Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

ERRATA

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BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
118, 170	Changed the sentence "Nonetheless, 35 years after the beginning of the model 80% of patients are still alive" to "Nonetheless, 35 years after the beginning of the model 20% of patients are still alive".
124	Removed text "If one assumes the same would happen in "real life", i.e. if one assumes that if the Hokusai-VTE trial had continued the recurrent events observed in the last period of analysis would be constant over time, this would mean that the favourable difference in the number of observed and estimated recurrent events for edoxaban is maintained throughout the rest of the analysis. This implies that for the remaining 49 years of the analysis, every year there would be an additional 3 events estimated, compared with the observed events. This would amount to a total of 147 additional events, which is quite significant"…"Nevertheless, if this assumption is valid, then this would lead to a number of nearly 150 overestimated recurrent events".
125	Changed the sentence "It can be observed how the probability of recurrent VTE for edoxaban is underestimated during the initial (short) period of the analysis, then peaking at around 6 months and finally how the difference in the probability of recurrence after 1 year is maintained in the economic model, favouring edoxaban, when compared with the hypothetically observed events in the trial." to "It can be observed how the probability of recurrent VTE for edoxaban is underestimated during the initial (short) period of the analysis, then peaking at around 3 months and finally how the difference in the probability of recurrence after 1 year is maintained in the economic model, favouring edoxaban, when compared with the hypothetically observed events in the trial (if assumed that the observed probability of recurrent events in the last period of the Hokusai-VTE trial would be constant over time after 1 year.)".
134	Changed the sentence "To note is that the post-hoc curves cross around month 9, with edoxaban presenting a higher risk of MB than warfarin until month 9, which then switches...Similarly to CRNMB there is an underestimation of the probability of MB in the first 9 months of the analysis. After month 10, the probability of MB is overestimated in the model." to "To note is that the post-hoc curves cross around month 7, with edoxaban presenting a higher risk of MB than warfarin until month 7, which then switches...There is an underestimation of the probability of MB in the first 6 months of the analysis. After month 7, the probability of MB is overestimated in the model."
135	Removed text "Nonetheless all transition probabilities after 1 year were assumed to be equal to the respective probability between the 99th day and the 364th day. If one assumes the same would happen in "real life", i.e. if one assumes that if the Hokusai-VTE trial had continued the bleeding events observed in the last period of analysis would be constant over time, then in the case of CRNMB events, there is a slight overestimation of the marginal effectiveness of edoxaban vs warfarin in terms of preventing bleedings and there is an overall overestimation in the total number of events; while in the case of MB, there is an underestimation of the marginal effectiveness (but an overestimation of the marginal effectiveness before 9 months) of edoxaban compared with warfarin after 12 months. In the case of bleeding events this is less relevant as after 12 months patients are only allowed to experience CRNMB and MB events when in the recurrent VTE state."

136	Removed “9” from the sentence “…in the initial 9 months of the analysis”.
125, 126, 132, 135, 136	Corrected scale in the graphs presented in Figure 9, Figure 10, Figure 11, Figure 12, Figure 13, Figure 15 and Figure 16, respectively.
199	Changed the sentences “clinical experts advised that the follow-up visits are often delivered by nurses” and “This analysis also considered the cost of follow-up visits based on non-consultant-led anticoagulation clinic attendance” to “clinical experts advised that the INR monitoring visits are likely to be delivered by nurses” and “This analysis also considered the cost of monitoring visits based on non-consultant-led anticoagulation clinic attendance”.
223	Removed text “Additionally, there is a lack of transparency in the OWSA reported. Not only have the tornado diagrams not been provided in the Excel model, but the macros running the OWSA in the model don’t work. Furthermore,”
237	Changed the value presented in Scenario 19.

Time horizon

The time horizon considered in the economic model was lifetime. The model was run for 1300 cycles, the equivalent to 50 years, by which time 99.9% of simulated patients had died.

Given that patients enter the model with an average age of 56 years, it would be expected that all patients would be dead before 50 years, when they would be 106 years. Nonetheless, 35 years after the beginning of the model 20% of patients are still alive. This implies that 20% of VTE patients would virtually survive until the age of 90. This indicates that survival is potentially overestimated in the economic model. This is discussed in Section 5.4.6 of the report.

Perspective and discounting

The company adopted an NHS and personal social services (PSS) perspective for the analysis, and applied a discount rate of 3.5% for costs and outcomes beyond the first year of the model. The ERG considers this to be appropriate and in line with the NICE reference case.

In conclusion, the ERG finds that there is lack of consistency in the approach followed by the company with regards to modelling specific VTE complications. Some of the model assumptions were also found to be clinically implausible. The approach undertaken raises the following concerns:

- The ERG is not convinced by the clinical plausibility of assuming that:
    - For patients experiencing recurrent VTE events or major bleeds, their QoL is only impacted during 2 weeks, after which they return to the QoL experienced before the events. This issue is related with the decision to combine 2-week cycles with tunnel state structures;
    - Patients return to their original anticoagulation therapy after a recurrent event (even though it is likely that the original therapy was not effective in preventing recurrence);
    - Patients experiencing recurrent VTE after (or at) 12 months do not receive anticoagulation treatment for more than 2 weeks. In clinical practice, patients off anticoagulation treatment who experience a recurrent VTE event will be given anticoagulation therapy (whether returning to their original therapy regimen or a new one) and are in fact likely to need anticoagulation therapy for the reminder of their lives;
    - The fact that CTEPH and stroke were considered treatment-related complications. The ERG's clinical experts advised that CTEPH is not an adverse event associated

is similar it is likely that the distribution of VTE recurrence over the different time periods will underestimate the consequences of VTE.

Table 29. Probability of recurrent VTE on edoxaban- Hokusai-VTE, safety population, on-treatment period

Time period	N	n	Probability	2-week probability used in the model	95% Confidence interval
From index event to 14 days	4118	30	0.729%	0.729%	0.469 to 0.988
From 15 days to 98 days	3967	21	0.529%	0.088%	0.304 to 0.755
From 99 days to 364 days	3614	17	0.470%	0.025%	0.247 to 0.693

Table 30. Probability of recurrent VTE on edoxaban obtained with NMA odd ratios

Time period	Probability	2-week probability used in the model
From index event to 14 days	0.473%	0.4731%
From 15 days to 98 days	0.919%	0.1537%
From 99 days to 364 days	0.379%	0.0200%

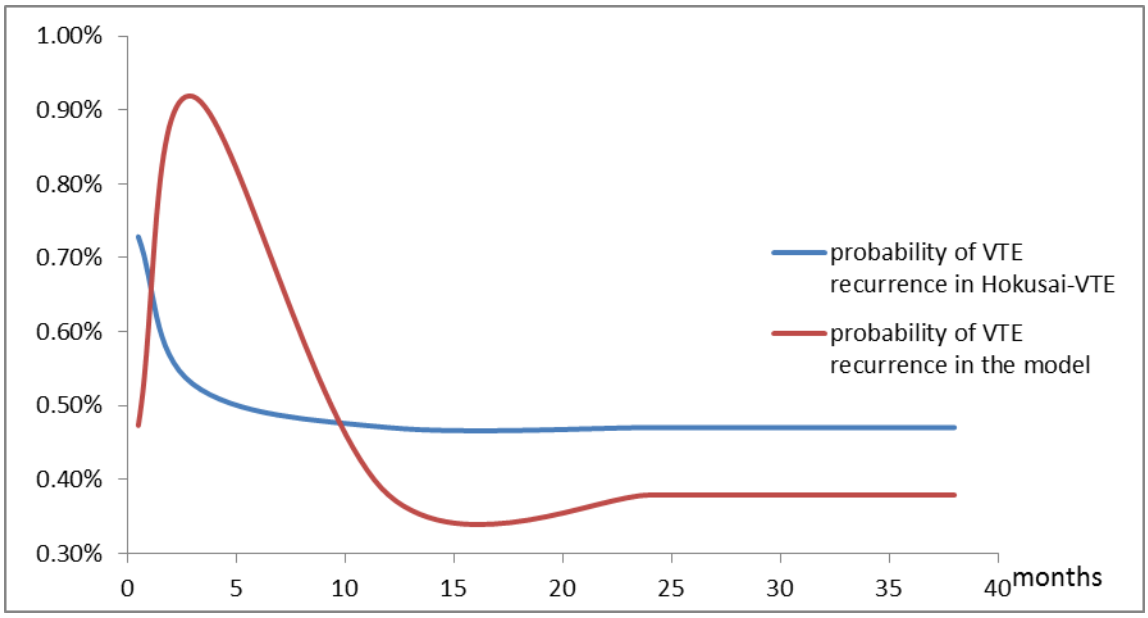
Table 31. Difference in the number of observed and estimated recurrent VTE events

Time period	Observed	Estimated	Difference
From index event to 14 days	30	19	-11
From 15 days to 98 days	21	38	17
From 99 days to 364 days	17	17	0
Total	68	74	6

It should also be mentioned that all transition probabilities after 1 year were assumed to be equal to the respective probability between the 99th day and the 364th day. The ERG is unclear why the company did not attempt to extrapolate the trial data and estimate the recurrence of VTE in the following years of the model. Furthermore, no clinical justification was provided by the company to support the assumption that the risk of recurrence would be maintained after 12 months.

Figure 9 below illustrates the issues reported in this subsection. It can be observed how the probability of recurrent VTE for edoxaban is underestimated during the initial (short) period of the analysis, then peaking at around 3 months and finally how the difference in the probability of recurrence after 1 year is maintained in the economic model, favouring edoxaban, when compared with the hypothetically observed events in the trial (if assumed that the observed probability of recurrent events in the last period of the Hokusai-VTE trial would be constant over time after 1 year.)

Figure 9. Difference in observed and estimated probability of recurrent VTE for edoxaban (produced by the ERG)



The combination of the issues raised is better explained by analysing Figure 10 and Figure 11 below. In Figure 10 the estimated recurrent VTE for warfarin and edoxaban can observed. As previously explained, the recurrence trend in warfarin was used as the baseline, and then the ORs obtained through the NMA (constant over time) were applied to obtain the recurrent VTE in the edoxaban arm. The consequence of this is that the curves are symmetrical and that there is a proportional difference in the risk throughout time (as PHs were assumed). However when we look at Figure 11, we can see the observed recurrence of VTE in the Hokusai-VTE trial for the warfarin and edoxaban arms of the trial. Not surprisingly, Figure 11 resembles Figure 9 as the probability of VTE recurrence in the model for edoxaban was modelled based on the probability of recurrence in the trial for warfarin.

The discrepancy between Figure 10 and Figure 11 is rather significant and casts doubt on the validity and the clinical plausibility of the modelled edoxaban arm in the economic model. This problem is related to the PH assumption made not only in the economic analysis but also in the Hokusai-VTE underlying statistical analysis and ultimately in the NMA.

Figure 10. VTE recurrence in the economic model (produced by the ERG)

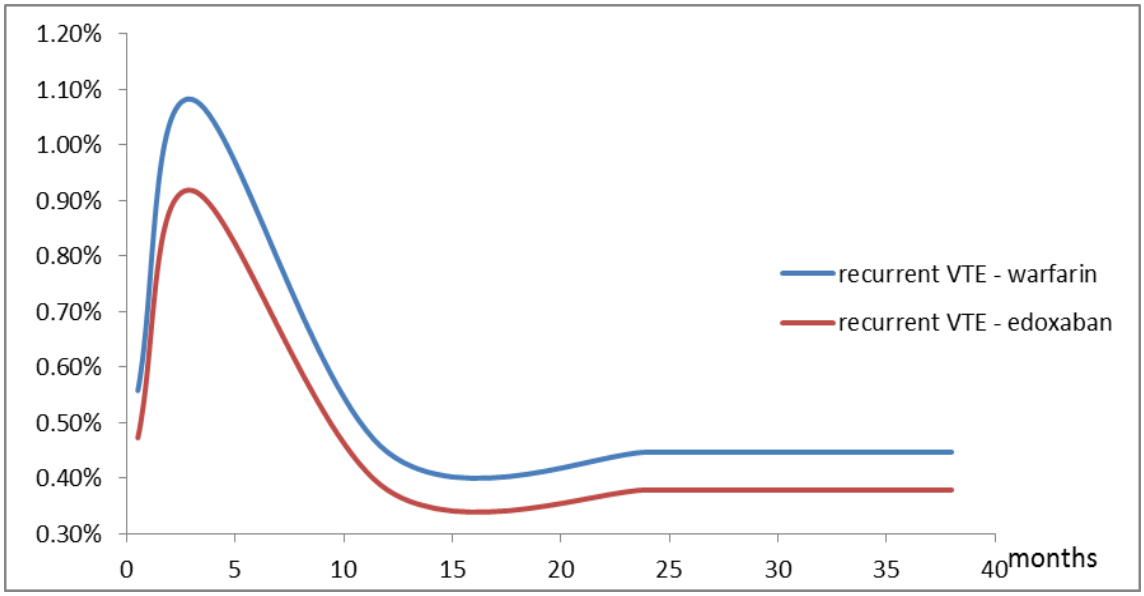
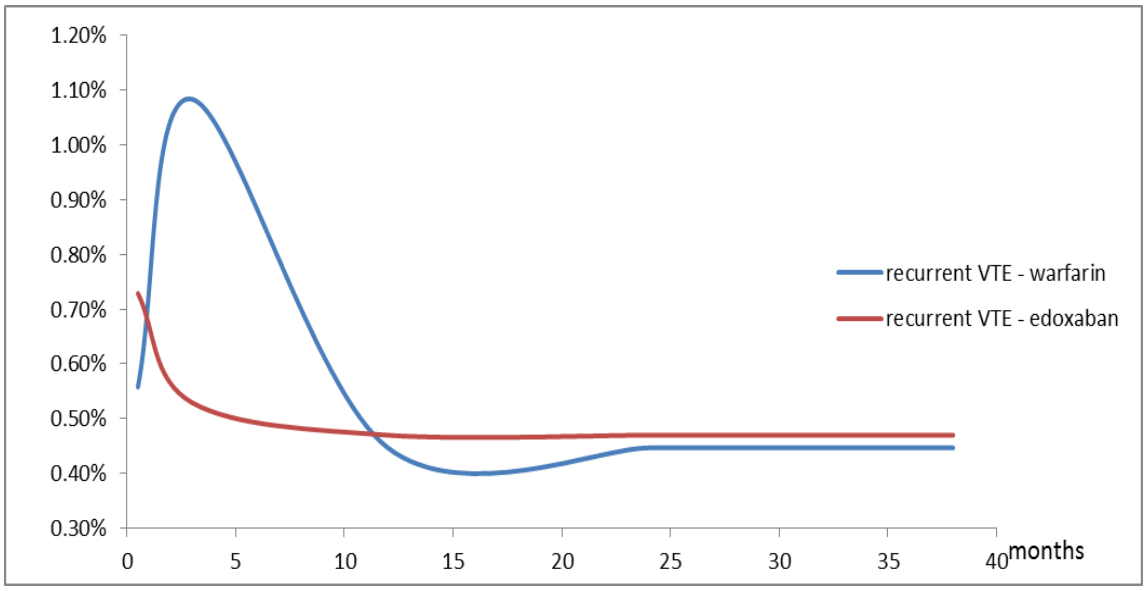


Figure 11. VTE recurrence in the Hokusai-VTE trial (produced by the ERG)



NMA estimates

The ORs estimates obtained from the NMA are calculated based on results at 6-months but are used in the economic model across the different time periods. As there is no significant difference in risk of recurrence between any of the NOACs and warfarin at 6-months, this could be interpreted as all of the NOACs having the same risk as warfarin over time.

The ERG considers that the non-inferiority design of the original trials included in the NMA has limited the opportunity for any NOAC in the network to have demonstrated a significant difference from any other treatment in the network, should one exist for prevention of VTE recurrence. In the

Figure 12. Probability of CRNMB on warfarin in the model (time-to-event analysis) and in the post-hoc analysis (phase-specific analysis) (produced by the ERG)

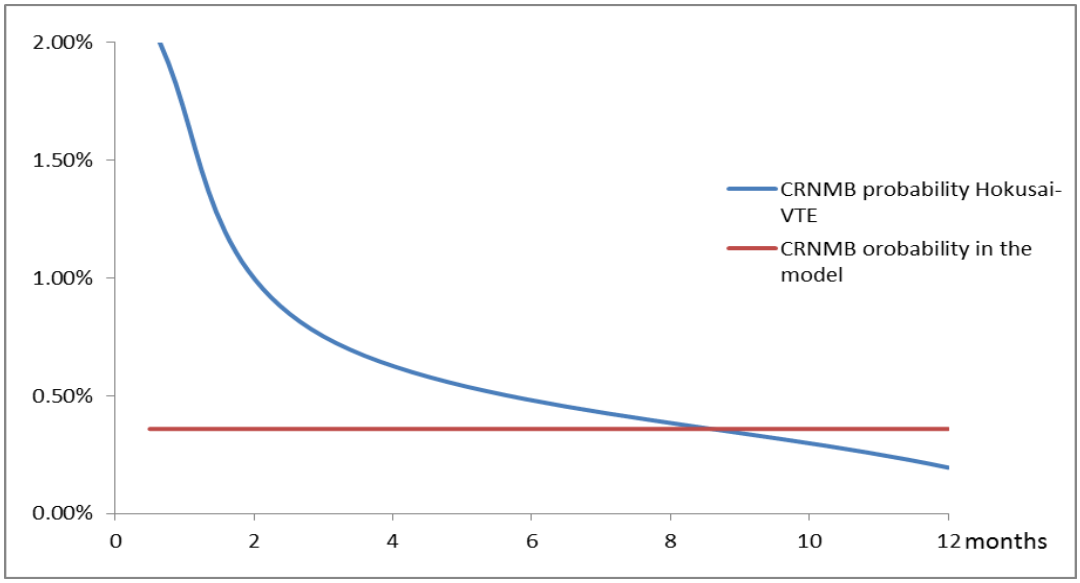


Figure 13. Probability of MB on warfarin in the model (time-to-event analysis) and in the post-hoc analysis (produced by the ERG)

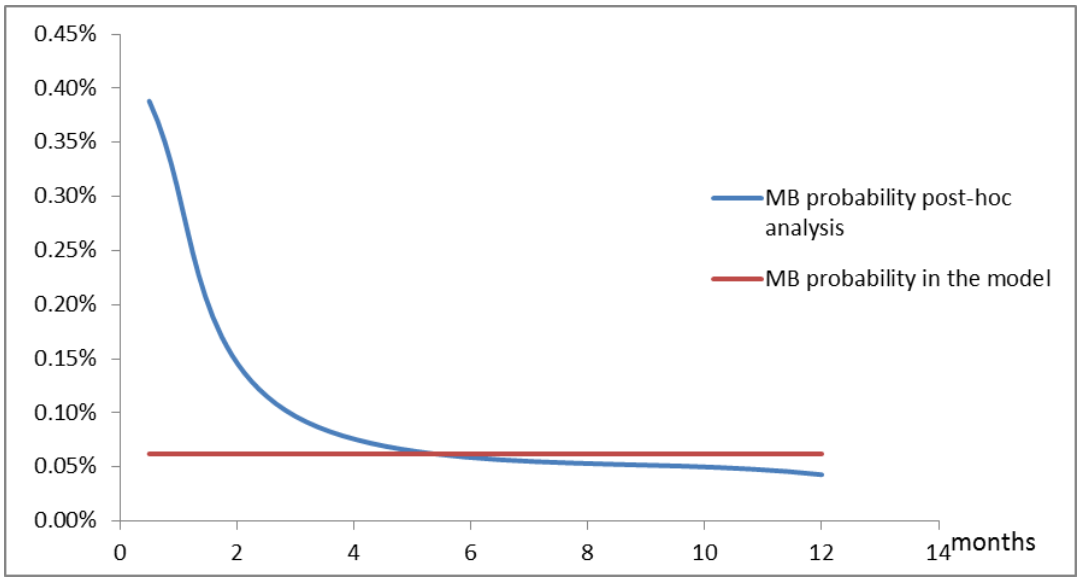


Table 39. Number of CRNMB events observed in time-to-event and phase-specific analysis and number of events in the model in the first 12 months

Treatment	Time-to-event analysis	Phase-specific analysis	Difference (time-to-event minus phase-specific)	Estimated	Difference (estimated minus time-to-event)	Difference (estimated minus phase-specific)
Warfarin	368	392	-24	376	8	-16
Edoxaban	298	324	-26	296	-2	-28
Difference	-70	-68	-	-80	-	-

Figure 14. KM curves for adjudicated major it CRNM bleeding events, safety analysis set, on-treatment period (reproduced from CS, Figure B8)

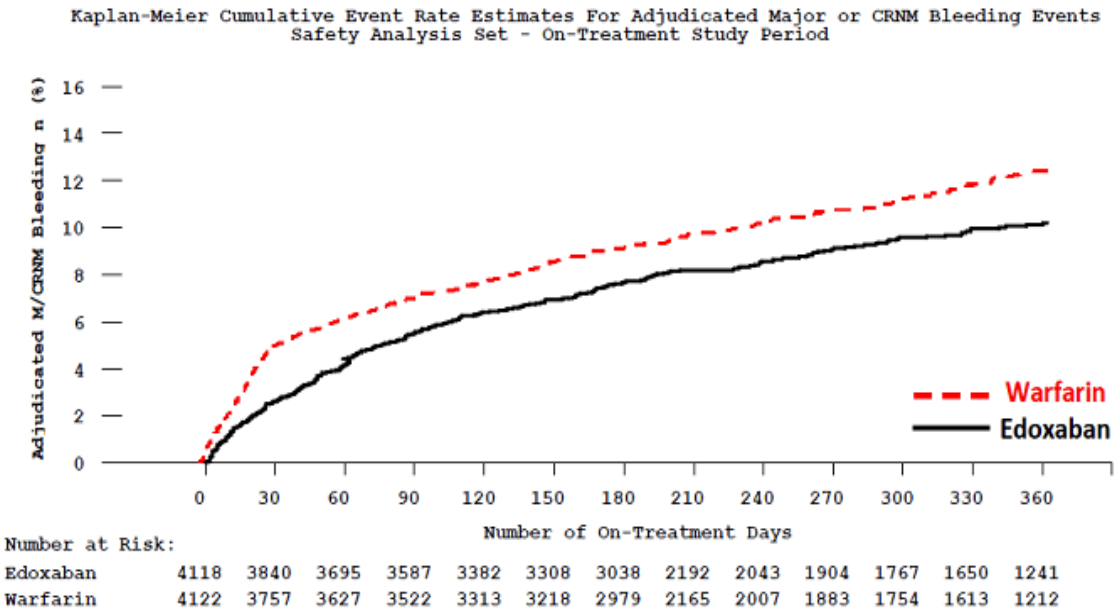


Figure 15 shows the difference in the CRNMB estimated curves for edoxaban and warfarin and the edoxaban and warfarin curves in the post-hoc analysis (phase-specific analysis). There is a substantial underestimation of the probability of CRNMB in the first 9 months of the analysis. After month 10, the probability of CRNMB is overestimated in the model. It can be observed how the post-hoc CRNMB curves seem to super-impose closer to 12 months. When comparing the difference in the number of estimated events between the warfarin and the edoxaban arms and the events observed in phase-specific analysis (Table 39) during the first 12 months of the analysis then this results in an overall underestimation of events in both arms (16 events in the warfarin arm and 28 events in the edoxaban arm). This difference comes from the difference in the phase-specific and the time-to-event analysis aforementioned.

Figure 16 shows the difference in the MB estimated curves for edoxaban and warfarin and the difference in the edoxaban and warfarin curves in the post-hoc analysis (phase-specific analysis). To note is that the post-hoc curves cross around month 7, with edoxaban presenting a higher risk of MB than warfarin until month 7, which then switches. This contradicts the KM curves presented in Figure 14. The nearly super-imposed model curves reflect the OR estimate of 0.942. There is an underestimation of the probability of MB in the first 6 months of the analysis. After month 7, the probability of MB is overestimated in the model. More precisely, and according to Table 39, there is in an underestimation of events in the warfarin arm of the model and an overestimation in the edoxaban arm of the model, exactly by the same number of events; 3 during the

first 12 months of the analysis. This difference is linked to the difference in the phase-specific and in the time-to-event analysis aforementioned.

Figure 15. Probability of CRNMB in the model and in the post-hoc analysis (produced by the ERG)

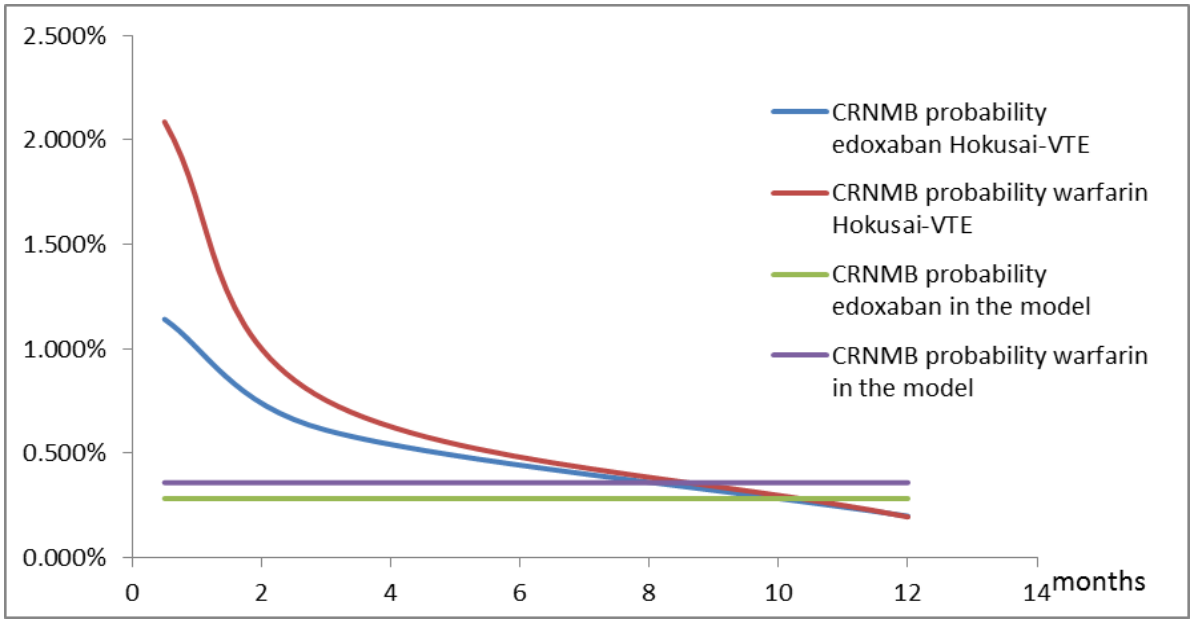
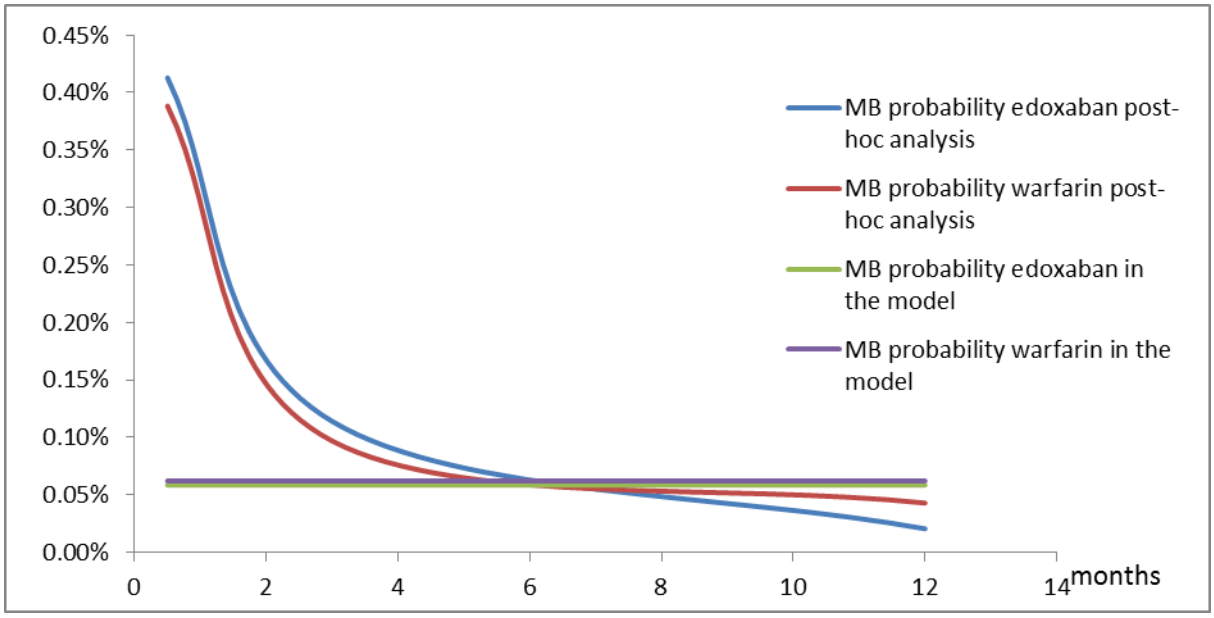


Figure 16. Probability of MB in the model and in the post-hoc analysis (produced by the ERG)



The difference between the KM curves and the post-hoc curves can be explained through several factors such as the fact that different methods of analysis were behind the curves (KM curves were derived by time-to-event analysis and the post-hoc curves were derived by phase-specific analysis) and the fact that the KM curves combine CRNMB and MB events, which seem to behave differently.

The discrepancy between the post-hoc curves and the estimated curves is substantial in the initial months of the analysis. Given that the edoxaban curves were modelled using ORs applied to the warfarin curves, the reason for this difference is the discrepancy between the post-hoc and the time-to-event curves in the warfarin arms of the model.

When comparing the difference in the number of events occurring in the model and in the time-to-event analysis (Table 39) there are 8 additional CRNMB events estimated in the warfarin arm of the model (compared to the time-to-event analysis in the Hokusai-VTE trial) and there are 2 fewer events estimated in the model during the initial 12 months. This means that there is a total difference in the number of events of 10, introducing bias into the analysis in favour of edoxaban.

In terms of MB events, there are 5 additional events estimated in the edoxaban arm of the model (compared to the time-to-event analysis in the Hokusai-VTE trial) and there is1 less event estimated in the warfarin arm of the model. This means that there is a total difference in the number of events of 6, introducing bias into the analysis against edoxaban.

The clinical experts also considered that, if treatment was extended beyond 12 months, the schedule modelled by the company would significantly overestimate the number of monitoring appointments typically required in clinical practice in subsequent years, which would consist of approximately 10 visits per year.

In addition, clinical experts advised that the INR monitoring visits are likely to be delivered by nurses.

In light of this, the ERG conducted a scenario analysis reducing the number of visits required in the first year (for the base case) to 3 visits per quarter after the initial 3 months and in the following years to 2 visits per quarter when lifelong treatment is assumed. This analysis also considered the cost of monitoring visits based on non-consultant-led anticoagulation clinic attendance rather than a weighted average of consultant and non-consultant led attendances. The results of this analysis are presented in Section 6.2.

NOAC monitoring

Clinical opinion sought by the ERG informed that there are some expected monitoring costs associated with edoxaban, dabigatran and rivaroxaban beyond what is considered standard monitoring for VTE patients. Patients on NOACs will visit their GP ideally to undergo an urea and electrolytes test. Therefore the monitoring costs associated with edoxaban are underestimated in the economic model.

The ERG conducted a scenario analysis to reflect different options for NOAC monitoring. As clinical opinion advised that this likely varies across clinical practice, the ERG undertook three scenarios, in accordance to the clinical advice received:

a) Average scenario: patients on NOACs receive an annual visit where they receive U&E;
b) Most conservative scenario: patients on NOACs have an annual appointment with their GP where they receive no tests;
c) Less conservative scenario: patients receive biannual visits where they receive U&E.

The results of this analysis are presented in Section 6.2.

5.1.1.1 Costs of index VTE and initial treatment

As explained in Section 5.4.2 all patients enter the model with index VTE and in the on treatment health state. During their treatment period patients incur the costs of diagnosis and hospitalisation (first cycle only) and treatment of the index VTE event. These are now described.

based on the assumption that the probability of these events might be different depending on the treatment received. As would be expected, when the probability of CTEPH or stroke is varied just in one arm of the economic model, the ICER changes substantially as these are expensive and serious conditions. However, varying the probability of these events in only one arm of the model doesn't have face validity, as there is no clinical rationale for CTEPH or stroke to be linked to the type of treatment received. By including irrelevant parameters in the analysis (but with a substantial impact on the ICER), and by presenting only the eight most influential parameters in the model, the company rendered their OWSA largely irrelevant. During clarification the ERG also asked the company to present total costs, total QALYs, and ICERs for the upper and lower value for each input listed; however these were not provided.

The ERG manually ran the scenario where the probability of VTE recurrence with edoxaban was changed to its upper limit on the 95% Confidence Interval range (1.174) and obtained an ICER of £7,181. This hasn't been reported in the list of inputs with "noteworthy" impact, which included ICERs from around £10,000 to around £5,000.

For utility values and utility decrements the company estimated 95% Confidence Intervals as low and high values, however the ERG is not clear how the standard deviations in the calculation presented were obtained. This was not reported by the company.

The ERG questions the appropriateness of varying the overall health state costs by +/-20%. The ERG believes this approach loses granularity because the specific costs or resource use within each health state that influence the results cannot be identified. The ERG notes that the resource use associated with warfarin monitoring should have been explicitly varied between plausible values, as this is expected to be a key model parameter.

Finally, it seems somewhat implausible that no parameter would influence the ICER of edoxaban vs rivaroxaban.

5.1.1.2 Probabilistic sensitivity analysis (PSA)

Parameter uncertainty was explored using PSA. Individual parameters within the model were assigned a distribution and the model was run for 2,000 simulations to generate total costs and QALYs. The inputs reportedly varied in the PSA and the assigned distributions are outlined in Table 94 the Appendix.

Probabilities, such as VTE-related death rate and event rates, were sampled from a beta distribution (bounded by 0 and 1). ORs were assumed to be distributed according to a lognormal distribution

18b	**NOAC patients receive an annual visit where they receive U&E**							
	Total costs (£)	£4,123	£4,033	£4,161	£4,061	£90	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£4,883	Dominant	Dominated
18c	**NOAC patients receive biannual visit where they receive U&E (less conservative approach)**							
	Total costs (£)	£4,168	£4,033	£4,206	£4,106	£135	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£7,315	Dominant	Dominated
19	**The number of INR monitoring visits for warfarin patients was reduced from 24 visits after 12 months to 10 visits per year (lifelong treatment scenario)**							
	Total costs (£)	£22,720	£15,192	£23,513	£22,698	£7,528	-£793	£23
	QALYs	12.54	12.36	12.55	12.62	0.19	0.00	-0.07
	ICER (compared with base case)					£40,359	£312,874	Dominated

Abbreviations used in the table: CG, clinical guideline; CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ICER, incremental cost-effectiveness ratio; INR, international normalised ratio; NOAC, novel oral anticoagulant; OR, odds ratio; PE, pulmonary embolism; PTS, post thrombotic syndrome; QALYs, quality-adjusted life years; QoL, quality of life; U&E, urea and electrolytes; VTE, venous thromboembolism,