Section A: Clarification on effectiveness data

A1. **Priority Request:** Please provide the clinical study reports for ARISTOTLE and AVERROES (references 67 and 68 in the manufacturer's submission).

Please see enclosed clinical study reports for ARISTOTLE and AVERROES. The ARISTOTLE CSR does not contain all of the supplemental tables and these have not been provided as they are very large files. These can be provided if required.

Inclusion and exclusion criteria for the AVERROES and ARISTOTLE trials

A2. Please clarify the rationale for including *a prior* systemic embolism in the inclusion criteria for ARISTOTLE and not in AVERROES.

Current AF management guidelines (including NICE CG36) recommend stratification of patients according to their risk of stroke, thereby to determine which patients with atrial fibrillation should be treated with oral VKAs rather than ASA[1]. VKA therapy is recommended for AF patients with a prior systemic embolism and therefore treatment with anti-platelet therapy such as ASA would be considered inadequate. As ARISTOTLE was conducted in warfarin suitable patients, subjects with a prior systemic embolism were included, whereas AVERROES included patients deemed unsuitable for warfarin and so this study excluded patients with prior systemic embolism.

A3. Please clarify whether people with AF due to reversible causes were excluded from AVERROES.

As described in section 4.2.2 of the AVERROES protocol,[2] patients with AF due to reversible causes such as thyrotoxicosis and pericarditis were excluded from participation in AVERROES.

A4. Please clarify whether people with mitral stenosis were excluded from AVERROES.

As described in section 4.2.2 of the AVERROES trial protocol, patients with AF due to valvular disease requiring surgery were excluded from participation in AVERROES as these patients would require formal anticoagulation with warfarin. Therefore, cases of mitral stenosis requiring surgery would be excluded. In cases of patients with mitral stenosis not requiring surgery, but who met all other inclusion criteria, the decision to include this patient would be at the Principal Investigator's clinical discretion. Table S.3.4B in the Clinical Study Report (see below) indicates that approximately [redacted] of patients in each AVERROES arm had mitral stenosis at baseline but these are likely to be mild given that the investigator did not feel they required surgery.

[redacted]

A5. Please clarify why an exclusion criteria based upon liver function was included in AVERROES.

Exclusion of subjects with pre-existing liver chemistry abnormalities was implemented for the protection of subjects while the safety profile of apixaban was under study in Phase 3. It was not the result of any preclinical or clinical observations with apixaban. Apixaban, like other oral anticoagulants, is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. The pharmacokinetics were studied formally in patients with Child-pugh scores A and B, which did not differ from healthy patients. It was not tested in patients with a Child-pugh score C, due to the risk of increased bleeding. It should also be noted that hepatic impairment is also a special warning for patients on aspirin, again due to increased bleeding risk.[3] In the AVERROES trial, there were no significant increase in the incidence of raised liver function tests when compared to aspirin and the results have established that apixaban has a low risk of drug-induced liver injury (see Table 6 below from p.10 of AVERROES CSR).

Baseline characteristics of the AVERROES and ARISTOTLE trial populations

A6. Please provide details of the number of patients, mean dose (and SD), and median dose (and the range) in each trial arm of AVERROES who at baseline were on:

i) non-study concomitant aspirin;

Investigators were strongly encouraged to stop open label ASA if patients were already taking ASA at randomisation. Those patients developing an indication for dual anti-platelet therapy (DAPT) could take open label ASA (up to 100mg OD) and clopidogrel and could continue study drug. At baseline [redacted] and [redacted] were taking ASA 30 days prior to study start in the apixaban and ASA arms respectively (see CSR Table S.3.4C below).

On the day of randomisation, 38% and 37.4% of patients were still on non-study ASA in the apixaban and ASA arms respectively (see CSR Table S.3.4D below).

[redacted]

Investigators were strongly encouraged to stop open label ASA if patients were already taking ASA at randomisation. Post study start, [redacted] of patients in each arm took non-study aspirin for more than [redacted] of the time during the study. The rates of non study aspirin dropped significantly and only a small percentage used the drug for longer than one week (see Table s.4.2B from CSR below). The mean, median and range of dosage is not reported in the CSR. The dose is likely to reflect the practice in the investigator unit and the study allowed for a dose range of 81mg to 324mg (up to 4 tablets of 81mg), with the vast majority settling for less than 162mg.[4]

[redacted]

ii) Clopidogrel:

Clopidogrel was used in [redacted] of patients in each arm 30 days prior to randomisation (see CSR Table S.3.4C above). This dropped to [redacted] and [redacted] in the apixaban and aspirin arms on the day of randomisation (see CSR Table S.3.4D above). The majority of patients were treated with clopidogrel for less than one week in both arms of the trial and the median duration was [redacted] weeks in the apixaban arm and [redacted] weeks in the aspirin arm (see Table s.4.2B in CSR below). The mean, median and range of doses is not reported in the CSR.

[redacted]

iii) NSAIDs;

Chronic (>3 months) daily NSAIDS was considered a restricted therapy in view of the increased risk of bleeding and the investigator was encouraged to consider stopping these after a careful risk benefit analysis. NSAIDS were used in [redacted] and [redacted] of apixaban and aspirin patients 30 days prior to randomisation (see CSR Table S.3.4C below).

[redacted]

This dropped to 1.9% and 2.3% of patients in the apixaban and ASA arms respectively on the day of randomisation (see CSR Table S.3.4D below).

[redacted]

The number of patients using NSAIDS during the study was low and similar in each arm and was unlikely to have any material effect on trial findings. The mean, median and range of doses is not reported in the CSR.

iv) other anti-platelet drugs e.g. dipyridamole.

Ticlopidine, another thienopyridine, was used in 0.3% and 0.5% of patients at 30 days prior to randomisation in the apixaban and ASA arms respectively (see CSR Table S.3.4C above). None were using ticlopidine on the day of randomisation (see CSR Table S.3.4D above). Dipyridamole was used in 0.2% and 0.4% patients 30 days prior to randomisation (see CSR Table S.3.4C above). Less than 0.1% and 0.1% remained on dipyridamole on the day of randomisation (see CSR Table S.3.4D above).The number of patients using other anti-platelet drugs during the study was low and similar in each arm and was unlikely to have any material effect on trial findings. The mean, median and range of doses is not reported in the CSR.

[redacted]

[redacted]

A7. Please provide details of the number of patients in each trial arm of ARISTOTLE who had atrial flutter at baseline.

Table 1: Medical history of randomised subjects

Subgroup	Apixaban, n (%)			Warfarin, n (%)		
		[redacted]			[redacted]	
Atrial Flutter		[redacted]			[redacted]	

Source: ARISTOTLE CSR: Table S.3.4B1

A8. Please provide the number of people in each trial arm at baseline in AVERROES who had a history of prior MI.

Data on prior history of MI is not available in aggregate form from the AVERROES CSR.

Trial populations and populations included in analysis

A9. **Priority question:** Please complete the table below for the ITT populations in (two tables in total):

i) ARISTOTLE;

Please see table below for the data and source for the ITT population. For haemorrhagic stroke the denominators (apixaban N=31; warfarin N=65) only include strokes without missing values for Rankin scale, with 9 patients having missing values in the apixaban arm, and 13 patients having missing values in the warfarin arm. For the individual severity sub-group endpoints, no statistical tests were performed as the trial was not powered for this. For the other fatal intracranial haemorrhage outcome an overall average was pooled from AVERROES and ARISTOTLE in the economic model due to small sample size. However, just the numbers in each treatment arm from ARISTOTLE are presented below. No statistical tests were performed on this as the trials were not powered for the endpoint. For ischaemic stroke the denominators (N=108 apixaban; N=108 warfarin) only include strokes without missing values for Rankin scale, 54 patients taking apixaban had missing values and 67 patients taking warfarin had missing values. For the individual ischaemic stroke severity sub-group endpoints, no statistical tests were performed as the trial was not powered for this. For other CV hospitalisation, data were not available in ARISTOTLE, therefore the same rate from AVERROES is assumed in the economic model. For the outcome of fatal other major bleeds, data was pooled from ARISTOTLE and AVERROES for the economic model due to small sample size. However, just the numbers in each treatment arm from ARISTOTLE are presented below.

Table 2: ARISTOTLE ITT population

Event	Apixaban		Warfarin		HR and 95% CI	p value	Source
	n	N	n	N			
Haemorrhagic stroke	40	9120	78	9081	0.51 (0.35–0.75)	<0.001	Granger et al. 2011, NEJM
Mild	7	31	13	65	NA	NA	ARISTOTLE secondary analysis
Moderate	10	31	10	65	NA	NA	ARISTOTLE secondary analysis
Severe	3	31	8	65	NA	NA	ARISTOTLE secondary analysis
Fatal	11	31	34	65	NA	NA	ARISTOTLE secondary analysis
Other fatal intracranial haemorrhage	2	12	4	44	NA	NA	ARISTOTLE secondary analysis
Ischaemic stroke	162	9120	175	9081	0.92 (0.74-1.13)	0.42	Granger et al. 2011, NEJM
Mild	57	108	49	108	NA	NA	ARISTOTLE secondary analysis
Moderate	23	108	32	108	NA	NA	ARISTOTLE secondary analysis
Severe	9	108	11	108	NA	NA	ARISTOTLE secondary analysis
Fatal	19	108	16	108	NA	NA	ARISTOTLE secondary analysis

Fatal systemic embolism	1	15	2	16	NA	NA	ARISTOTLE clinical study report pages 120, 138,
Other CV hospitalisation (as defined in the economic model)	NR	NR	NR	NR	NR	NR	NR
Other major bleeds (as defined in the economic model)	275	9088	340	9052	0.79 (0.68–0.93)	0.004	Granger et al. 2011, NEJM Table 3, ISTH major bleed breakdown
Non- ICH and non- GI related bleeds	170	275	221	340	NA	NA	Granger et al. 2011, NEJM Table 3, calculated from ISTH major bleed breakdown
Fatal other major bleeds	6	275	7	340	NA	NA	ARISTOTLE secondary analysis
Other cause mortality (as defined in the economic model)	528	9120	568	9081	0.92 (0.82-1.04)	0.185	ARISTOTLE secondary analysis
Other treatment discontinuations (as defined in the economic model)	2084	9120	2203	9081	0.93 (0.87 - 0.98)		ARISTOTLE secondary analysis

ii) AVERROES

Please see table below for the data and source for the ITT population. For the haemorrhagic stroke outcome, data were pooled for apixaban and aspirin due to small patient numbers in the model, although the numbers in each treatment arm are presented below for clarity. No statistical tests were performed on the different stroke severity categories for haemorrhagic and ischaemic stroke as the trial was not powered for this. For ischaemic stroke, the severity sub-categories include ischaemic and unspecified events, whereas the total ischaemic stroke numbers from the AVERROES publication exclude unspecified events. For the outcome of fatal systemic embolism, data was used from ARISTOTLE for the economic model since zero events were recorded for both treatment arms in AVERROES.

Table 3: AVERROES ITT population

	Apixaban		**Aspirin**				
Event	**n**	**N**	**n**	**N**	**HR and 95% CI**	**p value**	**Source**
Haemorrhagic stroke	6	2808	9	2791	0.67 (0.24-1.88)	0.45	Conolly et al. 2011, NEJM
Mild	1	6	0	9	NA	NA	AVERROES secondary analysis
Moderate	1	6	2	9	NA	NA	AVERROES secondary analysis
Severe	0	6	4	9	NA	NA	AVERROES secondary analysis
Fatal	4	6	3	9	NA	NA	AVERROES secondary analysis
Other fatal intracranial haemorrhage	1	5	1	2	NA	NA	AVERROES secondary analysis
Ischaemic stroke	35	2808	93	2791	0.37 (0.25-0.55)	<0.001	Conolly et al. 2011, NEJM
Mild	17	43	35	97	NA	NA	AVERROES secondary analysis
Moderate	12	43	37	97	NA	NA	AVERROES secondary analysis
Severe	5	43	15	97	NA	NA	AVERROES secondary analysis
Fatal	9	43	10	97	NA	NA	AVERROES secondary analysis

Fatal systemic embolism	0	2	0	13	NA	NA	AVERROES clinical study report pages 113, 135-141
Other CV hospitalisation (as defined in the economic model)	NR	2808	NR	2791	0.87 (0.74-1.01)		AVERROES secondary analysis
Other major bleeds (as defined in the economic model)	34	2808	18	2791	1.87 (1.06-3.31)		AVERROES secondary analysis
Non- ICH and non- GI related bleeds	22	34	11	18	NA	NA	AVERROES secondary analysis
Fatal other major bleeds	1	34	1	18	NA	NA	ARISTOTLE secondary analysis
Other cause mortality (as defined in the economic model)	94	2807	114	2790	0.83 (0.63-1.08)	0.168	AVERROES secondary analysis
Other treatment discontinuations (as defined in the economic model)	505	2808	555	2791	0.90 (0.81-1.01)		AVERROES secondary analysis

A10. Please provide the per protocol results for the primary efficacy outcome (stroke or SE) in ARISTOTLE.

According to the ARISTOTLE CSR section 3.6.2, the evaluable patient population was defined as the **s**ubset of randomised subjects, excluding full (if deviation occurred prior to randomization) or partial data (if deviation occurred after randomization) from subjects with protocol deviations expected to affect the primary efficacy endpoint. If a deviation occurred after randomization then the data up to the time of the deviation was included in the evaluable data set. Data for the evaluable population analysis up to 2 days after last dose is presented in the table below.

Table 4: Per protocol results for the primary efficacy outcome (stroke or SE) in ARISTOTLE

Apixaban N	Apixaban n	Warfarin N	Warfarin n	HR (95% CI)	p value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (2-sided p-value for superiority test)

HR: 0.69 (0.56, 0.86); p=0.0009 (2-sided p-value for superiority test)

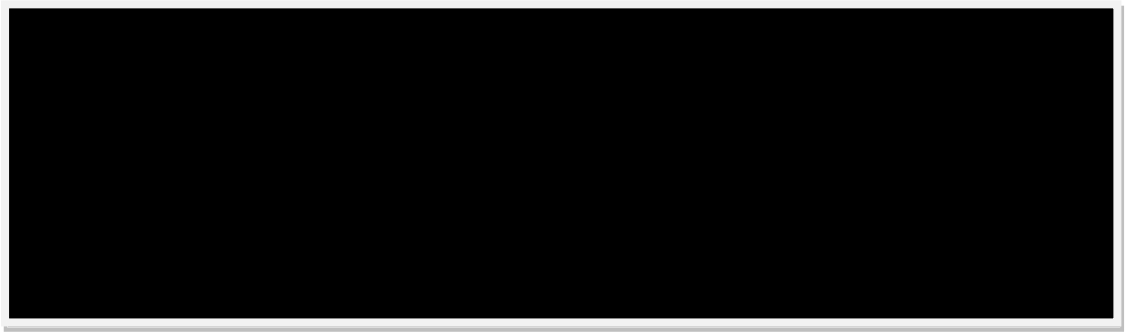
Source: ARISTOTLE CSR: Table 7.1.1.2

A11. Please clarify the numbers reported in Figure 4, page 51 of the manufacturer's submission (the Participant Flow for AVERROES) for patients discontinuing from both the apixaban and aspirin trial arms of AVERROES as the total numbers do not appear to equal the sum of the numbers reported for the individual reasons (subject request, AE, death and other reasons).

The total numbers discontinuing in the apixaban group (N=558) and the aspirin group (N=649) are both correct. However, the CSR states on p.73 (Table 5.1) that subjects were counted once in each category but may be counted in more than one discontinuation category. Therefore some subjects, who for example, were counted as discontinuing due to an AE, may also have been counted as discontinuing due to death, or for other reasons. For this reason the discontinuation sub-categories sum up to more than the total number of patients who discontinued in each treatment arm.

A12. Please provide details of the number of patients in each study arm in ARISTOTLE who experienced ≥1 study-drug interruption and the duration of the study drug interruptions.

Study interruptions were counted if they lasted 5 consecutive days or more. Table S4,1.C1 below from the ARISTOTLE CSR shows that [redacted] of subjects in the apixaban and [redacted] subjects in the warfarin arm interrupted their study treatment for 5 consecutive days or more, and provides reasons for the interruption .The duration of study drug interruptions is not reported in the CSR.



Subgroups

Stroke risk $CHAD_2$ scores

A13. **Priority Question:** Please complete the table below to provide the safety and efficacy results of ARISTOTLE and AVERROES by the following baseline $CHADS_2$ scores (six tables in total, three for each trial)

i) ≤1;

ii) 2;

iii) ≥3

Pre-specified sub-group analyses stratified by the above $CHADS_2$ risk categories were carried out for the primary efficacy outcome (stroke plus systemic embolism), major bleeding and all bleeding but not for any other secondary outcome as requested by the ERG. Analyses on other single-component secondary outcomes were not conducted, and such post-hoc analyses would be underpowered, given the smaller numbers of events involved, and therefore run the risk of producing spurious differences in treatment effect between different sub-groups. The ARISTOTLE CSR (section 7.1.2) states that a formal treatment-by-subgroup interaction testing was used as a tool to detect, rank, and evaluate those pre-specified subgroups where the efficacy effect might be found to vary. Because of the number of pre-specified analyses, there was high a priori risk for type 1 "false positive" results. None of the subgroup variables generated an interaction p-value <0.05. However, additional post-hoc sub-group analyses would be even more prone to produce spurious findings, and would be inadvisable to conduct.

Table 5: $CHADS_2$ ≤1 (ARISTOTLE)

Event	Apixaban		Warfarin		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Major bleeding						
All bleeding						

Sources: ARISTOTLE CSR: Figure 7.1.2; table S.5.4A); Figure 8.2.2; table S.6.2B; Table S.6.2D

Table 6: $CHADS_2$ =2 (ARISTOTLE)

Event	Apixaban		Warfarin		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Major bleeding						
All bleeding						

Sources: ARISTOTLE CSR: Figure 7.1.2; table S.5.4A; Figure 8.2.2; table S.6.2B; Table S.6.2D

Table 7: $CHADS_2$ ≥3 (ARISTOTLE)

Event	Apixaban		Warfarin		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Major bleeding						
All bleeding						

Sources: ARISTOTLE CSR: Figure 7.1.2; table S.5.4A (p.427); Figure 8.2.2); table S.6.2B; Table S.6.2D

Table 8: $CHADS_2$ ≤1 (AVERROES)

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Any bleeding						
Major bleeding						

Sources: AVERROES CSR: Figure 7.1.2; table S.5.4A (p.427); Figure 8.2.2); table S.6.2B; Table S.6.2D

Table 9: $CHADS_2$ =2 (AVERROES)

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism	[redacted]					
Any bleeding						
Major bleeding						

Sources: AVERROES CSR: Figure 7.1.2; table S.5.4A (p.427); Figure 8.2.2); table S.6.2B; Table S.6.2D

Table 10: $CHADS_2$ ≥3 (AVERROES)

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism	[redacted]					
Any bleeding						
Major bleeding						

Sources: AVERROES CSR: Figure 7.1.2; table S.5.4A (p.427); Figure 8.2.2); table S.6.2B; Table S.6.2D

A14. Please complete the table below to provide further details of the baseline $CHADS_2$ scores in both ARISTOTLE and AVERROES:

Table 11: Baseline $CHADS_2$ scores for ARISTOTLE and AVERROES

	ARISTOTLE		AVERROES	
$CHADS_2$ score	Apixaban	Warfarin	Apixaban	Aspirin
	n	n	n	n
0	[redacted]			
1				
2				
3				
4				
5				
6				

Sources: ARISTOTLE CSR Table 5.3.2.2; AVERROES CSR Table 5.3.2.2 B

A15. Please complete the table below to provide the results for the primary efficacy and safety outcomes for each $CHADS_2$ subgroup in:

For both trials $CHADS_2$ data was only reported for the individual score of 2. No other outcome data was available from the CSRs for individual $CHADS_2$ scores.

i) ARISTOTLE

Table 12: Primary efficacy and safety outcomes for $CHADS_2$ score of 2

Subgroup	Event	Apixaban		Comparator		HR and 95% CI	p value
		n	N	n	N		
	Primary efficacy outcome						
CHADS score = 2							
	Primary safety outcome						
CHADS score = 2							

Source: CSR Figure 7.1.2; Table S.6.2B; Figure 8.2.2

ii) AVERROES

Table 13: Primary efficacy and safety outcomes for $CHADS_2$ score of 2

Subgroup	Event	Apixaban		Comparator		HR and 95% CI	p value
		n	N	n	N		
	Primary efficacy outcome						
CHADS score =2							
	Primary safety outcome						
CHADS score =2							

Source: CSR Table S.5.4A; Table S.6.2B

% TTR

A16. Please provide the % TTR for each of the following region subgroups in ARISTOTLE:

i) North America;
ii) Latin America;
iii) Europe;
iv) Asia/Pacific;
v) US;
vi) Eastern EU;
vii) Western EU.

%TTR was not available from the CSR for individual patients, only by centre. Proportion of time in therapeutic range during the study period was calculated at country level, not by region. The table below provides a breakdown of this data. It

would be inappropriate to calculate a mean TTR by region by adding individual country TTRs and dividing by the total number of countries within a group.

Table 14: Proportion of time in specified INR range during the treatment period by region

Country	Proportion of time in specified INR range during the treatment period, %					
	INR <2.0		INR ≥2.0, ≤3.0		INR >3.0	
	Apixaban (Sham INR)	Warfarin	Apixaban (Sham INR)	Warfarin	Apixaban (Sham INR)	Warfarin
North America						
Canada						
USA						
Latin America						
Argentina						
Brazil						
Chile						
Columbia						
Mexico						
Peru						
Puerto Rico						
Europe						
Austria						
Belgium						
Czech Republic						
Denmark						
Finland						
France						
Germany						
Hungary						
Israel						
Italy						
Netherlands						
Norway						
Poland						
Romania						
Russia						
Spain						
Sweden						
Turkey						
UK						
Ukraine						
Asia/Pacific						
Australia						
China						
Hong Kong						
India						
Japan						
Malaysia						
Philippines						
Singapore						
South Korea						

Country	Proportion of time in specified INR range during the treatment period, %					
	INR <2.0		INR ≥2.0, ≤3.0		INR >3.0	
	Apixaban (Sham INR)	Warfarin	Apixaban (Sham INR)	Warfarin	Apixaban (Sham INR)	Warfarin
Taiwan	[redacted]					
Other						
South Africa	[redacted]					

Source: ARISTOTLE CSR, Table S.4.2B3

A17. Please provide the % TTR for the following age subgroups in ARISTOTLE:

i) <65 years;
ii) 65 to <75years;
iii) ≥75 years.

This data is not available from the CSR as analyses of these sub-groups were not conducted.

A18. Please provide the total number of people included in each analysis for each cTTR subgroup reported in tables 19 and 28 for each trial arm (i.e. apixaban and warfarin groups).

Data on number of people included in each analysis for each cTTR subgroup reported in tables 19 and 28 is not available from the CSR. Data on the events, effect sizes, and 95% confidence intervals was taken from a slide set and abstract presented at a conference as reported in the main submission. The numerator and denominator data is unavailable.

Region subgroups

A19. **Priority Question:** Please complete the table below to provide the safety and efficacy results of ARISTOTLE for the Western Europe subgroup (as defined in table 15, page 49 of the manufacturer's submission)

Pre-specified sub-group analyses stratified by the Western Europe region were carried out for the primary efficacy outcome (stroke plus systemic embolism) and major bleeding only, but not for any other secondary outcome as requested by the ERG. Analyses on other single-component secondary outcomes were not conducted, and such post-hoc analyses would be underpowered, given the smaller numbers of events involved, and therefore run the risk of producing spurious differences in treatment effect between different sub-groups. The ARISTOTLE CSR (section 7.1.2) states that a formal treatment-by-subgroup interaction testing was used as a tool to detect, rank, and evaluate those pre-specified subgroups where the efficacy effect might be found to vary. Because of the number of pre-specified analyses, there was high a priori risk for type 1 "false positive" results – the results for the two outcomes provided below should be viewed with caution in light of this as they are still likely to be underpowered. Furthermore, post-hoc sub-group analyses on additional secondary outcomes would be even more prone to produce spurious findings, and would be inadvisable to conduct.

Table 15: Safety and efficacy results of ARISTOTLE for the Western Europe subgroup

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: ARISTOTLE CSR Table: S.5.4D, Table: S.6.2Q

Other subgroups

A20. Please provide a breakdown of the reasons why people were taking 2.5 mg apixaban in both ARISTOTLE and AVERROES and the number of people for which each reason applies.

ARISTOTLE

831 patients took 2.5mg BD, 428 and 403 in the apixaban and warfarin arms respectively. Reasons for taking this dose are provided in the table below taken from the ARISTOTLE CSR.

[redacted]

AVERROES

361 patients took 2.5mg BD, 179 and 182 in the apixaban and ASA arms respectively (see Table s.3.3B1 in CSR).

[redacted]

A21. Please complete the table below to provide the safety and efficacy outcome data for the following subgroups (five tables in total):

For sub-questions a, b, d and e below pre-specified sub-group analyses were carried out for the primary efficacy outcome (stroke plus systemic embolism), major bleeding, and all bleeding only, but not for any other secondary outcome as requested by the ERG. Analyses on other single-component secondary outcomes were not conducted, and such post-hoc analyses would be underpowered, given the smaller numbers of events involved, and therefore run the risk of producing spurious differences in treatment effect between different sub-groups. The ARISTOTLE and AVERROES CSRs (section 7.1.2 in both) state that a formal treatment-by-subgroup interaction testing was used as a tool to detect, rank, and evaluate those pre-specified subgroups where the efficacy effect might be found to vary. Because of the number of pre-specified analyses, there was high a priori risk for type 1 "false positive" results – the results for the three outcomes provided for sub-questions a, b, and d below should be viewed with caution in light of this as they are still likely to be underpowered. Furthermore, post-hoc sub-group analyses on additional secondary outcomes would be even more prone to produce spurious findings, and would be inadvisable to conduct.

a. people on 2.5mg apixaban in ARISTOTLE;

Table 16: People on 2.5mg apixaban in ARISTOTLE

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: ARISTOTLE CSR Table S.5.4A , Table S.6.2D, Table S.6.2B

b. people on 5mg apixaban in ARISTOTLE;

Table 17: People on 5mg apixaban in ARISTOTLE

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Any bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Source: ARISTOTLE CSR Table S.5.4A , Table S.6.2D, Table S.6.2B

c. people on 2.5mg apixaban and aged over 80years in ARISTOTLE;

No data was reported on this sub-group in the CSR.

d. people <65years age in ARISTOTLE;

Table 18: People <65years age in ARISTOTLE

Event	Apixaban		Comparator		HR and 95% CI	p value
	n	N	n	N		
Stroke or systemic embolism						
Any bleeding						
Major bleeding						

Source: ARISTOTLE CSR Table S.5.4A , Table S.6.2D, Table S.6.2B

e. people contraindicated to warfarin in AVERROES.

Table 19: People contraindicated to warfarin in AVERROES

Reason VKA unsuitable	Apixaban, n/N	Aspirin, n/N	HR (95% CI)
Stroke or systemic embolism[†]			
Subject refused treatment with VKA (only reason)			
$CHADS_2$ score =1 and physician does not recommend VKA (only reason)			
All other reasons			
Any bleeding[‡]			
Subject refused treatment with VKA (only reason)			
$CHADS_2$ score =1 and physician does not recommend VKA (only reason)			
All other reasons			
Major bleeding[‡]			
Subject refused treatment with VKA (only reason)			
$CHADS_2$ score =1 and physician does not recommend VKA (only reason)			
All other reasons			

[†]Randomised subjects
[‡]Treated subjects
CRNM, clinically relevant non-major; VKA, vitamin K antagonist

Sources: AVERROES CSR, Stroke or systemic embolism: (Table: S.5.4A, Any bleeding: (Table: S.6.2D), Major bleeding: (Table: S.6.2B;)

A22. Please provide the results for all subgroups in AVERROES specified in table 15 for the primary efficacy outcome (stroke or SE).

Table 20: Primary efficacy outcome (stroke or SE) by subgroups in AVERROES

Subgroup	Total no. of patients	Apixaban (n/N)	Aspirin (n/N)	HR (95% CI)
VKA unsuitable				
Demonstrated	2215	17/1108	52/1107	0.33 (0.19, 0.56)
Expected	3383	34/1699	61/1684	0.55 (0.36, 0.84)
Reason VKA unsuitable				
Sub. Refused treatment with VKA	815	6/421	17/394	0.33 (0.13, 0.83)
CHADS2 score = 1 and physician does not recommend VKA	612	4/294	2/318	2.18 (0.40, 11.91)
All other reasons	4170	41/2091	94/2079	0.43 (0.30, 0.62)
Apixaban dose				
2.5 mg BD or placebo	361	3/179	12/182	0.26 (0.07, 0.93)
5 mg BD or placebo	5237	48/2628	101/2609	0.47 (0.33, 0.66)
Aspirin dose				
81 mg QD	3602	39/1816	85/1786	0.45 (0.31, 0.65)
162 mg QD	1468	11/718	20/750	0.57 (0.27, 1.20)
243 mg QD	133	1/73	2/60	0.41 (0.04, 4.48)
324 mg QD	377	0/193	5/184	<0.01
Geographic region				
North America	804	5/408	18/396	0.27 (0.10, 0.74)
Latin America	1185	8/589	31/596	0.25 (0.12, 0.55)
Europe	2507	23/1263	46/1244	0.49 (0.30, 0.81)
Asia pacific	1102	15/547	18/555	0.86 (0.43, 1.71)
Age				
<65 yr	1720	7/855	19/865	0.38 (0.16, 0.89)
65 to <75 yr	1987	24/1049	29/938	0.73 (0.43, 1.25)
≥75 yr	1891	20/903	65/988	0.34 (0.20, 0.56)
Gender				
Male	3277	26/1660	49/1617	0.52 (0.32, 0.83)
Female	2321	25/1147	64/1174	0.40 (0.25, 0.63)
Race				
White	4399	37/2221	93/2178	0.39 (0.26, 0.57)
Black/African American	36	0/10	0/26	NE
Asian	1085	14/541	18/544	0.79 (0.39, 1.59)
Other	78	0/35	2/43	<0.01
Ethnicity				
Hispanic/Latino	1116	6/557	30/559	0.20 (0.08, 0.47)
Not Hispanic/Latino	4420	45/2224	82/2196	0.54 (0.38, 0.78)
Weight				
≤60 kg	881	18/459	20/422	0.84 (0.44, 1.58)
>60 kg	4715	33/2348	93/2367	0.36 (0.24, 0.53)
BMI, kg/m^2				
≤28	2931	34/1446	56/1485	0.63 (0.41, 0.97)
>28-33	1666	14/854	40/812	0.33 (0.18, 0.61)
>33	992	3/503	17/489	0.17 (0.05, 0.57)

Level of renal impairment				
Severe or moderate	1084	13/545	32/539	0.40 (0.21, 0.76)
Mild	2149	22/1074	58/1075	0.37 (0.23, 0.61)
No impairment	1878	12/955	16/923	0.74 (0.35, 1.57)
No. of risk factors				
≤1	2162	13/1085	21/1077	0.61 (0.31, 1.22)
≥2	3436	38/1722	92/1714	0.41 (0.28, 0.60)
$CHADS_2$ score				
≤1	2142	12/1066	19/1076	0.63 (0.31, 1.30)
2	1973	23/1037	43/936	0.49 (0.29, 0.81)
≥3	1483	16/704	51/779	0.35 (0.20, 0.61)
Prior stroke or TIA				
Yes	764	10/390	33/374	0.29 (0.14, 0.60)
No	4834	41/2417	80/2417	0.51 (0.35, 0.74)
Age ≥75 years				
Yes	1891	20/903	65/988	0.34 (0.20, 0.56)
No	3707	31/1904	48/1803	0.61 (0.39, 0.96)
Diabetes mellitus				
Yes	1095	14/536	22/559	0.67 (0.34, 1.31)
No	4503	37/2271	91/2232	0.40 (0.27, 0.58)
Hypertension requiring treatment				
Yes	4837	46/2408	98/2429	0.47 (0.33, 0.67)
No	761	5/399	15/362	0.31 (0.11, 0.85)
Heart failure				
Yes	1810	19/920	35/890	0.52 (0.30, 0.91)
No	3788	32/1887	78/1901	0.41 (0.27, 0.62)

NE, not estimable

Source: AVERROES CSR: Figure 7.1.2 (p.104); Table S.5.4A

A23. Please provide the p value used to determine the presence of a significant between subgroup interaction in AVERROES. If the p value for between subgroup interaction in AVERROES was <0.10 (as it is in ARISTOTLE) then please suggest an explanation for the significant difference in treatment effect for age subgroups (p=0.08).

Sections 7.1.2 and 8.2.2 of the Clinical Study Report states: A formal treatment-by-subgroup interaction testing was used as a tool to detect, rank, and evaluate those subgroups where the efficacy effect might be found to vary. The treatment-by-subgroup interaction test is intended to help evaluate the degree of differential patterns across treatment groups for each grouping variable. In these analyses, there was no correction for multiplicity. Because of the number of analyses, there was high a priori risk for type 1 “false positive” results. If the number of subjects was ≤10 in either treatment group, a summary for that subgroup was not included in the test for subgroup-by-treatment interaction. None of the primary efficacy endpoint subgroup variables generated an interaction p-value <0.05, except for the ethnicity and weight subgroups. The p-value for the ethnicity group was 0.0349 and the p-value for the weight group was 0.0247. However, the HR for both ethnicity subgroups and both weight groups were <1, (i.e., the observed risk of stroke/SE was lower on apixaban than ASA for these subgroups).

The effect of age on exposure to apixaban has been formally studied in a pharmaco-kinetics (PK) study and slightly higher exposure was found in those >65 vs those <65 years of age. On the sole basis of age, no dose change is recommended. In this subgroup analysis, there seems to be numerically different results in the 65-75 age group with similar results in the <65 and >75 in terms of Hazard ratios. There is no correction for multiplicity when performing these pre specified subgroups analyses and this is likely a chance finding.

None of the subgroup variables generated an interaction p<0.05 for major bleeding or for the composite of major or CRNM bleeding (see Table s.6.2.F from CSR below). For all bleeding endpoints the only interaction p<0.05 was for prior Stroke/TIA subgroup; given the large number of comparisons performed this is likely a chance finding.

Network meta analysis

A24. **Priority Question:** Please provide the WinBUGS files containing the numerical trial data used for each of the outcomes assessed in the NMAs to enable validation of the results provided within the submission.

Please see attached zip file.

A25. **Priority Question:** Please provide the total residual deviance for the fixed and random effects models and the values of tau for the random effects model for each outcome assessed in the network meta analysis.

The residual deviance values for both the fixed and rand effect models are presented in the tables below. The average residual deviance is calculated by dividing the total deviance by the number of trial arms in each network. For the warfarin-suitable network the number of trial arms was seven whereas it is nine for the warfarin-unsuitable network (except for clinically relevant non-major bleeding where only four data points were available in the warfarin suitable analysis and six in the unsuitable). The closer the average residual deviance is to 1 the greater the fit of the data to the

model. As the tables below show, the total residual deviances closely match the number of arms in each network (i.e. average is close to 1) and so the data fit both models in both networks well.

Table 21: Residual deviance values from the fixed and random effect models for warfarin-suitable patients

Outcome	Basecase (RE-LY 2009 and ROCKET-AF ITT data) Fixed / random effect	SA1 (RE-LY 2010) Fixed / random effect	SA2 (ROCKET-AF OT data) Fixed / random effect
Any stroke	7.065 / 7.084	7.078 / 6.955	7.065 / 6.898
Haemorrhagic stroke	7.127 / 7.033	X	7.091 / 7.036
Ischaemic stroke	7.012 / 7.08	X	7.053 / 7.026
Disabling stroke	X	X	7.08 / 6.989
Non-disabling stroke	X	X	7.079 / 7.018
Stroke or systemic embolism	7.01 / 6.962	7.054 / 6.984	7.033 / 6.995
Systemic embolism	7.164 / 7.058	X	7.221 / 7.153
Fatal stroke	X	X	7.138 / 7.064
Major bleed	X	7.041 / 6.947	7.057 / 7.035
Any bleed	X	7.098 / 7.048	7.072 / 7.043
Gastrointestinal bleed	X	7.104 / 7.047	7.079 / 7.024
Clinically relevant non-major bleed	X	X	4.018 / 3.972*
Intracranial haemorrhage	X	7.1 / 7.054	7.101 / 6.989
MI	7.124 / 7.006	7.109 / 6.973	7.12 / 7.048
All cause mortality	7.035 / 6.968	X	7.061 / 6.979
Discontinuations	7.11 / 7.04	X	X

*Compared with only 4 data points as there was no RE-LY data available for this outcome

Table 22: Residual deviance values from the fixed and random effect models for warfarin unsuitable

Outcome	Basecase (RE-LY 2009 and ROCKET-AF ITT data) Fixed / random effect	SA1 (RE-LY 2010) Fixed / random effect	SA2 (ROCKET-AF OT data) Fixed / random effect
Any stroke	8.983 / 9.023	8.928 / 9.063	8.977 / 9.019
Haemorrhagic stroke	9.105 / 9.094	X	9.065 / 9.124
Ischaemic stroke	9.003 / 8.967	X	9.032 / 9.079
Disabling stroke^	X	X	X
Non-disabling stroke	X	X	9.112 / 9.013
Stroke or systemic embolism	9.054 / 9.075	9.029 / 8.97	9.09 / 9.154
Systemic embolism	9.178 / 9.032	X	9.204 / 9.207
Fatal stroke^	X	X	X
Major bleed	X	9.059 / 9.038	9.053 / 9.048
Any bleed	X	9.104 / 8.948	9.103 / 9.022
Gastrointestinal bleed	X	9.113 / 9.031	9.137 / 8.914
Clinically relevant non-major bleed	X	X	6.035 / 5.994*
Intracranial haemorrhage	X	9.068 / 8.989	9.114 / 9.002
Myocardial infarction	9.048 / 9.059	9.062 / 9.094	9.046 / 8.979
All cause mortality	9.048 / 9.05	X	9.037 / 8.952
Discontinuations	9.039 / 8.925	X	X

^No Net3 data available for disabling or fatal stroke; *Compared with only 6 data points as there was no RE-LY data available for this outcome

Table 23: Mean / median Tau values (95% CrI) from the random effect models: efficacy analyses

Please note that as mentioned in the main submission, the random effects model is not considered to be the most appropriate due to the difficulties in measuring between study heterogeneity based on the limited number of trials included in the analysis. In such cases, the random effects model can provide a poor estimate of the width of the distribution of intervention effects. Tau-squared is a heterogeneity parameter measuring cross-study variation. Therefore, if there is no variance between studies, tau-squared (and hence tau) takes a low (or zero) value. In the tables below, many of the mean values for tau are very large and fall outside the already wide 95% CrI. In addition, the CrIs are also wide. This suggests that some of the model iterations are poor estimates of the intervention effect.

Outcome	**Warfarin-suitable patients (Network 1)**			**Warfarin-unsuitable (Network 2)**		
	Basecase (RE-LY 2009 and ROCKET-AF ITT data)	**SA1 (RE-LY 2010)**	**SA2 (ROCKET-AF OT data)**	**Basecase (RE-LY 2009 and ROCKET-AF ITT data)**	**SA1 (RE-LY 2010)**	**SA2 (ROCKET-AF OT data)**
Any stroke	12140 / 0.1703 (0.042,121)	117 / 0.1609 (0.042,65)	11520 / 0.162 (0.042,101)	42 / 0.1557 (0.042,40)	69 / 0.1604 (0.042,69)	75 / 0.1548 (0.042,45)
Haemorrhagic stroke	73.51 / 0.1523 (0.042,38)	X	3025 / 0.1556 (0.042,53)	2709 / 0.1647 (0.042,112)	X	207 / 0.1566 (0.042,45)
Ischaemic stroke	3018 / 0.1611 (0.042,43.33)	X	40.6 / 0.1549 (0.042,42)	32800 / 0.1592 (0.042,63)	X	08600 / 0.1761 (0.042,345)
Disabling stroke^	X	X	286 / 0.1597 (0.042,70)	X	X	X

Non-disabling stroke	X	X	40430 / 0.1621 (0.042,116)	X	X	563 / 0.1618 (0.042,63)
Stroke or systemic embolism	131 / 0.1608 (0.042,82)	82 / 0.155 (0.042,47)	105 / 0.1616 (0.042,57)	5767 / 0.1578 (0.042,65)	5813 / 0.1587 (0.042,106)	6874 (0.1566 (0.042,171)
Systemic embolism	3032 / 0.1523 (0.042,52)	X	131 / 0.1544 (0.042,41)	271 / 0.1645 (0.042,87)	X	78 / 0.1594 (0.042,41)
Fatal stroke^	X	X	45 / 0.1523 (0.042,37)	X	X	X

Table 24: Mean / median Tau values (95% CrI) from the random effect models: safety analyses

Outcome	**Warfarin-suitable patients (Network 1)**			**Warfarin-unsuitable (Network 2)**		
	Basecase (RE-LY 2009 and ROCKET-AF ITT data)	**SA1 (RE-LY 2010)**	**SA2 (ROCKET-AF OT data)**	**Basecase (RE-LY 2009 and ROCKET-AF ITT data)**	**SA1 (RE-LY 2010)**	**SA2 (ROCKET-AF OT data)**
Major bleed	X	89 / 0.1637 (0.042,53)	702 / 0.1624 (0.042,64)	X	85 / 0.1526 (0.042,40)	70 / 0.1519 (0.042,36)
Any bleed	X	51 / 0.1607 (0.042,62)	201 / 0.1604 (0.042,34)	X	3710 / 0.1664 (0.042,83)	178 / 0.1712 (0.042,89)

Gastrointestinal bleed	X	29 / 0.1584 (0.042,51)	1181 / 0.1553 (0.042,54)	X	32 / 0.1553 (0.042,40)	384 / 0.1611 (0.042, 66)
Clinically relevant non-major bleed	X	X	202 / 0.1635 (0.042,65)	X	X	137 / 0.1607 (0.042,61)
Intracranial haemorrhage	X	527 / 0.1558 (0.042,49)	289 / 0.1595 (0.042,86)	X	935 / 0.1746 (0.042, 100)	91 / 0.1569 (0.042,89)
Myocardial infarction	3290 / 0.155 (0.042,50)	276 / 0.1631 (0.042,47)	84 / 0.1624 (0.042,62)	122 / 0.1527 (0.042,50)	71 / 0.1692 (0.042,74)	200 / 0.1625 (0.042,54)
All cause mortality	101 / 0.1587 (0.042,62)	X	12 / 0.1523 (0.042,39)	67 / 0.1716 (0.042,82)	X	8049 / 0.1619 (0.042,54)
Discontinuations	88 / 0.1592 (0.042,64)	X	X	628 / 0.167 (0.042,78)	X	X

Other clarifications on clinical effectiveness

A26. Please explain how the estimate that 80% of AF is non-valvular (page 20 of the manufacturer's submission) was calculated from reference 25.

The estimate was incorrect, the correct proportion having valvular disease is 26.3% and therefore the estimate of AF that is non-valvular from reference 25 should be 74%. However, there are a number of other potential estimates in the literature.

Realise-AF [5] is an international, cross-sectional survey of patients with AF, from 831 sites in 26 countries on 4 continents. Patients were eligible for analysis if they had at least 1 AF episode documented by standard electrocardiogram (ECG) or by Holter-ECG monitoring within the previous 12 months. AF was considered of valvular origin when it was associated with significant valvular heart disease. Overall, 2779 (26.3%) patients were found to have valvular AF, with 7629 (73.7%) having non-valvular AF. In the RECORDAF study, a worldwide, prospective observational survey of management of AF in 5604 unselected, community based patients, valvular heart disease was present in 19% of patients.[6] In a retrospective study of 120964 patients hospitalised for first-time AF in Denmark, 5047 (4.7%) had valvular heart disease.[7] Given the variation in valvular heart disease prevalence across these studies (5%-26%), an 80% prevalence of non-valvular AF is a reasonable estimate.

A27. A27 Please provide the numerical values for the total number of people included in each analysis (including the number of people in each treatment arm), the hazard ratio and 95% confidence interval for each of the subgroup results presented in the following figures in the manufacturer's submission:

i) Figure 6;
ii) Figure 8;
iii) Figure 12.

Table 25: Stroke or SE (Figure 6) - ARISTOTLE

Subgroup	Total no. of patients	Apixaban, n (N)	Warfarin, n (N)	HR (95% CI)
Prior use of warfarin or other VKA				
Yes	10401	102 (5208)	138 (5193)	0.73 (0.57, 0.95)
No	7800	110 (3912)	127 (3888)	0.86 (0.66, 1.11)
Age				
<65 yr	5471	51 (2731)	44 (2740)	1.16 (0.77, 1.73)
65 to <75 yr	7052	82 (3539)	112 (3513)	0.72 (0.54, 0.96)
≥75 yr	5678	79 (2850)	109 (2828)	0.71 (0.53, 0.95)
Sex				
Male	11785	132 (5886)	160 (5899)	0.82 (0.65, 1.04)
Female	6416	80 (3234)	105 (3182)	0.74 (0.56, 1.00)
Weight				
≤60 kg	1985	34 (1018)	52 (967)	0.63 (0.41, 0.97)
>60 kg	16154	177 (8070)	212 (8084)	0.83 (0.68, 1.01)
Type of AF				
Permanent or persistent	15412	191 (7744)	235 (7668)	0.80 (0.66, 0.97)
Paroxysmal	2786	21 (1374)	30 (1412)	0.72 (0.41, 1.25)
Prior stroke or TIA				
Yes	3436	73 (1694)	98 (1742)	0.76 (0.56, 1.03)

Subgroup	Total no. of patients	Apixaban, n (N)	Warfarin, n (N)	HR (95% CI)
No	14765	139 (7426)	167 (7339)	0.82 (0.65, 1.03)
Diabetes mellitus				
Yes	4547	57 (2284)	75 (2263)	0.75 (0.53, 1.05)
No	13654	155 (6836)	190 (6818)	0.81 (0.65, 1.00)
Heart failure				
Yes	5541	70 (2784)	79 (2757)	0.86 (0.63, 1.19)
No	12660	142 (6336)	186 (6324)	0.76 (0.61, 0.94)
$CHADS_2$ score				
≤1	6183	44 (3100)	51 (3083)	0.85 (0.57, 1.27)
2	6516	74 (3262)	82 (3254)	0.90 (0.66, 1.23)
≥3	5502	94 (2758)	132 (2744)	0.70 (0.54, 0.91)
Level of renal impairment				
Severe or moderate	3017	54 (1502)	69 (1515)	0.79 (0.56, 1.13)
Mild	7587	87 (3817)	116 (3770)	0.74 (0.56, 0.97)
No impairment	7518	70 (3761)	79 (3757)	0.88 (0.64, 1.21)
Apixaban dose				
2.5 mg BD or placebo	831	12 (428)	22 (403)	0.50 (0.25, 1.02)
5 mg BD or placebo	17370	200 (8692)	243 (8678)	0.82 (0.68, 0.98)
Geographic region				
North America	4474	42 (2249)	56 (2225)	0.75 (0.51, 1.13)
Latin America	3468	43 (1743)	52 (1725)	0.81 (0.54, 1.21)
Europe	7343	75 (3672)	77 (3671)	0.96 (0.70, 1.32)
Asia pacific	2916	52 (1456)	80 (1460)	0.65 (0.46, 0.92)
Aspirin use at randomisation				
Yes	5632	70 (2859)	94 (2773)	0.72 (0.53, 0.98)
No	12569	142 (6261)	171 (6308)	0.83 (0.67, 1.04)

AF, Atrial fibrillation; BD, twice daily; TIA, transient ischaemic attack; HR, Hazard ratio; vitamin K antagonist

Source: ARISTOTLE CSR Figure 7.1.2, Table S.5.4A

Table 26: Major bleed (Figure 12) - ARISTOTLE

Subgroup	Total no. of patients	Apixaban, n (N)	Warfarin, n (N)	HR (95% CI)
Prior use of warfarin or other VKA				
Yes	10376	185 (5196)	274 (5180)	0.66 (0.55, 0.80)
No	7764	142 (3892)	188 (3872)	0.73 (0.59, 0.91)
Age				
<65 yr	5455	56 (2723)	72 (2732)	0.78 (0.55, 1.11)
65 to <75 yr	7030	120 (3529)	166 (3501)	0.71 (0.56, 0.89)
≥75 yr	5655	151 (2836)	224 (2819)	0.64 (0.52, 0.79)
Sex				
Male	11747	225 (5868)	294 (5879)	0.76 (0.64, 0.90)
Female	6393	102 (3220)	168 (3173)	0.58 (0.45, 0.74)
Weight				
≤60 kg	1978	36 (1013)	62 (965)	0.55 (0.36, 0.83)
>60 kg	16102	290 (8043)	398 (8059)	0.72 (0.62, 0.83)
Type of AF				
Permanent or persistent	15361	283 (7715)	402 (7646)	0.68 (0.59, 0.80)
Paroxysmal	2776	44 (1371)	60 (1405)	0.73 (0.50, 1.08)
Prior stroke or TIA				
Yes	3422	77 (1687)	106 (1735)	0.73 (0.54, 0.98)
No	14718	250 (7401)	356 (7317)	0.68 (0.58, 0.80)
Diabetes mellitus				
Yes	4526	112 (2276)	114 (2250)	0.96 (0.74, 1.25)
No	13614	215 (6812)	348 (6802)	0.60 (0.51, 0.71)
Heart failure				
Yes	5527	87 (2777)	137 (2750)	0.61 (0.47, 0.80)
No	12613	240 (6311)	325 (6302)	0.73 (0.61, 0.86)
$CHADS_2$ score				
≤1	6169	76 (3093)	126 (3076)	0.59 (0.44, 0.78)
2	6492	125 (3246)	163 (3246)	0.76 (0.60, 0.96)
≥3	5479	126 (2749)	173 (2730)	0.70 (0.56, 0.88)
Level of renal impairment				
Severe or moderate	3005	73 (1493)	142 (1512)	0.50 (0.38, 0.67)
Mild	7565	157 (3807)	199 (3758)	0.76 (0.62, 0.94)
No impairment	7496	96 (3750)	119 (3746)	0.79 (0.61, 1.04)
Apixaban dose				
2.5 mg BD or placebo	826	20 (424)	37 (402)	0.50 (0.29, 0.86)
5 mg BD or placebo	17314	307 (8664)	425 (8650)	0.71 (0.61, 0.82)
Geographic region				
North America	4463	106 (2244)	137 (2219)	0.77 (0.60, 1.00)
Latin America	3460	60 (1739)	94 (1721)	0.60 (0.44, 0.84)
Europe	7313	110 (3657)	135 (3656)	0.80 (0.62, 1.02)
Asia pacific	2904	51 (1448)	96 (1456)	0.52 (0.37, 0.74)
Aspirin use at randomisation				
Yes	5608	129 (2846)	164 (2762)	0.75 (0.60, 0.95)
No	12532	198 (6242)	298 (6290)	0.66 (0.55, 0.79)

AF, Atrial fibrillation; BD, twice daily; TIA, transient ischaemic attack; HR, Hazard ratio; vitamin K antagonist

Source: ARISTOTLE CSR Figure 8.2.2, Table S.6.2B

Table 27: Stroke or SE (Figure 8) - AVERROES

Subgroup	Total no. of patients	Apixaban (n/N)	Aspirin (n/N)	HR (95% CI)
Age				
<65 yr	1720	7/855	19/865	0.38 (0.16, 0.89)
65 to <75 yr	1987	24/1049	29/938	0.73 (0.43, 1.25)
≥75 yr	1891	20/903	65/988	0.34 (0.20, 0.56)
Sex				
Male	3277	26/1660	49/1617	0.52 (0.32, 0.83)
Female	2321	25/1147	64/1174	0.40 (0.25, 0.63)
Estimated GFR (ml/min)				
<50	Not reported	Not reported	Not reported	Not reported
50 to <80	Not reported	Not reported	Not reported	Not reported
≥80	Not reported	Not reported	Not reported	Not reported
$CHADS_2$ score				
≤1	2142	12/1066	19/1076	0.63 (0.31, 1.30)
2	1973	23/1037	43/936	0.49 (0.29, 0.81)
≥3	1483	16/704	51/779	0.35 (0.20, 0.61)
Prior stroke or TIA				
Yes	764	10/390	33/374	0.29 (0.14, 0.60)
No	4834	41/2417	80/2417	0.51 (0.35, 0.74)
Study aspirin dose				
<162 mg daily	3602	39/1816	85/1786	0.45 (0.31, 0.65)
≥162 mg daily	1978	12/984	27/994	Not reported
Previous VKA use				
Yes	2215	17/1108	52/1107	0.33 (0.19, 0.56)
No	3383	34/1699	61/1684	0.55 (0.36, 0.84)
Patient refused VKA				
Yes	2092	16/Not reported	40/Not reported	Not reported
No	3506	35/Not reported	73/Not reported	Not reported
Heart failure				
Yes	1810	19/920	35/890	0.52 (0.30, 0.91)
No	3788	32/1887	78/1901	0.41 (0.27, 0.62)

Source: AVERROES Figure 7.1.2; Table S.5.4A

A28. Please provide the absolute values for the number of people in each trial arm experiencing an event and the total number in the analysis for the following outcomes reported in the text on page 55 of the manufacturer's submission:

i) death from cardiovascular causes;
ii) death from non-cardiovascular causes.

Please find absolute values as requested in the table below.

Table 28: Absolute values for death from CV & non-CV causes

Outcome	ARISTOTLE DATA		AVERROES DATA‡	
	Apixaban (n/N†)	Warfarin (n/N†)	Apixaban (n/N†)	Aspirin (n/N†)
Death from CV causes	[redacted]	[redacted]	[redacted]	[redacted]
Death from non-CV causes	[redacted]	[redacted]	[redacted]	[redacted]

CV, cardiovascular

†N reported in the CSR table as for the intended treatment period – Randomised subject‡Data reported as 'vascular or non-vascular death' in AVERROES CSR, compared with ARISTOTLE CSR, where the data is reported 'cardiovascular or non-cardiovascular death

Source: ARISTOTLE CSR: Table. 7.2.1, p.138, Table. 7.3A, p.111

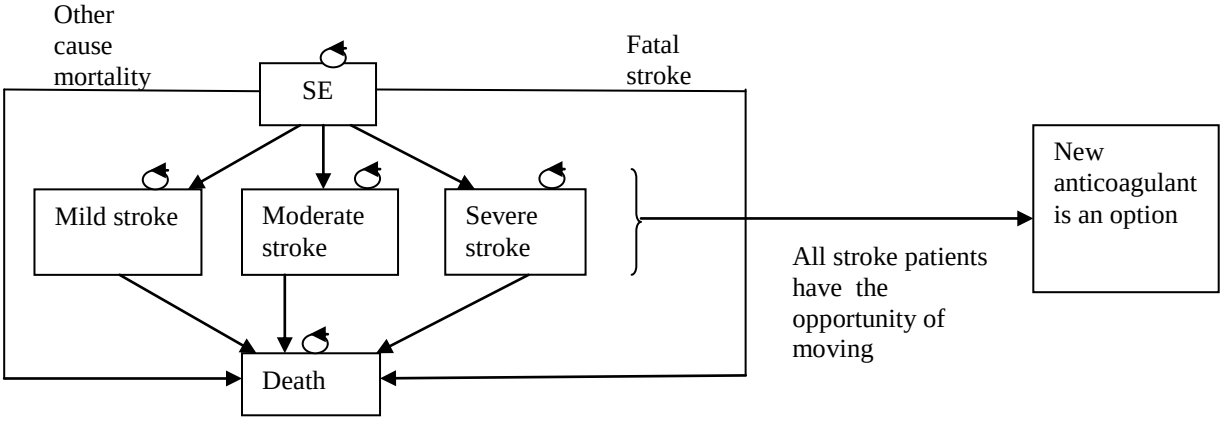
Section B: Clarification on cost-effectiveness data

Requested updates to the model

B1. **Priority request:** Please provide an Excel file with a version of the model allowing a scenario analysis in which patients experiencing an SE are exposed to the same risks as patients who have experienced an ischaemic stroke (i.e. subsequent stroke events).

The model has been amended to allow a scenario where patients experiencing a SE can experience a subsequent ischemic stroke (see updated model). However, we would like to stress that this analysis should be treated only as an exploratory scenario analysis as there are no data specifically for SE patients to support this modelling. In the model patients experiencing a first SE can go on to experience a subsequent mild, moderate, severe, or a fatal ischemic stroke and these data are taken from stroke patients. Patients experiencing a non-fatal stroke can die in subsequent cycles. The patient flow through the model is depicted graphically in the abbreviated Markov state diagram in Figure 1 below.

Figure 1: Abbreviated Markov state diagram
Model adaptation



To be consistent with the way recurrence is modelled in the stroke health states, secondary mild, moderate or severe stroke patients cannot move to a less severe stroke state. Instead, these patients are transferred to the recurrent stroke health states and remain there until death. The outcomes for these patients, e.g. number of events, costs and QALYs, are included in the recurrent events on the results sheet. This function of including/excluding recurrent events post SE is accessed via the dropdown menu in cell F65 on the settings page.

B2. **Priority request:** Within the submitted model, patients are modelled as surviving for up to 49 years (from 74 years to 123 years of age). Please provide an updated model which imposes a reasonable (e.g. 100 years) maximum survival for the AF patient population.

The model allows duration to be specified by the user. By specifying a 26 year duration (100 years -74 years) in cell F7 of the Settings page and selecting 26 from the drop down menu in cell F5 of the Results page the model will produce results for a 26 year period as requested (see updated model). This amendment has little or no impact on the ICERs produced by the model as the majority of patients have died before reaching 100 years of age. It is advisable when applying a model duration less than 'Life time' to select the half cycle correction method labelled "Half-cycle correction' in the drop down menu in cells F/G19 on the Settings page.

B3. **Priority request:** Please provide an updated model in which utility is adjusted for age as the model cohort ages.

The model has been adjusted to account for the impact of aging. A disutility of 0.00029 for each year of a patient's age is subtracted every year from the patient's health state utility.[8]

Assumptions

B4. Please provide an alternative version of Table 77 running the model under the assumption that other cause mortality is not treatment specific (i.e. no trial based other cause mortality).

Please note that there was a typographical error in the footnote of Tables 77 and 78 of the submission, patient characteristics from ARISTOTLE and AVERROES were not used in the analysis.

Table 29 below presents the alternative version of Table 77 of the submission (Table 30 below). Running a scenario with trial based mortality for the trial period switched off (cell E18 of the Death page set to 'No') results in the number of deaths from any cause increasing for both warfarin and apixaban. The difference in the number of all cause deaths between warfarin and apixaban is reduced, more than halving the all cause mortality advantage of apixaban. With trial based mortality applied there are 72 less all cause deaths with apixaban [66 recorded in the trial]), when trial based mortality is switched off and general AF all cause mortality is applied there are only 30 less deaths with apixaban. Therefore, using the trial based mortality is more appropriate as it produces predicted events similar to those observed in the trial.

Table 29: Model results compared with clinical data in VKA suitable population with other cause mortality not treatment specific

Outcome	ARISTOTLE Events‡			Model events†		
	Apixaban (N=9,120)	Warfarin (N=9,081)	Increment-al events on Warfarin	Apixaban (N=9,120)	Warfarin (N=9,081)	Incrementa l events on Warfarin
Primary outcome: stroke or SE	212	265	53	261	309	48
Stroke	199	250	51	241	287	46
Ischaemic or uncertain type	162	175	13	200	208	8
Haemorrhagic	40	78	38	41	79	38
SE	15	17	2	20	22	2
Death – any cause	603	669	66	795	825	30

Table 30: (Table 77 in original submission): Model results compared with clinical data in VKA suitable population

Outcome	ARISTOTLE Events‡			Model events†		
	Apixaban (N=9,120)	Warfarin (N=9,081)	Increment-al events on Warfarin	Apixaban (N=9,120)	Warfarin (N=9,081)	Incrementa l events on Warfarin
Primary outcome: stroke or SE	212	265	53	260§	307§	47
Stroke	199	250	51	240§	286§	46
Ischaemic or uncertain type	162	175	13	199	207	8
Haemorrhagic	40	78	38	41	79	38
SE	15	17	2	20	21	1
Death – any cause	603	669	66	593	665	72

Abbreviations: SE, systemic embolism; VKA, Vitamin K antagonist; yr, year.
†Approximation estimated at 1.84 years
§Sum of individual events

B5. It is noted that the reference used to inform the risk of incident death from MI reports risk according to gender for MI and stroke. However, the risk of incident death following stroke is not gender specific.

a) Please provide the rationale for using gender specific case fatality rates for MI and not for stroke

The number of myocardial infarctions in the AVERROES and ARISTOTLE trials was modest (AVERROES: apixaban = 24, aspirin = 28; ARISTOTLE: apixaban = 90, warfarin = 102) and as a result case fatality numbers were small. To ensure the cost effectiveness estimates were applicable to a UK population, data from Scarborough et. al.[9] based on a large number of patients (4,665 male and 4,342 female MI deaths) were used. As the data were available by gender it was implemented into the model by gender.

In an evaluation of stroke and systemic embolism prevention in anticoagulants it is imperative to use intervention specific data wherever possible. Some data for stroke

severity and stroke fatality was available for all new oral anticoagulant trials, but not by gender. In order to obtain all relevant modified Rankin scale (mRS) categories for the model it was necessary to weight the available data for dabigatran 150mg bd (switching to 110mg bd at 80 years), dabigatran 110mg bd and rivaroxaban with the proportions recorded for apixaban (see methods section of submission). Whilst ideally stroke fatality would be segregated by gender, this was decided against as the number of patients segregated by mRS score were too small in AVERROES and ARISTOTLE to result in meaningful and generalisable results, particularly for hemorrhagic strokes in the VKA unsuitable population (See tables 3 and 4, extracts from the secondary analysis of AVERROES[10] and ARRISTOTLE[11]). Additionally results from the Framingham Heart Study[12] found no significant difference in case fatality rates between genders.

Table 31: Stroke Severity Classification Associated with Ischemic or Unspecified Stroke

mRS classification	Apixaban	Aspirin
	n (%)	n (%)
0-2	[redacted]	[redacted]
3-4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]

Table 32: Stroke Severity Classification Associated with Hemorrhagic Stroke

mRS classification	Apixaban	Aspirin	Pooled Sample
	n	n	n (%)
0-2	[redacted]	[redacted]	[redacted]
3-4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]

b) Provide a scenario in which stroke case fatality is also varied by gender

The model has been adapted to allow a scenario in which stroke case fatality is varied by gender.

Parameter and model changes made for the scenario

1. The case fatality rates (CFR) for Scottish and English males and females were extracted from Table 2.6 of Scarborough et. al. (see Table 33).

Table 33: Case fatality rates taken from Scarborough

	Fatal Stroke Male (All ages)		Fatal Stroke Female (All ages)	
	N	%	N	%
England	7615	17.1	12119	24.7
Scotland	1009	18.7	1463	25.2

2. A weighted mean CFR for all males (England and Scotland) and all females was produced using the data in Table 33. Male CFR = 17.29% ([[7615*17.1]+[1009*18.7]]/[7615+ 1009]), female CFR = 24.75%.
3. The gender split of CFR in Scarborough et. al. is unusual at 39% male and 61% female. The percentage of female mortality would be expected to be lower at 52%-56%[9,13]. Therefore the gender split for all strokes rather than CFR was taken (see Table 33) to calculate a weighted mean CFR incidence rate of 21.2% (17.29%*48% [male] + 24.75%.*52% [female]). This result was then divided by the results in step 2 to give a gender relative risk (RR) (male = 0.82 [21.2%/17.29%]; female = 1.98 [21.2%/24.75%]).
4. The gender RRs (male = 0.82; female = 1.98) were applied to the CFRs used in the base case of the model. For example, the CFR for a VKA unsuitable patient receiving apixaban is [redacted], for males the CFR would be [redacted]
5. The mild, moderate and severe stroke percentages were recalibrated to reflect the change in the fatality percentage.

Model adaptation

A new sheet that details all the stroke severity distributions by gender has been added to the model "Stroke severity distributions" (see updated model). The calculations to obtain gender specific rates are outlined above. A macro sets the model to 100% females replaces the data for females and reports the results and repeats the process for males. The results are then weighed by the % of males and females in the model. The tables in cells B9:U23 of the 'stroke severity distributions' page summarises the key results for each comparator and are generated through use of the "Run CFR by gender button". More detailed results can be generated for the comparators selected on the 'settings' page from columns AE onwards of the "stroke severity distributions" page through use of the "Run detailed results for current comparators" button (Stroke severity distributions page).

B6. For those patients that are VKA suitable and do not receive warfarin as first line therapy, please explain the rationale for assuming that aspirin rather than warfarin is the second line treatment following an "other ICH" or major bleed event in the base case model.

Aspirin was selected as the second line treatment following an 'other ICH' or major bleed in the base case based on advice from clinical experts. As treatment discontinuation unrelated to stroke or bleeding is dealt with separately, 'other ICH' or major bleeding discontinuation is based on clinical grounds and not patient preference. Needing to discontinue one anticoagulant would mean that alternative anticoagulants would be contra-indicated. NICE clinical guideline 36 recommends aspirin in such circumstances, "where warfarin is not appropriate, aspirin should be given at 75 to 300 mg/day" (p16).[14]

Using aspirin as the second line treatment also provides the benefit of fairly comparing the new oral anticoagulants against warfarin, with the same treatment sequence. The same approach was employed in TA249,[15] dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation.

B7. Please clarify:

a) Whether data on other hospitalisation was collected in ARISTOTLE.

Data on CV hospitalisation was not collected in ARISTOTLE.

b) The rationale for assuming that the CV hospitalisation rate for warfarin does not differ from apixaban in the VKA suitable population.

As data on other CV hospitalisation (unrelated to stroke or MI) was not collected in the ARISTOTLE trial, it was assumed that the rate of other CV hospitalisation for apixaban would be the same as reported in the AVERROES trial.[10] It was conservatively assumed that the rate of other CV hospitalisation for warfarin patients would be no worse than that of apixaban.

c) The rationale for assuming that the CV hospitalisation rate for aspirin does differ from apixaban in the VKA unsuitable population.

As the AVERROES trial collected data on other CV hospitalisation it was possible to calculate rates for both apixaban and aspirin, and calculate the hazard ratio (See Table 34).**Error! Bookmark not defined.**

Table 34: CV hospitalizations unrelated to stroke or MI

	Apixaban	**Aspirin**	**Hazard Ratio (HR, 95% Confidence Interval)**
	Absolute Event Rate	**Absolute Event Rate**	
CV hospitalizations unrelated to stroke or MI	10.460	12.087	1.155 (0.992 - 1.345)

References

B8. Please clarify whether the risk adjustment factors summarised in Table 43 (p114/115) were identified systematically and provide details of the identification process.

A systematic review was not conducted to identify the risk adjustment factors summarised in Table 43 of the submission. The sources were identified from the reference list of Freeman et. al. [13].[16] The Freeman et. al. paper was identified in the systematic review of economic evaluations (section 7.1 and appendix 10 of the submission). Please note that the reference for MI in table 43 of the submission is incorrect, this should be Freeman et. al. and not Khan et al[17].

Other

B9. It is understood that data from the Friberg et al. study (identified in the "Targeted literature Review for the UK adaption of the Apixaban Atrial Fibrillation Cost- effectiveness Model") has been used to calculate a hazard ratio of 1.34 for other cause mortality in an AF patient population. Please provide a step by step calculation of this hazard ratio moving from raw data extracted from the paper to the final hazard ratio.

Annual rates of death for patients with paroxysmal, persistent and permanent AF as well as those of a matched general population were extracted from page 2349 (paragraph under the mortality section). The number of patients in each AF subgroup was obtained from Table 1, page 2348. Cause of death data was obtained from Table 3, page 2351.

Table 35: Data extracted from the Friberg et al. 2007 paper

Population	Annual mortality rate	Number of patients in subgroup	All Cause death (n)	Death due to MI)	Death due to all stroke	Death due to stroke and MI
General population	5%	N/A				
Paroxysmal AF	7%	888	111	18	11	29
Persistent AF	3%	618	27	6	2	8
Permanent AF	14%	1186	291	50	24	74

- To compare the annual rates due to events not modeled, reported annual rates of all-cause death were first converted to annual risk of mortality e.g. for paroxysmal AF (7%):
    - Annual risk of mortality = $1- e^{(-0.07)}$=6.76%
- MI- and stroke-induced deaths were calculated as percentage of total deaths by using observed number of deaths e.g. for paroxysmal AF:
    - (18+11)/111 = 29/111 = 26.13%
- The proportion of deaths due to stroke and MI was subtracted from the annual risk of mortality to calculate an "adjusted risk" excluding risk of death due to stroke and MI e.g for paroxysmal AF:
    - 6.76%*(1-26.13%)= 4.99%
- The risk was then converted back to a rate to enable calculation of a hazard ratio:
    - –ln (1-4.99%)=5.12%
- This process was repeated for persistent and permanent AF to obtain similar estimates as detailed in the table below:

Table 36: Calculations performed to obtain adjusted death rates

Population	Annual mortality risk	% of deaths attributed to Stroke and MI	Adjusted risk of death	Adjusted rate of death
Paroxysmal AF	6.76%	29/111 = **26.13**%	6.76%*(1-26.13%)=**4.99%**	-ln(1-4.99%)=**5.12%**
Persistent AF	2.96%	8/27 = **29.63%**	2.96%*(1-29.63%)=**2.08%**	-ln(1-2.08%)=**2.10%**
Permanent AF	13.06%	74/291 = **25.43%**	13.06%*(1-25.43%)=**9.74%**	-ln(1-9.74%)=**10.25%**

- An average adjusted death rates for paroxysmal, persistent and permanent AF was calculated weighing by patient numbers:
    - ((5.12%*888)+(2.10%*618)+(10.25%*1186))/(888+618+1186)=6.69%
    - The adjusted mortality rate for the AF population was compared to the overall mortality rate in the general population to obtain a hazard ratio of 1.34.
        - 6.69%/5.00% = 1.34
    - For purposes of comparison the weighed unadjusted mortality rate for AF was calculated to be 9.17%. The unadjusted HR would therefore be 1.83.

B10. Please provide step by step calculations for the following utility decrements:

a) Other ICH;

b) Other major bleeds;

c) CRNM bleeds;

Moving from raw data presented in the cited reference to the utility decrement value implemented in the economic model.

The decrements for the two major bleeds, other ICH and other major bleeds, were obtained using Table 1 on page 957 of the Thompson et al. paper.[18] The value of 0.841 for major bleed was subtracted from the value of 0.948 for 'on ward managed by general practitioner', resulting in a decrement value of 0.107.

The utility for CRNM was calculated by taking values from the supplementary appendix (enclosed) to Sullivan et al.[19] The decrement of 0.0582 was calculated by adding the decrement for 'ICD-9 599 Oth Urinary Tract Disor*' (Hematuria) 0.0054 to the decrement for two chronic conditions (NCC2; AF and Hematuria) 0.0528.

B11. The base case results in the VKA unsuitable population (presented in Table 80, p146) indicate that apixaban is extendedly dominated. Please clarify the rationale for concluding that apixaban is extendedly dominated.

The ERG are correct that this is an error. The intervention producing most QALYS can never be extendedly dominated.

B12. Please provide:

a) a step by step calculation of acute SE costs moving from raw data presented in the cited reference to the cost used in the economic model.

As there are no national schedule reference or tariff costs for systemic embolism it has been necessary to approximate the cost, as was done in the dabigatran and rivaroxaban single technology appraisals (STA).[15,20] The ERG reviewing the rivaroxaban STA suggested when discussing the post systemic embolism health state that minor stroke would make a suitable approximation for a systemic embolism.[21]

For acute systemic embolism the mean cost of a non-disabling minor stroke of £3,945 was taken from Table 3 of Luengo-Fernandez et. al.[22] This 2008/09 cost was inflated to a 2010/11 cost using the hospital and community health services pay and prices index (PPI); the 2008/09 value was multiplied by the proportion resulting from dividing the 2010/11 PPI by the 2008/09 PPI (£3,945*[276/267]=£4077.98.

For long-term maintenance cost of systemic embolism the mean post-acute non-disabling stroke cost of £2,135 was taken from Table 4 of Luengo-Fernandez et. al. This 2009/09 cost was inflated to a 2010/11 cost using the hospital and community health services pay and prices index (PPI); the 2008/09 value was multiplied by the proportion resulting from dividing the 2010/11 PPI by the 2008/09 PPI, and subsequently divided by 12 to provide a monthly cost (£2,135*[276/267]=£2206.97; £2,206.97/12= £183.91).

b) Sensitivity analysis values for acute and long term SE costs similar to the values presented in Tables 63 and 64 for ischaemic and haemorrhagic stroke.

Table 37: Systemic embolism acute costs (per episode) and long-term costs (per month)

	Cost	Sensitivity lower	Sensitivity upper	Source
Acute systemic embolism	£4077.98	£2,193.10	£5,962.90	Luengo-Fernandez et. al.
Long-term maintenance cost of systemic embolism	£183.91	£107.50	£260.30	Luengo-Fernandez et. al.

Section C: Textual clarifications and additional points

None

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