Questions for clarification

Clinical effectiveness

RE-LY trial

A1) PRIORITY From Table 34, page 88 of the manufacturer submission, it is clear that there is a substantial increase in the rate of bleeding at 65 years. Please provide:

- Justification for swapping from DE150 mg to DE110 mg at 80 years of age rather at a younger age.
- Evidence for the dose reduction at aged 80yrs.
- The method for deriving the overall effect for the sequence population.

Response:

As stated in the final scope, dabigatran etexilate (DBG) is to be assessed within its licensed indication. A recent article published in the Journal of the American College of Cardiology noted that "…novel oral anticoagulants with a better safety profile than vitamin K antagonists, such as dabigatran, may represent promising agents in the aging population with atrial fibrillation." [1] The DBG sequence regimens presented in our submission represent the most accurate estimate of the proposed use of each dose that is currently proposed by Boehringer Ingelheim for the summary of product characteristics (SPC). These regimens incorporating dose reduction at age 80 years were implemented based on interim feedback from the regulatory authority (European Medicines Agency – EMA). This exact posology was also reflected in the recent approval of DBG in Canada [2]. With this in mind, the most appropriate DBG regimens have been presented within the main submission and no further justification is required.

The relative treatment effect for the sequence population is based on a *post-hoc* subgroup analysis of the RE-LY trial, as presented in Tables 35, 36, 63 and 64 (Reference 80) of the main submission.

A2) PRIORITY There was a protocol amendment where investigators were cautioned against the use of quinidine (and other P-glycoprotein inhibitors) due to an increased rate of bleeding with dabigatran.

- Please comment on what the impact of being unable to utilise P-glycoprotein inhibitors would be on the use of dabigatran for, and the management of, atrial fibrillation in clinical practice.
- Please comment on any bias this change in recommendation may have on the trial results.

Response:

It is inaccurate to state that the protocol amendment was enacted as a result of an increased rate of bleeding. The protocol amendment [3] states that:

"[redacted]"

DBG was recently approved in both the US [4] and Canada. Neither the US nor Canadian label contains a general contraindication or dose-adjustment for concomitant use of P-glycoprotein inhibitors, e.g. from the Canadian product monograph [2]:

"P-gp inhibitors like verapamil, quinidine and amiodarone may be expected to increase systemic exposure to dabigatran, see Table below. The strong P- glycoprotein inhibitor ketoconazole, when administered orally, is contraindicated. If not otherwise specifically described, close clinical

surveillance (looking for signs of bleeding or anaemia), along with a sense of caution is required when dabigatran is co-administered with strong P-glycoprotein inhibitors."

See page 30 and 31 of the attached Canadian monograph for more detailed discussion of this issue [2]. Therefore it is not expected that the European SPC will preclude the concomitant use of P-glycoprotein inhibitors (with the exception of ketoconazole) with DBG in routine practice. Ketaconazole is a synthetic antifungal drug used to prevent and treat skin and fungal infections, especially in immunocompromised patients such as those with AIDS or those on chemotherapy. Therefore it is not a compound specifically used to treat patients with AF (or the usual comorbidities expected in patients with AF).

There is no indication that the results of RE-LY have been systematically changed due to this protocol amendment. This amendment is also in line with the regulatory views in Canada and the US.

A3) The RE-LY trial provides data for the risk of events while on warfarin or dabigatran. Please comment on the generalisability of the RE-LY trial to the UK population, including:

- How similar are the event rates from the RE-LY trial to those in the UK atrial fibrillation patient population and
- How similar are the characteristics of the patients in the RE-LY trial to the atrial fibrillation patients of the UK

Response:

A study by Rietbrock *et al* (2009) [5] examined the effectiveness of current practice in stroke prevention in atrial fibrillation in the UK, via an analysis of the General Practice Research Database (GPRD). This analysis showed that the incidence of stroke in current warfarin users was approximately 1.53 per 100 person-years, equating to a two-thirds risk reduction compared to no warfarin use. This corresponds well with the rate of stroke in warfarin patients studied in RE-LY (1.58% yearly event rate for stroke).

Further, extensive subgroup analyses were performed to examine whether the results of the RE-LY trial were applicable across various demographic and baseline characteristic. These subgroup analyses for the primary endpoint are presented in **Figure 1** and **Figure 2** for each DBG dose (taken from the QC Information Amendment, reference 1 in the main submission). No interaction was found for any baseline demographic factor, giving confidence that the results for the primary endpoint are generalisable.

Figure 1 Subgroup analyses for DBG 110mg bid (primary endpoint)

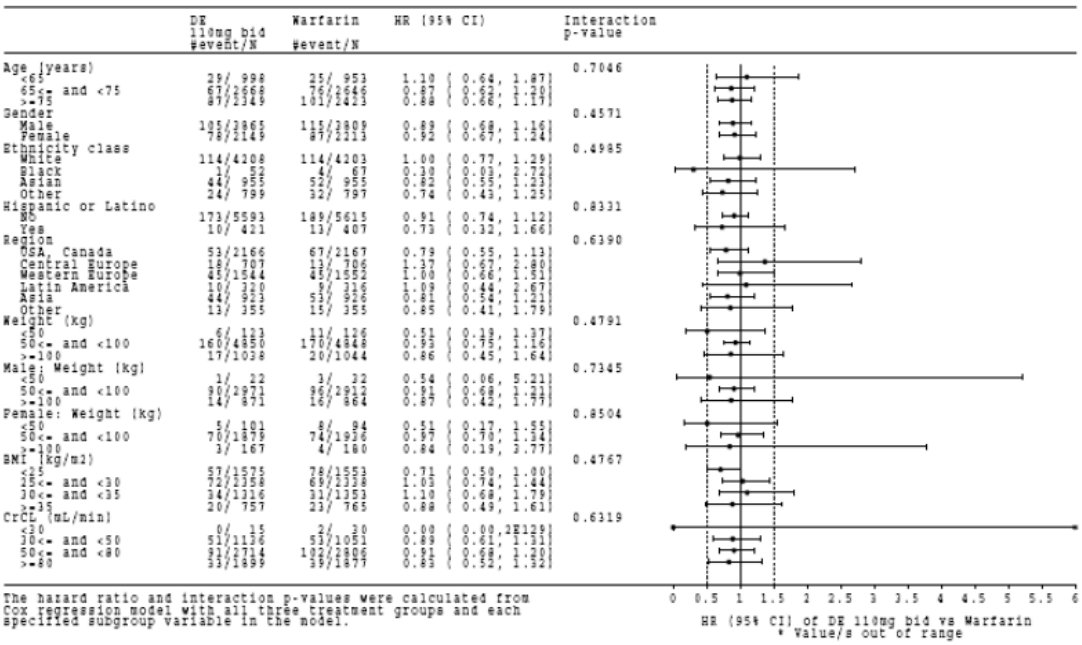
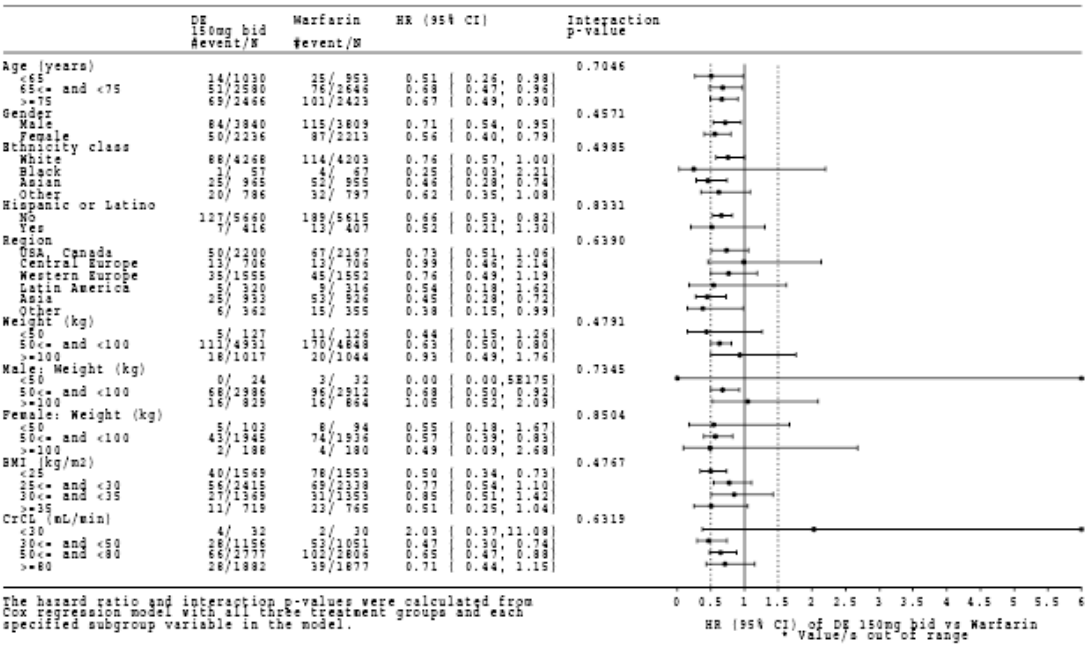


Figure 2 **Subgroup analyses for DBG 150mg bid (primary endpoint)**



Further, **Figure 3** and **Figure 4** (also from the same source) show the corresponding subgroup analyses for the major bleeding endpoint for both DBG doses. Similarly, no interaction was found (with one exception) which further demonstrates the generalisability of the clinical trial results. The only exception was that of age, further demonstrating the rationale for a stratification of dosing by age as discussed in A1 above.

Figure 3 **Subgroup analyses for DBG 110mg bid (major bleeding)**

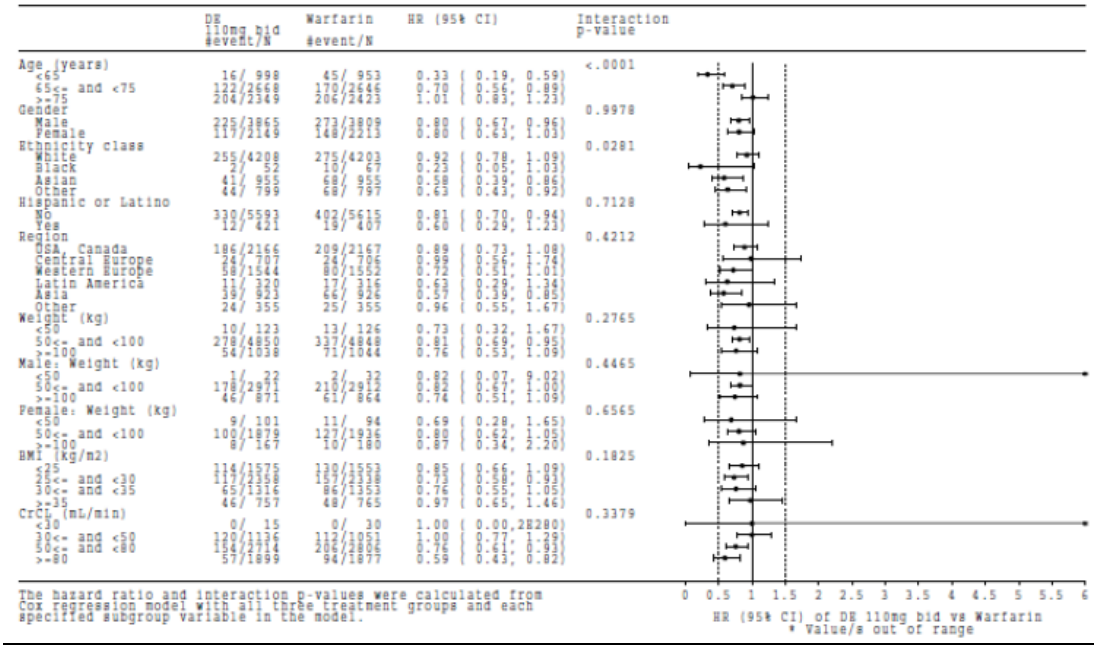
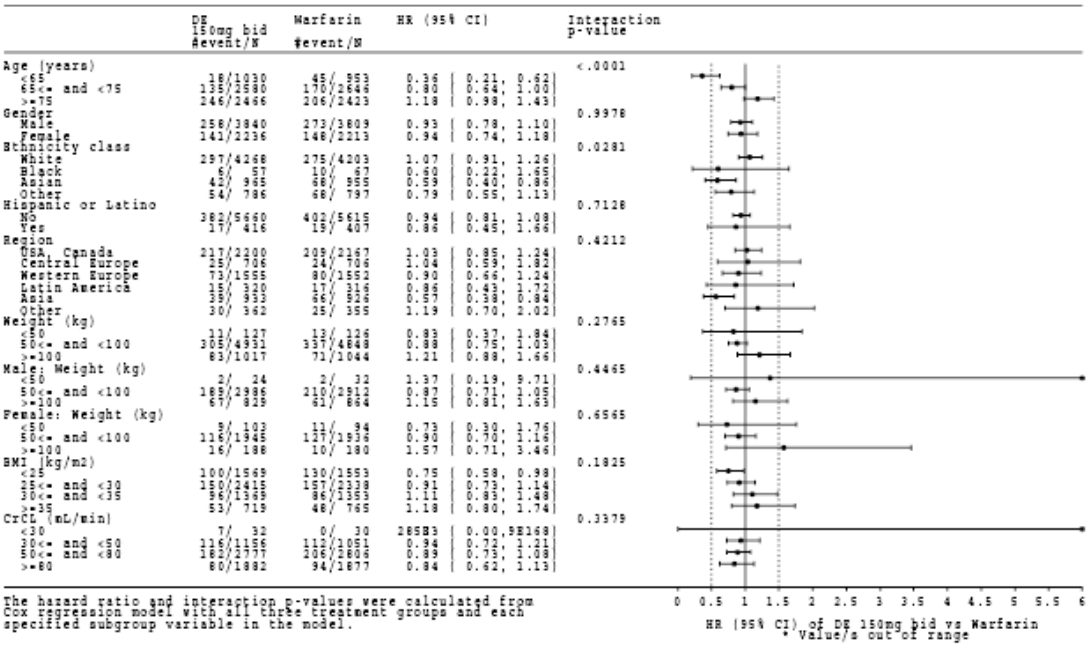


Figure 4 Subgroup analyses for DBG150mg bid (major bleeding)



A4) According to the clinical trial report (CTR), there were 846 patients with important protocol violations (that is they did not meet the entry requirements): 282 in the dabigatran 110mg group, 304 in the dabigatran 150mg group, and 260 in the warfarin group. According to Table 27 (page 71) in the manufacturers submission, the difference in the numbers of patients in the randomised/ITT population and the per protocol population were: 1194 in the dabigatran 110mg group, 1279 in the dabigatran 150mg group, and 910 in the warfarin group. Please explain these differences and the nature of the protocol violations.

Response:

The difference can be explained by the definition of the per protocol set (PPS). The PPS included all patients randomised *and* treated (i.e. patients eligible for the treated set) who did not have important protocol violations. The treated set included all randomised and treated subjects who were on study drug at least 70% of the time during the study or were on study drug at least 70% of the time prior to the onset of a stroke/systemic embolism. The final treated set comprised 15,266 patients and the final PPS comprised 14,730 patients. The difference between the two does not equal the number of patients with protocol violations (846) due to some patients meeting both reasons for exclusion.

The vast majority of protocol violations were due to patients not meeting the inclusion criteria as they had no additional risk factor for stroke (546 patients from 846 violations). The majority of other violations (193 patients) were due to the presence of an exclusion criterion, namely history of valve disorders.

A5) Please justify the protocol amendment for measuring quality of life in the RE-LY trial (measurements up to 12 months rather than up to 36 months).

Response:

The RE-LY study utilised a time-to-event trial design, and it is known that major QoL decrements in this indication will occur due to patients suffering a stroke. The disability associated with these events was assessed using a standard and validated disease-specific measure, i.e. the Modified Rankin Scale. With regards QoL assessments associated with anticoagulation treatment, it was determined that one year would be sufficient since this would result in less contamination from study events, leading to less chance of survivor bias.

A6) Please comment on why some analyses in the CTR report statistically significant p-values when the CI for the HR includes 1, and why there is such a large increase in the p-value in associated

analyses for very small differences in the HR and CI. For example, composite of stroke, systemic embolism, PE, MI, death and major bleed:

- DE 150 vs. warfarin: HR 0.91 (95% CI 0.82, 1.00), p=0.0393
- DE 110 vs. warfarin: HR 0.93 (95% CI 0.84, 1.02), p=0.1050

Response:

Although it appears that the upper bound of the 95% confidence interval exceeds 1 this is simply due to rounding. The upper bound of the confidence interval is in fact just below 1 and has been rounded up to the value 1.00 in order to present the results to 2 decimal places.

Due to the large sample size of the trial, with approximately 6,000 subjects per treatment arm, the estimated hazard ratios are quite precise. For this reason even a small change in the estimated hazard ratio can change the p-value by a seemingly large degree. Considering that that the estimated hazard ratio comparing DBG to warfarin is 2% lower in the DBG 150mg bid group than in the DBG 110mg bid group, and one confidence interval spans 1 and the other does not, the differences between the p-values for these two estimates is to be expected.

The values stated in the example are from the original analysis. The corresponding values from the re-analysis are as follows [6]:

- DBG 150mg bid vs. warfarin: HR 0.90 (95% CI 0.82, 0.99), p=0.0246
- DBG 110mg bid vs. warfarin: HR 0.92 (95% CI 0.84, 1.01), p=0.0968

MTC

A7) PRIORITY Please provide a justification for choosing the MTC (SAS) for the base-case instead of the results from the MTC (WinBUGs).

Response:

MTC is a statistical inference derived from a generalised linear model with random effects. In fact, the two separate MTC approaches (SAS and WinBUGS) fit the same statistical model with different computational algorithms.

Given the very nature of the WinBUGS algorithms, the results (point estimates) from WinBUGS may be very close to the real solution, but they never are the real solution. In SAS, PROC GLIMMIX arrives at the solution directly using likelihood based methods. In WinBUGS, different arbitrary analytical factors can affect the overall results (e.g. seed number, length of burning, length of the chain). In SAS (PROC GLIMMIX in this case), the same result is arrived at, regardless of the statistician running the analysis – i.e. the results are readily repeatable.

WinBUGS is a powerful software program that is particularly adaptable and useful in the cases where true Bayesian methods are needed and in cases where the amount of data is very small. In our MTCs, on the whole, the data sample is reasonably sized and it is not necessary to employ full Bayesian techniques; i.e. non-informative priors were used.

For the reasons above, and the fact we see results closer to the head to head input data within the SAS analyses, the SAS-based results were preferred as our base-case analysis, as they more closely reflect the underlying data, whereas the WinBUGS-based results tend to overestimate the variability of the relative treatment estimates.

Nevertheless, the economic model was tested using both MTC approaches and the effect on overall results was minimal. For completeness comparative deterministic ICERs are provided in **Table 1** below.

Table 1 Comparative ICERs for both MTC approaches

Analysis	SAS MTC	WinBUGs MTC
DBG sequence <80 vs. aspirin	£4,536	£4,937
DBG sequence <80 vs. A+C	£2,571	£3,830
DBG sequence >80 vs. aspirin	£3,719	£4,273
DBG sequence >80 vs. A+C	£2,038	£3,778
DBG 150mg bid vs. aspirin	£4,434	£4,676
DBG 150mg bid vs. A+C	£1,954	£3,322
DBG 110mg bid vs. aspirin	£9,397	£9,691
DBG 110mg bid vs. A+C	£6,213	£8,499

A8) PRIORITY Please provide a comparison of the different hazard ratios from the MTC (SAS), MTC (WinBUGs) analyses and the direct pairwise results and justify any discrepancies between them. A template is provided below to assist in reporting these results (See Appendix A).

Response:

The Appendix A table has been completed for the following endpoints:

- Ischaemic stroke
- All-cause mortality
- Myocardial infarction

NB: Some comparisons will not be immediately directly comparable due to the numerator and denominator being flipped for some estimates. This is due to reporting limitations in the original source data.

For WFN vs. ASA, the pairwise source is the BAFTA study (reference 97 in main submission).

For WFN vs. A+C, the pairwise source is the ACTIVE-W study (reference 91 in main submission).

For ASA vs. A+C, the pairwise source is the ACTIVE-A study (reference 39 in main submission).

All analyses show good consistency in the estimates between the pairwise results and the results of both MTCs. As noted above, the main difference between the MTCs is the degree of precision, i.e. the width of the confidence/uncertainty intervals. Comparative forest plots showing the various MTC results and the corresponding RE-LY results are shown in **Figure 14** to **Figure 19**.

A9) PRIORITY Please provide the WinBUGs code used for the MTC (WinBUGs).

Response:

The code is presented in Section 6.3 of the attached technical report [7].

A10) PRIORITY Please provide the statistics on model fit.

Response:

Firstly, model fit can be assessed informally via the comparison of results seen in the MTC versus those seen in the head to head trials. As seen in response to A7, the results presented in the SAS MTC analyses closely match those from the head to head data both for the point estimates of relative risks and also the confidence interval estimates.

In addition to the sense-check comparisons, **Table 2** also presents the estimates for the reduced chi-squared statistic; i.e. the generalised chi-square divided by the degrees of freedom used in the model. Estimates of the reduced chi-squared statistic close to 1.0 indicate a well fitting model, particularly with respect to the specified random effects.

Table 2 Reduced chi-squared statistic by endpoint

Endpoint	Statistic
All Stroke	0.97
Ischaemic Stroke	0.99
Haemorrhagic Stroke	0.91
Fatal or Disabling Stroke	0.95
Systemic Embolism	1.14
Mortality	0.95
Transient Ischaemic Attack	0.69
Intracranial Haemorrhage	0.80
Extracranial Haemorrhage	0.81
Minor Bleeds	1.39
Acute Myocardial Infarction	1.23
Cardiovascular Mortality	1.38
Any Bleeds	2.01

A11) PRIORITY Please provide testing for inconsistency (that is, variation in treatment effects between pair wise contrasts; frequentist pairwise analyses for the head to head trials in the network analyses).

Response:

Please refer to the response to A10.

A12) PRIORITY Please explain how the SAS code is dealing with the correlation within the multi-arm trials.

Response:

The correlation between treatment arms from the same trial is incorporated into the model by the trial specific random effects, regardless of the number of treatment arms within the trial. In our analyses, the input data to the model is presented as one observation per trial/treatment arm combination. The common problem of correlation within trials with >2 treatment arms becomes only an issue when treatment differences are modelled rather than absolute treatment effect estimates, as is the case in our analyses.

A13) PRIORITY Covariates were individually explored for four outcomes; please explain why these variables were explored in these four outcomes only, and not the other seven clinical outcomes presented in the MTC.

Response:

The endpoints explored with covariates were selected for pragmatic reasons. For the purposes of our analyses, it was determined that to explore the covariates for all endpoints would have been extensive, and that the effects could be reasonably examined by selecting a sample of endpoints. The endpoints selected were those that were deemed to be major model determinants.

A14) PRIORITY Trials with zero event arms were excluded from the MTC, please justify the exclusion of these trials.

Response:

Please refer to section 7.2 of the attached technical report.

Cost effectiveness

Treatment sequence

For questions B1-B4: Currently the economic model allows the evaluation of a restricted number of treatment sequences. Therefore please provide the information requested in order to allow the assessment of all treatment sequences which could be considered appropriate to UK clinical practice.

B1) PRIORITY The ERG wish to evaluate the potential cost-effectiveness of dabigatran (110mg and 150mg) used as either a first line treatment or as a second line treatment option following warfarin.

Please provide a revised model with the ability to choose any of the included treatments as either a first line or a second line treatment option.

Response:

Given that there are six treatments in the single dose model, each treatment arm could contain 25 $1^{st}/2^{nd}$-line combinations, enabling 600 pair-wise comparisons to be made. The complexity of this model and the time constraints for the response unfortunately preclude the provision of a new model.

The interventions provided in the model and the lines of therapy were based on clinical guidelines, current clinical practice and clinical expert opinion, and designed to model clinically feasible scenarios. Therefore most of the potential pair-wise comparisons would not be realistic or reflective of clinical practice. Hence the choice of active comparators as WFN 1^{st} /ASA 2^{nd}, ASA 1^{st} /NT 2^{nd}, and A+C 1^{st} /ASA 2^{nd}.

The decision not to include anticoagulants as both first and second line treatments was taken based on clinical advice. Whilst the SPC for DBG had not yet been finalised, it is expected that patients contraindicated for warfarin (due to haematological reasons) would also be contraindicated to DBG.

Further, this step would also result in an unmanageable level of complexity in the model as the reason why a patient was discontinued from DBG/WFN would be needed, and whether they can be switched to WFN/DBG. This would result in unsupported assumptions and therefore a pragmatic approach was taken whereby the alternative clinical pathways were modelled and compared. Additionally, the RE-LY trial randomised patients that were eligible for anticoagulation therapy and was a head-to-head study. No clinical efficacy and safety evidence has been generated that would provide data for patients having failed an initial anticoagulation treatment and then progressing to the next. As pointed out before, it is also unknown how many patients would remain eligible for anticoagulation therapy once they 'failed' the first treatment choice.

In summary the economic model is designed to answer the relevant decision problem: is replacing warfarin with dabigatran etexilate cost-effective? This requires comparable treatment sequencing in both arms of the respective model.

B2) PRIORITY Please provide the base-case cost-effectiveness results comparing dabigatran 110mg and 150mg when used as either a first line treatment or as a second-line treatment following warfarin. Please present these results for both the single and sequential dose models.

Response:

Please refer to the response to B1 above. This is impractical and can not be modelled as it is not clear which patients withdrawn from DBG/WFN would move to WFN/DBG.

Therefore the pragmatic approach was taken to compare alternative clinical therapy scenarios where for clinical reasons DBG is seen as a replacement to WFN in suitable patients. This is also reflecting the data generated by the RE-LY trial which provides the highest level of head-to-head evidence.

B3) PRIORITY Please consider incorporating a third line of treatment in the model, which will allow the user to choose any sequence of treatment and provide a revised model with this additional functionality.

Response:

As noted above the complexity of the model and the time constraints for the response prohibit the provision of an updated model with this functionality.

B4) PRIORITY Please analyse and provide the base-case cost-effectiveness results of the comparison between these two specific treatment sequences: Dabigatran → Warfarin → Aspirin → No treatment in comparison with Warfarin → Aspirin → No treatment. Please present these results for both the single and sequential dose models for dabigatran 110mg and 150mg.

Response:

Please refer to the responses above.

In summary these changes are not implemented for the following reasons:

- Practical reasons (time limitations)
- Complexity of the existing model
- Expert clinical advice on the currently modelled treatment sequences
- Lack of data/clinically invalid

Further, in spite of these limitations, we strongly believe that sufficient evidence has been presented to make the case that DBG is a cost-effective option ahead of WFN. Given the PSA and other sensitivity analysis presented in the main submission, these results appear robust and variation in lines of therapy would not be expected to change the conclusions.

Pairwise comparisons

B5) PRIORITY Please provide the results of the cost-effectiveness analysis using simultaneous comparisons between dabigatran (150mg and 110mg) and all comparators, namely:

- Fully incremental comparison of the ICERs
- Cost-effectiveness acceptability curves
- Probability of cost-effectiveness at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.
- For all patients and separately for patients aged <80 and 80+.

Response:

The model is currently not structured to enable comparisons between 150mg bid and 110mg bid. Restructuring the model would enable this comparison, however this would be complex and time consuming. It is also not reflective of the expected posology according to the draft SPC currently under EMA review and already approved in Canada [2].

As an approximation, deterministic results can be compared, and are shown in **Table 3** for the single-dose model. This results in extended dominance of DBG 150mg bid over DBG 110mg bid.

Table 3 Incremental analysis for all treatments in the single-dose model

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,080	7.082	Baseline			
WFN	£15,583	7.283	£503	0.201	£2,502	£2,502
A+C	£16,070	7.061	£990	-0.021	D	D
DBG 150mg bid	£16,923	7.497	£1,843	0.415	£4,441	£6,262
DBG 110mg bid	£18,385	7.433	£3,305	0.351	£9,416	ED

D – dominated; ED – extended dominated.

This result is expected as patients on DBG 150mg bid experience fewer strokes and therefore lower levels of long-term disability than patients on DBG 110mg bid.

These comparisons can not and should not be made in the sequence model as the clinical data used is specific to dose and age. The average age in the sequence model < 80 years is 69.1 years and the average age in the sequence model ≥ 80 years is 82.9 years. Therefore both costs and QALYs differ substantially between analyses. Adapting the sequential model so that the 110mg bid dose could be used in patients < 80 years and the 150mg bid dose in patients ≥ 80 years is not appropriate as this is not the expected labelled posology.

However, an additional deterministic analysis can be produced to compare the results from the sequential model to the single-dose model. This involves setting the initial conditions in the sequence model to those in the single-dose model (i.e. age at model entry, % male, $CHADS_2$ and previous stroke distribution). This produces the results in **Table 4**.

Table 4 Incremental analysis for all treatments from the single-dose and sequential models using initial conditions from the single-dose model

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,080	7.082	Baseline			
WFN	£15,583	7.283	£503	0.201	£2,502	£2,502
A+C	£16,070	7.061	£990	-0.021	D	D
DBG 150mg bid	£16,923	7.497	£1,843	0.415	£4,441	£6,262
Sequence model	£17,767	7.449	£2,687	0.367	£7,313	ED
DBG 110mg bid	£18,385	7.433	£3,305	0.351	£9,416	ED

D – dominated; ED – extended dominated.

Whilst DBG 150mg bid has extended dominance over both the DBG 110mg bid and the sequence model, it should be noted that all three are cost-effective compared to treatments available in current clinical practice.

Treatment adherence and discontinuation

B6) PRIORITY Page 166 of the manufacturer's submission states "To represent this discontinuation rate for first-line treatment, Kaplan-Meier curves from the RE-LY trial were fitted to Weibull distributions for DBG and WFN (Table 82)". Please provide the original Kaplan-Meier curves for treatment discontinuation.

Response:

Kaplan-Meier curves are provided in and **Figure 5** to **Figure 13.**

B7) PRIORITY Please also provide the Kaplan-Meier probabilities of discontinuation at 30 days, 90 days, 1 year and 2 years.

Response:

Treatment adherence (discontinuation) KM estimates (RE-LY total population):
30 days DBG 110mg bid: [redacted] % ([redacted] %) DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
90 days DBG 110mg bid: [redacted] % ([redacted] %) DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
360 days DBG 110mg bid: [redacted] % ([redacted] %) DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
720 days DBG 110mg bid: [redacted] % ([redacted] %) DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)

Treatment adherence (discontinuation) KM estimates (RE-LY >=80y population)
30 days DBG 110mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
90 days DBG 110mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
360 days DBG 110mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
720 days DBG 110mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)

Treatment adherence (discontinuation) KM estimates (RE-LY <80y population)
30 days DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
90 days DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
360 days DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)
720 days DBG 150mg bid: [redacted] % ([redacted] %) WFN: [redacted] % ([redacted] %)

B8) PRIORITY Please provide additional justification for using a Weibull distribution for treatment discontinuation of first-line treatments rather than alternative distributions. Provide the results of fitting the Kaplan-Meier curves for treatment discontinuation to different distributions including, log logistic, log normal, Gompertz and exponential. Results should include the goodness of fit statistics and parametric estimates.

Response:

Treatment discontinuation due to non-adherence was considered in the model using trial and published studies to inform predictions from model start through to 6 years. After 6 years the discontinuation due to non-adherence is assumed to be 0 based on feedback from the clinical panel who indicated that patients who have remained adherent to drug for that length of time are likely to

remain adherent. This assumption is supported by published studies [8-9] that indicate a plateauing of treatment non-adherence by six years.

The Weibull function was used to describe treatment discontinuation in the base case because this distribution fit the empiric RE-LY data well and allowed predictions beyond the median trial follow-up of 2 years up to 6 years. Additionally, for the aspirin arm, which was not in the RE-LY trial, the data were only available from a published survival graph and so a Weibull distribution could be estimated.

Two general approaches were tested further and are described here. 1) Different parametric survival functions were fitted to the empiric data, and 2) the empiric data were used to inform the first two years, and then a constant hazard based on the average of the second year was used to estimate discontinuation beyond year 2, i.e. the median duration of the trial.

The fit statistics of the parametric functions, summarised using Akaike Information Criteria, and visual inspection indicate that overall the Weibull and Lognormal distributions best fit the data (see **Table 5**) and **Figure 5** to **Figure 13**. The results in **Table 5** (low values relate a better fit) suggest that the fits for Weibull, Lognormal, Loglogistic and Gamma are broadly similar across datasets, whereas the Exponential model has a poorer fit.

Table 5 Comparison of Akaike Information Criteria

	Exponential	Weibull	Lognormal	Loglogistic	Gamma
RE-LY All					
110 mg	9654	9116	9085	9111	9125
150 mg	10163	9598	9563	9592	9608
Warfarin	7915	7709	7753	7716	7705
<80					
110 mg	7602	7191	7166	7187	7199
150 mg	7824	7390	7367	7386	7397
Warfarin	6246	6084	6119	6089	6082
80+					
110 mg	2010	1889	1884	1889	1893
150 mg	2277	2154	2142	2151	2160
Warfarin	1641	1601	1611	1603	1601

Figure 5 **Adherence Curve of Single Dose Dabigatran 110mg bid**

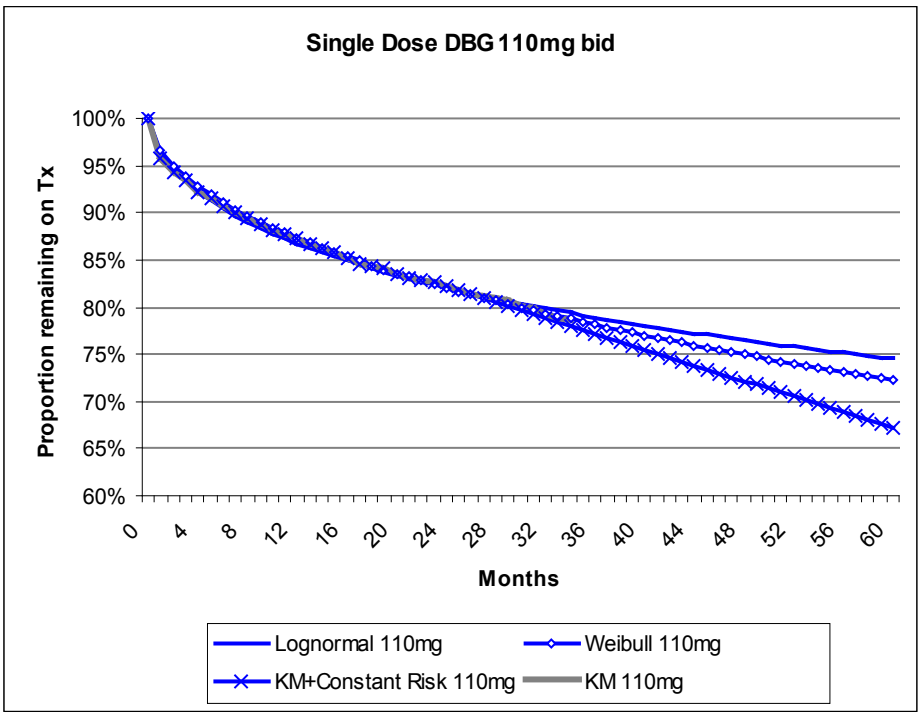


Figure 6 **Adherence Curve of Single Dose Dabigatran 150mg bid**

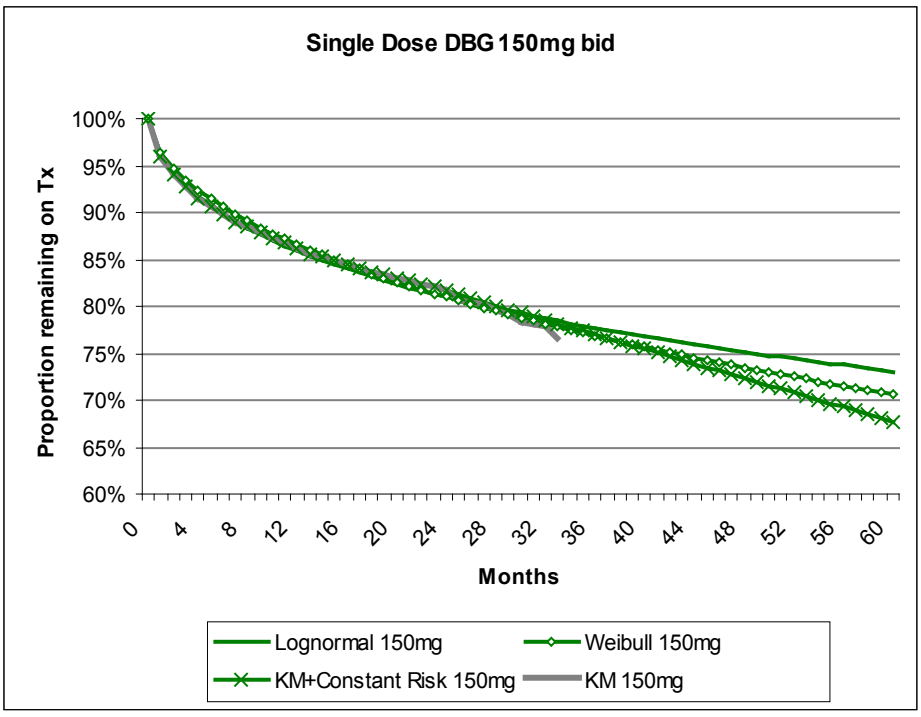


Figure 7 **Adherence Curve of Single Dose Warfarin**

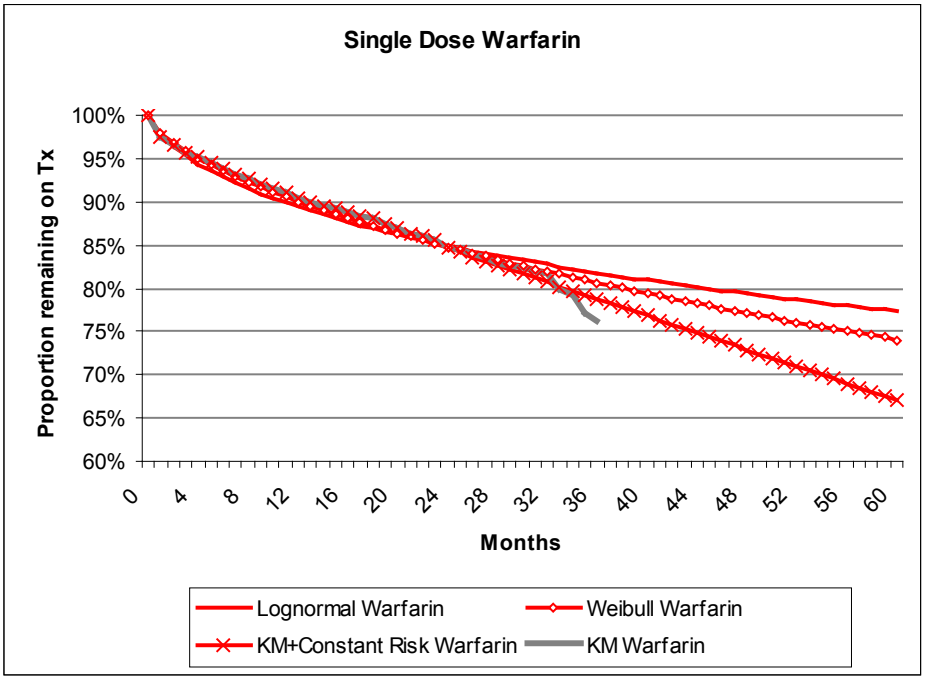


Figure 8 **Adherence Curve of Sequence Dose Dabigatran 110mg bid (Population Age<80)**

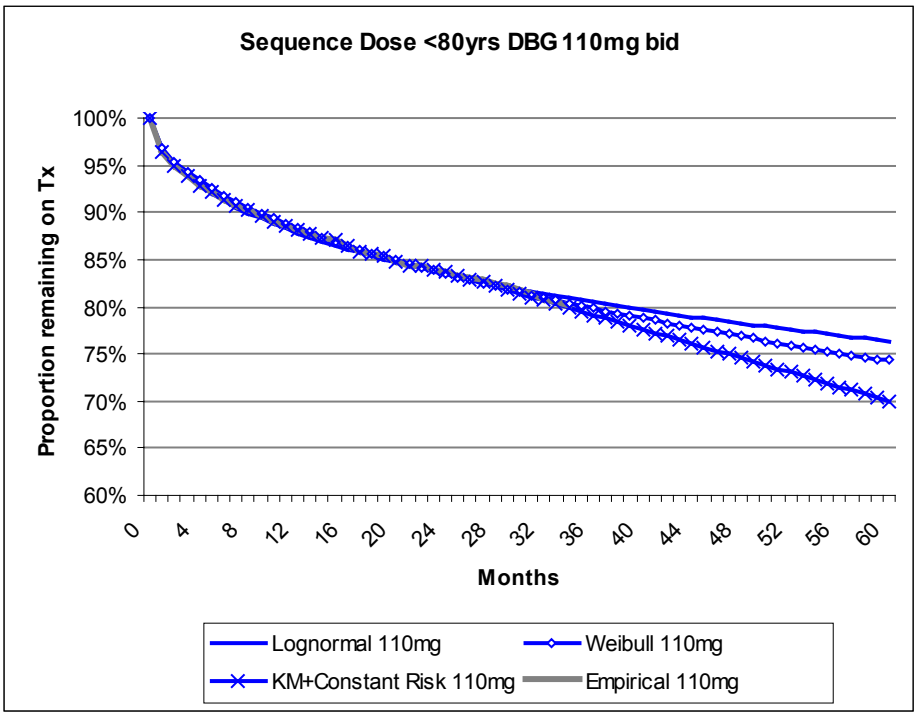


Figure 9 **Adherence Curve of Sequence Dose Dabigatran 150mg bid (Population Age<80)**

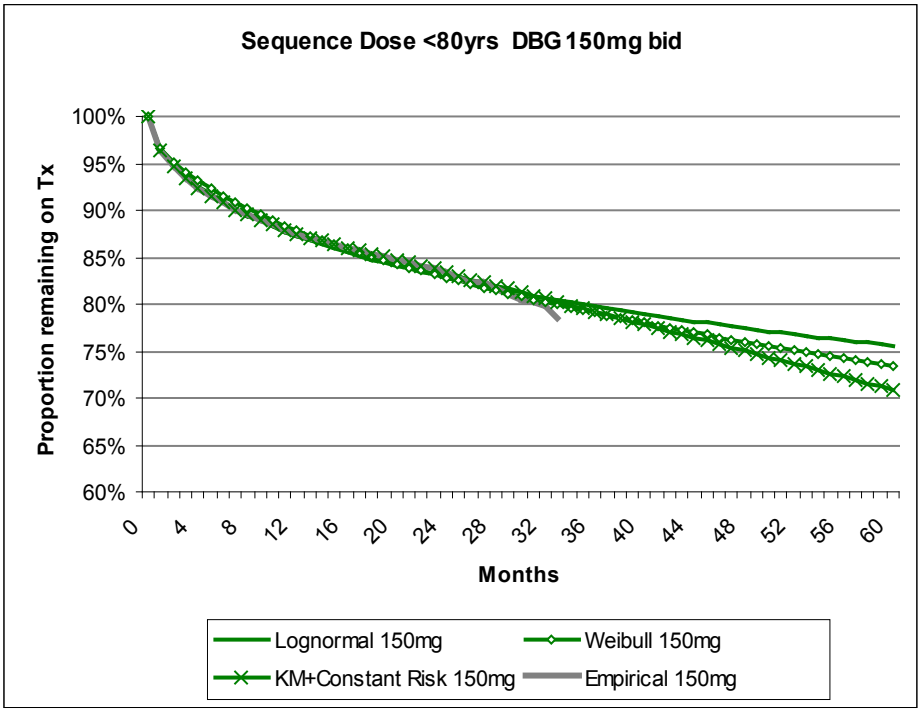


Figure 10 **Adherence Curve of Sequence Dose Warfarin (Population Age<80)**

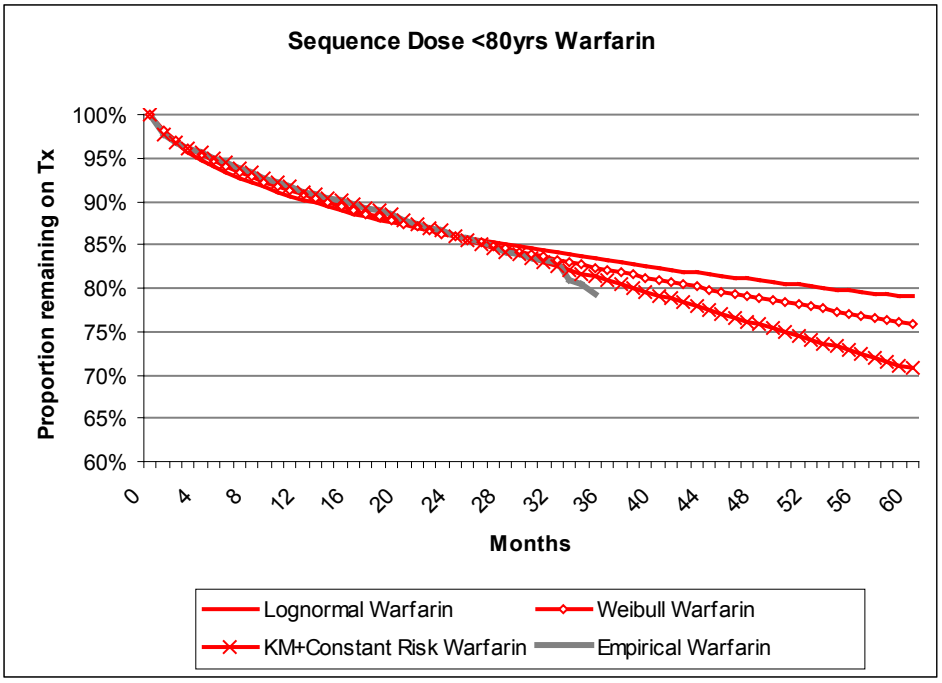


Figure 11 **Adherence Curve of Sequence Dose Dabigatran 110mg bid (Population Age 80+)**

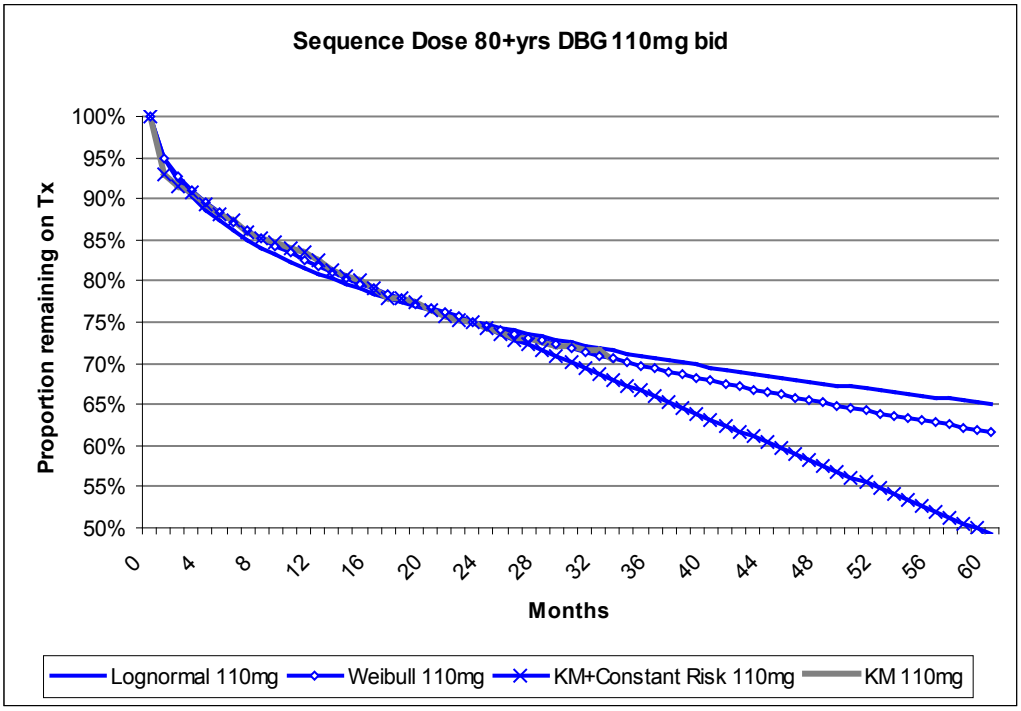


Figure 12 **Adherence Curve of Sequence Dose Dabigatran 150mg bid (Population Age 80+)**

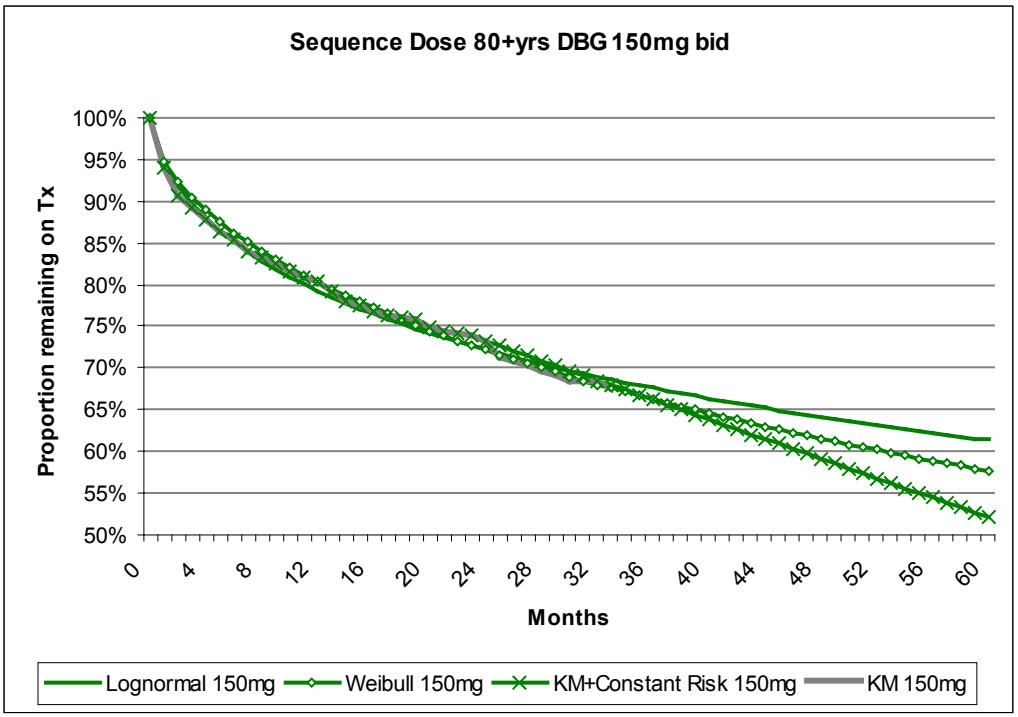
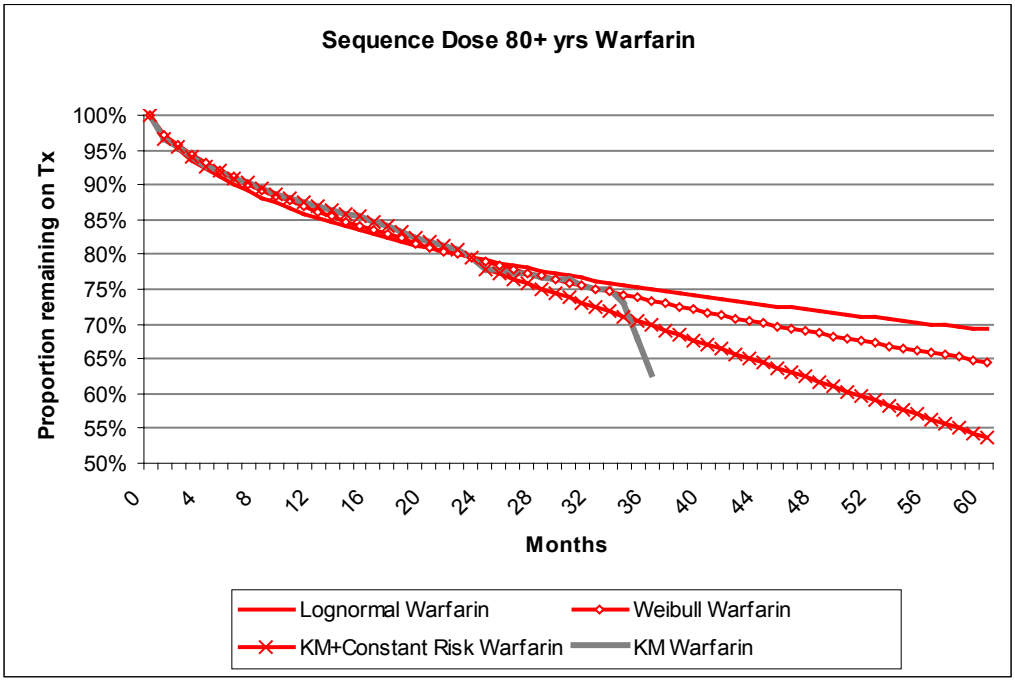


Figure 13 Adherence Curve of Sequence Dose Warfarin (Population Age 80+)



B9) PRIORITY Please also present additional sensitivity analysis for the cost-effectiveness results using alternative survival distributions as well as using the Kaplan-Meier curves followed by constant discontinuation after 2 years. Please present the results of these sensitivity analyses for both the single and sequential dose models.

Response:

The Weibull and lognormal functions were implemented in the model, along with the KM + constant hazard rate assumption. The parameters for the Weibull and lognormal functions are presented in **Table 6**.

Table 6 Parameters of Weibull and Lognormal Functions

	Weibull		Lognormal	
	Intercept	Weibull Shape	Intercept	Scale
RE-LY All				
110 mg	9.5824	0.5426	9.8589	3.5573
150 mg	9.4467	0.546	9.6596	3.4912
Warfarin	9.3549	0.6527	9.9367	3.2333
<80				
110 mg	9.744	0.5436	10.1016	3.6051
150 mg	9.6792	0.541	10.008	3.6046
Warfarin	9.5011	0.6491	10.1721	3.3025
80+				
110 mg	8.8448	0.5456	8.7962	3.3091
150 mg	8.5569	0.5707	8.396	3.0574
Warfarin	8.7484	0.6694	8.9919	2.9494

As incremental cost per QALY results indicate (**Table 7**), the impact of these different approaches for estimating the treatment discontinuation have a minimal impact on the ICER for both the single dose and dose sequence models.

Table 7 Comparison of ICERs in Different Scenarios

ICER (£)	Lognormal	Weibull	KM+Constant Risk
Single dose	6,305	6,264	5,947
Sequence dose; <80 RE-LY population	7,405	7,314	6,969
Sequence dose; 80+ RE-LY population	8,032	7,873	8,004

B10) PRIORITY Discontinuation from aspirin is currently estimated by applying the absolute discontinuation rates from the Mant et al (2007) paper. Please present an additional sensitivity analysis using the relative effect of discontinuation for aspirin compared to warfarin from the same paper (2007) applied to the RE-LY data (warfarin) to obtain a new estimate for aspirin discontinuation rates. Present the results of these sensitivity analyses for both the single and sequential dose models.

Response:

Thirty-three percent of WFN patients discontinued and 24% of ASA patients discontinued, therefore the relative risk was 1.375. Therefore for this sensitivity analysis, withdrawal from WFN was 37.5% higher than for ASA. The results of this sensitivity analysis are shown in **Table 8**. Note that only the comparison to ASA is shown.

Table 8 Sensitivity analysis with discontinuation rate for ASA relative to WFN

Model	Base case	Sensitivity analysis
150 mg bid vs ASA	£4,434	£5,935
110 mg bid vs ASA	£9,397	£12,545
<80 sequence model, DBG vs ASA	£4,536	£5,997
80+ sequence model, DBG vs ASA	£3,719	£5,000

B11) PRIORITY The adherence curves used in the sequence models do not appear to match those presented in the report (figure 20 and figure 21, page 168). Please justify this discrepancy and discuss any implications this may have for the cost-effectiveness results.

Response:

This is due to a simple oversight. The incorrect curves were copied into the main submission, however the curves shown in the economic model are correct and these are the rates used in the analyses. Please accept our apologies for the error.

B12) PRIORITY Please clarify the meaning and model implications to the expression “permanent discontinuation” used in table 69, page 154 of the manufacturer’s submission to refer to the effect on treatment status from haemorrhagic stroke and intracranial haemorrhage events. Please also provide a sensitivity analysis in which the discontinuation due to events is varied between 0% and 100%.

Response:

Permanent discontinuation means a permanent withdrawal from both 1st and 2nd line treatments. For these patients costs and outcomes are then based on ‘no treatment’. 100% of patients permanently discontinue following an ICH or HS event. This was based on expert advice and clinical practice. Intracranial bleeding leaves patients vulnerable to the adverse effects of anticoagulation and antiplatelet treatment, as bleeding into the previous event site is particularly damaging. It should also be noted that such patients who suffer an intracranial bleeding while on anticoagulation or antithrombotic therapy, would be “re-exposed” to the treatment that –at least in the case of ICH- is very likely to have caused the harm.

The Canadian product monograph for DBG [2] also states that ‘As with all anticoagulants, PRADAX [DBG] should be used with caution in circumstances associated with an increased risk of bleeding.’ In the US label [4], DBG is contraindicated in patients with active pathological bleeding.

It should also be noted that this assumption is made in the publication on which the model is based (Sorensen *et al*. reference 111 in the main submission), co-authored by leading clinical experts in this field and published prior to the availability of the results from RE-LY; thus minimising potential bias.

Model structure

B13) Please comment further on the justification of modelling acute myocardial infarction as an acute event with only one-off costs and disutility, and with no consequences beyond 3-months. Please discuss any potential biases with the current approach.

Response:

A decision not to include AMI was initially recommended by the clinical expert panel convened early in the model design phase, prior to the outcomes of RE-LY being released. Following the results from RE-LY, it was clear that it would be appropriate to include AMI as an event. However, post-event costs and disutilites were not included for a number of reasons:

- Clinical expert opinion suggested that patients, if not immediately suffering a fatal event (which is modelled), would recover within 3 months, mostly without permanent (neurological) disabilities, which cannot be said for strokes. This is supported by results from a study by Parikh *et al* [10] which states that AMI case fatality rates for 30day, 1yr and 5yr do not largely change over these time periods.
- History of AMI has been shown in a recent German study (Schweikert *et al*. Eur Heart J, 2009) [11] to have limited impact on HRQoL as measured by EQ-5D for patients at least 65 years of age, which is the primary population of interest in this study.

Whilst the inclusion of long-term follow-up costs and disutility would be expected to decrease the cost-effectiveness of DBG, this would not be expected to be a large effect, given that the sensitivity analysis revealed that AMI is not a key model driver (Table 146, No. 35-36, 57-58 in the main submission document). Also, the rate of AMI is quite low overall in the RE-LY population and not significantly different across treatment arms.

Furthermore, the economic model already has a high degree of complexity and it was necessary to make some simplifying assumptions for pragmatic reasons. That is, inclusion of this extra degree of complexity would be extremely time and labour-intensive which, on the balance of probability, would be unlikely to add a great deal of extra information to the overall conclusions.

B14) Please provide additional justification for the exclusion of pulmonary embolism from the economic model. Please discuss any potential biases with the current approach.

Response:

The rates of pulmonary embolism were low, and similar to those observed for systemic embolism. The sensitivity analyses of systemic embolism (Table 146, No. 32-33, 47-48 in the main submission document) showed very little impact of variation in these on the overall cost-effectiveness. Given similar costs and outcomes for this event, similar results would be expected.

In addition, prevention of stroke and systemic embolism refers to arterial embolism. Pulmonary embolisms result from venous, not aterial, clots. Accordingly PE was excluded from the model for pragmatic reasons.

B15) Please provide additional justification for switching stroke status to a 'yes' following a transient ischaemic attack.

Response:

The most common cause of a TIA in patients with AF is a blood clot formed in the heart that occludes an artery in the brain. In a TIA, the blockage period is short lived with no permanent damage. Ischaemic strokes have similar cause therefore patients who have had TIA have an elevated risk of stroke. This is reflected in stroke risk algorithms such as $CHADS_2$ which assigns the same score to a TIA as a stroke. TIA is also specifically mentioned as a criterion for 'high risk' in the NICE stroke risk stratification algorithm in the NICE clinical guideline (reference 4 in the main submission).

It should be noted that switching stroke status to 'yes' incurs no additional costs or disabilities to the patient and only changes the risk of stroke.

B16) Please comment on why all non- intracranial haemorrhage events incur only a one-off cost and disutility.

Response:

Patients experience follow-up disability costs and disutilities following an IS/HS and ICH as a result of loss of brain function following the acute event. This does not occur for ECH where patients are expected to either suffer a fatal event or recover once appropriate therapy has been initiated and the bleeding subsided. Thus, long-term disability and disutility are not expected to be cost or utility drivers. This assumption is conservative for DBG as major bleedings were highest for WFN. Additionally, this assumption had to be made in light of the complexity of the model and the heterogeneity of bleeding events and their therapy in patients.

B17) Please justify why only one event can occur in each 3-month cycle in the model.

Response:

The frequency of events in the model was assumed to be no more than one per cycle due to distribution of events observed in RE-LY.

Including multiple events per cycle would have increased the complexity of the model considerably, as well as introducing additional assumptions relating to costs and utilities for simultaneous events, as well as a huge amount of redundancy in the model as many events would be unlikely to occur simultaneously (e.g. having ischaemic and bleeding events simultaneously).

The approach taken appears justified in the comparisons between the data and the model outputs in Section 6.7.1 of the main submission.

B18) Page 244 of the manufacturer's submission. When real-world warfarin INR distribution is changed to trial-like warfarin INR distribution, as expected the ICER is equal to the ICER in the base-case. However, changing the proportion of individuals on target range to 100% provides different ICERs for trial-like and real-world WFN: trial-like – ICER=£49,301/QALY; real-world=£60,259/QALY. Please justify the reasons behind these results, including:

- How the different warfarin scenarios impact the economic model?
- Does the choice of scenario have an influence on any inputs besides the proportion of individuals in each INR range?

Response:

The ICERs with trial-like warfarin (TW) are only affected by the TW INR control specified, while the real-world warfarin (RW) ICERs are influenced by both the TW and the RW ICERs (note that the ICER for RW improves when we assume that TW had better control). This behaviour is as designed to allow the RW control to reflect its deviation from the TW control. Manipulating the TW control is not a designed feature of the model and those results should not be considered meaningful. If the question is "what is the ICER of DBG compared to perfect INR control" the model is designed to evaluate that by changing the RW INR control to 100%, but still leaving the TW control as specified in the RE-LY data.

However, it should be noted that the cost of INR monitoring is based on the average patient, and that the cost of perfect INR control would be expected to be substantially higher. Therefore this would invalidate the ICERs derived using this assumption. More importantly, whilst realising that this is most likely a validation step, it is important to note that there is no evidence to suggest that clinical practice has ever managed to attain an average TTR (time in therapeutic range) approaching 100%, and therefore this comparison is not clinically relevant.

Model programming

B19) When the cost and utilities values are reset using the VBA button 'Reset Model Inputs' the parameter inputs no longer match those included in the base case analysis. Please confirm that the model is using the preferred base case parameter inputs and correct the stored inputs on each sheet if necessary.

Response:

We can confirm that the model is using the correct parameters and the stored inputs have been corrected.

Textual clarification and additional points

C1) Please explain the following discrepancies between the CTR and the main submission (see below table):

- The incidence of MI and PE
- The HR and CIs

Outcome	110 vs. WFN HR (95% CI)		150 vs. WFN HR (95% CI)	
	CTR	Submission	CTR	Submission
Composite Stroke/SE	0.91 (0.75, 1.12)	0.90 (0.74, 1.10)	0.66 (0.53, 0.82)	0.65 (0.52, 0.81)
Ischaemic stroke	1.14 (0.91, 1.44)	1.13 (0.89, 1.42)	0.76 (0.58, 0.98)	0.75 (0.58, 0.97)
MI	1.35 (0.98, 1.87)	1.29 (0.96, 1.75)	1.38 (1.00, 1.91)	1.27 (0.94, 1.71)

Response:

We will require some more clarification on this query as it is unclear which "CTR" is being referred to. Reference 1 to the main submission (RE-LY QC Information Amendment) is the primary data source for the RE-LY trial used throughout the submission and the values in this source match those in the submission. See Table 15.2.1.1: 3, Table 15.2.1.1: 8 and Table 15.2.6.1: 1 in the Information Amendment to match the source data with that presented in the submission. Please also refer to the correction letter published on November 4th 2010 in the New England Journal of Medicine [12].

The original CTR was compiled prior to the RE-LY trial re-evaluation and is therefore not referred to as a primary data source in the submission. A revised CTR including the re-evaluation is now available [6].

Appendix A

Figures in upper part of matrix (in bold) are the direct pairwise results and figures in lower part of the matrix are the MTC results for all possible pairwise comparisons. NA = not applicable

(i) MTC (SAS) analyses compared to direct pairwise results – Ischaemic stroke

Ischaemic stroke	**DBG 150mg**	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**1.50 (1.17, 1.92)**	**0.75 (0.58, 0.97)**	NA	NA
DBG 110mg	1.45 (1.09, 1.92)	*	**1.13 (0.89, 1.42)**	NA	NA
WFN	0.77 (0.58, 1.03)	1.12 (0.86, 1.45)	*	**0.30 (0.13, 0.63)**	**2.17 (1.51, 3.13)**
ASA	0.48 (0.27, 0.84)	0.69 (0.40, 1.20)	0.62 (0.38, 1.01)	*	**0.68 (0.57, 0.80)**
A+C	0.37 (0.23, 0.61)	0.54 (0.33, 0.87)	0.48 (0.32, 0.73)	0.78 (0.41, 1.48)	*

(ii) MTC (WinBUGs) analyses compared to direct pairwise results - Ischaemic stroke

Ischaemic stroke	**DBG 150mg**	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**1.50 (1.17, 1.92)**	**0.75 (0.58, 0.97)**	NA	NA
DBG 110mg	1.45 (0.77, 4.08)	*	**1.13 (0.89, 1.42)**	NA	NA
WFN	0.80 (0.50, 1.65)	1.15 (0.72, 4.34)	*	**0.30 (0.13, 0.63)**	**2.17 (1.51, 3.13)**
ASA	0.49 (0.23, 1.05)	0.70 (0.34, 2.14)	0.60 (0.33, 1.00)	*	**0.68 (0.57, 0.80)**
A+C	0.41 (0.21, 1.35)	0.59 (0.29, 3.43)	0.51 (0.29, 1.27)	0.86 (0.39, 3.00)	*

(i) MTC (SAS) analyses compared to direct pairwise results - Mortality

Mortality	**DBG 150mg**	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**1.03 (0.90, 1.17)**	**0.88 (0.77, 1.00)**	NA	NA
DBG 110mg	1.03 (0.89, 1.19)	*	**0.91 (0.80, 1.03)**	NA	NA
WFN	0.89 (0.77, 1.03)	0.92 (0.79, 1.06)	*	**0.95 (0.72, 1.26)**	**1.01 (0.81, 1.26)**
ASA	0.83 (0.64, 1.07)	0.85 (0.66, 1.10)	0.93 (0.76, 1.14)	*	**0.98 (0.89, 1.08)**
A+C	0.88 (0.66, 1.18)	0.91 (0.68, 1.21)	0.99 (0.77, 1.27)	1.06 (0.77, 1.47)	*

(ii) MTC (WinBUGs) analyses compared to direct pairwise results - Mortality

Mortality	**DBG 150mg**	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**1.03 (0.90, 1.17)**	**0.88 (0.77, 1.00)**	NA	NA
DBG 110mg	1.03 (0.75, 1.44)	*	**0.91 (0.80, 1.03)**	NA	NA
WFN	0.90 (0.69, 1.22)	0.92 (0.70, 1.32)	*	**0.95 (0.72, 1.26)**	**1.01 (0.81, 1.26)**
ASA	0.82 (0.58, 1.18)	0.85 (0.59, 1.28)	0.91 (0.71, 1.16)	*	**0.98 (0.89, 1.08)**
A+C	0.90 (0.60, 1.52)	0.93 (0.60, 1.59)	1.01 (0.73, 1.48)	1.10 (0.74, 1.78)	*

(i) MTC (SAS) analyses compared to direct pairwise results – Acute Myocardial Infarction

Myocardial infarction	**DBG 150mg**	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**1.02 (0.77, 1.35)**	**1.27 (0.94, 1.71)**	NA	NA
DBG 110mg	1.02 (0.73, 1.43)	*	**1.29 (0.96, 1.75)**	NA	NA
WFN	1.28 (0.90, 1.83)	1.31 (0.92, 1.86)	*	**0.96 (0.44, 2.11)**	**1.58 (0.94, 2.67)**
ASA	0.91 (0.49, 1.69)	0.93 (0.50, 1.72)	0.71 (0.42, 1.19)	*	**0.78 (0.59, 1.03)**
A+C	0.87 (0.44, 1.70)	0.89 (0.45, 1.73)	0.68 (0.38, 1.20)	0.96 (0.44, 2.08)	*

(ii) MTC (WinBUGs) analyses compared to direct pairwise results – Acute Myocardial Infarction

Myocardial infarction	**DBG 150mg**	**DBG 110mg**	**WFN**	**ASA**	**A+C**
DBG 150mg	*	**1.02 (0.77, 1.35)**	**1.27 (0.94, 1.71)**	NA	NA
DBG 110mg	1.02 (0.39, 2.61)	*	**1.29 (0.96, 1.75)**	NA	NA
WFN	1.31 (0.67, 3.30)	1.35 (0.62, 3.18)	*	**0.96 (0.44, 2.11)**	**1.01 (0.81, 1.26)**
ASA	0.82 (0.34, 2.10)	0.84 (0.34, 2.06)	0.63 (0.31, 1.10)	*	**0.78 (0.59, 1.03)**
A+C	0.98 (0.37, 3.94)	1.01 (0.33, 3.55)	0.75 (0.32, 1.86)	1.22 (0.45, 3.78)	*

Figure 14 Ischaemic stroke MTC analyses for DBG 150mg bid

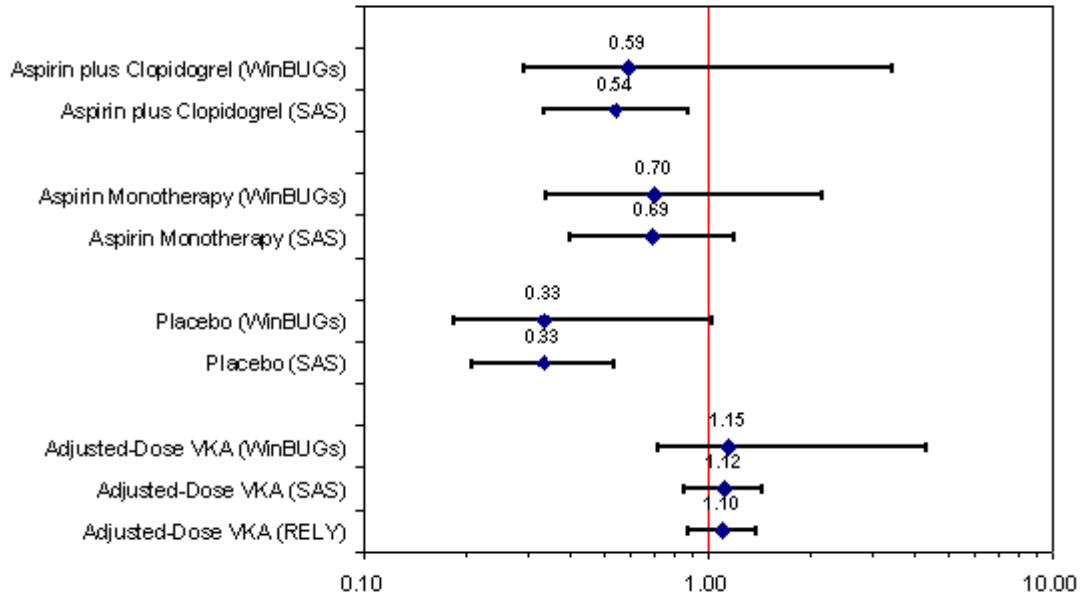


Figure 15 Ischaemic stroke MTC analyses for DBG 110mg bid

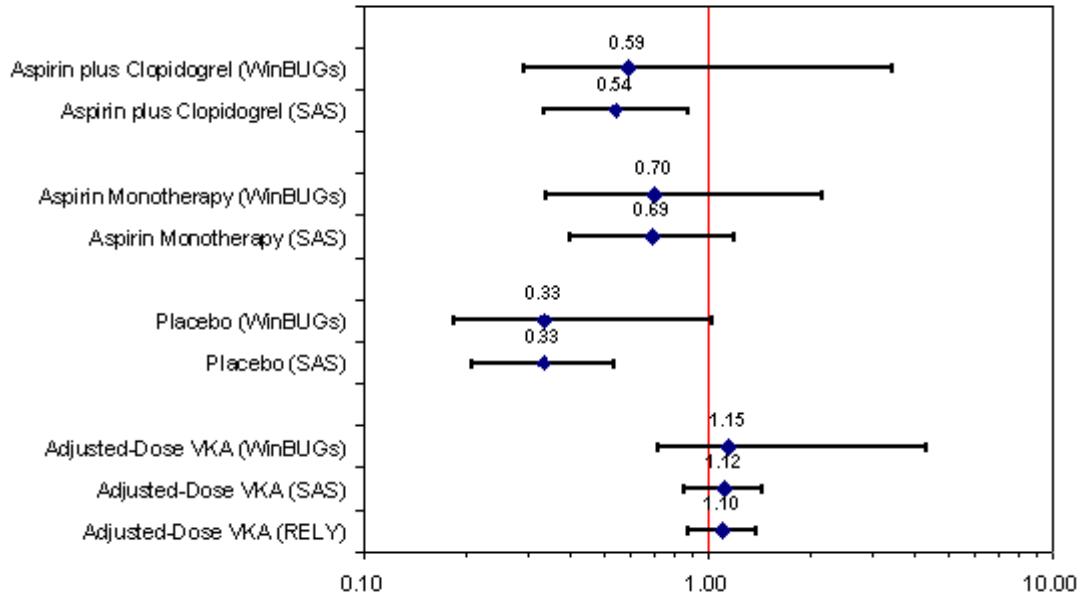


Figure 16 Mortality MTC analyses for DBG 150mg bid

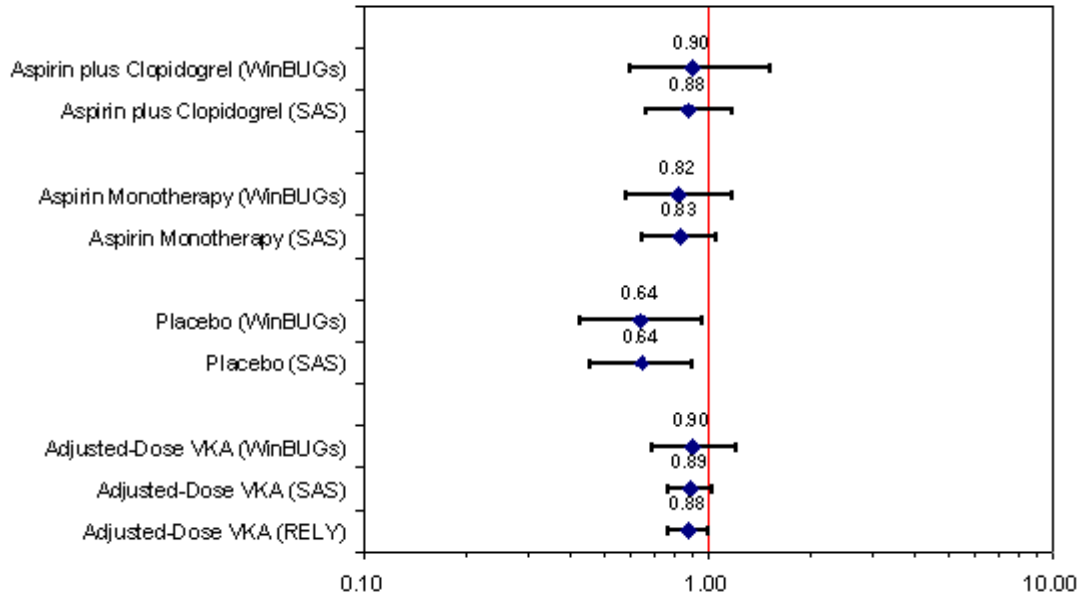


Figure 17 Mortality MTC analyses for DBG 110mg bid

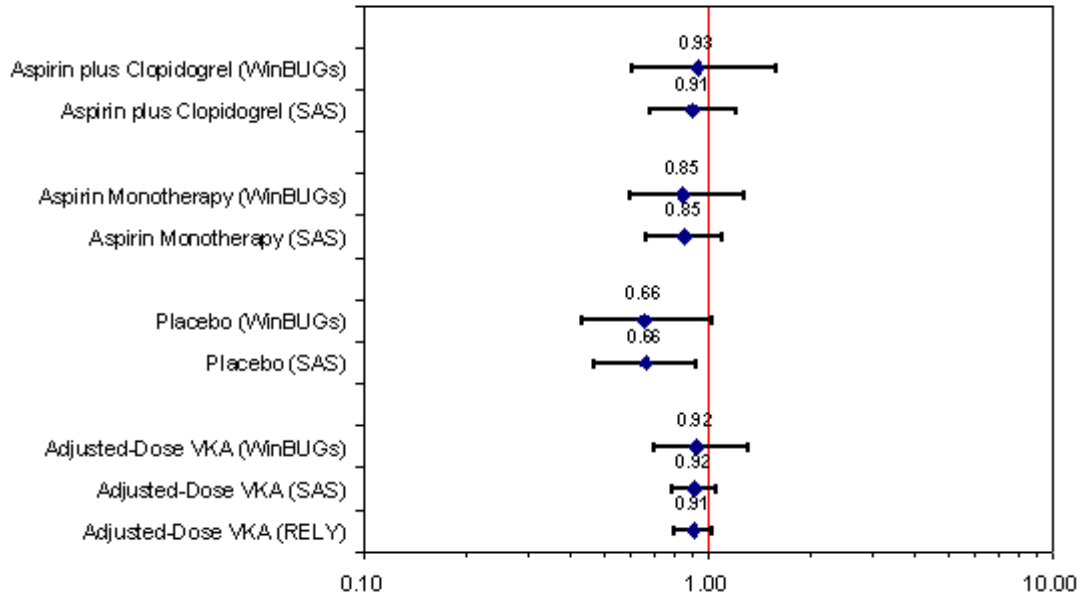


Figure 18 Acute MI MTC analyses for DBG 150mg bid

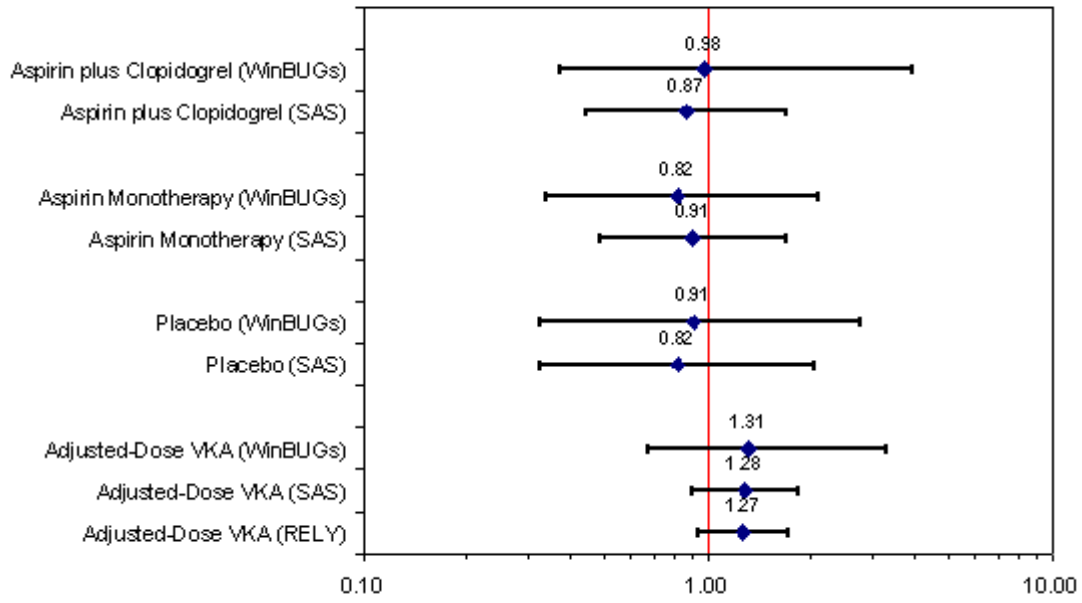
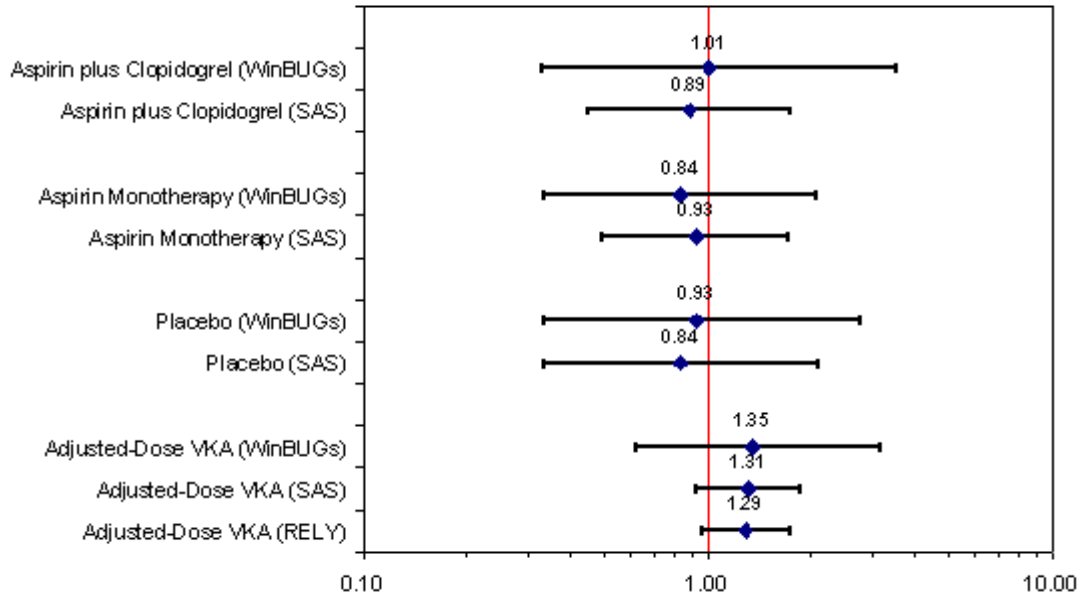


Figure 19 Acute MI MTC analyses for DBG 110mg bid



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