costs of administering anticoagulation treatments
2. **Monitoring costs** – routine GP/nurse visits, renal function, INR monitoring (VKA)
3. **Costs of VTE recurrence** – resource use associated with hospitalisation and diagnostic procedures
4. **Costs of bleeding** – resource use associated with hospitalisation, reversal agents and long-term rehabilitation costs (intracranial haemorrhage)
5. **Costs of CTEPH** – resource use associated with diagnosis and treatment of CTEPH following a PE
6. **Costs of PTS** – resource use associated with diagnosis and treatment of PTS following a DVT
7. **Costs of cancer (subgroup analysis only)** – resource use associated with hospitalisation and treatment for cancer (weighted across prostate, breast, lung and colorectal)

Drug costs

Drug costs were based on the NHS Drug Tariff and dosing information on the summary of product characteristics for each drug. If more than one relevant preparation was available, Prescription Cost Analysis (PCA) data were used to estimate a weighted average cost.

Table 28: Cost per pack for drugs in the model

Drug	Cost per pack[(a)]	Doses per pack
Apixaban 2.5 mg tablets	£57.00	60
Apixaban 5 mg tablets	£53.20	56
Aspirin 75 mg	£0.86 [(b)]	28
Dabigatran 150 mg	£51.00	60
Edoxaban 60 mg tablets	£49.00	28
Fondaparinux 10 mg pre-filled syringe	£11.65	1
Heparin sodium, 5,000 IU/0.2 ml ampoule	£37.35	10
Rivaroxaban 10 mg tablets	£54.00	30
Rivaroxaban 15 mg tablets	£50.40	28
Rivaroxaban 20 mg tablets	£50.40	28
Warfarin 3 mg tablets	£0.86	28
Warfarin 5 mg tablets	£0.94	28

(a) NHS Drug Tariff November 2019
(b) Weighted average based on PCA July 2019

Table 29: Cost and prescription data for LMWH

Chemical name	Items dispensed	Cost per syringe[a]
Dalteparin	6,970 [b]	
Dalteparin - 10,000 IU	17.10%	£5.65
Dalteparin - 12,500 IU	29.77%	£7.06
Dalteparin - 15,000 IU	31.23%	£8.47
Dalteparin - 18,000 IU	21.89%	£10.16
Enoxaparin	7,383[b]	
Enoxaparin - 80 mg	27.09%	£5.51
Enoxaparin - 100 mg	31.74%	£7.23
Enoxaparin - 120 mg	25.94%	£8.79
Enoxaparin - 150 mg	15.23%	£9.99
Tinzaparin	4,243 [b]	
Tinzaparin - 8,000 IU	3.56%	£4.76
Tinzaparin - 10,000 IU	18.71%	£5.95
Tinzaparin - 12,000 IU	21.52%	£7.14
Tinzaparin - 14,000 IU	27.10%	£8.33
Tinzaparin - 16,000 IU	11.34%	£9.52
Tinzaparin - 18,000 IU	17.77%	£10.71

(a) NHS Drug Tariff November 2019
(b) PCA July 2019

For VKA-containing regimens (LMWH/VKA, UFH/VKA, fondaparinux/VKA) the duration of parenteral anticoagulation was assumed to be 10 days administered alongside oral VKA, which was assumed to be warfarin in all cases. Prior to initiating treatment on dabigatran or edoxaban, patients require 5 days of parenteral anticoagulation, which was assumed to be LMWH.

LMWH dosing is determined by body weight and renal clearance. Data from Barba 2005, a registry based study assessing the impact of body weight on clinical outcome after VTE, was used to inform the distribution of weight and number of patients with VTE in 3 categories (<50 kg, 50 kg to 100 kg and >100 kg). These values were used to estimate an overall mean weight and standard deviation. A lognormal distribution was used to produce an overall distribution of weight, which provided a good fit to the original proportion of patients falling into each of the 3 weight categories. This distribution was used to calculate the proportion of patients requiring each pre-filled syringe dose for dalteparin, enoxaparin and tinzaparin. In addition, the assumption was made that there is some inefficiency in prescribing with 15% of patients receiving a pre-filled syringe one dosage increment higher than they require. The committee estimated that 85% of patients using LMWH pre-filled syringes, fondaparinux pre-filled syringes and UFH self-administer their treatment. Of the remaining 15%, half will be visited by a district nurse and the other half will attend an appointment with a nurse at a health centre (50% band 5 nurse time and 50% band 6 nurse time). UFH was assumed to be administered twice daily subcutaneously using single dose ampoules.

Table 30: Administration costs

Resource[(a)]	Cost
District nurse	£41.73
GP practice nurse - band 5 - 10 mins	£9.80
GP practice nurse - band 6 - 10 mins	£12.30

(a) PSSRU 2018

A summary of the drug cost per cycle for each strategy is shown in Table 31 for the initial treatment period and Table 32 for the extended therapy period.

Table 31: Drug cost per cycle in the initial treatment period

	Dose	Individual drug cost	Total drug cost	Administration cost[(a)]
LMWH/VKA				
Cycle 1	10 days parenteral LMWH[(a)] Warfarin: 10 mg/day for 2 days and 6 mg/day thereafter	£59.13 £5.62	£64.75	£39.61
Cycle 2+	Warfarin: 6 mg/day	-	£5.61	-
UFH/VKA				
Cycle 1	UFH 5,000 IU twice daily for 10 days Warfarin: 10 mg/day for 2 days and 6 mg/day thereafter	£74.70 £5.62	£80.32	£79.22
Cycle 2+	Warfarin: 6 mg/day	-	£5.61	-
Fondaparinux/VKA				
Cycle 1	Fondaparinux 1 injection/day for 10 days Warfarin: 10 mg/day for 2 days and 6 mg/day thereafter	£116.53 £5.62	£122.15	£39.61
Cycle 2+	Warfarin: 6 mg/day	-	£5.61	-
Rivaroxaban				
Cycle 1	15 mg twice daily for days 1-21 and 20 mg/day thereafter	-	£202.05	-
Cycle 2+	20 mg/day	-	£164.25	-
Dabigatran				
Cycle 1	5 days parenteral LMWH[(a)] Dabigatran 150 mg twice daily thereafter	£29.57 £146.62	£176.19	£19.81
Cycle 2+	150 mg twice daily	-	£155.13	-
Apixaban				
Cycle 1	10 mg twice daily for days 1-7 and 5 mg twice daily thereafter	-	£186.68	-
Cycle 2+	5 mg twice daily	-	£173.38	-
Edoxaban				
Cycle 1	5 days parenteral LMWH[(a)] Edoxaban 60 mg/day thereafter	£29.57 £150.94	£180.51	£19.81
Cycle 2+	60 mg/day	-	£159.69	-

	Dose	Individual drug cost	Total drug cost	Administration cost[(a)]
LMWH (cancer subgroup)				
All cycles	1 injection/day for duration of treatment	-	£539.62	£361.44

(a) Assuming nurse administration in 15% of patients for LMWH, UFH and fondaparinux
(b) LMWH dosage calculated based on patient weight distribution form Barba 2005

Table 32: Drug costs per cycle in the extended therapy period

Drug	Dose	Cost per cycle
Aspirin	75 mg/day	£2.82
VKA (warfarin) standard	6 mg/day	£5.61
VKA (warfarin) low	5 mg/day	£3.06
Apixaban 2.5 mg	2.5 mg twice daily	£173.38
Apixaban 5 mg	5 mg twice daily	£173.38
Edoxaban	60 mg/day	£159.69
Dabigatran	150 mg twice daily	£155.13
Rivaroxaban 10 mg	10 mg/day	£164.25
Rivaroxaban 20 mg	20 mg/day	£164.25

People who experienced a recurrent VTE while off treatment were assumed to return to the same treatment that they received for the index event at the start of the model. People who experienced a recurrent VTE while on treatment were assumed to switch to another treatment. For simplicity, this was modelled as a weighted average of the costs and effectiveness of all treatment comparators.

Monitoring and routine healthcare costs

VKA-containing regimens

During the first 3 months of treatment on VKA-containing regimens, patients were assumed to attend an initial GP visit, 10 INR monitoring visits (90% with a band 5 nurse in the community and 10% with a band 6 nurse in secondary care) and a follow-up GP visit at 3 months. In subsequent cycles, 1 INR monitoring visit was assumed.

DOACs

During the first 3 months of treatment with a DOAC, patients were assumed to attend an initial double GP visit (to allow more time to explain dosing as there are no INR monitoring visits) and a follow-up GP visit at 3 months. In subsequent cycles the number of GP visits is determined by individual's renal function: once a year if normal renal function, twice a year for people with stage 3 chronic kidney disease (CKD) and four times a year for people with stage 4 or 5 CKD (Ocak 2013).

LMWH alone (cancer subgroup)

During the first 3 months of treatment with LMWH alone for the cancer subgroups analysis, patients were assumed to attend 2 GP visits and have a blood test to check platelet count due to the risk of heparin-induced thrombocytopenia. In subsequent cycles, the number of GP visits is determined by individual's renal function as described above for the DOACs.

Treatment switching

In the sequencing analysis, people who switch to aspirin in the extended phase of treatment were assumed to attend 2 GP visits per year for follow-up and platelet monitoring. For strategies in which people switch to no treatment in the extended phase, it was assumed no monitoring costs would be incurred. For other treatment strategies involving a change of drug between the initial and extended phases, for example switching from one DOAC to another DOAC or from a DOAC to a VKA, monitoring costs on the new treatment were assumed to be equivalent to what was assumed for the first cycle of the same drug in the initial treatment phase.

The unit costs of monitoring and routine healthcare visits are shown in Table 33. The monitoring cost per cycle associated with each treatment is reported in Table 34.

Table 33: Unit costs of monitoring and healthcare visits

Resource	Costs	Source
GP visit	£37.00	PSSRU 2018
Anticoagulation clinic - band 5 nurse - 10 mins	£14.83	PSSRU 2018
Secondary care nurse visit - band 6 - 10 mins	£18.33	PSSRU 2018
Full blood count [Haematology, DAPS05]	£2.51	NHS Reference Costs 2017/18

Table 34: Cost of monitoring and routine healthcare visits per cycle

Resource	Cost per cycle
VKA-containing strategies (INR monitoring)	
Cycle 1	£225.83
Cycle 2 onwards	£15.18
DOACs	
Cycle 1	£111.00
Cycle 2 onwards	£15.11
LMWH alone (cancer subgroup)	
Cycle 1	£79.01
Cycle 2 onwards	£15.11
Aspirin	
Cycle 3 onwards	£10.02

Costs of VTE recurrence

In the event of a recurrent DVT, the committee estimated that 90% of patients would be managed as outpatients and the remainder as inpatients. Outpatient management was

assumed to consist of an emergency medicine category 3 investigation with category 4 treatment, vascular ultrasound scan, D-dimer test, and blood test (based on NHS Reference Costs 2017/18).

In the event of a recurrent PE, the committee estimated that 20% of patients would be managed as outpatients and the remainder as inpatients. Outpatient management was assumed to consist of an emergency medicine category 3 investigation with category 4 treatment, ECG, D-dimer, blood test and lung scan (computed tomography pulmonary angiogram in 80% of cases, ventilation/perfusion scan in 20% of cases).

Table 35: Inpatient and outpatient costs for treatment of recurrent VTE

Resource	Cost[(a)]
Inpatient costs	
Deep vein thrombosis [YQ51A to YQ51E]	£636.46
Pulmonary embolism [DZ09J to DZ09Q]	£1,411.51
Outpatient cost components	
Emergency medicine category 3 investigation with category 4 treatment [VB02Z]	£394.50
Vascular ultrasound scan [RD47Z]	£66.36
Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over [RD21A]	£106.12
Lung Ventilation or Perfusion Scan, 19 years and over [RN18A]	£311.07
Electrocardiogram Monitoring or Stress Testing [EY51Z]	£118.76
D-dimer test	£10.82
Directly accessed pathology services - haematology [DAPS05]	£2.51
Proportion outpatient versus inpatient for treatment of recurrence	
DVT recurrences managed as outpatients/inpatients	90%/10%
PE recurrences managed as outpatients/inpatients	20%/80%
Calculated costs per VTE recurrence	
Deep vein thrombosis	£490.42
Pulmonary embolism	£1,263.15

(a) NHS Reference Costs 2017/18

Bleeding events

The short-term cost of managing a major ICB consisted of the NHS Reference Cost for haemorrhagic cerebrovascular disorders plus 14 rehabilitation sessions for stroke. The cost of managing a major ECB was based on a weighted average of NHS Reference Costs for gastrointestinal bleeds. The cost of managing a CRNMB was assumed to consist of an emergency medicine category 2 investigation with category 2 treatment.

Table 36: Short-term cost of managing bleeding events

Events	Cost[(a)]
ICB	
Haemorrhagic cerebrovascular disorders [AA23C to AA23G]	£2,985.08
Rehabilitation for stroke [VC04Z]	£387.61

Events	Cost[a]
ECB	
Gastrointestinal bleed [FD03A to FD03H]	£1,212.89
Gastrointestinal bleed (single and multiple interventions) [FD03A to FD03E]	£2,950.08
CRNMB	
Emergency medicine category 2 investigation with category 2 treatment - non-admitted VB07Z]	£184.49

(a) NHS Reference Costs 2017/18

Long-term costs following a major ICB were sourced from Wardlaw 2006 and inflated to current values.

Table 37: Long-term costs for post-ICB state

Resource	Cost	Source
First year - dependent state	£30,307.36	Wardlaw 2006
First year - independent state	£5,059.71	Wardlaw 2006
Second year onwards - dependent state	£15,377.60	Wardlaw 2006
Second year onwards - independent state	£1,192.91	Wardlaw 2006
Proportion of patients in independent state (GOS >3)[a]	40.50%	Rosand 2004
First year cost - overall	£20,082.06	Calculated
Second year onwards cost - overall	£9,632.80	Calculated

(a) GOS = Glasgow Outcome Scale (1=death, 2=persistent vegetative, 3=severe disability, 4=moderate disability, 5=good recovery)

In the event of a major bleed, there was committee consensus that reversal agents would be administered. The model takes into account the cost associated with reversal agents but does not take into account any potential differences in the effectiveness of the reversal agents.

Table 38: Reversal agent dose and unit cost

Reversal agent	Unit cost	Dose	Source
Vitamin K - phytomenadione 10 mg/1 ml[a]	£0.38	5 to 10mg	NHS Drug Tariff November 2019
Octaplex - 1,000 IU vial (40 ml)	£416.50	INR 2-2.5 - 0.9-1.3ml/kg[b] INR 2.5-3 - 1.3-1.6ml/kg[b]	Monthly Index of Medical Specialities (MIMS)
Beriplex - 1,000 IU vial (40 ml)	£600.00	INR 2.0-3.9 - 25 IU/kg[b]	Monthly Index of Medical Specialities (MIMS)
Idarucizumab - 2.5 g/50 ml	£1,200.00	5g	NICE evidence summary 73
Protamine sulfate	£3.52	50mg	Electronic market information tool (eMIT) November 2019

(a) Assumes an average of 1.5 vials per patient
(b) Average body weight 72 kg

Table 39 summarises the committee's consensus on the proportion of major bleeds that would be treated with a reversal agent and the average cost per reversal for each anticoagulant.

Table 39: Proportion of people who would receive a reversal agent and the average cost per reversal

Anticoagulant	Reversal agent for ICB	Reversal agent for ECB	Weighted average cost per reversal
Apixaban	PCC[(a)] (100%)	PCC[(a)] (60%)	£1280.31
Dabigatran	Idarucizumab (100%)	Idarucizumab (60%)	£2400.00
Edoxaban	PCC[(a)] (100%)	PCC[(a)] (60%)	£1280.31
Rivaroxaban	PCC[(a)] (100%)	PCC[(a)] (60%)	£1280.31
VKA (warfarin)	Vitamin K IV (100%) PCC[(a)] (90%)	Vitamin K IV (100%) PCC[(a)] (50%)	£1152.85
LMWH	Protamine sulfate (100%)	Protamine sulfate (60%)	£3.52

(a) PCC = prothrombin complex concentrate (assumes 50% Beriplex/50% Octaplex)

CTEPH

CTEPH can be treated surgically by carrying out a procedure known as pulmonary endarterectomy. However, not all patients with CTEPH are suitable for this procedure; other treatment options include balloon pulmonary angioplasty and medical management with the drug riociguat. A proportion of patients who undergo surgery also receive riociguat.

The probability of being eligible for pulmonary endarterectomy (59.5%) was taken from Delcroix 2016, an analysis of a multicentre European registry including people with operable and inoperable CTEPH. The probability of receiving balloon pulmonary angioplasty conditional on being ineligible for pulmonary endarterectomy was assumed to be 20%.

The costs for management of CTEPH were split into 5 categories: diagnosis, surgical procedures, medication, routine healthcare resource use, and unplanned healthcare resource use. The unit costs of resources associated with CTEPH are shown in Table 40.

- Diagnosis consists of a clinical examination (GP visit and non-consultant-led respiratory medicine outpatient visit), ventilation/perfusion scan in 20% of patients, outpatient visit (consultant-led respiratory medicine outpatient visit), computed tomography pulmonary angiogram (CTPA), right-heart catheterisation, and magnetic resonance imaging (MRI) pulmonary angiogram in 80% of patients.
- For surgical procedures, the cost of pulmonary endarterectomy was taken from the NICE guideline NG89 economic analysis (based on information from Papworth Hospital, the UK's only centre for the procedure). For balloon pulmonary angioplasty, the cost was based on the NHS England tariff and it was assumed 4 procedures would be required based on committee input.
- For medical management of CTEPH, the committee indicated that riociguat is the only drug currently used to treat CTEPH. It was assumed that 30% of patients who undergo

pulmonary endarterectomy (committee consensus), 41% of patients who undergo balloon pulmonary angioplasty (Inami 2017), and the remaining inoperable patients would receive riociguat.

- Based on committee consensus, it was assumed that patients would require 5 annual appointments in the first year after diagnosis and 3 in the subsequent years. These were assumed to be a consultant-led, non-admitted face-to-face attendance, follow-up, respiratory medicine from NHS Reference Costs 2016/17.
- Unplanned healthcare resource use for CTEPH is dependent on functional class (NICE Guideline NG89). The proportion of patients in each functional class (2, 3 or 4) was taken from Schweikert 2014: patients in functional class 2 were assumed to require 1 outpatient visit and 1-day ward assessment per year; patients in functional class 3 were assumed to require 1 outpatient visit and 2-day ward assessments per year and patients in functional class 4 were assumed to require 1 outpatient visit, 2-day ward assessments and 4 hospital admissions per year.

Table 40: Costs for CTEPH-related resource use

Resource	Cost	Source
Diagnosis		
Clinical examination - Non-consultant-led, non-Admitted Face-to-Face Attendance, First, Respiratory medicine [WF01B - 340]	£133.81	NHS Reference Costs 2017/18
Referral/outpatient visit - Consultant-led, non-Admitted Face-to-Face Attendance, First, Respiratory medicine [WF01B - 340]	£207.58	NHS Reference Costs 2017/18
Right heart catheterisation - weighted average of standard cardiac catheterisation procedures [EY43A to EY43F]	£1,725.60	NHS Reference Costs 2017/18
MRI pulmonary angiogram - weighted average of magnetic resonance imaging scan of one area (excluding under 19 years old) [RD01A, RD02A, RD03Z]	£142.76	NHS Reference Costs 2017/18
Surgical procedures		
Pulmonary endarterectomy	£23,579.00	NG89 Economic analysis
Balloon pulmonary angioplasty	£5,969.00	NHS England tariff
Drugs (annual cost)		
Riociguat	£26,003.60[(a)]	BNF 2019
Hospital attendances (routine and unplanned)		
Outpatient visit - Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up, Respiratory Medicine [WF01A - 340]	£145.88	NHS Reference Costs 2017/18
Day ward assessment - weighted average of heart failure or shock, day case [EB03A to EB03E]	£401.62	NHS Reference Costs 2017/18
Hospital admission - weighted average of heart failure or shock, elective inpatient, non-elective long stay, and non-elective short stay [EB03A to EB03E]	£1,867.80	NHS Reference Costs 2017/18

(a) Calculated as 3 Riociguat tablets per day for a year, based on the BNF price of £23.75 per tablet

PTS

It was assumed that patients who were experiencing symptoms of PTS would require an initial vascular surgery appointment for diagnosis. The committee provided estimates of ongoing resource use for management of PTS. Patients with severe ulcerating PTS were assumed to attend 2 vascular surgery appointments and 2 nurse visits per week for compression bandaging. For those with no ulceration, 4 nurse visits and 1 GP appointment per year was assumed.

Table 41: Unit costs of resources related to PTS

Resource	Cost	Source
Diagnosis		
First attendance - consultant-led - non-admitted face-to-face [WF01B] and non-admitted multidisciplinary [WF02B]	£178.91	NHS Reference Costs 2017/18
Routine costs		
Band 5 nurse - 10 mins	£14.83	PSSRU 2018
Consultant review visit - consultant-led - non-admitted face-to-face [WF01A] and non-admitted multidisciplinary [WF02A]	£138.54	NHS Reference Costs 2017/18
GP visit	£37.00	PSSRU 2018

Cancer

For the cancer subgroup analysis, the model takes into account costs of hospital care associated with cancer. The costs for colorectal, lung and prostate cancers were informed by Hall 2015. This study analysed patient-level data from individuals within 6 months of cancer diagnosis in an NHS Trust. Hospital costs associated with lung cancer were informed by the economic analysis for the NICE Guideline NG122 on lung cancer. A weighted average cost across all 4 cancers was calculated based on the proportions of colorectal, lung, prostate and breast cancer patients who experienced a VTE in an analysis of registry data from California (Chew 2006).

Table 42: Hospital care costs for people with cancer

	Cost per cycle	Source	Proportion[(a)]
Lung Cancer	£2,543.47	NG122	35.13%
Breast Cancer	£2,519.00	Hall 2015	19.27%
Colorectal Cancer	£2,528.60	Hall 2015	25.94%
Prostate cancer	£744.40	Hall 2015	19.66%
Average cancer cost	£2,181.23	Calculated	

(a) Chew 2006

Sensitivity analyses

In order to explore uncertainty on model results, we conducted both deterministic and probabilistic sensitivity analyses. The impact of changes in parameter estimates individually

on the model results was explored by performing one-way sensitivity analyses. The mean of the input parameter of interest was replaced by the lower and upper bound of the 95% confidence interval, when available, otherwise it was altered by a plausible range. The impact of these changes on the expected incremental net benefits for relevant pairwise comparisons is reported using tornado diagrams.

Additional sensitivity analyses were undertaken to explore the following assumptions and parameters (results are reported in appendix B):

- Varying the duration of treatment in people with unprovoked VTE (3, 6, 12 months)
- Using relative effects for the initial treatment phase based on separate NMAs for DVT and PE
- Using calibrated and uncalibrated baseline estimates for VTE recurrence and survival
- Lower discontinuation rate at 6 and 12 months
- Higher spontaneous discontinuation rate for DOACs compared to VKA
- Alternative sources of baseline bleeding rates
- Setting the effectiveness for edoxaban in the extended therapy phase to the average of the other DOACs

For probabilistic sensitivity analysis, we assigned probability distributions to model input parameters reflecting uncertainty surrounding point estimates, defined by standard error/confidence intervals and type of parameter. The particular distribution assigned to each type of model parameter reflects the nature of the data. Probabilities are parameterised using a beta distribution, to reflect the fact that these values must lie between 0 and 1. Costs are given a gamma distribution, as these values are bound at 0 but theoretically have no upper limit. Mean differences are assigned a normal distribution, as these values are not bound at either end of the number continuum. Relative risks, odds ratios, and rate ratios are assigned a lognormal distribution, in order to reflect the fact that these parameters are asymmetrically distributed (i.e. values between 0 and 1 favour one comparator, whereas values between 1 and infinity favour the other). Utilities, as with probabilities, are assigned a beta distribution. To account for uncertainty in the estimates of relative treatment effects from the NMAs, CODA outputs containing 10,000 iterations for each outcome were generated in WinBUGS.

Monte Carlo simulation was used to randomly sample 1,000 times from the CODAs and distributions for all parameters and costs and QALYs recorded each time. This process allowed uncertainty around model results to be characterised in terms of the proportion of iterations in which each comparator is cost effective at a particular threshold.

Results

Results are reported for the following:

- **Base-case analysis** – people remain on the same treatment for the initial and extended phases
- **Sequencing analysis** – considers treatment switching between the initial and extended phases
- **Cancer subgroup analysis**

For each analysis, results are reported separately for treatment of DVT and treatment of PE. For each treatment strategy, we report the number of VTE recurrences and bleeding events, a breakdown of costs by category, total costs, total QALYs and expected net monetary benefit at a threshold value for £20,000/QALY. For these results, strategies are ordered from most QALYs to least QALYs.

We also report incremental cost-effectiveness results by ordering strategies from least costly to most costly and calculating incremental cost-effectiveness ratios (ICERs) for non-dominated strategies. Probabilistic results are presented graphically as cost-effectiveness acceptability curves (CEACs), which show the probability of each strategy being cost effective over a range of threshold values. For ease of interpretation, when comparing a large number of strategies, such as in the sequencing analysis, all strategies are included in the calculation of probabilities but only those strategies that have a >3% probability of being cost effective are shown in the figures.

The results of additional sensitivity analyses using alternate assumptions or data sources for specific parameters can be found in appendix B.

Base-case analysis

Base-case analysis (no switching) – DVT

Table 43 shows key outcomes and costs for each strategy in the base-case analysis for DVT assuming no treatment switching. Overall, DOACs have higher treatment costs but lower monitoring costs and lower rates of bleeding than VKA strategies. Edoxaban results in the lowest number of VTE recurrences (by a small margin) but it should be noted that edoxaban is the only DOAC that did not have a separate extended therapy trial so this result is based on the assumption that the relative effects from the initial treatment phase would continue in the extended therapy phase. Apixaban is associated with lower rates of both major bleeds and CRNMB.

Deterministic incremental cost-effectiveness results for this scenario are shown in Table 44. Apixaban is the strategy that produces the most QALYs and an ICER of £1,802/QALY compared to LMWH/VKA. All other strategies are dominated.

Figure 5 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban and rivaroxaban). The relative effects of the drugs on the outcome major bleeding have the most influence on the incremental net monetary benefit. However, over the range of

values tested, apixaban always remains the optimal strategy. Figure 6 shows the uncertainty surrounding the model results over a range of cost-effectiveness thresholds from £0 to £50,000 per QALY. The bold line indicates the strategy that generates the highest net monetary benefit at a given threshold. Apixaban is cost effective at a threshold of £20,000/QALY with a probability of 97.5%.

Table 45 summarises an additional analysis showing the probability that each of the 7 treatments is more cost effective in pairwise comparisons with each of the other treatments based on net monetary benefit. This shows that apixaban has a high probability of being more cost effective in pairwise comparisons with each of the other treatments. Rivaroxaban also has a high probability of being more cost effective in most comparisons, with the exception of the pairwise comparison with apixaban. Unfractionated heparin/VKA has a low probability of being cost effective compared with all other treatments.

Table 43: Key outcomes and costs for the base-case analysis (no treatment switching) – DVT

	Events[a]			Costs							
Strategy	**Recurrent VTE**	**Major bleeds**	**CRNMB**	**Treatment**	**Monitoring**	**Recurrent VTE**	**Major bleeding**	**CRNMB**	**Total QALYs[b]**	**Total costs[b]**	**NMB £20K/QALY**
Apixaban	29.25	1.35	11.36	£605	£211	£280	£90	£24	7.550	£1,527	£149,467
Rivaroxaban	29.46	2.19	19.21	£601	£211	£281	£159	£39	7.531	£1,601	£149,010
Dabigatran	30.27	2.68	13.58	£580	£212	£287	£214	£29	7.518	£1,632	£148,718
Edoxaban[c]	28.70	2.94	16.89	£591	£210	£276	£221	£35	7.516	£1,631	£148,691
LMWH/VKA	29.56	3.36	20.05	£228	£334	£282	£251	£41	7.504	£1,445	£148,641
Fondaparinux/VKA	29.44	3.65	17.27	£289	£333	£282	£275	£36	7.498	£1,519	£148,445
UFH/VKA	31.08	4.15	20.31	£291	£336	£294	£314	£42	7.482	£1,585	£148,061

(a) Per 100 people in the model
(b) Discounted values
(c) No extended therapy trial

Table 44: Deterministic incremental cost-effectiveness results for the base-case analysis (no treatment switching) - DVT

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
LMWH/VKA	£1,445	7.504			
Fondaparinux/VKA	£1,519	7.498	£74	-0.006	dominated
Apixaban	£1,527	7.550	£82	0.045	£1,802
UFH/VKA	£1,585	7.482	£59	-0.067	dominated
Rivaroxaban	£1,601	7.531	£74	-0.019	dominated
Edoxaban[a]	£1,631	7.516	£104	-0.034	dominated
Dabigatran	£1,632	7.518	£106	-0.032	dominated

(a) No extended therapy trial

Figure 5: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban vs. rivaroxaban based on incremental net monetary benefit at a threshold of £20,000/QALY – DVT

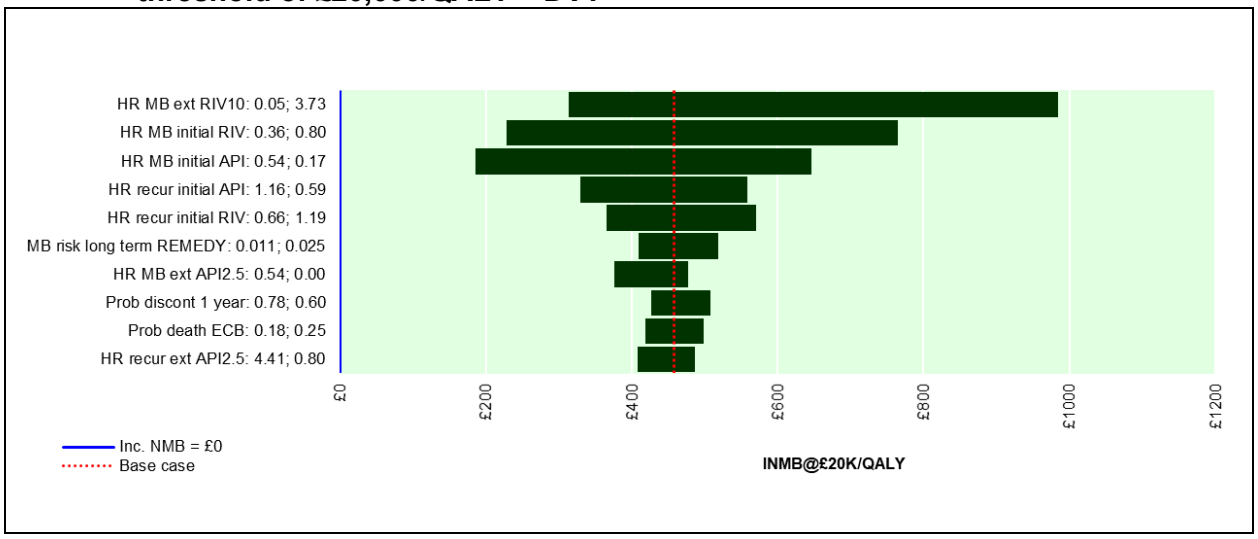
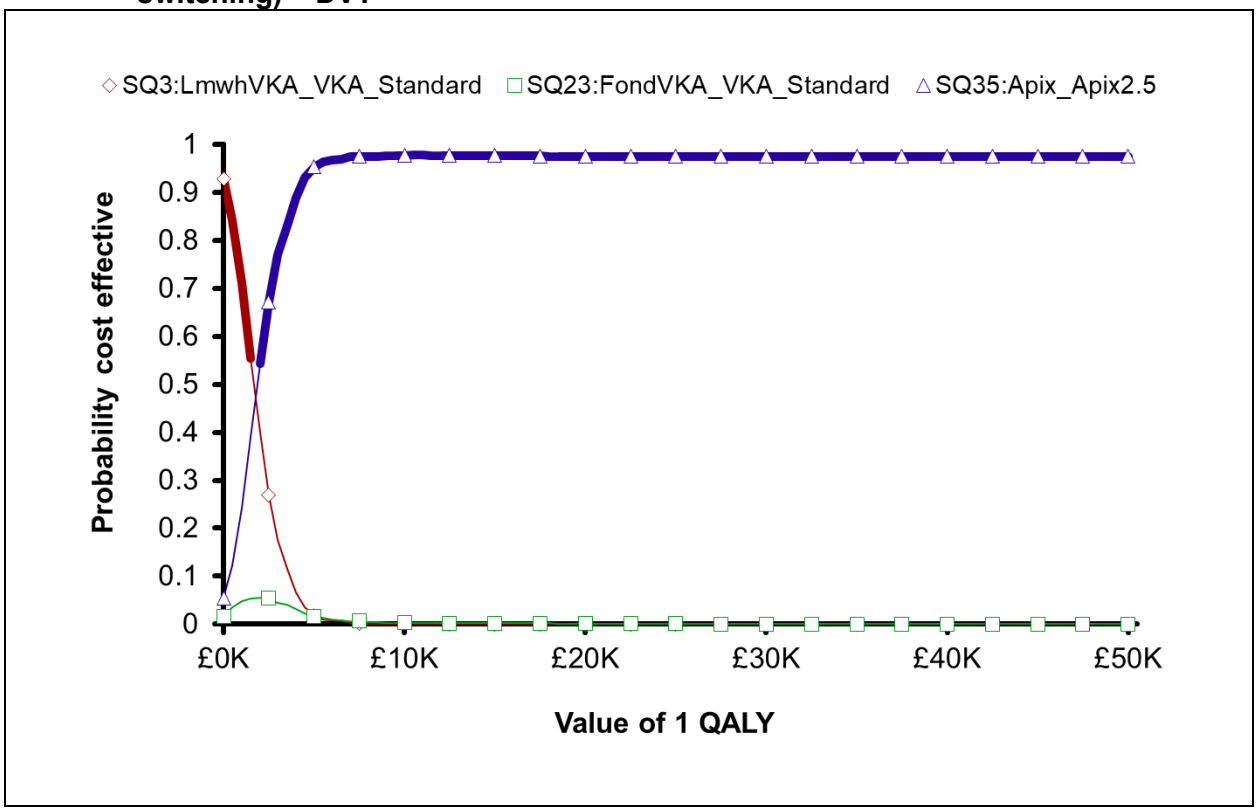


Figure 6: Cost-effectiveness acceptability curve for the base-case analysis (no treatment switching) – DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Table 45: Pairwise comparison of probability more cost effective for the base-case analysis – DVT

	LMWH/VKA	UNF/VKA	FOND/VKA	APIXABAN	DABIGATRAN	EDOXABAN	RIVAROXABAN
LMWH/VKA		0.01	0.30	1.00	0.64	0.55	0.94
UNF/VKA	0.99		0.88	1.00	0.96	0.90	0.98
FOND/VKA	0.71	0.12		1.00	0.75	0.69	0.93
APIXABAN	0.00	0.00	0.00		0.00	0.00	0.02
DABIGATRAN	0.36	0.04	0.25	1.00		0.42	0.83
EDOXABAN	0.45	0.10	0.31	1.00	0.58		0.87
RIVAROXABAN	0.06	0.02	0.07	0.98	0.17	0.13	

Note: Each cell shows the probability that the treatment in the column is more cost effective than the treatment in the row based on net monetary benefit. Columns with values closer to 1 (more green) indicate the treatment in that column is likely to be more cost effective than other treatments whereas columns with values closer to 0 (more red) indicate that the treatment in that column is likely to be less cost effective than the other treatments.

Base -case analysis (no switching) PE

Table 46 shows the key outcomes and costs in the base-case analysis for PE. The results for PE are consistent with those for DVT. Apixaban is the most cost-effective strategy with an ICER of £1,660/QALY compared to LMWH/VKA (Table 47).

One-way and probabilistic sensitivity analyses for PE show similar results to DVT. Apixaban remains the optimal strategy over the range of parameter values tested in all one-way sensitivity analyses (Figure 7) and has 97% probability of being cost effective at a threshold of £20,000/QALY (Figure 8).

Table 48 summarises the probability that each of the 7 treatments is more cost effective in pairwise comparisons with each of the other treatments based on net monetary benefit. Similar to the DVT results, this shows that apixaban has a high probability of being more cost effective in pairwise comparisons with each of the other treatments. Rivaroxaban also has a high probability of being more cost effective in most comparisons, with the exception of the pairwise comparison with apixaban. Unfractionated heparin/VKA has a low probability of being cost effective compared with all other treatments.

Table 46: Key outcomes and costs for the base-case analysis (no treatment switching) – PE

	Events[a]			Costs							
Strategy	**Recurrent VTE**	**Major bleeds**	**CRNMB**	**Treatment**	**Monitoring**	**Recurrent VTE**	**Major bleeding**	**CRNMB**	**Total QALYs[b]**	**Total costs[b]**	**NMB at £20K/QALY**
Apixaban	21.22	1.18	10.14	£557	£188	£264	£82	£21	7.447	£3,044	£145,893
Rivaroxaban	21.45	2.00	17.83	£553	£188	£266	£150	£36	7.427	£3,116	£145,434
Edoxaban[c]	20.82	2.74	15.56	£544	£187	£260	£211	£32	7.414	£3,143	£145,146
Dabigatran	22.35	2.48	12.32	£533	£190	£275	£204	£25	7.412	£3,149	£145,094
LMWH/VKA	21.71	3.15	18.66	£194	£309	£269	£240	£38	7.401	£2,968	£145,044
Fondaparinux/VKA	21.58	3.43	15.93	£254	£309	£268	£263	£32	7.395	£3,039	£144,859
UFH/VKA	23.25	3.93	18.91	£257	£311	£284	£302	£38	7.375	£3,107	£144,396

(a) Per 100 people in the model
(b) Discounted values
(c) No extended therapy trial

Table 47: Deterministic incremental cost-effectiveness results for the base-case analysis (no treatment switching) - PE

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
LMWH/VKA	£2,968	7.401			
Fondaparinux/VKA	£3,039	7.395	£72	-0.006	dominated
Apixaban	£3,044	7.447	£77	0.046	£1,660
UFH/VKA	£3,107	7.375	£63	-0.072	dominated
Rivaroxaban	£3,116	7.427	£71	-0.019	dominated
Edoxaban[a]	£3,143	7.414	£98	-0.032	dominated
Dabigatran	£3,149	7.412	£104	-0.035	dominated

(a) No extended therapy trial

Figure 7: One-way sensitivity analysis (top 10 most influential parameters) for apixaban vs. rivaroxaban based on incremental net monetary benefit at a threshold of £20,000/QALY - PE

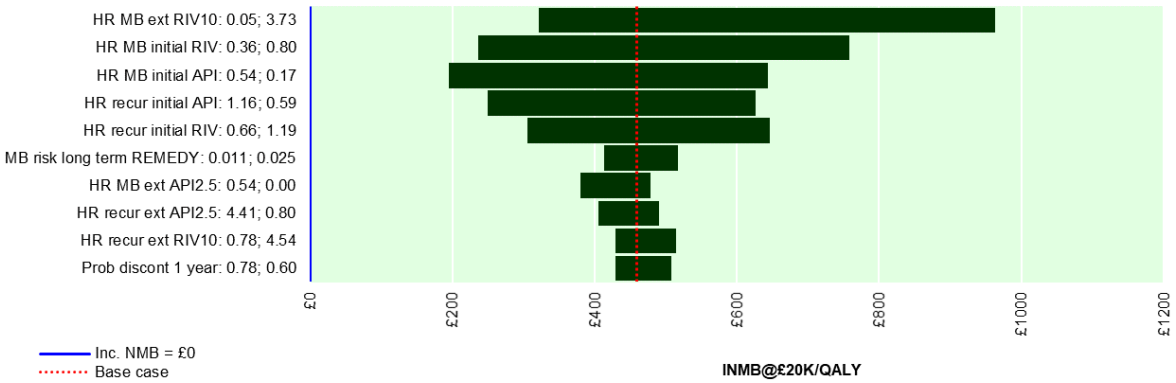
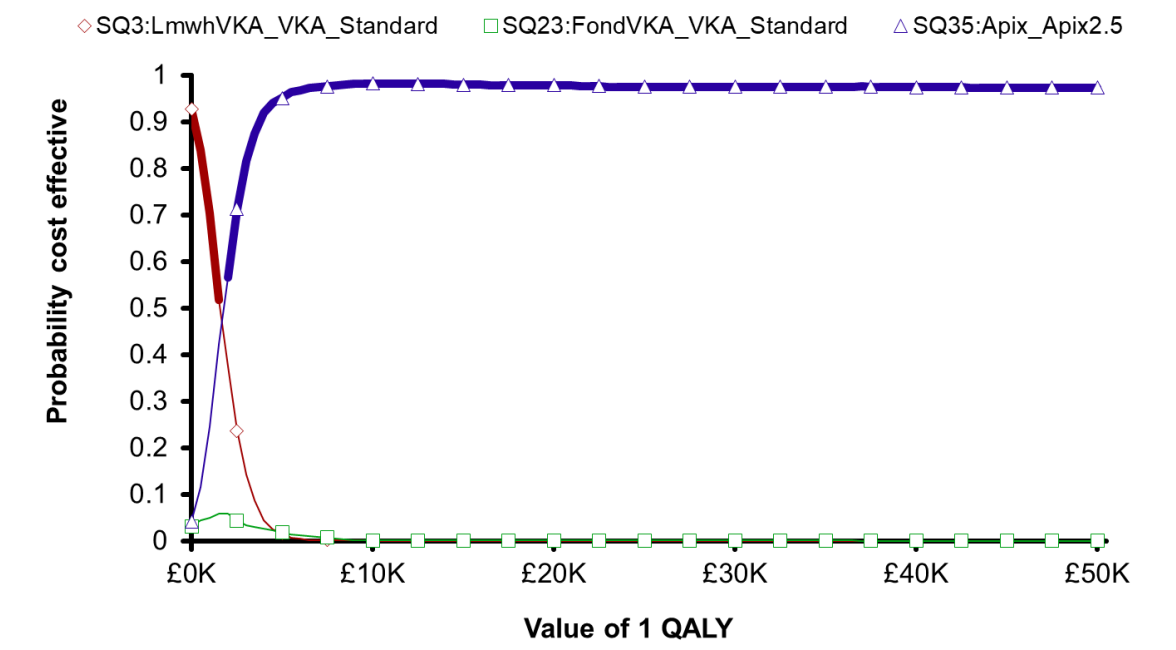


Figure 8: Cost-effectiveness acceptability curve for the base-case analysis (no treatment switching) - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Table 48: Pairwise comparison of probability more cost effective for the base-case analysis – PE

	LMWH/VKA	UNF/VKA	FOND/VKA	APIXABAN	DABIGATRAN	EDOXABAN	RIVAROXABAN
LMWH/VKA		0.00	0.27	1.00	0.62	0.58	0.93
UNF/VKA	1.00		0.93	1.00	0.97	0.92	0.99
FOND/VKA	0.73	0.08		1.00	0.72	0.69	0.93
APIXABAN	0.00	0.00	0.00		0.00	0.00	0.02
DABIGATRAN	0.38	0.03	0.28	1.00		0.45	0.85
EDOXABAN	0.42	0.08	0.31	1.00	0.55		0.84
RIVAROXABAN	0.07	0.01	0.07	0.98	0.15	0.16	

Note: Each cell shows the probability that the intervention in the column is more cost effective than the intervention in the row based on net monetary benefit. Columns with values closer to 1 (more green) indicate the intervention in that column is likely to be more cost effective than other interventions whereas columns with values closer to 0 (more red) indicate that the intervention in that column is likely to be less cost effective than the other interventions.

Sequencing analysis

Sequencing analysis (all strategies) - DVT

Table 49 shows key outcomes and costs for all 70 strategies assuming treatment switching from any initial treatment to any extended therapy is possible following a DVT index event. The sequence of apixaban as initial treatment followed by apixaban (5 mg twice daily) in the extended therapy phase generates the most QALYs. The QALY differences between strategies that begin with the same initial treatment are generally very small. The sequences of apixaban as initial treatment followed by no treatment, aspirin and VKA standard in the extended therapy phase all generate similar QALYs and the strategies apixaban followed by apixaban (5 mg twice daily) and apixaban followed by apixaban (2.5 mg twice daily) generate virtually identical costs as well as QALYs. The ICER for the sequence apixaban followed by apixaban (5 mg twice daily) versus apixaban followed by VKA standard is £26,161/QALY (Table 50).

Figure 9 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban followed by VKA standard versus apixaban followed by no treatment). There is uncertainty in relation to a number of baseline parameters in the model, in particular the risk of long-term major bleeding, which could affect the relative ranking of the 2 strategies.

Table 49: Key outcomes and costs for the sequencing analysis (all strategies) - DVT

Strategy	Events[a]			Costs					Total QALYs[b]	Total costs[b]	NMB at £20K/QALY	Rank (NMB)
	Recurrent VTE	Major bleeds	CRNMB	Treatment	Monitoring	Recurrent VTE	Major bleeding	CRNMB				
SQ36:Apix_Apix5	29.28	1.33	11.63	£605	£211	£280	£88	£25	7.550	£1,526	£149,476	4
SQ35:Apix_Apix2.5	29.25	1.35	11.36	£605	£211	£280	£90	£24	7.550	£1,527	£149,467	5
SQ37:Apix_Dabig	29.04	1.52	11.97	£582	£210	£278	£106	£25	7.547	£1,517	£149,413	7
SQ38:Apix_Edox	28.90	1.63	12.56	£587	£210	£277	£113	£27	7.545	£1,527	£149,368	8
SQ39:Apix_Riv10	29.22	1.62	12.15	£593	£211	£279	£113	£26	7.544	£1,535	£149,343	9
SQ33:Apix_VKA_Standard	28.93	1.68	13.01	£398	£210	£277	£118	£27	7.543	£1,351	£149,517	1
SQ34:Apix_ASA	30.63	1.45	12.31	£400	£210	£290	£96	£26	7.543	£1,358	£149,506	3
SQ31:Apix_NoTreat	31.53	1.35	11.07	£400	£190	£296	£88	£24	7.543	£1,341	£149,510	2
SQ40:Apix_Riv20	29.31	1.72	12.72	£592	£211	£280	£121	£27	7.541	£1,544	£149,284	10
SQ32:Apix_VKA_low	29.64	1.68	13.08	£397	£211	£282	£116	£28	7.541	£1,361	£149,467	6
SQ66:Riv_Apix5	29.52	1.90	18.70	£613	£211	£282	£135	£38	7.537	£1,592	£149,141	14
SQ65:Riv_Apix2.5	29.50	1.92	18.44	£613	£211	£282	£137	£38	7.536	£1,593	£149,133	15
SQ67:Riv_Dabig	29.29	2.09	19.04	£590	£211	£280	£153	£39	7.533	£1,583	£149,080	17
SQ68:Riv_Edox	29.14	2.20	19.61	£596	£210	£279	£160	£40	7.531	£1,592	£149,035	18
SQ69:Riv_Riv10	29.46	2.19	19.21	£601	£211	£281	£159	£39	7.531	£1,601	£149,010	19
SQ63:Riv_VKA_Standard	29.18	2.25	20.06	£409	£210	£279	£164	£41	7.530	£1,420	£149,181	11
SQ64:Riv_ASA	30.85	2.02	19.37	£412	£211	£292	£143	£40	7.530	£1,427	£149,170	13
SQ61:Riv_NoTreat	31.73	1.93	18.15	£411	£190	£298	£134	£37	7.529	£1,410	£149,175	12
SQ70:Riv_Riv20	29.55	2.29	19.77	£600	£211	£282	£167	£40	7.528	£1,610	£148,952	20
SQ62:Riv_VKA_low	29.87	2.25	20.12	£409	£211	£284	£163	£41	7.528	£1,429	£149,132	16
SQ56:Edox_Apix5	29.08	2.64	15.98	£608	£210	£279	£196	£33	7.521	£1,630	£148,797	27
SQ55:Edox_Apix2.5	29.06	2.66	15.72	£608	£210	£279	£198	£33	7.521	£1,631	£148,789	28
SQ46:Dabig_Apix5	30.49	2.48	13.25	£602	£213	£289	£196	£28	7.521	£1,641	£148,778	30
SQ45:Dabig_Apix2.5	30.47	2.50	12.99	£602	£213	£289	£198	£27	7.521	£1,642	£148,770	31
SQ57:Edox_Dabig	28.85	2.84	16.32	£586	£210	£277	£214	£34	7.518	£1,621	£148,736	33
SQ47:Dabig_Dabig	30.27	2.68	13.58	£580	£212	£287	£214	£29	7.518	£1,632	£148,718	34
SQ58:Edox_Edox	28.70	2.94	16.89	£591	£210	£276	£221	£35	7.516	£1,631	£148,691	35

Strategy	Events[a]			Costs					Total QALYs[b]	Total costs[b]	NMB at £20K/QALY	Rank (NMB)
	Recurrent VTE	Major bleeds	CRNMB	Treatment	Monitoring	Recurrent VTE	Major bleeding	CRNMB				
SQ48:Dabig_Edox	30.13	2.78	14.15	£585	£212	£286	£221	£30	7.516	£1,641	£148,674	36
SQ59:Edox_Riv10	29.02	2.93	16.49	£596	£210	£278	£220	£34	7.515	£1,639	£148,666	37
SQ49:Dabig_Riv10	30.44	2.77	13.75	£590	£213	£289	£220	£29	7.515	£1,650	£148,649	38
SQ53:Edox_VKA_Standard	28.74	2.99	17.34	£404	£210	£276	£225	£36	7.515	£1,458	£148,838	21
SQ54:Edox_ASA	30.41	2.76	16.65	£407	£210	£289	£204	£34	7.515	£1,465	£148,827	23
SQ43:Dabig_VKA_Standard	30.16	2.83	14.59	£401	£212	£287	£225	£31	7.514	£1,471	£148,818	24
SQ44:Dabig_ASA	31.81	2.60	13.91	£403	£212	£299	£204	£29	7.514	£1,477	£148,808	26
SQ51:Edox_NoTreat	31.29	2.67	15.43	£406	£189	£295	£196	£32	7.514	£1,448	£148,831	22
SQ41:Dabig_NoTreat	32.68	2.51	12.70	£403	£192	£305	£196	£27	7.514	£1,461	£148,812	25
SQ60:Edox_Riv20	29.11	3.03	17.05	£595	£210	£279	£228	£35	7.513	£1,648	£148,608	42
SQ52:Edox_VKA_low	29.43	2.99	17.40	£404	£211	£281	£224	£36	7.513	£1,467	£148,788	29
SQ50:Dabig_Riv20	30.53	2.87	14.31	£589	£213	£289	£228	£30	7.513	£1,659	£148,592	46
SQ42:Dabig_VKA_low	30.84	2.82	14.65	£400	£213	£292	£224	£31	7.512	£1,480	£148,770	32
SQ6:LmwhVKA_Apix5	29.89	3.02	18.72	£428	£334	£285	£223	£38	7.511	£1,614	£148,601	43
SQ5:LmwhVKA_Apix2.5	29.87	3.03	18.46	£429	£334	£285	£224	£38	7.510	£1,615	£148,593	44
SQ7:LmwhVKA_Dabig	29.66	3.21	19.05	£406	£334	£283	£240	£39	7.507	£1,606	£148,541	47
SQ8:LmwhVKA_Edox	29.52	3.31	19.61	£411	£334	£282	£247	£40	7.506	£1,615	£148,497	48
SQ9:LmwhVKA_Riv10	29.83	3.30	19.21	£416	£334	£284	£246	£39	7.505	£1,623	£148,472	49
SQ26:FondVKA_Apix5	29.77	3.30	15.94	£490	£334	£284	£246	£33	7.505	£1,689	£148,404	54
SQ25:FondVKA_Apix2.5	29.75	3.32	15.68	£490	£334	£284	£248	£33	7.504	£1,690	£148,397	55
SQ3:LmwhVKA_VKA_Stand	29.56	3.36	20.05	£228	£334	£282	£251	£41	7.504	£1,445	£148,641	39
SQ4:LmwhVKA_ASA	31.19	3.14	19.37	£230	£334	£295	£230	£40	7.504	£1,451	£148,631	41
SQ1:LmwhVKA_NoTreat	32.06	3.04	18.17	£230	£314	£301	£222	£37	7.504	£1,435	£148,635	40
SQ10:LmwhVKA_Riv20	29.92	3.40	19.77	£416	£334	£285	£254	£40	7.502	£1,632	£148,416	53
SQ2:LmwhVKA_VKA_low	30.23	3.35	20.11	£227	£335	£287	£250	£41	7.502	£1,454	£148,593	45
SQ27:FondVKA_Dabig	29.55	3.49	16.27	£468	£334	£282	£264	£34	7.501	£1,680	£148,344	57
SQ28:FondVKA_Edox	29.40	3.59	16.83	£473	£333	£281	£271	£35	7.499	£1,690	£148,300	58
SQ29:FondVKA_Riv10	29.71	3.59	16.43	£478	£334	£284	£270	£34	7.499	£1,698	£148,275	59

Strategy	Events[a]			Costs					Total QALYs[b]	Total costs[b]	NMB at £20K/QALY	Rank (NMB)
	Recurrent VTE	Major bleeds	CRNMB	Treatment	Monitoring	Recurrent VTE	Major bleeding	CRNMB				
SQ23:FondVKA_VKA_Stand	29.44	3.65	17.27	£289	£333	£282	£275	£36	7.498	£1,519	£148,445	50
SQ24:FondVKA_ASA	31.08	3.42	16.59	£291	£334	£294	£254	£34	7.498	£1,526	£148,434	52
SQ21:FondVKA_NoTreat	31.95	3.33	15.39	£291	£313	£300	£246	£32	7.497	£1,510	£148,438	51
SQ30:FondVKA_Riv20	29.80	3.69	16.99	£477	£334	£284	£278	£35	7.496	£1,707	£148,219	60
SQ22:FondVKA_VKA_low	30.12	3.64	17.33	£288	£335	£287	£273	£36	7.496	£1,528	£148,396	56
SQ16:UnfVKA_Apix5	31.40	3.82	19.02	£486	£337	£296	£286	£39	7.489	£1,750	£148,022	64
SQ15:UnfVKA_Apix2.5	31.38	3.83	18.77	£487	£337	£296	£288	£38	7.488	£1,751	£148,015	65
SQ17:UnfVKA_Dabig	31.19	4.00	19.34	£465	£336	£295	£303	£40	7.485	£1,742	£147,964	67
SQ18:UnfVKA_Edox	31.05	4.10	19.88	£470	£336	£294	£310	£41	7.484	£1,751	£147,921	68
SQ19:UnfVKA_Riv10	31.34	4.09	19.50	£475	£337	£296	£309	£40	7.483	£1,759	£147,897	69
SQ13:UnfVKA_VKA_Stand	31.08	4.15	20.31	£291	£336	£294	£314	£42	7.482	£1,585	£148,061	61
SQ14:UnfVKA_ASA	32.67	3.93	19.65	£294	£336	£306	£293	£40	7.482	£1,592	£148,051	63
SQ11:UnfVKA_NoTreat	33.51	3.84	18.49	£293	£317	£312	£286	£38	7.482	£1,576	£148,055	62
SQ20:UnfVKA_Riv20	31.43	4.19	20.04	£474	£337	£297	£317	£41	7.480	£1,767	£147,842	70
SQ12:UnfVKA_VKA_low	31.74	4.14	20.37	£291	£337	£299	£313	£42	7.480	£1,594	£148,014	66

(a) Per 100 people in the model
(b) Discounted values
(c) No extended therapy trial

Table 50: Deterministic incremental cost-effectiveness results for the sequencing analysis (all strategies) – DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ31:Apix_NoTreat	£1,341	7.543			
SQ33:Apix_VKA_Standard	£1,351	7.543	£10	0.001	£12,052
SQ34:Apix_ASA	£1,358	7.543	£7	0.000	dominated
SQ32:Apix_VKA_low	£1,361	7.541	£10	-0.002	dominated
SQ61:Riv_NoTreat	£1,410	7.529	£59	-0.014	dominated
SQ63:Riv_VKA_Standard	£1,420	7.530	£69	-0.013	dominated
SQ64:Riv_ASA	£1,427	7.530	£75	-0.014	dominated
SQ62:Riv_VKA_low	£1,429	7.528	£78	-0.015	dominated
SQ1:LmwhVKA_NoTreat	£1,435	7.504	£84	-0.040	dominated
SQ3:LmwhVKA_VKA_Standard	£1,445	7.504	£94	-0.039	dominated
SQ51:Edox_NoTreat	£1,448	7.514	£97	-0.029	dominated
SQ4:LmwhVKA_ASA	£1,451	7.504	£100	-0.039	dominated
SQ2:LmwhVKA_VKA_low	£1,454	7.502	£103	-0.041	dominated
SQ53:Edox_VKA_Standard	£1,458	7.515	£107	-0.029	dominated
SQ41:Dabig_NoTreat	£1,461	7.514	£110	-0.030	dominated
SQ54:Edox_ASA	£1,465	7.515	£113	-0.029	dominated
SQ52:Edox_VKA_low	£1,467	7.513	£116	-0.031	dominated
SQ43:Dabig_VKA_Standard	£1,471	7.514	£120	-0.029	dominated
SQ44:Dabig_ASA	£1,477	7.514	£126	-0.029	dominated
SQ42:Dabig_VKA_low	£1,480	7.512	£129	-0.031	dominated
SQ21:FondVKA_NoTreat	£1,510	7.497	£158	-0.046	dominated
SQ37:Apix_Dabig	£1,517	7.547	£166	0.003	ext. dom.
SQ23:FondVKA_VKA_Standard	£1,519	7.498	£168	-0.045	dominated
SQ24:FondVKA_ASA	£1,526	7.498	£175	-0.045	dominated
SQ36:Apix_Apix5	£1,526	7.550	£175	0.007	£26,161
SQ38:Apix_Edox	£1,527	7.545	£1	-0.005	dominated
SQ35:Apix_Apix2.5	£1,527	7.550	£1	0.000	dominated
SQ22:FondVKA_VKA_low	£1,528	7.496	£2	-0.054	dominated
SQ39:Apix_Riv10	£1,535	7.544	£9	-0.006	dominated
SQ40:Apix_Riv20	£1,544	7.541	£18	-0.009	dominated
SQ11:UnfVKA_NoTreat	£1,576	7.482	£50	-0.069	dominated
SQ67:Riv_Dabig	£1,583	7.533	£57	-0.017	dominated
SQ13:UnfVKA_VKA_Standard	£1,585	7.482	£60	-0.068	dominated
SQ66:Riv_Apix5	£1,592	7.537	£66	-0.013	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ14:UnfVKA_ASA	£1,592	7.482	£66	-0.068	dominated
SQ68:Riv_Edox	£1,592	7.531	£66	-0.019	dominated
SQ65:Riv_Apix2.5	£1,593	7.536	£67	-0.014	dominated
SQ12:UnfVKA_VKA_low	£1,594	7.480	£68	-0.070	dominated
SQ69:Riv_Riv10	£1,601	7.531	£75	-0.020	dominated
SQ7:LmwhVKA_Dabig	£1,606	7.507	£80	-0.043	dominated
SQ70:Riv_Riv20	£1,610	7.528	£84	-0.022	dominated
SQ6:LmwhVKA_Apix5	£1,614	7.511	£88	-0.039	dominated
SQ8:LmwhVKA_Edox	£1,615	7.506	£89	-0.044	dominated
SQ5:LmwhVKA_Apix2.5	£1,615	7.510	£89	-0.040	dominated
SQ57:Edox_Dabig	£1,621	7.518	£95	-0.032	dominated
SQ9:LmwhVKA_Riv10	£1,623	7.505	£97	-0.045	dominated
SQ56:Edox_Apix5	£1,630	7.521	£104	-0.029	dominated
SQ58:Edox_Edox	£1,631	7.516	£105	-0.034	dominated
SQ55:Edox_Apix2.5	£1,631	7.521	£105	-0.029	dominated
SQ10:LmwhVKA_Riv20	£1,632	7.502	£106	-0.048	dominated
SQ47:Dabig_Dabig	£1,632	7.518	£106	-0.033	dominated
SQ59:Edox_Riv10	£1,639	7.515	£113	-0.035	dominated
SQ46:Dabig_Apix5	£1,641	7.521	£115	-0.029	dominated
SQ48:Dabig_Edox	£1,641	7.516	£115	-0.034	dominated
SQ45:Dabig_Apix2.5	£1,642	7.521	£116	-0.029	dominated
SQ60:Edox_Riv20	£1,648	7.513	£122	-0.037	dominated
SQ49:Dabig_Riv10	£1,650	7.515	£124	-0.035	dominated
SQ50:Dabig_Riv20	£1,659	7.513	£133	-0.038	dominated
SQ27:FondVKA_Dabig	£1,680	7.501	£154	-0.049	dominated
SQ26:FondVKA_Apix5	£1,689	7.505	£163	-0.045	dominated
SQ28:FondVKA_Edox	£1,690	7.499	£164	-0.051	dominated
SQ25:FondVKA_Apix2.5	£1,690	7.504	£164	-0.046	dominated
SQ29:FondVKA_Riv10	£1,698	7.499	£172	-0.051	dominated
SQ30:FondVKA_Riv20	£1,707	7.496	£181	-0.054	dominated
SQ17:UnfVKA_Dabig	£1,742	7.485	£216	-0.065	dominated
SQ16:UnfVKA_Apix5	£1,750	7.489	£224	-0.061	dominated
SQ18:UnfVKA_Edox	£1,751	7.484	£225	-0.066	dominated
SQ15:UnfVKA_Apix2.5	£1,751	7.488	£225	-0.062	dominated
SQ19:UnfVKA_Riv10	£1,759	7.483	£233	-0.067	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ20:UnfVKA_Riv20	£1,767	7.480	£241	-0.070	dominated

(a) No extended therapy trial

Figure 9: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban followed by VKA standard vs. apixaban followed by no treatment based on incremental net monetary benefit at a threshold of £20,000/QALY – DVT

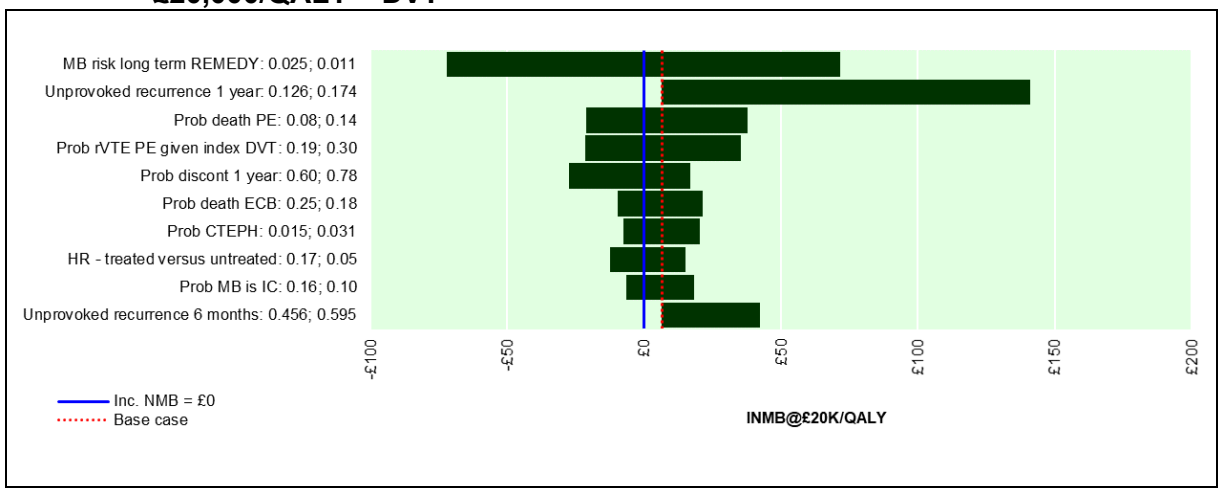
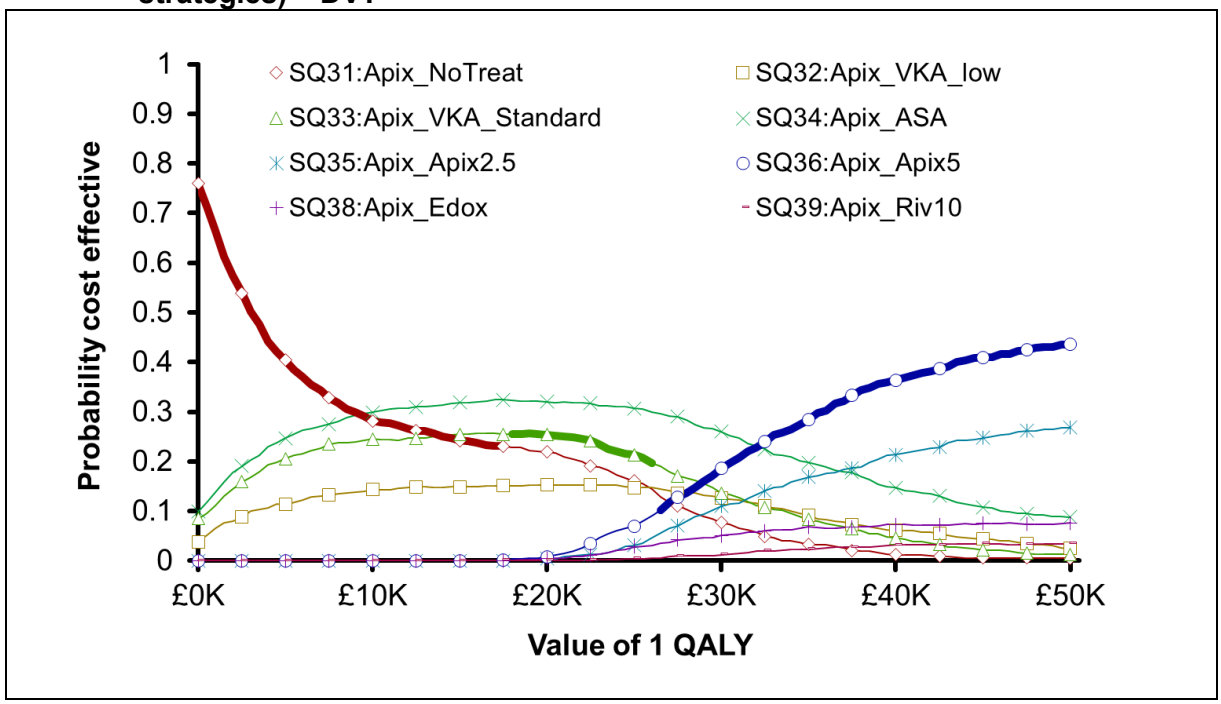


Figure 10: Cost-effectiveness acceptability curve for the sequencing analysis (all strategies) – DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

At a threshold value of £20,000/QALY, the strategy with the highest probability of being cost effective is the sequence apixaban followed by aspirin (32%) but the strategy with the highest net monetary benefit is the sequence apixaban followed by VKA standard, which has a 25% probability of being the most cost effective strategy (Figure 10). Compared to the base-case analysis, there is more uncertainty in the results. No strategy achieves >50% probability of being cost effective over the range of threshold values shown.

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) – DVT

Prior to running the model, the committee noted that a person would not normally switch from a DOAC as initial treatment to a VKA as extended therapy unless there were specific clinical concerns, for example with tolerability of a DOAC. This is because switching to a VKA would require the introduction of INR monitoring visits that patients may find unacceptable and so it was felt that this sequence was unlikely to be a clinically relevant option for the majority of patients.

Table 51 presents the non-dominated incremental cost-effectiveness results if all treatment strategies that involve switching from a DOAC to a VKA are removed from the decision space. In addition, given the virtually identical costs and QALYs for the different apixaban doses in the extended therapy phase, only strategies at the licensed dose of 2.5 mg twice daily have been retained to simplify interpretation of the CEACs.

The least costly strategy is now apixaban followed by no treatment. Apixaban followed by apixaban (2.5 mg twice daily) is the only strategy that is not dominated, with an ICER of £26,009/QALY compared to apixaban followed by no treatment.

The strategy apixaban followed by aspirin is not on the cost-effectiveness frontier in the deterministic analysis because it is extendedly dominated but at a threshold value of £20,000/QALY, it is the strategy with the highest probability of being cost effective. This is due to the small incremental differences in costs and QALYs and considerable uncertainty around this result.

Figure 11 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban followed by no treatment versus apixaban followed by aspirin). The results were sensitive to a number of baseline model parameters as well as the size of the treatment effect for aspirin on both VTE recurrence and major bleeding.

Table 51: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) - DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ31:Apix_NoTreat	£1,341	7.543			
SQ35:Apix_Apix2.5	£1,527	7.550	£185	0.007	£26,009

Figure 11: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban followed by no treatment vs. apixaban followed by aspirin based on incremental net monetary benefit at a threshold of £20,000/QALY - DVT

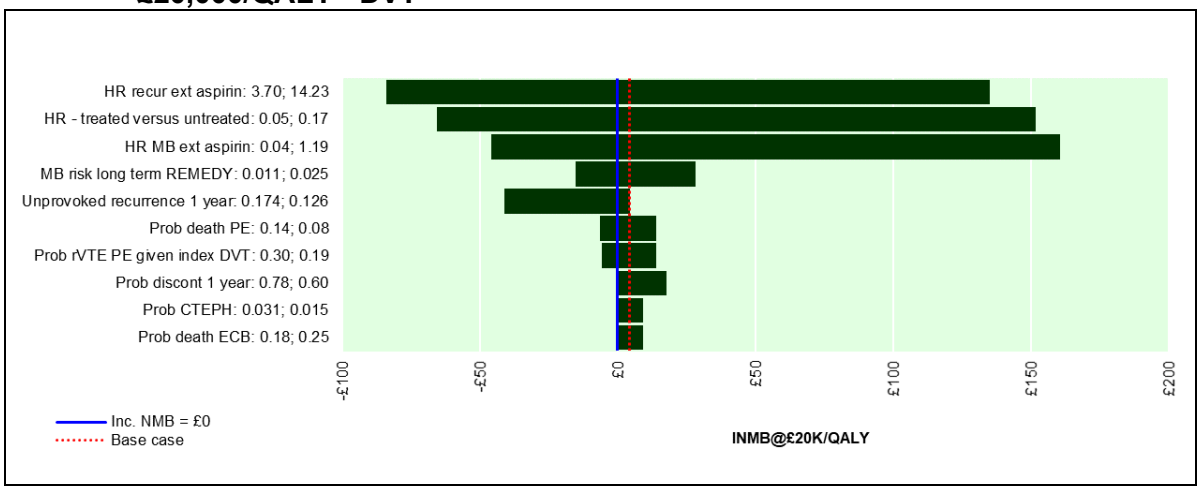
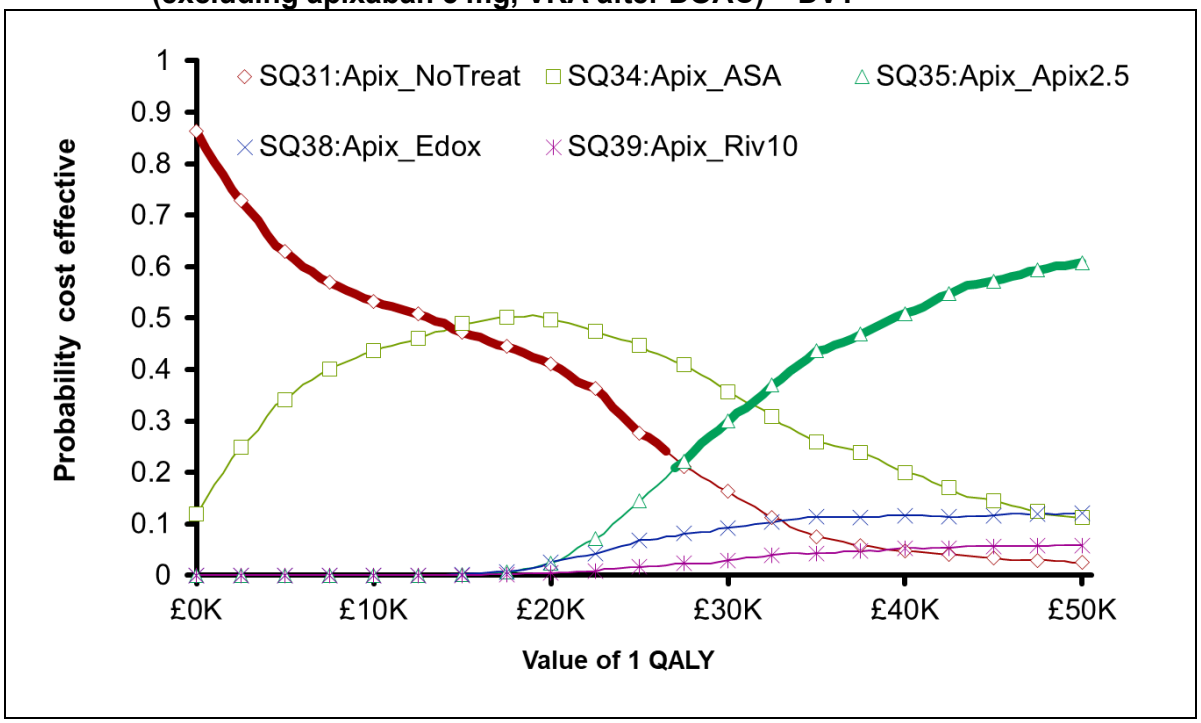


Figure 12: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) – DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment and aspirin) – DVT

Results of the extended therapy NMAs showed that aspirin was less effective for the outcome VTE recurrence than DOACs or VKA and the committee felt that in clinical practice, aspirin would not be an appropriate option for long-term secondary prevention in all patients, particularly those who have had more than one VTE and are at a higher risk of recurrence. Similarly, no treatment is unlikely to be an appropriate option for these people in the extended phase.

Table 52 presents the non-dominated incremental cost-effectiveness results when strategies containing no treatment or aspirin in the extended phase are also removed from the decision space. The least costly strategy is now LMWH/VKA followed by VKA standard. Apixaban followed by apixaban (2.5 mg twice daily) remains the strategy that generates the most QALYs, with an ICER of £3,035/QALY compared to apixaban followed by dabigatran.

In one-way sensitivity analyses for the pairwise comparison of apixaban followed by apixaban (2.5mg twice daily) versus apixaban followed by dabigatran, results were sensitive to the relative effect of the drugs on major bleeding in the extended therapy phase.

The probabilistic results show that apixaban followed by apixaban (2.5mg twice daily) has a 63% probability of being cost effective at a threshold of £20,000/QALY (Figure 14)

Table 52: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ3:LmwhVKA_VKA_Standard	£1,445	7.504			
SQ37:Apix_Dabig	£1,517	7.547	£72	0.042	£1,709
SQ35:Apix_Apix2.5	£1,527	7.550	£10	0.003	£3,035

Figure 13: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban followed by apixaban 2.5mg vs, apixaban followed by dabigatran based on incremental net monetary benefit at a threshold of £20,000/QALY - DVT

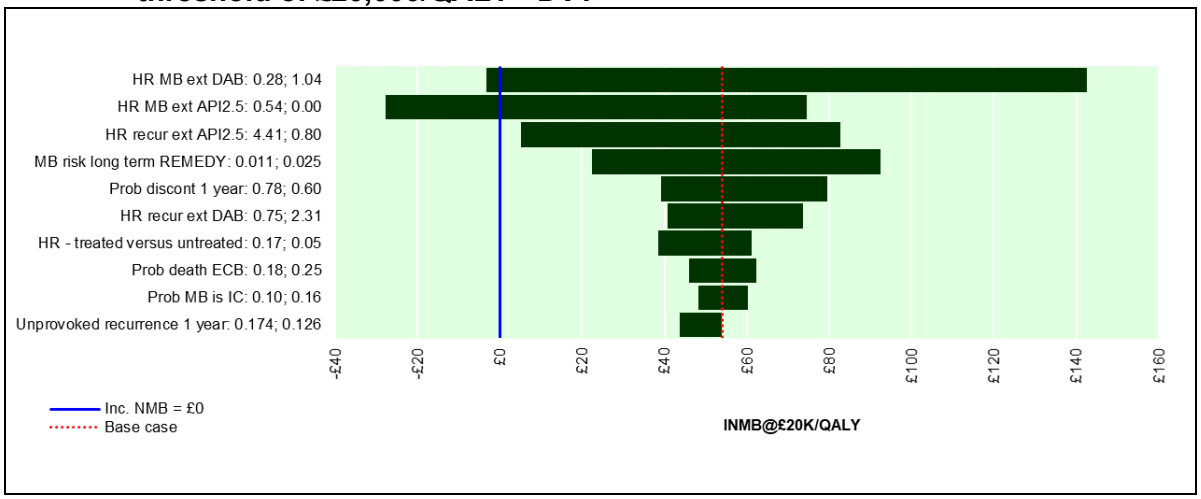
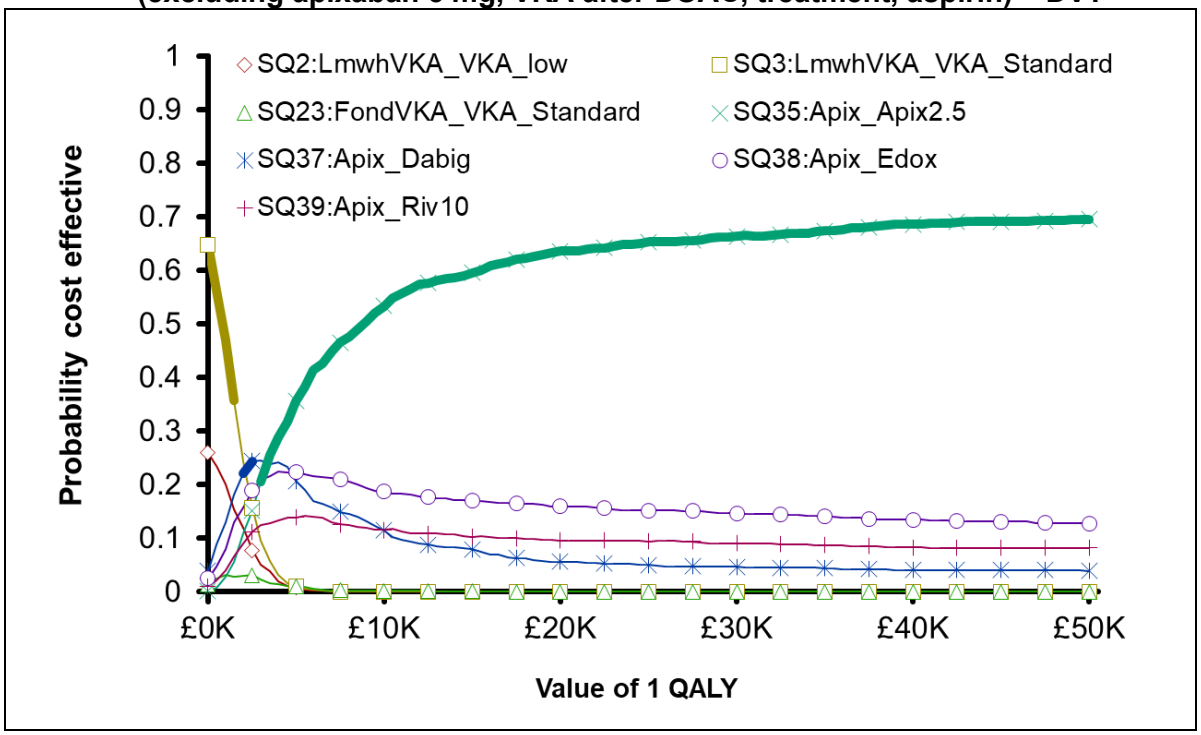


Figure 14: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, treatment, aspirin) – DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (separate incremental results by initial treatment strategy) - DVT

The committee was also interested in understanding what is the most cost-effective extended therapy for a given initial treatment. Therefore, incremental cost-effectiveness results were presented separately for all strategies that begin with LMWH/VKA, apixaban, dabigatran, edoxaban or rivaroxaban as initial treatment. As before, these results omit strategies that were deemed by the committee not to be clinically relevant for the majority of patients, in other words excluding the following extended therapy options: VKA after a DOAC, aspirin and no treatment. Apixaban 5mg twice daily as an extended therapy was also omitted to simplify interpretation of incremental results given that it produced identical costs and QALYs to apixaban 2.5mg twice daily.

Table 53 shows that when LMWH/VKA is used in the initial treatment phase, the strategy of switching to apixaban in the extended therapy phase generates the most QALYs, with an ICER of £27,826/QALY in comparison to the strategy of remaining on a VKA. That is to say, if a person starts on LMWH/VKA in the initial treatment phase, switching to any DOAC in the extended phase is unlikely to be cost effective. For strategies that start with a DOAC as initial treatment, dabigatran as extended therapy is the least costly strategy but apixaban 2.5 mg as extended therapy generates more QALYs with an ICER of approximately £3,050/QALY. In practical terms, this suggests that regardless of the choice of DOAC in the initial treatment phase, switching to apixaban for secondary prevention is likely to be cost effective.

Table 53: Deterministic cost-effectiveness results for the sequencing analysis (separate incremental results for a given initial treatment) – DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA as initial treatment					
SQ3:LmwhVKA_VKA_Standard	£1,445	7.504			
SQ2:LmwhVKA_VKA_low	£1,454	7.502	£9	-0.002	dominated
SQ7:LmwhVKA_Dabig	£1,606	7.507	£161	0.003	ext. dom.
SQ8:LmwhVKA_Edox[(a)]	£1,615	7.506	£170	0.001	dominated
SQ5:LmwhVKA_Apix2.5	£1,615	7.510	£170	0.006	£27,826
SQ9:LmwhVKA_Riv10	£1,623	7.505	£8	-0.006	dominated
SQ10:LmwhVKA_Riv20	£1,632	7.502	£17	-0.008	dominated
Apixaban as initial treatment					
SQ37:Apix_Dabig	£1,517	7.547			
SQ38:Apix_Edox[(a)]	£1,527	7.545	£10	-0.002	dominated
SQ35:Apix_Apix2.5	£1,527	7.550	£10	0.003	£3,035
SQ39:Apix_Riv10	£1,535	7.544	£8	-0.006	dominated
SQ40:Apix_Riv20	£1,544	7.541	£17	-0.008	dominated
Dabigatran as initial treatment					
SQ47:Dabig_Dabig	£1,632	7.518			
SQ48:Dabig_Edox[(a)]	£1,641	7.516	£9	-0.002	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ45:Dabig_Apix2.5	£1,642	7.521	£9	0.003	£3,043
SQ49:Dabig_Riv10	£1,650	7.515	£8	-0.006	dominated
SQ50:Dabig_Riv20	£1,659	7.513	£17	-0.008	dominated
Edoxaban as initial treatment					
SQ57:Edox_Dabig	£1,621	7.518			
SQ58:Edox_Edox[(a)]	£1,631	7.516	£9	-0.002	dominated
SQ55:Edox_Apix2.5	£1,631	7.521	£10	0.003	£3,045
SQ59:Edox_Riv10	£1,639	7.515	£8	-0.006	dominated
SQ60:Edox_Riv20	£1,648	7.513	£17	-0.008	dominated
Rivaroxaban as initial treatment					
SQ67:Riv_Dabig	£1,583	7.533			
SQ68:Riv_Edox	£1,592	7.531	£9	-0.002	dominated
SQ65:Riv_Apix2.5	£1,593	7.536	£10	0.003	£3,039
SQ69:Riv_Riv10	£1,601	7.531	£8	-0.006	dominated
SQ70:Riv_Riv20	£1,610	7.528	£17	-0.008	dominated

(a) No extended therapy trial

Sequencing analysis (all strategies) - PE

Table 54 shows key outcomes and costs for all 70 strategies assuming treatment switching from any initial treatment to any extended therapy is possible following a PE. The sequence of apixaban as initial treatment followed by apixaban (5 mg twice daily) in the extended therapy phase generates the most QALYs. Similar to the results for DVT, the sequence of apixaban as initial treatment followed by no treatment in the extended therapy phase is the least costly strategy. The QALY differences between strategies that begin with the same initial treatment are very small. In particular, as seen in the DVT analysis, the strategies apixaban followed by apixaban (5 mg twice daily) and apixaban followed by apixaban (2.5 mg twice daily) generate virtually identical costs and QALYs.

The ICER for the sequence apixaban followed by VKA standard versus apixaban followed by no treatment is £4,300/QALY and the ICER for apixaban followed by apixaban (5 mg twice daily) versus apixaban followed by VKA standard is £27,247/QALY (Table 55); all other strategies are either dominated or extendedly dominated, including the strategy apixaban followed by aspirin, despite this strategy having the second highest net monetary benefit.

Figure 15 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban followed by VKA standard versus apixaban followed by aspirin).There is considerable uncertainty about the effect of aspirin on both VTE recurrence and major bleeding and the tornado diagram shows that this could affect the relative ranking of the 2 strategies in terms of net monetary benefit. Results are also sensitive to the baseline estimate for the long-term risk of major bleeding sourced from the warfarin arm of the RE-

MEDY trial (Schulman 2013) as well as the hazard ratio for LMWH/VKA that was applied to the baseline long-term risk of VTE recurrence while off treatment.

At a threshold value of £20,000/QALY, the strategy with the highest probability of being cost effective is the sequence apixaban followed by VKA standard but Figure 16 shows there is considerable uncertainty in the results.

Table 54: Key outcomes and costs for the sequencing analysis (all strategies) - PE

	Events[a]			Costs								
Strategy	**Recurrent VTE**	**Major bleeds**	**CRNMB**	**Treatment**	**Monitoring**	**Recurrent VTE**	**Major bleeding**	**CRNMB**	**Total QALYs[b]**	**Total costs[b]**	**NMB at £20K/QALY**	**Rank (NMB)**
SQ36:Apix_Apix5	21.23	1.16	10.40	£557	£188	£264	£80	£22	7.447	£3,044	£145,901	4
SQ35:Apix_Apix2.5	21.22	1.18	10.14	£557	£188	£264	£82	£21	7.447	£3,044	£145,893	5
SQ37:Apix_Dabig	21.07	1.35	10.74	£535	£188	£262	£98	£22	7.444	£3,035	£145,844	7
SQ38:Apix_Edox	20.97	1.45	11.30	£540	£187	£261	£105	£23	7.442	£3,044	£145,803	8
SQ33:Apix_VKA_Standard	21.00	1.50	11.74	£357	£187	£261	£109	£24	7.441	£2,874	£145,946	1
SQ39:Apix_Riv10	21.19	1.44	10.90	£545	£188	£263	£104	£23	7.441	£3,052	£145,774	9
SQ34:Apix_ASA	22.17	1.27	11.01	£358	£187	£273	£88	£23	7.440	£2,878	£145,915	2
SQ32:Apix_VKA_low	21.48	1.49	11.78	£356	£188	£266	£108	£24	7.439	£2,882	£145,889	6
SQ40:Apix_Riv20	21.25	1.54	11.45	£544	£188	£264	£112	£24	7.439	£3,060	£145,716	10
SQ31:Apix_NoTreat	22.81	1.18	9.81	£357	£169	£279	£80	£21	7.438	£2,863	£145,903	3
SQ66:Riv_Apix5	21.49	1.72	17.34	£565	£188	£266	£126	£35	7.433	£3,108	£145,559	14
SQ65:Riv_Apix2.5	21.47	1.74	17.09	£565	£188	£266	£128	£34	7.433	£3,109	£145,551	15
SQ67:Riv_Dabig	21.33	1.91	17.67	£543	£188	£265	£144	£35	7.430	£3,099	£145,503	17
SQ68:Riv_Edox	21.23	2.01	18.23	£548	£188	£264	£150	£37	7.429	£3,108	£145,462	18
SQ63:Riv_VKA_Standard	21.26	2.06	18.66	£369	£188	£264	£154	£37	7.427	£2,941	£145,603	11
SQ69:Riv_Riv10	21.45	2.00	17.83	£553	£188	£266	£150	£36	7.427	£3,116	£145,434	19
SQ64:Riv_ASA	22.41	1.83	17.94	£369	£187	£275	£134	£36	7.426	£2,945	£145,573	12
SQ61:Riv_NoTreat	23.04	1.74	16.76	£368	£170	£281	£126	£34	7.425	£2,930	£145,561	13
SQ62:Riv_VKA_low	21.73	2.05	18.70	£367	£188	£269	£153	£38	7.425	£2,949	£145,547	16
SQ70:Riv_Riv20	21.51	2.10	18.37	£553	£188	£267	£158	£37	7.425	£3,124	£145,377	20
SQ56:Edox_Apix5	21.08	2.45	14.68	£561	£187	£263	£187	£30	7.419	£3,143	£145,242	24
SQ55:Edox_Apix2.5	21.06	2.47	14.42	£561	£187	£263	£188	£29	7.419	£3,143	£145,235	25
SQ57:Edox_Dabig	20.92	2.64	15.01	£539	£187	£261	£204	£30	7.416	£3,134	£145,186	28
SQ46:Dabig_Apix5	22.50	2.29	11.99	£555	£190	£276	£187	£25	7.415	£3,157	£145,149	31
SQ45:Dabig_Apix2.5	22.49	2.31	11.74	£555	£190	£276	£188	£24	7.415	£3,158	£145,142	33
SQ58:Edox_Edox	20.82	2.74	15.56	£544	£187	£260	£211	£32	7.414	£3,143	£145,146	32
SQ53:Edox_VKA_Standard	20.85	2.79	15.99	£364	£187	£261	£215	£32	7.413	£2,975	£145,287	21
SQ59:Edox_Riv10	21.04	2.73	15.17	£549	£187	£262	£210	£31	7.413	£3,151	£145,117	35

	Events[a]			Costs								
Strategy	**Recurrent VTE**	**Major bleeds**	**CRNMB**	**Treatment**	**Monitoring**	**Recurrent VTE**	**Major bleeding**	**CRNMB**	**Total QALYs[b]**	**Total costs[b]**	**NMB at £20K/QALY**	**Rank (NMB)**
SQ54:Edox_ASA	22.01	2.56	15.27	£365	£186	£272	£194	£31	7.412	£2,979	£145,257	22
SQ47:Dabig_Dabig	22.35	2.48	12.32	£533	£190	£275	£204	£25	7.412	£3,149	£145,094	36
SQ52:Edox_VKA_low	21.32	2.78	16.03	£362	£188	£265	£213	£33	7.411	£2,983	£145,231	26
SQ48:Dabig_Edox	22.25	2.58	12.87	£538	£189	£274	£210	£26	7.411	£3,157	£145,054	38
SQ60:Edox_Riv20	21.10	2.83	15.71	£548	£187	£263	£218	£32	7.411	£3,159	£145,061	37
SQ51:Edox_NoTreat	22.63	2.47	14.10	£363	£169	£278	£186	£29	7.410	£2,964	£145,245	23
SQ49:Dabig_Riv10	22.46	2.57	12.47	£543	£190	£276	£210	£26	7.410	£3,165	£145,026	40
SQ43:Dabig_VKA_Standard	22.28	2.63	13.29	£360	£190	£274	£214	£27	7.409	£2,992	£145,193	27
SQ44:Dabig_ASA	23.42	2.40	12.58	£361	£189	£285	£194	£26	7.408	£2,996	£145,163	29
SQ41:Dabig_NoTreat	24.03	2.31	11.42	£360	£172	£291	£186	£24	7.407	£2,981	£145,152	30
SQ42:Dabig_VKA_low	22.75	2.62	13.33	£359	£190	£278	£213	£27	7.407	£3,000	£145,138	34
SQ6:LmwhVKA_Apix5	21.93	2.82	17.36	£388	£309	£271	£213	£35	7.407	£3,132	£145,000	43
SQ50:Dabig_Riv20	22.53	2.66	13.01	£542	£190	£276	£217	£27	7.407	£3,173	£144,970	46
SQ5:LmwhVKA_Apix2.5	21.92	2.84	17.11	£388	£309	£271	£214	£34	7.406	£3,133	£144,993	44
SQ7:LmwhVKA_Dabig	21.78	3.00	17.69	£366	£309	£269	£230	£36	7.403	£3,123	£144,946	47
SQ8:LmwhVKA_Edox	21.68	3.10	18.23	£371	£309	£268	£236	£37	7.402	£3,132	£144,905	48
SQ3:LmwhVKA_VKA_Standard	21.71	3.15	18.66	£194	£309	£269	£240	£38	7.401	£2,968	£145,044	39
SQ9:LmwhVKA_Riv10	21.89	3.09	17.84	£376	£309	£270	£236	£36	7.401	£3,140	£144,878	49
SQ26:FondVKA_Apix5	21.81	3.10	14.63	£448	£309	£270	£236	£30	7.401	£3,204	£144,815	54
SQ25:FondVKA_Apix2.5	21.79	3.12	14.38	£448	£309	£270	£237	£29	7.401	£3,205	£144,808	55
SQ4:LmwhVKA_ASA	22.84	2.93	17.95	£195	£308	£280	£220	£36	7.399	£2,971	£145,015	41
SQ1:LmwhVKA_NoTreat	23.45	2.83	16.80	£194	£291	£286	£212	£34	7.398	£2,956	£145,003	42
SQ2:LmwhVKA_VKA_low	22.17	3.14	18.69	£193	£310	£273	£239	£38	7.398	£2,975	£144,989	45
SQ10:LmwhVKA_Riv20	21.95	3.18	18.38	£375	£309	£271	£243	£37	7.398	£3,148	£144,822	52
SQ27:FondVKA_Dabig	21.65	3.28	14.96	£427	£309	£268	£253	£30	7.398	£3,195	£144,760	57
SQ28:FondVKA_Edox	21.55	3.38	15.51	£431	£309	£267	£259	£32	7.396	£3,204	£144,720	58
SQ23:FondVKA_VKA_Standard	21.58	3.43	15.93	£254	£309	£268	£263	£32	7.395	£3,039	£144,859	50
SQ29:FondVKA_Riv10	21.77	3.37	15.11	£437	£309	£269	£259	£31	7.395	£3,212	£144,692	59
SQ24:FondVKA_ASA	22.72	3.21	15.22	£255	£308	£279	£243	£31	7.394	£3,043	£144,829	51
SQ22:FondVKA_VKA_low	22.05	3.43	15.97	£253	£310	£272	£262	£32	7.393	£3,047	£144,804	56

	Events[a]			Costs								
Strategy	**Recurrent VTE**	**Major bleeds**	**CRNMB**	**Treatment**	**Monitoring**	**Recurrent VTE**	**Major bleeding**	**CRNMB**	**Total QALYs[b]**	**Total costs[b]**	**NMB at £20K/QALY**	**Rank (NMB)**
SQ30:FondVKA_Riv20	21.83	3.47	15.65	£436	£309	£270	£266	£32	7.393	£3,220	£144,636	60
SQ21:FondVKA_NoTreat	23.33	3.12	14.07	£254	£291	£284	£235	£29	7.392	£3,028	£144,818	53
SQ16:UnfVKA_Apix5	23.46	3.60	17.65	£445	£312	£286	£275	£36	7.381	£3,267	£144,353	64
SQ15:UnfVKA_Apix2.5	23.45	3.62	17.41	£445	£312	£285	£277	£35	7.381	£3,268	£144,346	65
SQ17:UnfVKA_Dabig	23.32	3.78	17.97	£424	£312	£284	£292	£36	7.378	£3,259	£144,300	67
SQ18:UnfVKA_Edox	23.22	3.87	18.50	£429	£311	£283	£298	£37	7.376	£3,267	£144,260	68
SQ13:UnfVKA_VKA_Standard	23.25	3.93	18.91	£257	£311	£284	£302	£38	7.375	£3,107	£144,396	61
SQ19:UnfVKA_Riv10	23.43	3.87	18.12	£434	£312	£285	£297	£37	7.375	£3,275	£144,233	69
SQ14:UnfVKA_ASA	24.35	3.71	18.22	£257	£311	£294	£282	£37	7.374	£3,110	£144,367	62
SQ11:UnfVKA_NoTreat	24.94	3.62	17.10	£256	£294	£300	£275	£35	7.373	£3,096	£144,356	63
SQ12:UnfVKA_VKA_low	23.70	3.92	18.95	£255	£312	£288	£301	£38	7.373	£3,114	£144,342	66
SQ20:UnfVKA_Riv20	23.49	3.96	18.64	£433	£312	£286	£305	£38	7.373	£3,283	£144,179	70

(a) Per 100 people in the model
(b) Discounted values
(c) No extended therapy trial

Table 55: Deterministic incremental cost-effectiveness results for the sequencing analysis (all strategies) - PE

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ31:Apix_NoTreat	£2,863	7.438			
SQ33:Apix_VKA_Standard	£2,874	7.441	£12	0.003	£4,300
SQ34:Apix_ASA	£2,878	7.440	£3	-0.001	dominated
SQ32:Apix_VKA_low	£2,882	7.439	£8	-0.002	dominated
SQ61:Riv_NoTreat	£2,930	7.425	£55	-0.016	dominated
SQ63:Riv_VKA_Standard	£2,941	7.427	£67	-0.014	dominated
SQ64:Riv_ASA	£2,945	7.426	£70	-0.015	dominated
SQ62:Riv_VKA_low	£2,949	7.425	£74	-0.016	dominated
SQ1:LmwhVKA_NoTreat	£2,956	7.398	£82	-0.043	dominated
SQ51:Edox_NoTreat	£2,964	7.410	£90	-0.031	dominated
SQ3:LmwhVKA_VKA_Standard	£2,968	7.401	£93	-0.040	dominated
SQ4:LmwhVKA_ASA	£2,971	7.399	£97	-0.042	dominated
SQ2:LmwhVKA_VKA_low	£2,975	7.398	£101	-0.043	dominated
SQ53:Edox_VKA_Standard	£2,975	7.413	£101	-0.028	dominated
SQ54:Edox_ASA	£2,979	7.412	£105	-0.029	dominated
SQ41:Dabig_NoTreat	£2,981	7.407	£107	-0.034	dominated
SQ52:Edox_VKA_low	£2,983	7.411	£109	-0.030	dominated
SQ43:Dabig_VKA_Standard	£2,992	7.409	£118	-0.032	dominated
SQ44:Dabig_ASA	£2,996	7.408	£121	-0.033	dominated
SQ42:Dabig_VKA_low	£3,000	7.407	£125	-0.034	dominated
SQ21:FondVKA_NoTreat	£3,028	7.392	£154	-0.049	dominated
SQ37:Apix_Dabig	£3,035	7.444	£161	0.003	ext. dom.
SQ23:FondVKA_VKA_Standard	£3,039	7.395	£165	-0.046	dominated
SQ24:FondVKA_ASA	£3,043	7.394	£168	-0.047	dominated
SQ36:Apix_Apix5	£3,044	7.447	£169	0.006	£27,247
SQ38:Apix_Edox	£3,044	7.442	£0	-0.005	dominated
SQ35:Apix_Apix2.5	£3,044	7.447	£1	0.000	dominated
SQ22:FondVKA_VKA_low	£3,047	7.393	£3	-0.055	dominated
SQ39:Apix_Riv10	£3,052	7.441	£8	-0.006	dominated
SQ40:Apix_Riv20	£3,060	7.439	£16	-0.008	dominated
SQ11:UnfVKA_NoTreat	£3,096	7.373	£52	-0.075	dominated
SQ67:Riv_Dabig	£3,099	7.430	£55	-0.017	dominated
SQ13:UnfVKA_VKA_Standard	£3,107	7.375	£63	-0.072	dominated
SQ66:Riv_Apix5	£3,108	7.433	£64	-0.014	dominated
SQ68:Riv_Edox	£3,108	7.429	£64	-0.019	dominated

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ65:Riv_Apix2.5	£3,109	7.433	£65	-0.014	dominated
SQ14:UnfVKA_ASA	£3,110	7.374	£67	-0.073	dominated
SQ12:UnfVKA_VKA_low	£3,114	7.373	£70	-0.074	dominated
SQ69:Riv_Riv10	£3,116	7.427	£72	-0.020	dominated
SQ7:LmwhVKA_Dabig	£3,123	7.403	£79	-0.044	dominated
SQ70:Riv_Riv20	£3,124	7.425	£80	-0.022	dominated
SQ6:LmwhVKA_Apix5	£3,132	7.407	£88	-0.041	dominated
SQ8:LmwhVKA_Edox	£3,132	7.402	£88	-0.045	dominated
SQ5:LmwhVKA_Apix2.5	£3,133	7.406	£89	-0.041	dominated
SQ57:Edox_Dabig	£3,134	7.416	£90	-0.031	dominated
SQ9:LmwhVKA_Riv10	£3,140	7.401	£96	-0.046	dominated
SQ56:Edox_Apix5	£3,143	7.419	£99	-0.028	dominated
SQ58:Edox_Edox	£3,143	7.414	£99	-0.033	dominated
SQ55:Edox_Apix2.5	£3,143	7.419	£100	-0.028	dominated
SQ10:LmwhVKA_Riv20	£3,148	7.398	£104	-0.049	dominated
SQ47:Dabig_Dabig	£3,149	7.412	£105	-0.035	dominated
SQ59:Edox_Riv10	£3,151	7.413	£107	-0.034	dominated
SQ46:Dabig_Apix5	£3,157	7.415	£114	-0.032	dominated
SQ48:Dabig_Edox	£3,157	7.411	£114	-0.037	dominated
SQ45:Dabig_Apix2.5	£3,158	7.415	£114	-0.032	dominated
SQ60:Edox_Riv20	£3,159	7.411	£115	-0.036	dominated
SQ49:Dabig_Riv10	£3,165	7.410	£121	-0.038	dominated
SQ50:Dabig_Riv20	£3,173	7.407	£129	-0.040	dominated
SQ27:FondVKA_Dabig	£3,195	7.398	£152	-0.049	dominated
SQ26:FondVKA_Apix5	£3,204	7.401	£160	-0.046	dominated
SQ28:FondVKA_Edox	£3,204	7.396	£160	-0.051	dominated
SQ25:FondVKA_Apix2.5	£3,205	7.401	£161	-0.047	dominated
SQ29:FondVKA_Riv10	£3,212	7.395	£168	-0.052	dominated
SQ30:FondVKA_Riv20	£3,220	7.393	£176	-0.054	dominated
SQ17:UnfVKA_Dabig	£3,259	7.378	£215	-0.069	dominated
SQ18:UnfVKA_Edox	£3,267	7.376	£223	-0.071	dominated
SQ16:UnfVKA_Apix5	£3,267	7.381	£223	-0.066	dominated
SQ15:UnfVKA_Apix2.5	£3,268	7.381	£224	-0.067	dominated
SQ19:UnfVKA_Riv10	£3,275	7.375	£231	-0.072	dominated
SQ20:UnfVKA_Riv20	£3,283	7.373	£239	-0.074	dominated

(a) No extended therapy trial

Figure 15: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban followed by VKA standard vs. apixaban followed by aspirin based on incremental net monetary benefit at a threshold of £20,000/QALY – PE

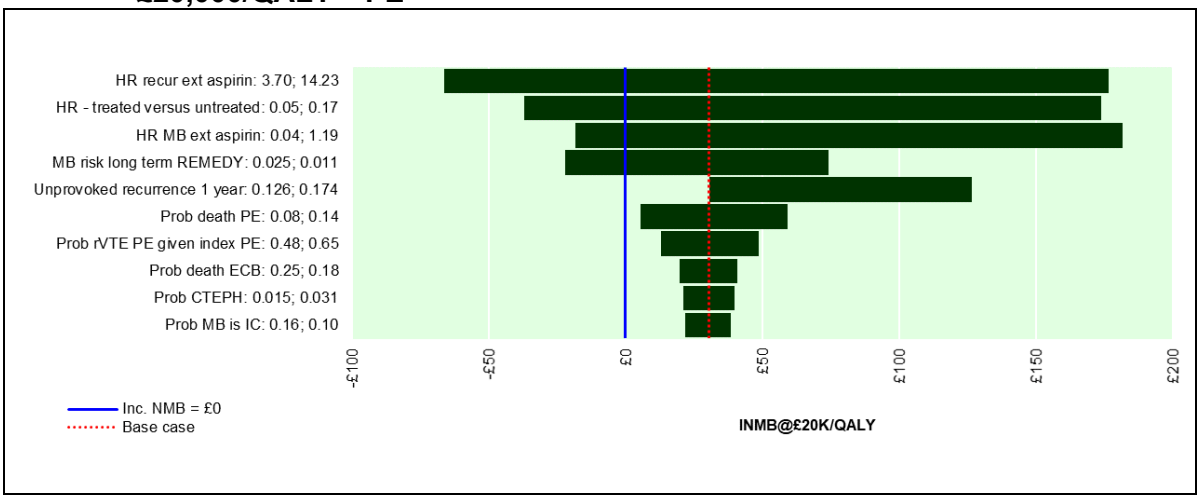
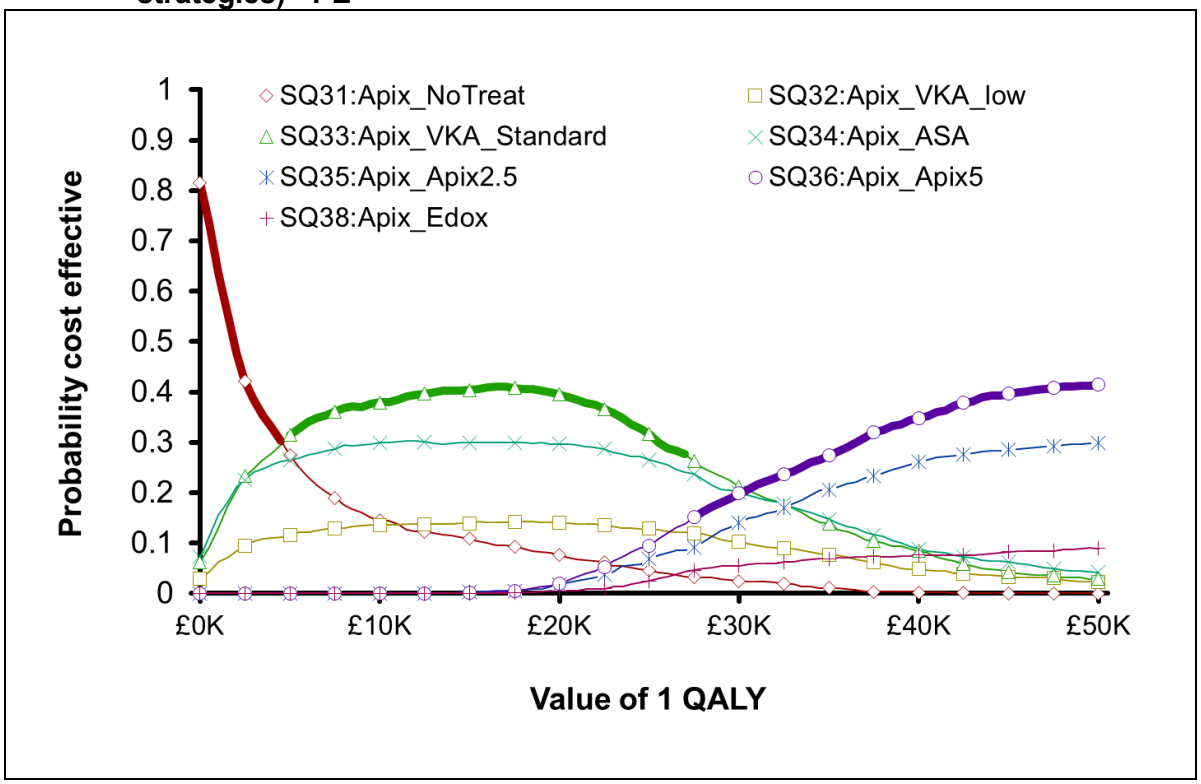


Figure 16: Cost-effectiveness acceptability curve for the sequencing analysis (all strategies) - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) - PE

Table 56 presents the non-dominated incremental cost-effectiveness results if all treatment strategies that involve switching from a DOAC to a VKA are removed from the decision space as the committee felt these strategies were unlikely to be clinically relevant options for the majority of patients. In addition, given the virtually identical costs and QALYs for the different apixaban doses in extended therapy, only strategies at the licensed dose of 2.5 mg twice daily for extended therapy have been retained to simplify interpretation of the CEACs.

The least costly strategy is now apixaban followed by no treatment. Apixaban followed by aspirin and apixaban followed by apixaban (2.5 mg twice daily) are the only other strategies that are not dominated.

Figure 17 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban followed by aspirin versus apixaban followed by no treatment). Similar to the same analysis for DVT, the results were sensitive to a number of baseline model parameters as well as the size of the treatment effect for aspirin on both VTE recurrence and major bleeding.

The probabilistic results show that apixaban followed aspirin has a 51% probability of being cost effective at a threshold of £20,000/QALY (

Figure 18).

Table 56: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC)

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ31:Apix_NoTreat	£2,863	7.438			
SQ34:Apix_ASA	£2,878	7.440	£15	0.001	£11,134
SQ35:Apix_Apix2.5	£3,044	7.447	£167	0.007	£23,035

Figure 17: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban followed by aspirin vs. apixaban followed by no treatment based on incremental net monetary benefit at a threshold of £20,000/QALY - PE

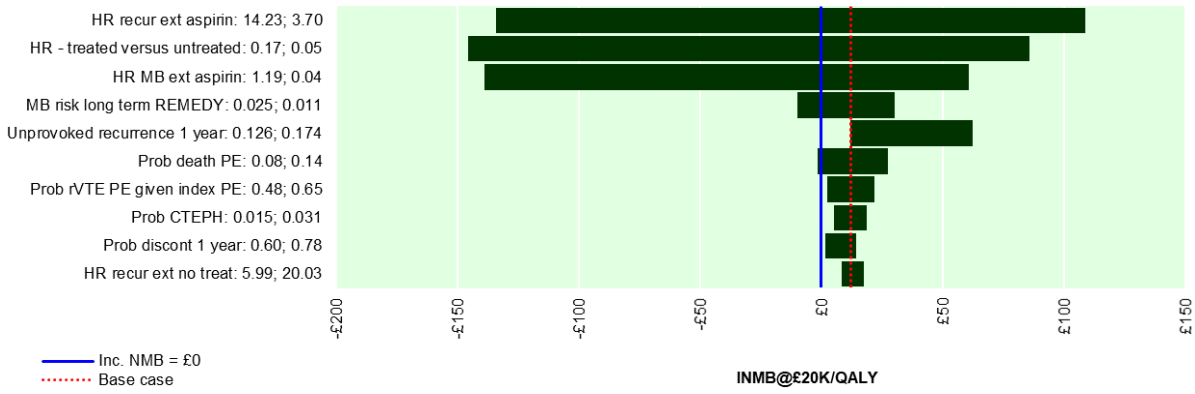
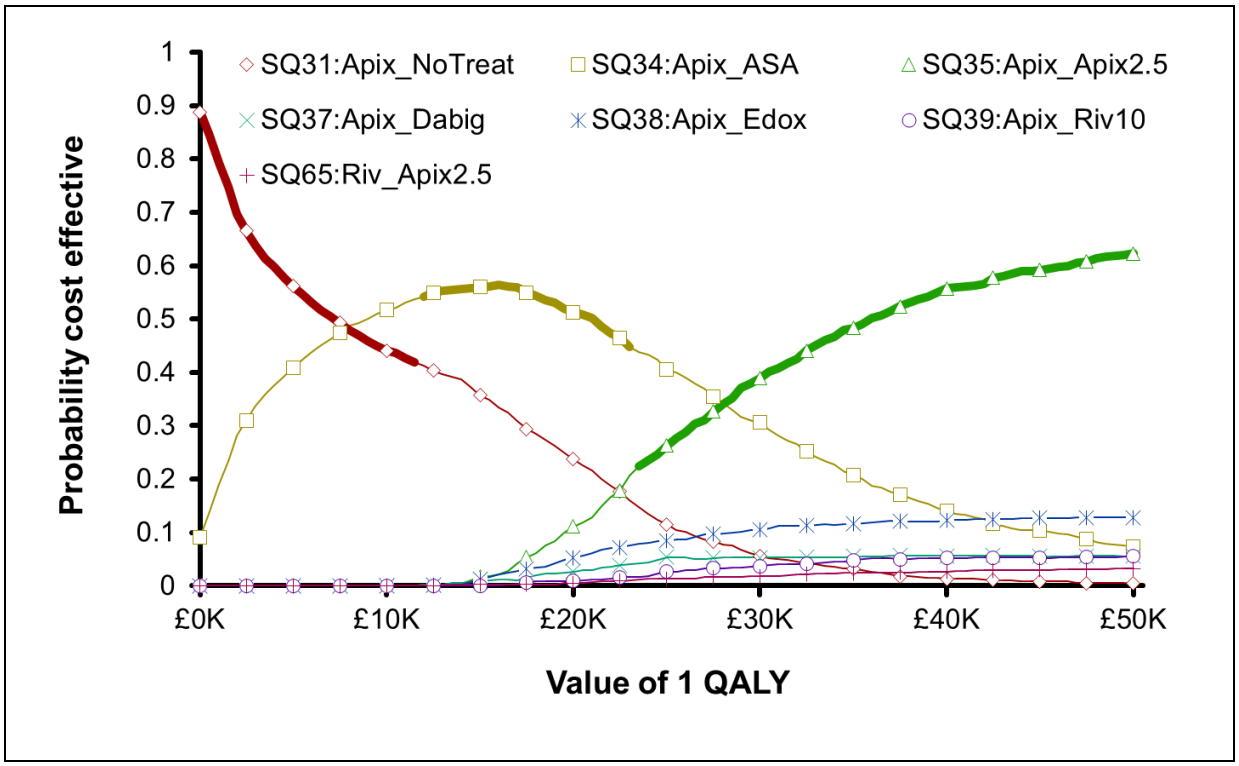


Figure 18: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, no VKA after DOAC) – PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – PE

Table 57 presents the non-dominated incremental cost-effectiveness results when strategies containing no treatment or aspirin in the extended phase are also removed from the decision space. The least costly strategy is now LMWH/VKA followed by VKA standard. Apixaban followed by apixaban (2.5 mg twice daily) is the most cost-effective strategy, with an ICER of £3,283/QALY compared to apixaban followed by dabigatran.

In one-way sensitivity analyses for the pairwise comparison of apixaban followed by apixaban (2.5mg twice daily) versus apixaban followed by dabigatran (Figure 19), results were sensitive to the relative effect of the drugs on major bleeding in the extended therapy phase as well as the effect of apixaban on VTE recurrence in the extended therapy phase.

Figure 20 shows the CEAC for this scenario, apixaban followed by apixaban 2.5 mg has a 61% probability of being cost effective.

Table 57: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – PE

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ3:LmwhVKA_VKA_Standard	£2,968	7.401			

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ37:Apix_Dabig	£3,035	7.444	£67	0.043	£1,551
SQ35:Apix_Apix2.5	£3,044	7.447	£10	0.003	£3,283

Figure 19: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban followed by apixaban 2.5 mg vs. apixaban followed by dabigatran based on incremental net monetary benefit at a threshold of £20,000/QALY – PE

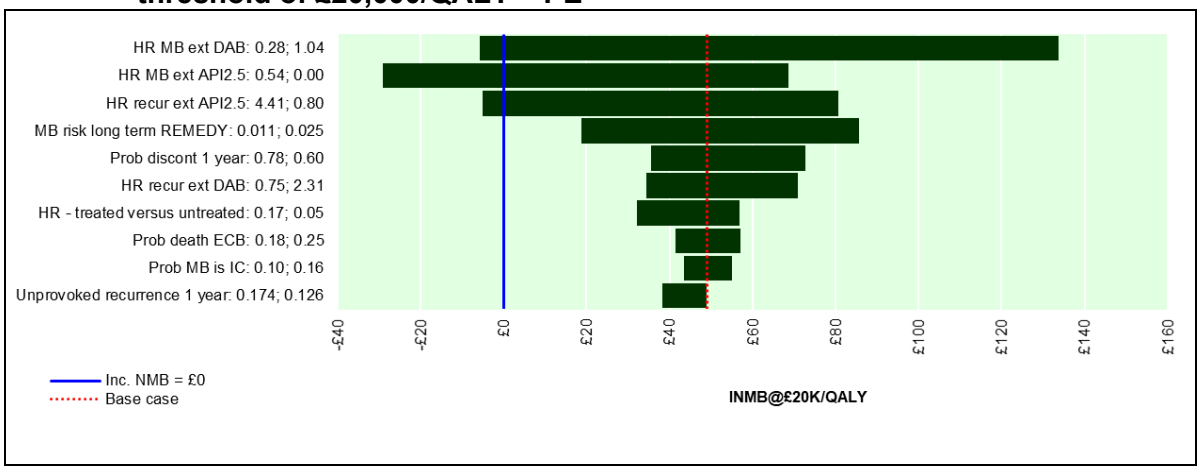
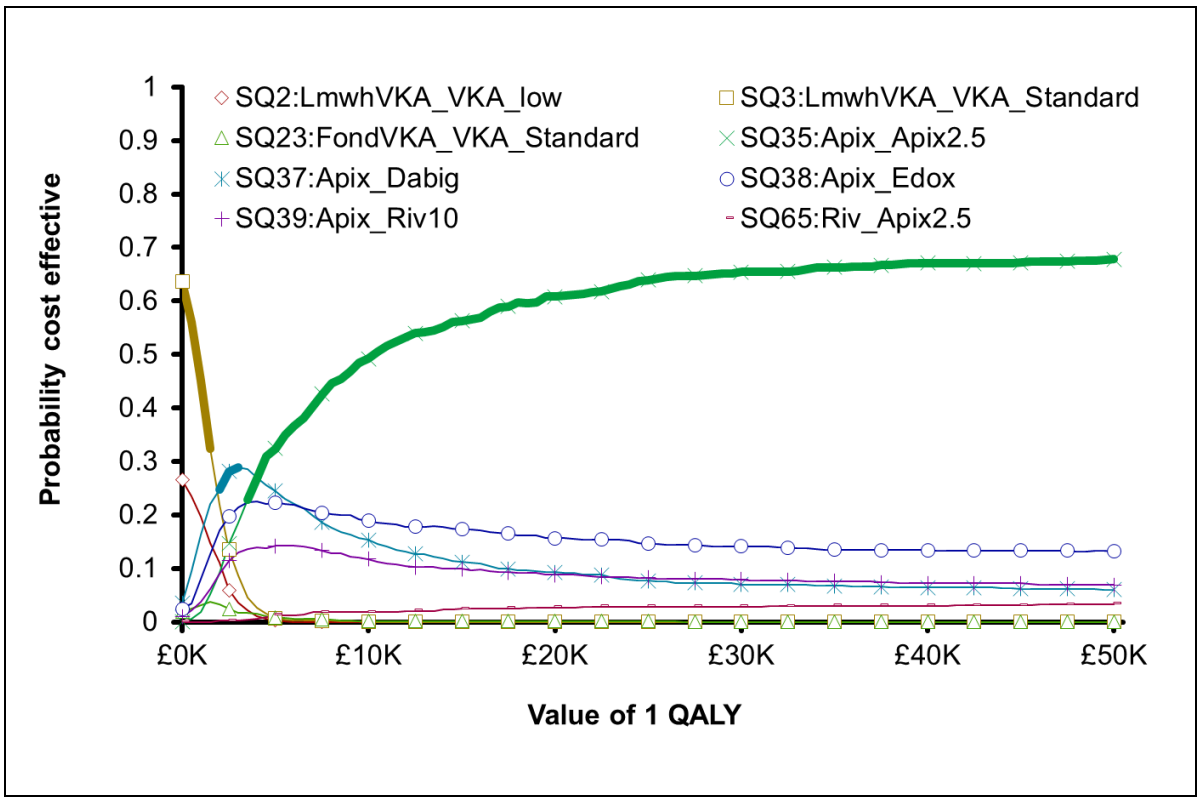


Figure 20: Cost-effectiveness acceptability curve for the sequencing analysis overall population (excluding apixaban 5 mg, no VKA after DOAC, no treatment, no aspirin) – PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (separate incremental results by initial treatment strategy) – PE

Table 58 shows the results of separate incremental cost-effectiveness results for strategies starting with LMWH/VKA, apixaban, dabigatran, edoxaban or rivaroxaban. The results for PE are consistent with those for DVT. When LMWH/VKA is used in the initial treatment phase, switching to apixaban in the extended therapy phase generates the most QALYs and an ICER of £28,969/QALY in comparison to the strategy of remaining on a VKA and is therefore unlikely to be cost effective. For all other initial treatment strategies, apixaban 2.5 mg is the most cost-effective option in the extended therapy phase.

Table 58: Deterministic cost-effectiveness results for the sequencing analysis (separate incremental results for a given initial treatment) – PE

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA as initial treatment					
SQ3:LmwhVKA_VKA_Standard	£2,968	7.401			

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ2:LmwhVKA_VKA_low	£2,975	7.398	£7	-£0	dominated
SQ7:LmwhVKA_Dabig	£3,123	7.403	£156	£0	ext. dom.
SQ8:LmwhVKA_Edox[(a)]	£3,132	7.402	£164	£0	dominated
SQ5:LmwhVKA_Apix2.5	£3,133	7.406	£165	£0	£28,969
SQ9:LmwhVKA_Riv10	£3,140	7.401	£7	-£0	dominated
SQ10:LmwhVKA_Riv20	£3,148	7.398	£15	-£0	dominated
Apixaban as initial treatment					
SQ37:Apix_Dabig	£3,035	7.444			
SQ38:Apix_Edox[(a)]	£3,044	7.442	£9	-0.002	dominated
SQ35:Apix_Apix2.5	£3,044	7.447	£10	0.003	£3,283
SQ39:Apix_Riv10	£3,052	7.441	£7	-0.006	dominated
SQ40:Apix_Riv20	£3,060	7.439	£16	-0.008	dominated
Dabigatran as initial treatment					
SQ47:Dabig_Dabig	£3,149	7.412			
SQ48:Dabig_Edox[(a)]	£3,157	7.411	£9	-0.002	dominated
SQ45:Dabig_Apix2.5	£3,158	7.415	£9	0.003	£3,291
SQ49:Dabig_Riv10	£3,165	7.410	£7	-0.005	dominated
SQ50:Dabig_Riv20	£3,173	7.407	£15	-0.008	dominated
Edoxaban as initial treatment					
SQ57:Edox_Dabig	£3,134	7.416			
SQ58:Edox_Edox[(a)]	£3,143	7.414	£9	-0.002	dominated
SQ55:Edox_Apix2.5	£3,143	7.419	£10	0.003	£3,292
SQ59:Edox_Riv10	£3,151	7.413	£7	-0.006	dominated
SQ60:Edox_Riv20	£3,159	7.411	£15	-0.008	dominated
Rivaroxaban as initial treatment					
SQ67:Riv_Dabig	£3,099	7.430			
SQ68:Riv_Edox[(a)]	£3,108	7.429	£9	-0.002	dominated
SQ65:Riv_Apix2.5	£3,109	7.433	£9	0.003	£3,287
SQ69:Riv_Riv10	£3,116	7.427	£7	-0.005	dominated
SQ70:Riv_Riv20	£3,124	7.425	£16	-0.008	dominated

(a) No extended therapy trial

Subgroup analysis

Cancer subgroup – DVT

Table 59 presents the key costs and outcomes for the cancer population with a DVT. LMWH given alone has higher treatment costs than all other strategies. Rivaroxaban has the lowest

rate of VTE recurrence. Edoxaban and dabigatran have the highest rates of major bleeding and apixaban has the lowest.

Table 60 reports the incremental deterministic cost-effectiveness results with 4 out of the 8 strategies positioned on the cost-effectiveness frontier and with LMWH as an outlier due to its much higher cost. This is graphically represented on the cost-effectiveness plane in Figure 21. Apixaban generates the most QALYs with an ICER of £12,727/QALY compared to rivaroxaban.

Figure 22 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban and rivaroxaban). The results are sensitive to the relative effects of the drugs on both VTE recurrence and major bleeding.

Compared to the DVT analysis for the general population, the cost-effectiveness results in the cancer subgroup are considerably more uncertain. In probabilistic sensitivity analysis, apixaban has a 49% probability of being cost effective at a threshold of £20,000/QALY (Figure 23). Although LMWH alone generated approximately the same total QALYs as rivaroxaban, it has a 0% probability of being cost effective because of its high cost in comparison to other treatments.

Table 61 summarises an additional analysis showing the probability that each of the 8 treatments is more cost effective in pairwise comparisons with each of the other treatments based on net monetary benefit. In the pairwise comparison of apixaban and rivaroxaban (if these were the only 2 treatment options), apixaban has a 61% probability of being more cost effective whereas rivaroxaban has a 39% probability of being more cost effective, reinforcing that there is greater uncertainty in the results of the cancer subgroup analysis compared to the general population.

Table 59: Key outcomes and costs for the cancer population - DVT

Strategy	Events[a]			Costs						Total QALYs[c]	Total costs[c]	NMB at £20K/QALY
	Recurrent VTE	Major bleeds	CRNMB	Treatment	Monitoring	Recurrent VTE	Major bleeding	CRNMB	Other[b]			
Apixaban	17.06	3.70	19.26	£919	£166	£230	£161	£50	£19,845	1.426	£19,794	£8,722
LMWH	15.58	5.17	17.14	£2,566	£131	£217	£175	£45	£19,743	1.418	£21,287	£7,077
Rivaroxaban	13.08	5.53	35.41	£845	£161	£196	£239	£88	£19,734	1.418	£19,697	£8,666
LMWH/VKA	20.00	5.51	28.53	£685	£287	£256	£228	£72	£19,681	1.412	£19,650	£8,592
Fondaparinux/VKA[d]	19.79	6.04	23.84	£741	£287	£254	£250	£61	£19,643	1.409	£19,678	£8,504
UFH/VKA	22.21	6.09	16.34	£790	£290	£275	£251	£43	£19,620	1.407	£19,713	£8,421
Dabigatran	18.93	8.25	46.12	£925	£166	£248	£421	£114	£19,476	1.396	£19,803	£8,122
Edoxaban	13.70	10.00	23.44	£845	£161	£201	£430	£60	£19,376	1.390	£19,538	£8,264

(a) Per 100 people in the model
(b) Including cancer treatment costs
(c) Discounted values
(d) No data in the cancer population

Table 60: Deterministic incremental cost-effectiveness results for the cancer population - DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
Edoxaban	£19,538	1.390			
LMWH/VKA	£19,650	1.412	£112	0.022	£5,080
Fondaparinux/VKA[a]	£19,678	1.409	£28	-0.003	dominated
Rivaroxaban	£19,697	1.418	£47	0.006	£7,716
UFH/VKA	£19,713	1.407	£16	-0.011	dominated
Apixaban	£19,794	1.426	£97	0.008	£12,727
Dabigatran	£19,803	1.396	£9	-0.030	dominated
LMWH	£21,287	1.418	£1,494	-0.008	dominated

(a) No data in the cancer population

Figure 21: Cost-effectiveness plane for the cancer population - DVT

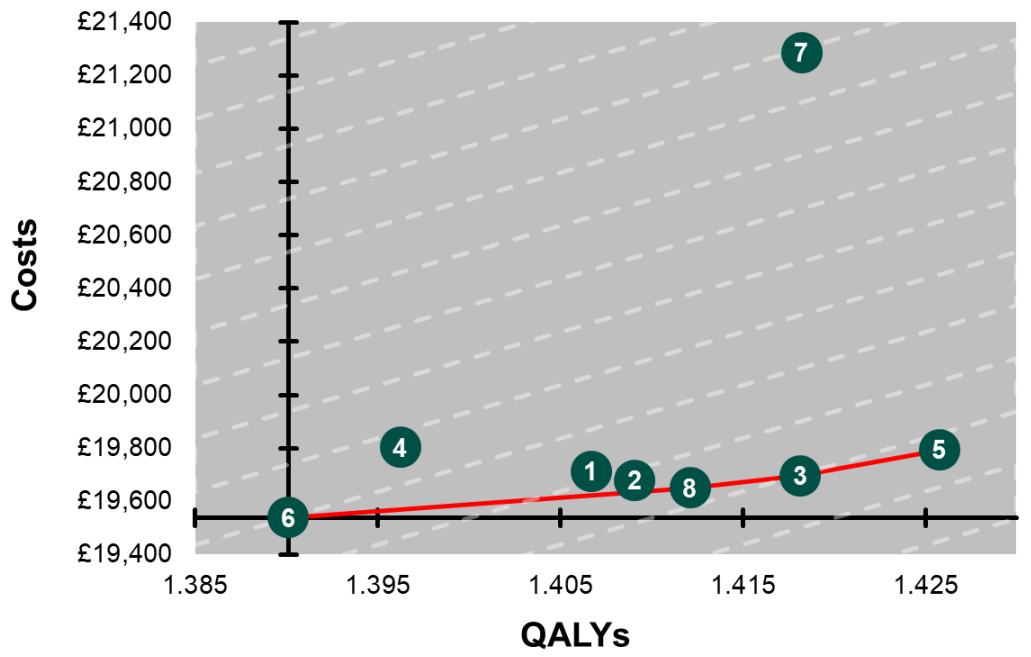


Figure 22: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban vs. rivaroxaban based on incremental net monetary benefit at a threshold of £20,000/QALY in the cancer population - DVT

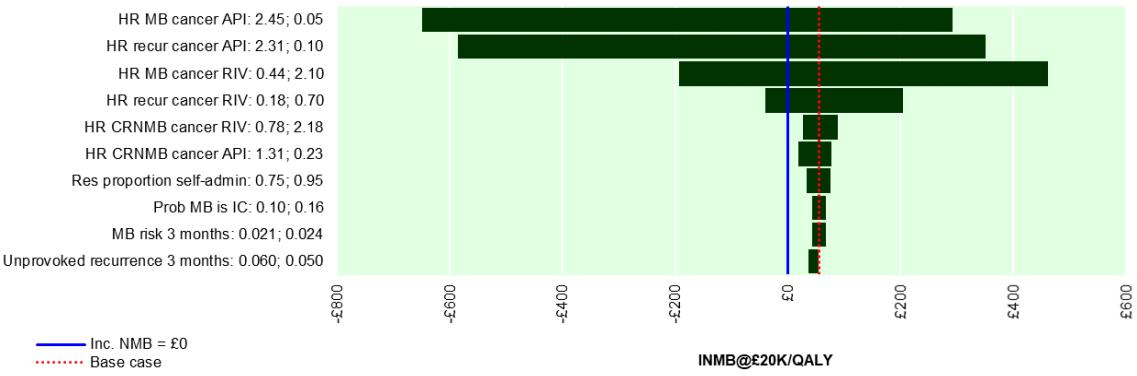
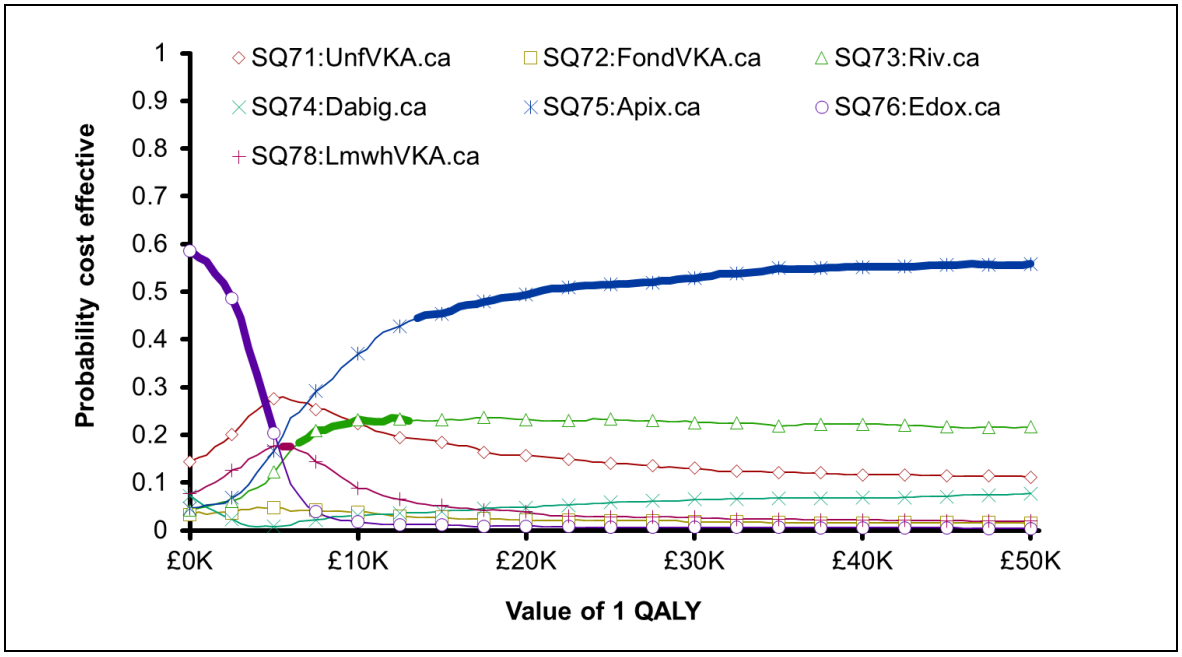


Figure 23: Cost-effectiveness acceptability curve for the cancer population - DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Table 61: Pairwise comparison of probability more cost effective for the cancer population – DVT

	LMWH/VKA	UNF/VKA	FOND/VKA	RIVAROXABAN	DABIGATRAN	APIXABAN	EDOXABAN	LMWH
LMWH/VKA		0.43	0.26	0.68	0.23	0.72	0.14	0.00
UNF/VKA	0.57		0.51	0.66	0.34	0.72	0.31	0.01
FOND/VKA	0.75	0.49		0.77	0.32	0.76	0.26	0.00
RIVAROXABAN	0.33	0.34	0.24		0.17	0.61	0.10	0.00
DABIGATRAN	0.78	0.66	0.69	0.83		0.83	0.51	0.07
APIXABAN	0.28	0.28	0.24	0.39	0.17		0.13	0.00
EDOXABAN	0.86	0.69	0.74	0.90	0.49	0.87		0.01
LMWH	1.00	0.99	1.00	1.00	0.93	1.00	0.99	

Note: Each cell shows the probability that the intervention in the column is more cost effective than the intervention in the row based on net monetary benefit. Columns with values closer to 1 (more green) indicate the intervention in that column is likely to be more cost effective than other interventions whereas columns with values closer to 0 (more red) indicate that the intervention in that column is likely to be less cost effective than the other interventions

Cancer subgroup – PE

The key outcomes and costs for treatment of PE in people with cancer are broadly consistent with those for DVT (Table 62). Rivaroxaban has the lowest rate of VTE recurrence and apixaban has the lowest rate of major bleeding. As with DVT, 4 out of the 8 strategies are positioned on the cost-effectiveness frontier and the ICER for apixaban versus rivaroxaban is £15,378/QALY (Table 63).

Figure 25 shows the impact of changing the value of one parameter at a time on the results of the pairwise comparison for the 2 strategies with the highest expected net monetary benefit (apixaban and rivaroxaban). The base case incremental net monetary benefit between the two strategies for PE is even smaller than for DVT and the results are sensitive to the relative effects of the drugs on both VTE recurrence and major bleeding.

In probabilistic sensitivity analysis, apixaban has a 51% probability of being cost effective at a threshold of £20,000/QALY (Figure 26).

Table 64 summarises an additional analysis showing the probability that each of the 8 treatments is more cost effective in pairwise comparisons with each of the other treatments based on net monetary benefit. In the pairwise comparison of apixaban and rivaroxaban (if these were the only 2 treatment options), apixaban has a 61% probability of being more cost effective whereas rivaroxaban has a 39% probability of being more cost effective. Apart from this, the pairwise probabilities that apixaban and rivaroxaban are more cost effective compared to each of the other treatment options are broadly similar.

Table 62: Key outcomes and costs for the cancer population – PE

Strategy	Events[a]			Costs								
	Recurrent VTE	Major bleeds	CRNMB	Treatment	Monitoring	Recurrent VTE	Major bleeding	CRNMB	Other[b]	Total QALYs[c]	Total costs[c]	NMB at £20K/QALY
Apixaban	14.17	3.54	18.58	£801	£158	£234	£152	£47	£19,721	1.402	£19,599	£8,434
Rivaroxaban	10.23	5.36	34.66	£729	£153	£190	£229	£85	£19,641	1.397	£19,521	£8,411
LMWH	12.74	4.99	16.51	£2,441	£123	£218	£166	£42	£19,630	1.395	£21,094	£6,807
LMWH/VKA	17.08	5.32	27.73	£566	£278	£268	£218	£69	£19,537	1.386	£19,440	£8,285
Fondaparinux/VKA[d]	16.90	5.85	23.08	£621	£278	£266	£240	£58	£19,499	1.383	£19,469	£8,199
UFH/VKA	19.29	5.88	15.63	£669	£280	£294	£241	£41	£19,458	1.379	£19,493	£8,097
Dabigatran	16.05	8.04	45.18	£806	£158	£257	£409	£111	£19,340	1.371	£19,598	£7,826
Edoxaban	10.95	9.79	22.79	£730	£153	£198	£418	£57	£19,281	1.368	£19,363	£8,005

(a) Per 100 people in the model
(b) Including cancer treatment costs
(c) Discounted values
(d) No data in the cancer population

Table 63: Deterministic incremental cost-effectiveness results for the cancer population - PE

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Edoxaban	£19,363	1.368			
LMWH/VKA	£19,440	1.386	£78	0.018	£4,340
Fondaparinux/VKA[a]	£19,469	1.383	£29	-0.003	dominated
UFH/VKA	£19,493	1.379	£52	-0.007	dominated
Rivaroxaban	£19,521	1.397	£81	0.010	£7,826
Dabigatran	£19,598	1.371	£77	-0.025	dominated
Apixaban	£19,599	1.402	£78	0.005	£15,378
LMWH	£21,094	1.395	£1,496	-0.007	dominated

(a) No data in the cancer population

Figure 24: Cost-effectiveness plane for the cancer population - PE

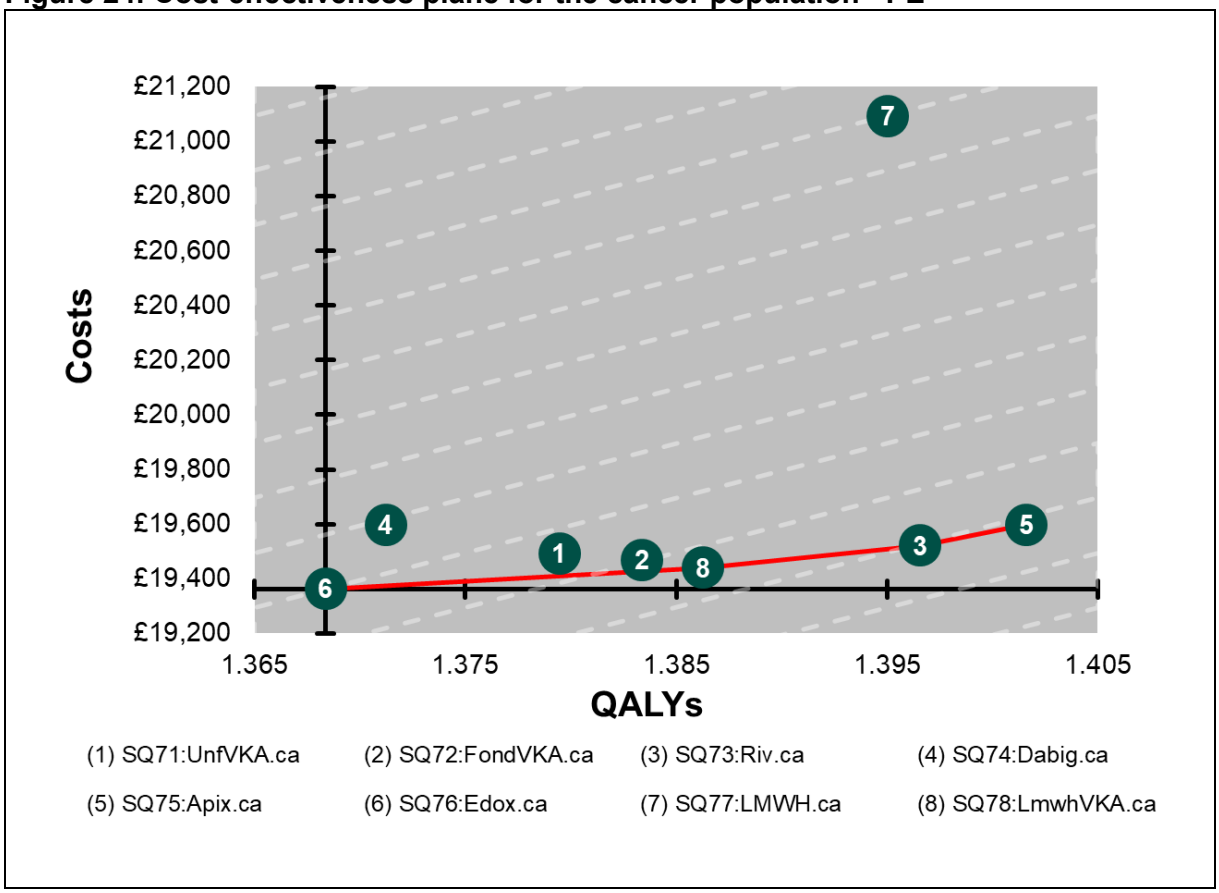


Figure 25: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban vs. rivaroxaban based on incremental net monetary benefit at a threshold of £20,000/QALY - cancer population - PE

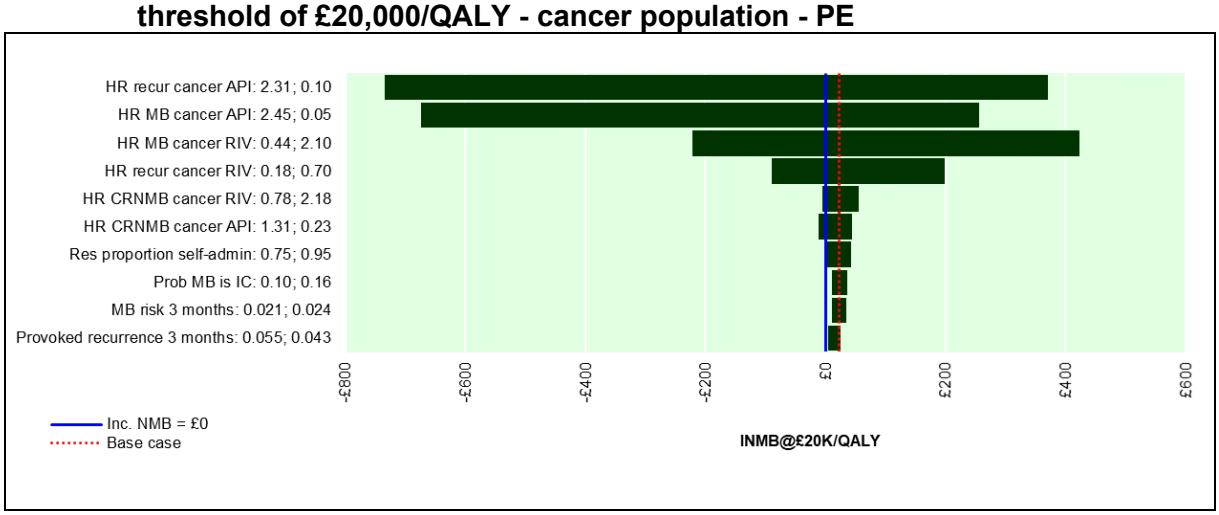
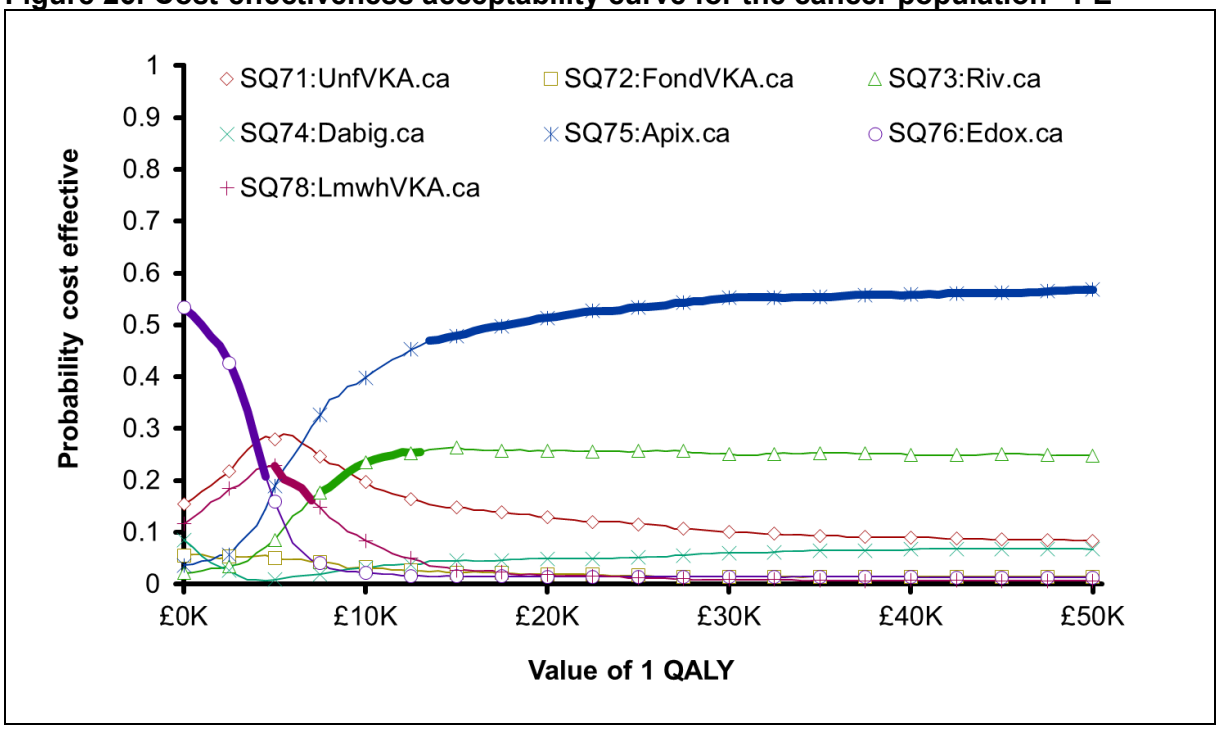


Figure 26: Cost-effectiveness acceptability curve for the cancer population - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Table 64: Pairwise comparison of probability more cost effective for the cancer population – PE

	LMWH/VKA	UNF/VKA	FOND/VKA	RIVAROXABAN	DABIGATRAN	APIXABAN	EDOXABAN	LMWH
LMWH/VKA		0.41	0.26	0.77	0.24	0.76	0.20	0.00
UNF/VKA	0.59		0.51	0.72	0.38	0.75	0.39	0.02
FOND/VKA	0.74	0.49		0.83	0.31	0.80	0.32	0.00
RIVAROXABAN	0.23	0.28	0.17		0.16	0.61	0.10	0.00
DABIGATRAN	0.76	0.62	0.69	0.84		0.83	0.55	0.09
APIXABAN	0.24	0.25	0.20	0.39	0.17		0.13	0.01
EDOXABAN	0.80	0.61	0.68	0.90	0.45	0.87		0.01
LMWH	1.00	0.98	1.00	1.00	0.91	0.99	0.99	

Note: Each cell shows the probability that the intervention in the column is more cost effective than the intervention in the row based on net monetary benefit. Columns with values closer to 1 (more green) indicate the intervention in that column is likely to be more cost effective than other interventions whereas columns with values closer to 0 (more red) indicate that the intervention in that column is likely to be less cost effective than the other interventions

Summary

The summary below is limited to the results of the cost-effectiveness analysis for pharmacological treatments for confirmed DVT and PE. For a complete discussion of the committee's deliberations of both the clinical and cost-effectiveness evidence and how these informed the recommendations, please see the Committee discussion of the evidence contained in evidence review D.

Cost-effectiveness results

We developed a cost-effectiveness model to compare different pharmacological treatments for people with a confirmed diagnosis of DVT or PE. In the base case, the model assumes that people who experienced a provoked VTE receive treatment for 3 months and people who experienced an unprovoked VTE receive long-term (extended) therapy of an indefinite duration but takes into account spontaneous discontinuation over time.

Results of the base-case cost-effectiveness analysis, in which people are assumed to remain on the same treatment in the initial and extended therapy phases, showed that apixaban has a high probability of being cost effective. This is because apixaban achieves the biggest reduction in both major bleeding and CRNMB as well as having a favourable effect on VTE recurrence and as a consequence generates the most QALYs. Compared to LMWH/VKA, apixaban has a higher acquisition cost but these costs are partially offset through fewer monitoring visits and lower resource use associated with managing major bleeding events, resulting in an ICER of £1,802/QALY for DVT index events and £1,660/QALY for PE index events. In probabilistic sensitivity analysis, apixaban has a >95% probability of being cost effective to treat both DVTs and PEs. After apixaban, rivaroxaban ranks next best for the outcome major bleeding and generates the second highest total QALYs and expected net monetary benefit. Total costs for rivaroxaban are approximately £70 higher than apixaban; the cost of the two drugs is similar and the difference in total costs between the drugs is driven by the difference in major bleeding as reported in the NMA.

If the economic analysis is expanded to consider the option of switching from any initial treatment to any extended therapy, the sequence of apixaban followed by VKA standard has the highest net monetary benefit but probabilistic sensitivity analyses for both DVT and PE showed that there is considerable uncertainty around this result. In addition, prior to running the model, the committee noted that this sequence was unlikely to be relevant to the majority of patients in current clinical practice because a person would not normally switch from a DOAC as initial treatment to warfarin as extended therapy unless there were specific clinical concerns. When all sequences of a DOAC followed by a VKA were removed from the decision space, the sequence apixaban followed by aspirin had the highest probability of being cost effective. Although aspirin was not as effective as a VKA or DOACs for the outcome VTE recurrence, it also did not significantly increase the risk of major bleeding compared to placebo and has a low acquisition cost compared to other treatments. The committee agreed that aspirin could improve outcomes and lower costs compared to no treatment in the extended therapy phase but did not consider either of these to be appropriate options for all patients following a VTE, especially those at higher risk of VTE recurrence. When strategies with aspirin, no treatment and switching from a DOAC to a VKA were removed from the decision space, the strategy with the highest probability of being cost effective was to start on apixaban as initial treatment and remain on apixaban in the extended therapy phase. It was noted that the difference in QALYs for all sequences

beginning with the same initial treatment were generally very small. This is because there is greater uncertainty surrounding relative treatment effects in the extended phase and because the choice of treatment in the initial treatment phase (when the baseline risk of both VTE recurrence and bleeding are highest) has a much bigger impact on total QALYs.

In people with cancer and VTE, apixaban generated the most QALYs and had the highest probability of being cost effective for both DVTs and PEs but there was more uncertainty in these results compared to the base-case analysis in the overall VTE population. Rivaroxaban had a slightly lower rate of VTE recurrence and a slightly higher rate of major bleeding compared to apixaban and overall had the second highest expected net monetary benefit. LMWH alone was more costly compared to all other treatments and although it generated more total QALYs than LMWH/VKA, it had a 0% probability of being cost effective for both DVTs and PEs.

There are a number of important limitations to bear in mind when interpreting the results of this economic analysis. At the time of this analysis, there were no head-to-head RCTs comparing DOACs identified in the published literature. Although the committee agreed it was appropriate to undertake NMAs to synthesise direct and indirect evidence and to use these results to inform the economic analysis, the committee expressed concerns about potential heterogeneity of the patient populations in the different DOAC trials (see evidence report D for a more detailed discussion). Some of these concerns related to differences in exclusion criteria regarding bleeding risk, which was shown in a number of one-way sensitivity analyses to be an influential parameter in the economic model. There was a gap in the evidence base for edoxaban, which was the only DOAC that did not have an extended therapy trial and therefore required additional assumptions to be made. For the full sequencing analysis, we compared up to 70 different strategies but in the absence of sequencing trials for all combinations, it was necessary to assume treatment effects were independent in the initial and extended phases.

Comparison with other cost-utility analyses

A systematic review of the published literature identified 7 cost-utility analyses for the treatment and secondary prevention of VTE in the UK context. Four out of 7 of the analyses compared one of the DOACs to LMWH/VKA and were all funded by the manufacturer of the DOAC that was the main intervention of interest in each of the analyses (Bamber 2015, Lanitis 2017, Jugrin 2015, Clay 2018). These models made different assumptions about the duration of treatment, ranging from 3 months to lifelong. In all cases, the authors concluded that the DOAC either dominated LMWH/VKA or was cost effective with an ICER below £20,000/QALY. A fifth cost-utility analysis, funded by the manufacturer of dabigatran, compared dabigatran with rivaroxaban given for 6 months as initial treatment and an additional 6-12 months as extended therapy; the analysis concluded that dabigatran dominated rivaroxaban (Jugrin 2016). The sixth cost-utility analysis, funded by the manufacturer of apixaban, compared apixaban, rivaroxaban, dabigatran and LMWH/VKA given for 6 months and concluded that apixaban dominated the other DOACs and produced an ICER of £2,520/QALY compared to LMWH/VKA (Lanitis 2016).

The only published study (Sterne 2017) that was not funded by a manufacturer undertook NMAs and developed a Markov model to evaluate the cost effectiveness of apixaban, dabigatran, edoxaban, rivaroxaban and LMWH/warfarin for the acute treatment of VTE (6 months of anticoagulation), and the cost effectiveness of apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, aspirin, dabigatran, rivaroxaban, warfarin and “no

pharmacotherapy" for the secondary prevention of VTE (lifelong anticoagulation). In Sterne 2017, separate model structures were built for the extended therapy phase (secondary prevention) and the initial treatment phase (acute treatment) and the decision problems were modelled sequentially, assuming that the most cost-effective comparator in secondary prevention would be used after acute treatment. This approach is in contrast to our analysis, which models all potential combinations of initial treatments and extended therapies to determine what is the most cost-effective sequence overall.

There were a number of other differences between our analysis and the Sterne 2017 model. Firstly, the approach to modelling major ICBs differed. In our model, relative effects of each treatment on major bleeding in the initial and extended phases were obtained from RCTs and an assumption about the proportion of major bleeds that were intracranial was sourced from the literature and assumed to be the same for all treatments in the cost-effectiveness analysis. In the Sterne 2017 analysis, due to a lack of data, the risk of a non-fatal ICB during the initial treatment period was assumed to be the same for all DOACs and was estimated by performing a pairwise meta-analysis versus warfarin. For extended therapy, the risk of ICB in Sterne 2017 was taken from trials conducted in atrial fibrillation patients. Secondly, our model stratified VTE events depending on whether they were provoked or unprovoked in nature and applied different baseline rates for the long-term risk of recurrence (obtained from Prandoni 2007) and different assumptions about treatment duration for provoked (3 months) versus unprovoked events (indefinite, long-term treatment). This means that in the base case, the effectiveness of extended therapy in our model is being applied in people who have experienced unprovoked events, which are associated with a higher baseline risk of recurrence. In the Sterne 2017 model, the baseline risk of recurrence (no pharmacotherapy) during the extended therapy phase appears to be based on the entire Prandoni 2007 cohort, without differentiating between provoked and unprovoked events. Thirdly, our model allowed people to discontinue treatment following a bleeding event or to discontinue treatment spontaneously during the extended therapy phase as there was evidence from the literature that persistence with anticoagulation therapy declined over time. In the base case, the Sterne 2017 model assumed that patients could only discontinue treatment during the extended therapy phase after an ICB. Finally, there were differences in terms of the RCTs that were included in both the initial and extended therapy NMAs that could have impacted the estimates of relative treatment effects. Despite these differences, the Sterne 2017 model reached a similar conclusion to our analysis that apixaban has the highest probability of being cost effective for the initial treatment of VTE. In the extended therapy phase, Sterne 2017 concluded that there was uncertainty about whether aspirin or no pharmacotherapy was most cost effective and the authors did not explore incremental cost-effectiveness results with those strategies removed from the decision space.

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Appendix A – Full list of model parameters

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Baseline population				
Starting age	65.5	0.109	Martinez 2014	Normal
Sex (% male)	44.37%	0.003	Martinez 2014	Beta
Proportion DVTs which are provoked	0.405	0.004	Martinez 2014	Beta
Proportion of PEs which are provoked	0.437	0.004	Martinez 2014	Beta
Proportion of patients treated for longer than 6 months	56.35%	0.037	Prandoni 2002	Beta
VTE recurrence				
Short-term recurrence (first 3 months)				
Provoked VTE	4.44%	0.003	Martinez 2014	Beta
Unprovoked VTE	4.98%	0.003	Martinez 2014	Beta
Long-term recurrence (cumulative)				
Provoked VTE - 6 months	1.65%	0.015	Prandoni 2007	Beta
Provoked VTE - 1 year	4.88%	0.009	Prandoni 2007	Beta
Provoked VTE - 10 years	13.42%	0.027	Prandoni 2007	Beta
Unprovoked VTE - 6 months	3.93%	0.010	Prandoni 2007	Beta
Unprovoked VTE - 1 year	11.09%	0.012	Prandoni 2007	Beta
Unprovoked VTE - 10 years	31.00%	0.035	Prandoni 2007	Beta
Relative effects				
DVT versus PE - hazard ratio	1.44	0.173	Prandoni 2007	Lognormal
Proportion of VTEs which are DVT in Prandoni 2007	0.660	0.012	Prandoni 2007	Beta
DVT versus overall recurrence - hazard ratio	1.116		Calculated	
PE versus overall recurrence - hazard ratio	0.775		Calculated	
Treated versus untreated long term - hazard ratio	0.0978	0.036	NMA	Lognormal
Type of recurrent VTE				
Prob of recurrent VTE being PE in patients with index DVT	24.40%	0.027	Prandoni 2007	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Prob of recurrent VTE being PE in patients with index PE	56.56%	0.045	Prandoni 2007	Beta
Split of provoked/unprovoked recurrent VTE				
Prob of recurrent VTE being provoked in patients with provoked index VTE	41.95%	0.003	Martinez 2014	Beta
Prob of recurrent VTE being provoked in patients with unprovoked index VTE	0.00%		Committee consensus	
Recurrence in cancer patients				
Additional risk of recurrence in patients with cancer - hazard ratio	3.2	0.266	Prandoni 2002	Lognormal
Bleeding				
Short-term major bleeding risk (first 3 months)				
Probability of major bleed	2.24%	0.001	Nieto 2010	Beta
Proportion of major bleeds which are intracranial	13.00%	0.014	Nieto 2010	Beta
Long-term major bleeding risk				
RE-MEDY data				
Long-term bleeding probability (exposure = 473 days)	1.75%	0.003	Schulman 2013	Beta
COMMAND data				
Cumulative major bleeding				
3 months	2.90%	0.004	Yamashita 2018	Beta
3 years	7.20%	0.007	Yamashita 2018	Beta
Cumulative discontinuation				
3 months	5.60%	0.006	Yamashita 2018	Beta
6 months	11.30%	0.009	Yamashita 2018	Beta
1 year	21.40%	0.011	Yamashita 2018	Beta
3 years	33.50%	0.013	Yamashita 2018	Beta
Cumulative major bleeding adjusted for discontinuation				
3 months	2.98%		Calculated	
3 years	8.83%		Calculated	
Clinically relevant non-major bleeding				
RE-MEDY data				
Clinically relevant bleeding	10.18%	0.008	Schulman 2014	Beta
Bleeding in cancer patients				

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Additional risk of bleeding in patients with cancer - hazard ratio	2.2	0.313	Prandoni 2002	Lognormal
Mortality				
Probability of death from model events				
PE - Bach 2016	10.68%	0.016	Bach 2016	Beta
PE - Janata 2002	14.84%	0.021	Janata 2002	Beta
Major intracranial bleed	47.89%	0.059	Nieto 2010	Beta
Major extracranial bleed	21.26%	0.019	Nieto 2010	Beta
Long-term probability of death from CTEPH				
CTEPH treated with pulmonary endarterectomy - 1 year	7.00%	0.013	Delcroix 2016	Beta
CTEPH treated with pulmonary endarterectomy - 3 years	11.00%	0.015	Delcroix 2016	Beta
CTEPH medically managed - 1 year	12.00%	0.020	Delcroix 2016	Beta
CTEPH medically managed - 3 years	30.00%	0.031	Delcroix 2016	Beta
CTEPH treated with balloon angioplasty - 1 year	2.94%	0.020	Mizoguchi 2012	Beta
Age of patients with CTEPH from studies				
Age of patients treated with pulmonary endarterectomy	60	0.821	Delcroix 2016	Gamma
Age of patients medically managed	67	0.965	Delcroix 2016	Gamma
Age of patients treated with balloon angioplasty	60	0.821	Committee consensus	Gamma
Proportion of CTEPH patients receiving each treatment				
Proportion of patients treated with pulmonary endarterectomy	59.50%	0.019	Delcroix 2016	Beta
Proportion of patients ineligible for pulmonary endarterectomy who receive balloon angioplasty	20.00%	0.051	Committee consensus	Beta
Long-term probability of death from intracranial bleed				
Major intracranial bleed - SMR - 1st year	4.73	0.044	Bronnum-Hansen 2001	Lognormal
Major intracranial bleed - SMR - years 1-5	2.31	0.035	Bronnum-Hansen 2002	Lognormal
Mortality – Cancer subgroup				
Cancer mortality (without VTE)				
Prostate cancer				
Localised				
Year 1	2.70%	0.001	Chew 2006	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Year 2	5.80%	0.001	Chew 2006	Beta
Regional				
Year 1	2.60%	0.002	Chew 2006	Beta
Year 2	6.60%	0.003	Chew 2006	Beta
Remote				
Year 1	25.10%	0.007	Chew 2006	Beta
Year 2	45.90%	0.008	Chew 2006	Beta
Breast cancer				
Localised				
Year 1	1.80%	0.001	Chew 2006	Beta
Year 2	4.40%	0.001	Chew 2006	Beta
Regional				
Year 1	4.40%	0.002	Chew 2006	Beta
Year 2	12.40%	0.003	Chew 2006	Beta
Remote				
Year 1	43.60%	0.011	Chew 2006	Beta
Year 2	62.00%	0.011	Chew 2006	Beta
Lung cancer				
Localised				
Year 1	24.60%	0.005	Chew 2006	Beta
Year 2	41.20%	0.006	Chew 2006	Beta
Regional				
Year 1	46.20%	0.005	Chew 2006	Beta
Year 2	68.70%	0.005	Chew 2006	Beta
Remote				
Year 1	81.10%	0.003	Chew 2006	Beta
Year 2	92.70%	0.002	Chew 2006	Beta
Colon/rectum cancer				
Localised				

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Year 1	8.30%	0.003	Chew 2006	Beta
Year 2	13.30%	0.003	Chew 2006	Beta
Regional				
Year 1	14.50%	0.003	Chew 2006	Beta
Year 2	26.30%	0.004	Chew 2006	Beta
Remote				
Year 1	59.90%	0.006	Chew 2006	Beta
Year 2	80.00%	0.005	Chew 2006	Beta
Effect of VTE on mortality (HRs)				
Prostate cancer				
Localised	5.6	0.205	Chew 2006	Lognormal
Regional	4.7	0.459	Chew 2006	Lognormal
Remote	2.8	0.307	Chew 2006	Lognormal
Breast cancer				
Localised	6.6	0.296	Chew 2006	Lognormal
Regional	2.4	0.317	Chew 2006	Lognormal
Remote	1.8	0.247	Chew 2006	Lognormal
Lung cancer				
Localised	3.1	0.194	Chew 2006	Lognormal
Regional	2.9	0.107	Chew 2006	Lognormal
Remote	2.5	0.041	Chew 2006	Lognormal
Colon/rectum cancer				
Localised	3.2	0.285	Chew 2006	Lognormal
Regional	2.2	0.145	Chew 2006	Lognormal
Remote	2	0.088	Chew 2006	Lognormal
Relative proportion of cancer types in patients with VTE and cancer				
Prostate cancer				
Localised	13.85%	0.007	Chew 2006	Lognormal
Regional	3.97%	0.004	Chew 2006	Lognormal

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Remote	1.84%	0.003	Chew 2006	Lognormal
Breast cancer				
Localised	9.23%	0.006	Chew 2006	Lognormal
Regional	7.78%	0.006	Chew 2006	Lognormal
Remote	2.26%	0.003	Chew 2006	Lognormal
Lung cancer				
Localised	3.63%	0.004	Chew 2006	Lognormal
Regional	8.25%	0.006	Chew 2006	Lognormal
Remote	23.25%	0.009	Chew 2006	Lognormal
Colon/rectum cancer				
Localised	4.62%	0.004	Chew 2006	Lognormal
Regional	13.38%	0.007	Chew 2006	Lognormal
Remote	7.95%	0.006	Chew 2006	Lognormal
Adverse events				
CTEPH				
Probability of CTEPH	2.30%	0.004	Ende-Varhaar 2017	Beta
CTEPH in unprovoked versus provoked PE - odds ratio	4.1	0.348	Ende-Varhaar 2017	Lognormal
Proportion of patients with unprovoked PE - "all comer" studies	36.00%	0.014	Ende-Varhaar 2017	Beta
Proportion of patients with unprovoked PE - "survivor" studies	48.00%	0.009	Ende-Varhaar 2017	Beta
PTS				
Probability of severe PTS	0.053030303	0.010	Prandoni 1997	Beta
Probability of moderate/mild PTS	0.172348485	0.016	Prandoni 1997	Beta
Treatment discontinuation - inputs				
Overall discontinuation (cumulative)				
Prob of discontinuation at 3 months	17.00%	0.023	Vora 2016	Beta
Prob of discontinuation at 6 months	38.00%	0.020	Vora 2016	Beta
Prob of discontinuation at 1 year	69.00%	0.046	Vora 2016	Beta
Discontinuation due to events				
Prob due to major intracranial bleed	33.33%	0.167	Committee consensus	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Prob due to major extracranial bleed	33.33%	0.167	Committee consensus	Beta
Prob due to NMCR bleed	10.00%	0.05	Committee consensus	Beta
Relative discontinuation - DOACs versus VKA				
DOAC discontinuation at 2 months	20.00%	0.015	Dronkers 2018	Beta
VKA discontinuation at 2 months	9.10%	0.004	Dronkers 2018	Beta
HR - DOAC versus VKA discontinuation	1.0	0.023	Vora 2016	Beta
Second line treatment weighting				
Relative use of anticoagulants				
LMWH/VKA	47.05%	4.33E-04	PCA June 2018	Dirichlet
Rivaroxaban	22.41%	3.61E-04	PCA June 2018	Dirichlet
Dabigatran	2.64%	1.39E-04	PCA June 2018	Dirichlet
Apixaban	26.22%	3.81E-04	PCA June 2018	Dirichlet
Edoxaban	1.68%	1.11E-04	PCA June 2018	Dirichlet
Relative use of anticoagulants in cancer subgroup				
LMWH/VKA	5.00%		Committee consensus	
Rivaroxaban	6.35%		Committee consensus	
Dabigatran	0.75%		Committee consensus	
Apixaban	7.43%		Committee consensus	
Edoxaban	0.48%		Committee consensus	
LMWH	80.00%		Committee consensus	
Drugs - resource use				
Parenteral treatment - general				
Duration of parenteral treatment				
Days of parenteral treatment - warfarin	10	2.551	Committee consensus	Gamma
Days of parenteral treatment - dabigatran and edoxaban	5	1.020	Committee consensus	Gamma
LMWH				
Self-administration of parenteral treatment				
Proportion of patients who self-administer parenteral treatment	85.00%	0.051	Committee consensus	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Proportion of patients requiring nurse administration who require a district nurse visit	50.00%	0.051	Committee consensus	Beta
Proportion of nurses who are band 4	50.00%	0.051	Committee consensus	Beta
Inefficiency in prescription of parenteral pre-filled syringes				
Proportion of patients who receive a higher dose than required	15.00%	0.051	Committee consensus	Beta
Relative usage of LMWH pre-filled syringes				
Dalteparin	37.48%	0.004	PCA July 2019	Dirichlet
Enoxaparin	39.70%	0.004	PCA July 2019	Dirichlet
Tinzaparin	22.82%	0.003	PCA July 2019	Dirichlet
Patients' weight distribution (for calculating doses of LMWH)				
Mean weight by category				
< 50 kg	45	0.246	Barba 2005	Gamma
50 kg - 100 kg	73	0.120	Barba 2006	Gamma
> 100 kg	112	0.642	Barba 2007	Gamma
Monitoring and routine healthcare visits - resource use				
INR monitoring				
Number of monitoring appointments				
Cycle 1	10	2.041	Committee consensus	Gamma
Cycle 2 onwards	1	0.128	Committee consensus	Gamma
Staff providing monitoring				
Proportion of appointments with band 5 nurse in community	0.9	0.026	Committee consensus	Gamma
Self-monitoring				
Proportion of patients who self-monitor	0	0.026	Assumption	Beta
DOAC monitoring				
Initial appointment				
Length of initial GP appointment (relative to single appointment)	2	0.255	Committee consensus	Gamma
Number of follow-up appointments (annual)				
Normal renal function	1	0.128	Committee consensus	Gamma
CKD <3	2	0.255	Committee consensus	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
CKD 4 or 5	4	0.510	Committee consensus	Gamma
Proportion of patients with CKD				
Normal renal function	37.89%	0.010	Ocak 2013	Dirichlet
CKD <3	61.46%	0.010	Ocak 2013	Dirichlet
CKD 4 or 5	0.65%	0.002	Ocak 2013	Dirichlet
Recurrent VTE - resource use				
Proportion of patients treated as outpatients				
DVT	0.9	0.026	Committee Consensus	Beta
PE	0.2	0.026	Committee Consensus	Beta
Proportion of PE patients receiving CTPA rather than V/Q				
Proportion of CTPA scans	0.8	0.051	Committee Consensus	Beta
Bleeding event – resource use				
Proportion of patients in independent state (GOS >3)	0.41	0.024	Rosand 2004	Beta
Events				
Number of rehab sessions for intracranial bleed	14	2.041	Committee consensus	Gamma
Reversal agent use				
VKA-based regimens				
Proportion of intracranial bleeds treated with vitamin K	100%		Committee Consensus	
Proportion of extracranial bleeds treated with vitamin K	100%		Committee Consensus	
Proportion of intracranial bleeds treated with PCC	90%	0.026	Committee Consensus	Beta
Proportion of extracranial bleeds treated with PCC	50%	0.051	Committee Consensus	Beta
DOACs (except dabigatran)				
Proportion of intracranial bleeds treated with PCC	100%		Committee Consensus	
Proportion of extracranial bleeds treated with PCC	60%	0.051	Committee Consensus	Beta
Dabigatran				
Proportion of intracranial bleeds treated with idarucizumab	100%		Committee Consensus	
Proportion of extracranial bleeds treated with idarucizumab	60%	0.051	Committee Consensus	Beta
PCC product use				
Proportion of PCC usage which is Octaplex	50%	0.051	Assumption	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Proportion of low-dose Octaplex use	50%	0.051	Assumption	Beta
LMWH alone				
Proportion of intracranial bleeds treated with protamine sulfate	100%		Committee Consensus	
Proportion of extracranial bleeds treated with protamine sulfate	60%	0.051	Committee Consensus	Beta
Reversal agent dose				
Vitamin K - ampoules used	1.5	0.255	Assumption	Gamma
Octaplex - INR 2 to 2.5 - 0.9 to 1.3 ml/kg body weight	80		Octaplex prescribing information	
Octaplex - INR 2.5 to 3 - 1.3 to 1.6 ml/kg body weight	105		Octaplex prescribing information	
Beriplex - INR 2.0 to 3.9 - 25 IU/kg body weight	1811		Beriplex prescribing information	
PCC - number of doses	1.25	0.128	Assumption	Gamma
Idarucizumab	2	2.041	Committee consensus	Gamma
Protamine sulfate	1		Maximum dose in BNF	
CTEPH - resource use				
Diagnosis - proportion of patients receiving each resource				
Clinical examination	100%		Committee consensus	
Ventilation/perfusion scan	20%	0.051	Committee consensus	Beta
Referral/outpatient visit	100%		Committee consensus	
CTPA	100%		Committee consensus	
Right heart catheterisation	100%		Committee consensus	
MRI pulmonary angiogram	80%	0.051	Committee consensus	Beta
Surgical procedures				
Number of balloon pulmonary angioplasty procedures required	4		Committee consensus	
Drug use in patients not surgically treated				
Proportion of patients treated with riociguat	100%		Committee consensus	
Drug use in patients treated with pulmonary endarterectomy				
Proportion of patients treated with riociguat	30%	0.051	Committee consensus	Beta
Drug use in patients treated with balloon pulmonary angioplasty				

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Proportion of patients on medication after BPA (1.5-3.5 years)	41% %	0.040	Inami 2017	Beta
Routine healthcare appointments				
First year after diagnosis	5.00	1.020	Committee consensus	Gamma
Second year after diagnosis onwards	3.00	0.510	Committee consensus	Gamma
Proportion of patients within each functional class				
Class II	0.27	0.041	Schweizkert 2014	Beta
Class III	0.59	0.045	Schweizkert 2014	Beta
Class IV	0.14	0.032	Schweizkert 2014	Beta
Unplanned healthcare resource use				
Class II				
Outpatient visits	1.00	0.255	Committee consensus	Gamma
Day ward assessment	1.00	0.255	Committee consensus	Gamma
Hospital admissions	0.00			
Class III				
Outpatient visits	1.00	0.255	Committee consensus	Gamma
Day ward assessment	2.00	0.255	Committee consensus	Gamma
Hospital admissions	0.00			
Class IV				
Outpatient visits	1.00	0.255	Committee consensus	Gamma
Day ward assessment	2.00	0.255	Committee consensus	Gamma
Hospital admissions	4.00	0.510	Committee consensus	Gamma
PTS - resource use				
Ulceration				
10-year probability of developing ulcer	0.048	0.007	Committee consensus	Beta
Nurse visits for compression bandaging	26	1.531	Committee consensus	Gamma
Consultant review visits	2	0.255	Committee consensus	Gamma
No ulceration				
Nurse visits per year	4	0.510	Committee consensus	Gamma
GP visits per year	1	0.128	Committee consensus	Gamma

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Cancer costs				
Lung Cancer				
Progressed (monthly cost)	£912	91.188	NICE Guideline NG122	Gamma
Progression free (monthly cost)	£292	29.241	NICE Guideline NG122	Gamma
Breast Cancer				
Weighted Breast Cancer Cost (15 months)	£12,595	562.510	Hall 2015	Gamma
Colorectal Cancer				
Weighted Colorectal Cancer Cost (15 months)	£12,643	719.401	Hall 2015	Gamma
Prostate cancer				
Weighted Prostate Cancer Cost (15 months)	£3,722	241.076	Hall 2015	Gamma
Utility scores				
Utilities for VTE recurrence				
DVT				
Baseline	0.710	0.006	Cohen 2014	Beta
1 month	0.790	0.010	Cohen 2014	Beta
3 months	0.840	0.009	Cohen 2014	Beta
6 months	0.850	0.009	Cohen 2014	Beta
PE				
Baseline	0.670	0.009	Cohen 2014	Beta
1 month	0.750	0.014	Cohen 2014	Beta
3 months	0.790	0.013	Cohen 2014	Beta
6 months	0.810	0.014	Cohen 2014	Beta
Utilities for bleeding				
Major bleeding				
Current health (baseline)	0.950	0.012	Locadia 2004	Beta
Major intracranial bleed	0.330	0.026	Locadia 2004	Beta
Major extracranial bleed	0.650	0.012	Locadia 2004	Beta
Long-term intracranial bleeding				
Disutility of stroke - all stroke	0.180	0.026	Luengo-Fernandez 2013	Normal

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
CRNMB				
Disutility (muscular bleeding)	0.040	0.015	Locadia 2004	Normal
Utility for CTEPH	0.560	0.017	Meads 2008	Beta
Utilities for PTS				
Severe PTS	0.930	0.009	Lenert 1997	Beta
Moderate PTS	0.980	0.005	Lenert 1997	Beta
Utilities for cancer				
Lung Cancer				
Metastatic NSCLC	0.653	0.022	Nafees 2008	Beta
Breast cancer				
Breast Cancer - Metastatic disease (stable)	0.715	0.050	Lloyd 2006	Beta
Colorectal cancer				
Colorectal cancer - Metastatic disease	0.820	0.019	Farkkila 2012	Beta
Colorectal cancer - Palliative care	0.643	0.051	Farkkila 2012	Beta
Prostate Cancer				
Prostate cancer - metastatic disease	0.740	0.028	Torvinen 2012	Beta
Prostate cancer - Palliative	0.590	0.056	Torvinen 2012	Beta
Duration of disutility				
Event				
DVT (months)	1.00	0.128	Committee consensus	Gamma
PE (months)	1.00	0.128	Committee consensus	Gamma
Major intracranial bleed (months)	3.00	0.255	Committee consensus	Gamma
Major extracranial bleed (months)	1.00	0.128	Committee consensus	Gamma
Non-major clinically relevant bleed (days)	2.00	0.510	Committee consensus	Gamma
Population utility norms				
Men				
54 < age < 65	0.780	0.020	Kind 1999	Beta
64 < age < 75	0.780	0.019	Kind 1999	Beta
74 < age	0.750	0.027	Kind 1999	Beta

Parameter	Point estimate	Standard error	Source	Distribution used in PSA
Women				
54 < age < 65	0.810	0.015	Kind 1999	Kind 1999
64 < age < 75	0.780	0.016	Kind 1999	Kind 1999
74 < age	0.710	0.019	Kind 1999	Kind 1999

Appendix B – Results of additional sensitivity analyses

Sensitivity analyses for key model assumptions

A number of additional sensitivity analyses were run for the main analysis (no switching) to explore the impact of alternative assumptions and data sources for key input parameters. The table below reports deterministic ICERs for apixaban vs. LMWH/VKA and shows that in all cases, apixaban remains cost effective, with all other options dominated.

Parameter varied in sensitivity analysis	ICER (£/QALY)	
	DVT	PE
Base-case analysis results	**£1,802**	**£1,660**
Duration of treatment for unprovoked VTEs (base case is indefinite treatment)		
3 months	dominates	dominates
6 months	dominates	dominates
12 months	£424	£290
Relative treatment effects for DVT and PE		
Using separate treatment effects from DVT and PE NMAs	£3,628	£1,152
Model calibration		
No calibration for mortality and VTE recurrence	£643	£657
Discontinuation rate		
Probability of discontinuation at 6 and 12 months reduced by 20%	£3,829	£3,577
Higher discontinuation on DOACs vs. VKA (HR = 2.339 Dronkers 2018)	dominates	dominates
Baseline bleeding rates		
Alternate sources of baseline bleeding rate: COMMAND study (major bleeding)	£1,549	£1,435

Edoxaban as extended therapy

No RCT evidence was identified to inform the effectiveness of edoxaban as an extended therapy. In the base case analysis of the model, treatment effects for edoxaban in the extended phase were assumed to be the same as the initial phase. We tested an alternative scenario in which the treatment effects for edoxaban on VTE recurrence, major bleeding and CRNMB were set to the average values of the other DOACs in the extended phase. The tables below report incremental cost-effectiveness for DVT and PE assuming no switching. For DVT, edoxaban is now the most expensive strategy; it generates fewer total QALYs than the other DOACs and remains dominated so the overall conclusions remain the same as the base case. For PE, the total costs for edoxaban have increased slightly but the ordering of treatments by cost and the overall conclusions remain the same as the base case.

Deterministic incremental cost-effectiveness results for DVT (effectiveness of edoxaban in the extended therapy phase is set to average of the other DOACs)

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA	£1,445	7.504			
Fondaparinux/VKA	£1,519	7.498	£74	-0.006	dominated
Apixaban	£1,527	7.550	£82	0.045	£1,802
UFH/VKA	£1,586	7.482	£59	-0.067	dominated
Rivaroxaban	£1,601	7.531	£74	-0.019	dominated
Dabigatran	£1,632	7.517	£106	-0.032	dominated
Edoxaban	£1,635	7.515	£109	-0.035	dominated

Deterministic incremental cost-effectiveness results for PE (effectiveness of edoxaban in the extended therapy phase is set to average of the other DOACs)

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA	£2,968	7.401			
Fondaparinux/VKA	£3,039	7.395	£72	-0.006	dominated
Apixaban	£3,044	7.447	£77	0.046	£1,660
UFH/VKA	£3,107	7.375	£63	-0.072	dominated
Rivaroxaban	£3,116	7.427	£71	-0.019	dominated
Edoxaban	£3,147	7.413	£102	-0.034	dominated
Dabigatran	£3,149	7.412	£104	-0.035	dominated

Threshold analyses for apixaban versus rivaroxaban

In the Committee discussion of the evidence (see evidence review D), it was noted that differences in the inclusion and exclusion criteria for the DOAC trials could potentially impact the estimates of relative treatment effects, in particular for major bleeding. In the base-case cost-effectiveness results, apixaban and rivaroxaban were consistently ranked as first and second in terms of net monetary benefit. We undertook threshold analyses to explore the impact of varying (1) the estimate of the relative treatment effect (hazard ratio) for rivaroxaban for major bleeding in the initial treatment phase and (2) the cost of rivaroxaban on the incremental net monetary benefit when comparing apixaban and rivaroxaban.

Parameter	Base case value (95% CrI)	Threshold value[(a)]
DVT		
Hazard ratio for major bleeding rivaroxaban vs. LMWH/VKA	0.548 (0.364 to 0.796)	0.182
Cost rivaroxaban (20mg tablets, 28 per pack)	£50.40 per pack	-95%
PE		
Hazard ratio for major bleeding rivaroxaban vs. LMWH/VKA	0.318 (0.167 to 0.535)	0.170
Cost rivaroxaban (20mg tablets, 28 per pack)	£50.40 per pack	-98%

(a) Value at which the incremental net monetary benefit for apixaban vs. rivaroxaban = £0

In addition, the impact of varying both the hazard ratio for major bleeding for rivaroxaban and the cost of rivaroxaban on incremental net monetary benefit is shown in two-way sensitivity analyses below.

Two-way sensitivity analysis showing incremental net monetary benefit for apixaban versus rivaroxaban (DVT)

% reduction in cost of rivaroxaban	Hazard ratio major bleeding (rivaroxaban versus LMWH/VKA)					
	0.10	0.20	0.30	0.40	0.50	0.60
0%	-£102	£23	£148	£273	£398	£522
-10%	-£151	-£25	£100	£225	£350	£474
-20%	-£199	-£73	£52	£177	£302	£426
-30%	-£247	-£122	£4	£129	£254	£378
-40%	-£296	-£170	-£45	£81	£205	£330
-50%	-£344	-£218	-£93	£32	£157	£282
-60%	-£392	-£266	-£141	-£16	£109	£234
-70%	-£441	-£315	-£189	-£64	£61	£186
-80%	-£489	-£363	-£237	-£112	£13	£138

Note: Each cell shows the incremental net monetary benefit for apixaban versus rivaroxaban when varying both the hazard ratio for rivaroxaban for major bleeding and the cost of rivaroxaban. Negative values (orange cells) indicate scenarios in which rivaroxaban is more cost effective and positive values (blue cells) indicate scenarios in which apixaban is more cost effective.

Two-way sensitivity analysis showing incremental net monetary benefit for apixaban versus rivaroxaban (PE)

% reduction in the cost of rivaroxaban	Hazard ratio major bleeding (rivaroxaban versus LMWH/VKA)					
	0.1	0.20	0.30	0.40	0.50	0.60
0%	-£85	£37	£158	£280	£401	£522
-10%	-£132	-£10	£112	£233	£354	£475
-20%	-£179	-£57	£65	£140	£308	£429
-30%	-£226	-£104	£18	£140	£261	£382
-40%	-£273	-£151	-£29	£93	£214	£335
-50%	-£320	-£198	-£76	£46	£167	£289
-60%	-£367	-£244	-£122	-£1	£121	£242
-70%	-£414	-£291	-£169	-£47	£74	£195
-80%	-£461	-£338	-£216	-£94	£27	£149

Note: Each cell shows the incremental net monetary benefit for apixaban versus rivaroxaban when varying both the hazard ratio for rivaroxaban for major bleeding and the cost of rivaroxaban. Negative values (orange cells) indicate scenarios in which rivaroxaban is more cost effective and positive values (blue cells) indicate scenarios in which apixaban is more cost effective.