Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

ERG's response to Bayer's comments on ACD

BMJ Technology Assessment Group

Evidence Review Group (ERG) comments on Bayer's responses to the Appraisal Committee Document (ACD) for Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

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In summary, the ERG considers the key points to be:

- The cost of monitoring associated with warfarin;
- The stratification of warfarin patients by level of INR control;
- The manufacturer's use of a treatment-related disutility for warfarin.

1 ASSESSMENT OF THE MANUFACTURER'S ACD RESPONSE

The Appraisal Committee requested revised cost-effectiveness analyses of rivaroxaban versus warfarin (Box 1).

Box 1. Revised cost-effectiveness analysis requested by appraisal committee

For the second Appraisal Committee meeting, the manufacturer of rivaroxaban should provide revised cost-effectiveness analyses comparing rivaroxaban with warfarin as follows:

- The characteristics of the cohort in the model should represent people with atrial fibrillation in the UK. Therefore ideally the baseline risks of events in the patient cohort in the model should be derived from the General Practice Research Database or the UK GP practice-based survey (Gallagher et al. 2008).
- The analyses should use clinical-effectiveness data from the safety-on-treatment population of the ROCKET-AF trial, and use all point estimates from this trial regardless of statistical significance.
- The effect of the low proportion of time in therapeutic range on warfarin in the ROCKET-AF trial should be accounted for by considering subgroup analyses by country or centre.
- The analyses should incorporate a fixed annual warfarin international normalised ratio (INR) monitoring cost of £242 per person.

The manufacturer provided an updated economic model that addressed the first two requests for:

- A model cohort representative of people with atrial fibrillation in the UK;
- Analysis based on point estimates derived from the safety-on-treatment population of ROCKET-AF.

The request for an examination of the effect of the low time in therapeutic range (TTR) seen in ROCKET-AF was addressed as an amendment to the manufacturer's base case, rather than as a subgroup analysis.

The manufacturer contested the Appraisal Committee's request for the use of a "fixed annual warfarin international normalised ratio (INR) monitoring cost of £242 per person"; commenting that, the costs recommended by the Appraisal Committee did not take into account new research. However, the manufacturer provided a sensitivity analysis incorporating this cost.

In addition to the adjustments requested by the Appraisal Committee, the manufacturer also amended the model to include:

- A disutility associated with warfarin treatment;
- Real world discontinuation rates for warfarin and rivaroxaban;
- 90-day case fatality rates for major stroke and intracranial bleed.

Furthermore, the manufacturer has conducted an additional indirect comparison of rivaroxaban versus aspirin. The manufacturer's additional indirect comparison uses only trials comparing rivaroxaban to warfarin and warfarin to aspirin, in order to reduce the network heterogeneity. The updated indirect comparison is used in the updated model to provide results for rivaroxaban versus aspirin.

1.1 Representative model cohort

a) Baseline distribution

The manufacturer has altered the distribution of patients at baseline across $CHADS_2$ scores from the distribution observed in ROCKET-AF to the distribution reported in Gallagher et al.[1] The difference between these patient populations is summarised in Table 1.

Table 1. Previous and updated baseline $CHADS_2$ score distributions

Risk category ($CHADS_2$ score)	Original model distribution (%)	Updated model distribution (%)
Low risk (0-1)	0	35
Moderate risk (2-3)	13	35
High risk (4+)	87	30
Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled).		

b) Event rates according to baseline risk

In association with the adjustment of the baseline distribution of patients by $CHADS_2$ score, the manufacturer also updated the risk of stroke. In the original model the risk of stroke used in the comparison of rivaroxaban with warfarin (based on ROCKET-AF) did not vary by baseline $CHADS_2$ score. However, in the manufacturer's updated model the risk of stroke is dependent on baseline $CHADS_2$ score (summarised in Table 2).

Table 2. Stroke risk by $CHADS_2$ score at baseline used in manufacturer's updated model

Risk category ($CHADS_2$ score)	Quarterly risk of stroke	Source
Low risk (0-1)	0.0005	Bayer GPRD study (data for ischaemic stroke events in warfarin-treated patients). A relative risk of 0.4 is applied to the risk of stroke in patients at moderate risk of stroke
Moderate risk (2-3)	0.0011	ROCKET-AF safety-on-treatment analysis
High risk (4+)	0.0036	Bayer GPRD study (data for ischaemic stroke events in warfarin-treated patients). A relative risk of 3.2 is applied to the risk of stroke in patients at moderate risk of stroke
Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); GPRD, General practice research database; ROCKET-AF, Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.		

The risk of stroke, calculated using a weighted average of stroke risk by patients $CHADS_2$ score distribution at baseline, is applied throughout the model. It is important to note that, with the exception of patients experiencing a stroke (ischaemic or haemorrhagic), patients are not stratified by stroke risk after baseline. Patients who experience ischaemic or haemorrhagic stroke are assumed to be at high risk, regardless of their previous $CHADS_2$ score.

1.2 Safety-on-treatment population

All the manufacturer's revised analyses are based on point estimates obtained from analysis of the safety-on-treatment population of ROCKET-AF.

1.3 Examining the effect of the low time in therapeutic range (TTR) observed in ROCKET-AF

The Appraisal Committee requested a subgroup analysis by country or centre to investigate the effect of the low TTR observed in ROCKET-AF. The manufacturer states in their response to the ACD that: "In the revised cost-effectiveness analysis, the event rate in the warfarin arm has been revised to reflect the time in therapeutic range achieved in trial centres in Western Europe." The manufacturer provided no further clarification on how this change had been implemented.

On inspection of the manufacturer's updated model, the ERG observed that the approach taken to model warfarin patients had changed significantly from that used in the original model. In the updated model, patients are separated into three categories of INR control: below 2; between 2 and 3; and above 3 (Table 3). However, in the original model, the efficacy of warfarin was not disaggregated by TTR, with the mean efficacy observed in ROCKET-AF applied to all patients throughout the model. Moreover, in the updated model, the effectiveness of warfarin to prevent stroke and systemic embolism varies with level of INR control. Similarly, the risk of bleeding events differs with level of INR control. The risks used in the updated model are summarised in Table 4.

Table 3. Proportion of patients by INR category

INR category	Proportion of patients in each category	Source
Below 2	21.9	ROCKET-AF, Western Europe analysis
Between 2 and 3	60.6	
Above 3	17.5	
Abbreviations used in table: INR, International normalised ratio; ROCKET-AF, Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation		

Table 4. Safety and efficacy of warfarin based on level of INR control used in the manufacturer's updated model

Event	Quarterly event risk by INR		
	<2	2-3	>3
Ischaemic stroke	0.60	0.24	0.24
Systemic embolism	0.07	0.05	0.02
Minor bleed	2.64	2.73	4.37
Major bleed	0.61	0.63	1.01
Intracranial bleed	0.16	0.19	0.24
Abbreviations used in table: INR, International normalised ratio.			

The implementation of analyses based on level of INR control constitutes an extensive change to the model structure, a change which, *ceteris paribus* (all else being equal) results in an increase in the

ICER of £3,742. The ERG was unable to fully validate this structural change, because of time constraints and the late arrival of the Excel file.

1.4 Monitoring costs associated with warfarin

As discussed above, the manufacturer contested the Appraisal Committee's request for the use of a "fixed annual warfarin international normalised ratio (INR) monitoring cost of £242 per person"; commenting that, the costs recommended by the Appraisal Committee did not take into account new research.

a) New research submitted by the manufacturer

The manufacturer submitted a detailed breakdown of the calculation of the cost of warfarin monitoring in primary care. The cost of warfarin monitoring in primary care was calculated as [redacted] per annum, based on [redacted] visits per year (on average). All estimates of resource use were taken from a real world survey commissioned by the manufacturer. The main components of the cost associated with warfarin monitoring in primary care were from home visits ([redacted] of total cost) and subsequent clinic visits ([redacted] of total cost). Subsequent clinic visits incurred costs of [redacted] per visit, based on 8 minutes of a nurse's time; whereas home visits incurred a cost of [redacted] per visit. A grade 7 community nurse was assumed to carry out both home and subsequent clinic visits. The ERG notes that if the annual number of visits is [redacted] to 20, the cost of warfarin monitoring in primary care, based on the manufacturer's calculations, becomes £283.94.

b) Costs used in the manufacturer's updated model

The updated model submitted by the manufacturer, used the same unit costs as the original model. However, the number of visits required for the re-initiation of warfarin had been reduced from 7 to 5 per 3-month cycle. Therefore, the costs associated with warfarin monitoring in primary care used in the manufacturer's updated model were:

- £175.50 for initiation of warfarin (calculated as a weighted average of naïve and experienced patients);
- £135 for maintenance on warfarin;
- £135 for re-initiation of warfarin.

This is equivalent to an annual cost of warfarin monitoring in primary care of £580 (one initiation cycle plus 3 maintenance or re-initiation cycles). The ERG notes that this is substantially higher than the primary care costs proposed by the manufacturer in the response to the ACD.

The ERG applied the primary care monitoring cost of [redacted] to the updated model (by using a cost of £16.47 for subsequent primary care visits). The manufacturer's revised ICER rose to £5,853.

c) Sensitivity analysis

The manufacturer presented the results of sensitivity analyses using a cost of £242 for warfarin monitoring in primary care. The ERG was unable to replicate the manufacturer's results because no details were provided on how this cost had been implemented in the manufacturer's model. However, the ERG used a cost of £11.26 for subsequent primary care visits, which yielded annual warfarin monitoring costs of £242 as requested by the Appraisal Committee. This resulted in an ICER of £9,729 for rivaroxaban versus warfarin, based on the manufacturer's updated model.

1.5 Warfarin treatment-related disutility

The original model submitted in support of this STA assumed that no disutility was associated with any of the treatments considered. However, the manufacturer's updated model includes a disutility associated with warfarin treatment; all other therapies are assumed to incur no disutility. The manufacturer's rationale for the addition of a treatment-related disutility for warfarin is based on the acknowledgement of the Appraisal Committee that: "anxiety about the difficulty of keeping the INR within the satisfactory therapeutic range" was one of the main concerns facing people with atrial fibrillation.[2] The manufacturer provides no rationale for the maintenance of the assumption that no disutility is associated with rivaroxaban, aspirin or dabigatran.

The treatment-related disutility applied to warfarin patients in the manufacturer's updated model is 0.01; the disutility was calculated by multiplying the utility of stable patients (0.779)[3] by the weighted average utility of warfarin patients managed in a GP or hospital setting (0.946).[4] Removal of this disutility has a substantial impact on the ICER, increasing it nearly 3-fold, from £2,869 to £10,764. The ERG considers that the application of a disutility to warfarin treatment, in the absence of any disutility associated with rivaroxaban treatment, will bias the analysis in favour of rivaroxaban. Furthermore, the ERG notes that no evidence has been presented to suggest there is no disutility associated with rivaroxaban treatment. Moreover, the ERG is aware of evidence of a disutility associated with another oral anticoagulant, dabigatran.[5]

1.6 Real world discontinuation rates

In addition to the updated analyses requested by the Appraisal Committee, the manufacturer also updated the discontinuation rates used in the model with "real-world" discontinuation rates. Warfarin discontinuation rates from the GPRD[6] are used in the updated model and a relative risk of "real-world" discontinuation is used to update the discontinuation rates of rivaroxaban (summarised in Table 5). The manufacturer presented all analyses including and excluding the updating of discontinuation rates. Results indicate that the ICERs were not sensitive to discontinuation.

Table 5. Discontinuation rates used in the manufacturer's original and updated models

Model	Treatment	Cycle	Discontinuation rate (%)	Calculation/source
Original	Rivaroxaban	Initial	8.90	ROCKET-AF
		Subsequent	4.39	
	Warfarin	Initial	8.00	
		Subsequent	4.46	
Updated	Rivaroxaban	Initial	10.57	Calculated by applying a relative risk of 1.19 obtained from GPRD[6] to discontinuation rate of 8.90% observed in ROCKET-AF
		Subsequent	4.43	Calculated by applying a relative risk of 1.01 obtained from GPRD[6] to discontinuation rate of 4.39% observed in ROCKET-AF
	Warfarin	Initial	9.50	GPRD[6]
		Subsequent	4.50	GPRD[6]

Abbreviations used in this table: GPRD, General practice research database; ROCKET-AF, Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

1.7 The use of 90-day case fatality

The original model used 30-day case fatality rates to inform the risk of death from major ischaemic stroke or intracranial bleed. The manufacturer has updated the 30-day case fatality rates with 90-day case fatality rates. The rationale for this is that 90-day case fatality rates are more in line with the cycle length of 3 months used in the manufacturer's model. The ERG agrees with the manufacturer that 90-day case fatality rates are more suitable for use in the manufacturer's model.

1.8 Additional amendments recommended by the ERG

In addition to the amendments submitted by the manufacturer in the updated model, the ERG considers that adjustments are needed to:

a) account for an increased risk of stroke following systemic embolism (SE);

b) update the mortality risk associated with MI to an appropriate risk for patients in a post-statin era.

a) Increased risk of stroke post-SE

As observed in the ERG's original report, systemic embolism is categorised as a temporary event within the manufacturer's model. In order to approximate a post-SE health state (which would account for the increased risk of stroke following an SE), the ERG has amended the manufacturer's updated model such that following after a systemic embolism patients transition into the post-minor stroke health state.

b) Post-statin era MI mortality

The manufacturer's updated model continues to use a risk of death from MI (2.68% per quarter) derived from a paper published in 1986.[7] The ERG has updated the risk of death from MI to 0.27% per quarter, as reported in a study by Pedersen et al., published in 2005.[8]

1.9 Indirect comparison of rivaroxaban with aspirin

In the manufacturer's response to the ACD, results from a new indirect comparison for the comparison of rivaroxaban with aspirin using warfarin as a common comparator are presented. The manufacturer justifies the reason for inclusion of this new analysis as it being an attempt to address the comments from the Appraisal Committee regarding the large amount of heterogeneity present in the network meta-analysis in the manufacturer's original submission. The manufacturer reports that statistically significant heterogeneity in the new analysis is limited to two endpoints; major bleeding and extracranial bleeding. The ERG notes that there is substantial clinical heterogeneity in the trials included in the manufacturer's indirect comparison due to the inclusion of trials assessing various doses of aspirin and also trials with differing warfarin target INR values. In an attempt to address the issues of clinical and statistical heterogeneity in the manufacturer's original submission, the ERG conducted an NMA including only trials with comparable dosing of warfarin and aspirin, which resulted in a more homogenous dataset with the fixed effects model being preferred for all outcomes assessed.

The results of the manufacturer's indirect comparison and the ERG's network meta-analysis for the comparison of rivaroxaban versus aspirin are presented in Table 6. The overall results of the two analyses are generally consistent with each other, showing a general trend towards reduction in ischaemic stroke, systemic embolism and myocardial infarction with rivaroxaban and an increase in all bleeding-related outcomes with rivaroxaban. The only results that reach statistical significance are reduction in systemic embolism with rivaroxaban using the manufacturer's indirect comparison (RR

0.19; 95% CI 0.04 to 0.93) and increase in minor extracranial bleeds with rivaroxaban using the ERG's NMA (OR 1.96; 95% CI 1.13 to 3.21).

Table 6. Results from the indirect comparison conducted by the manufacturer compared with results from the NMA conducted by the ERG for the comparison of rivaroxaban with aspirin (RR/OR <1 favours rivaroxaban; RR/OR >1 favours aspirin)

Outcome	Manufacturer Indirect Comparison RR (95% CI)	ERG's NMA Mean OR (95% CrI)
Ischaemic stroke	[redacted]	0.63 (0.35 to 1.03)
Systemic embolism	[redacted]	0.47 (0.04 to 1.97)
Major extracranial bleed	[redacted]	1.87† (0.88 to 3.60)
Minor extracranial bleed	[redacted]	1.96* (1.13 to 3.21)
Intracranial bleed	[redacted]	1.86 (0.57 to 4.81)
Myocardial infarction	[redacted]	0.69 (0.33 to 1.28)
Discontinuation	[redacted]	3.11‡ (0.61 to 10.25)

*Statistically significant at the 5% level.

†Excluding WASPO[9] as this outcome was identified by the investigators as likely to be specific to the population studied and is therefore not generalisable to a wider population.

‡Excluding AFASAK-I[10] as this outcome was identified by the investigators as likely to be skewed by patients not being adequately informed of the frequency of blood tests in the warfarin group.

Abbreviations used in table: 95% CI, 95% Confidence Interval; 95% CrI, 95% Credible Interval; ERG, Evidence Review Group; NMA, network meta-analysis; OR, odds ratio; vs, versus.

However, the ERG maintains that the population in ROCKET-AF are people eligible for treatment with warfarin and thus the ERG considers that there are not clinical data available for the efficacy of rivaroxaban in people who are unsuitable for warfarin treatment and thus rivaroxaban cannot be compared with aspirin in this population. Moreover, the trials used in the indirect comparison presented by the manufacturer include warfarin as a direct comparator for aspirin, and thus the patients in the trials must have been suitable for anticoagulation with warfarin. The ERG considers that the results from the analyses conducted by the manufacturer and ERG represent the comparison of rivaroxaban with aspirin in a population suitable for treatment with warfarin.

1.10 Further analyses and comments

a) Rivaroxaban versus dabigatran

The manufacturer reported in their response to the ACD that they consider that dabigatran 110mg dose should have been included in the ERG's NMA presented in the ERG report; the ERG's original NMA included only the dabigatran 150mg dose. The ERG would like to clarify that the reason for omission of this dose from the ERG's NMA was because the ERG did not receive a functioning model comparing rivaroxaban to a dabigatran sequence regimen. The ERG has re-run its NMA to include the dabigatran 110mg data from RE-LY, and notes that the results generated are generally consistent with the results from the manufacturer's original submission. The results from the ERG's updated NMA and the manufacturer's original NMA for dabigatran 110mg and 150mg compared with rivaroxaban are presented in Table 7.

Table 7. Results from the NMA conducted by the manufacturer and the NMA conducted by the ERG for the comparison of rivaroxaban with dabigatran (OR <1 favours rivaroxaban; OR >1 favours dabigatran)

Outcome	Dabigatran 110mg Mean OR (95% CrI)		Dabigatran 150mg Mean OR (95% CrI)	
	Manufacturer NMA	ERG NMA	Manufacturer NMA	ERG NMA
Ischaemic stroke	[redacted]	0.82 (0.59 to 1.11)	[redacted]	1.20 (0.84 to 1.66)
Systemic embolism	[redacted]	0.36* (0.09 to 0.95)	[redacted]	0.42 (0.10 to 1.11)
Major extracranial bleed	[redacted]	1.21† (0.96 to 1.49)	[redacted]	1.06† (0.85 to 1.32)
Minor extracranial bleed	[redacted]	1.40* (1.24 to 1.57)	[redacted]	1.18* (1.05 to 1.32)
Intracranial bleed	[redacted]	2.23* (1.24 to 3.76)	[redacted]	1.67 (0.95 to 2.70)
Myocardial infarction	[redacted]	0.60* (0.38 to 0.89)	[redacted]	0.59* (0.38 to 0.88)
Discontinuation	-	0.80*‡ (0.71 to 0.90)	-	0.76*‡ (0.68 to 0.89)

*Statistically significant at the 5% level.

†Excluding WASPO[9] as this outcome was identified by the investigators as likely to be specific to the population studied and is therefore not generalisable to a wider population.

‡Excluding AFASAK-I[10] as this outcome was identified by the investigators as likely to be skewed by patients not being adequately informed of the frequency of blood tests in the warfarin group.

Abbreviations used in table: 95% CI, 95% Confidence Interval; 95% CrI, 95% Credible Interval; ERG, Evidence Review Group; NMA, network meta-analysis; OR, odds ratio; vs, versus.

The results show a general trend in reduction of systemic embolism, myocardial infarction and treatment discontinuation with rivaroxaban when compared with either dabigatran 110mg or dabigatran 150mg. By contrast, there is a general trend towards an increase in all the bleeding

outcomes with rivaroxaban when compared with either the dabigatran 110mg or dabigatran 150mg dose. The results for the outcome of ischaemic stroke suggest that rivaroxaban is favoured in the comparison of rivaroxaban versus dabigatran 110mg, whereas in the comparison of rivaroxaban with dabigatran 150mg, dabigatran 150mg appears to be favoured.

Although none of the results reaches statistical significance in the manufacturer's NMA, several are statistically significant in the ERG's NMA. The statistically significant results in the ERG's NMA are as follows:

- reduction of systemic embolism with rivaroxaban compared with dabigatran 110mg;
- increase in minor extracranial bleed with rivaroxaban compared with dabigatran 110mg and 150mg;
- increase in intracranial bleed with rivaroxaban compared with dabigatran 110mg;
- reduction in myocardial infarction with rivaroxaban compared with dabigatran 110mg and 150mg;
- reduction in treatment discontinuations with rivaroxaban compared with dabigatran 110mg and 150mg.

The ERG also considers it important to note that in the trial informing the rivaroxaban MI data set, (ROCKET-AF), significantly more people had a history of prior MI at baseline in the warfarin group compared with the rivaroxaban group ($p < 0.05$).

In summary, the ERG considers that, compared with dabigatran 110mg, rivaroxaban is associated with greater reduction in stroke and systemic embolism but more adverse bleeding events. By contrast, compared with dabigatran 150mg, rivaroxaban is associated with a non-significant reduction in systemic embolism and a non-significant increase in ischaemic stroke as well as increased adverse bleeding events.

The Appraisal Committee acknowledged the large amount of uncertainty present in the indirect comparison of rivaroxaban and dabigatran and consequently did not consider the comparison any further. The manufacturer has responded to this decision by the Appraisal Committee with a re-iteration of the argument for taking a cost-minimisation approach. The manufacturer's rationale for using a cost-minimisation approach is that there is no statistically significant difference between the interventions. The ERG maintains the position that a cost minimisation approach is not appropriate for the comparison of rivaroxaban with dabigatran. The ERG recommends that any comparison of these two therapies uses point estimates and full probabilistic analysis.

In addition, the manufacturer has raised the issue of comparing rivaroxaban with dabigatran in line with the marketing authorisation of dabigatran. The marketing authorisation of dabigatran states that the lower dose of 110mg bid must be used in patients over 80 years of age. The manufacturer states that the comparison of rivaroxaban and the dabigatran sequence regimen (150mg bid followed by 110mg bid for patients over 80 years of age) results in the dominance of rivaroxaban 51.4% of the time and the dominance of dabigatran 26.6% of the time. However, the ERG is unable to validate this analysis because no functioning model comparing rivaroxaban to a dabigatran sequence regimen has been received.

b) Suspension of risk

In the ACD response, the manufacturer states that "The description of 'suspension of risk of events' is inaccurate. The risk of certain clinical events in the post-event states are still accounted for within the model; that is, the consequences of the event (cost and disutility) are being attributed to each arm according to the clinical data in all subsequent cycles. The patients are simply accruing these pay-offs in the post-event state rather by creating new health states to account for these events."

The ERG has previously addressed this point in the response to the manufacturer's factual accuracy check of the original ERG report. The ERG maintains the position that the risk of events is unnecessarily suspended in the model. The ERG understands the point raised by the manufacturer that "the risk of certain clinical events in the post-event health states are still accounted for". However, this is not the same issue as that raised by the ERG on the suspension of risk. The manufacturer's model suspends the risk of further events following the occurrence of a temporary or permanent event. In that, following a permanent event a person can only transition to a post-event health state or die. Similarly, following a temporary event in the model, a person can only transition to the initiation or stable AF health states or die. Therefore, at the time when patients are most at risk of further events no risk of further events is applied. The impact of this is likely to be to bias against the more effective comparator.

2 ERG VALIDATION OF MODEL REVISIONS

A formal validation of the manufacturer's revised economic model was not possible given the time constraints of the commentary process, the extensive restructuring carried out by the manufacturer and the late arrival of the Excel file. Therefore, validation has been largely limited to the replication of the manufacturer's original base case.

Additional cross checks have been carried out to verify the implementation of:

- stroke risks dependent on the distribution of patients across $CHADS_2$ scores at baseline;
- the disutility associated with warfarin;
- the use of "real-world" discontinuation rates.

A limited check of the stratification of patients by level of INR control has also been carried out.

The ERG was able to replicate the ICER of rivaroxaban versus warfarin based on the safety-on-treatment population (using all estimates of effect regardless of statistical significance) to within £13, suggesting a high degree of consistency between the original and updated models. In addition, the cross checks of the manufacturer's amendments provided extra validation of the manufacturer's description. The implementation of the stratification of patients by INR control was not well described in the manufacturer's ACD response and constituted significant restructuring of the model. Although, the limited check of the stratification of patients by level of INR control indicated that the restructure had been correctly implemented. However, given the high level of impact that this restructure has on the model results, further validation is recommended.

2.1 Manufacturer's revisions

The manufacturer has submitted a revised base case for rivaroxaban versus warfarin in the licensed and poorly controlled patient populations.

These revised analyses include the following amendments:

- The use of a patient distribution based on Gallagher et al.[1];
- The adjustment of stroke risk based on baseline distribution of patients across $CHADS_2$ scores;
- Stratification of warfarin patients by level of INR control;
- Adjustment of the number of re-initiation visits (from 7 to 5);

- Disutility associated with warfarin therapy;
- Real-world discontinuation rates;
- The use of 90-day case fatalities.

The cumulative impact of removing these amendments is displayed in Tables 8 for rivaroxaban versus warfarin in the licensed population.

Table 8. Rivaroxaban versus warfarin, replication of original model results

Scenario	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's updated base case	**Rivaroxaban**	**6,916**	**7.241**	**705**	**0.246**	**2,869**
	Warfarin	**6,210**	**6.995**	**-**	**-**	**-**
Incremental removal of manufacturer's amendments						
Gallagher et al.[1] patient distribution (by $CHADS_2$ score)	Rivaroxaban	8,398	7.088	776	0.236	3,292
	Warfarin	7,622	6.852	-	-	-
Risk of stroke adjusted by baseline $CHADS_2$ score	Rivaroxaban	8,661	7.060	788	0.234	3,374
	Warfarin	7,872	6.826	-	-	-
Modelling warfarin efficacy by INR	Rivaroxaban	8,661	7.060	681	0.245	2,782
	Warfarin	7,979	6.815	-	-	-
Adjusted number of re-initiation visits	Rivaroxaban	8,661	7.060	629	0.245	2,570
	Warfarin	8,031	6.815	-	-	-
Disutility associated with warfarin	Rivaroxaban	8,661	7.060	629	0.073	8,639
	Warfarin	8,031	6.987	-	-	-
Real world discontinuation rates	Rivaroxaban	8,721	7.060	645	0.0742	8,697
	Warfarin	8,076	6.986	-	-	-
90-day case fatality	Rivaroxaban	8,784	7.068	628	0.072	8,745
	Warfarin	8,156	6.997	-	-	-
Manufacturer's original SOT point estimate result	**Rivaroxaban**	**8,834**	**7.071**	**633**	**0.073**	**8,732**
	Warfarin	**8,200**	**6.998**	**-**	**-**	**-**

Abbreviations used in table: $CHADS_2$, Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (doubled); ICER, Incremental cost effectiveness ratio; INR, International normalised ratio; SOT, Safety-on-treatment; QALY, Quality adjusted life year.

Of the amendments submitted in the manufacturer's updated model, the ERG accepts:

- The use of a patient distribution based on Gallagher et al.[1];
- The adjustment of stroke risk based on baseline distribution of patients across $CHADS_2$ scores;
- Adjustment of the number of re-initiation visits (from 7 to 5);
- The use of 90-day case fatalities.

In addition to these amendments, the ERG also considers that adjustments are needed to account for:

- the increased risk of stroke post-systemic embolism;
- the use of a post-statin era mortality associated with MI.

Table 9 displays the incremental impact of each of the amendments listed above. Scenario analyses are presented to consider the impact of:

- the stratification of patients by level of INR control;
- using the cost of monitoring recommended by the Appraisal Committee;
- using the cost of monitoring submitted by the manufacturer.

Table 9. Rivaroxaban versus warfarin, ERG revised base case

Scenario	Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Manufacturer's original SOT point estimate result	**Rivaroxaban**	**8,834**	**7.071**	**633**	**0.073**	**8,732**
	Warfarin	**8,200**	**6.998**	**-**	**-**	**-**
Incremental addition of amendments						
Gallagher et al.[1] patient distribution (by $CHADS_2$ score)	Rivaroxaban	8,757	7.068	642	0.072	8,960
	Warfarin	8,116	6.997	-	-	-
Risk of stroke adjusted by baseline $CHADS_2$ score	Rivaroxaban	7,043	7.248	618	0.070	8,856
	Warfarin	6,424	7.178	-	-	-
Adjusted number of re-initiation visits	Rivaroxaban	7,043	7.248	658	0.070	9,421
	Warfarin	6,385	7.178	-	-	-
90-day case fatality	Rivaroxaban	6,989	7.240	672	0.072	9,330
	Warfarin	6,317	7.168	-	-	-
Increased risk of stroke post-SE	Rivaroxaban	7,022	7.237	669	0.074	9,044
	Warfarin	6,353	7.163	-	-	-
Post statin era MI mortality risk	Rivaroxaban	7,226	7.325	659	0.061	10,727
	Warfarin	6,567	7.263	-	-	-
Inclusion of warfarin monitoring costs requested by the AC	Rivaroxaban	7,226	7.325	1,815	0.061	29,537
	Warfarin	5,411	7.263	-	-	-
The revised base-case	**Rivaroxaban**	**7,226**	**7.325**	**1,815**	**0.061**	**29,537**
	Warfarin	**5,411**	**7.263**	**-**	**-**	**-**
Further scenario analysis						
The revised base case (including AC requested costs and stratification of warfarin patients by INR)	Rivaroxaban	7,226	7.325	1,867	0.056	33,378
	Warfarin	5,359	7.269	-	-	-
The revised base case using the manufacturer's updated costs	Rivaroxaban	7,226	7.325	1,432	0.061	23,314
	Warfarin	5,794	7.263	-	-	-
The revised base case using the manufacturer's updated costs and stratification of warfarin patients by INR	Rivaroxaban	7,226	7.325	1,485	0.056	26,551
	Warfarin	5,741	7.269	-	-	-
Abbreviations used in table: AC, Appraisal committee; $CHADS_2$, Congestive heart failure, Hypertension, Age,						

Diabetes and history of Stroke or TIA (doubled); ICER, Incremental cost effectiveness ratio; INR, International normalised ratio; MI, Myocardial infarction; SE, Systemic embolism; SOT, Safety-on-treatment; QALY, Quality adjusted life year.

Generally, the model amendments considered relevant by the ERG have a minor impact on the overall ICER. However, the issue of the cost of monitoring with warfarin is clearly an important one. Using the annual cost of monitoring in primary care (submitted by the manufacturer as part of the ACD response), increases the ICER by nearly £13,000. Similarly, using the annual cost of monitoring in primary care requested by the Appraisal Committee increases the ICER by nearly £20,000. In addition, the stratification of patients by level of INR control has a moderate impact on the overall ICER, increasing it between £3,000 and £4,000, in favour of warfarin.

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