National Institute for Health and Care Excellence

Guideline version (Draft)

# 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*

*Evidence review*

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*These evidence reviews were developed by the NICE Guideline Updates Team*

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ISBN:

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# 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.

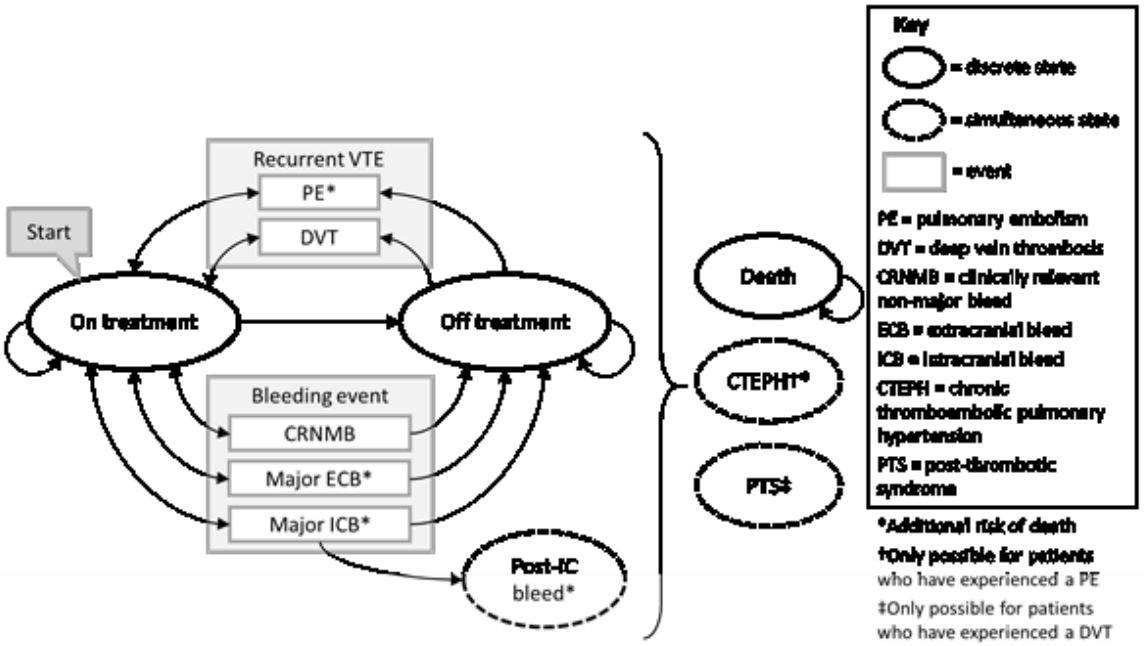
## Model structure

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 or extracranial bleeds.

### *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 |

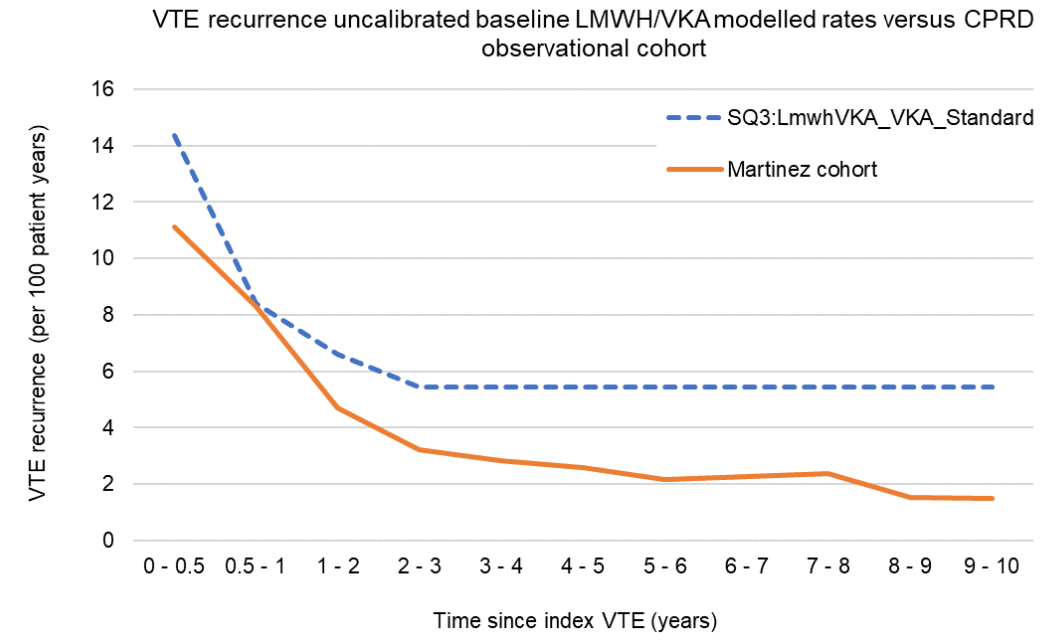
## Model calibration

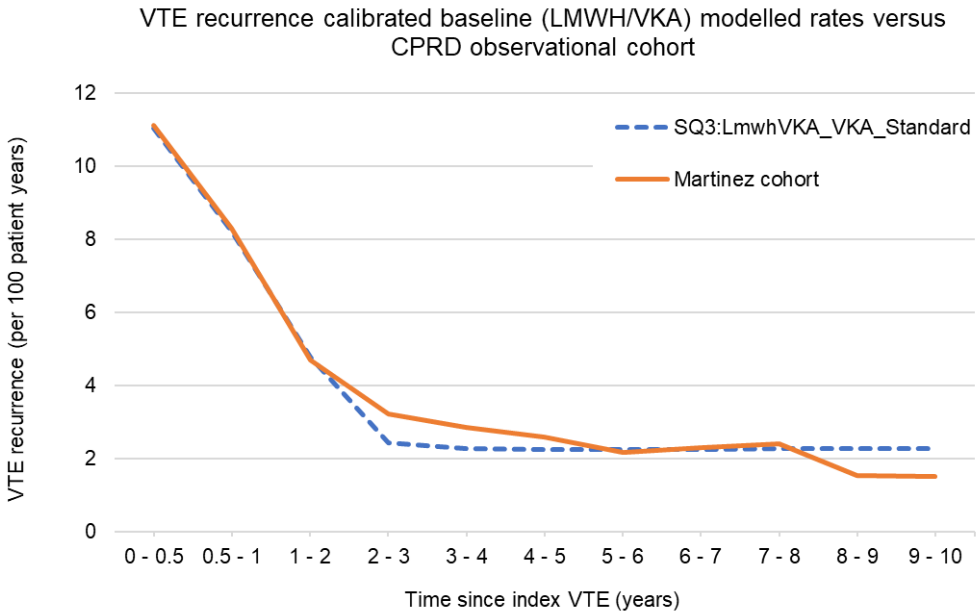
The baseline rates for VTE recurrence and mortality for the reference regimen (LMWH/VKA) that were generated by the model were compared to estimates from the Martinez 2014 CPRD observational cohort study. As there were some differences in the modelled estimates compared to the empirical data, calibration 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**




1

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**

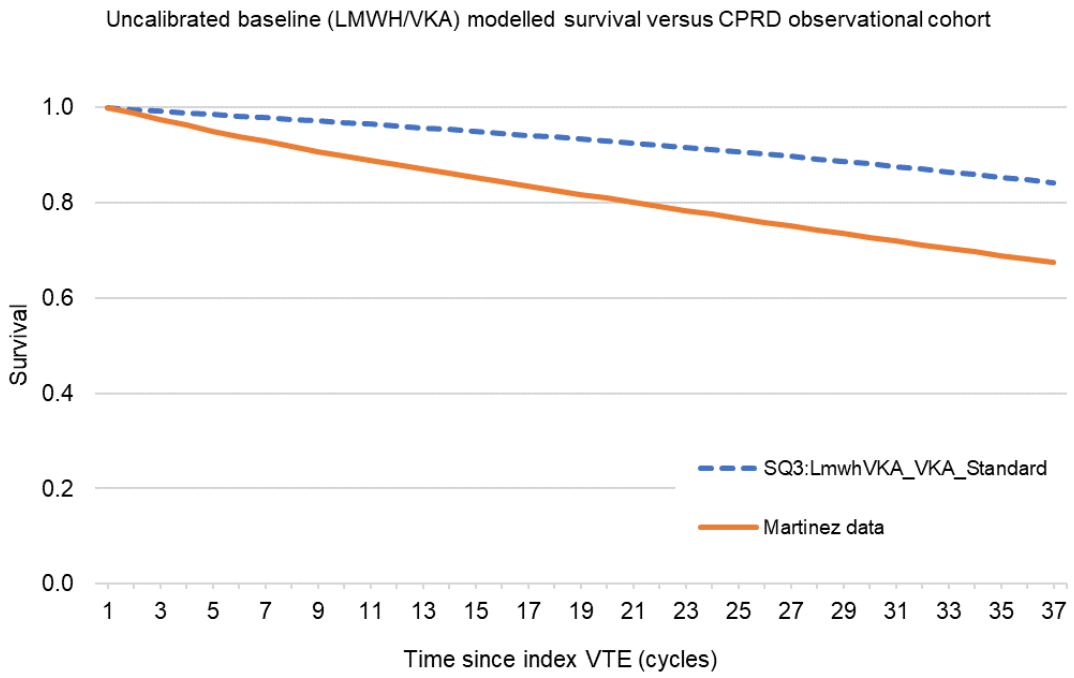
| | Calibration factor |
|---|---|
| Short-term VTE recurrence – 3 months | 0.9053 |
| Long-term VTE recurrence – 6 months | 0.3933 |
| Long-term VTE recurrence – 1 year | 0.7390 |
| Long-term VTE recurrence – 10 years | 0.5962 |

**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**



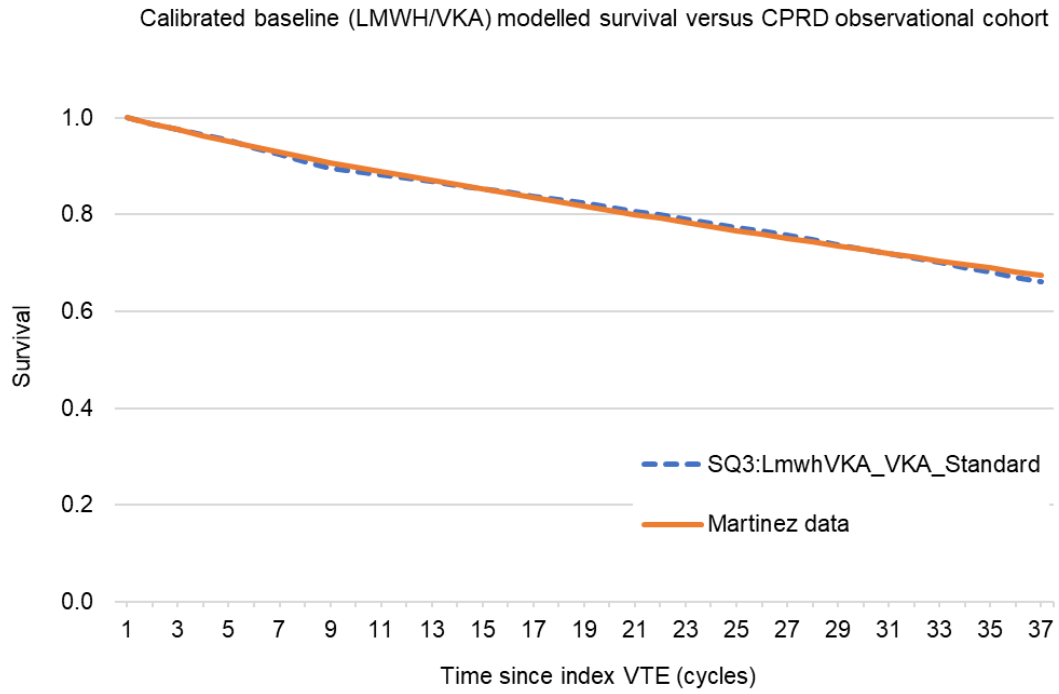



**Table 12: Calibration factors for survival**

| | 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<br>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<br>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**

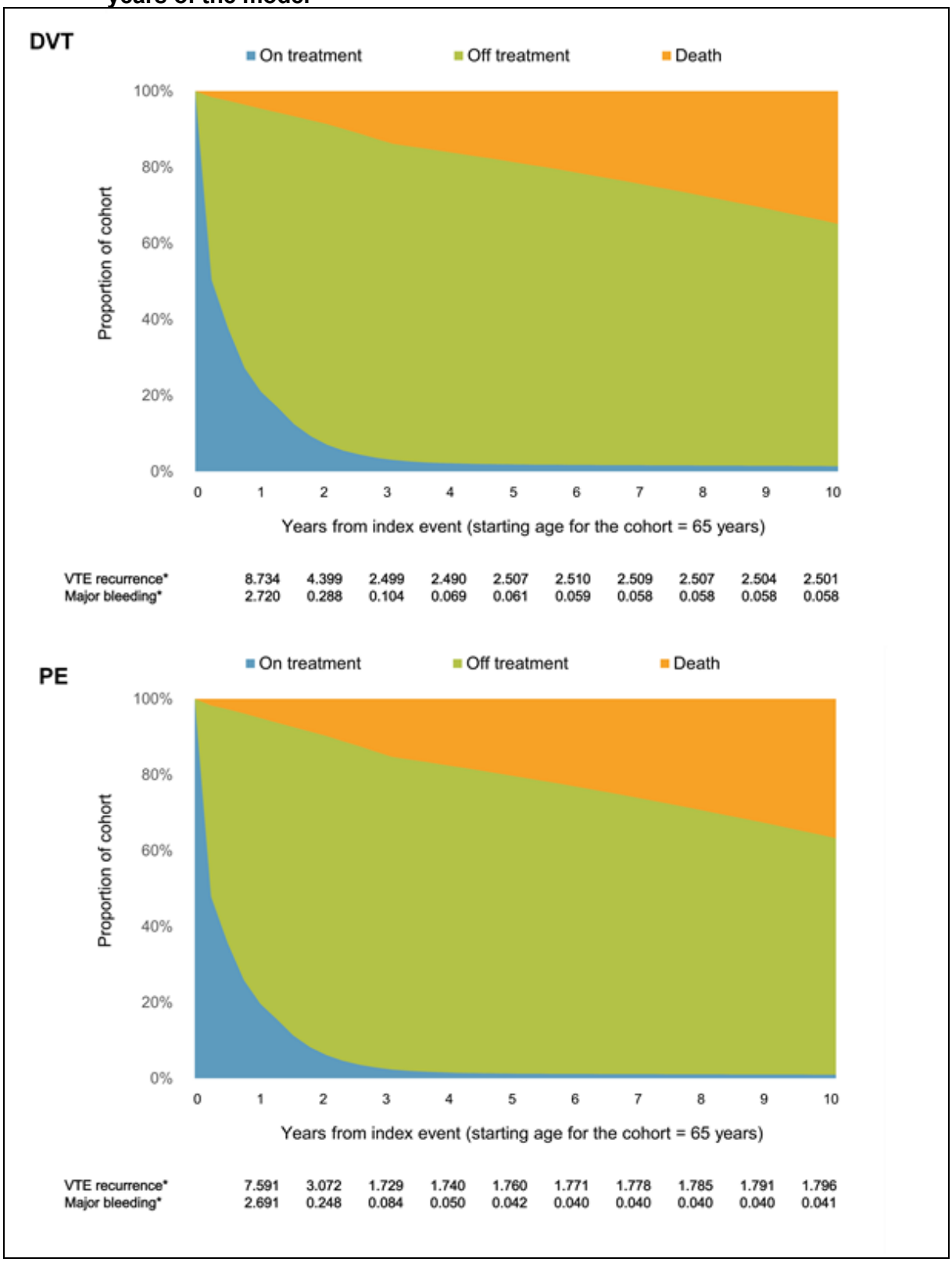
| | Event | Source |
|---|---|---|
| Cycle 1 | Major bleed | Nieto 2013 |
| | CRNMB | Applied HR from Schulman 2013 vs. major bleed |
| Cycle 2 onwards | Major bleed | Schulman 2013 |
| | CRNMB | Applied HR from Schulman 2013 vs. major bleed |

**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 pack[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 | £12.3 |

*(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]<br>Warfarin: 10 mg/day for 2 days and 6 mg/day thereafter | £59.14<br>£5.62 | £64.76 | £39.61 |
| Cycle 2+ | Warfarin: 6 mg/day | - | £5.61 | - |
| **UFH/VKA** | | | | |
| Cycle 1 | UFH 5,000 IU twice daily for 10 days<br>Warfarin: 10 mg/day for 2 days and 6 mg/day thereafter | £74.70<br>£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<br>Warfarin: 10 mg/day for 2 days and 6 mg/day thereafter | £116.53<br>£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]<br>Dabigatran 150 mg twice daily thereafter | £49.37<br>£146.63 | £196.00 | £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]<br>Edoxaban 60 mg/day thereafter | £49.37<br>£150.94 | £1200.31 | £19.66 |
| Cycle 2+ | 60 mg/day | - | £159.69 | - |

| | Dose | Individual drug cost | Total drug cost | Administration cost[(a)] |
|---|---|---|---|---|
| **LMWH (cancer subgroup only)** | | | | |
| 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).

### 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 |
| **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 |
| **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]<br>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 |

*(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 | ICB | ECB | 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 |

| Anticoagulant | ICB | ECB | Average cost per reversal |
|---|---|---|---|
| Rivaroxaban | PCC[(a)] (100%) | PCC[(a)] (60%) | £1280.31 |
| VKA (warfarin) | Vitamin K IV (100%)<br>PCC[(a)] (90%) | Vitamin K IV (100%)<br>PCC[(a)] (50%) | £1152.85 |

*(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 £2,993/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 95%.

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 | 29.254 | 1.346 | 11.363 | £605 | £211 | £280 | £145 | £24 | 7.550 | £1,581 | £149,413 |
| Rivaroxaban | 29.457 | 2.190 | 19.207 | £601 | £211 | £281 | £159 | £39 | 7.531 | £1,601 | £149,010 |
| Dabigatran | 30.270 | 2.675 | 13.582 | £580 | £212 | £287 | £214 | £29 | 7.518 | £1,632 | £148,718 |
| Edoxaban[c] | 28.704 | 2.938 | 16.892 | £591 | £210 | £276 | £221 | £35 | 7.516 | £1,631 | £148,691 |
| LMWH/VKA | 29.557 | 3.360 | 20.051 | £228 | £334 | £282 | £251 | £41 | 7.504 | £1,445 | £148,641 |
| Fondaparinux/VKA | 29.441 | 3.649 | 17.272 | £289 | £333 | £282 | £275 | £36 | 7.498 | £1,519 | £148,445 |
| UFH/VKA | 31.083 | 4.150 | 20.311 | £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 | £1,581 | 7.550 | £136 | 0.045 | £2,993 |
| UFH/VKA | £1,585 | 7.482 | £5 | -0.067 | dominated |
| Rivaroxaban | £1,601 | 7.531 | £20 | -0.019 | dominated |
| Edoxaban[a] | £1,631 | 7.516 | £50 | -0.034 | dominated |
| Dabigatran | £1,632 | 7.518 | £51 | -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**

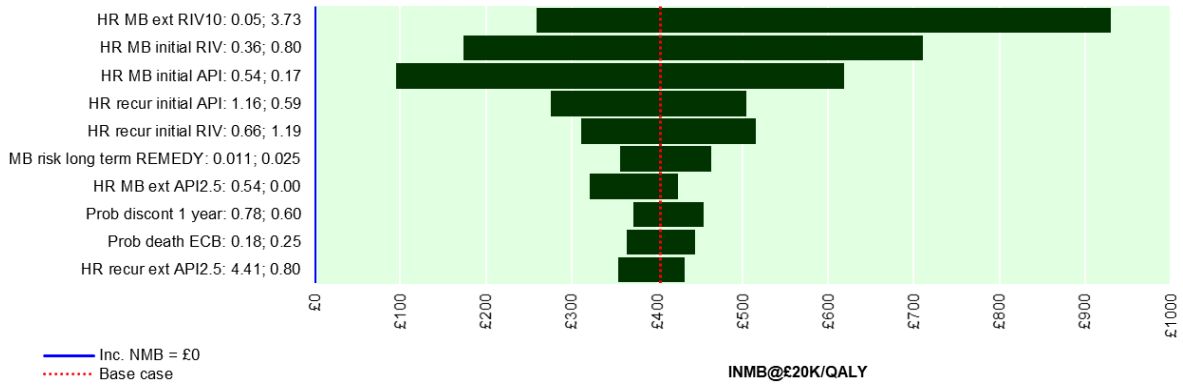
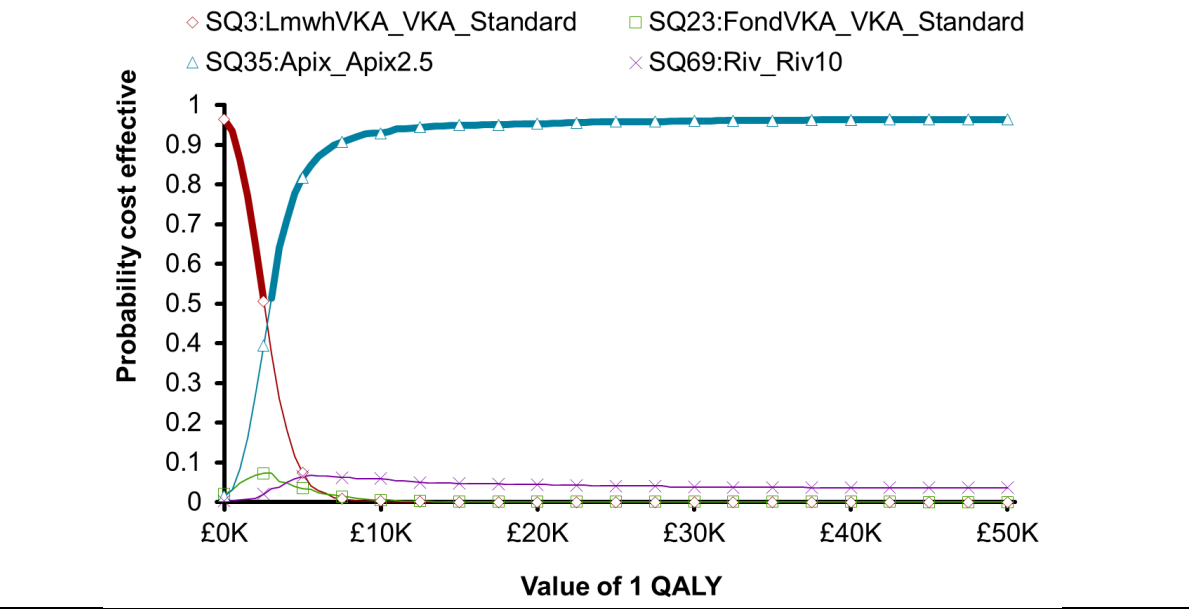



**Figure 6: Cost-effectiveness acceptability curve for the base-case analysis (no treatment switching) – DVT**




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

1

**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 | 0.28 | 1.00 | 0.67 | 0.53 | 0.94 |
| **UNF/VKA** | 0.99 | | 0.88 | 1.00 | 0.98 | 0.89 | 0.99 |
| **FOND/VKA** | 0.72 | 0.12 | | 1.00 | 0.78 | 0.68 | 0.94 |
| **APIXABAN** | 0.00 | 0.00 | 0.00 | | 0.01 | 0.00 | 0.04 |
| **DABIGATRAN** | 0.33 | 0.03 | 0.22 | 0.99 | | 0.38 | 0.82 |
| **EDOXABAN** | 0.47 | 0.11 | 0.32 | 1.00 | 0.62 | | 0.89 |
| **RIVAROXABAN** | 0.06 | 0.02 | 0.06 | 0.96 | 0.18 | 0.11 | |

*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 £2,808/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 93% 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 | 21.215 | 1.177 | 10.142 | £557 | £188 | £264 | £136 | £21 | 7.447 | £3,098 | £145,840 |
| Rivaroxaban | 21.447 | 2.001 | 17.829 | £553 | £188 | £266 | £150 | £36 | 7.427 | £3,116 | £145,434 |
| Edoxaban[c] | 20.824 | 2.737 | 15.564 | £544 | £187 | £260 | £211 | £32 | 7.414 | £3,143 | £145,146 |
| Dabigatran | 22.350 | 2.479 | 12.317 | £533 | £190 | £275 | £204 | £25 | 7.412 | £3,149 | £145,094 |
| LMWH/VKA | 21.707 | 3.150 | 18.656 | £194 | £309 | £269 | £240 | £38 | 7.401 | £2,968 | £145,044 |
| Fondaparinux/VKA | 21.580 | 3.434 | 15.928 | £254 | £309 | £268 | £263 | £32 | 7.395 | £3,039 | £144,859 |
| UFH/VKA | 23.246 | 3.925 | 18.908 | £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 | £3,098 | 7.447 | £130 | 0.046 | £2,808 |
| UFH/VKA | £3,107 | 7.375 | £9 | -0.072 | dominated |
| Rivaroxaban | £3,116 | 7.427 | £18 | -0.019 | dominated |
| Edoxaban[a] | £3,143 | 7.414 | £45 | -0.032 | dominated |
| Dabigatran | £3,149 | 7.412 | £51 | -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**

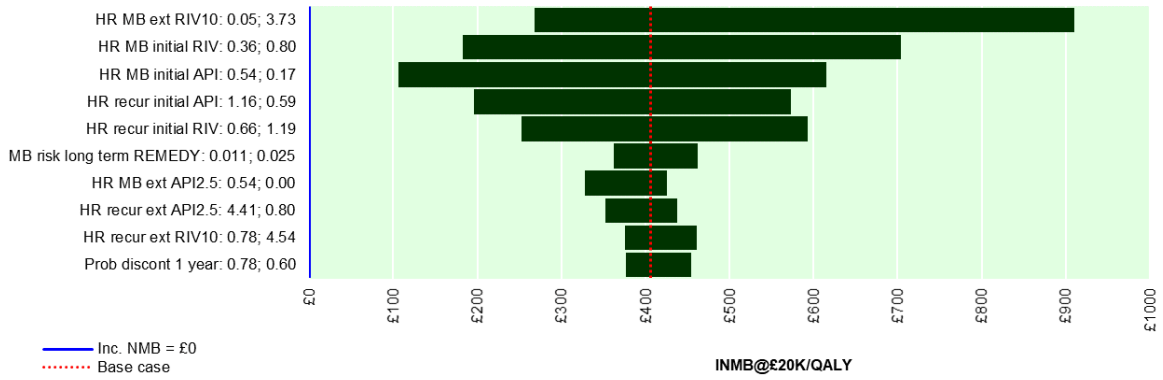
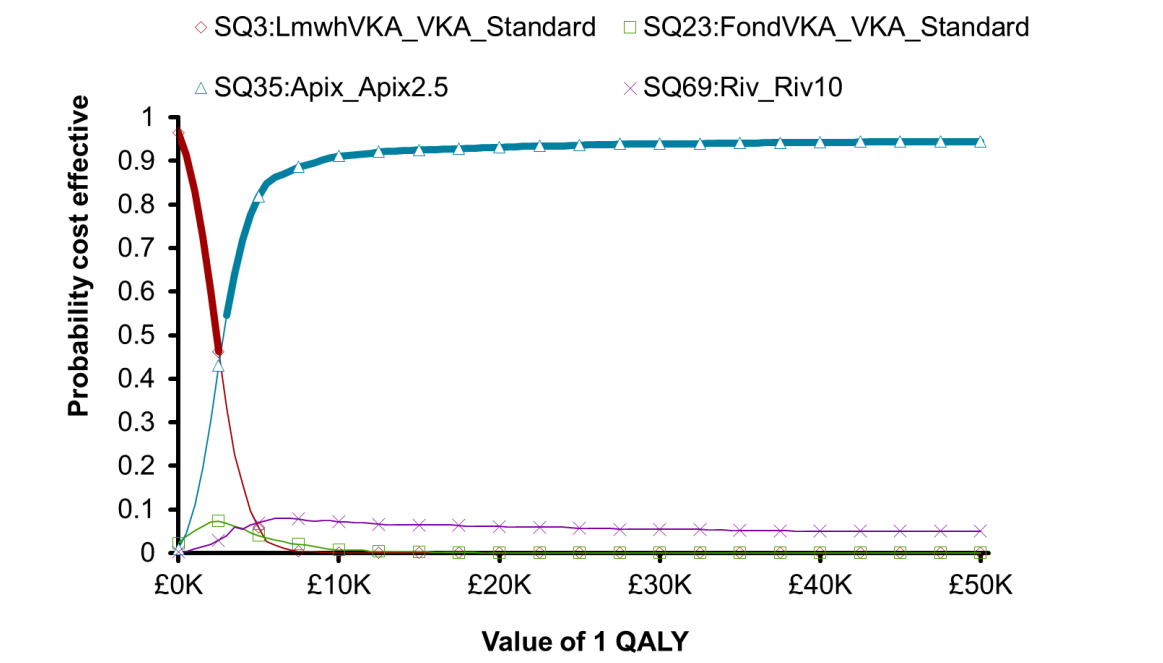



**Figure 8: Cost-effectiveness acceptability curve for the base-case analysis (no treatment switching) - PE**




*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 | 0.29 | 1.00 | 0.63 | 0.57 | 0.94 |
| **UNF/VKA** | 1.00 | | 0.91 | 1.00 | 0.97 | 0.93 | 0.99 |
| **FOND/VKA** | 0.71 | 0.09 | | 1.00 | 0.73 | 0.70 | 0.95 |
| **APIXABAN** | 0.00 | 0.00 | 0.00 | | 0.01 | 0.00 | 0.06 |
| **DABIGATRAN** | 0.37 | 0.03 | 0.27 | 0.99 | | 0.47 | 0.85 |
| **EDOXABAN** | 0.43 | 0.07 | 0.30 | 1.00 | 0.53 | | 0.86 |
| **RIVAROXABAN** | 0.06 | 0.01 | 0.05 | 0.94 | 0.15 | 0.14 | |

*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 | 29.276 | 1.326 | 11.633 | £605 | £211 | £280 | £143 | £25 | 7.550 | £1,580 | £149,421 | 4 |
| SQ35:Apix_Apix2.5 | 29.254 | 1.346 | 11.363 | £605 | £211 | £280 | £145 | £24 | 7.550 | £1,581 | £149,413 | 5 |
| SQ37:Apix_Dabig | 29.044 | 1.523 | 11.973 | £582 | £210 | £278 | £161 | £25 | 7.547 | £1,571 | £149,359 | 7 |
| SQ38:Apix_Edox[c] | 28.896 | 1.626 | 12.559 | £587 | £210 | £277 | £168 | £27 | 7.545 | £1,581 | £149,314 | 8 |
| SQ39:Apix_Riv10 | 29.215 | 1.620 | 12.147 | £593 | £211 | £279 | £168 | £26 | 7.544 | £1,589 | £149,288 | 9 |
| SQ33:Apix_VKA_Stand | 28.935 | 1.683 | 13.015 | £398 | £210 | £277 | £173 | £27 | 7.543 | £1,405 | £149,463 | 1 |
| SQ34:Apix_ASA | 30.632 | 1.450 | 12.309 | £400 | £210 | £290 | £151 | £26 | 7.543 | £1,412 | £149,452 | 3 |
| SQ31:Apix_NoTreat | 31.529 | 1.351 | 11.067 | £400 | £190 | £296 | £143 | £24 | 7.543 | £1,395 | £149,456 | 2 |
| SQ40:Apix_Riv20 | 29.308 | 1.722 | 12.724 | £592 | £211 | £280 | £176 | £27 | 7.541 | £1,598 | £149,230 | 10 |
| SQ32:Apix_VKA_low | 29.637 | 1.677 | 13.076 | £397 | £211 | £282 | £171 | £28 | 7.541 | £1,415 | £149,412 | 6 |
| SQ66:Riv_Apix5 | 29.517 | 1.901 | 18.702 | £613 | £211 | £282 | £135 | £38 | 7.537 | £1,592 | £149,141 | 14 |
| SQ65:Riv_Apix2.5 | 29.495 | 1.921 | 18.437 | £613 | £211 | £282 | £137 | £38 | 7.536 | £1,593 | £149,133 | 15 |
| SQ67:Riv_Dabig | 29.289 | 2.095 | 19.036 | £590 | £211 | £280 | £153 | £39 | 7.533 | £1,583 | £149,080 | 17 |
| SQ68:Riv_Edox[c] | 29.144 | 2.196 | 19.611 | £596 | £210 | £279 | £160 | £40 | 7.531 | £1,592 | £149,035 | 18 |
| SQ69:Riv_Riv10 | 29.457 | 2.190 | 19.207 | £601 | £211 | £281 | £159 | £39 | 7.531 | £1,601 | £149,010 | 19 |
| SQ63:Riv_VKA_Stand | 29.182 | 2.252 | 20.059 | £409 | £210 | £279 | £164 | £41 | 7.530 | £1,420 | £149,181 | 11 |
| SQ64:Riv_ASA | 30.848 | 2.023 | 19.366 | £412 | £211 | £292 | £143 | £40 | 7.530 | £1,427 | £149,170 | 13 |
| SQ61:Riv_NoTreat | 31.729 | 1.926 | 18.146 | £411 | £190 | £298 | £134 | £37 | 7.529 | £1,410 | £149,175 | 12 |
| SQ70:Riv_Riv20 | 29.548 | 2.290 | 19.774 | £600 | £211 | £282 | £167 | £40 | 7.528 | £1,610 | £148,952 | 20 |
| SQ62:Riv_VKA_low | 29.871 | 2.246 | 20.119 | £409 | £211 | £284 | £163 | £41 | 7.528 | £1,429 | £149,132 | 16 |
| SQ56:Edox_Apix5 | 29.077 | 2.642 | 15.982 | £608 | £210 | £279 | £196 | £33 | 7.521 | £1,630 | £148,797 | 27 |
| SQ55:Edox_Apix2.5 | 29.055 | 2.662 | 15.716 | £608 | £210 | £279 | £198 | £33 | 7.521 | £1,631 | £148,789 | 28 |
| SQ46:Dabig_Apix5 | 30.494 | 2.484 | 13.252 | £602 | £213 | £289 | £196 | £28 | 7.521 | £1,641 | £148,778 | 30 |
| SQ45:Dabig_Apix2.5 | 30.473 | 2.503 | 12.990 | £602 | £213 | £289 | £198 | £27 | 7.521 | £1,642 | £148,770 | 31 |
| SQ57:Edox_Dabig | 28.849 | 2.836 | 16.316 | £586 | £210 | £277 | £214 | £34 | 7.518 | £1,621 | £148,736 | 33 |
| SQ47:Dabig_Dabig | 30.270 | 2.675 | 13.582 | £580 | £212 | £287 | £214 | £29 | 7.518 | £1,632 | £148,718 | 34 |
| SQ58:Edox_Edox[c] | 28.704 | 2.938 | 16.892 | £591 | £210 | £276 | £221 | £35 | 7.516 | £1,631 | £148,691 | 35 |
| SQ48:Dabig_Edox[c] | 30.127 | 2.776 | 14.150 | £585 | £212 | £286 | £221 | £30 | 7.516 | £1,641 | £148,674 | 36 |

| 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 | | | | |
| SQ59:Edox_Riv10 | 29.017 | 2.932 | 16.487 | £596 | £210 | £278 | £220 | £34 | 7.515 | £1,639 | £148,666 | 37 |
| SQ49:Dabig_Riv10 | 30.436 | 2.770 | 13.751 | £590 | £213 | £289 | £220 | £29 | 7.515 | £1,650 | £148,649 | 38 |
| SQ53:Edox_VKA_Stand | 28.742 | 2.994 | 17.340 | £404 | £210 | £276 | £225 | £36 | 7.515 | £1,458 | £148,838 | 21 |
| SQ54:Edox_ASA | 30.409 | 2.765 | 16.646 | £407 | £210 | £289 | £204 | £34 | 7.515 | £1,465 | £148,827 | 23 |
| SQ43:Dabig_VKA_Stand | 30.164 | 2.831 | 14.592 | £401 | £212 | £287 | £225 | £31 | 7.514 | £1,471 | £148,818 | 24 |
| SQ44:Dabig_ASA | 31.809 | 2.605 | 13.908 | £403 | £212 | £299 | £204 | £29 | 7.514 | £1,477 | £148,808 | 26 |
| SQ51:Edox_NoTreat | 31.291 | 2.667 | 15.425 | £406 | £189 | £295 | £196 | £32 | 7.514 | £1,448 | £148,831 | 22 |
| SQ41:Dabig_NoTreat | 32.679 | 2.508 | 12.703 | £403 | £192 | £305 | £196 | £27 | 7.514 | £1,461 | £148,812 | 25 |
| SQ60:Edox_Riv20 | 29.108 | 3.032 | 17.054 | £595 | £210 | £279 | £228 | £35 | 7.513 | £1,648 | £148,608 | 42 |
| SQ52:Edox_VKA_low | 29.432 | 2.987 | 17.400 | £404 | £211 | £281 | £224 | £36 | 7.513 | £1,467 | £148,788 | 29 |
| SQ50:Dabig_Riv20 | 30.526 | 2.868 | 14.311 | £589 | £213 | £289 | £228 | £30 | 7.513 | £1,659 | £148,592 | 46 |
| SQ42:Dabig_VKA_low | 30.845 | 2.824 | 14.651 | £400 | £213 | £292 | £224 | £31 | 7.512 | £1,480 | £148,770 | 32 |
| SQ6:LMWH/VKA_Apix5 | 29.886 | 3.015 | 18.718 | £428 | £334 | £285 | £223 | £38 | 7.511 | £1,614 | £148,601 | 43 |
| SQ5:LMWH/VKA_Apix2.5 | 29.865 | 3.035 | 18.458 | £429 | £334 | £285 | £224 | £38 | 7.510 | £1,615 | £148,593 | 44 |
| SQ7:LMWH/VKA_Dabig | 29.663 | 3.205 | 19.046 | £406 | £334 | £283 | £240 | £39 | 7.507 | £1,606 | £148,541 | 47 |
| SQ8:LLMWH/VKA_Edox[c] | 29.520 | 3.305 | 19.611 | £411 | £334 | £282 | £247 | £40 | 7.506 | £1,615 | £148,497 | 48 |
| SQ9:LMWHVKA_Riv10 | 29.827 | 3.299 | 19.214 | £416 | £334 | £284 | £246 | £39 | 7.505 | £1,623 | £148,472 | 49 |
| SQ26:FondVKA_Apix5 | 29.771 | 3.303 | 15.937 | £490 | £334 | £284 | £246 | £33 | 7.505 | £1,689 | £148,404 | 54 |
| SQ25:FondVKA_Apix2.5 | 29.750 | 3.323 | 15.676 | £490 | £334 | £284 | £248 | £33 | 7.504 | £1,690 | £148,397 | 55 |
| SQ3:LMWHVKA_VKA_Stand | 29.557 | 3.360 | 20.051 | £228 | £334 | £282 | £251 | £41 | 7.504 | £1,445 | £148,641 | 39 |
| SQ4:LMWH/VKA_ASA | 31.194 | 3.136 | 19.370 | £230 | £334 | £295 | £230 | £40 | 7.504 | £1,451 | £148,631 | 41 |
| SQ1:LMWH/VKA_NoTreat | 32.060 | 3.039 | 18.172 | £230 | £314 | £301 | £222 | £37 | 7.504 | £1,435 | £148,635 | 40 |
| SQ10:LMWH/VKA_Riv20 | 29.917 | 3.397 | 19.771 | £416 | £334 | £285 | £254 | £40 | 7.502 | £1,632 | £148,416 | 53 |
| SQ2:LMWH/VKA_VKA_low | 30.234 | 3.354 | 20.110 | £227 | £335 | £287 | £250 | £41 | 7.502 | £1,454 | £148,593 | 45 |
| SQ27:FondVKA_Dabig | 29.548 | 3.494 | 16.265 | £468 | £334 | £282 | £264 | £34 | 7.501 | £1,680 | £148,344 | 57 |
| SQ28:FondVKA_Edox[c] | 29.405 | 3.594 | 16.832 | £473 | £333 | £281 | £271 | £35 | 7.499 | £1,690 | £148,300 | 58 |
| SQ29:FondVKA_Riv10 | 29.712 | 3.588 | 16.434 | £478 | £334 | £284 | £270 | £34 | 7.499 | £1,698 | £148,275 | 59 |
| SQ23:FondVKA_VKA_Stand | 29.441 | 3.649 | 17.272 | £289 | £333 | £282 | £275 | £36 | 7.498 | £1,519 | £148,445 | 50 |
| SQ24:FondVKA_ASA | 31.082 | 3.424 | 16.590 | £291 | £334 | £294 | £254 | £34 | 7.498 | £1,526 | £148,434 | 52 |

| 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 | | | | |
| SQ21:FondVKA_NoTreat | 31.949 | 3.327 | 15.389 | £291 | £313 | £300 | £246 | £32 | 7.497 | £1,510 | £148,438 | 51 |
| SQ30:FondVKA_Riv20 | 29.802 | 3.686 | 16.992 | £477 | £334 | £284 | £278 | £35 | 7.496 | £1,707 | £148,219 | 60 |
| SQ22:FondVKA_VKA_low | 30.120 | 3.642 | 17.331 | £288 | £335 | £287 | £273 | £36 | 7.496 | £1,528 | £148,396 | 56 |
| SQ16:UFH/VKA_Apix5 | 31.402 | 3.816 | 19.018 | £486 | £337 | £296 | £286 | £39 | 7.489 | £1,750 | £148,022 | 64 |
| SQ15:UFH/VKA_Apix2.5 | 31.381 | 3.834 | 18.765 | £487 | £337 | £296 | £288 | £38 | 7.488 | £1,751 | £148,015 | 65 |
| SQ17:UFH/VKA_Dabig | 31.185 | 4.000 | 19.336 | £465 | £336 | £295 | £303 | £40 | 7.485 | £1,742 | £147,964 | 67 |
| SQ18:UFH/VKA_Edox[c] | 31.047 | 4.097 | 19.885 | £470 | £336 | £294 | £310 | £41 | 7.484 | £1,751 | £147,921 | 68 |
| SQ19:UFH/VKA_Riv10 | 31.345 | 4.091 | 19.500 | £475 | £337 | £296 | £309 | £40 | 7.483 | £1,759 | £147,897 | 69 |
| SQ13:UFH/VKA_VKA_Stand | 31.083 | 4.150 | 20.311 | £291 | £336 | £294 | £314 | £42 | 7.482 | £1,585 | £148,061 | 61 |
| SQ14:UFH/VKA_ASA | 32.671 | 3.932 | 19.651 | £294 | £336 | £306 | £293 | £40 | 7.482 | £1,592 | £148,051 | 63 |
| SQ11:UFH/VKA_NoTreat | 33.511 | 3.839 | 18.488 | £293 | £317 | £312 | £286 | £38 | 7.482 | £1,576 | £148,055 | 62 |
| SQ20:UFH/VKA_Riv20 | 31.432 | 4.186 | 20.040 | £474 | £337 | £297 | £317 | £41 | 7.480 | £1,767 | £147,842 | 70 |
| SQ12:UFH/VKA_VKA_low | 31.740 | 4.144 | 20.369 | £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 | £1,395 | 7.543 | | | |
| SQ33:Apix_VKA_Standard | £1,405 | 7.543 | £10 | 0.001 | £12,053 |
| SQ61:Riv_NoTreat | £1,410 | 7.529 | £5 | -0.014 | dominated |
| SQ34:Apix_ASA | £1,412 | 7.543 | £7 | 0.000 | dominated |
| SQ32:Apix_VKA_low | £1,415 | 7.541 | £10 | -0.002 | dominated |
| SQ63:Riv_VKA_Standard | £1,420 | 7.530 | £15 | -0.013 | dominated |
| SQ64:Riv_ASA | £1,427 | 7.530 | £21 | -0.014 | dominated |
| SQ62:Riv_VKA_low | £1,429 | 7.528 | £24 | -0.015 | dominated |
| SQ1:LMWH/VKA_NoTreat | £1,435 | 7.504 | £30 | -0.040 | dominated |
| SQ3:LMWH/VKA_VKA_Standard | £1,445 | 7.504 | £40 | -0.039 | dominated |
| SQ51:Edox_NoTreat | £1,448 | 7.514 | £43 | -0.029 | dominated |
| SQ4:LMWH/VKA_ASA | £1,451 | 7.504 | £46 | -0.039 | dominated |
| SQ2:LMWH/VKA_VKA_low | £1,454 | 7.502 | £49 | -0.041 | dominated |
| SQ53:Edox_VKA_Standard | £1,458 | 7.515 | £53 | -0.029 | dominated |
| SQ41:Dabig_NoTreat | £1,461 | 7.514 | £56 | -0.030 | dominated |
| SQ54:Edox_ASA | £1,465 | 7.515 | £59 | -0.029 | dominated |
| SQ52:Edox_VKA_low | £1,467 | 7.513 | £62 | -0.031 | dominated |
| SQ43:Dabig_VKA_Standard | £1,471 | 7.514 | £66 | -0.029 | dominated |
| SQ44:Dabig_ASA | £1,477 | 7.514 | £72 | -0.029 | dominated |
| SQ42:Dabig_VKA_low | £1,480 | 7.512 | £75 | -0.031 | dominated |
| SQ21:FondVKA_NoTreat | £1,510 | 7.497 | £104 | -0.046 | dominated |
| SQ23:FondVKA_VKA_Standard | £1,519 | 7.498 | £114 | -0.045 | dominated |
| SQ24:FondVKA_ASA | £1,526 | 7.498 | £121 | -0.045 | dominated |
| SQ22:FondVKA_VKA_low | £1,528 | 7.496 | £123 | -0.047 | dominated |
| SQ37:Apix_Dabig | £1,571 | 7.547 | £166 | 0.003 | ext. dom. |
| SQ11:UFH/VKA_NoTreat | £1,576 | 7.482 | £171 | -0.062 | dominated |
| SQ36:Apix_Apix5 | £1,580 | 7.550 | £175 | 0.007 | £26,161 |
| SQ38:Apix_Edox[(a)] | £1,581 | 7.545 | £1 | -0.005 | dominated |
| SQ35:Apix_Apix2.5 | £1,581 | 7.550 | £1 | 0.000 | dominated |
| SQ67:Riv_Dabig | £1,583 | 7.533 | £3 | -0.017 | dominated |
| SQ13:UFH/VKA_VKA_Standard | £1,585 | 7.482 | £5 | -0.068 | dominated |
| SQ39:Apix_Riv10 | £1,589 | 7.544 | £9 | -0.006 | dominated |
| SQ66:Riv_Apix5 | £1,592 | 7.537 | £12 | -0.013 | dominated |
| SQ14:UFH/VKA_ASA | £1,592 | 7.482 | £12 | -0.068 | dominated |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| SQ68:Riv_Edox[a] | £1,592 | 7.531 | £12 | -0.019 | dominated |
| SQ65:Riv_Apix2.5 | £1,593 | 7.536 | £13 | -0.014 | dominated |
| SQ12:UFH/VKA_VKA_low | £1,594 | 7.480 | £14 | -0.070 | dominated |
| SQ40:Apix_Riv20 | £1,598 | 7.541 | £18 | -0.009 | dominated |
| SQ69:Riv_Riv10 | £1,601 | 7.531 | £21 | -0.020 | dominated |
| SQ7:LMWH/VKA_Dabig | £1,606 | 7.507 | £26 | -0.043 | dominated |
| SQ70:Riv_Riv20 | £1,610 | 7.528 | £30 | -0.022 | dominated |
| SQ6:LMWH/VKA_Apix5 | £1,614 | 7.511 | £34 | -0.039 | dominated |
| SQ8:LMWH/VKA_Edox[a] | £1,615 | 7.506 | £35 | -0.044 | dominated |
| SQ5:LMWH/VKA_Apix2.5 | £1,615 | 7.510 | £35 | -0.040 | dominated |
| SQ57:Edox_Dabig | £1,621 | 7.518 | £41 | -0.032 | dominated |
| SQ9:LMWH/VKA_Riv10 | £1,623 | 7.505 | £43 | -0.045 | dominated |
| SQ56:Edox_Apix5 | £1,630 | 7.521 | £50 | -0.029 | dominated |
| SQ58:Edox_Edox[a] | £1,631 | 7.516 | £51 | -0.034 | dominated |
| SQ55:Edox_Apix2.5 | £1,631 | 7.521 | £51 | -0.029 | dominated |
| SQ10:LMWH/VKA_Riv20 | £1,632 | 7.502 | £52 | -0.048 | dominated |
| SQ47:Dabig_Dabig | £1,632 | 7.518 | £52 | -0.033 | dominated |
| SQ59:Edox_Riv10 | £1,639 | 7.515 | £59 | -0.035 | dominated |
| SQ46:Dabig_Apix5 | £1,641 | 7.521 | £61 | -0.029 | dominated |
| SQ48:Dabig_Edox[a] | £1,641 | 7.516 | £61 | -0.034 | dominated |
| SQ45:Dabig_Apix2.5 | £1,642 | 7.521 | £62 | -0.029 | dominated |
| SQ60:Edox_Riv20 | £1,648 | 7.513 | £68 | -0.037 | dominated |
| SQ49:Dabig_Riv10 | £1,650 | 7.515 | £70 | -0.035 | dominated |
| SQ50:Dabig_Riv20 | £1,659 | 7.513 | £78 | -0.038 | dominated |
| SQ27:FondVKA_Dabig | £1,680 | 7.501 | £100 | -0.049 | dominated |
| SQ26:FondVKA_Apix5 | £1,689 | 7.505 | £109 | -0.045 | dominated |
| SQ28:FondVKA_Edox[a] | £1,690 | 7.499 | £110 | -0.051 | dominated |
| SQ25:FondVKA_Apix2.5 | £1,690 | 7.504 | £110 | -0.046 | dominated |
| SQ29:FondVKA_Riv10 | £1,698 | 7.499 | £118 | -0.051 | dominated |
| SQ30:FondVKA_Riv20 | £1,707 | 7.496 | £126 | -0.054 | dominated |
| SQ17:UFH/VKA_Dabig | £1,742 | 7.485 | £162 | -0.065 | dominated |
| SQ16:UFH/VKA_Apix5 | £1,750 | 7.489 | £170 | -0.061 | dominated |
| SQ18:UFH/VKA_Edox[a] | £1,751 | 7.484 | £171 | -0.066 | dominated |
| SQ15:UFH/VKA_Apix2.5 | £1,751 | 7.488 | £171 | -0.062 | dominated |
| SQ19:UFH/VKA_Riv10 | £1,759 | 7.483 | £179 | -0.067 | dominated |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| SQ20:UFH/VKA_Riv20 | £1,767 | 7.480 | £187 | -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**

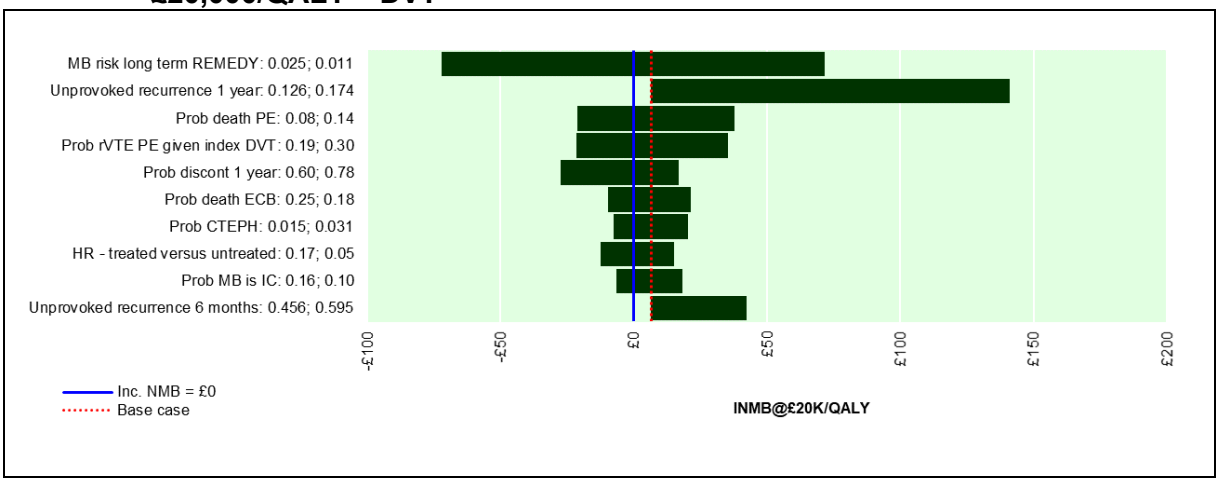
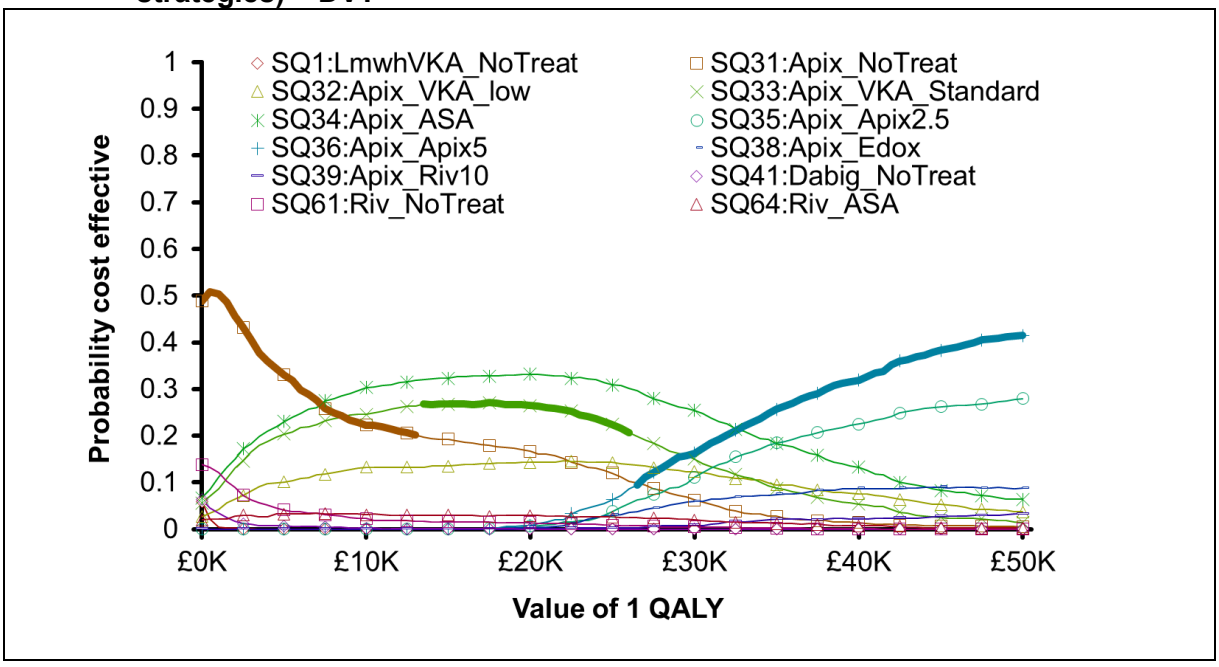



**Figure 10: Cost-effectiveness acceptability curve for the sequencing analysis (all strategies) – DVT**




*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 (33%) but the strategy with the highest net monetary benefit is the sequence apixaban followed by VKA standard, which has a 27% 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 | £1,395 | 7.543 | | | |
| SQ35:Apix_Apix2.5 | £1,581 | 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**

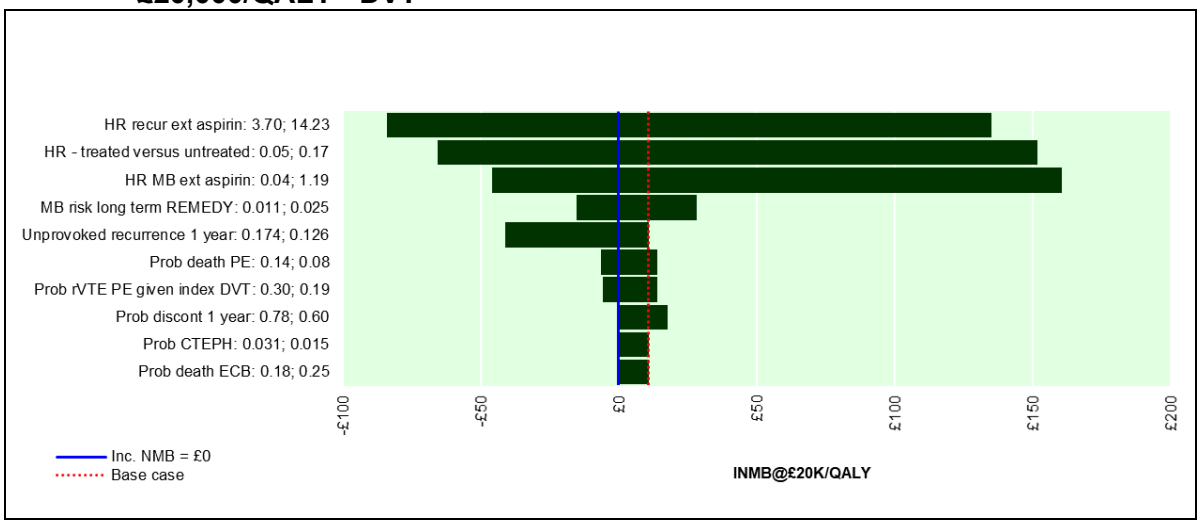
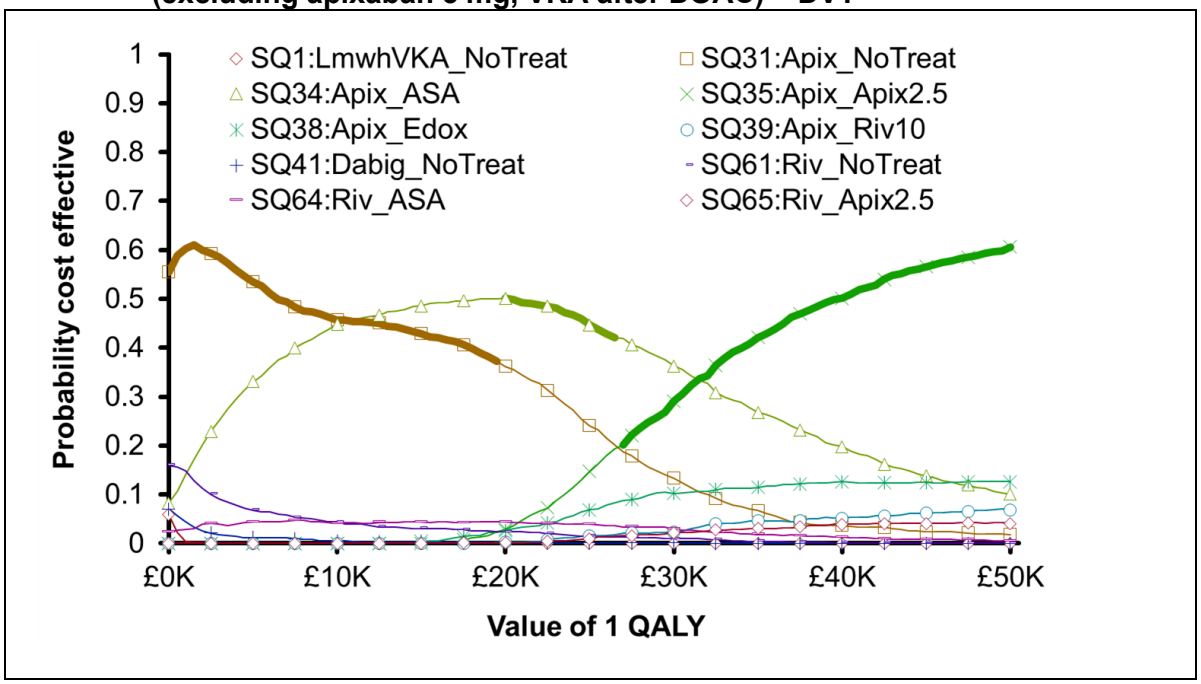



**Figure 12: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) – DVT**




1 *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 61% 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 | £1,571 | 7.547 | £126 | 0.042 | £2,990 |
| SQ35:Apix_Apix2.5 | £1,581 | 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**

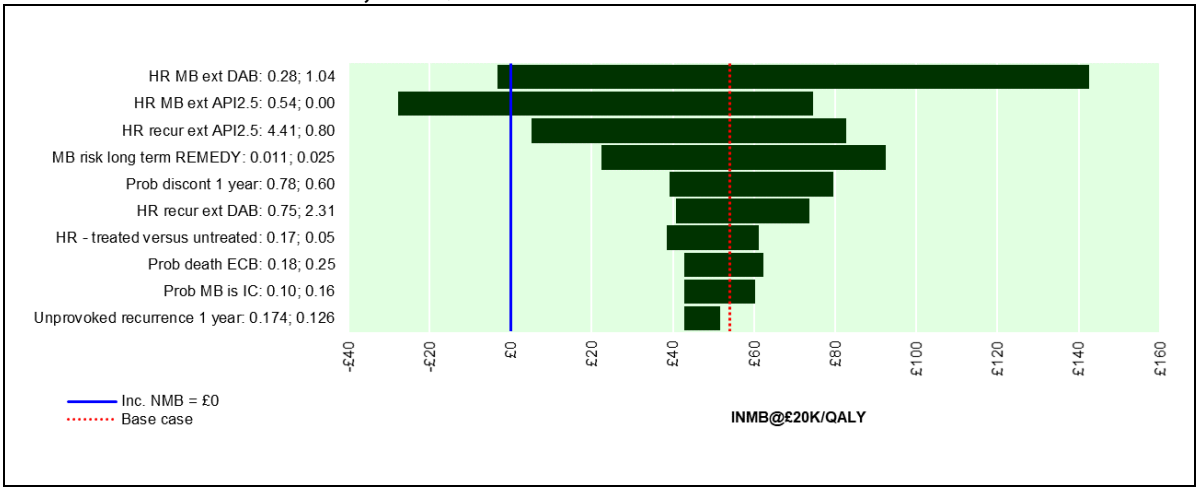
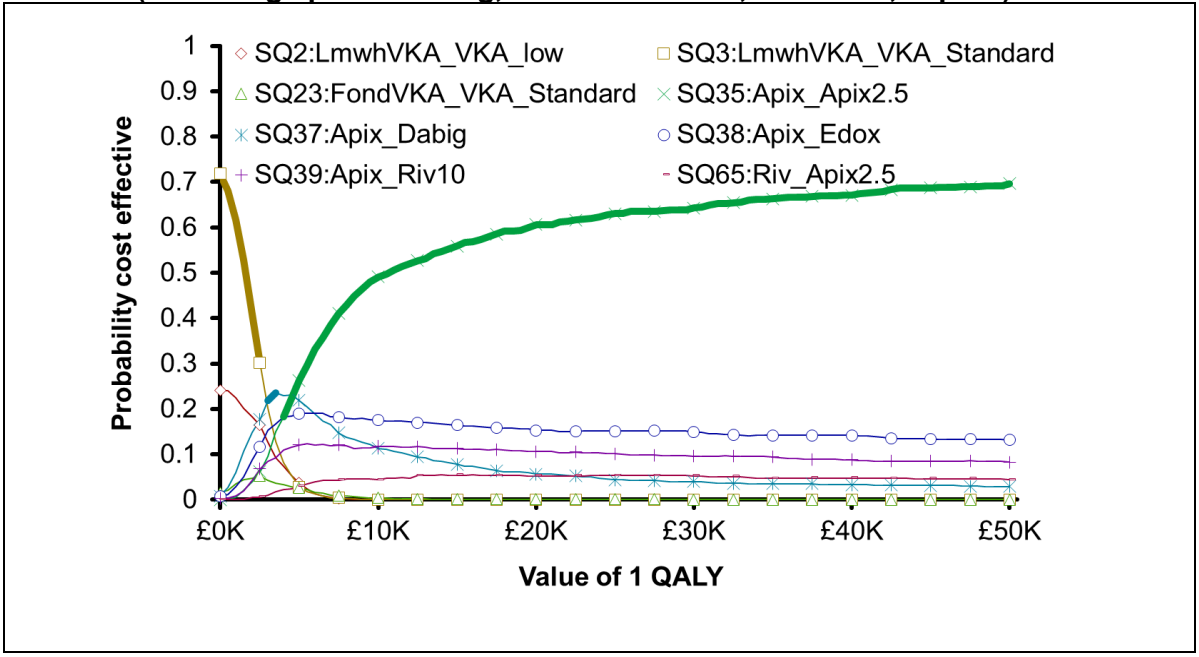



**Figure 14: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, treatment, aspirin) – DVT**




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

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

4 The committee was also interested in understanding what is the most cost-effective extended
5 therapy for a given initial treatment. Therefore, incremental cost-effectiveness results were
6 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 | £1,571 | 7.547 | | | |
| SQ38:Apix_Edox[(a)] | £1,581 | 7.545 | £10 | -0.002 | dominated |
| SQ35:Apix_Apix2.5 | £1,581 | 7.550 | £10 | 0.003 | £3,035 |
| SQ39:Apix_Riv10 | £1,589 | 7.544 | £8 | -0.006 | dominated |
| SQ40:Apix_Riv20 | £1,598 | 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 |
| 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 |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| 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 £4,305/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; no strategy achieves >50% probability of being cost effective over the range of threshold values shown.

**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 | 21.230 | 1.157 | 10.400 | £557 | £188 | £264 | £134 | £22 | 7.447 | £3,097 | £145,847 | 4 |
| SQ35:Apix_Apix2.5 | 21.215 | 1.177 | 10.142 | £557 | £188 | £264 | £136 | £21 | 7.447 | £3,098 | £145,840 | 5 |
| SQ37:Apix_Dabig | 21.072 | 1.348 | 10.735 | £535 | £188 | £262 | £152 | £22 | 7.444 | £3,088 | £145,791 | 7 |
| SQ38:Apix_Edox[c] | 20.970 | 1.448 | 11.303 | £540 | £187 | £261 | £159 | £23 | 7.442 | £3,097 | £145,749 | 8 |
| SQ39:Apix_Riv10 | 21.189 | 1.441 | 10.898 | £545 | £188 | £263 | £158 | £23 | 7.441 | £3,105 | £145,721 | 9 |
| SQ33:Apix_VKA_Standard | 20.997 | 1.503 | 11.739 | £357 | £187 | £261 | £163 | £24 | 7.441 | £2,927 | £145,893 | 1 |
| SQ34:Apix_ASA | 22.174 | 1.270 | 11.007 | £358 | £187 | £273 | £142 | £23 | 7.440 | £2,931 | £145,862 | 2 |
| SQ40:Apix_Riv20 | 21.253 | 1.538 | 11.450 | £544 | £188 | £264 | £166 | £24 | 7.439 | £3,113 | £145,663 | 10 |
| SQ32:Apix_VKA_low | 21.480 | 1.494 | 11.780 | £356 | £188 | £266 | £162 | £24 | 7.439 | £2,935 | £145,836 | 6 |
| SQ31:Apix_NoTreat | 22.807 | 1.175 | 9.813 | £357 | £169 | £279 | £134 | £21 | 7.438 | £2,916 | £145,850 | 3 |
| SQ66:Riv_Apix5 | 21.487 | 1.722 | 17.341 | £565 | £188 | £266 | £126 | £35 | 7.433 | £3,108 | £145,559 | 14 |
| SQ65:Riv_Apix2.5 | 21.473 | 1.742 | 17.087 | £565 | £188 | £266 | £128 | £34 | 7.433 | £3,109 | £145,551 | 15 |
| SQ67:Riv_Dabig | 21.332 | 1.910 | 17.670 | £543 | £188 | £265 | £144 | £35 | 7.430 | £3,099 | £145,503 | 17 |
| SQ68:Riv_Edox[c] | 21.232 | 2.008 | 18.227 | £548 | £188 | £264 | £150 | £37 | 7.429 | £3,108 | £145,462 | 18 |
| SQ69:Riv_Riv10 | 21.447 | 2.001 | 17.829 | £553 | £188 | £266 | £150 | £36 | 7.427 | £3,116 | £145,434 | 19 |
| SQ63:Riv_VKA_Standard | 21.258 | 2.062 | 18.656 | £369 | £188 | £264 | £154 | £37 | 7.427 | £2,941 | £145,603 | 11 |
| SQ64:Riv_ASA | 22.414 | 1.833 | 17.937 | £369 | £187 | £275 | £134 | £36 | 7.426 | £2,945 | £145,573 | 12 |
| SQ70:Riv_Riv20 | 21.510 | 2.097 | 18.372 | £553 | £188 | £267 | £158 | £37 | 7.425 | £3,124 | £145,377 | 20 |
| SQ62:Riv_VKA_low | 21.733 | 2.053 | 18.696 | £367 | £188 | £269 | £153 | £38 | 7.425 | £2,949 | £145,547 | 16 |
| SQ61:Riv_NoTreat | 23.036 | 1.740 | 16.763 | £368 | £170 | £281 | £126 | £34 | 7.425 | £2,930 | £145,561 | 13 |
| SQ56:Edox_Apix5 | 21.079 | 2.451 | 14.677 | £561 | £187 | £263 | £187 | £30 | 7.419 | £3,143 | £145,242 | 24 |
| SQ55:Edox_Apix2.5 | 21.064 | 2.470 | 14.423 | £561 | £187 | £263 | £188 | £29 | 7.419 | £3,143 | £145,235 | 25 |
| SQ57:Edox_Dabig | 20.923 | 2.639 | 15.006 | £539 | £187 | £261 | £204 | £30 | 7.416 | £3,134 | £145,186 | 28 |
| SQ46:Dabig_Apix5 | 22.503 | 2.295 | 11.992 | £555 | £190 | £276 | £187 | £25 | 7.415 | £3,157 | £145,149 | 31 |
| SQ45:Dabig_Apix2.5 | 22.489 | 2.313 | 11.741 | £555 | £190 | £276 | £188 | £24 | 7.415 | £3,158 | £145,142 | 33 |
| SQ58:Edox_Edox[c] | 20.824 | 2.737 | 15.564 | £544 | £187 | £260 | £211 | £32 | 7.414 | £3,143 | £145,146 | 32 |
| SQ59:Edox_Riv10 | 21.039 | 2.730 | 15.166 | £549 | £187 | £262 | £210 | £31 | 7.413 | £3,151 | £145,117 | 35 |
| SQ53:Edox_VKA_Standard | 20.850 | 2.790 | 15.993 | £364 | £187 | £261 | £215 | £32 | 7.413 | £2,975 | £145,287 | 21 |

| | 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)** |
| SQ47:Dabig_Dabig | 22.350 | 2.479 | 12.317 | £533 | £190 | £275 | £204 | £25 | 7.412 | £3,149 | £145,094 | 36 |
| SQ54:Edox_ASA | 22.006 | 2.562 | 15.274 | £365 | £186 | £272 | £194 | £31 | 7.412 | £2,979 | £145,257 | 22 |
| SQ60:Edox_Riv20 | 21.102 | 2.826 | 15.709 | £548 | £187 | £263 | £218 | £32 | 7.411 | £3,159 | £145,061 | 37 |
| SQ52:Edox_VKA_low | 21.325 | 2.782 | 16.033 | £362 | £188 | £265 | £213 | £33 | 7.411 | £2,983 | £145,231 | 26 |
| SQ48:Dabig_Edox[c] | 22.251 | 2.577 | 12.867 | £538 | £189 | £274 | £210 | £26 | 7.411 | £3,157 | £145,054 | 38 |
| SQ51:Edox_NoTreat | 22.629 | 2.469 | 14.099 | £363 | £169 | £278 | £186 | £29 | 7.410 | £2,964 | £145,245 | 23 |
| SQ49:Dabig_Riv10 | 22.464 | 2.570 | 12.474 | £543 | £190 | £276 | £210 | £26 | 7.410 | £3,165 | £145,026 | 40 |
| SQ43:Dabig_VKA_Standard | 22.277 | 2.629 | 13.290 | £360 | £190 | £274 | £214 | £27 | 7.409 | £2,992 | £145,193 | 27 |
| SQ44:Dabig_ASA | 23.418 | 2.404 | 12.580 | £361 | £189 | £285 | £194 | £26 | 7.408 | £2,996 | £145,163 | 29 |
| SQ50:Dabig_Riv20 | 22.526 | 2.664 | 13.010 | £542 | £190 | £276 | £217 | £27 | 7.407 | £3,173 | £144,970 | 46 |
| SQ42:Dabig_VKA_low | 22.746 | 2.621 | 13.330 | £359 | £190 | £278 | £213 | £27 | 7.407 | £3,000 | £145,138 | 34 |
| SQ41:Dabig_NoTreat | 24.032 | 2.312 | 11.422 | £360 | £172 | £291 | £186 | £24 | 7.407 | £2,981 | £145,152 | 30 |
| SQ6:LMWH/VKA_Apix5 | 21.932 | 2.817 | 17.364 | £388 | £309 | £271 | £213 | £35 | 7.407 | £3,132 | £145,000 | 43 |
| SQ5:LMWH/VKA_Apix2.5 | 21.918 | 2.836 | 17.115 | £388 | £309 | £271 | £214 | £34 | 7.406 | £3,133 | £144,993 | 44 |
| SQ7:LMWH/VKA_Dabig | 21.779 | 3.001 | 17.688 | £366 | £309 | £269 | £230 | £36 | 7.403 | £3,123 | £144,946 | 47 |
| SQ8:LMWH/VKA_Edox[c] | 21.682 | 3.098 | 18.235 | £371 | £309 | £268 | £236 | £37 | 7.402 | £3,132 | £144,905 | 48 |
| SQ26:FondVKA_Apix5 | 21.806 | 3.100 | 14.634 | £448 | £309 | £270 | £236 | £30 | 7.401 | £3,204 | £144,815 | 54 |
| SQ9:LMWH/VKA_Riv10 | 21.893 | 3.091 | 17.844 | £376 | £309 | £270 | £236 | £36 | 7.401 | £3,140 | £144,878 | 49 |
| SQ25:FondVKA_Apix2.5 | 21.791 | 3.119 | 14.383 | £448 | £309 | £270 | £237 | £29 | 7.401 | £3,205 | £144,808 | 55 |
| SQ3:LMWH/VKA_VKA_Standard | 21.707 | 3.150 | 18.656 | £194 | £309 | £269 | £240 | £38 | 7.401 | £2,968 | £145,044 | 39 |
| SQ4:LMWH/VKA_ASA | 22.842 | 2.926 | 17.950 | £195 | £308 | £280 | £220 | £36 | 7.399 | £2,971 | £145,015 | 41 |
| SQ10:LMWH/VKA_Riv20 | 21.955 | 3.185 | 18.377 | £375 | £309 | £271 | £243 | £37 | 7.398 | £3,148 | £144,822 | 52 |
| SQ2:LMWH/VKA_VKA_low | 22.174 | 3.142 | 18.695 | £193 | £310 | £273 | £239 | £38 | 7.398 | £2,975 | £144,989 | 45 |
| SQ1:LMWH/VKA_NoTreat | 23.453 | 2.835 | 16.797 | £194 | £291 | £286 | £212 | £34 | 7.398 | £2,956 | £145,003 | 42 |
| SQ27:FondVKA_Dabig | 21.653 | 3.284 | 14.958 | £427 | £309 | £268 | £253 | £30 | 7.398 | £3,195 | £144,760 | 57 |
| SQ28:FondVKA_Edox[c] | 21.555 | 3.381 | 15.506 | £431 | £309 | £267 | £259 | £32 | 7.396 | £3,204 | £144,720 | 58 |
| SQ29:FondVKA_Riv10 | 21.766 | 3.374 | 15.115 | £437 | £309 | £269 | £259 | £31 | 7.395 | £3,212 | £144,692 | 59 |
| SQ23:FondVKA_VKA_Standard | 21.580 | 3.434 | 15.928 | £254 | £309 | £268 | £263 | £32 | 7.395 | £3,039 | £144,859 | 50 |
| SQ24:FondVKA_ASA | 22.718 | 3.209 | 15.221 | £255 | £308 | £279 | £243 | £31 | 7.394 | £3,043 | £144,829 | 51 |
| SQ30:FondVKA_Riv20 | 21.828 | 3.468 | 15.649 | £436 | £309 | £270 | £266 | £32 | 7.393 | £3,220 | £144,636 | 60 |

| | 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)** |
| SQ22:FondVKA_VKA_low | 22.048 | 3.425 | 15.968 | £253 | £310 | £272 | £262 | £32 | 7.393 | £3,047 | £144,804 | 56 |
| SQ21:FondVKA_NoTreat | 23.330 | 3.117 | 14.065 | £254 | £291 | £284 | £235 | £29 | 7.392 | £3,028 | £144,818 | 53 |
| SQ16:UFH/VKA_Apix5 | 23.465 | 3.602 | 17.653 | £445 | £312 | £286 | £275 | £36 | 7.381 | £3,267 | £144,353 | 64 |
| SQ15:UFH/VKA_Apix2.5 | 23.451 | 3.620 | 17.411 | £445 | £312 | £285 | £277 | £35 | 7.381 | £3,268 | £144,346 | 65 |
| SQ17:UFH/VKA_Dabig | 23.316 | 3.780 | 17.967 | £424 | £312 | £284 | £292 | £36 | 7.378 | £3,259 | £144,300 | 67 |
| SQ18:UFH/VKA_Edox[c] | 23.222 | 3.874 | 18.499 | £429 | £311 | £283 | £298 | £37 | 7.376 | £3,267 | £144,260 | 68 |
| SQ19:UFH/VKA_Riv10 | 23.426 | 3.868 | 18.119 | £434 | £312 | £285 | £297 | £37 | 7.375 | £3,275 | £144,233 | 69 |
| SQ13:UFH/VKA_VKA_Standard | 23.246 | 3.925 | 18.908 | £257 | £311 | £284 | £302 | £38 | 7.375 | £3,107 | £144,396 | 61 |
| SQ14:UFH/VKA_ASA | 24.348 | 3.708 | 18.222 | £257 | £311 | £294 | £282 | £37 | 7.374 | £3,110 | £144,367 | 62 |
| SQ20:UFH/VKA_Riv20 | 23.487 | 3.959 | 18.637 | £433 | £312 | £286 | £305 | £38 | 7.373 | £3,283 | £144,179 | 70 |
| SQ12:UFH/VKA_VKA_low | 23.699 | 3.917 | 18.946 | £255 | £312 | £288 | £301 | £38 | 7.373 | £3,114 | £144,342 | 66 |
| SQ11:UFH/VKA_NoTreat | 24.941 | 3.618 | 17.103 | £256 | £294 | £300 | £275 | £35 | 7.373 | £3,096 | £144,356 | 63 |

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

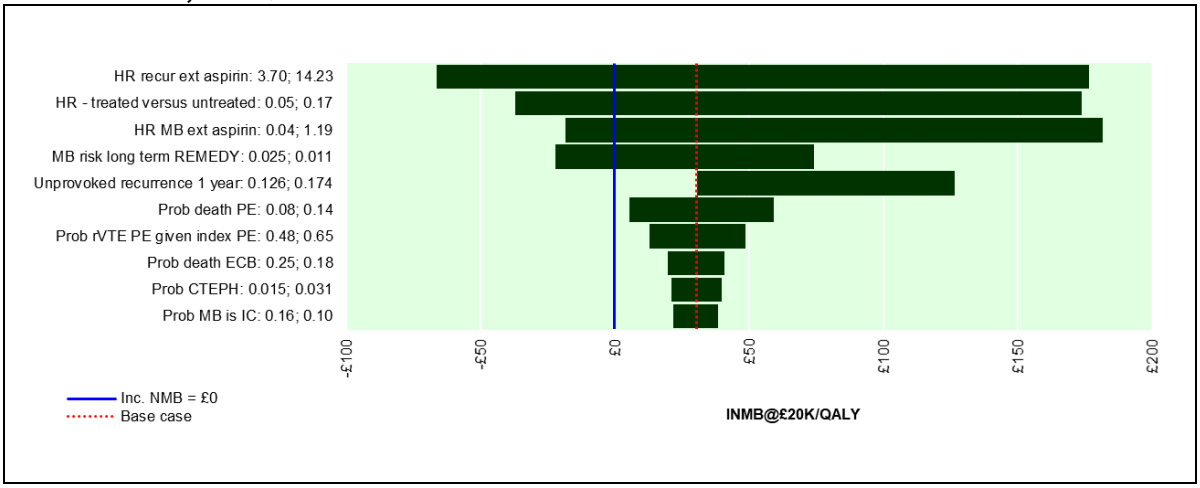
**Table 55: Deterministic incremental cost-effectiveness results for the sequencing analysis (all strategies) - PE**

| | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| Strategy | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| SQ31:Apix_NoTreat | £2,916 | 7.438 | | | |
| SQ33:Apix_VKA_Standard | £2,927 | 7.441 | £12 | 0.003 | £4,305 |
| SQ61:Riv_NoTreat | £2,930 | 7.425 | £2 | -0.016 | dominated |
| SQ34:Apix_ASA | £2,931 | 7.440 | £3 | -0.001 | dominated |
| SQ32:Apix_VKA_low | £2,935 | 7.439 | £8 | -0.002 | dominated |
| SQ63:Riv_VKA_Standard | £2,941 | 7.427 | £14 | -0.014 | dominated |
| SQ64:Riv_ASA | £2,945 | 7.426 | £17 | -0.015 | dominated |
| SQ62:Riv_VKA_low | £2,949 | 7.425 | £21 | -0.016 | dominated |
| SQ1:LmwhVKA_NoTreat | £2,956 | 7.398 | £29 | -0.043 | dominated |
| SQ51:Edox_NoTreat | £2,964 | 7.410 | £37 | -0.031 | dominated |
| SQ3:LmwhVKA_VKA_Standard | £2,968 | 7.401 | £40 | -0.040 | dominated |
| SQ4:LmwhVKA_ASA | £2,971 | 7.399 | £44 | -0.042 | dominated |
| SQ2:LmwhVKA_VKA_low | £2,975 | 7.398 | £48 | -0.043 | dominated |
| SQ53:Edox_VKA_Standard | £2,975 | 7.413 | £48 | -0.028 | dominated |
| SQ54:Edox_ASA | £2,979 | 7.412 | £52 | -0.029 | dominated |
| SQ41:Dabig_NoTreat | £2,981 | 7.407 | £53 | -0.034 | dominated |
| SQ52:Edox_VKA_low | £2,983 | 7.411 | £56 | -0.030 | dominated |
| SQ43:Dabig_VKA_Standard | £2,992 | 7.409 | £65 | -0.032 | dominated |
| SQ44:Dabig_ASA | £2,996 | 7.408 | £68 | -0.033 | dominated |
| SQ42:Dabig_VKA_low | £3,000 | 7.407 | £72 | -0.034 | dominated |
| SQ21:FondVKA_NoTreat | £3,028 | 7.392 | £100 | -0.049 | dominated |
| SQ23:FondVKA_VKA_Standard | £3,039 | 7.395 | £112 | -0.046 | dominated |
| SQ24:FondVKA_ASA | £3,043 | 7.394 | £115 | -0.047 | dominated |
| SQ22:FondVKA_VKA_low | £3,047 | 7.393 | £119 | -0.048 | dominated |
| SQ37:Apix_Dabig | £3,088 | 7.444 | £161 | 0.003 | ext. dom. |
| SQ11:UnfVKA_NoTreat | £3,096 | 7.373 | £168 | -0.068 | dominated |
| SQ36:Apix_Apix5 | £3,097 | 7.447 | £169 | 0.006 | £27,247 |
| SQ38:Apix_Edox | £3,097 | 7.442 | £0 | -0.005 | dominated |
| SQ35:Apix_Apix2.5 | £3,098 | 7.447 | £1 | 0.000 | dominated |
| SQ67:Riv_Dabig | £3,099 | 7.430 | £2 | -0.017 | dominated |
| SQ39:Apix_Riv10 | £3,105 | 7.441 | £8 | -0.006 | dominated |
| SQ13:UnfVKA_VKA_Standard | £3,107 | 7.375 | £10 | -0.072 | dominated |
| SQ66:Riv_Apix5 | £3,108 | 7.433 | £11 | -0.014 | dominated |
| SQ68:Riv_Edox | £3,108 | 7.429 | £11 | -0.019 | dominated |
| SQ65:Riv_Apix2.5 | £3,109 | 7.433 | £12 | -0.014 | dominated |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| SQ14:UnfVKA_ASA | £3,110 | 7.374 | £13 | -0.073 | dominated |
| SQ40:Apix_Riv20 | £3,113 | 7.439 | £16 | -0.008 | dominated |
| SQ12:UnfVKA_VKA_low | £3,114 | 7.373 | £17 | -0.074 | dominated |
| SQ69:Riv_Riv10 | £3,116 | 7.427 | £19 | -0.020 | dominated |
| SQ7:LmwhVKA_Dabig | £3,123 | 7.403 | £26 | -0.044 | dominated |
| SQ70:Riv_Riv20 | £3,124 | 7.425 | £27 | -0.022 | dominated |
| SQ6:LmwhVKA_Apix5 | £3,132 | 7.407 | £35 | -0.041 | dominated |
| SQ8:LmwhVKA_Edox | £3,132 | 7.402 | £35 | -0.045 | dominated |
| SQ5:LmwhVKA_Apix2.5 | £3,133 | 7.406 | £36 | -0.041 | dominated |
| SQ57:Edox_Dabig | £3,134 | 7.416 | £37 | -0.031 | dominated |
| SQ9:LmwhVKA_Riv10 | £3,140 | 7.401 | £43 | -0.046 | dominated |
| SQ56:Edox_Apix5 | £3,143 | 7.419 | £46 | -0.028 | dominated |
| SQ58:Edox_Edox | £3,143 | 7.414 | £46 | -0.033 | dominated |
| SQ55:Edox_Apix2.5 | £3,143 | 7.419 | £46 | -0.028 | dominated |
| SQ10:LmwhVKA_Riv20 | £3,148 | 7.398 | £51 | -0.049 | dominated |
| SQ47:Dabig_Dabig | £3,149 | 7.412 | £52 | -0.035 | dominated |
| SQ59:Edox_Riv10 | £3,151 | 7.413 | £54 | -0.034 | dominated |
| SQ46:Dabig_Apix5 | £3,157 | 7.415 | £60 | -0.032 | dominated |
| SQ48:Dabig_Edox | £3,157 | 7.411 | £60 | -0.037 | dominated |
| SQ45:Dabig_Apix2.5 | £3,158 | 7.415 | £61 | -0.032 | dominated |
| SQ60:Edox_Riv20 | £3,159 | 7.411 | £62 | -0.036 | dominated |
| SQ49:Dabig_Riv10 | £3,165 | 7.410 | £68 | -0.038 | dominated |
| SQ50:Dabig_Riv20 | £3,173 | 7.407 | £76 | -0.040 | dominated |
| SQ27:FondVKA_Dabig | £3,195 | 7.398 | £99 | -0.049 | dominated |
| SQ26:FondVKA_Apix5 | £3,204 | 7.401 | £107 | -0.046 | dominated |
| SQ28:FondVKA_Edox | £3,204 | 7.396 | £107 | -0.051 | dominated |
| SQ25:FondVKA_Apix2.5 | £3,205 | 7.401 | £108 | -0.047 | dominated |
| SQ29:FondVKA_Riv10 | £3,212 | 7.395 | £115 | -0.052 | dominated |
| SQ30:FondVKA_Riv20 | £3,220 | 7.393 | £123 | -0.054 | dominated |
| SQ17:UnfVKA_Dabig | £3,259 | 7.378 | £162 | -0.069 | dominated |
| SQ18:UnfVKA_Edox | £3,267 | 7.376 | £170 | -0.071 | dominated |
| SQ16:UnfVKA_Apix5 | £3,267 | 7.381 | £170 | -0.066 | dominated |
| SQ15:UnfVKA_Apix2.5 | £3,268 | 7.381 | £171 | -0.067 | dominated |
| SQ19:UnfVKA_Riv10 | £3,275 | 7.375 | £178 | -0.072 | dominated |
| SQ20:UnfVKA_Riv20 | £3,283 | 7.373 | £186 | -0.074 | dominated |

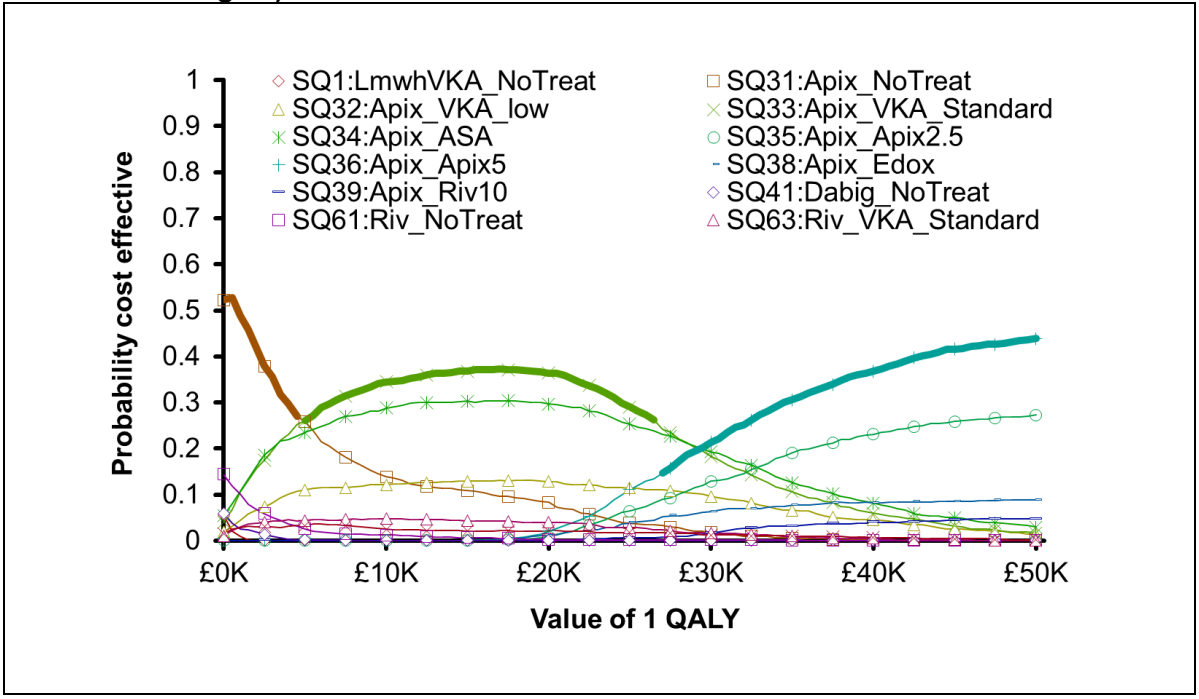
*(a) No extended therapy trial*

**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**




1

**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*

2

## 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 | £2,916 | 7.438 | | | |
| SQ34:Apix_ASA | £2,931 | 7.440 | £15 | 0.001 | £11,143 |
| SQ35:Apix_Apix2.5 | £3,098 | 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**

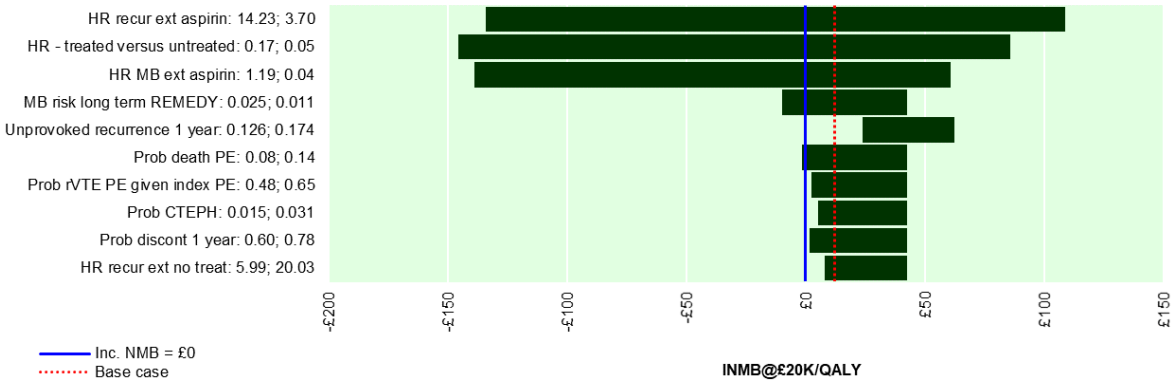
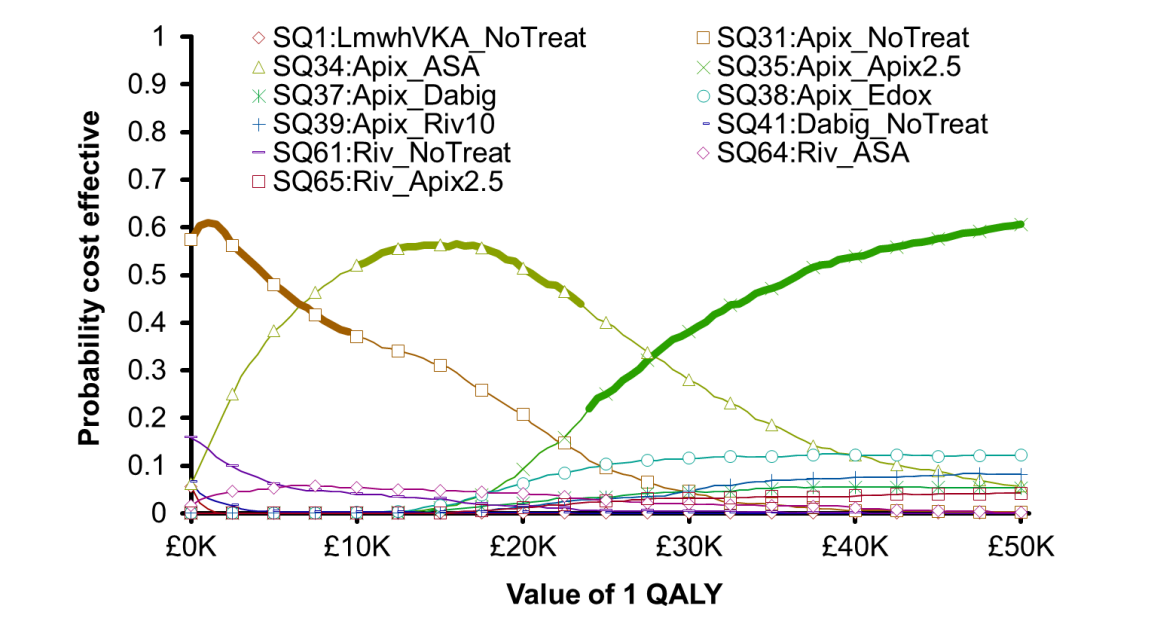



**Figure 18: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, no VKA after DOAC) – PE**




*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 57% 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 | | | |
| SQ37:Apix_Dabig | £3,088 | 7.444 | £120 | 0.043 | £2,776 |
| SQ35:Apix_Apix2.5 | £3,098 | 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**

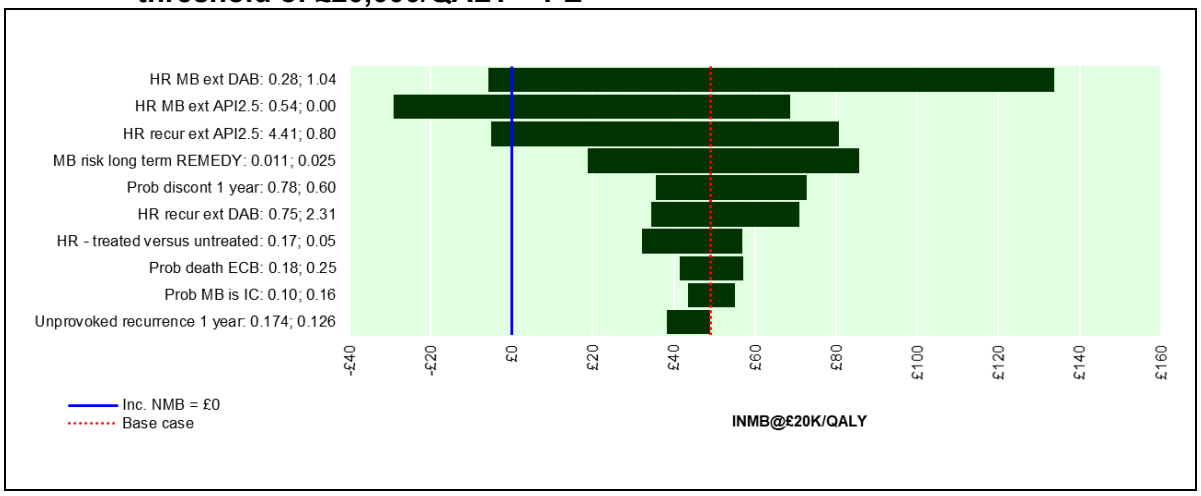
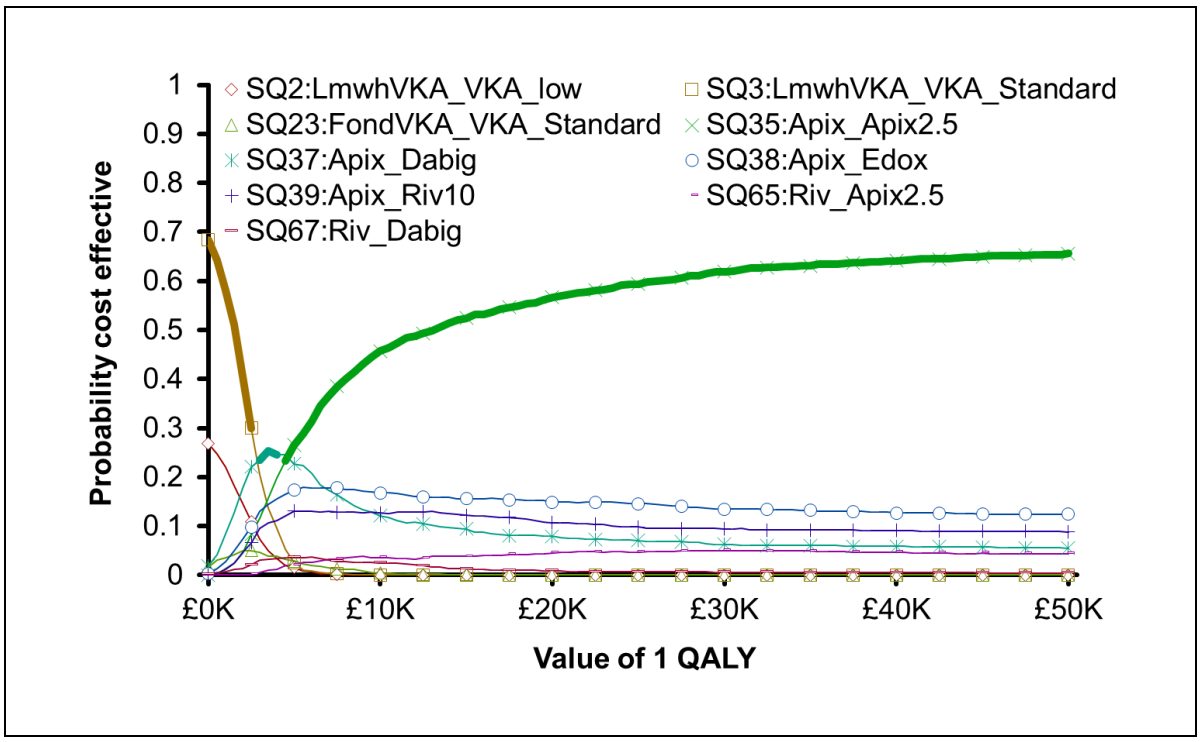


**Figure 20: Cost-effectiveness acceptability curve for the sequencing analysis overall population (excluding apixaban 5 mg, no VKA after DOAC, no treatment, no aspirin) – PE**




*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 | | | |
| SQ2:LmwhVKA_VKA_low | £2,975 | 7.398 | £7 | -£0 | dominated |
| SQ7:LmwhVKA_Dabig | £3,123 | 7.403 | £156 | £0 | ext. dom. |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| 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 | £3,088 | 7.444 | | | |
| SQ38:Apix_Edox[(a)] | £3,097 | 7.442 | £9 | -0.002 | dominated |
| SQ35:Apix_Apix2.5 | £3,098 | 7.447 | £10 | 0.003 | £3,283 |
| SQ39:Apix_Riv10 | £3,105 | 7.441 | £7 | -0.006 | dominated |
| SQ40:Apix_Riv20 | £3,113 | 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 is the most expensive treatment and is more than 3 times the cost of DOACs and more than 4 times the cost of VKA containing 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 3 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. Note that although rivaroxaban produces the second highest net monetary benefit, it is extendedly dominated. Apixaban generates the most QALYs with an ICER of £11,526/QALY compared to LMWH/VKA.

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 52% 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 65% probability of being more cost effective whereas rivaroxaban has a 35% 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 | 17.362 | 3.713 | 20.692 | £759 | £188 | £235 | £173 | £56 | £18,270 | 1.425 | £19,681 | £8,821 |
| LMWH | 15.861 | 5.174 | 18.446 | £2,416 | £304 | £222 | £234 | £50 | £18,154 | 1.418 | £21,381 | £6,972 |
| Rivaroxaban | 13.310 | 5.539 | 36.484 | £712 | £180 | £200 | £249 | £93 | £18,170 | 1.418 | £19,603 | £8,749 |
| LMWH/VKA | 20.357 | 5.524 | 30.220 | £505 | £312 | £262 | £241 | £79 | £18,123 | 1.411 | £19,523 | £8,705 |
| Fondaparinux/VKA[d] | 20.148 | 6.053 | 25.507 | £562 | £312 | £260 | £263 | £68 | £18,087 | 1.408 | £19,551 | £8,616 |
| UFH/VKA | 22.609 | 6.099 | 18.223 | £594 | £317 | £281 | £265 | £51 | £18,066 | 1.406 | £19,575 | £8,544 |
| Dabigatran | 19.272 | 8.262 | 47.714 | £752 | £191 | £253 | £434 | £120 | £17,931 | 1.396 | £19,680 | £8,231 |
| Edoxaban | 13.949 | 10.003 | 24.571 | £707 | £181 | £206 | £440 | £65 | £17,843 | 1.390 | £19,441 | £8,350 |

*(a) Per 100 people in the model*
*(b) Discounted values*
*(c) Includes cancer treatment costs*
*(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 | £19,441 | 1.390 | | | |
| LMWH/VKA | £19,523 | 1.411 | £81 | 0.022 | £3,725 |
| Fondaparinux/VKA[a] | £19,551 | 1.408 | £29 | -0.003 | dominated |
| UFH/VKA | £19,575 | 1.406 | £52 | -0.005 | dominated |
| Rivaroxaban | £19,603 | 1.418 | £81 | 0.006 | ext. dom. |
| Dabigatran | £19,680 | 1.396 | £157 | -0.016 | dominated |
| Apixaban | £19,681 | 1.425 | £158 | 0.014 | £11,526 |
| LMWH | £21,381 | 1.418 | £1,700 | -0.008 | dominated |

*(a) No data in the cancer population*

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

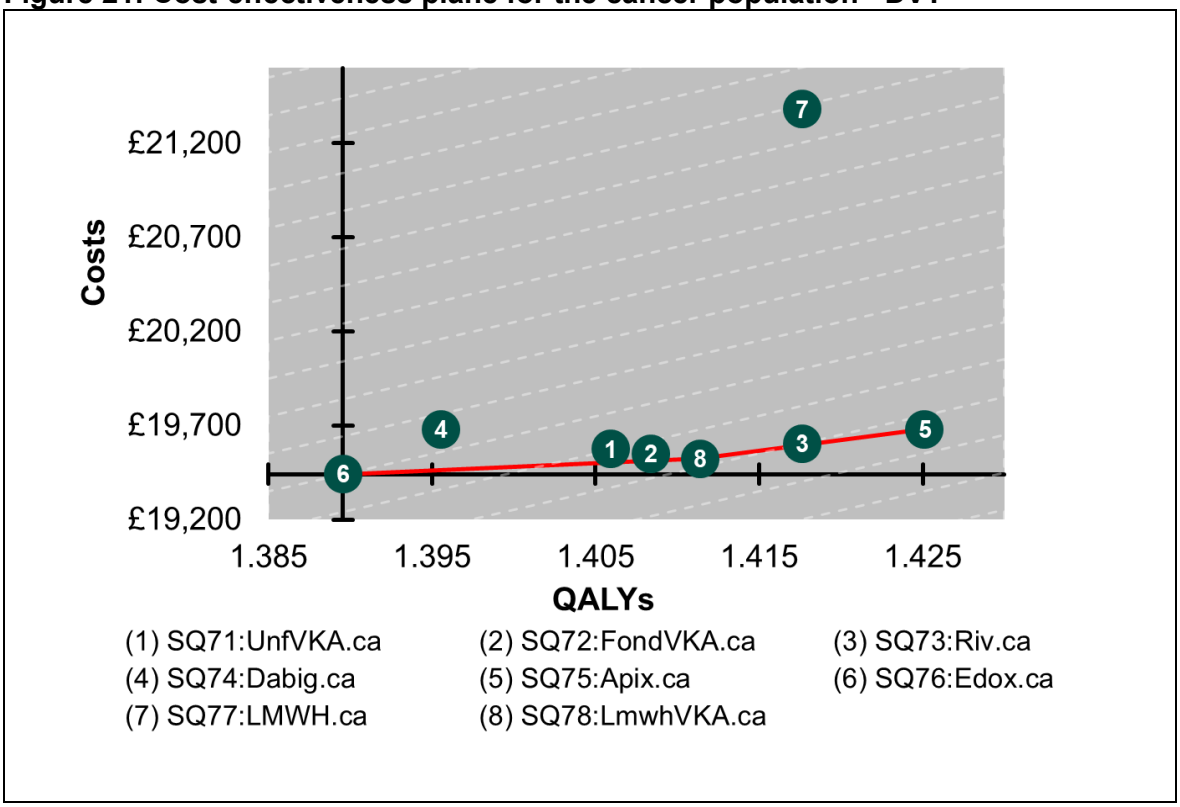



**Figure 22: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban vs. rivaroxaban based on incremental net monetary benefit at a threshold of £20,000/QALY in the cancer population - DVT**

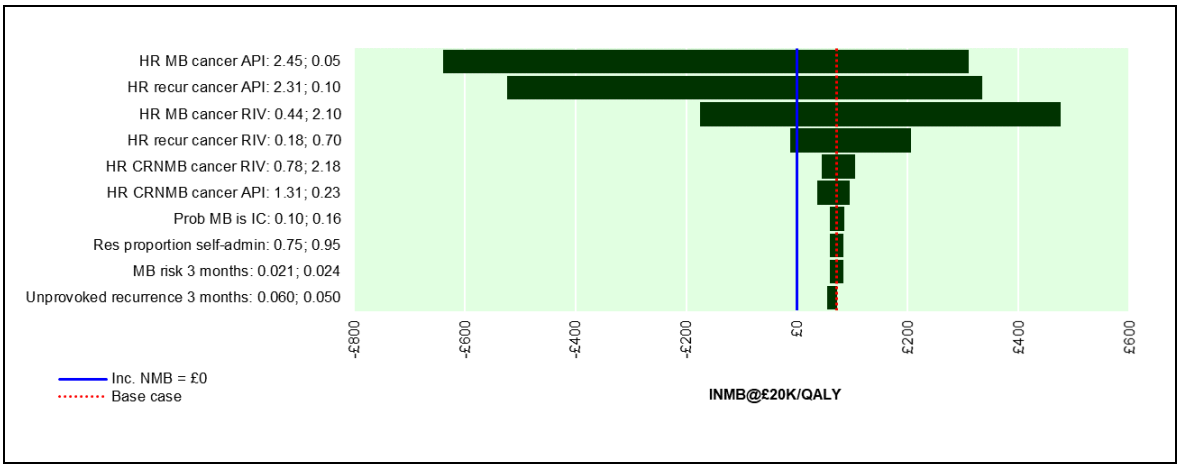
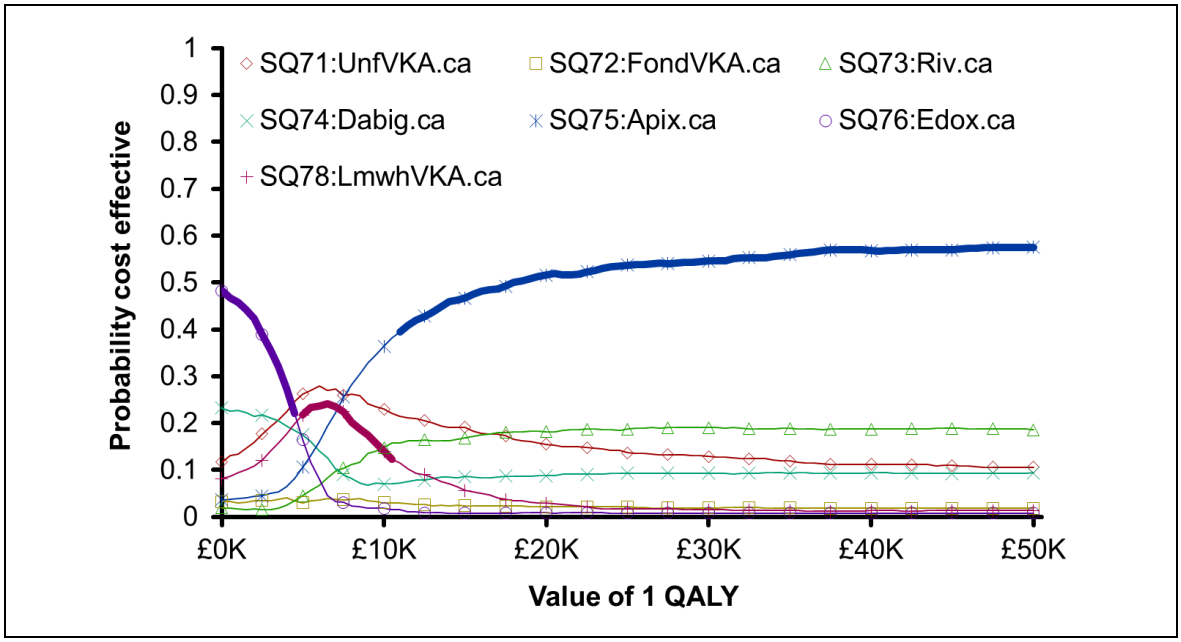


**Figure 23: Cost-effectiveness acceptability curve for the cancer population - DVT**




*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** | | 0.41 | 0.23 | 0.66 | 0.27 | 0.73 | 0.12 | 0.00 |
| **UNF/VKA** | 0.59 | | 0.50 | 0.65 | 0.41 | 0.72 | 0.30 | 0.00 |
| **FOND/VKA** | 0.77 | 0.51 | | 0.76 | 0.37 | 0.79 | 0.24 | 0.00 |
| **RIVAROXABAN** | 0.34 | 0.35 | 0.24 | | 0.24 | 0.65 | 0.11 | 0.00 |
| **DABIGATRAN** | 0.73 | 0.59 | 0.63 | 0.76 | | 0.80 | 0.44 | 0.02 |
| **APIXABAN** | 0.27 | 0.28 | 0.22 | 0.35 | 0.20 | | 0.13 | 0.01 |
| **EDOXABAN** | 0.88 | 0.70 | 0.77 | 0.89 | 0.56 | 0.87 | | 0.00 |
| **LMWH** | 1.00 | 1.00 | 1.00 | 1.00 | 0.98 | 1.00 | 1.00 | |

*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. In contrast to DVT, rivaroxaban is now an additional strategy on the cost-effectiveness frontier for PE. The ICER for apixaban versus rivaroxaban is £11,939/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 49% 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 59% probability of being more cost effective whereas rivaroxaban has a 41% 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 | | | | | | Total QALYs[c] | Total costs[c] | NMB at £20K/QALY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Recurrent VTE | Major bleeds | CRNMB | Treatment | Monitoring | Recurrent VTE | Major bleeding | CRNMB | Cancer[b] | | | |
| Apixaban | 14.409 | 3.543 | 19.728 | £678 | £175 | £238 | £161 | £51 | £18,208 | 1.401 | £19,511 | £8,510 |
| Rivaroxaban | 10.406 | 5.368 | 35.472 | £632 | £167 | £193 | £236 | £88 | £18,137 | 1.396 | £19,452 | £8,471 |
| LMWH | 12.954 | 4.998 | 17.531 | £2,328 | £290 | £222 | £221 | £46 | £18,104 | 1.395 | £21,211 | £6,680 |
| LMWH/VKA | 17.378 | 5.328 | 29.118 | £423 | £298 | £273 | £229 | £74 | £18,041 | 1.386 | £19,338 | £8,374 |
| Fondaparinux/VKA[d] | 17.188 | 5.854 | 24.458 | £480 | £298 | £271 | £250 | £63 | £18,007 | 1.383 | £19,368 | £8,287 |
| UFH/VKA | 19.626 | 5.891 | 17.206 | £512 | £302 | £299 | £252 | £47 | £17,968 | 1.379 | £19,380 | £8,195 |
| Dabigatran | 16.323 | 8.046 | 46.477 | £670 | £177 | £262 | £419 | £116 | £17,857 | 1.371 | £19,501 | £7,911 |
| Edoxaban | 11.133 | 9.800 | 23.657 | £627 | £168 | £202 | £426 | £61 | £17,807 | 1.368 | £19,290 | £8,068 |

*(a) Per 100 people in the model*
*(b) Includes 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 | £19,290 | 1.368 | | | |
| LMWH/VKA | £19,338 | 1.386 | £48 | 0.018 | £2,728 |
| Fondaparinux/VKA[a] | £19,368 | 1.383 | £30 | -0.003 | dominated |
| UFH/VKA | £19,380 | 1.379 | £41 | -0.007 | dominated |
| Rivaroxaban | £19,452 | 1.396 | £114 | 0.011 | £10,830 |
| Dabigatran | £19,501 | 1.371 | £49 | -0.026 | dominated |
| Apixaban | £19,511 | 1.401 | £59 | 0.005 | £11,939 |
| LMWH | £21,211 | 1.395 | £1,700 | -0.007 | dominated |

*(a) No data in the cancer population*

1

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

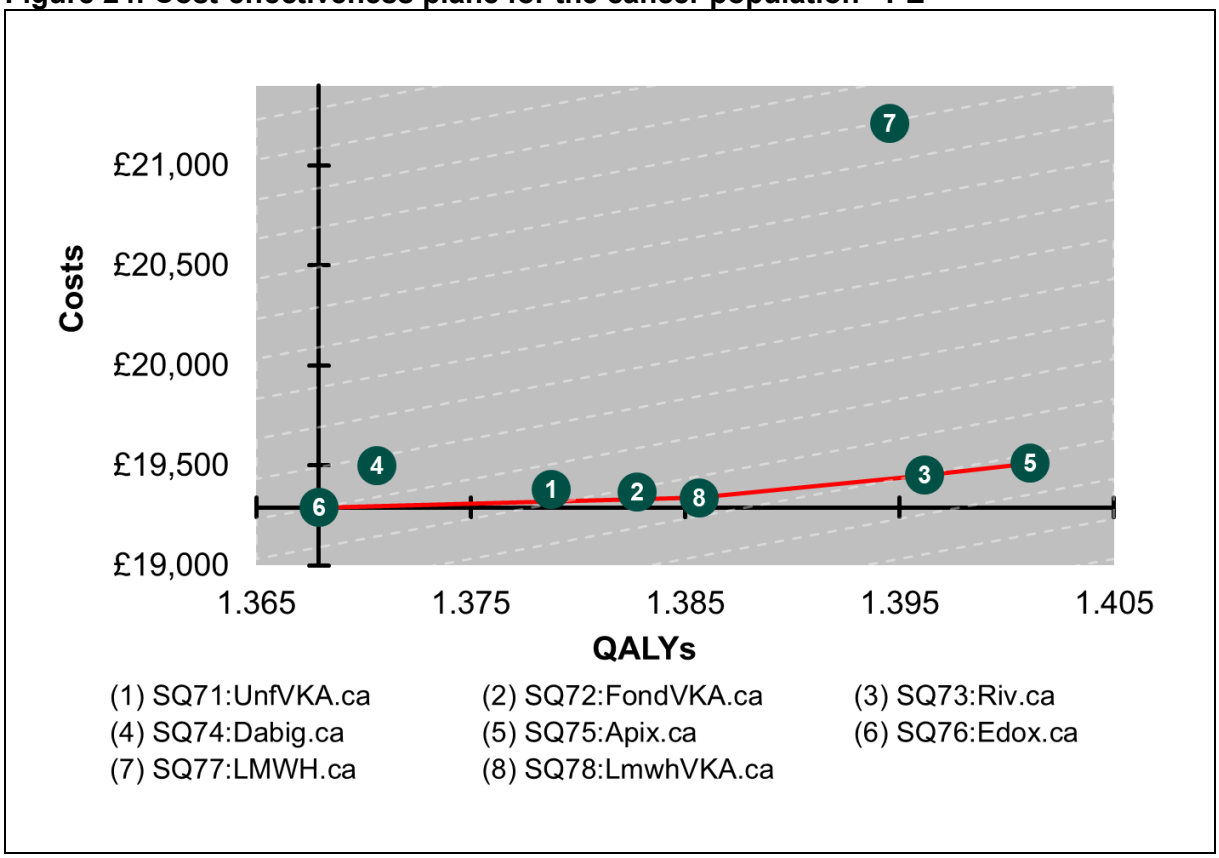



**Figure 25: Results of one-way sensitivity analysis (top 10 most influential parameters) for apixaban vs. rivaroxaban based on incremental net monetary benefit at a threshold of £20,000/QALY - cancer population - PE**

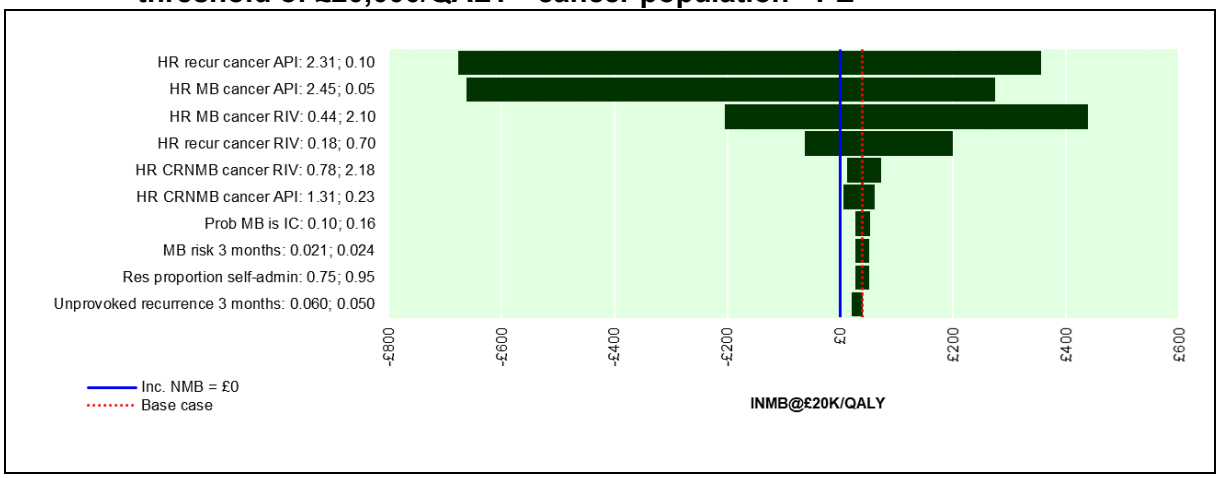
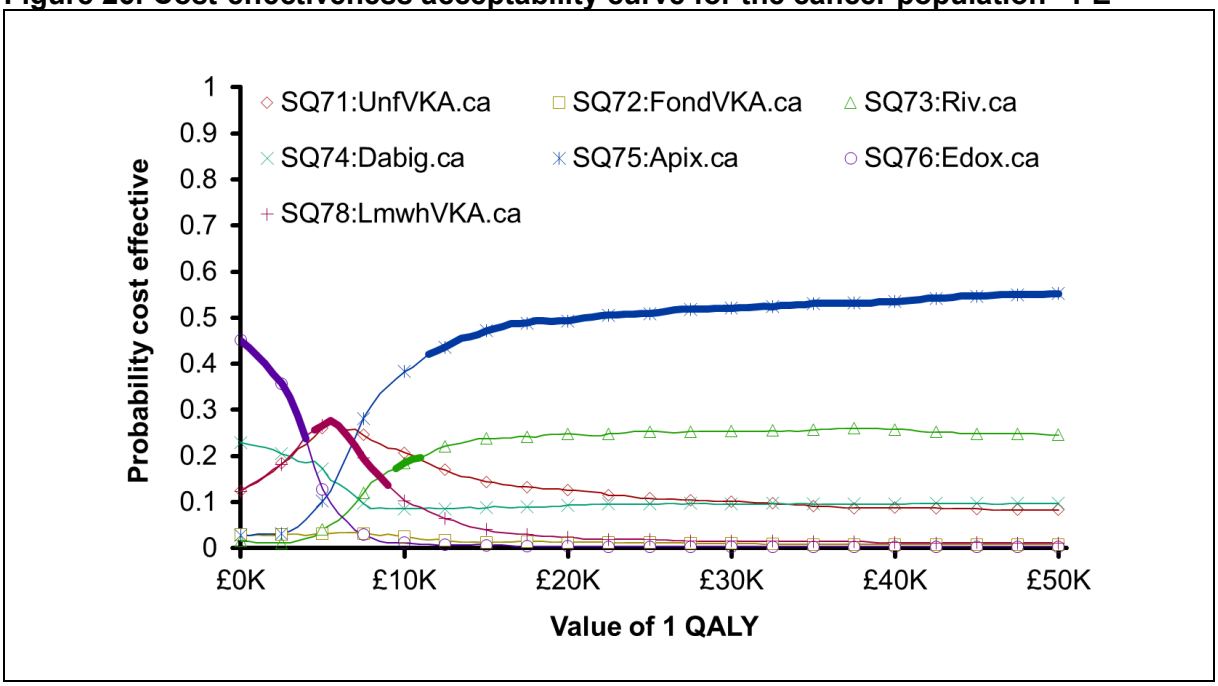


**Figure 26: Cost-effectiveness acceptability curve for the cancer population - PE**




*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** | | 0.40 | 0.25 | 0.76 | 0.36 | 0.76 | 0.17 | 0.00 |
| **UNF/VKA** | 0.60 | | 0.52 | 0.73 | 0.46 | 0.74 | 0.38 | 0.00 |
| **FOND/VKA** | 0.75 | 0.48 | | 0.81 | 0.45 | 0.80 | 0.29 | 0.00 |
| **RIVAROXABAN** | 0.24 | 0.27 | 0.19 | | 0.24 | 0.59 | 0.08 | 0.00 |
| **DABIGATRAN** | 0.64 | 0.54 | 0.55 | 0.76 | | 0.76 | 0.43 | 0.02 |
| **APIXABAN** | 0.24 | 0.27 | 0.20 | 0.41 | 0.24 | | 0.14 | 0.01 |
| **EDOXABAN** | 0.83 | 0.62 | 0.71 | 0.92 | 0.57 | 0.86 | | 0.00 |
| **LMWH** | 1.00 | 1.00 | 1.00 | 1.00 | 0.98 | 1.00 | 1.00 | |

*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 £2,993/QALY for DVT index events and £2,808/QALY for PE index events. In probabilistic sensitivity analysis, apixaban has a >90% 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 only marginally higher than apixaban (approximately £20); 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.

# References

Bach AG, Taute BM, Baasai N et al. (2016) 30-Day mortality in acute pulmonary embolism: prognostic value of clinical scores and anamnestic features. PLoS ONE 11: 1-10. Available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0148728

Bamber L, Muston D, McLeod E, Guillermin A, Lowin J, and Patel R. (2015). Cost-effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. Thrombosis Journal 13: 20

Barba R, Marco J, Martin-Alvarez H et al. (2005) The influence of extreme body weight on clinical outcome of patients with venous thromboembolism: findings from a prospective registry (RIETE). Journal of Thrombosis and Haemostasis 3: 856-862

British National Formulary 2019. Available at https://bnf.nice.org.uk/

Bronnum-Hansen H, Davidseb M and Thorvaldsen P (2001) Long-term survival and causes of death after stroke. Stroke 32: 2131-2136

Chew HK, Wun T, Harvey D et al. (2006) incidence of venous thromboembolism and its effect on survival among patients with common cancers. Archives of Internal Medicine 166: 458-464

Clay, E., Jamotte, A., Verhamme, P., Cohen, A. T., Van Hout, B. A., and Gumbs, P. (2018). Cost-effectiveness of edoxaban compared to warfarin for the treatment and secondary prevention of venous thromboembolism in the UK. Journal of Market Access & Health Policy, 6(1): 1495974

Delcroix M, Lang I, Pepke-Zaba et al. (2016) Long-term outcome of patients with chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 133: 859-871

Department of health NHS reference costs 2016/17. Available at https://www.gov.uk/government/collections/nhs-reference-costs

Dronkers AEA, Lijfering WM, Teichert M et al. (2018) Persistence to direct oral anticoagulants for acute venous thromboembolism. Thrombosis research 167: 135-141

Electronic Medicines Compendium (2017) Summary product characteristics: Octaplex. Available at https://www.medicines.org.uk/emc/product/6566/smpc

Electronic Medicines Compendium (2018) Summary product characteristics: Beriplex. Available at https://www.medicines.org.uk/emc/product/6354/smpc

Ende-Verhaar YM, Cannegieter SC, Noordegraaf AV et al. (2017) Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 49: 1-11

Farkkila N, Sintonen H, Saarto T eta l. (2012) Health-related quality of life in colorectal cancer. Colorectal Disease 15: 215-222

Hall PS, Hamilton P, Meads Dm et al. (2015) Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. British Journal of cancer 112: 948-956

Inami T, Kataoka M, Yanagisawa R et al. (2016) Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Circulation 134: 2030-2032

Jugrin A V, Ustyugova A, Urbich M, Lamotte M, and Sunderland T. (2015). The cost-utility of dabigatran etexilate compared with warfarin in treatment and extended anticoagulation of acute VTE in the UK. Thrombosis & Haemostasis, 114(4): 778-92

Jugrin A V, Hosel V, Ustyugova A, De Francesco, M , Lamotte M, and Sunderland T. (2016). Indirect comparison and cost-utility of dabigatran etexilate and rivaroxaban in the treatment and extended anticoagulation of venous thromboembolism in a UK setting. Journal of Medical Economics, 19(1):1-10

Kearon C, Gent M, Hirsh J et al. (1999) A comparison of three months of anticoagulation for a first episode of idiopathic venous thromboembolism. The New England Journal of Medicine 12: 901-907

Khorana AA (2010) Venous thromboembolism and prognosis in cancer. Thrombosis Research 125(6): 490-493

Kind P, Hardman G and Macran S (1999) UK Population Norms for EQ-5D. University of York. Available at https://www.york.ac.uk/che/pdf/DP172.pdf

Klok F, Kooiman J, Huisman MV et al. (2014) Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review. European Respiratory Journal 45: 201-201

Lanitis T, Leipold R, Hamilton M, Rublee D, Quon P, Browne C, and Cohen A T. (2016). Cost-effectiveness of Apixaban Versus Other Oral Anticoagulants for the Initial Treatment of Venous Thromboembolism and Prevention of Recurrence. Clinical Therapeutics, 38(3): 478-93

Lanitis T, Leipold R, Hamilton M, Rublee D, Quon P, Browne C, and Cohen A T. (2017). Cost-effectiveness of apixaban versus low molecular weight heparin/vitamin k antagonist for the treatment of venous thromboembolism and the prevention of recurrences. BMC Health Services Research, 17(1): 74

Lernet LA and Soetikno RM (1997) Automated computer interviews to elicit utilities Potential applications in the treatment of deep vein thrombosis. Journal of the American Medical Informatics Association 4: 49-56

Locadia M, Bossuyt PMM, Stalmeier PFM et al. (2004) Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. PhD Thesis, 57-76.

Lloyd A, Nafees B, Narewske J et al. (2006) Health state utilities for metastatic breast cancer. British Journal of Cancer 95: 683-690

Luengo-Fernandez R, Gray AM, Bull L et al. (2013) Quality of life after TIA and stroke – Ten years results of the Oxford Vascular Study. American Academy of Neurology 81: 1588-1595

Martinez C, Cohen AT, Bamber L et al. (2014) Epidemiology of first recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Blood Coagulation, Fibrinolysis and Cellular Haemostasis 112: 255-263

Mitchell M, Muftakhidinov B, Winchen T et al. "Engauge Digitizer Software." Available at http://markummitchell.github.io/engauge-digitizer

Mizoguchi H, Ogawa A, Munemasa M et al. (2012) Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circulation: Cardiovascular Interventiona 5: 748-755

Meads DM, McKenna SP, Doughty N et al. (2008) The responsiveness and validity of the CAMPHOR utility index. Eur Respir J 32: 1513-1519

Nafees B, Stafford M, Gavriel S et al. (2008) Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes 6: 1-10

NHS Business Services Authority - Drug tariff 2019. Available at https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

NHS Business Services Authority (2018) Prescription Cost Analysis (PCA) data. Available at https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data

National Institute for Health and Care Excellence (2018) Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism [NG89]. Available at https://www.nice.org.uk/guidance/ng89

National Institute for Health and Care Excellence (2016) Reversal of the anticoagulation effect of dabigatran: idarucizumab Evidence summary [ESNM73]. Available at https://www.nice.org.uk/advice/esnm73/chapter/full-evidence-summary

National Institute for Health and Care Excellence (2019) Lung cancer: diagnosis and management [NG122]. Available at https://www.nice.org.uk/guidance/ng122

National Institute for Health and Care Excellence (2015) Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. Committee papers [TA355]. Available at https://www.nice.org.uk/guidance/ta355/documents/atrial-fibrillation-nonvalvular-edoxaban-tosylate-id624-committee-papers2

Nieto JA, Solano R, Ruiz-Ribo MD et al. (2010) Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. Journal of Thrombosis and Haemostasis 8: 1216-1222

Okak G, Lijfering WM, Verduijn M et al. (2013) Risk of venous thrombosis in patients with chronic kidney disease: identification of high-risk groups. Journal of Thrombosis and Haemostasis 11: 627-633

Personal Social Services Research Unit (2017) Unit costs of health and social care. Available at https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/

Pengo V, Lensing AWA, Prins MH et al. (2004) Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. New England Journal of Medicine 359: 2257-2264

Prandoni P, Villalta S, Bagatella P et al. (1997) The clinical course of deep vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 82: 423-428

Prandoni P, Lensing AWA, Piccioli A et al. (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 15: 3484-3488

Prandoni P, Noventa F, Ghirarduzzi A et al. (2007) The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 92: 199-205

Rosand J, Eckman MH, Knudsen KA et al. (2004) The Effect of Warfarin and Intensity of Anticoagulation on Outcome of Intracerebral Hemorrhage. Archives of Internal Medicine 164: p880-884

Schulman S, Kearon C, Kakkar AK et al. (2013) Extended use of dabigatran, warfarin or placebo in venous thromboembolism. New England Jornal of Medicine 368: 709-718

Schweikert B, Pittrow D, Vizza CD et al. (2014) Demographics, clinical characteristics, health resource utilization and cost of chronic thromboembolic pulmonary hypertension patients: retrospective results from six European countries. Health Services Research 14: 1-7

Sterne J A, Bodalia P N, Bryden P A, Davies P A, Lopez-Lopez J A, Okoli G N, Thom H H, Caldwell D M, Dias S, Eaton D, Higgins J P, Hollingworth W, Salisbury C, Savovic J, Sofat R, Stephens-Boal A, Welton N J, and Hingorani A D. (2017). Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technology Assessment, 21(9): 1-386

Torvinen S, Farkkila N, Sintonen H et al. (2012) Health-related quality of life in prostate cancer. Acta Oncologica 52: 1094-1101

Vora P, Soriano-Gabarro M, Suzart K et al. (2016) Limited evidence on persistence with anticoagulants, and its effect on the risk of recurrence of venous thromboembolism: a systematic review of observational studies. Patients Preference and Adherence 10: 1657-1665

Wardlaw JM, Chappell FM, Stevenson M et al. (2006) Accurate, practical and cost-effective assessment of carotid stenosis in the UK. Health Technology Assessment 10(30)

Yamashita Y, Morimoto T, Amano H et al. (2018) Anticoagulation therapy for venous thromboembolism in the real world – from the COMMAND VTE registry. Circulation Journal 82: 1262-1270

# 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 treatments** | | | | |
| **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 |
| **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 |
| 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 |

| Parameter | Point estimate | Standard error | Source | Distribution used in PSA |
|---|---|---|---|---|
| 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 |
| 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 |

| Parameter | Point estimate | Standard error | Source | Distribution used in PSA |
|---|---|---|---|---|
| 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 |
| Proportion of low-dose Octaplex use | 50% | 0.051 | Assumption | 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 | |

| Parameter | Point estimate | Standard error | Source | Distribution used in PSA |
|---|---|---|---|---|
| PCC - number of doses | 1.25 | 0.128 | Assumption | Gamma |
| Idarucizumab | 2 | 2.041 | Committee consensus | Gamma |
| **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** | | | | |
| 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 |

| Parameter | Point estimate | Standard error | Source | Distribution used in PSA |
|---|---|---|---|---|
| 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 |
| **Cancer costs** | | | | |
| **Lung Cancer** | | | | |
| Progressed (monthly cost) | £912 | 91.188 | NICE Lung Cancer Model | Gamma |
| Progression free (monthly cost) | £292 | 29.241 | NICE Lung Cancer Model | 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** | | | | |

| Parameter | Point estimate | Standard error | Source | Distribution used in PSA |
|---|---|---|---|---|
| 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 |
| 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 | | | | |

| Parameter | Point estimate | Standard error | Source | Distribution used in PSA |
|---|---|---|---|---|
| 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 |
| **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** | **£2,993** | **£2,808** |
| Duration of treatment for unprovoked VTEs (base case is indefinite treatment) | | |
| 3 months | dominates | dominates |
| 6 months | dominates | dominates |
| 12 months | £1,744 | £1,544 |
| Relative treatment effects for DVT and PE | | |
| Using separate treatment effects from DVT and PE NMAs | £6,266 | £1,659 |
| Model calibration | | |
| No calibration for mortality and VTE recurrence | £1,580 | £1,550 |
| Discontinuation rate | | |
| Probability of discontinuation at 6 and 12 months reduced by 20% | £4,925 | £4,641 |
| 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) | £2,700 | £2,547 |

## 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. Edoxaban is now the most expensive strategy; it generates fewer total QALYs than the other DOACs and remains dominated so the overall conclusions of the base case analysis remain the same.

**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 | | | |

| Strategy | Absolute | | Incremental | | |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | ICER (£/QALY) |
| Fondaparinux/VKA | £1,519 | 7.498 | £74 | -0.006 | dominated |
| Apixaban | £1,581 | 7.550 | £136 | 0.045 | £2,993 |
| UFH/VKA | £1,586 | 7.482 | £5 | -0.067 | dominated |
| Rivaroxaban | £1,601 | 7.531 | £20 | -0.019 | dominated |
| Dabigatran | £1,632 | 7.517 | £51 | -0.032 | dominated |
| Edoxaban | £1,635 | 7.515 | £54 | -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 | £3,098 | 7.447 | £130 | 0.046 | £2,808 |
| UFH/VKA | £3,107 | 7.375 | £9 | -0.072 | dominated |
| Rivaroxaban | £3,116 | 7.427 | £18 | -0.019 | dominated |
| Dabigatran | £3,147 | 7.413 | £49 | -0.034 | dominated |
| Edoxaban | £3,149 | 7.412 | £51 | -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) | 0.225 |
| Cost rivaroxaban (20mg tablets, 28 per pack) | £50.40 per pack | -84% |
| **PE** | | |
| Hazard ratio for major bleeding rivaroxaban vs. LMWH/VKA | 0.318 (0.167 to 0.535) | 0.213 |
| Cost rivaroxaban (20mg tablets, 28 per pack) | £50.40 per pack | -87% |

*(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) | | | | | |
|---|---|---|---|---|---|---|
| | 0.20 | 0.30 | 0.40 | 0.50 | 0.60 | 0.70 |
| 0% | -£31 | £94 | £219 | £344 | £468 | £592 |
| -10% | -£79 | £46 | £171 | £296 | £420 | £544 |
| -20% | -£128 | -£2 | £123 | £248 | £372 | £496 |
| -30% | -£176 | -£50 | £75 | £199 | £324 | £448 |
| -40% | -£224 | -£99 | £27 | £151 | £276 | £400 |
| -50% | -£272 | -£147 | -£22 | £103 | £228 | £352 |
| -60% | -£321 | -£195 | -£70 | £55 | £180 | £304 |
| -70% | -£369 | -£243 | -£118 | £7 | £132 | £256 |
| -80% | -£417 | -£291 | -£166 | -£41 | £84 | £208 |

*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) | | | | | |
|---|---|---|---|---|---|---|
| | 0.20 | 0.30 | 0.40 | 0.50 | 0.60 | 0.70 |
| 0% | -£16 | £105 | £227 | £348 | £469 | £589 |
| -10% | -£63 | £58 | £180 | £301 | £422 | £543 |
| -20% | -£110 | £12 | £133 | £254 | £375 | £496 |
| -30% | -£157 | -£35 | £86 | £208 | £329 | £450 |
| -40% | -£204 | -£82 | £40 | £161 | £282 | £403 |
| -50% | -£251 | -£129 | -£7 | £114 | £235 | £356 |
| -60% | -£298 | -£176 | -£54 | £68 | £189 | £310 |
| -70% | -£344 | -£222 | -£101 | £21 | £142 | £263 |
| -80% | -£391 | -£269 | -£147 | -£26 | £95 | £216 |

*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.*