NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

October 2009

Contents

List of tables and figures

Glossary of commonly used terms

A+C	Aspirin plus clopidogrel
AF	Atrial fibrillation
AMI/MI	(Acute) myocardial infarction
ASA	Aspirin monotherapy
CI	Confidence interval
DBG	Dabigatran etexilate
ECH	Extracranial haemorrhage
GI	Gastrointestinal
HS	Haemorrhagic stroke
ICH	Intracranial haemorhage
IS	Ischaemic stroke
MTC	Mixed treatment comparison
PSA	Probabilistic sensitivty analysis
SD	Standard deviation
SE	Systemic embolism/Standard error
TIA	Transient ischamic attack
VKA	Vitamin K antagonist
WFN	Warfarin

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126]' rather than 'One trial[126]').

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see 'Related procedures for evidence submission', appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Product Details

- Approved name of technology: Dabigatran etexilate
- Brand name: Pradaxa
- Therapeutic class: Oral anticoagulant
- Formulation: 110mg and 150mg hard capsules
- Dosing regimen: Either 110mg or 150mg twice daily
- Course length: Unlimited
- Pack size: 60 capsules
- Cost: £2.52 per daily dose

Mechanism of Action

The oral pro-drug dabigatran etexilate is rapidly converted to its active form, dabigatran. Dabigatran is a synthetic reversible thrombin inhibitor, which binds to thrombin with a high affinity and specificity. The pro-drug itself has no anticoagulant activity.

Indication

Prevention of stroke and systemic embolism in adult patients with atrial fibrillation.

Marketing Status

Dabigatran etexilate (DBG) does not currently have UK marketing authorisation for the indication detailed in this submission. The dossier for regulatory approval was submitted to the EMEA in January 2010 and will be considered through the centralised procedure. Marketing authorisation is currently expected in March 2011.

Comparators

The main comparator is the current standard of care for patients at moderate to high risk of stroke, dose-adjusted warfarin (WFN). Secondary analyses will also compare DBG with both aspirin monotherapy and dual anti-platelet therapy (aspirin plus clopidogrel) in patients who are unable or unwilling to receive WFN but are eligible for DBG.

Source of clinical evidence

For the primary comparison versus WFN, the key clinical evidence comes from the pivotal RE-LY study, the largest RCT ever conducted in this therapeutic area. For the secondary comparisons, a mixed treatment analysis was peformed.

Summary of clinical evidence – RE-LY

The key results of the RE-LY trial are summarised in **Table 1** and **Table 2**.

Overall, the RE-LY trial not only achieved but surpassed the pre-specified non-inferiority objective for efficacy. Good statistical power was achievable with the original planned recruitment of 15,000 patients, however actual recruitment of over 18,000 subjects ensured even greater power. The demonstration of a dose-response for the primary endpoint, where DBG 110mg bid was shown to be less effective than DBG 150mg bid but non-inferior to WFN is further support of the findings.

The superiority of DBG 150mg bid over WFN was reflected in all components of the primary endpoint (stroke and systemic embolism). For the composite primary endpoint itself, the relative risk reductions were 35% and 10% for the 150mg bid and 110mg bid respectively compared to WFN, with 150mg bid having a p-value of 0.0001 for superiority versus WFN.

For ischaemic stroke, the relative risk reduction for the 150mg bid dose was 25% compared to WFN and was significant (p=0.0296). Haemorrhagic stroke was significantly decreased by two-thirds compared to WFN for both doses (p-value <0.0001) and did not show dose-response. Given the usual trade-off between thromboembolic risk reduction and haemorrhagic risk increase, this is an extremely desirable and groundbreaking result.

The treatment effects of DBG were further reflected in all specified secondary endpoints. The risk reductions on stroke/systemic embolism and death was 17% for DBG 150mg bid, which was statistically significant (p-value = 0.0015). Both doses also reduced the risk of all cause mortality, the risk reductions by DBG 110mg bid and DBG 150mg bid were 9% (p-value = 0.1308) and 12% (p-value = 0.0517), respectively. Most of this effect was due to vascular death. This is an important finding since WFN reduces mortality in AF subjects compared to placebo. An additional reduction in mortality over and above the effect of WFN is clinically important and further substantiates the clinical value of DBG.

The rate of symptomatic MI was not statistically significantly different across the three groups. Rates of silent MI were similar between the treatment groups.

Table 1 Summary of efficacy results from RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Stroke/SE (Primary endpoint)	**183**	**1.54%**	**134**	**1.11%**	**202**	**1.71%**	**0.90 (0.74 – 1.10)**	**0.65* (0.52 – 0.81)**
Ischaemic stroke only	152	1.28%	103	0.86%	134	1.14%	1.13 (0.89 – 1.42)	0.75* (0.58 – 0.97)
Haemorrhagic stroke only	14	0.12%	12	0.10%	45	0.38%	0.31* (0.17 – 0.56)	0.26* (0.14 – 0.49)
Stroke/SE/All-cause death (Secondary endpoint)	**577**	**4.85%**	**520**	**4.32%**	**613**	**5.20%**	**0.93 (0.83 – 1.04)**	**0.83* (0.74 – 0.93)**
All-cause death only	446	3.75%	438	3.64%	487	4.13%	0.91 (0.80 – 1.03)	0.88 (0.77 – 1.00)
Stroke/SE/PE/MI (including silent MI)/Vascular death (Secondary endpoint)	**507**	**4.26%**	**443**	**3.68%**	**513**	**4.35%**	**0.98 (0.87 – 1.11)**	**0.84* (0.74 – 0.96)**
Total MI	98	0.82%	97	0.84%	75	0.64%	1.29 (0.96 – 1.75)	1.27 (0.94 – 1.71)
Vascular death only	289	2.43%	274	2.28%	317	2.69%	0.90 (0.77 – 1.06)	0.85* (0.72 – 0.99)

ITT analysis set: DBG 110mg - N = 6,015, subject-years = 11,899; DBG 150mg - N = 6,076, subject-years = 12,033; WFN - N = 6,022, subject-years = 11,794

* Denotes statistically significant in favour of DBG

Source: [1]

Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; ITT, intention to treat; MI, myocardial infarction; PE, pulmonary embolism; SE, systemic embolism; TIA, transient ischaemic attack; WFN, warfarin

Table 2 Summary of safety results from RE-LY

Outcome	DBG 110mg		DBG 150mg		WFN		Hazard Ratio DBG 110mg v WFN (95% CI)	Hazard Ratio DBG 150mg v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Major bleeding	342	2.87%	399	3.32%	421	3.57%	0.80* (0.70 – 0.93)	0.93 (0.81 – 1.07)
Life threatening major bleeding	147	1.24%	179	1.49%	218	1.85%	0.67* (0.54 – 0.82)	0.80* (0.66 – 0.98)
Intracranial haemorrhage (including haemorrhagic stroke)	27	0.23%	38	0.32%	90	0.76%	0.30* (0.19 – 0.45)	0.41* (0.28 – 0.61)
GI major bleeding	134	1.14%	186	1.57%	125	1.07%	1.07 (0.84 – 1.36)	1.47^ (1.17 – 1.85)
GI life-threatening bleeding	67	0.57%	94	0.79%	57	0.49%	1.17 (0.82 – 1.67)	1.62^ (1.17 – 2.26)
ALT/AST>3xULN	118	2.0%	106	1.7%	125	2.1%	0.98 (0.76 – 1.26)	0.88 (0.68 – 1.14)
ALT/AST>5xULN	36	0.6%	45	0.7%	50	0.8%	0.75 (0.49 – 1.15)	0.93 (0.62 – 1.40)
ALT/AST>3xULN and total bilirubin >2xULN	11	0.2%	14	0.2%	21	0.4%	0.55 (0.26 – 1.13)	0.69 (0.35 – 1.36)

ITT analysis set: DBG 110mg - N = 6,015, subject-years = 11,899; DBG 150mg - N = 6,076, subject-years = 12,033; WFN - N = 6,022, subject-years = 11,794

* Denotes statistically significant in favour of DBG. ^ Denotes statistically significant in favour of warfarin

Source: [1]

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase;DBG, dabigatran etexilate; GI, gastrointestinal; LFT, liver function test; ULN, upper limit of normal; WFN, warfarin

A lower yearly event rate for major bleeds was observed with DBG treatment compared with WFN. Subjects treated with DBG 110mg had a significantly lower rate of major bleeds compared with WFN (p=0.0026). The rate of major bleeds with DBG 150mg compared to WFN was not statistically significantly different (p=0.3146). There was a significantly lower rate of life-threatening bleeds, haemorrhagic stroke and ICH for both doses of DBG compared with WFN as follows:

Life threatening bleed

- DBG 110mg compared to WFN (p=0.0001)
- DBG 150mg compared to WFN (p=0.0305)

ICH (including haemorrhagic stroke)

- DBG 110mg compared to WFN (p<0.0001)
- DBG 150mg compared to WFN (p<0.0001)

There was no evidence of any incremental liver toxicity with DBG, indeed the rates of increased liver function enzymes were slightly higher with in the WFN group than either of the DBG groups.

Overall, this study demonstrated that both doses of DBG were clearly non-inferior to WFN and that DBG 150mg bid was superior to WFN for the primary efficacy endpoint. In addition both doses of DBG significantly reduced the occurrence of the most serious haemorrhagic events compared to WFN which, when considered alongside the significant reduction in ischaemic stroke with DBG 150mg bid, represents an unprecedented result in this therapeutic area.

Summary of clinical evidence – MTC

The key results of the MTC are summarised in **Table 3**.

The statistically significant findings from the MTC analyses for each DBG scenario versus aspirin monotherapy are as follows:

- Significant superiority of DBG 110mg bid for all stroke, fatal or disabling stroke and TIA
- Significant superiority of DBG 150mg bid for all stroke, ischaemic stroke and fatal or disabling stroke

The statistically significant findings from the MTC analyses for each DBG scenario versus aspirin plus clopidogrel are as follows:

- Significant superiority of DBG 110mg bid for ischaemic stroke, systemic embolism, minor bleeding and any bleeding
- Significant superiority of DBG 150mg bid for all stroke, ischaemic stroke, fatal or disabling stroke, systemic embolism, minor bleeding and any bleeding

Table 3 Summary of results from the MTC

Outcome	RR versus aspirin monotherapy (95% CI)	RR versus aspirin plus clopidogrel (95% CI)	RR versus placebo (95% CI)
DBG 110mg bid			
All stroke	0.52* (0.28 – 0.96)	0.55 (0.30 – 1.00)	0.35* (0.17 – 0.71)
Ischaemic stroke	0.69 (0.40 – 1.20)	0.54* (0.33 – 0.87)	0.33* (0.21 – 0.54)
Mortality	0.85 (0.66– 1.10)	0.91 (0.68 – 1.21)	0.66* (0.47 – 0.93)
ECH	0.84 (0.34 – 2.09)	0.87 (0.52 – 1.44)	1.58 (0.25 – 10.02)
AMI	0.93 (0.50 – 1.72)	0.89 (0.45 – 1.73)	0.84 (0.33 – 2.09)
Vascular mortality	0.90 (0.63 – 1.29)	0.81 (0.57 – 1.14)	1.13 (0.72 – 1.80)
DBG 150mg bid			
All stroke	0.37* (0.20 – 0.69)	0.39* (0.21 – 0.72)	0.25* (0.12 – 0.51)
Ischaemic stroke	0.48* (0.27 – 0.84)	0.37* (0.23 – 0.61)	0.23* (0.14 – 0.38)
Mortality	0.83 (0.64 – 1.07)	0.88 (0.66 – 1.18)	0.64* (0.45 – 0.91)
ECH	0.96 (0.39 – 2.37)	0.99 (0.60 – 1.63)	1.80 (0.28 – 11.38)
AMI	0.91 (0.49 – 1.69)	0.87 (0.44 – 1.70)	0.82 (0.33 – 2.05)
Vascular mortality	0.85 (0.59– 1.21)	0.76 (0.54 – 1.07)	1.07 (0.67 – 1.69)

*Denotes statistically significant in favour of DBG
Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; TIA, transient ischaemic attack; VKA, vitamin K antagonist

Economic Evaluation

The economic evaluation estimated the cost-effectiveness of DBG compared to WFN, aspirin and aspirin plus clopidogrel for stroke prevention in patients with atrial fibrillation (AF). Based on the results of the evaluation it is concluded that the use of DBG is clearly and consistently cost-effective across all comparisons and analyses.

An economic model employing Markov processes was constructed to approximate the disease pathway of patients with AF of sufficiently high risk of stroke to be eligible for anticoagulation treatment. The model included all relevant clinical outcomes and incorporated health states stratified by line of treatment, history of stroke and disability level. Appropriately for a chronic disease with lifelong consequences, the economic model tracked the costs and outcomes accumulated by patients until their deaths. Quality-adjusted

life years (QALYs) were calculated using event and health state (dis-)utilities derived from the published literature, permitting a cost-utility analysis (CUA).

Principle clinical parameters were derived from the pivotal RE-LY trial or a bespoke mixed treatment comparison (MTC) based on a network meta-analysis. Other model parameters including cost data were sourced from published studies or other standard sources. Where appropriate, model parameters were assigned distributions to facilitate probabilistic sensitivity analysis (PSA).

Four DBG regimens were examined by the economic model. Two of these regimens mirrored the per protocol use of DBG in the RE-LY trial, i.e. either 110mg or 150mg bid in all eligible patients. Two further *post-hoc* regimens were examined that mimic the likely intended use of the two doses in line with the clear dose-response demonstrated in RE-LY:

1. Patients aged less than 80 years only initiated on DBG 150mg bid and switching to DBG 110mg bid at age 80 (DBG sequence < 80 years)
2. Patients aged more than 80 years only initiated on DBG 110mg b.i.d (DBG sequence ≥ 80 years)

These regimens are intended to optimise the most appropriate use of each dose in younger or older patients, thereby maximising the capacity to benefit from the varying characteristics of the two doses. Each regimen was compared to WFN (primary analysis) for all eligible patients and to aspirin or aspirin plus clopidogrel (secondary analysis) for eligible patients who are unable or unwilling to receive WFN.

Incremental results of economic model for the four DBG regimens are presented in **Table 4** to **Table 7**.

Table 4 Base case PSA of the single dose model for DBG 150mg bid

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,279	7.029	Baseline			
A+C	£15,315	7.014	£36	-0.014	dominated	dominated
WFN	£15,566	7.267	£287	0.238	£1,206	£1,206
DBG 150mg bid	£17,092	7.459	£1,813	0.430	£4,211	£7,940

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 5 Base case PSA of the single dose model for DBG 110mg bid

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,279	7.029	Baseline			
A+C	£15,315	7.014	£36	-0.014	dominated	dominated
WFN	£15,566	7.267	£287	0.238	£1,206	£1,206
DBG 110mg bid	£18,210	7.434	£2,931	0.405	£7,238	£15,867

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 6 Base case PSA of the sequence model for patients under 80 years

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
A+C	£16,696	7.512	Baseline			
ASA	£16,836	7.540	£140	0.028	£5,002	Extended dominance
WFN	£17,057	7.804	£361	0.293	£1,234	£1,234
DBG	£18,820	8.030	£2,125	0.519	£4,097	£7,811

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 7 Base case PSA of the sequence model for patients at least age 80 years

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
A+C	£8,971	3.868	Baseline			
WFN	£9,092	4.000	£121	0.132	£916	£916
ASA	£9,355	3.899	£384	0.030	£12,597	Extended dominance
DBG	£10,041	4.080	£1,070	0.212	£5,048	£11,912

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

The pairwise ICERs for DBG compared to each alternative are summarised in **Table 8**.

Table 8 Pair wise comparisons for DBG from the deterministic and probabilistic model

Intervention	Comparator	Analysis	Inc. Cost	Inc. QALY	ICER
DBG 150mg bid	ASA	PSA	£1,813	0.430	£4,211
		Det	£1,843	0.416	£4,434
	WFN	PSA	£1,526	0.192	£7,940
		Det	£1,340	0.214	£6,264
	A+C	PSA	£1,777	0.445	£3,995
		Det	£853	0.437	£1,954
DBG 110mg bid	ASA	PSA	£2,931	0.405	£7,238
		Det	£3,305	0.352	£9,397
	WFN	PSA	£2,644	0.167	£15,867
		Det	£2,802	0.150	£18,691
	A+C	PSA	£2,895	0.419	£6,905
		Det	£2,315	0.373	£6,213
Seq <80	ASA	PSA	£1,984	0.491	£4,045
		Det	£2,125	0.468	£4,536
	WFN	PSA	£1,763	0.226	£7,811
		Det	£1,773	0.242	£7,314
	A+C	PSA	£2,125	0.519	£4,097
		Det	£1,283	0.499	£2,571
Seq ≥ 80	ASA	PSA	£686	0.182	£3,779
		Det	£703	0.189	£3,719
	WFN	PSA	£949	0.080	£11,912
		Det	£832	0.106	£7,873
	A+C	PSA	£1,070	0.212	£5,048
		Det	£450	0.221	£2,038

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; Det, deterministic model; PSA, probabilistic sensitivity analysis; Seq, sequence model; WFN, warfarin

Finally, the probability that DBG is cost-effective in each analysis, as generated by the PSA, is presented in **Table 9**.

Table 9 Probability of cost-effectiveness at different willingness to pay thresholds

Intervention	Comparator	WTP: £20,000 per QALY	WTP: £30,000 per QALY
DBG 150mg bid	ASA	100%	100%
	WFN	93%	98%
	A+C	100%	100%
DBG 110mg bid	ASA	97%	99%
	WFN	67%	84%
	A+C	98%	100%
Seq < 80	ASA	100%	100%
	WFN	96%	99%
	A+C	100%	100%
Seq ≥ 80	ASA	92%	95%
	WFN	69%	77%
	A+C	92%	96%

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; Seq, sequence model; WFN, warfarin; WTP, willingness to pay

Both the evaluations for the proposed use of the two doses and the single dose analyses fall well within the thresholds for cost-effectiveness and therefore represent good value-for-money. The ICERs for patients receiving the 150mg bid dose are lower reflecting the significant reduction in ischaemic stroke and the substantial saving that can be made through the reduction in long term disability. The 110mg dose had similar ischaemic stroke efficacy to WFN but a better safety profile. Whilst the relative difference in haemorrhagic stroke and intracranial haemorrhage is large, there are relatively few of these events compared to ischaemic stroke.

In the secondary comparisons, the additional clinical benefit of DBG comfortably offsets the additional incremental cost. This result is not unexpected given that aspirin and aspirin plus clopidogrel are known to be inferior to WFN. Even though the incremental costs are higher in this comparison compared to the primary analysis, the incremental QALYs are substantially higher. For all analyses, cost-effectiveness is rapidly achieved.

For all comparisons, the incremental cost-effectiveness ratios (ICERs) are below the benchmark £20,000 per QALY gained in each analysis. This is not a trivial result when set in the context of a relatively high cost new chemical entity compared to a well-established, proven and inexpensive generic comparator. The achievement of such impressive cost-effectiveness results when it is known that DBG must concede a significant incremental cost of medication, gives an indication of the huge additional clinical benefit that DBG can offer.

Accordingly, across all analyses the results are driven by the relatively lower number of catastrophic events estimated in the DBG regimens compared to the comparators. This includes the analysis in patients over the age of 80, where it would be expected that the case for an anticoagulant would be hardest to prove in patients with elevated risk of major

bleeding. However the results show that despite being relatively rare events, the relative treatment effect of DBG with respect to haemorrhagic stroke and intracranial haemorrhage is such that over 400 additional such events are prevented in the 10,000 patient modelled cohort. The knock-on effect of preventing so many serious clinical events has a significant effect on the relative costs and outcomes estimated by the economic model.

Therefore even in the analyses considering only the DBG 110mg bid dose, where there is no additional benefit in prevention of ischaemic stroke compared to WFN, this effect is sufficiently large to make the economic case for DBG 110mg bid. This is an important result given that very elderly patients are those most likely to be treated sub-optimally, and that DBG 110mg bid is shown to be a clinically and cost-effective alternative.

If the above effect provides the foundation for the results, the additional effect seen in analyses considering the DBG 150mg bid dose provides further benefit in other catastrophic events that further boosts the cost-effectiveness of DBG. The 150mg bid dose provides an almost “free” benefit by significantly reducing both ischaemic stroke and haemorrhagic stroke/intracranial haemorrhage, resulting in ICERs that are significantly and consistently below £10,000 per QALY gained with a high level of probability.

The key modelling assumption underpinning these results is that of continued benefit. The economic model assumes that the relative treatment effects continue beyond the two-year horizon of the RE-LY trial. However there is no evidence to suggest that this assumption will not hold, indeed the Kaplan-Meier curves for ischaemic stroke, haemorrhagic stroke and intracranial haemorrhage from RE-LY indicate that benefit did not wane over time and that this is likely to be a safe assumption.

In the secondary comparison, the results show that DBG is clearly superior to both aspirin monotherapy and aspirin plus clopidogrel in patients eligible for anticoagulation but unable or unwilling to receive WFN. The above outlined effects are magnified in that both DBG doses provide significant benefits in ischaemic stroke and haemorrhagic stroke/intracranial haemorrhage. These effects once again swamp other considerations in terms of both costs and outcomes when a long-term perspective is taken.

The modelling approach is commensurate with the goal of treatment being the prevention of events which may (or may not) occur at any given point in the future. The decision to anticoagulate a patient in this indication is one made for life, therefore it would be perverse to truncate the model at some arbitrary time horizon. It is wholly appropriate that lifetime costs and benefits are considered when judging the cost-effectiveness of the alternatives.

It will be unavoidable that a new chemical entity, when compared to three extremely low-cost generic alternatives, will result in a relatively large increase in upfront spending on medication. It is imperative therefore that this is placed in the above context and considered against the hugely significant clinical benefits (and cost savings) that can be achieved in the medium to long-term.

Further, the true incremental cost of DBG will depend on the ability of local anticoagulation services to adapt to the introduction of a product that does not require INR monitoring. As DBG is taken up, it will be essential that services are able to release efficiencies in order to realise the full economic benefit of DBG.

To summarise, the economic evaluation demonstrates that DBG offers new and important clinical benefits with respect to potentially catastrophic thromboembolic and haemorrhagic events that cannot be achieved with current alternatives. It also offers a rare opportunity to the NHS to redesign an antiquated treatment pathway whilst simultaneously improving clinical outcomes and economic efficiency. DBG can therefore be regarded as a cost-effective use of NHS resources with a high degree of confidence as a first-line treatment for the prevention of stroke in patients with atrial fibrillation.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

- Approved name: Dabigatran etexilate
- Brand name: Pradaxa
- Therapeutic class: Oral anticoagulant

1.2 What is the principal mechanism of action of the technology?

The oral pro-drug dabigatran etexilate is rapidly converted to its active form, dabigatran. Dabigatran is a synthetic reversible thrombin inhibitor, which binds to thrombin with a high affinity and specificity. The pro-drug itself has no anticoagulant activity.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

No, dabigatran etexilate (DBG) does not currently have UK marketing authorisation for the indication detailed in this submission. The dossier for regulatory approval was submitted to the EMEA in January 2010 and will be considered through the centralised procedure. Marketing authorisation is currently expected in March 2011.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

Not applicable at this stage.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The indication is “prevention of stroke and systemic embolism in adult patients with atrial fibrillation”.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The RELY-ABLE study [2] is an ongoing extension of the pivotal RE-LY trial. The purpose of RELY-ABLE is to assess the long-term safety (major bleeding is the primary outcome) of DBG 110mg bid and 150mg bid in 6,200 patients who completed the RE-LY trial. The study is due to complete in July 2011.

There are no other studies due to report in the next 12 months which will provide additional evidence.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

As per the response to question 1.3, our current estimation is that DBG will become available following marketing authorisation in March 2011.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

No, DBG does not yet have regulatory approval for this indication outside the UK. However an FDA advisory panel voted unanimously in favour of recommending DBG for use in this indication on September 20th 2010 [3]. The FDA will issue a final decision by October 19th 2010.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yes. Our submission to the Scottish Medicines Consortium was made on September 6th 2010.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 10 Unit costs of technology being appraised

Pharmaceutical formulation	Hard capsules
Acquisition cost (excluding VAT)	£2.52 per day
Method of administration	Oral
Doses	110mg and 150mg capsules
Dosing frequency	Either 110mg or 150mg twice daily
Average length of a course of treatment	Chronic treatment, lifelong
Average cost of a course of treatment	Dependent on individual factors
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Unlimited
Dose adjustments	None

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other therapies are likely to be routinely administered as part of a course of treatment.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia[4]. It is characterised by uncoordinated atrial activation with consequent deterioration of mechanical function. AF is triggered by premature depolarisations arising in the region of the pulmonary veins and propagates in an irregular and unsynchronised pattern. The resulting pattern of ventricular activation is irregular.

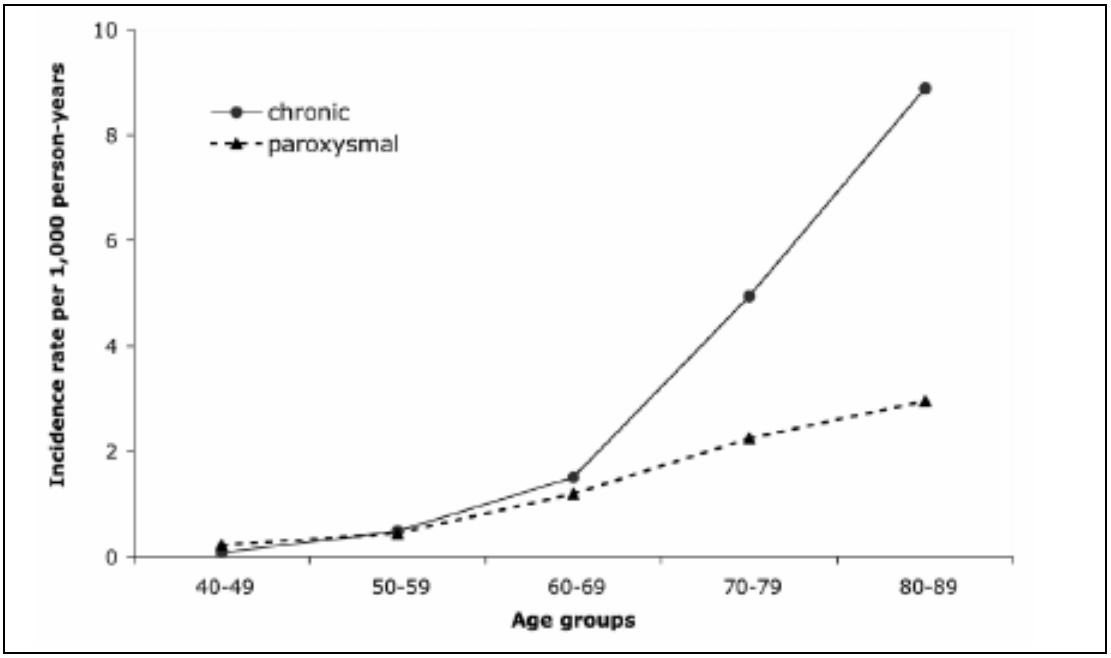
Patients are categorised based on their most frequent presentation, although the categories of AF are not mutually exclusive:

- Paroxysmal AF – duration less than 7 days and terminates spontaneously
- Persistent AF – duration > 7 days and would last indefinitely if not cardioverted
- Permanent AF – duration > 7 days and sinus rhythm not possible

An individual patient may have several episodes of paroxysmal AF and occasional persistent AF. Over time, paroxysmal AF may become persistent; likewise, both paroxysmal and persistent AF may become permanent.

A cohort study using the UK General Practice Research Database (GPRD)[5] estimated the incidence rate of paroxysmal and chronic AF (defined as an episode of AF not converting to sinus rhythm within 1 week) in the general practice setting. The incidence of chronic AF was highest in the oldest patient groups (**Figure 1**). Conversely, patients with paroxysmal AF were younger and had fewer co-morbid conditions than patients with chronic AF. This age difference likely reflects the progressive nature of AF.

Figure 1 Incidence of AF (rate per 1,000 person-years) by temporal classification and patient age[5]



AF is the leading cause of ischaemic stroke[6]. It is associated with a hypercoagulable state and a predisposition to thrombus formation (thrombogenesis). The majority (66-75%) of strokes in patients with non-valvular AF are cardioembolic in origin[7-9]. In this case, ischaemic stroke occurs when a thrombus forms in the heart then travels via the cerebral arteries, blocking blood flow to the brain. Thrombus formation as a result of stasis in the left atrial appendage is thought to represent the main source of disabling cardioembolic strokes in patients with AF.

AF is an independent predictor of stroke, with an annual risk that is approximately 5-fold higher than patients in sinus rhythm. However, this risk is not homogeneous, ranging from an annual risk of 1% in patients aged over 65 years old with no risk factors, to over 12% per year in patients who have a history of prior stroke, transient ischaemic attack or thromboembolism[4].

2.2 How many patients are assumed to be eligible? How is this figure derived?

Data from the Quality and Outcomes Framework (QOF) database reveal that there were 732,508 patients registered with diagnosed AF in England in 2008/09[10], equating to a prevalence rate of 1.35%. The corresponding figures for Wales were 51,963 and 1.65%[11].

Current consensus guidelines recommend that patients are stratified based on their risk of stroke. A number of clinical classification schemes have been proposed for predicting the risk of stroke in patients with AF.

The main internationally recognised schemes are:

- American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) [12]
- American College of Chest Physicians (ACCP) [7]
- Atrial Fibrillation Investigators (AFI) [13]
- European Society of Cardiology[14]
- Stroke Prevention in Atrial Fibrillation Investigators (SPAF) [15]
- $CHADS_2$ [16, 17]
- Framingham Heart Study [18]
- NICE [4, 19]

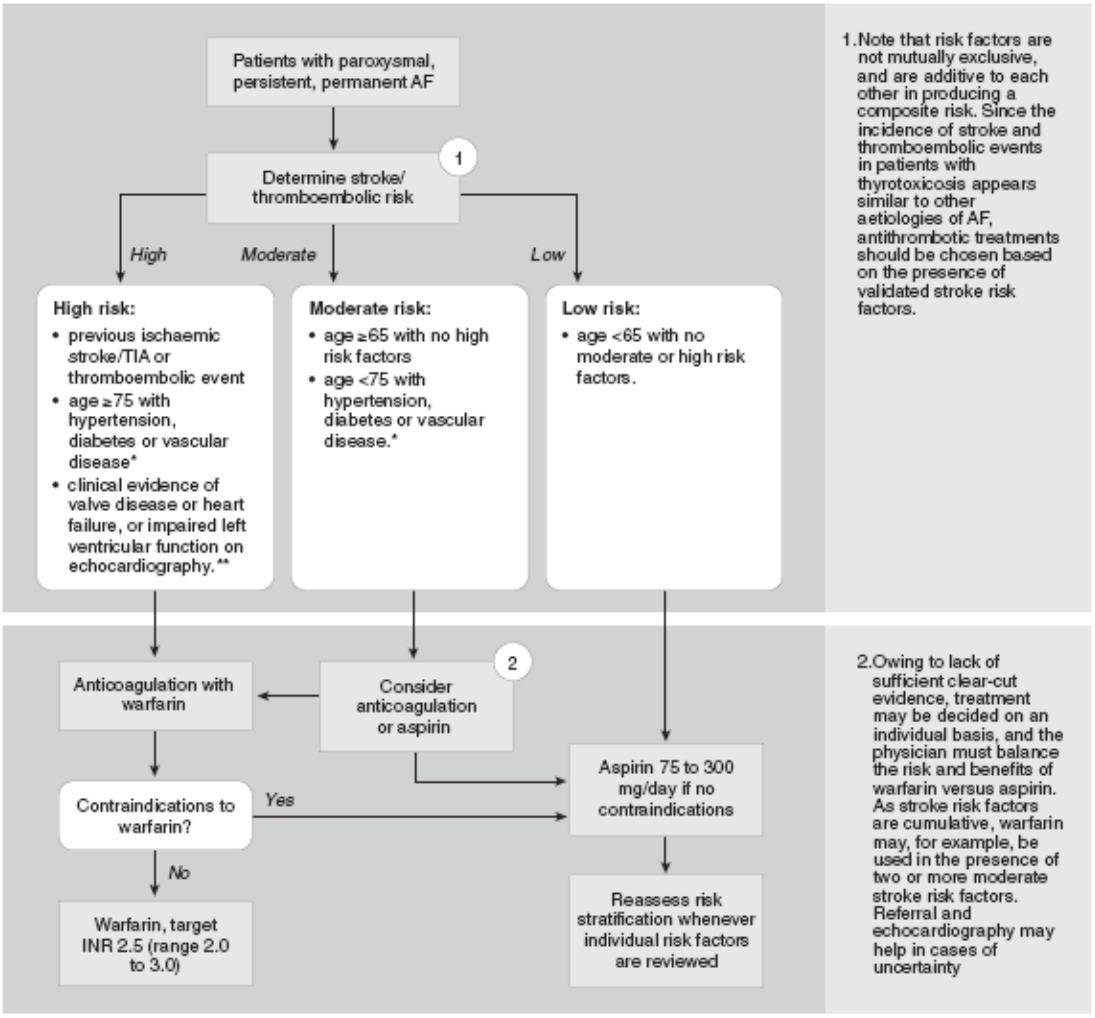
There is clear consistency between these risk stratification schemes regarding the factors that increase risk of stroke:

- advanced age
- prior stroke or transient ischemic attack (TIA)
- hypertension
- diabetes

However, there is some variation between schemes concerning the impact of individual factors on overall risk, i.e. whether the presence of a particular risk factor puts a patient at low, moderate or high risk of stroke.

The NICE risk algorithm (**Figure 2**) illustrates one such variation.

Figure 2 NICE stroke risk stratification algorithm[4]



According to this algorithm, eligibility for anticoagulation therapy is reserved for those at moderate and high risk. Ostensibly, this means any AF patient who is aged 65 or older, or has one of the other independent risk factors, is eligible. The costing template which accompanies the NICE guideline[20] estimated that 86.5% of patients would fulfil these criteria. Application of this percentage to the QOF data above results in an estimation of 678,318 AF patients in England and Wales potentially eligible for anticoagulation treatment in 2008/09.

It is worth noting that, as AF prevalence is known to rise with increasing age, it is highly likely that the prevalence of AF will also continue to increase over time as the average age of the population goes up. In addition, significant numbers of AF patients remain undiagnosed. Should diagnosis of AF improve in the coming years then this will also lead to an increase in the pool of eligible patients.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE clinical guideline 36: Atrial Fibrillation[19].

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The pertinent part of the AF clinical pathway depicting the context in which DBG will be used has been presented above in **Figure 2**. The pathway will change only with regards the two boxes concerning anticoagulation with warfarin:

- *Contraindication to warfarin?* Instead consider contraindication to DBG
- *Warfarin, target INR 2.5 (range 2.0 to 3.0).* Instead treat with DBG which requires no anticoagulation monitoring.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Treatment with dose-adjusted warfarin (WFN) has a narrow therapeutic window which requires that patients are closely monitored to ensure that their dosing regimen is providing a balanced level of anticoagulation. Patients receive frequent blood tests in order to calculate their International Normalised Ratio (INR). Current consensus recommends that treatment should target an INR of 2.5, whilst keeping the patient within the range of 2.0-3.0.

A number of factors affect the ability to maintain INR within the target therapeutic range:

- *Variable response of patients to WFN.* There is a wide variation between patients in response to WFN resulting in different dose requirements for different patients.
- WFN has many drug-drug and drug-food interactions (see **Table 11** and **Table 12**)
- *The dosing regimen is complex, requiring patient education, increasing risk of overdose or underdose.* In the UK there are four different strength WFN tablets available (0.5mg, 1mg, 3mg and 5mg)[21]. Patients are often given supplies of several strengths to allow adjustment based on INR results and they may have to take several tablets (or cut tablets in half) to reach the required dose. This may increase the risk of accidental under or overdose.

Table 11 Drug-drug interactions that may affect the anticoagulant effect of warfarin[22]

Reduced anticoagulant effect	Possible reduced anticoagulant effect	Anticoagulant effect may be reduced or enhanced	Enhanced anticoagulant effect	Possible enhanced anticoagulant effect
• Barbiturates • Carbamazepine • Enteral foods containing vitamin K • Griseofulvin • Primidone • Raloxifene • Rifamycins • St John's wort • Sucralfate • Vitamin K	• Acitretin • Aprepitant • Atorvastatin* • Azathioprine • Mercaptopurine • Mitotane • Rowachol®	• Atazanavir • Bosentan** • Colestyramine • Corticosteroids • Fosamprenavir • Neomycin • Nevirapine • Oestrogens • Orlistat** • Penicillins • Phenytoin • Progestogens • Ritonavir • Sulphonylureas • Tricyclic anti-depressants • Ubidecarenone	• Amiodarone • Anabolic steroids • Aspirin • Azapropazone • Chloramphen-icol • Cimetidine • Ciprofloxacin • Clarithromycin • Clopidogrel • Danazol • Dipyridamole • Disulfiram • Entacapone • Erlotinib • Erythromycin • Fibrates • Fluconazole • Fluorouracil • Flutamide • Fluvastatin • Glucosamine • High-dose corticosteroids • Itraconazole • Ketoconazole • Ketorolac • Metronidazole • Miconazole • Mirtazapine • Nalidixic acid • Norfloxacin • Ofloxacin • Propafenone • Sibutramine • Simvastatin • Sitaxentan • Sulfinpyrazone • Sulphonamides • Tamoxifen • Testolactone • Testosterone • Thyroid hormones • Tramadol • Voriconazole • Zafirlukast	• Allopurinol • Azithromycin • Aztreonam • Bicalutamide • Celecoxib • Cephalosporins • Chloral* • Dextropropoxy-phene • Diclofenac • Esomeprazole • Etodolac • Etoposide • Etoricoxib • Exenatide • Ezetimibe • Flurbiprofen • Ibuprofen • Ifosfamide • Iloprost • Imatinib • Influenza vaccine • Lactulose • Leflunomide • Levamisole • Levofloxacin • Mefenamic acid • Meloxicam • Memantine • Methylphenidate • NSAIDs • Omeprazole • Pantoprazole • Paracetamol (prolonged regular use) • Parecoxib • Piroxicam • Proguanil • Ritonavir • Rosuvastatin • Saquinavir • Sorafenib • SSRI anti-depressants • Sulindac • Tetracyclines • Tigecycline • Toremifene • Triclofos* • Trimethoprim • Valproate • Venlafaxine

*Transient enhancement/reduction of anticoagulant effect possible
**Monitoring of anticoagulant effect recommended by manufacturer

Table 12 Drug-food interactions that may affect the anticoagulant effect of warfarin[23]

Level of causation	Potentiation	Inhibition
Highly probable	▪ Alcohol ▪ **Fish oil** ▪ **Mango**	▪ Food with high-vitamin K content, such as broccoli, cabbage and spinach ▪ Large amounts of avocado
Probable	▪ **Grapefruit juice**	▪ *Soy milk*
Possible	▪ Cranberry juice	▪ **Sushi containing seaweed**

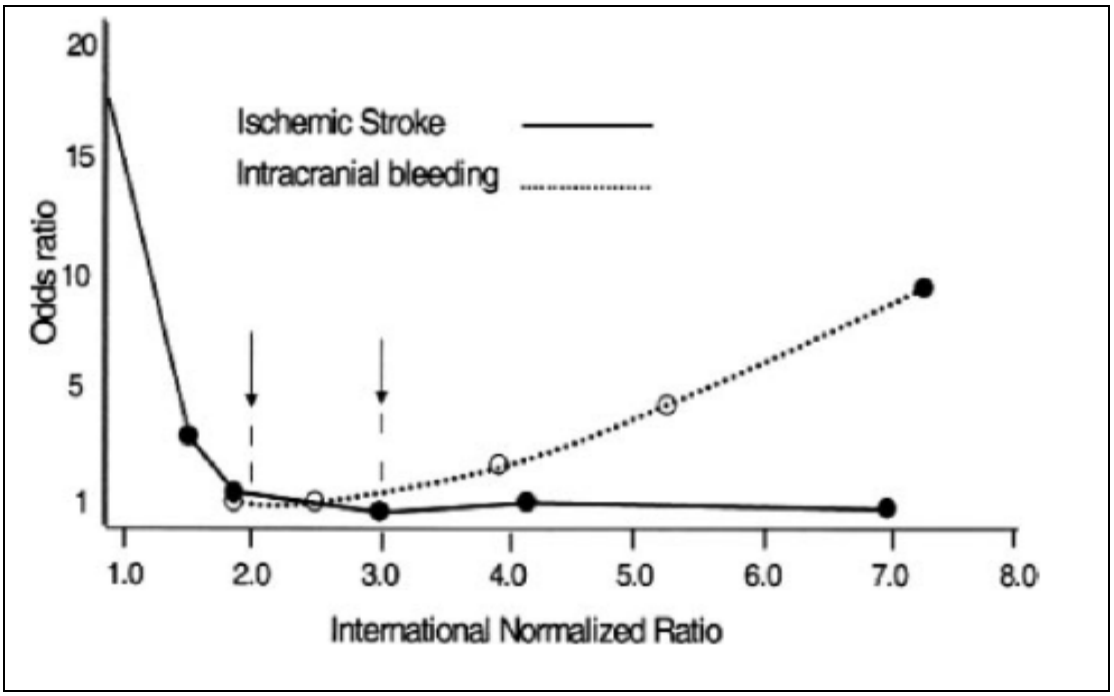
Bold = moderate interaction; *italics* = minor interaction; regular = non-clinical interaction (increase or decrease in VKA levels without change in INR or clinical status)

Considering these limitations of WFN therapy it is perhaps not surprising that patients do not always stay within the therapeutic range. A study of routine activity records and INR measurements was conducted in South Wales to establish how well AF patients treated with WFN are maintained within the target INR range and the relationship between INR control and clinical outcomes[24, 25]. The authors concluded that suboptimal anticoagulation was associated with poor clinical outcomes, but that good control was difficult to achieve and maintain.

Even in the setting of a university teaching hospital, where patients may be assumed to be relatively well controlled, patients treated with WFN were outside the target INR range 32.1% of the time, with 15.4% of values >3.0 and 16.7% of values <2.0[24]. These average figures disguise the wide variation in time spent out of target range: the quartile with the worst control spent 71.6% of their time out of target range compared with only 16.3% of time out of range in the best controlled quartile. A multivariate logistic regression model showed that a 10% increase in time out of range was associated with an increased risk of mortality (odds ratio (OR) 1.29, P<0.001) and of ischaemic stroke (OR 1.10, P=0.006) and other thromboembolic events (OR 1.12, P<0.001). The rate of hospitalisation was also higher when INR was outside the target range. The difference in life expectancy between the upper and lower quartiles of control was 19.4 months (P<0.001).

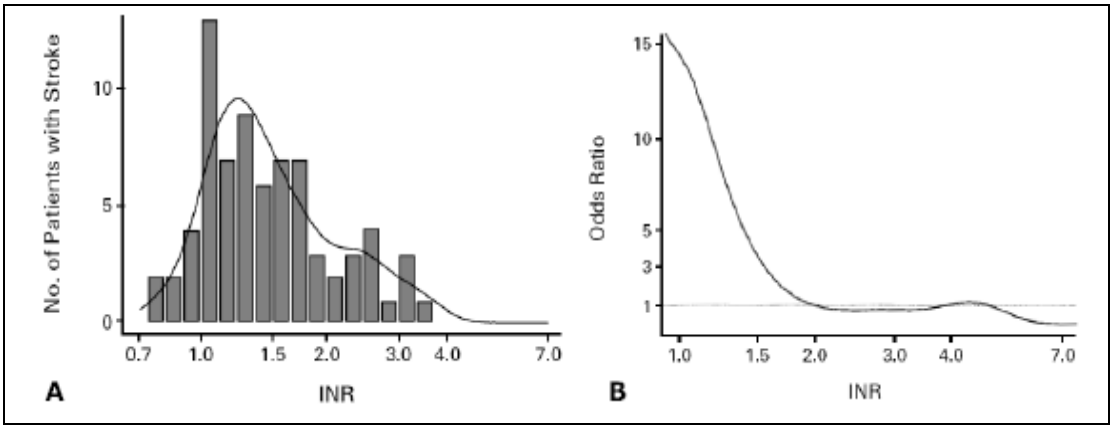
A systematic review and meta-analysis of 21 studies in patients with non-valvular AF receiving WFN reported that an INR less than 2.0 was associated with an odds ratio (OR) for ischaemic events of 5.07 and that an INR greater than 3.0 was associated with an odds ratio for bleeding events of 3.21[26]. This effect is clearly illustrated in **Figure 3**.

Figure 3 Relationship between INR control and risk of ischaemic stroke or intracranial bleeding [12]



The risk of stroke rises rapidly as INR falls below 2.0, with more than two-thirds of ischaemic strokes in patients taking VKAs occurring at INR levels below 2.0. In 74 patients with AF hospitalised for ischaemic stroke while taking a VKA, the odds of stroke compared with the risk at an INR of 2.0 doubled at an INR of 1.7, tripled at an INR of 1.5 and increased six-fold at an INR of 1.3 (**Figure 4**)[27].

Figure 4 Increased risk of stroke at low INR levels [27]



Furthermore, as compared with an INR greater than 2.0, an INR less than 2.0 has been shown to independently increase the odds of a severe stroke (odds ratio 1.9, 95% CI 1.1-3.4) and the risk of death within 30 days (hazard ratio 3.4, 95% CI 1.1-10.1)[28].

On the flip side, the major determinants of WFN-induced bleeding are:[29]

- Intensity of the anticoagulant effect
- Patient characteristics or co-morbid conditions
- Concomitant use of drugs that interfere with haemostasis
- Length of therapy.

Van Walraven and colleagues conducted a retrospective cohort study in eastern Ontario using population-based administrative databases to measure the proportion of serious haemorrhagic and thromboembolic events that would be avoided if anticoagulation was perfect[30]. During the study period, totalling 6,422 years of exposure time, patients on anticoagulant therapy spent 14.2% of the time with INR values greater than 3.0. The population-attributable risk of critically high anticoagulation intensity for serious haemorrhagic events was 25.6% in patients who had received anticoagulation therapy and 2.0% in the entire elderly population. This would translate into an annual decrease of 67 serious haemorrhagic events in eastern Ontario alone if time spent with critically high INRs was avoided. Similarly, the population-attributable risk of critically high INRs for lethal haemorrhages was 28.1% and 1.8% for the anticoagulated and entire population, respectively[30].

There is no increase in efficacy at INR levels greater than 3.0, but a sharp increase in the risk of intracranial haemorrhage (ICH) is seen at INRs of 3.5 - 4.0 and above. ICH is the only haemorrhagic complication that regularly produces deficits at least as great as those produced by the ischaemic strokes that treatment is intended to prevent[7]. The risk of severe morbidity or mortality is substantially higher from ICH than from other types of major haemorrhagic complications associated with WFN[31].

Fang and colleagues identified 72 intracranial and 98 major extracranial haemorrhagic complications related to WFN use in more than 15,300 person-years of WFN exposure. At hospital discharge, 76% of patients with ICH had severe disability or had died, compared with 3% of those with extracranial haemorrhages such as GI bleeds. In this cohort study, the majority of deaths (88%) and disability among survivors from WFN-associated haemorrhage were due to ICH[31].

Although the incidence of ICH is low (typically between 0.1% and 0.6%)[12], the relative odds of ICH increase with patient age and anticoagulation intensity. Increased risk is particularly apparent in those patients aged greater than 85 years and at INRs greater than 3.5[32].

Even in the absence of a major bleeding event, an asymptomatic high INR or minor bleed often requires urgent management to restore the patient to the target INR range. A retrospective analysis of 7,400 UK-based VKA-treated patients found 325 bleeding events and asymptomatic high INRs requiring treatment over a 10-month period, costing a total of £367,850. The average cost of treating major and minor bleeds was £4,584 and £715, respectively[33]. A prospective audit of the frequency and severity of over-anticoagulation and bleeding was carried out at the anticoagulation service of a district hospital in the UK serving 3,900 anticoagulant patients. Over a 23-month period, 297 bleeding episodes (73 major and 224 minor) and 146 asymptomatic high INRs were recorded. Admission to hospital was necessary for 152 patients and 23 died; five as a result of the bleeding episode. The average cost for an asymptomatic high INR was £414, minor bleed was £793 and major bleed was £6,011[34].

Perhaps the problems associated with INR control are best illustrated by the fact that WFN is the second most common cause of hospital admissions for adverse drug reactions in the UK[35].

Further, despite recommendations for anticoagulant therapy in AF patients at moderate to high risk of stroke, studies have highlighted the fact that WFN is under-used in clinical practice. One UK study[36] estimated that 47% of male and 60% of female patients who were otherwise eligible for WFN, did not receive it. The costing template accompanying NICE clinical guideline 36 suggested (conservatively) that 56% of all AF patients should receive WFN, which would be a 26% increase on the status quo (the template estimated that only 30% of all AF patients received WFN)[20].

A retrospective cohort study[37] examined treatment initiation and factors that influence the choice of thromboprophylaxis in 18,459 patients with chronic AF in the UK primary care setting. Factors reducing the likelihood of WFN initiation were advanced age, history of dementia and history of falls. Conversely, aspirin was more likely to be initiated in elderly patients than their younger counterparts. Contrary to current guideline recommendations, there was no correlation between stroke risk ($CHADS_2$ scores) and initiation of WFN or aspirin after adjusting for age and gender.

Therefore it is possible to conclude that although WFN is effective when a patient is well-controlled, the evidence suggests that the individual nature of WFN response means many patients in routine practice are frequently outside the therapeutic range and may suffer poorer outcomes as a consequence. In addition, many patients currently receive sub-optimal

therapy (e.g. aspirin or no treatment) for a variety of reasons even though the evidence indicates that they should receive WFN.

2.6 Please identify the main comparator(s) and justify their selection.

The main comparator is the current standard of care for patients at moderate to high risk of stroke, dose-adjusted warfarin (WFN). No other vitamin-K antagonist is routinely used in UK clinical practice. Aspirin is also recommended for patients at low risk of stroke in whom it is estimated the potential risks of WFN outweigh the potential benefits. However in patients eligible for WFN, aspirin has been shown to be inferior to WFN[38]. There are currently no other licensed alternatives for this indication.

Therefore this submission will present a primary analysis comparing DBG to WFN. There will also be secondary analyses comparing DBG with both aspirin monotherapy and dual anti-platelet therapy (aspirin plus clopidogrel) in patients who are unable or unwilling to receive WFN but are eligible for DBG. Aspirin plus clopidogrel (A+C) has been examined in the ACTIVE-A study[39] in this patient population and is also due to be appraised by NICE[40].

Data will also be presented for DBG versus a putative placebo or "no treatment" alternative. This will provide an estimate of the relative clinical effectiveness of DBG to background disease progression and permits the calculation of numbers needed to treat/harm (NNT/NNH). This comparison is presented for illustrative purposes only and will not be considered in the economic evaluation.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

As with all anticoagulants, the primary safety concern is bleeding. Clinical protocols exist for the emergency management of major bleeding episodes therefore it is not necessary to describe here any individual medicine which may be prescribed.

The only other adverse event that was significantly more common with DBG than with WFN was dyspepsia or gastritis-like symptoms (including abdominal discomfort). In these cases, standard therapies for the treatment of these symptoms, such as antacids and proton pump inhibitors, may be administered.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The main resource use associated with DBG is the acquisition cost of the medicine itself. It does not require resource of any other kind in terms of administration, monitoring or tests over and above routine practice.

2.9 Does the technology require additional infrastructure to be put in place?

No. On the contrary, since DBG does not require anticoagulation monitoring, its introduction will allow the NHS to re-examine the significant existing infrastructure associated with the use of WFN.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No specific equity or equality issues were raised in NICE clinical guideline 36.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

The final scope for this appraisal notes that:

"Consideration should be given to the advantage of dabigatran in terms of its lower requirement for therapeutic monitoring."

This addition to the final scope was a result of the agreement of consultees that DBG, due to less therapeutic monitoring required, could potentially improve access to treatment for people for whom therapeutic monitoring is difficult. This correlates with the points raised in the response to Section 2.5 which outlined that some patients currently receive sub-optimal care.

DBG has predictable pharmacodynamics and pharmacokinetics and consequently does not require anticoagulation monitoring[41]. Quite apart from the clinical and economic case demonstrated in this submission, for this reason alone the introduction of DBG has the potential to revolutionise the way the NHS provides anticoagulation services.

Moreover, initiation on WFN is a life-changing event for most patients. The most obvious inconvenience relates to the time demands required to comply with the schedule of INR monitoring. At the extremes this may be in the form of hours spent waiting in an over-crowded urban outpatient clinic, or the time taken to travel many miles to the nearest clinic in a remote rural area. Some patients may be needle-phobic. Others may find the constant changing of dose (and therefore combination of WFN tablets to be taken and/or cut in half)

confusing. Use of WFN is further complicated by numerous drug-drug and drug-food interactions, meaning patients must avoid or moderate their intake of several common foods, dietary supplements and over-the-counter medications [22].

DBG is taken in a fixed, oral formulation and has far fewer such interactions. There is evidence to suggest that patients would prefer to be initiated on a product like DBG to avoid the inconvenience of INR monitoring and WFN interactions [42].

The introduction of DBG, a product that provides all the clinical benefits of well-controlled WFN and more, but has a predictable anticoagulant effect and does not require INR monitoring, has the potential to shift the paradigm of stroke prevention in patients with AF.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

As outlined above, sub-optimal care in this context can be described as an AF patient who should otherwise receive WFN, but actually receives some other therapy (e.g. aspirin). As noted above in the response to question 2.5, it has been demonstrated in one UK study that there was no correlation between stroke risk ($CHADS_2$ scores) and initiation of WFN or aspirin, contrary to current guidelines[37]. Therefore it is entirely plausible that there is a group of patients who receive aspirin but would be eligible for DBG.

To address this, a mixed treatment comparison has been performed allowing estimated relative clinical parameters for DBG, aspirin monotherapy and aspirin plus clopidogrel (A+C) to be presented. Further, based on the mixed treatment comparison, a secondary analysis comparing DBG to aspirin and A+C for such patients will be presented in the economic evaluation. The MTC further permits a clinical comparison and NNT/NNH analysis versus a putative placebo or “no treatment” comparator.

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with AF who are at moderate to high risk of stroke or systemic embolism	As in final scope, however definitions of moderate to high risk can differ slightly between guidelines.	The definition of moderate considered in the submission is that defined by the RE-LY trial [43] which required patients to have one additional risk factor for stroke from a pre-defined list (other than AF). This definition is broadly in line with other risk stratification systems advocated by international guidelines[7, 14, 19].
Intervention	Dabigatran etexilate	As in final scope (both DBG 110mg bid and 150mg bid doses presented).	
Comparator(s)	▪ Warfarin ▪ Antiplatelet agents in people whom warfarin is inappropriate	As in final scope. Warfarin is the comparator for the primary analysis. Comparisons versus aspirin monotherpay and aspirin plus clopidogrel are also presented as are secondary analyses for patients whom warfarin is not appropriate (or not received) AND in whom DBG may be appropriate. No other agents are licensed or routinely used for this indication therefore no other comparisons are presented.	
Outcomes	• stroke • non-central nervous system embolism • myocardial infarction	As in final scope. Each of these outcomes is considered.	

	• mortality • adverse effects of treatment including haemorrhage • health-related quality of life.		
Economic analysis	Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As in the final scope. Results are expressed in terms of incremental cost per QALY gained. Various time horizons are presented with lifetime being that of the primary analysis (appropriate for a chronic condition and to account for the potential lifelong consequences of stroke and intracranial haemorrhage). Costs are considered from the NHS and PSS perspective.	
Subgroups to be considered	People who have not been previously treated with warfarin.	As in the final scope. Comparative evidence is presented for the subgroups of patients who are either warfarin-naïve or warfarin experienced. The economic analysis is presented both for all eligible patients and by age stratification as per the likely intended use of the two DBG doses.	The likely posology of the two doses is as follows: • Patients under the age of 80-years initiated on DBG 150mg bid and switched to DBG 110mg bid at age 80 • Patients over the age of 80 initiated on DBG 110mg bid
Special considerations, including issues related to equity or equality	The potential advantage of dabigatran in terms of its lower requirement for therapeutic monitoring.	These equity and equality issues are addressed in the submission.	

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A comprehensive search strategy was designed to retrieve relevant clinical data from published literature. This included searches of literature databases, searching of conference abstracts and searches of the manufacturer's internal literature databases. Trials in-progress were also identified, in order to highlight future studies which may be published and provide additional data for the treatments of interest.

The following databases were examined up to August 2010:

- Medline (including Medline® In-Process)
- Embase
- Cochrane Clinical Trials Register

Filters based on those suggested by SIGN were adapted for use in Embase.com search interface and validated in-house. No study design filter is required for the search of Cochrane Library as this database has a built-in filter for clinical trials. No study design filter was used for Medline® In-Process via Pubmed.

Clinical keywords and medical subject headings were used to search for disease and interventions. The search strategies used for each database are presented in Appendix 2.

The following conference proceedings and journals were hand searched 2007-2009 (or 2010 if the conference had taken place by the date of the search)

- European Stroke Conference
- European Society of Cardiology congress
- International Stroke Conference
- American College of Cardiology Annual Scientific Session
- American Heart Association Scientific Sessions

Other data sources searched were:

- Manufacturer's internal databases: BILIT, pre-BILIT and IDEA
- Clinicaltrials.gov

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

To be included in this review, trials had to meet the eligibility criteria as defined in **Table 13** and **Table 14**. There was no date limitation on studies.

Table 13 Inclusion criteria

Category	Criteria	Rationale
Study design	Studies must be published randomised controlled trials or observational studies	RCTs are considered the gold standard of clinical evidence. Observational studies provide evidence within clinical practice, and as such may offer valuable additional evidence. Therefore both types of study are applicable for inclusion.
Population	Studies must be conducted in human adult patients (≥18 years) with atrial fibrillation	Although AF affects both children and adults, DBG will not be used in people under the age of 18. Therefore only patients aged 18 years or above are relevant to the review.
Disease	Atrial fibrillation	As per decision problem
Intervention	Studies must contain DBG and compare it to another treatment modality (which may include placebo).	Only studies assessing the clinical effectiveness of DBG for the prevention of stroke in AF patients are relevant to the decision problem.
Indication	Studies must investigate stroke prevention in patients with AF.	As per decision problem
Language restrictions	Only English language papers are considered	This restriction is unlikely to limit results substantially due to data availability in English language.

Abbreviations: DBG, dabigatran etexilate; RCT, randomised controlled trial.

Table 14 Exclusion criteria

Study design	Studies that are non-randomised controlled trials or observational
Population	Studies conducted in human patients less than 18 years of age, studies in animals or in-vitro
Disease	Studies not including patients with atrial fibrillation
Intervention	Studies not investigating DBG or not comparative
Indication	Studies not investigating stroke prevention in patients with AF
Language restrictions	Non-English language publications

Abbreviation: DBG, dabigatran etexilate

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into an MS Excel database.

First pass of citations

Citations were first screened based on the abstract supplied with each citation. Each abstract was screened by two independent reviewers with any discrepancies resolved by a third reviewer. Those that did not match the eligibility criteria were excluded at this 'first pass'. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. In instances when it was not possible to include or exclude citations based on the abstract, full-text copies were ordered. Full-text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.

Second pass of citations

The eligibility criteria were applied to the full-text citations using the same double screening and reconciliation method as described above, and the data presented in the studies included after this stage were extracted to data extraction grids.

Extraction strategy

Data from trials were extracted independently by two reviewers, with any discrepancies resolved by a third reviewer. The extraction grid used is shown in Appendix 2. Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction grid. Each publication was referenced in the grid to recognise that more than one publication may have contributed to the entry.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Searches of the databases and conference proceedings yielded 280 separate citations. In addition 20 trials were identified from Clinicaltrials.gov, of which three were relevant for inclusion. Of four conference abstracts identified, three were from the ACC conference 2010. All totals are presented in **Table 15**.

Table 15 Final numbers retrieved from searches

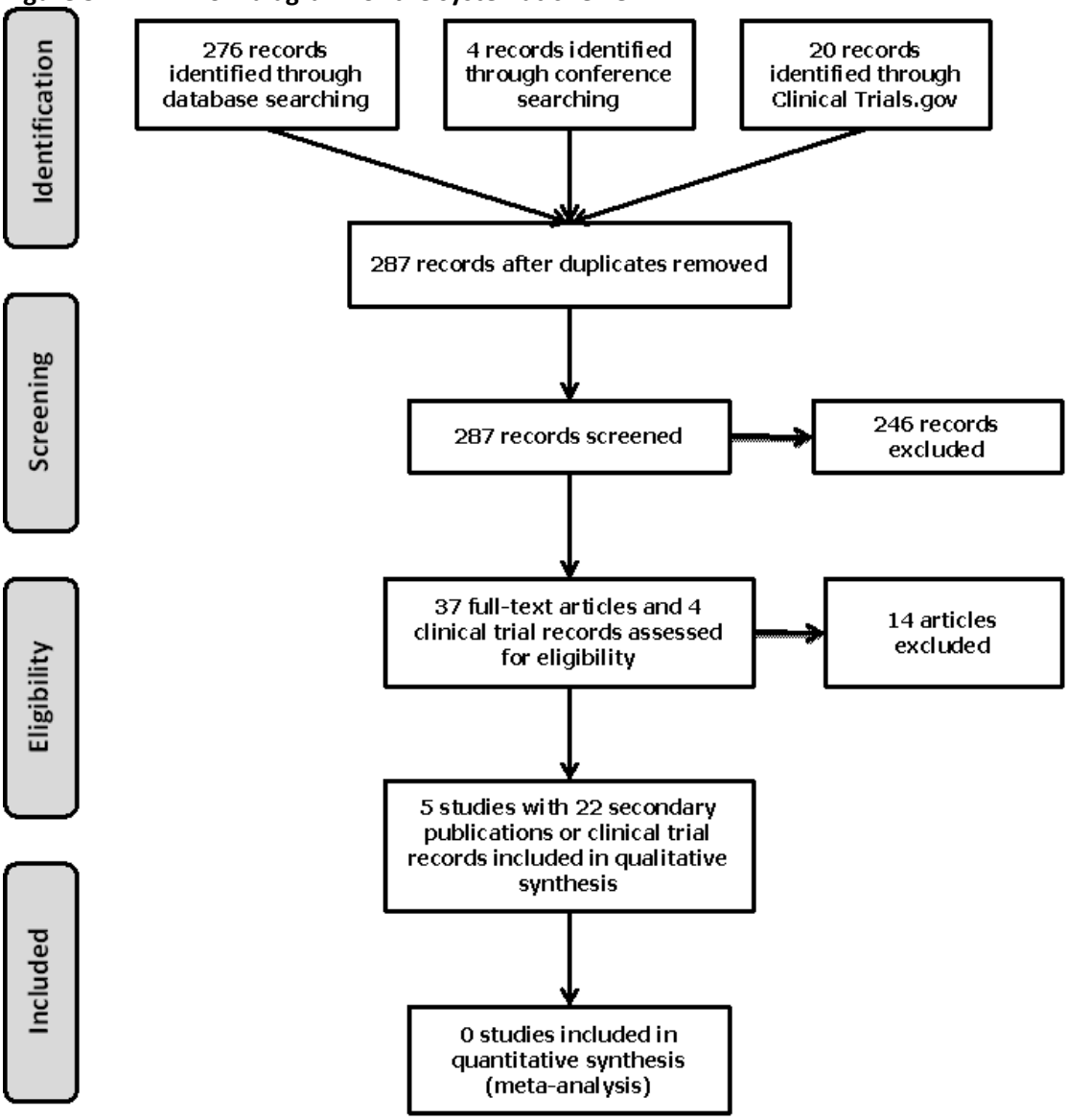
Source	Number of citations
Cochrane	8
Medline and Embase	130
Medline ® In-Process	40
BILIT and pre-BILIT	19
Conference searching	4
Clinicaltrials.gov	20
IDEA	79
Total	300

Due to the overlap of coverage between the databases, nine of the abstracts were found to be duplicates. Following a first review of the abstracts, 37 potentially relevant references and four clinical trial records were identified. Full-text reports of these citations were obtained for more detailed evaluation.

Following detailed examination of the full-text reports, fourteen studies were excluded leaving 27 citations that met the inclusion/exclusion criteria for this review. Some references reported data on the same study and were therefore linked together, resulting in five primary studies linked to 22 secondary publications.

The flow of studies through the review is shown in **Figure 5**.

Figure 5 Flow diagram for the systematic review



The reasons for study exclusion at second pass are presented in **Table 16** and a list of those excluded at second pass is presented in **Table 17**.

Table 16 Reasons for exclusion at second pass

Reason	Number of citations
Copy / duplicate	5
Review / editorial	8
Disease area (i.e. not AF)	1

Table 17 Studies excluded at second pass

Reference	Title	Principle author	Journal	Reasons for exclusion
[44]	Stroke: more protection for patients with atrial fibrillation	Albers G.W.	*Lancet Neurology* (2010) 9:1 (2-4)	Review/editorial
[45]	Atrial fibrillation - All change!	Savelieva I.	*Clinical Medicine*, Journal of the Royal College of Physicians of London (2007) 7:4 (374-379)	Review/editorial
[46]	Co administration of dabigatran etexilate and atorvastatin: assessment of potential impact on pharmacokinetics and pharmacodynamics.	Stangier J.	American journal of cardiovascular drugs: drugs, devices, and other interventions, 2009 9 (1) 59-68	Disease (not AF)
[47]	Does dabigatran improve stroke-prevention in atrial fibrillation?	Eikelboom JW.	*J Thromb Haemost*	Review/editorial
[48]	Does dabigatran improve stroke-prevention in atrial fibrillation?	Stollberger C.	*J Thromb Haemost*	Review/editorial
[49]	Dabigatran: safer, more effective and easier to use than warfarin		*Cardiovasc J Afr*	Review/editorial
[41]	Pharmacology, Pharmacokinetics, and Pharmacodynamics of Dabigatran Etexilate, an Oral Direct Thrombin Inhibitor	Stangier J.	*Clin Appl Thromb Hemost*	Review/editorial
[50]	Abstract 4629: Long-Term Open Label Extension of the Prevention of Embolic and Thrombotic Events on Dabigatran in Atrial Fibrillation (PETRO- Ex study)	Nagarakanti R.	*Circulation*. 2008;118:S_922.	Copy/duplicate
[51]	Direct thrombin inhibitors	Di Nisio M.	*NEJM* (2005) 353:10 (1028-1040). Date of Publication: 8 Sep 2005	Review/editorial
[52]	Dabigatran compared to warfarin in patients with atrial fibrillation and prior TIA or stroke: results of RE-LY	Diener HC.	35th Int Stroke Conf 2010, San Antonio, 23 - 26 Feb 2010 , (2010)	Copy/duplicate
[52]	Dabigatran compared to warfarin in patients with atrial fibrillation and prior TIA or stroke: results of RE-LY	Diener HC.	35th Int Stroke Conf 2010, San Antonio, 23 - 26 Feb 2010 , (2010)	Copy/duplicate
[53]	RELY study of stroke prevention in atrial fibrillation (Randomized Evaluation of Long-term anticoagulant therapY): dabigatran compared to warfarin in 18,113 patients with atrial fibrillation at risk of stroke	Connolly SJ.	European Society of Cardiology (ESC) Cong 2009, Barcelona, 29 Aug - 2 Sep 2009 (Oral Presentation) , (2009)	Copy/duplicate
[54]	Dabigatran challenges warfarin's superiority for stroke prevention in atrial fibrillation.	Schwartz NE.	*Stroke* 2010; 41: 1307-1309	Review/Editorial
[54]	Efficacy and safety of dabigatran compared to warfarin at different levels of INR control for stroke prevention in 18,113 patients with atrial fibrillation in the RE-LY trial.	Wallentin L.	82nd Sci Sess 2009 of the American Heart Association (AHA), Orlando, 14 - 18 Nov 2009 (Oral Presentation) , (2009)	Copy/duplicate

A list of linked studies is shown in **Table 18**. Primary studies are shown in bold, those not in bold are secondary linked studies.

Table 18 List of primary studies and linked references

Study	Principle Author	Citation	Reference
RE-LY	**Connolly S.J.**	***NEJM* (2009) 361:12 (1139-1151). Date of Publication: 17 Sep 2009**	**43**
	Boehringer Ingelheim Pharmaceuticals	ClinicalTrials.gov Identifier: NCT00**262600**	55
	Ezekowitz M.D.	*Am Heart J* (2009) 157:5 (805-810.e2)	56
	Connolly S.J.	*Eur J Heart Fail* (2009) 11:12 (1215)	57
	Wallentin L..	82nd Sci Sess of the American Heart Association (AHA), Orlando, 14 - 18 Nov 2009 *Circulation* 120 (21), 2158	58
	Ezekowitz M.	Mtg of the European Heart Rhythm Association, Berlin, 21 - 24 Jun 2009 *Europace* 11 (Suppl 2)	59
	Diener HC.	35th Int Stroke Conf, San Antonio, 23 - 26 Feb 2010	52
	Oldgren J.	*JACC* March 9, 2010 Volume 55, issue 10 (Suppl 1)	60
	Koti MJ.	*JACC* March 9, 2010 Volume 55, issue 10 (Suppl 1)	61
	Healey JS.	*JACC* March 9, 2010 Volume 55, issue 10 (Suppl 1)	62
	Boehringer Ingelheim International GmbH	Doc No: U07-3249-01	63
	Diener HC.	62nd Ann Mtg of the American Academy of Neurology (AAN), Toronto, 10 - 17 Apr 2010 Neurology 74 (9) (Suppl 2), A281 (2010)	64
	Diener HC.	20th Mtg of the European Neurological Society (ENS), Berlin, 19 - 23 Jun 2010 J Neurol 257 (Suppl 1), S31 (2010)	65
	Connolly SJ.	European Society of Cardiology (ESC) Cong 2009, Barcelona, 29 Aug - 2 Sep 2009 (Oral Presentation) , (2009)	53
RELY-ABLE	**Boehringer Ingelheim Pharmaceuticals**	**ClinicalTrials.gov Identifier: NCT00808067**	**66**
PETRO	**Ezekowitz MD.**	***Am J Cardiol* 2007 100 (9) 1419-26**	**67**
	Stangier J.	Journal of Thrombosis and Haemostasis 2005 3 (Suppl 1)	68
	Wallentin LC.	European Heart Journal 2005 26 (Suppl) 482-483	69
	Boehringer Ingelheim bv	Doc No: U06-1615-02	70
PETRO-Ex	**Nagarakanti R.**	**Sci Sess of the American Heart Association, New Orleans, 8 - 12 Nov 2008 (Poster)**	**50**
	Boehringer Ingelheim Pharmaceuticals	ClinicalTrials.gov Identifier: NCT00157248	71
	Nagarakanti R.	Sci Sess of the American Heart Association, New Orleans, 8 - 12 Nov 2008 (Oral Presentation)	72
	The PETRO-ex Investigators	*Cerebrovasc Dis* 2006 21 (Suppl 4) 2	73
	Boehringer Ingelheim Pharmaceuticals, Inc.	Doc No: U06-3419-02	74
	Boehringer Ingelheim Pharmaceuticals, Inc.	Doc No: U09-3247-01	75
1160.49	**Nippon Boehringer Ingelheim Co., Ltd.**	**Doc No: U07-3126**	**76**
	Boehringer Ingelheim Pharmaceuticals	ClinicalTrials.gov Identifier: NCT01136408	77

Complete list of relevant RCTs

5.2.3 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Details of all RCTs which consider DBG in adults with AF at risk of stroke are shown in **Table 19**. Of these five studies, only RE-LY[43], PETRO[67] and 1160.49[76] compare DBG with other therapies.

5.2.4 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

All of RE-LY[43], PETRO[67] and 1160.49[76] compare DBG with an intervention relevant to the decision problem. It should be noted at the outset that PETRO and study 1160.49 are phase-II dose-finding studies with primary safety objectives. The pivotal RE-LY study provides all of the meaningful evidence on the clinical effectiveness of DBG in this indication.

5.2.5 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

PETRO-Ex[72] was an open-label extension of PETRO in which only patients receiving DBG were observed over an extended period. Further, many patients in PETRO-Ex switched dosing group either at the start of the study or during follow-up. Therefore PETRO-Ex can be reasonably excluded from further discussion as it is an extension of a phase-II dose-finding study which considers only various doses of DBG and has no comparator relevant to the decision problem. The summary results of PETRO-Ex are presented in Appendix 14 for information.

Similarly, RELY-ABLE[2] is an ongoing long-term extension of the RE-LY study which considers only the DBG treatment groups. The RELY-ABLE trial is not due to complete until July 2011 and therefore cannot be discussed further here.

Table 19 List of relevant RCTs

Trial	Intervention	Comparator	Population	Primary study reference
RE-LY	• DBG 110mg bid (N = 6,015) • DBG 150mg bid (N = 6,076)	Adjusted dose warfarin, target INR 2.0-3.0 (N = 6,022)	18,113 patients randomised	[43]
RELY-ABLE	• DBG 110mg bid • DBG 150mg bid	None	Estimated enrolment of 6,200	[2]
PETRO	• DBG 50 mg bid (N=58) • DBG 50 mg bid + ASA 81 mg od (N=20) • DBG 50 mg bid + ASA 325 mg od (N=27) • DBG 150 mg bid (N=99) • DBG 150 mg bid + ASA 81 mg od (N=34) • DBG 150 mg bid + ASA 325 mg od (N=33) • DBG 300 mg bid (N=98) • DBG 300 mg bid + ASA 81 mg od (N=33) • DBG 300 mg bid + ASA 325 mg od (N=30)	Adjusted dose warfarin, target INR 2.0-3.0 (N = 70)	502 patients randomised	[67]
PETRO-Ex	All patients were initially maintained on the same DBG doses as in PETRO except the 50mg bid dose group who were switched to 150mg od. Due to higher frequency of major bleeding events in 300mg bid group and thromboembolic events in 150mg od group, these patients were subsequently switched to DBG 300mg od or 150mg bid.	None. The warfarin patient arm from PETRO (n=70) was discontinued.	361 patients rolled over from PETRO study	[72]
1160.49	• DBG 110mg bid • DBG 150mg bid	Adjusted dose warfarin, target INR 2.0-3.0 (1.6 to 2.6 for patients aged 70 or over)	174 patients randomised	[76]

Abbreviations: ASA, aspirin; bid, twice daily dosing; DBG, dabigatran etexilate; INR, International Normalised Ratio; od, once-daily dosing

List of relevant non-RCTs

5.2.6 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No studies of non-RCT type were identified through the searches.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

The CONSORT checklist detailing which section of the submission deals with each item is presented in **Table 20**.

Table 20 Consort 2010 checklist

Section/Topic	Item number	Checklist item	Reported in section/table
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5.3.2/**Table 23**
	2b	Specific objectives or hypotheses	5.3.2/5.3.6/**Table 23**
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	**Table 23**
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5.3.6
Participants	4a	Eligibility criteria for participants	**Table 22**
	4b	Settings and locations where the data were collected	**Table 23**
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5.3.5/**Table 23**
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	5.3.6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation	8a	Method used to generate the random allocation sequence	Appendix 3/**Table 23**
Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5.3.6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5.3.7
Results			
Participant flow	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5.3.8/**Figure 6**/**Figure 7/Figure 8**
	13b	For each group, losses and exclusions after randomisation, together with reasons	5.3.8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	**Table 23**
	14b	Why the trial ended or was stopped	N/A

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

PETRO [67, 70]

Synopsis

The PETRO study was a 12-week study of DBG, alone or in combination with aspirin (ASA), compared to warfarin (INR 2.0-3.0) in patients with AF. The trial was designed as a 3 x 3 factorial of three doses of DBG (50, 150, and 300 mg bid) and two doses of ASA (81 and 325mg od or nil), plus warfarin (WFN) as an active control group (ten treatments in total). Only the 150mg bid dose is relevant to the decision problem of this submission.

This study was designed to identify a DBG dose with and without concomitant ASA that appeared safe (as measured by bleeding) and potentially effective (inhibition of D-dimer generation) for further study in a large-scale phase-III trial.

1160.49 [76]

Synopsis

This was a phase II study to assess the safety and efficacy of DBG in Japanese patients with non-valvular AF in comparison to WFN. Although this trial was designed to be comparable with PETRO, the doses selected for the phase-III RE-LY trial had already been selected prior to the start of 1160.49. Therefore the doses studied in 1160.49 do match with those in the RE-LY trial.

RE-LY [1, 43, 63]

Synopsis

RE-LY was the pivotal trial for DBG in this indication. It was a large, randomised, parallel group, active-controlled, non-inferiority trial of two blinded doses of DBG (110mg bid and 150mg bid) compared with open-label WFN (target INR of 2.0 to 3.0) for the prevention of stroke and systemic embolism in patients with non-valvular AF and at least one additional risk factor for stroke. It was specified in the statistical analysis plan that superiority testing was to be performed if the non-inferiority condition was met.

Important note regarding amended/updated RE-LY study data

After database lock on August 15th 2009, several additional primary efficacy and safety outcome events were identified during routine clinical site closure visits. These included two systemic embolic events and eight major haemorrhages. Subsequently, after discussions with the FDA, the primary and secondary efficacy and safety data were checked for consistency, and the study database was re-evaluated for possible underreporting of events. To achieve this, all free text, outcomes, and adverse event fields in the database were searched with multiple algorithms to identify any symptom that might suggest the possibility of any primary or secondary event or bleeding. This included examination of all decreases in haemoglobin of greater than 2 g/dL between visits, other markers of potential bleeding, new pathological Q waves on routine ECGs and any report of weakness or other symptoms that might be potentially related to a stroke.

This process resulted in the identification of 81 new events in 80 patients. These included one stroke, one systemic embolic event, four clinical myocardial infarctions, one pulmonary embolism, five transient ischemic attacks and 69 major haemorrhages (**Table 21**).

Although silent myocardial infarction, defined as the new appearance of pathological Q waves on ECG, was part of the RE-LY definition of myocardial infarction, none were reported by investigators during the course of the study. However, in review of the routine ECG reports, 28 cases fulfilling the criteria for silent myocardial infarction were identified.

All of these newly identified events were adjudicated in a blinded fashion and in accordance with the study protocol. Double data entry of all INR data was performed for validation. This resulted in a change in the mean time in therapeutic range of warfarin patients from 64.2% to 64.4%.

Table 21 Additional confirmed subjects with events from RE-LY re-evaluation

Endpoint	DBG 110mg bid	DBG 150mg bid	Warfarin	Total
Stroke	0	0	1	1
SE	0	0	1	1
Death	0	0	0	0
TIA	3	1	1	5
MI	1	0	3	4
PE	0	0	1	1
Major Bleed	18	28	22	68
Subtotal	**22**	**29**	**29**	**80**
Silent MI	11	8	9	28
Total	**33**	**37**	**38**	**108**

Source: [1]

Abbreviations: DBG, dabigatran etexilate; MI, myocardial infarction; PE, pulmonary embolism; SE, systemic embolism; TIA, transient ischaemic attack

The new adjudicated clinical events (N=81) and silent MIs (N=28), together with 22 events from a previous post-database lock sensitivity analysis, were merged and integrated in a combined outcomes re-analysis. *Importantly, it is this re-analysis that is presented in Section 5.5 and 5.9 of the submission, not the original published analysis* [1]. The re-analysis was finalised in April 2010 and shared with regulatory authorities including EMA and FDA at that time. It is due to be published as an addendum to the original publication in the New England Journal of Medicine in due course.

It is extremely important to note that following the re-analysis the primary efficacy and safety conclusions of RE-LY remain unchanged. DBG at the higher dose is superior to WFN for the prevention of stroke/systemic embolism with comparable rates of major bleeding. The lower dose is superior to WFN with respect to the rate of major bleeding and comparable for the prevention of stroke/systemic embolism. Importantly, both doses significantly reduce the most serious bleeding event, intracranial haemorrhage. The re-analyses corrected significant minor errors in the database and oversights in the plausibility evaluation of the first analysis but have confirmed and partly strengthened the study results and reliability of the conclusions from RE-LY.

The designs of each study are summarised in **Table 23**.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

The eligibility criteria for each study are shown in **Table 22**. In the 1160.49 study [76], 174 patients were randomised only in Japan, compared to 502 patients enrolled in four countries in the PETRO study [67, 70] and 18,133 patients in 44 countries in the RE-LY trial [1, 43, 63]. The major differences in the eligibility criteria were the initial requirement for patients to have coronary artery disease (CAD) in the PETRO study until protocol amendment, after which a history of CAD was considered as an additional risk factor for stroke. Also, in the PETRO study patients were only included if they had received treatment with WFN or other VKA prior to inclusion. This was not an inclusion criterion for the RE-LY trial or the 1160.49 study.

Table 22 Eligibility criteria in the RCTs

	Inclusion criteria	Exclusion criteria

PETRO	• Documented AF with coronary artery disease plus one or more of the following:
	  • Hypertension requiring medical treatment
	  • Diabetes mellitus (type 1 or 2)
	  • Symptomatic heart failure or left ventricular dysfunction (ejection fraction <40%)
	  • Previous stroke or transient ischaemic attack
	  • Age >75 years
	• Treatment with warfarin or other vitamin K dependent anticoagulants for at least 8 weeks prior to inclusion.
	• After entry of approximately half of the patients, the requirement for coronary artery disease was removed to facilitate recruitment.
		• Mitral stenosis
		• Prosthetic heart valves
		• Planned cardioversion
		• Recent MI (within last month)
		• Recent stroke or TIA
		• Coronary stent placement within 6 months
		• Any contraindication to or another indication for anticoagulant therapy
		• Major haemorrhage in the past 6 months
		• Severe renal impairment (glomerular filtration rate ≤30 ml/min)
		• Abnormal liver function
		• Risk of pregnancy
		• Investigational drug use within 30 days
		• Any other condition that would not allow participation in the study

1160.49	• Patients of at least 20 years age with non-valvular atrial fibrillation (paroxysmal, persistent or permanent) diagnosed from electrocardiogram at least twice within 1 year.
	• Patients with additional risk factor for thromboembolism with one or more of the following conditions/events:
	  • Hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg)
	  • Diabetes mellitus (types 1 or 2)
	  • Left-sided heart failure (symptomatic congestive heart failure or left ventricular ejection fraction <40%)
	  • Previous ischemic stroke or transient ischemic attack
	  • Age ≥75 years
	  • History of coronary artery disease
		• Valvular heart disease or history of prosthetic valve replacement or valve surgery
		• Patients who were to receive electric defibrillation or pharmacological defibrillation during the study period
		• Patients who developed stroke or transient ischemic attack within 30 days before the date of informed consent
		• Patients who developed myocardial infarction or were admitted to hospital due to acute coronary syndrome or for percutaneous transluminal coronary angioplasty within 3 months before the date of informed consent or patients underwent coronary stenting within 6 months before the date of informed consent
		• Atrial myxoma or left ventricular thrombosis
		• Contraindication to anticoagulant therapies such as:
		  - Previous intra-cranial, intra-ocular, spinal/intraspinal, retroperitoneal or non-traumatic intra-articular haemorrhage
		  - Gastrointestinal haemorrhage within 3 months before the date of informed consent
		  - Peptic ulcers within 30 days before the date of informed consent
		  - Major bleeding with warfarin at the therapeutic range
		  - Patients requiring the continuous therapy of an oral non-steroidal anti-inflammatory drug (excluding aspirin of 100mg or less as a daily dose)
		  - Haemorrhagic diseases
		• Patients scheduled for major surgery or invasive procedure which may cause bleeding or patients having major surgery within 6 weeks

		before the date of informed consent • Major bleeding from non-gastrointestinal organs within 6 months before the date of informed consent • Uncontrolled hypertension • Patients requiring anticoagulant therapy for deep vein thrombosis or pulmonary embolism or thrombolytic therapy • Patients with endocarditis; a history of clinically significant renal diseases or with a creatinine value exceeding 1.2 times the upper limit of the standard range; a history of clinically significant hepatic diseases or with liver function test values exceeding the upper limit of the standard range • Patients with a haemoglobin level of less than 10 g/dL; a platelet count of less than 10 x 104 /µL • Patients with malignancy • Patients having received another investigational drug within 30 days
RE-LY	• Patients aged >18 years at baseline with AF documented by electrocardiography performed at screening or within 6 months prior to screening, and at least one of the following characteristics: • History of stroke, TIA or systemic embolism • Left ventricular ejection fraction <40% • Symptomatic heart failure • Age ≥ 75 years • Age ≥ 65 years and one of the following: • Diabetes mellitus on treatment • Documented coronary artery disease • Hypertension requiring medical treatment	• History of heart valve disorders • Severe, disabling stroke within the previous 6 months or any stroke within the previous 14 days • Conditions associated with increased risk of bleeding • Contraindication to warfarin treatment • Reversible causes of atrial fibrillation • Planning of pulmonary vein ablation or surgery for cure of AF • Severe renal impairment • Active infective endocarditis • Active liver disease • Women who are pregnant or of childbearing potential who do not use medically accepted form of contraception • Anaemia • Patients with transaminase elevation upon exposure to ximelagatran • Patients who have received investigational drug in the past 30 days • Patients considered unreliable, with low life expectancy (less than duration of trial) or any condition which would not allow safe participation in the study

Sources: [63, 70, 76]

Table 23 Comparative summary of methodology of the RCTs

	PETRO [67, 70]	1160.49 [76]	RE-LY [1, 43, 63]
Scientific rationale	Treatment of AF patients with oral anticoagulants substantially reduces the risk of stroke but has the downside to induce major bleeding events. Depending on the dose and titration level of warfarin, this risk dramatically increases and therefore, only a narrow therapeutic window of an INR range of 2-3 is left to provide sufficient benefit without increased risk of bleeding. In order to meet this narrow therapeutic window, treatment with VKAs requires regular monitoring and dose adjustments during treatment, which results in substantial underuse in clinical practice [78]. DBG, which is given as a fixed dose and does not require monitoring, may be an alternative to warfarin.		
	This study was designed to attempt to identify a dose of DBG with and without concomitant ASA that appeared safe (as measured by bleeding) and potentially effective (inhibition of D-dimer generation) for further study in large-scale phase-III trials.	Phase II study to assess safety (e.g., the incidence of bleeding events) and efficacy of DBG in Japanese patients with NVAF with comparison to warfarin. The results were intended to be compared to those of the PETRO study	The trial was designed to evaluate whether 110mg bid and 150mg bid of DBG are non-inferior to adjusted dose warfarin (target INR of 2.0 to 3.0) in the prevention of stroke and systemic embolism in non-valvular AF patients with at least 1 additional risk factor for stroke.
Clinical phase	Phase II	Phase II	Phase III
Location of study	Multi-centre, international (Denmark, Netherlands, Sweden, United States)	Japan	Multi-centre, international in 44 countries (including: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Finland, France, Greece, Hong Kong (China), Hungary, India, Israel, Italy, Japan, South Korea, Malaysia, Mexico, the Netherlands, Norway, Peru, Philippines, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, South Africa, Spain, Taiwan, Turkey, Ukraine, United Kingdom, United States)
Study design	Randomised, parallel group trial in subjects with non-rheumatic atrial fibrillation (paroxysmal, persistent, or permanent) who also had an additional risk factor for thromboembolic events. The trial was double-blind with respect to DBG treatment but was open-label for concomitant ASA treatment, and for patients randomised to warfarin. The trial had a 3 x 3 factorial design with 3 doses of DBG and 2 doses of ASA, with an additional treatment group randomised to warfarin alone.	Open-label, multicentre, randomised, parallel-group comparison study in patients with non-valvular atrial fibrillation (paroxysmal, persistent or permanent) were to be randomised to DBG 110mg bid, DBG 150mg bid or warfarin in a 1:1:1 ratio. The patients were to receive study drugs for 12 weeks.	Prospective Randomised Open trial with Blinded outcome Evaluation (PROBE) study with 2 doses of DBG (110mg bid, 150mg bid) compared to adjusted-dose warfarin therapy, INR 2.0-3.0. Approximately 6,000 subjects per treatment group were randomised over 2 years with a further year of follow-up to a common termination. A key element of the PROBE design was to use blinded adjudicators to reduce potential bias in the evaluation and classification of important study outcome events.

	PETRO [67, 70]	1160.49 [76]	RE-LY [1, 43, 63]
Objective	To evaluate the safety of different doses of DBG, alone or in combination with ASA, as determined by the rates of bleeding and other adverse events. A secondary objective of this trial was to evaluate the anticoagulant effect of different doses of DBG, based on the reduction of plasma concentrations of D-dimer, a laboratory marker for activated coagulation in AF patients, and to correlate bleeding and other events with PK and PD data.	To evaluate the safety of DBG administered orally at doses of 110 and 150mg, twice daily, for 12 weeks in Japanese patients with non-valvular atrial fibrillation (paroxysmal, persistent or permanent) in comparison with warfarin.	To demonstrate that the efficacy and safety of 2 blinded doses (110mg bid and 150mg bid) of DBG are non-inferior to adjusted dose warfarin (target INR 2-3) for the prevention of stroke and systemic embolism in subjects with non-valvular AF with at least 1 additional risk factor for stroke. As pre-specified in the statistical analysis plan, superiority testing was to be performed to compare DBG with warfarin for the primary endpoint once non-inferiority was established.
Duration of study	6th October 2003 to 3rd November 2004	10th November 2005 to 4th September 2006	22nd December 2005 to 15th March 2009
Methods of randomisation	The treatment allocation was determined according to the randomisation code provided using ClinPro/LBL Version 6.0 release 5 software. Randomisation was stratified by country; each country received a multiple of all treatments, and corresponding treatment assignment envelopes, in the ratio 2:3:3:4. This resulted in a block size that is a multiple of 28 (the actual figure, unknown to the investigators, was 28); the number of treatment kits containing a combination of DBG and ASA was a multiple of 24 (again, the actual figure was 24). These figures were unknown to the investigators in order to make calculations of the block size impossible.	The randomisation code was provided by Bell System (a registration centre) with validated software. Randomisation was based on permuted blocks with a block size of six. Eligible patients were randomly assigned in a 1:1:1 ratio to receive DBG 110mg bid, DBG 150mg bid or warfarin. After obtaining written consent on Visit 1, the investigator facsimiled a patient registration form to the registration centre, when the patient was eligible. Before Visit 2, the registration centre facsimiled a confirmation form including randomised treatment to the investigator. The investigator dispensed the study drug according to the randomised treatment.	Randomisation was to have taken place within 14 days of the screening visit. Subjects were randomly allocated to 1 of 3 treatment groups —DBG 110 bid, DBG 150mg bid, or warfarin, — with equal probability (allocation ratio of 1:1:1). The randomisation was done through an IVRS located at the central coordinating centre. The randomisation was done with a random block size of 3, 6, and 9, and the randomisation schedule was generated by using validated software. The doses of DBG were blinded.

	PETRO [67, 70]	1160.49 [76]	RE-LY [1, 43, 63]
Method of blinding	If a patient was randomised to DBG, such patients entered the double-blind treatment period, i.e., the patients and trial site personnel did not know what dose level of DBG the patient was receiving. As a result of increased bleeding risk in the highest 300mg bid DBG dose group with ASA (81mg or 325mg) the Steering Committee and DSMB decided to unblind this treatment for several patients. Warfarin and aspirin treatment was open-label.	The study was open label.	DBG 110mg and 150mg capsules were identical in appearance and were administered in a blinded manner. Warfarin was administered open-label. The randomisation code was kept by the Trial Coordinating Centre. All personnel involved in the conduct of the trial were blinded to treatment assignments until database lock. An independent Event Adjudication Committee was established for the blinded adjudication of primary and secondary outcome events and major bleeding. An Adjudication Committee Charter, under which the blinded evaluation of endpoints was to be carried out, governed their activities.
Intervention	1) DBG 50mg bid; N = 58 2) DBG 50mg bid + ASA 81mg od; N = 20 3) DBG 50mg bid + ASA 325mg od; N = 27 4) DBG 150mg bid; N = 99 5) DBG 150mg bid + ASA 81mg od; N = 34 6) DBG 150mg bid + ASA 325mg od; N = 33 7) DBG 300mg bid; N = 98 8) DBG 300mg bid + ASA 81mg od; N = 33 9) DBG 300mg bid + ASA 325mg od; N = 30	1) DBG 110mg bid; N = 53 2) DBG 150mg bid; N = 59	1) DBG 110mg bid; N = 6,015 2) DBG 150mg bid; N = 6,076
Comparator	1) Adjusted dose warfarin od, target INR 2.0-3.0; N = 70	1) Adjusted dose warfarin od, target INR 2.0-3.0 (1.6 – 2.6 for patients over the age of 70); N = 62	1) Adjusted dose warfarin od, target INR 2.0-3.0; N = 6,022

Primary outcomes	There was no primary efficacy endpoint.
	The primary safety endpoint was the frequency of any bleeding. Bleeding events were classified as follows:
	• Major bleeds
	• Minor bleeds, further subdivided into
	  • Clinically relevant bleeds
	  • "Nuisance" bleeds
		There was no primary efficacy endpoint.
		The primary safety endpoint was the frequency of bleeding. Bleeding events were classified as follows:
		• Major bleeds
		• Minor bleeds, further subdivided into
		  • Clinically relevant bleeds
		  • "Nuisance" bleeds
		
		Others:
		• Incidence and severity of adverse events
		• Discontinuation of study drug due to adverse events
		• Changes in laboratory test values
			Incidence of all stroke (including haemorrhagic) or systemic embolism

	PETRO [67, 70]	1160.49 [76]	RE-LY [1, 43, 63]
Secondary outcomes	Secondary endpoints were as follows: • Change from baseline in the plasma concentration of D-dimer. • Frequency and severity of adverse events other than bleeding • Composite endpoint of ischemic stroke (fatal or non fatal), transient ischemic attack, systemic thromboembolism, myocardial infarction (fatal or non fatal), other major adverse cardiac event and all cause mortality. • Frequency of individual components of clinical outcome events: • ischemic stroke, fatal and non-fatal • transient ischemic attack • systemic thromboembolism • myocardial infarction, fatal and non-fatal • other major adverse cardiac event • death, all causes • Clinically relevant changes in laboratory tests for safety • The pharmacokinetics of DBG, assessed by steady-state plasma concentrations. • Anticoagulant effects (aPTT, ECT, soluble fibrin) and 11-dehydro-thromboxane B2 measurements.	Secondary endpoints were as follows: • A composite clinical endpoint including the incidence of ischemic or haemorrhagic stroke (fatal or non-fatal), transient ischemic attacks, systemic embolism, myocardial infarction (fatal or non-fatal), other major adverse cardiac events, and death • The incidence of the following thromboembolic events: • Ischemic or haemorrhagic stroke (fatal or non-fatal) • Transient ischemic attack • Systemic embolism • Myocardial infarction, fatal and non-fatal • Other major adverse cardiac event • Death • Anticoagulant effects - For DBG; D-Dimer, soluble fibrin, aPTT, ECT, INR, 11-dehydro-thromboxane B2 - For warfarin; D-Dimer, soluble fibrin, 11-dehydro-thromboxane B2	The secondary endpoints were: • Composite of all stroke (including haemorrhagic), systemic embolism, and all death. • Composite of all stroke (including haemorrhagic), systemic embolism, pulmonary embolism, myocardial infarction and vascular death Additional endpoints were: • Individual occurrence or composites of any of ischemic stroke (fatal and non-fatal), systemic embolism, pulmonary embolism, myocardial infarction, TIAs, vascular death, all deaths, and hospitalisations • Net Clinical Benefit as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, myocardial infarction, all cause deaths, and major bleed. Safety endpoints were: • Major bleeding, satisfying one or more of the following criteria: • Reduction in haemoglobin levels of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells • Symptomatic bleeding in a critical area or organ: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding Major bleeds were classified as life-threatening if they met one or more of the following criteria: • Fatal, symptomatic intracranial bleed; reduction in haemoglobin levels of at least 50 g/L; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; necessitated surgical intervention • Minor bleeding (bleeding events not meeting the criteria for major bleeding) • Other adverse events including hepatic toxicity

	PETRO [67, 70]	1160.49 [76]	RE-LY [1, 43, 63]
Duration of follow-up	Visit schedule: 1) Screening (day -7 to -4) 2) Baseline (day 0, max of 1 week after visit 1) 3) Within 1 week of visit 2 (day 4 to 7) 4) Within 2 weeks of visit 2 (day 10-14) 5) 4 weeks from visit 2 (day 28) 6) 8 weeks from visit 2 (day 56) 7) 12 weeks from visit 2 (day 84) 8) Final visit, week 13 (7 days from visit 7)	Visit schedule: 1) Screening (day -14 to -7) 2) Baseline (day 0, max of 2 weeks after visit 1) 3) 1 week from initiation (day 7 $\pm$ 3) 4) 2 weeks from initiation (day 14 $\pm$ 3) 5) 4 weeks from initiation (day 28 $\pm$ 3) 6) 8 weeks from initiation (day 56 $\pm$ 3) 7) 12 weeks from initiation (day 84 $\pm$ 3) 8) Final visit, 2 weeks $\pm$ 1 (14 days $\pm$ 7) from visit 7	Visit schedule: 1) Screening 2) Baseline/randomisation within 14 days of screening 3) to 14) Follow-up visits. Two weeks after randomisation, all subjects were to have had a telephone visit to evaluate safety and outcome events. The subjects were to return to the clinic for regularly scheduled follow-up visits 1, 3, 6, 9, and 12 months from randomisation and then every 4 months for the duration of the trial up to a maximum of month 36. Visit "98") Final follow-up visit procedures were to be performed whenever a subject discontinued participation in the study, either prematurely or according to the protocol. The duration of treatment was expected to be a median of 20-24 months, with a minimum of 12 months' treatment after the last subject was randomised and a maximum treatment of approximately 3 years. Actual median study follow-up was 23.7 months

Sources: [63, 70, 76]

Abbreviations: aPTT, activated partial thromboplastin time; ASA, aspirin; DBG, dabigatran etexilate; DSMB, Drug Safety Monitoring Board; ECT, ecarin clotting time; INR, International Normalised Ratio; TIA, transient ischaemic attack; VKA, vitamin K antagonist

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

PETRO [67, 70]

Table 24 presents the baseline characteristics of the 502 patients randomised in the PETRO study. In general, there were no large differences between the treatment groups in PETRO in terms of baseline demographic and disease characteristics.

1160.49 [76]

The baseline characteristics of the participants of study 1160.49 are presented in **Table 25**. The proportion of females in the DBG 110 mg bid group was relatively higher than those of the other groups. The mean creatinine clearance in the WFN group was larger than those of the DBG groups. The proportion of concomitant aspirin in the WFN group was higher than those of the DBG groups. However these differences are likely explained by the size of the study.

RE-LY [1, 43, 63]

Table 26 details the baseline characteristics of the patients in each of the three treatment groups in the RE-LY trial. In general, there were no large differences between the treatment groups in terms of baseline demographic and disease characteristics.

The major differences between the studies in terms of patient characteristics at baseline were a higher percentage of males in the PETRO [67, 70] and 1160.49 studies [76] compared to RE-LY [1, 43, 63]. The types of AF were equally distributed amongst patients in RE-LY whereas patients with paroxysmal AF were less prominent in the PETRO and 1160.49 studies. There were higher proportions of WFN-experienced patients in PETRO (inclusion criterion) and 1160.49 than in RE-LY, which was designed to split WFN-experienced and naïve patients 50/50.

Table 24 Baseline characteristics of participants (PETRO)

Parameter	DBG 50 mg (n=105)	DBG 150 mg (n=166)	DBG 300 mg (n=161)	Warfarin (n=70)	p-value for equality of groups
Mean age, yrs (SD)	70 (8.8)	70 (8.1)	69.5 (8.4)	69 (8.3)	0.7
Female	21 (20%)	31 (18.7%)	28 (17.4%)	11 (15.7%)	0.9
Weight, kg (SD)	88.6 (17.2)	89.4 (17.0)	90.0 (17.3)	92.0 (21.1)	NR
Median duration of disease, yrs (IQ range)	3.6 (6.9)	3.9 (6.6)	6.4 (4.3)	3.4 (5.0)	0.4
Previous TIA or stroke	19 (18%)	29 (17.5%)	26 (16%)	13 (18.6%)	1.0
Hypertension	70 (66.7%)	118 (71%)	119 (74%)	49 (70%)	0.6
Diabetes	27 (25.7%)	45 (27%)	39 (24%)	15 (21.4%)	0.8
Heart failure	35 (33.3%)	52 (31.3%)	36 (22.4%)	24 (34.3%)	0.1
CAD	64 (61%)	104 (63%)	96 (59.6%)	42 (60%)	1.0
Current/former smoker	76 (72.4%)	120 (72.3%)	116 (72%)	53 (75.7%)	1.0
Beta-blockers	69 (65.7%)	121 (73%)	110 (68.3%)	49 (70%)	0.6
ACE inhibitor/ARB	70 (66.7%)	116 (69.8%)	112 (69.5%)	57 (81.4%)	0.2
Verapamil/dilatiazem	16 (15%)	31 (18.7%)	34 (21%)	14 (20%)	0.7
Other calcium inhibitors	26 (24.7%)	37 (2.3%)	38 (23.6%)	14 (20%)	0.9
Amiodarone	9 (8.5%)	9 (5.4%)	13 (8%)	6 (8.5%)	0.7
Digoxin	46 (43.8%)	75 (45%)	66 (41%)	32 (45.7%)	0.9
Diuretic	59 (56%)	89 (53.6%)	97 (60%)	44 (63%)	0.5
Statin	58 (55%)	100 (60%)	95 (59%)	37 (53%)	0.7

Source: [67]

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; DBG, dabigatran etexilate; IQ, interquartile; SD, standard deviation; TIA, transient ischaemic attack

Table 25 Baseline characteristics of participants (1160.49)

Parameter	DBG 110 mg bid (n=[redacted])	DBG 150 mg bid (n=[redacted])	Warfarin (n=[redacted])
Mean age, yrs (SD)	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Weight, kg (SD)	[redacted]	[redacted]	[redacted]
Type of AF	[redacted]	[redacted]	[redacted]
Mean CrCl, mL/min (SD)	[redacted]	[redacted]	[redacted]
Previous TIA or stroke	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]
LVD or symptomatic heart failure	[redacted]	[redacted]	[redacted]
CAD	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]
Warfarin experienced	[redacted]	[redacted]	[redacted]

Source: [76]

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CrCl, creatinine clearance; DBG, dabigatran etexilate; LVD, left ventricular dysfunction; SD, standard deviation; TIA, transient ischaemic attack

Table 26 Baseline characteristics of participants (RE-LY)

Parameter	DBG 110 mg bid (n=6,015)	DBG 150 mg bid (n=6,076)	Warfarin (n=6,022)
Mean age, yrs (SD)	71.4 (8.6)	71.5 (8.8)	71.6 (8.6)
Male	3,865 (64.3%)	3,840 (63.2%)	3,809 (63.3%)
Weight, kg (SD)	82.9 (19.8)	82.4 (19.3)	82.6 (19.6)
Duration of disease	<3 mo: 1,843 (30.6%) 3 mo – 2 yrs: 1,324 (22.0%) >2yrs: 2,842 (47.2%)	<3 mo: 1,854 (30.5%) 3 mo – 2 yrs: 1,344 (22.1%) >2yrs: 2,875 (47.3%)	<3 mo: 1,929 (32.0%) 3 mo – 2 yrs: 1,315 (21.8%) >2yrs: 2,776 (46.1%)
Type of AF	Persistent: 1,950 (32.4%) Paroxysmal: 1,928 (32.1%) Permanent: 2,131 (35.4%)	Persistent: 1,909 (31.4%) Paroxysmal: 1,977 (32.5%) Permanent: 2,188 (36.0%)	Persistent: 1,930 (32.0%) Paroxysmal: 2,036 (33.8%) Permanent: 2,055 (34.1%)
$CHADS_2$ score	0: 151 (2.5%) 1: 1,809 (30.1%) 2: 2,088 (34.7%) 3+: 1,966 (32.7%) Mean: 2.1	0: 146 (2.4%) 1: 1,815 (29.9%) 2: 2,136 (35.2%) 3+: 1,979 (32.6%) Mean: 2.1	0: 155 (2.6%) 1: 1,707 (28.3%) 2: 2,229 (37.0%) 3+: 1,931 (32.1%) Mean: 2.1
Mean CrCl, mL/min (SD)	73.0 (27.7)	72.7 (28.2)	73.0 (27.4)
Long-term VKA therapy	3,008 (50.0%)	3,047 (50.1%)	2,929 (48.6%)
Previous cardioversion	1,658 (27.6%)	1,683 (27.7%)	1,651 (27.4%)
Previous ablation	119 (2.0%)	136 (2.2%)	132 (2.2%)
Diabetes	1,409 (23.4%)	1,402 (23.1%)	1,410 (23.4%)
Hypertension	4,738 (78.8%)	4,795 (78.9%)	4,750 (78.9%)
Previous stroke	761 (12.7%)	756 (12.4%)	756 (12.6%)
Previous TIA	548 (9.1%)	587 (9.7%)	528 (8.8%)
Prior MI	1,008 (16.8%)	1,029 (16.9%)	968 (16.1%)
Heart failure	1,937 (32.2%)	1,934 (31.8%)	1,922 (31.9%)
Aspirin	2,384 (39.6%)	2,338 (38.5%)	2,431 (40.4%)
Anti-hypertensive	4,830 (80.3%)	4,895 (80.6%)	4,784 (79.4%)
Beta-Blocker	3,789 (63.0%)	3,887 (64.0%)	3,722 (61.8%)
Amiodarone	647 (10.8%)	672 (11.1%)	657 (10.9%)
Statins	2,702 (44.9%)	2,682 (44.1%)	2,673 (44.4%)
Proton-pump inhibitor	847 (14.1%)	878 (14.5%)	842 (14.0%)
H_2-receptor antagonist	239 (4.0%)	257 (4.2%)	262 (4.4%)

Source: [1]

Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance; DBG, dabigatran etexilate; MI, myocardial infarction; SD, standard deviation; TIA, transient ischaemic attack

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

PETRO [67, 70]

Efficacy Outcomes

Since the objective of the study was dose exploration the PETRO study had no primary efficacy endpoint. Secondary efficacy outcomes were as follows:

- A composite clinical endpoint of any thromboembolic or cardiac event, including the incidence of ischemic stroke (fatal + non-fatal), TIAs, systemic embolism, myocardial infarction (fatal + non-fatal), other major adverse cardiac events and all-cause mortality
- Net clinical cost (NCC) as measured by the composite clinical endpoint of stroke/TIA/systemic embolism/MI/death plus major bleeds
- The occurrence rates of:
    - stroke (fatal and non-fatal)
    - TIAs
    - systemic embolism
    - myocardial infarction (fatal and non-fatal)
    - other major cardiac events
    - all cause mortality
- Various pharmacodynamic/-kinetic parameters such as D-dimer, soluble fibrin, 11-dehydrothromboxane, aPTT, ECT and DBG plasma concentrations

Safety Endpoints

The following safety endpoints were assessed:

1. Cumulative incidence of any bleeding event (primary safety endpoint)
2. Cumulative incidence of bleeding, classified as major or minor bleeding. Minor bleeds were further differentiated into clinically relevant and nuisance bleeds.
3. Incidence and severity of other adverse events, including clinically relevant changes in laboratory parameters, vital signs, physical examinations, and ECG changes
4. Discontinuation of treatment due to adverse events

5. Systematic changes in laboratory parameters

Bleeding Events

Bleeding events were classified as major or minor according to the outcome, the loss of blood, and the severity and rate of bleeding. Minor bleeding was further subdivided into clinically relevant and nuisance bleeds.

A major bleeding event was defined as any bleed fulfilling one of the following conditions:

- Fatal or life-threatening
- Retroperitoneal, intracranial, intraocular, or intra-spinal bleeding (verified by objective testing)
- Bleeding requiring surgical treatment
- Clinical overt bleeding leading to a transfusion of ≥ 2 units of packed cells or whole blood
- Clinically overt bleeding leading to a fall in haemoglobin of ≥ 20 g/L

In case of a major bleeding event, the patient was to be withdrawn from the study.

A minor bleeding event was any bleed that did not qualify as a major bleed. A minor bleed was further categorised as clinically relevant if it fulfilled one of the following criteria:

- Skin hematoma ≥ 25 cm^2
- Spontaneous nose bleed > 5 minutes duration
- Macroscopic haematuria, either spontaneous or, if associated with an intervention, lasting more than 24 hours
- Spontaneous rectal bleeding (more than spotting on toilet paper)
- Gingival bleeding > 5 minutes
- Bleeding leading to hospitalisation
- Bleeding leading to a transfusion of < 2 units of packed cells or whole blood
- Any other bleeding event considered clinically relevant by the investigator

All minor bleeding events not fulfilling one of the criteria for clinically relevant were classified as nuisance bleeds. Withdrawal of the patient from further participation in the study was to be considered in the event of a clinically relevant bleeding event.

1160.49 [76]

Efficacy Outcomes

The primary objective of this study was safety evaluation. Secondary efficacy outcomes were as follows:

- A composite clinical endpoint including the incidence of ischemic or haemorrhagic stroke (fatal + non-fatal), TIAs, systemic embolism, myocardial infarction (fatal + non-fatal), other major adverse cardiac events and death
- The occurrence rates of:
    - Ischaemic or haemorrhagic stroke (fatal and non-fatal)
    - TIAs
    - Systemic embolism
    - Myocardial infarction (fatal and non-fatal)
    - Other major cardiac events
    - Death
- Anticoagulation effects
- Various pharmacodynamic/-kinetic parameters such as D-dimer, soluble fibrin, 11-dehydrothromboxane, aPTT, ECT and DBG plasma concentrations

Safety Endpoints

Bleeding events were the primary focus of the safety analysis. These events were classified as follows:

- Major bleeding
- Minor bleeding (subdivided into)
    - Clinically relevant (or significant) bleeding
    - Nuisance bleeding

Other adverse events were also recorded along with a variety of laboratory test values.

Bleeding Events

Major bleeding was defined as any bleed fulfilling one of the following conditions:

- Fatal or life-threatening
- Retroperitoneal, intracranial, intraocular, or intraspinal bleeding (verified by objective testing)
- Bleeding requiring surgical treatment
- Clinically overt bleeding leading to a transfusion (erythrocyte component transfusion or whole blood transfusion) of 4.5 units (equal to 2 units in EU/US) or more
- Clinically overt bleeding leading to a fall in haemoglobin of at least 2 g/dL

Minor bleeding was any bleed that did not qualify as a major bleed. Minor bleeding was further categorised as clinically relevant if it fulfilled one of the following criteria. All minor bleeding events not fulfilling one of the criteria for clinically relevant were classified as nuisance bleeds.

- A skin haematoma of at least 25 cm^2
- Spontaneous nose bleed lasting for more than 5 minutes
- Macroscopic haematuria (either spontaneous or, if associated with an intervention, lasting more than 24 hours)
- Spontaneous rectal bleeding (more than spotting on toilet paper)
- Gingival bleeding lasting for more than 5 minutes
- Bleeding leading to hospitalisation
- Bleeding leading to blood transfusion (erythrocyte component transfusion or whole blood transfusion) of less than 4.5 units (equal to 2 units in EU/US)
- Any other bleeding considered clinically relevant by the investigator

RE-LY [1, 43, 63]

Efficacy Outcomes

The primary endpoint of the RE-LY study was as follows:

- Incidence of stroke (including haemorrhagic) or non-Central Nervous System (CNS) systemic embolism

Secondary efficacy endpoints were as follows:

- Incidence of stroke (including haemorrhagic), systemic embolism, all death
- Incidence of stroke (including haemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular deaths (includes deaths from bleeding)

Other efficacy endpoints:

- Individual or composite occurrences of ischaemic stroke (fatal and non-fatal), systemic embolism, pulmonary embolism, acute myocardial infarction, TIAs, vascular death (includes deaths from bleeding), all deaths, and hospitalisations
- Net Clinical Benefit (NCB) as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, all cause deaths, and major bleeds

Stroke was defined as an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. The stroke was categorised as ischaemic or haemorrhagic or cause unknown (based on CT or magnetic resonance (MR) scanning or autopsy). Fatal stroke was defined as death from any cause within 30 days of stroke. Severity of a stroke was assessed by modified Rankin score (mRs) at discharge from hospital and at 3 to 6 months post-event.

Systemic embolism was an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina, or grafts), and must have been documented by angiography, surgery, scintigraphy, or autopsy.

In subjects who did not undergo percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) a **myocardial infarction (MI)** was defined in patients who fulfilled at least 2 of the following 3 criteria:

1) Typical prolonged severe chest pain or related symptoms or signs (e.g., ST changes of T-wave inversion in the ECG) suggestive of myocardial infarction.
2) Elevation of troponin or creatinine kinase-muscle brain (CK-MB) to more than the ULN or if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level.
3) Development of significant Q-waves in at least 2 adjacent ECG leads.

In subjects who underwent PCI within 24 hours **MI** was defined as follows:

- Elevation of troponin or CK-MB to more than 3xULN or if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.

In subjects who underwent CABG within 72 hours **MI** was defined as follows:

- Elevation of CKMB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads.

Silent MI was retrospectively diagnosed by the appearance of significant new Q-waves between study visits. In such cases, the date of the event was recorded as the midpoint between the 2 study visits. MI may also have been demonstrated at autopsy.

Deaths were classified as being vascular (including bleeding) or non-vascular, due to other specified causes (e.g., malignancy), or of unknown etiology.

Safety Endpoints

All reported major bleeding events, bleeds requiring discontinuation of study medication, hospitalisations, or other medical intervention, were forwarded for adjudication by a committee blinded to treatment allocation. The overall objective was to categorise each reported bleed as major or minor.

Additional safety parameters that were to be assessed included intracerebral haemorrhage, other intracranial haemorrhage, elevations of liver function tests, the presence of hepatic dysfunction, and other adverse events.

Bleeding Events

Subjects were to be assessed for signs and symptoms of bleeding. Bleeding was classified as major or minor by using the following guidelines. Major bleeds were further sub-classified as life-threatening or other major bleeds.

Major bleeding must have satisfied one or more of the following criteria:

- Bleeding associated with a reduction in haemoglobin levels of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells
- Symptomatic bleeding in a critical area or organ: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding

Major bleeds were classified as life-threatening if they met one or more of the following criteria:

- Fatal, symptomatic intracranial bleed; reduction in haemoglobin levels of at least 50 g/L; transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents; necessitated surgical intervention

Minor bleeds were clinical bleeds that did not fulfil the criteria for major bleeds. Minor bleeds were classified as either being associated or not being associated with study medication discontinuation (temporary or permanent).

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

PETRO [67, 70]

Since this was a dose exploration study, no formal statistical hypotheses were tested and no sample size or power calculations were reported. All statistics were simply descriptive.

1160.49 [76]

No formal statistical hypotheses were tested and no sample size or power calculations were reported. All statistics were simply descriptive.

RE-LY [1, 43, 63]

This trial assumed a yearly event rate in the primary endpoint of 1.6% for both DBG and WFN, with 5,000 subjects per treatment group to be recruited in 2 years and followed up for 1 additional year to achieve 150 events per treatment group. Within these parameters, each comparison had approximately 90% power to conclude the non-inferiority of DBG to WFN at a one-sided α=0.025 level (without adjusting for multiple comparisons) based on the derived non-inferiority margin of 1.46. With a total of 15,000 subjects randomised to the two DBG doses and WFN at a 1:1:1 ratio, to achieve a total of 450 events, using the Hochberg procedure to compare each DBG dose to WFN, the trial had approximately 84% power to conclude the non-inferiority of both DBG doses to WFN using the non-inferiority margin of 1.46.

A total of 15,000 subjects were recruited in less than 2 years (18 months). If the recruitment was stopped at that time, the last randomised subject would have had to be followed up for more than one year to achieve the planned total number of events, if the actual event rate was as expected. In addition, based on the results from other published studies, the actual event rate could be less than 1.6%. Because of these concerns, the RE-LY operational committee (comprised mainly of academic leaders and only a minority representation from the sponsor) decided to continue the recruitment as planned until the originally scheduled “last patient in” date. As a result, a total of 18,113 subjects were randomised. It was expected that if the actual event rate was as planned, the statistical power would be increased.

The primary endpoint was assessed by the time to the first occurrence of stroke or systemic embolism. The statistical model for the primary efficacy analysis was the Cox proportional hazard model including treatment as a factor in the model. The hazard ratio and its confidence limits were determined for evaluating the non-inferiority of DBG over WFN. The Cox regression model was also used for other time-to-event analyses.

The null hypothesis was that the hazard ratio of DBG versus WFN was larger than or equal to the specified non-inferiority margin δ = 1.46. The alternative hypothesis was that the hazard ratio of DBG versus WFN was less than 1.46. The upper bound of the confidence interval (CI) of the hazard ratio of DBG versus WFN was compared to the non-inferiority margin for the non-inferiority testing.

Since there were two comparisons of DBG versus WFN, the Hochberg procedure was used to handle the multiple comparisons. Accordingly the DBG dose with the largest hazard ratio versus WFN was to be tested first for non-inferiority at α=0.025 (one-sided) level. If non-inferiority was concluded from this comparison, then the non-inferiority versus WFN for both DBG doses would be claimed.

Otherwise, the non-inferiority for this dose would not be claimed and the other DBG dose would be compared to WFN at α=0.0125 (one-sided) level for non-inferiority.

As specified in the statistical analysis plan, superiority testing was to be performed to compare DBG to WFN for the primary endpoint if the non-inferiority claim was established.

Four analysis sets were defined for the efficacy analyses: the randomised/ITT set, the safety set (SAF), the treated set, and the per-protocol set (PPS).

The ITT set included all randomised subjects in the treatment groups to which they were assigned, regardless of whether the subjects received study medication or not.

The SAF set included all randomised subjects who received at least one dose of study medication. Subjects were stratified by the randomised treatment.

The treated set included all randomised subjects who took the randomised study medication for ≥70% of the time in the study or prior to the onset of a primary outcome event.

The PPS included all subjects who were randomised and treated and did not have important protocol violations.

The various data sets that were used for each analysis are summarised in **Table 27**.

Table 27 Analysis sets in RE-LY

Endpoint	Randomised Set	Safety Set	Treated Set	Per Protocol Set
Primary endpoint	X	X (sensitivity)	X (sensitivity)	X (sensitivity)
Important secondary endpoint	X	X		
Other secondary endpoint	X			
Adverse events		X		
Bleeding	X	X (sensitivity)		
Liver function tests		X		
Demographic/baseline characteristics	X			
Compliance		X		
Patient numbers	DBG 110: 6,015 DBG 150: 6,076 WFN: 6,022	DBG 110: 5,983 DBG 150: 6,059 WFN: 5,998	DBG 110: 4,995 DBG 150: 4,988 WFN: 5,283	DBG 110: 4,821 DBG 150: 4,797 WFN: 5,112

Source: [63]
Abbreviations: DBG, dabigatran etexilate; WFN, warfarin

The time to the occurrence of the primary endpoint event was computed as (event date – randomisation date) + 1. Subjects who did not have primary endpoint events during the trial period were considered to be censored. The time to censoring was computed as (study termination date – randomisation date) + 1. For subjects who had more than one primary endpoint event during the trial, the time to the first occurrence of the primary endpoint event was used for the primary efficacy

analysis. All adjudicated and/or un-refuted events were used. The proportional hazards assumptions were not formally tested, but they were investigated.

Yearly event rates were computed for outcome events, by treatment group, descriptively. These were crude assessments of the occurrence of events. More accurate assessments were provided by Kaplan-Meier curves. The yearly event rate for a treatment group was computed as the total number of events that occurred in that treatment group divided by the total subject exposure in years (subject years) in that group. For a given subject, exposure was computed from the date of randomisation to the date of study termination, using the randomised set.

For a more accurate assessment, the subject exposure should be computed from the date of randomisation or treatment start to the date of the first occurrence of an event, if an event occurred, or to the date of study medication or treatment stop if no event occurred. However, this calculation would provide different subject exposure years for different events, which can be confusing in many cases. Since the event rate for outcome events and bleeds was low, an estimate using the total subject exposure provides a very close result to that calculated using the exposure computed from the time of randomisation/treatment start date to the time of first occurrence of an event.

The randomised set was used for the secondary analyses. The safety set was used for some secondary endpoints as sensitivity analyses. Secondary analyses were performed for the time to the first occurrence of the composite endpoints.

All secondary outcomes were analysed using the Cox regression model with treatment as the factor in the model. The hazard ratio of each DBG dose versus WFN and the 95% CI of the hazard ratio were provided for each of the composite endpoints.

Summary statistics (frequency, percentage, yearly event rate) were provided by treatment group for each component of the composite endpoints.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

PETRO [67, 70]

No relevant subgroup analyses were planned or reported.

1160.49 [76]

No relevant subgroup analyses were planned or reported.

RE-LY [1, 43, 63]

Subgroup analyses were planned for the primary outcome event, the secondary endpoint stroke/systemic embolism/all cause deaths and bleeding events using the Cox regression model. The model included factors for treatment, subgroup, and treatment by subgroup interaction. The randomised set was used. The hazard ratio, 95% CI of the hazard ratio, and the p-value for testing interactions were reported.

It was hypothesised that subjects previously exposed to WFN or other VKA therapy prior to randomisation may respond differently to WFN treatment from those who were not previously exposed. To explore this, subjects were categorised into groups based on their history of VKA use prior to randomisation. A treatment by VKA use history interaction was anticipated.

Except for the baseline VKA use subgroup, no heterogeneity between treatment groups was expected across other subgroups. The primary outcome was evaluated as exploratory analyses across all other subgroups. However due to the large number of subgroup analyses performed, some treatment by subgroup interactions may turn out to be statistically significant by chance. These subgroups were as follows:

1. Previous VKA use class (naive/experienced): Subjects were considered VKA naïve if they had received 2 months or less of any VKA in their life time up to the time of randomization; experienced if more than 2 months.
2. Age (years): <65, ≥65, and <75, ≥75
3. Body Mass Index (BMI, kg/m2): <30, ≥30, and <35, ≥35
4. Gender: male, female
5. CrCL (mL/min): <30, ≥30, and <50, ≥50, and <80, ≥80
6. Weight (kg): <50, ≥50, and <100, ≥100
7. Ethnicity class: White, Black, Asian, Other
8. Hispanic or Latino: no or yes (defined based on countries and ancestral origins)
9. Baseline aspirin therapy: no or yes
10. Occurrence of previous stroke or TIA: no or yes
11. Geographic region: North America, Western Europe, Central Europe, Latin America, Asia, or Other.
12. Symptomatic heart failure (NYHA class ≥2): no or yes
13. Left Ventricular Ejection Fraction (LVEF) ≤40%: no or yes

14. Age ≥65 years and diabetes mellitus on treatment: no or yes
15. Age ≥65 years and documented CAD: no or yes
16. Age ≥65 years and hypertension: no or yes

The following subgroups were not specified in the protocol but were specified in the statistical analysis plan as additional subgroups:

17. VKA use status at randomization: on VKA or not on VKA
18. CHADS2 score
19. Baseline aspirin + clopidogrel use: no or yes
20. Baseline dipyridamole use: no or yes
21. Baseline diltiazem use: no or yes
22. Baseline amiodarone use: no or yes
23. Baseline statin use: no or yes
24. Baseline angiotensin receptor blocker (ARB) use: no or yes
25. Baseline other NSAID use: no or yes
26. Baseline antithrombotic use: no or yes
27. Baseline anti-hypertensive use: no or yes
28. Baseline beta blocker/calcium channel blocker/drug used in AF: no or yes
29. Baseline metabolic/anti-inflammatory: no or yes
30. Baseline P-glycoprotein (gp) inhibitors: no or yes
31. Baseline other medication use: no or yes
32. Centre INR control: based on the average percent of time the INR was in the range of 2-3 among all WFN subjects in the respective centre:
    A. INR control: <60% of time or ≥60% of time
    B. INR control: <65% of time or ≥65% of time

The primary subgroup analysis is analysis 1 which will be presented in the submission. Due to the volume of potential subgroup analyses, in the interests of brevity only a selection of the other subgroup analyses will be presented in the submission.

Further, given the clear dose-response demonstrated by the two DBG doses it was clear that one or other of the doses may be more appropriate in patients of differing risk profiles. Therefore a *post-*

hoc subgroup analysis was performed which targets each dose within a specific patient population as per the current proposed posology.

The analysis stratified use of the two DBG doses as follows:

a) Patients aged less than 80 years at baseline initiated on DBG 150mg bid and switched to DBG 110mg bid at age 80 (Denoted as "DBG Sequence")

b) Patients aged more than 80 years at baseline initiated on DBG 110mg bid (Denoted as "DBG >80")

This analysis, alongside the main "all patients" analysis, will inform the principle analyses of the economic evaluation presented in Section 6.

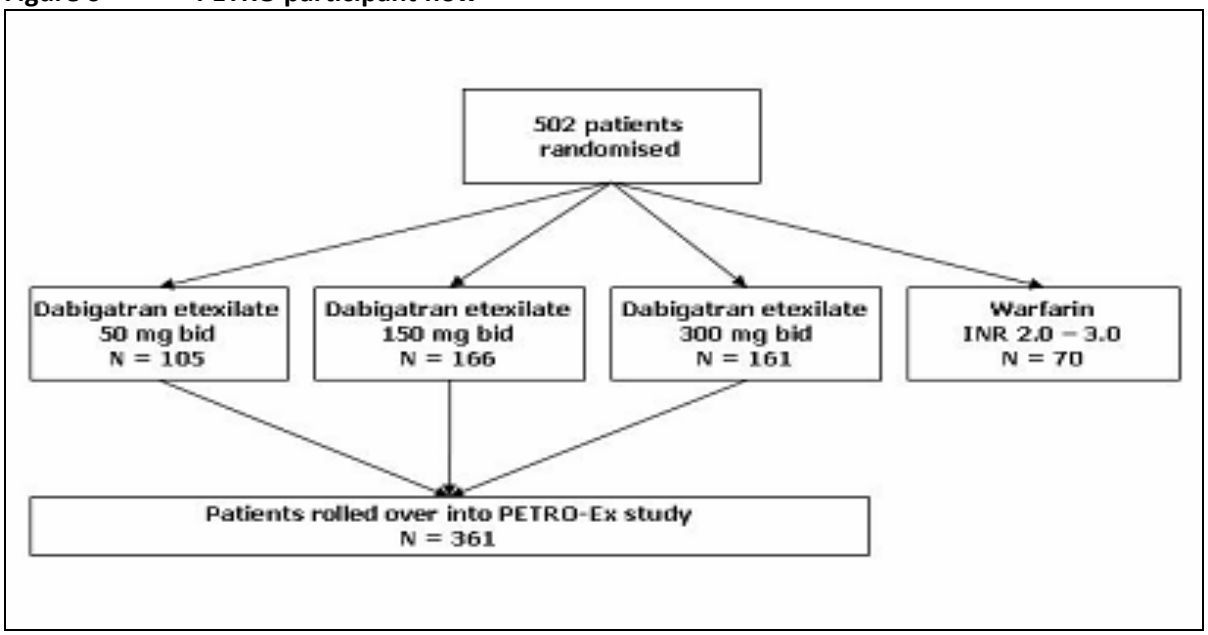
Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

PETRO [67, 70]

Figure 6 illustrates the participant flow in the PETRO study. A total of 593 patients were enrolled, of which 502 were randomised.

Figure 6 PETRO participant flow



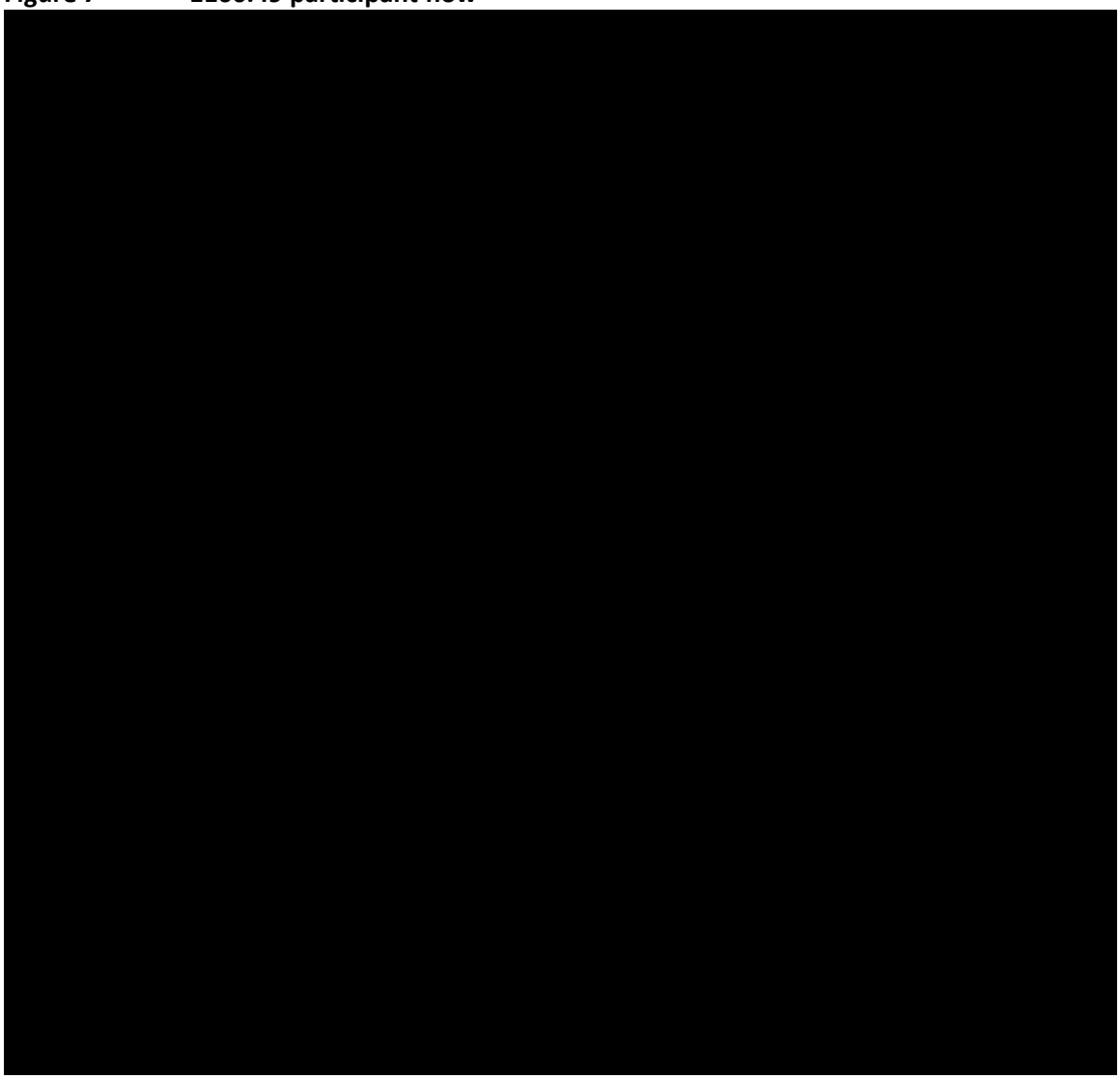
Abbreviations: bid, twice daily dosing; INR, International Normalised Ratio

Twelve patients with glomerular filtration rates≤50 ml/min underwent down -titration to once daily DBG (one patient in group 50mg bid, five patients in group 150mg bid, six patients in group 300mg bid). These patients were analysed according to the group to which they were initially assigned.

1160.49 [76]

A total of [redacted] patients were enrolled, of which 174 were randomised ([redacted] to DBG 110mg bid, [redacted] to DBG 150mg bid, [redacted] to WFN). [redacted] patients in the 110mg bid group, [redacted] in the 150mg bid group, and [redacted] in the WFN group received treatment. [redacted] patients ([redacted]%) in the 110mg bid group, [redacted] patients ([redacted]%) in the 150mg bid group, and [redacted] patients ([redacted]%) in the WFN group were prematurely discontinued from the study, mainly because of adverse events (**Figure 7**).

Figure 7 1160.49 participant flow

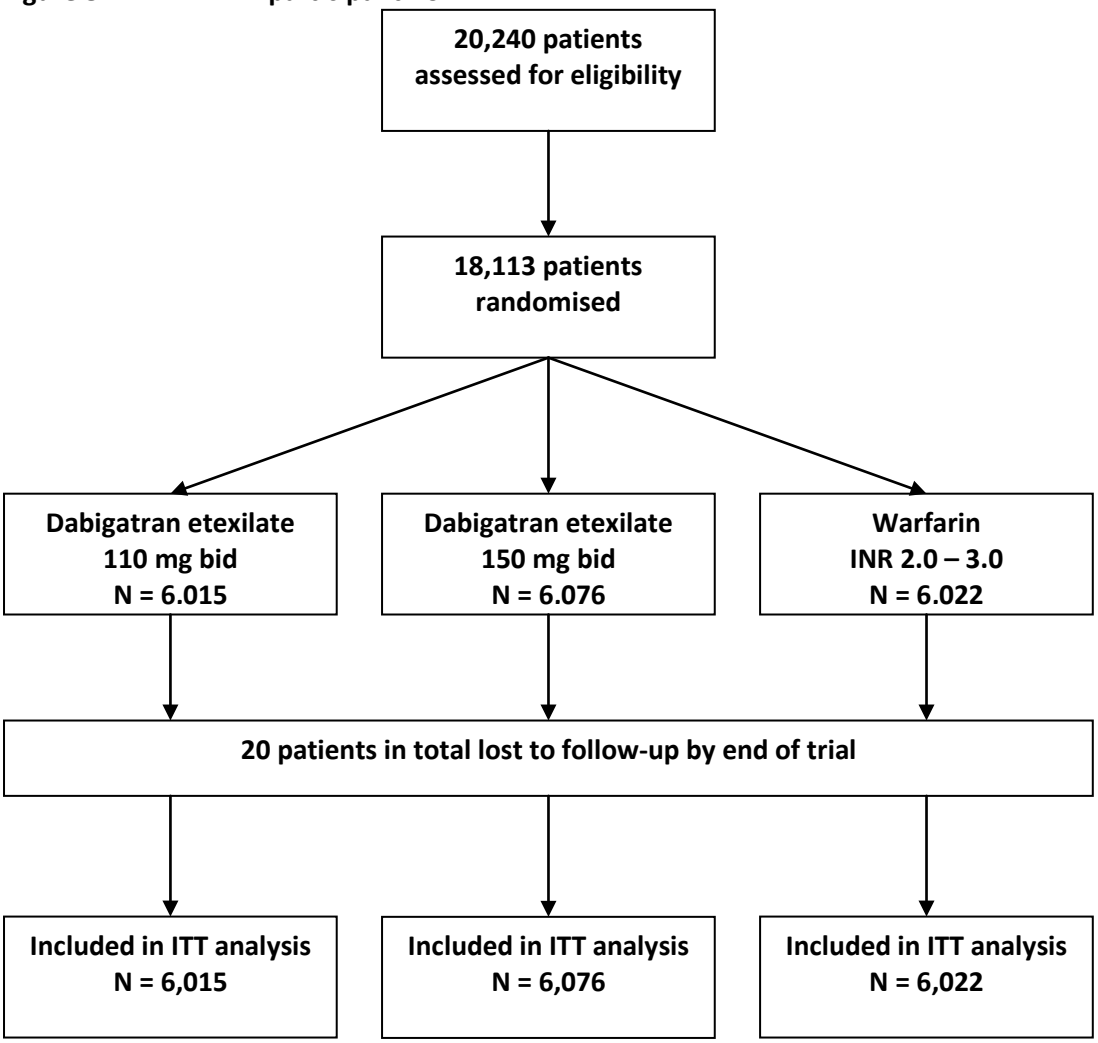


Abbreviations: bid, twice daily dosing; DBG, dabigatran etexilate

RE-LY [1, 43, 63]

Figure 8 illustrates the participant flow in the RE-LY study. A total of 20,240 patients were assessed for eligibility, of which 18,113 were randomised.

Figure 8 RE-LY participant flow



Abbreviations: bid, twice daily dosing; INR, International Normalised Ratio; ITT, intention to treat

5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?

- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 28 summarises the full quality assessment of the three RCTs presented in Appendix 3.

Table 28 Summary of the critical appraisal of the RCTs

	PETRO	1160.49	RE-LY
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	No	No	Yes, where blinding was appropriate.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants (no). Outcomes assessors (yes).	Care providers and participants (no). Outcomes assessors (yes).	Care providers and participants (partially). Outcomes assessors (yes).
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

PETRO [67, 70]

Only two thromboembolic events occurred during the 12-week treatment period, and neither occurred with the DBG dose studied in PETRO that is relevant to the decision problem (DBG 150mg bid). Therefore presentation of these results is trivial.

Other secondary endpoints evaluated the pharmacokinetic and pharmacodynamic properties of DBG and their interrelationship. These analyses are not relevant to the decision problem and are not presented. Safety analyses from PETRO will be presented in Section 5.9.

1160.49 [76]

[redacted]

Other secondary endpoints evaluated the pharmacokinetic and pharmacodynamic properties of DBG and their interrelationship. These analyses are not relevant to the decision problem and are not presented. Safety analyses from study 1160.49 will be presented in Section 5.9.

RE-LY [1, 43, 63]

Table 29 to Table 31 presents the results of the efficacy analyses from RE-LY for the primary and secondary endpoints. **Figure 10** to **Figure 12** present the Kaplan-Meier curves for major endpoints.

DBG compliance was calculated as the number of capsules taken, divided by the number of capsules that should have been taken. The calculation was based on expected use, and therefore days when DBG was temporarily or permanently discontinued were not considered in the calculation. Adequate compliance was defined as within 80-120%.INR control was assessed by the percentage of time the INR was in the required target range of 2-3. A linear interpolation using the Rosendaal method was performed[79]. Days in the first week after randomisation and the days while study WFN was temporarily or permanently stopped were excluded.

Non-inferiority of both DBG doses compared to WFN was demonstrated for the primary endpoint. The upper bound of both 95% CIs was below 1.46, the protocol specified margin, for both doses. The p-value for the non-inferiority test, using 1.46, was <0.0001 for both doses. Relative risk reductions for DBG 110mg and DBG 150mg were 10% and 35%, respectively, in comparison to WFN.

DBG 150mg bid was superior to WFN for the primary endpoint as demonstrated in a superiority test, that compared DBG and WFN after non-inferiority was established (p=0.0001). Non-inferiority was also demonstrated for both doses at the lower margin of 1.38 (p<0.0001 for both doses), the preferred margin of the FDA. A Kaplan-Meier plot of time to first stroke or SE is presented in **Figure 9**.

For ischemic stroke DBG 150mg bid was superior to WFN, while DBG 110mg bid was not statistically different from WFN. The Kaplan-Meier estimates show that DBG 150mg bid separated early in the study from the other treatment groups and remained below both WFN and DBG 110mg bid throughout the study (**Figure 10**).

The frequency of haemorrhagic strokes in the DBG groups was less than one third of that seen in the WFN group. As seen in the Kaplan-Meier estimates (**Figure 11**), both DBG doses reduced haemorrhagic strokes significantly compared to WFN. The risk reductions were 69% and 74%, respectively for DBG 110mg bid and DBG 150mg bid, and were highly statistically significant (p-value <0.0001). The Kaplan Meier curves appear to diverge almost from the beginning of the study and continued to diverge until the end of the study.

“Other stroke” refers to strokes with uncertain classification. These are usually events with no imaging available to categorise the event. For the purposes of the MTC and economic model presented later in the submission, these events were added to ischaemic stroke. Rates of SE were low and similar across the treatment groups.

The results for the secondary composite endpoint of stroke, SE and all cause death showed the same pattern as for the primary endpoint: DBG 110mg bid was similar to WFN; DBG 150mg bid was superior to WFN.

As shown in the Kaplan-Meier estimate for all cause death (**Figure 12**), the DBG groups diverged from WFN at approximately 16 months after randomisation. DBG 110mg bid and DBG 150mg bid reduced the risk of all cause death by 9% and 12% (relative risk reduction), respectively, in comparison to WFN. The reduction in all cause death was significant for DBG 150mg bid (p-value = 0.0475).

DBG 150mg bid had a statistically significant reduction in reducing the risk of the stroke, SE, PE, MI and vascular death composite endpoint when compared to WFN (relative risk reduction of 15%, p-value 0.0093). DBG 110mg bid was comparable to WFN for the same endpoint. Rates of PE were low and similar across the treatment groups.

Although the rates of symptomatic, clinical (and therefore) total MI were numerically higher for both doses of DBG compared to WFN, neither difference (for either endpoint) was statistically significant. The rates of silent MI were low and similar between the three treatment groups.

More than 60% of all deaths were attributed to vascular causes. DBG 110mg bid and DBG 150mg bid reduced the risk of vascular death by 10% and 16%, respectively, in comparison to WFN. The reduction in vascular death was significant for DBG 150 (p=0.0386).

For the ischaemic stroke, SE, PE, MI, TIA, hospitalisation or all-cause death composite endpoint statistical analysis showed that the DBG 110mg bid provided more benefit and that DBG 150mg bid was not statistically different in comparison to WFN for this composite endpoint (p-values=0.0024 and 0.3083), respectively, with corresponding risk reductions of 8% and 3%.

The rates of TIA were lower with both DBG doses compared to WFN. Subjects treated with DBG 110mg bid had the lowest rate of hospitalisation, which was significantly lower when compared with WFN (p=0.0209). This difference was due, in part, to a lower rate of hospitalisations for cardiovascular (non-outcome) events.

The risk reduction in net clinical benefit was 8% and 10% for DBG 110mg bid and DBG 150mg bid, respectively, the latter of which was statistically significant (p = 0.0254).

Table 29 Results of the efficacy analysis for treatment compliance and time in therapeutic range from RE-LY

Outcome	DBG 110mg bid compliance (SD)	DBG 150mg bid compliance (SD)	WFN TTR
Compliance/TTR	94.8% (11.3)	94.6% (11.7)	64.4% (19.8)

Analysis set: DBG 110mg - N = 5,725; DBG 150mg - N = 5,781 (includes all subjects who had compliance data available at any time during the study). WFN - N = 5,789 (subjects who have INR data at each 3 month timepoint are evaluated, this is the overall analysis of all INR data at each timepoint)
Source: [1]
Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; ITT, intention to treat; SD, standard deviation; SE, systemic embolism; TTR, time in therapeutic range; WFN, warfarin

Table 30 Results of the efficacy analysis for the primary endpoint and its components from RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Stroke/SE (Primary endpoint)	**183**	**1.54%**	**134**	**1.11%**	**202**	**1.71%**	**0.90 (0.74 – 1.10)**	**0.65* (0.52 – 0.81)**
Ischaemic stroke only	152	1.28%	103	0.86%	134	1.14%	1.13 (0.89 – 1.42)	0.75* (0.58 – 0.97)
Haemorrhagic stroke only	14	0.12%	12	0.10%	45	0.38%	0.31* (0.17 – 0.56)	0.26* (0.14 – 0.49)
Other stroke	7	0.06%	9	0.07%	10	0.08%		
SE only	15	0.13%	13	0.11%	21	0.18%		

ITT analysis set: DBG 110mg - N = 6,015, subject-years = 11,899; DBG 150mg - N = 6,076, subject-years = 12,033; WFN - N = 6,022, subject-years = 11,794
* Denotes statistically significant in favour of DBG
Source: [1]
Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; ITT, intention to treat; SE, systemic embolism; WFN, warfarin

Table 31 Results of the efficacy analysis for the secondary endpoints and their components from RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Stroke/SE/All-cause death (Secondary endpoint)	**577**	**4.85%**	**520**	**4.32%**	**613**	**5.20%**	**0.93 (0.83 – 1.04)**	**0.83* (0.74 – 0.93)**
All-cause death only	446	3.75%	438	3.64%	487	4.13%	0.91 (0.80 – 1.03)	0.88 (0.77 – 1.00)
Stroke/SE/PE/MI (including silent MI)/Vascular death (Secondary endpoint)	**507**	**4.26%**	**443**	**3.68%**	**513**	**4.35%**	**0.98 (0.87 – 1.11)**	**0.84* (0.74 – 0.96)**
PE only	14	0.12%	18	0.15%	12	0.10%		
Symptomatic, clinical MI only	87	0.73%	89	0.74%	66	0.56%	1.30 (0.95 – 1.80)	1.32 (0.96 – 1.81)
Silent MI only	11	0.09%	8	0.07%	9	0.08%		
Total MI	98	0.82%	97	0.84%	75	0.64%	1.29 (0.96 – 1.75)	1.27 (0.94 – 1.71)
Vascular death only	289	2.43%	274	2.28%	317	2.69%	0.90 (0.77 – 1.06)	0.85* (0.72 – 0.99)
Ischaemic stroke/SE/PE/MI/TIA/hospitalisation or all-cause death	2,479	20.83%	2,603	21.63%	2,632	22.32%	0.92* (0.87 – 0.97)	0.97 (0.92 – 1.03)
TIA only	74	0.62%	87	0.72%	99	0.84%		
Hospitalisation only	2,312	19.43%	2,430	20.19%	2,458	20.84%	0.93* (0.87 – 0.99)	0.98 (0.92 – 1.04)
Net clinical benefit (Stroke/SE/PE/MI/ all-cause death or major bleed)	863	7.34%	848	7.11%	925	7.91%	0.92 (0.84 – 1.01)	0.90* (0.82 – 0.99)

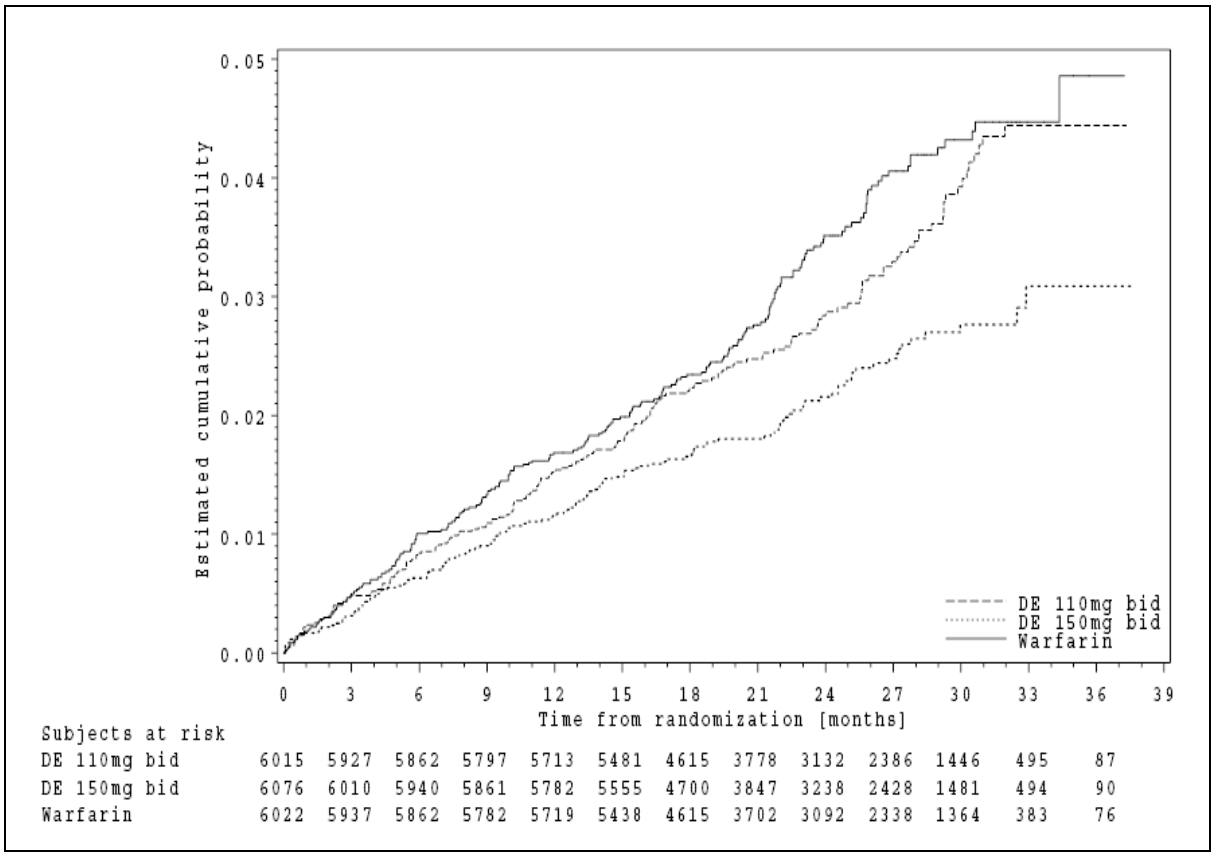
ITT analysis set: DBG 110mg - N = 6,015, subject-years = 11,899; DBG 150mg - N = 6,076, subject-years = 12,033; WFN - N = 6,022, subject-years = 11,794

* Denotes statistically significant in favour of DBG

Source: [1]

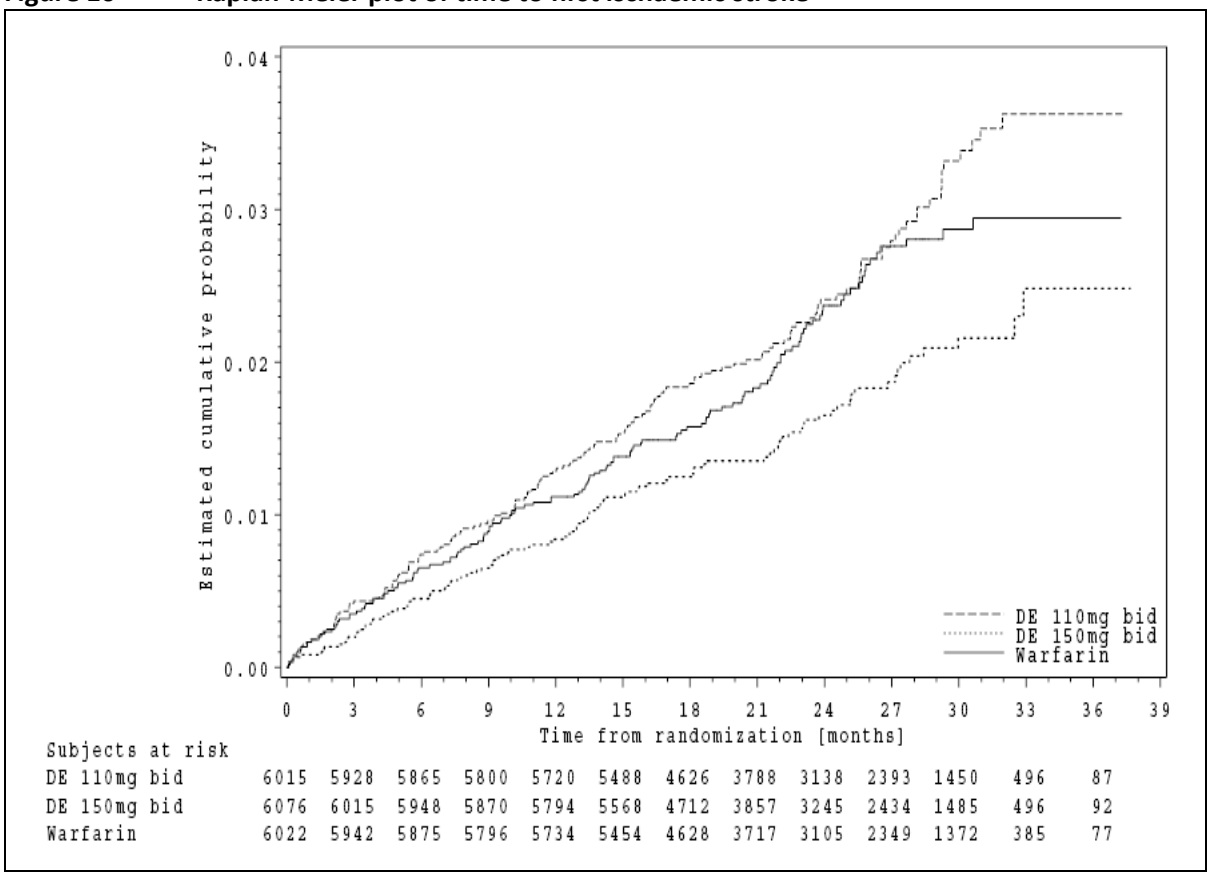
Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; ITT, intention to treat; MI, myocardial infarction; PE, pulmonary embolism; SE, systemic embolism; TIA, transient ischaemic attack; WFN, warfarin

Figure 9 Kaplan-Meier plot of time to first stroke/SE [1]



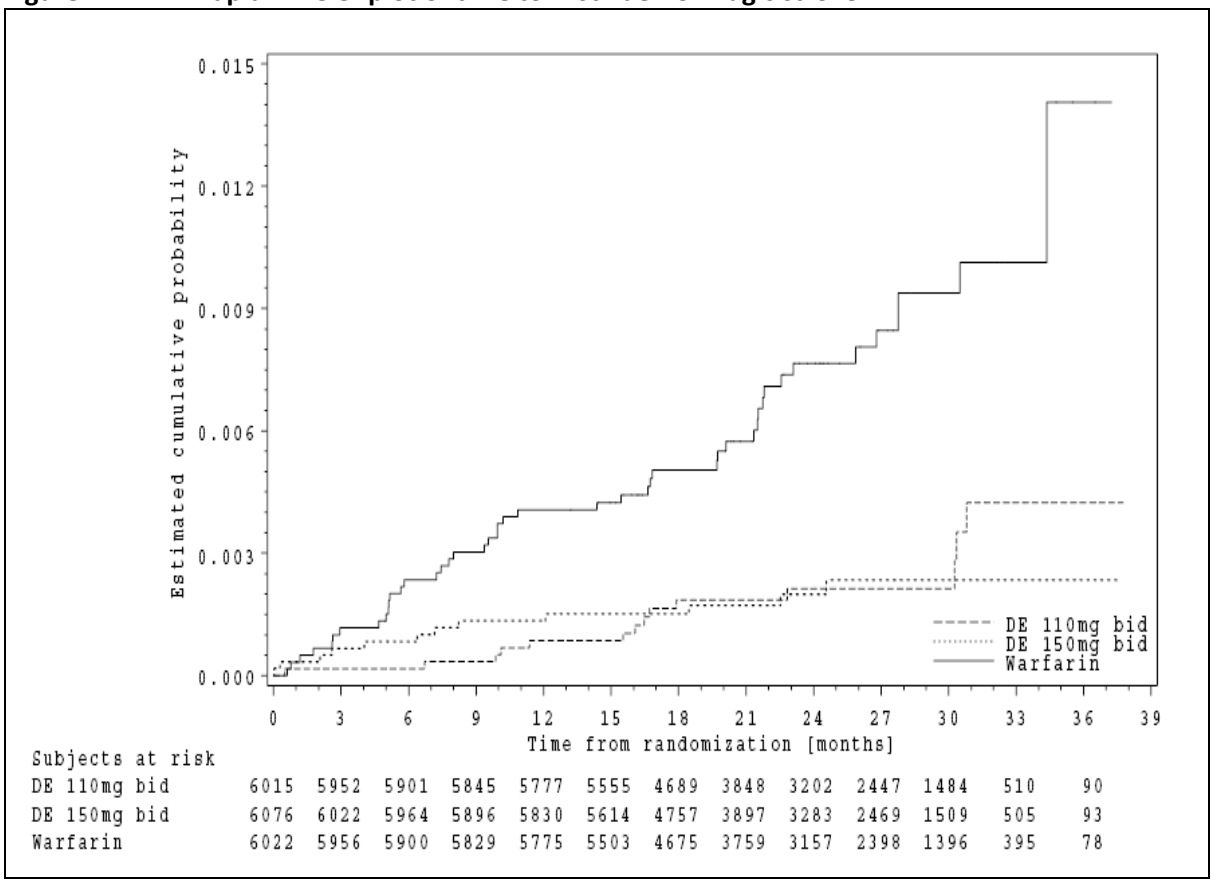
Abbreviation: DE, dabigatran etexilate

Figure 10 Kaplan-Meier plot of time to first ischaemic stroke [1]



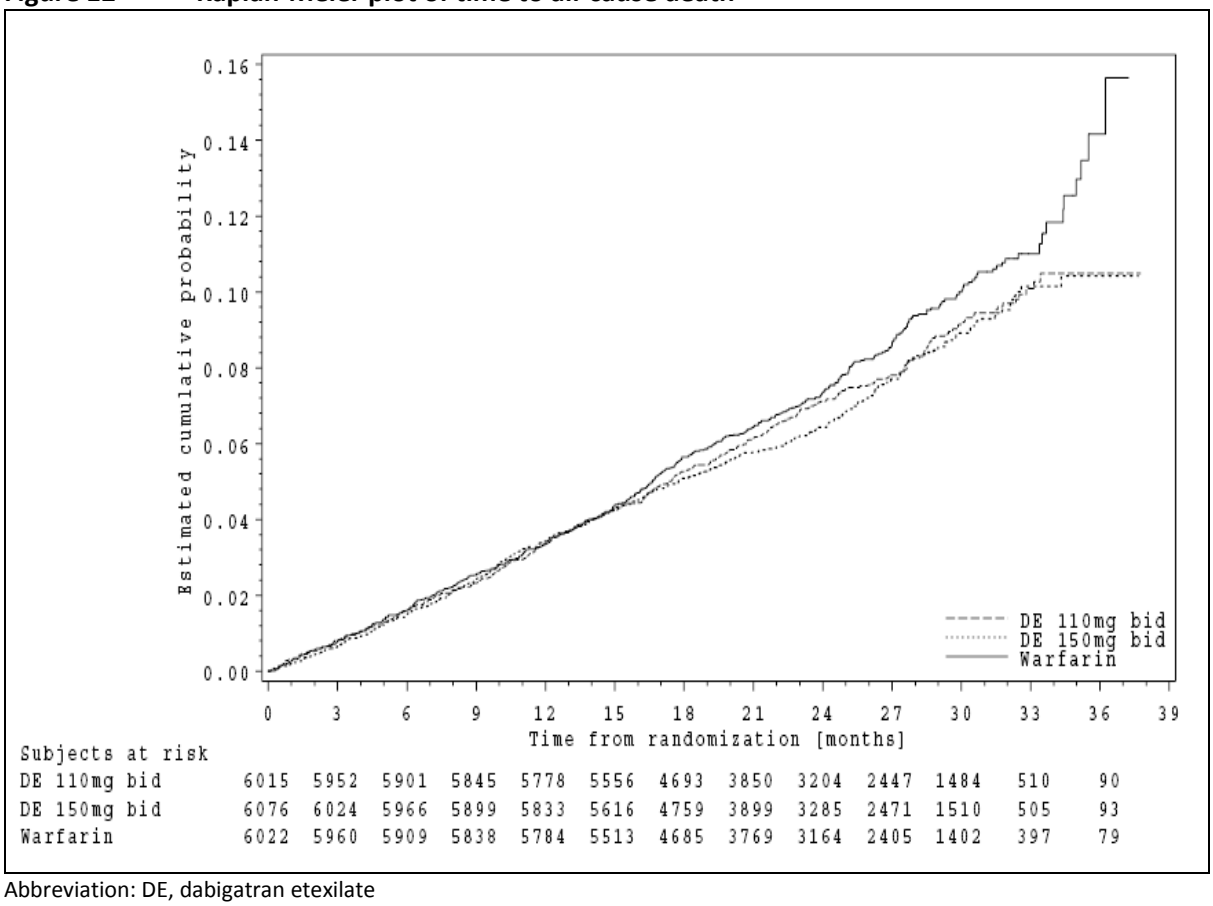
Abbreviation: DE, dabigatran etexilate

Figure 11 Kaplan-Meier plot of time to first haemorrhagic stroke [1]



Abbreviation: DE, dabigatran etexilate

Figure 12 Kaplan-Meier plot of time to all-cause death [1]



Abbreviation: DE, dabigatran etexilate

Table 32 and Table 33 presents the results of the subgroup analysis which stratified the results of the RE-LY trial by prior WFN experience level for the primary and secondary efficacy endpoints.

The DBG 150mg bid group demonstrated higher risk reduction than WFN for both VKA naïve and VKA experienced subjects in terms of the primary endpoint. There was no treatment by VKA use interaction (p-value =0.8691). For the secondary endpoint of stroke, SE and all-cause death DBG 150mg bid was superior to WFN for both VKA experienced and naïve subjects. DBG 110mg bid was non-inferior to WFN in reducing the occurrences of stroke or SE for both VKA-experienced and naïve subjects. No interaction was observed implying that the treatment effect of both doses is independent of VKA treatment history.

Results from other selected pre-defined subgroups for the primary endpoint are summarised in **Table 34**. These results show that the trends demonstrated in the overall results are generally maintained across the various subgroups.

In addition a further analysis of the RE-LY trial data, stratified by the age cut-off of 80 years was required for the purposes of the economic model. The reasons for this precise data cut will be outlined in the upcoming sections. **Table 35** and **Table 36** present these analyses.

Table 32 Efficacy results of the primary endpoint (stroke/SE) by VKA-experience subgroup from RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
VKA-naïve	89	1.57%	61	1.07%	97	1.69%	0.93 (0.70 – 1.24)	0.63* (0.46 – 0.87)
VKA-experienced	94	1.51%	73	1.15%	105	1.74%	0.87 (0.66 – 1.15)	0.63* (0.49 – 0.89)
p-value for interaction								0.8691

ITT analysis set (naïve): DBG 110mg bid - N = 3,005, subject-years = 5,659; DBG 150mg bid - N = 3,028, subject-years = 5,700; WFN - N = 3,093, subject-years = 5,744
ITT analysis set (experienced): DBG 110mg bid - N = 3,008, subject-years = 6,236; DBG 150mg bid - N = 3,047, subject-years = 6,331; WFN - N = 2,929, subject-years = 6,050
* Denotes statistically significant in favour of DBG
Source: [1]
Abbreviations: DBG, dabigatran etexilate; SE, systemic embolism; VKA, vitamin K antagonist; WFN, warfarin

Table 33 Efficacy results of the secondary endpoint (stroke/SE/all-cause death) by VKA-experience subgroup from RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
VKA-naïve	301	5.32%	266	4.67%	300	5.22%	1.02 (0.87 – 1.19)	0.89 (0.75 – 1.05)
VKA-experienced	276	4.43%	254	4.01%	313	5.17%	0.85 (0.73 – 1.00)	0.77* (0.69 – 0.91)
p-value for interaction								0.2696

ITT analysis set (naïve): DBG 110mg bid - N = 3,005, subject-years = 5,659; DBG 150mg bid - N = 3,028, subject-years = 5,700; WFN - N = 3,093, subject-years = 5,744
ITT analysis set (experienced): DBG 110mg bid - N = 3,008, subject-years = 6,236; DBG 150mg bid - N = 3,047, subject-years = 6,331; WFN - N = 2,929, subject-years = 6,050
* Denotes statistically significant in favour of DBG
Source: [1]
Abbreviations: DBG, dabigatran etexilate; SE, systemic embolism; VKA, vitamin K antagonist; WFN, warfarin

Table 34 Efficacy results of the primary endpoint for selected pre-defined subgroups

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Age < 65 years	29	1.47%	14	0.69%	25	1.35%	1.10 (0.64 – 1.87)	0.51* (0.26 – 0.98)
65 < Age < 75	67	1.26%	51	0.98%	76	1.45%	0.87 (0.62 – 1.20)	0.68* (0.47 – 0.96)
Age > 75	87	1.89%	69	1.43%	101	2.15%	0.88 (0.66 – 1.17)	0.67* (0.49 – 0.90)
Male	105	1.36%	84	1.10%	115	1.53%	0.89 (0.68 – 1.16)	0.71* (0.54 – 0.95)
Female	78	1.86%	50	1.14%	87	2.03%	0.92 (0.67 – 1.24)	0.56* (0.40 – 0.79)
BMI < 25	57	1.89%	40	1.33%	78	2.65%	0.71 (0.50 – 1.55)	0.50* (0.34 – 0.73)
25 < BMI < 30	72	1.54%	56	1.16%	69	1.49%	1.03 (0.74 – 1.44)	0.77 (0.54 – 1.10)
30 < BMI < 35	34	1.28%	27	0.99%	31	1.16%	1.10 (0.68 – 1.79)	0.85 (0.51 – 1.42)
BMI > 35	20	1.32%	11	0.76%	23	1.49%	0.88 (0.49 – 1.61)	0.51 (0.25 – 1.04)
Ethnicity class - white	114	1.35%	88	1.03%	114	1.36%	1.00 (0.77 – 1.29)	0.76 (0.51 – 1.00)
Ethnicity class – black	1	1.01%	1	0.83%	4	3.29%	0.30 (0.03 – 2.72)	0.25 (0.03 – 2.21)
Ethnicity class – Asian	44	1.36%	25	1.34%	52	2.91%	0.82 (0.55 – 1.23)	0.46* (0.28 – 0.74)
Ethnicity class – other	24	1.57%	20	1.32%	32	2.13%	0.74 (0.43 – 1.25)	0.62 (0.35 – 1.08)
Hispanic or Latino – No	173	1.55%	127	1.12%	189	1.70%	0.91 (0.74 – 1.12)	0.66 (0.53 – 0.82)
Hispanic or Latino – Yes	10	1.38%	7	0.97%	13	1.88%	0.73 (0.32 – 1.66)	0.52 (0.21 – 1.30)
CrCL (ml/min) < 30	0	0.00%	4	7.61%	2	3.75%	No RR possible	2.03 (0.37 – 11.08)
30 < CrCL (ml/min) < 50	51	2.40%	28	1.27%	53	2.69%	0.89 (0.61 – 1.31)	0.47* (0.30 – 0.74)
50 < CrCL (ml/min) < 80	91	1.69%	66	1.21%	102	1.87%	0.91 (0.68 – 1.20)	0.65* (0.47 – 0.88)

CrCL (ml/min) > 80	33	0.86%	28	0.73%	39	1.03%	0.83 (0.52 – 1.32)	0.71 (0.44 – 1.15)
Regions – USA, Canada	53	1.19%	50	1.11%	67	1.51%	0.79 (0.55 – 1.13)	0.73 (0.51 – 1.06)
Regions – Central Europe	18	1.31%	13	0.96%	13	0.96%	1.37 (0.67 – 2.80)	0.99 (0.46 – 2.14)
Regions – Western Europe	45	1.45%	35	1.11%	45	1.46%	1.00 (0.66 – 1.51)	0.76 (0.49 – 1.19)
Regions – Latin America	10	1.82%	5	0.91%	9	1.68%	1.09 (0.44 – 2.67)	0.54 (0.18 – 1.62)
Regions – Asia	44	2.50%	25	1.39%	53	3.06%	0.81 (0.54 – 1.21)	0.45* (0.28 – 0.72)
Regions – Other	13	1.95%	6	0.88%	15	2.27%	0.85 (0.41 – 1.79)	0.38* (0.15 – 0.99)

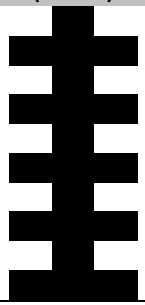
ITT analysis set: Please refer to the clinical trial report [1] for details of the subject-years for each subgroup
* Denotes statistically significant in favour of DBG
Source: [80]
Abbreviations: CI, confidence interval; CrCL, creatinine clearance; DBG, dabigatran etexilate; ITT, intention to treat; MI, myocardial infarction; RR, relative risk; SE, systemic embolism; TIA, transient ischaemic attack; WFN, warfarin

Table 35 Efficacy results for the less than 80 years of age subgroup

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Ischaemic stroke	[redacted]	[redacted]	83	0.83%	106	1.07%	[redacted]	0.77 (0.58 – 1.03)
Haemorrhagic stroke	[redacted]	[redacted]	7	0.07%	33	0.33%		0.21* (0.09 – 0.47)
SE	[redacted]	[redacted]	10	0.10%	15	0.15%		0.66 (0.30 – 1.47)
TIA	[redacted]	[redacted]	67	0.67%	72	0.73%		0.92 (0.66 – 1.29)
MI	[redacted]	[redacted]	74	0.74%	58	0.59%		1.26 (0.89 – 1.78)

ITT analysis set: DBG 110mg bid - N = 5,044, subject-years = 10,034; DBG 150mg bid - N = 5,019, subject-years = 10,014; WFN - N = 5,034, subject-years = 9,881
* Denotes statistically significant in favour of DBG
Source: [80]
Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; ITT, intention to treat; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack; WFN, warfarin

Table 36 Efficacy results for the greater than 80 years of age subgroup

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Ischaemic stroke	30	1.61%			37	1.93%	0.82 (0.51 – 1.33)	
Haemorrhagic stroke	3	0.20%			12	0.58%	0.26* (0.07 – 0.91)	
SE	3	0.20%			6	0.19%	0.51 (0.13 – 2.06)	
TIA	12	0.46%			27	1.03%	0.45* (0.23 – 0.89)	
MI	23	1.19%			17	0.90%	1.39 (0.74 – 2.60)	

ITT analysis set: DBG 110mg bid - N = 917, subject-years = 1,866; DBG 150mg bid - N = 1,057, subject-years = 2,019; WFN - N = 988, subject-years = 1,913

* Denotes statistically significant in favour of DBG

Source: [80]

Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; ITT, intention to treat; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack; WFN, warfarin

Efficacy Summary

Overall, the RE-LY trial not only achieved but surpassed the pre-specified non-inferiority objective for efficacy. Good statistical power was achievable with the original planned recruitment of 15,000 patients, however actual recruitment of over 18,000 subjects ensured even greater power. The demonstration of a dose-response for the primary endpoint, where DBG 110mg bid was shown to be less effective than DBG 150mg bid but non-inferior to WFN is further support of the findings.

The superiority of DBG 150mg bid over WFN was reflected in all components of the primary endpoint. For the composite primary endpoint itself, the relative risk reductions were 35% and 10% for the 150mg bid and 110mg bid respectively compared to WFN, with 150mg bid having a p-value of 0.0001 for superiority versus WFN.

For ischaemic stroke, the relative risk reduction for the 150mg bid dose was 25% compared to WFN and was significant (p=0.0296). Haemorrhagic stroke was significantly decreased by two-thirds compared to WFN for both doses (p-value <0.0001) and did not show dose-response. Given the usual trade-off between thromboembolic risk reduction and haemorrhagic risk increase, this is an extremely desirable and groundbreaking result.

Stroke severity is a key determinant of disability and sequelae. Strokes in subjects with AF tend to be more disabling than other strokes. In RE-LY, approximately 50% of the strokes were disabling based on evaluations 3-6 months after the events (a Rankin score of 3-6). Whether using the initial Rankin score or the Rankin score at 3-6 months, both doses of DBG and WFN have approximately the same incidences of disabling and non-disabling stroke. Therefore the effect of DBG is not restricted to milder strokes and it can be stated with confidence that the reduction in strokes with DBG versus WFN is clinically meaningful.

The treatment effects of DBG were further reflected in all specified secondary endpoints. The risk reductions on stroke/SE and death was 17% for DBG 150mg bid, which was statistically significant (p-value = 0.0015). Both doses also reduced the risk of all cause mortality, the risk reductions by DBG 110mg bid and DBG 150mg bid were 9% (p-value = 0.1308) and 12% (p-value = 0.0517), respectively. Most of this effect was due to vascular death. This is an important finding since WFN reduces mortality in AF subjects compared to placebo. An additional reduction in mortality over and above the effect of WFN is clinically important and further substantiates the clinical value of DBG.

When vascular death is incorporated into a composite outcome with other important clinical outcomes, namely PE, MI, stroke and SE, the benefits of DBG compared to WFN are maintained, with the high dose superior to WFN (p=0.0096).

Further the rate of hospitalisation was lower with DBG than WFN. DBG 110mg bid had significantly fewer hospitalisations than WFN (p-value =0.0209) and annualised rates for all hospitalisations in the DBG groups were relatively lower (39.5%, 41.6% and 42.6% for DBG 110mg bid, DBG 150mg bid and WFN, respectively).

The rate of symptomatic MI was not statistically significantly different across the three groups (yearly event rates of 0.73%, 0.74% and 0.56% for DBG 110mg bid, DBG 150mg bid and WFN, respectively). Rates of silent MI were similar between the treatment groups.

The imbalance observed in the number of MIs was in large part due to the incidence of MI reported after treatment discontinuation. The number of subjects with reported MI more than 6 days after stopping study drug was higher in the DBG treatment group when compared with WFN (17, 20, and 12 MIs for DBG 110mg bid, DBG 150mg bid, and WFN, respectively).

Overall, this study demonstrated that both doses of DBG were clearly non-inferior to WFN and that DBG 150mg bid was superior to WFN for the primary efficacy endpoint. In addition both doses of DBG significantly reduced the occurrence of haemorrhagic stroke compared to WFN which, when considered alongside the significant reduction in ischaemic stroke with DBG 150mg bid, represents an unprecedented result in this therapeutic area.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

It would not appropriate or meaningful to meta-analyse a very large phase-III trial such as RE-LY with two small and short phase-II trials such as PETRO and 1160.49 due to the differences in study duration and methodology.

PETRO and study 1160.49 were small (502 and 174 patients randomised respectively) safety/dose exploration studies with no primary efficacy endpoint and only a handful of thromboembolic events between them. Much of the safety data from PETRO relates to dosing regimens for DBG which were not pursued into phase-III. Both PETRO and study 1160.49 were only 12 weeks in duration. The value of the safety data from PETRO and 1160.49 in this context is merely descriptive and is outlined in Section 5.9.

In contrast, RE-LY is a large (over 18,000 patients randomised) multi-national phase-III pivotal trial, with median duration of two years. The differences in duration and study objective mean that a meta-analysis of the three trials would not be appropriate.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

To facilitate the comparison with aspirin monotherapy and aspirin plus clopidogrel (A+C), a mixed treatment comparison (MTC) incorporating a network meta-analysis was performed.

The MTC aimed to capture (systematic review) and synthesise (meta-analyse) all relevant information for treatments used in the prevention of stroke in patients with AF. It was ultimately

intended that the MTC would provide important treatment effect estimates for inclusion in the economic model presented in Section 6.

There are existing meta-analyses in this field [38, 81, 82]; this MTC built on these reviews and additionally included recently published trial data on DBG from RE-LY. A formal literature review was performed to capture important trials that may not have been included in previous reviews. MTC methodology has been used to robustly assess the relative efficacy and safety of the treatments of interest and to investigate whether some covariates affect the overall results.

The MTC was performed before the early cessation of the AVERROES study [83]. At the time of writing, data from this study are not yet published and therefore it is not possible to include the study in the MTC.

The primary objective of this research was to provide estimates of relative efficacy and safety of all the treatments of interest through indirect comparisons with all other comparators (RRs). The MTC was adjusted for some potentially important covariates where possible.

The secondary objectives included the following:

- Estimate risk for each treatment within each outcome: The economic model required estimates of the risk of events, to which the RRs could be applied. A robust estimate of treatment/outcome risk was obtained by pooling event rates from all relevant trials.
- Summarise INR control for adjusted-dose WFN: That is, for trials that studied adjusted-dose WFN, identify the target 'therapeutic' range (TTR), and determine the proportion of time that patients were recorded as within range (%TTR).
- Summarise treatment effect relative to placebo: A final objective—to summarise each treatment's effect relative to placebo for each outcome using number-needed-to-treat (NNT) methodology—was added during the analyses.

A systematic literature review was performed according to QUOROM (Quality of Reporting of Meta-analyses). Searches encompassed electronic medical databases and the Internet (specified sites):

- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews
    - The Cochrane Central Register of Controlled Trials
    - Database of Abstracts of Reviews of Effectiveness
- MEDLINE and MEDLINE In-Process (using PubMed platform)
- EMBASE (using Dialog Platform)
- BIOSIS (using Dialog Platform)

No restrictions were applied on publication dates and language. Search terms included combinations of free text and Medical Subject Headings (MeSH). Full listings of search terms are provided in Appendix 4. Three sets of terms were used:

- Health condition of interest (Disease): terms for AF
- Intervention(s): for example, aspirin, DBG, WFN
- Study type (s): for example, RCTs

Appropriate terms were combined and iterative searches were conducted using other relevant terms and concepts as needed.

Bibliographic reference lists of included articles, systematic reviews and meta-analyses were searched for further studies of interest. Studies identified from database searches, bibliographic references, and additional studies known to be of importance were considered part of the overall search results. Non–English-language literature that met the inclusion criteria were translated into English and further considered for inclusion.

The inclusion/exclusion criteria were based on a strategy to identify study types of interest within the population/disease condition of interest, and for the interventions of interest. Inclusion or exclusion of studies was performed by two researchers, and differences in recommended action (include or exclude) were resolved in discussion with a third researcher.

The initial objective of this systematic review was to identify treatments used in the prevention of stroke in NVAF and to compare these treatments across several important outcomes. However initial searches did not retrieve all known relevant trials due to inconsistencies in the medical definitions and indexing used in the trials for NVAF patients. Therefore, there was a deviation from the original protocol and the objective of this systematic review was changed to include all trials on AF patients, without the NVAF search restriction.

Inclusion and exclusion criteria for the review are listed in **Table 37** and **Table 38**.

Table 37 Inclusion criteria

Category	Criteria	Rationale
Study design	RCTs	RCTs are considered the gold standard of clinical evidence.
Population	Adult patients with AF being treated for the prevention of stroke	Although AF affects both children and adults, DBG will not be used in people under the age of 18. Therefore only patients aged 18 years or above are relevant to the review.
Intervention	At least one of: 1. Placebo 2. Adjusted-dose warfarin 3. Fixed low-dose warfarin 4. Fixed low-dose warfarin + aspirin 5. Aspirin monotherapy 6. Aspirin + clopidogrel 7. Ximelagatran 8. Other vitamin K antagonists (i.e., dicoumarol, phenindione, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione, or tioclomarol; all to be rolled into the adjusted-dose warfarin group or excluded in the analyses) 9. Dabigatran etexilate a. 150mg bid b. 110mg bid a. Sequence	This list covers all licensed and unlicensed pharmacological treatments that may be used for the indication under consideration. Further, the review includes the comparators relevant to the decision problem (warfarin and antiplatelet agents). Ximelagatran, an oral direct thrombin inhibitor, was withdrawn in February 2006 due to concerns over hepatic safety. Ximelagatran was included in the MTC only to maximise the known available data for adjusted-dose warfarin (i.e., the comparator in SPORTIF III and V) [84, 85]. Three doses are used in the MTC for DBG: the 150mg bid and 110mg bid reflect the patient groups in the RE-LY trial; Sequence reflects the posology in the licensed indication and is derived for use in the economic evaluation in Section 6
Language restrictions	None.	

Abbreviation: DBG, dabigatran etexilate; MTC, mixed treatment comparison; RCT, randomised controlled trial

Table 38 Exclusion criteria

Study design	• Phase I studies • Non-randomised studies • Open-label follow-up studies • Reviews, letters, and comment articles
Population	Trials that included only patients with atrial flutter
Intervention	Studies not investigating at least one of the listed treatments

Systematic reviews and meta-analyses of clinical trials were identified during the searches in order that their reference lists can be checked for additional trials.

The inclusion and exclusion criteria were based on a strategy to identify study types of interest within the population/disease condition of interest, and for the interventions of interest. Inclusion or exclusion of studies was performed by two researchers, and differences in recommended action (include or exclude) were resolved in discussion with a third researcher.

Included Outcomes

The following outcomes were meta-analysed, those marked with an asterisk were required for the economic model:

1. All stroke (ischaemic or haemorrhagic)
2. Ischaemic stroke*
3. Haemorrhagic stroke*

4. Fatal or disabling stroke
5. Systemic embolism*
6. Pulmonary embolism[1]
7. All cause mortality
8. Transient ischaemic attack*
9. Intracranial haemorrhage*
10. Extracranial haemorrhage*
11. Minor bleeds*
12. Acute myocardial infarction*
13. Cardiovascular mortality
14. Any bleeds (major or minor)

Only trials that clearly reported the outcomes were to be included in each outcome's meta-analysis. Where outcome definition was unclear or not reported the use of proxy outcomes data (e.g., subdural haematoma instead of intracranial haemorrhage) was considered and noted.

The database searches yielded a total of 1,486 titles (**Table 39**). Of these, 357 records were duplicates; hence, 1,129 titles were eligible for further screening (Level 1).

Table 39 Final numbers retrieved from searches

Source	Number of citations
Cochrane	228
Embase	818
Medline/Medline In-Process	342
BIOSIS	98
Total	1,486

After level 1 screening, a total of 55 studies were identified to receive full-text screening (clinical studies = 53, hand search = 2). Ten reviews were searched for any additional trials, and one additional study was identified. Finally, one further study was added that was published after the literature searches were complete (RE-LY, published on 30 August 2009). The main reasons for exclusion were irrelevant study type, intervention, and population (**Figure 13**).

After level 2 screening of 57 full-text articles (**Table 40**), data was extracted from 26 full-text articles. Data extraction was performed by two separate researchers, and inconsistencies were resolved by a third researcher. The references for these studies and reasons for exclusion where appropriate are given in Appendix 4. The actual extracted data used in the analyses is also presented in Appendix 4.

[1] Pulmonary embolism was reported in only one trial and subsequently was not analysed within these meta-analyses.

Table 40 Search results

Stage of Review	Number of Articles
Number of articles identified from searches	1,129
Number potentially of interest after title and abstract review	55
Number potentially of interest after adding references identified from review articles	56
Number potentially of interest after adding RE-LY publication	57
Excluded due to not having 2 treatments of interest	4
Excluded due to having inappropriate trial design	6
Excluded due to having no outcome data	5
Excluded due to trial being a short-term phase 2 trial	3
Excluded due to being a discussion/commentary paper	6
Excluded due to being a duplicate	3
Excluded due to being a trial design article	2
Excluded due to being a subgroup or pooled analysis	2
Final number of articles from which data were extracted	26

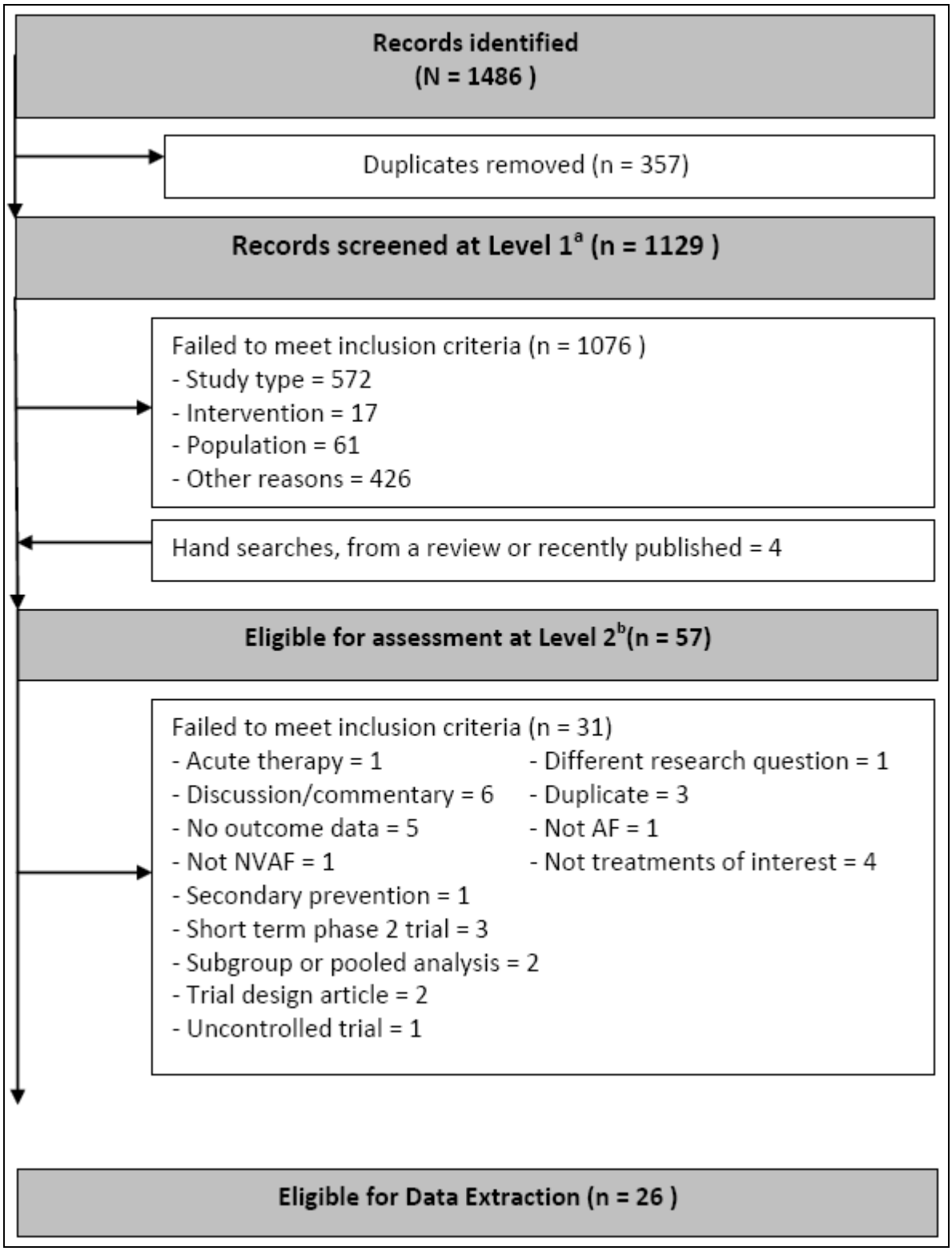
Of the 26 articles from which data was extracted, three articles [86-88] were excluded from the meta-analyses because they scored two or less on the Jadad quality scale. In addition, two trials each were reported over two articles, yielding a total of 21 trials for inclusion in the meta-analyses. Finally, one further trial [39] included only patients who were ineligible for anticoagulation; therefore, this trial was excluded from the primary meta-analyses but was reintroduced in a sensitivity analysis.

During full-text review of the retrieved articles, the scope of included treatments and outcomes was expanded to allow for additional important data for the meta-analyses. The following additional treatments were identified during the full-text review:

- Idraparinux, a synthetic pentasaccharide administered via once-weekly subcutaneous injection. This compound is not licensed for this indication in the UK and its phase-III trial was halted early due to excess bleeding rates[89].
- Indobufen, an oral platelet aggregation inhibitor, not licensed for this indication in the UK.
- Triflusal, an oral platelet aggregation inhibitor, not licensed for this indication in the UK.

To construct the MTC, trials were selected that enabled connected networks of treatments. A trial must have had at least 2 of the 12 included treatments to be included in the meta-analyses.

Figure 13 QUORUM Flow diagram



Abbreviation: NVAF, non-valvular atrial fibrillation

Key: a. Level 1 screening = Title and abstract screening; b. Level 2 screening = Full-text screening.

For each outcome, all pair-wise comparisons were estimated in the analyses. The distribution of the number of trials included in at least one of the outcomes' meta-analysis, by treatment, is shown in **Table 41**.

Table 41 Number of trials included in the meta-analyses

Meta-analyses criteria	Number of Trials
Number of articles from which data was extracted	26
Number of unique trials across the articles	24
Number of trials excluded due to Jadad score of 2 or less	3
Number of trials excluded due to including only patients ineligible for anticoagulation	1
Final number of trials for inclusion in the primary meta-analyses	20
By treatment:	
Aspirin + clopidogrel	1
Aspirin monotherapy	6
Dabigatran etexilate 110mg bid	1
Dabigatran etexilate 150mg bid	1
Adjusted-dose VKA	20
Fixed low-dose warfarin	2
Fixed low-dose warfarin + aspirin	2
Idraparinux	1
Indobufen	1
Placebo	6
Triflusal	1
Ximelagatran	2

Abbreviation: VKA = vitamin K antagonist

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

The list of included studies along with baseline characteristics of participants is presented in **Table 42**. The network of evidence is illustrated in **Figure 14**. The number of trials included in the meta-analyses of each outcome, stratified by treatment, is presented in **Table 43**.

Table 42 Included trials with baseline characteristics

Trial	Primary Author (Year)	Trial Name (if Available)	Treatment	Dose	% of Time in INR	Jadad Total Score	Mean Length of Follow-up (Months)	Number Randomised	Mean Age (years)	% Male	Primary Reference
1	Albers (2005)	SPORTIF V	Dose-adjusted VKA	INR: 2.0 - 3.0	0.680	5	20	1962	71.6	69.0	84
			Ximelagatran	36mg BID	n/a	5	20	1960	71.6	69.6	
2	Bousser (2008)	AMADEUS	Dose-adjusted VKA (warfarin or acenocoumarol)	INR: 2.0 - 3.0	0.630	3	11.1	2293	70.2	65.5	89
			Idraparinux	1.5-2.5mg/week	n/a	3	10.2	2283	70.1	67.5	
3	Connolly (1991)	CAFA	Dose-adjusted VKA	INR: 2.0 - 3.0	0.437	5	15.2	187	68	75.9	90
			Placebo	n/a	n/a	5	15.2	191	67.4	73.3	
4	Connolly (2006)	ACTIVE W	Aspirin + clopidogrel	75-100mg/day + 75mg/day	n/a	3	15.36	3335	70.2	66.5	91
			Dose-adjusted VKA (country specific VKA)	INR: 2.0 - 3.0	0.638	3	15.36	3371	70.2	65.6	
5	Connolly (2009a) (Included only for sensitivity analysis)	ACTIVE A	Aspirin + clopidogrel	75-100mg/day + 75mg/day	n/a	5	43.2	3772	70.9	58.6	39
			Aspirin monotherapy	n/a	n/a	5	43.2	3782	71.1	57.8	
6	Connolly (2009b)	RE-LY	Dabigatran 110mg bid	110mg BID	n/a	3	24	6015	71.4	64.3	43
			Dabigatran 150mg bid	150mg BID	n/a	3	24	6076	71.5	63.2	
			Dose-adjusted VKA	INR: 2.0 - 3.0	0.640	3	24	6022	71.6	63.3	
7	Ezekowitz (1992)	n/a	Dose-adjusted VKA	INR: 1.4 - 2.8	0.560	5	21.6	260	67	100.0	92
			Placebo	n/a	n/a	5	20.4	265	67	100.0	
8	Gullov (1998)	AFASAK 2	Aspirin monotherapy	300mg/day	n/a	3	42	169	73.1	65.1	93
			Dose-adjusted VKA	INR: 2.0 - 3.0	0.730	3	42	170	73.2	57.1	
			Fixed low dose warfarin	1.25mg/day	n/a	3	42	167	74.2	59.3	
			Fixed low dose warfarin + aspirin	1.25mg/day	n/a	3	42	171	72.7	59.1	
9	Hellemons (1999)	n/a	Aspirin monotherapy	150mg/day	n/a	3	33.4	141	70.8	47.5	94
			Dose-adjusted VKA (phenprocoumon)	INR: 2.5 - 3.5	0.480	3	36.7	131	70	44.3	
10	Kistler (1990)	BAATAF	Dose-adjusted VKA	INR: 1.5 - 2.7	0.830	3	26.4	212	68.5	74.5	95

Trial	Primary Author (Year)	Trial Name (if Available)	Treatment	Dose	% of Time in INR	Jadad Total Score	Mean Length of Follow-up (Months)	Number Randomised	Mean Age (years)	% Male	Primary Reference
			Placebo	optional aspirin	n/a	3	26.4	208	67.5	70.2	
11	Koudstaal (1993)	EAFT	Dose-adjusted VKA	INR: 2.5 - 4.0	nr	5	27.6	225	71	55.1	96
			Placebo	n/a	n/a	5	27.6	214	70	57.9	
			Aspirin monotherapy	75mg/day	n/a	3	32.4	485	81.5	54.4	
12	Mant (2007)	BAFTA	Dose-adjusted VKA	INR: 2.0 - 3.0	0.670	3	32.4	488	81.5	54.7	97
			Dose-adjusted VKA	INR: 2.0 - 4.5	0.710	3	15.6	210	65	73.8	
13	Mcbride (1991)	SPAF	Placebo	n/a	n/a	3	15.6	211	66	70.1	98
			Aspirin monotherapy	325mg/day	n/a	3	27.6	545	70	70.1	
14	Mcbride (1994)	SPAF II	Dose-adjusted VKA	INR: 2.0 - 4.5	0.860	3	27.6	555	70	70.1	99
			Dose-adjusted VKA	INR: 2.0 - 3.0	0.610	3	13.2	523	71	59.1	
15	Mcbride (1996)	SPAF III	Fixed low dose warfarin + aspirin	0.5-3.0mg/day	n/a	3	13.2	521	72	62.0	100
			Dose-adjusted VKA	INR: 2.0 - 3.5	0.835	3	12	454	72.2	48.5	
16	Morocutti (1997)	SIFA	Indobufen	400mg/day	n/a	3	12	462	72.8	45.5	101
			Dose-adjusted VKA	INR: 2.0 - 3.0	0.660	3	17.4	1703	70.1	70.2	
17	Olsson (2003)	SPORTIF III	Ximelagatran	36mg BID	n/a	3	17.4	1704	70.3	68.0	85
			Dose-adjusted VKA	INR: 2.0 - 3.0	0.700	3	14.3	153	73.6	49.0	
18	Pengo (1998)	n/a	Fixed low dose warfarin	1.25mg/day	n/a	3	14.6	150	74.7	41.3	102
19	Pérez-Gómez (2004)	NASPEAF	Dose-adjusted VKA (acenocumarol)	INR: 2.0 - 3.0	0.650	3	28.8	237	69.6	54.4	103
			Triflusal	600mg/day	n/a	3	29.4	242	69.9	57.0	
			Aspirin monotherapy	75mg/day	n/a	5	24	336	nr	54.8	
20	Petersen (1989)	AFASAK	Dose-adjusted VKA	INR: 2.8 - 4.2	0.420	5	24	335	nr	52.5	104
			Placebo	n/a	n/a	5	24	336	nr	53.6	
			Aspirin monotherapy	300mg/day	n/a	3	12	39	82.6	53.8	
21	Rash (2007)	WASPO	Dose-adjusted VKA	INR: 2.0 - 3.0	0.692	3	12	36	83.5	38.9	105

Abbreviations: BID, twice daily dosing; INR, International Normalised Ratio; VKA, vitamin-K antagonist

Two trial-specific data issues required extra consideration in terms of their inclusion or exclusion in the analyses:

Trial 9: Hellemons (1999) [94]

This trial included two separate arms of dose adjusted VKA: one whose target INR was 1.1 to 1.6 and the other whose target INR was 2.5 to 3.5. It would not be valid to pool these arms, and including two separate adjusted-dose VKA arms would cause logistical problems for the meta-analyses. Therefore, we excluded the arm with target INR of 1.1 to 1.6 and agreed to include only the adjusted-dose VKA arm whose target INR overlapped the standard range of 2.0 to 3.0.

Trial 10: BAATAF (1990) [95]

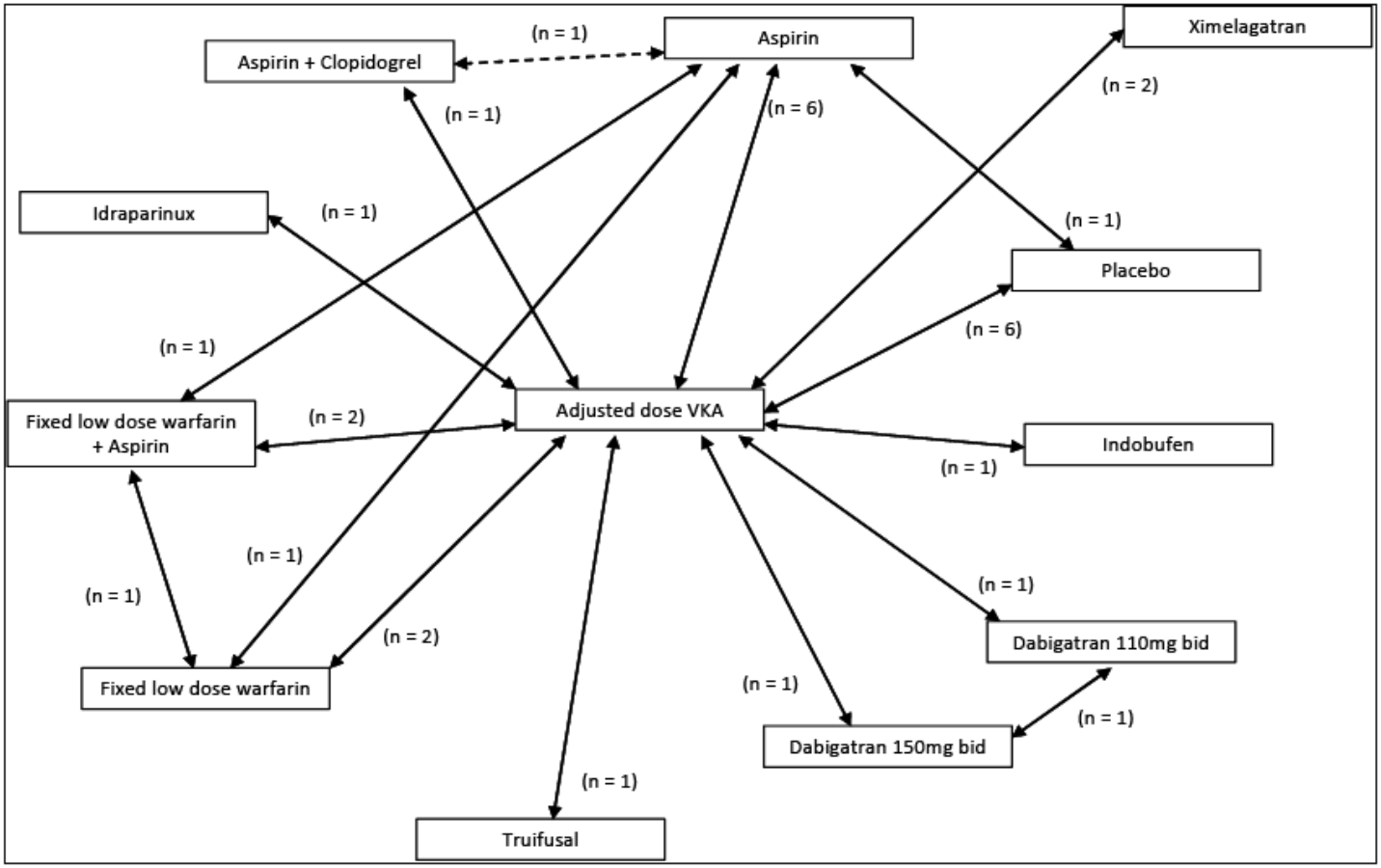
This trial included an adjusted-dose VKA group and a control group; the control group was 'allowed' to take aspirin. In the control group, 46% of all control person time was contributed by regular aspirin takers in this trial. It was agreed that the control group should be entered as placebo because other placebo groups may also be allowed to take aspirin as needed (although this may not be explicitly stated in the articles).

Table 43 Number of trials included in the meta-analysis of each outcome, by treatment

Outcome	Aspirin + Clop	Aspirin Mono-therapy	DBG 110mg bid	DBG 150mg bid	Adjusted -Dose VKA	Fixed Low-Dose Warfarin	Fixed Low-Dose Warfarin + Aspirin	Idraparinux	Indobufen	Placebo	Triflusal	Ximelagatran
At least one outcome	1	6	1	1	20	2	2	1	1	6	1	2
All stroke	1	4	1	1	11	1	1	1	1	2	1	1
Ischaemic stroke	1	3	1	1	16	2	2	1	1	5		2
Haemorrhagic stroke	1		1	1	6			1	1			2
Fatal or disabling stroke	1	5	1	1	14	1	2		1	4		2
Systemic embolism	1	5	1	1	15	2	2			4	1	2
Mortality	1	5	1	1	17	1	2	1	1	4	1	2
Transient ischemic attack		5	1	1	13	1	2			4	1	2
Intracranial haemorrhage	1	4	1	1	11	2	2	1			1	1
Extracranial haemorrhage	1	2	1	1	9	1	2	1		1		2
Minor bleeds	1	2	1	1	12	1	1	1	1	4	1	1
Acute MI	1	4	1	1	16	2	2	1	1	3	1	2
CV mortality	1	5	1	1	16	2	2	1	1	5	1	
Any bleeds	1	5	1	1	16	2	2	1		4	1	2

Abbreviations: BID, twice daily dosing; CV = cardiovascular; DBG, dabigatran etexilate; MI = myocardial infarction; VKA = vitamin K antagonist.

Figure 14 Network diagram



Notes:

1) The dotted line between Aspirin + Clopidogrel and Aspirin indicates that this link is only included as a sensitivity analysis.

2) This network diagram shows the number of trials that include direct comparisons between treatments for at least one endpoint. The network diagram for each individual analysis endpoint would be smaller than that shown as not all trials presented data on all analysis endpoints.

Abbreviations: bid, twice daily dosing; VKA = vitamin K antagonist.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

Due to the volume of data created by 20 selected trials, 15 endpoints and 12 treatments, a summary of the data involved in this MTC is presented in **Table 44** and **Table 45** only for the treatments of relevance to this submission. This table presents the pooled risks for each treatment stratified by outcome, which provides the background data for the calculation of RRs. The full set of extracted data used in the analyses is presented in Appendix 4.

Table 44 Individual pooled risks by outcome (part 1)

Outcome	DBG 110mg bid			DBG 150mg bid			DBG sequence*			Adjusted dose VKA		
	Cases	At risk	Pooled risk (95% CI)	Cases	At risk	Pooled risk (95% CI)	Cases	At risk	Pooled risk (95% CI)	Cases	At risk	Pooled risk (95% CI)
All stroke	171	6,015	0.028 (0.024,0.033)	122	6,076	0.020 (0.017,0.024)	121	5,990	0.020 (0.017,0.024)	421	15,238	0.028 (0.020,0.035)
Ischaemic stroke	159	6,015	0.026 (0.022,0.030)	111	6,076	0.018 (0.015,0.022)	113	5,990	0.019 (0.015,0.022)	372	18,245	0.020 (0.015,0.026)
Haemorrhagic stroke	14	6,015	0.002 (0.001,0.004)	12	6,076	0.002 (0.001,0.003)	10	5,990	0.002 (0.001,0.003)	70	15,619	0.004 (0.001,0.008)
Fatal or disabling stroke	103	6,015	0.017 (0.014,0.020)	76	6,076	0.013 (0.010,0.015)	75	5,990	0.013 (0.010,0.015)	278	16,411	0.017 (0.012,0.022)
Systemic embolism	15	6,015	0.002 (0.001,0.004)	13	6,076	0.002 (0.001,0.003)	13	5,990	0.002 (0.001,0.003)	37	16,267	0.002 (0.001,0.003)
Mortality	446	6,015	0.074 (0.068,0.081)	438	6,076	0.072 (0.066,0.079)	429	5,990	0.072 (0.065,0.078)	1,267	18,685	0.068 (0.050,0.085)
TIA	74	6,015	0.012 (0.010,0.015)	87	6,076	0.014 (0.011,0.017)	79	5,990	0.013 (0.010,0.016)	188	12,683	0.015 (0.012,0.017)
ICH	16	6,015	0.003 (0.001,0.004)	26	6,076	0.004 (0.003,0.006)	21	5,990	0.004 (0.002,0.005)	112	15,725	0.007 (0.005,0.009)
ECH	317	6,015	0.053 (0.047,0.058)	364	6,076	0.060 (0.054,0.066)	345	5,990	0.058 (0.052,0.063)	619	16,607	0.037 (0.021,0.053)
Minor bleeding	1,566	6,015	0.260 (0.249,0.271)	1,787	6,076	0.294 (0.283,0.306)	1,698	5,990	0.283 (0.272,0.295)	3,733	15,135	0.247 (0.146,0.347)
AMI	98	6,015	0.016 (0.013,0.019)	97	6,076	0.016 (0.013,0.019)	97	5,990	0.016 (0.013,0.019)	209	18,566	0.011 (0.008,0.014)
Vascular mortality	289	6,015	0.048 (0.043,0.053)	274	6,076	0.045 (0.040,0.050)	260	5,990	0.043 (0.038,0.049)	665	15,447	0.043 (0.030,0.056)
Any bleeding	1,754	6,015	0.292 (0.280,0.303)	1,993	6,076	0.328 (0.316,0.340)	1,902	5,990	0.318 (0.306,0.329)	4,647	18,191	0.255 (0.156,0.355)

Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; TIA, transient ischaemic attack; VKA, vitamin K antagonist

*DBG sequence refers to a weighted-average post-hoc subgroup analysis of the RE-LY data including patients less than 80 years on 150mg bid and patients older than 80 on 110mg bid. This reflects the posology in the licensed indication and is constructed for the purposes of the economic evaluation in Section 6.

Table 45 Individual pooled risks by outcome (part 2)

Outcome	Aspirin monotherapy			Aspirin plus clopidogrel			Placebo/no treatment		
	Cases	At risk	Pooled risk (95% CI)	Cases	At risk	Pooled risk (95% CI)	Cases	At risk	Pooled risk (95% CI)
All stroke	89	1,131	0.079 (0.025,0.132)	100	3,335	0.030 (0.024,0.036)	66	550	0.120 (0.000,0.293)
Ischaemic stroke	46	855	0.054 (0.027,0.080)	90	3,335	0.027 (0.021,0.032)	97	1,089	0.089 (0.043,0.135)
Haemorrhagic stroke	No data			5	3,335	0.001 (0.000,0.003)	No data		
Fatal or disabling stroke	96	1,676	0.057 (0.029,0.086)	58	3,335	0.017 (0.013,0.022)	39	1,023	0.038 (0.009,0.067)
Systemic embolism	9	1,676	0.005 (0.003,0.008)	18	3,335	0.005 (0.003,0.008)	9	952	0.009 (0.003,0.015)
Mortality	206	1,379	0.149 (0.084,0.215)	159	3,335	0.048 (0.040,0.055)	100	898	0.111 (0.044,0.179)
TIA	29	1,574	0.018 (0.009,0.028)	No data			15	1,003	0.015 (0.008,0.022)
ICH	8	1,340	0.006 (0.002,0.010)	11	3,335	0.003 (0.001,0.005)	No data		
ECH	25	654	0.038 (0.029,0.047)	101	3,335	0.030 (0.024,0.036)	4	265	0.015 (0.000,0.030)
Minor bleeding	30	208	0.144 (0.114,0.175)	568	3,335	0.170 (0.158,0.183)	96	878	0.109 (0.054,0.164)
AMI	41	1,340	0.031 (0.026,0.036)	36	3,335	0.011 (0.007,0.014)	11	690	0.016 (0.009,0.023)
Vascular mortality	95	1,676	0.057 (0.039,0.075)	120	3,335	0.036 (0.030,0.042)	43	1,217	0.035 (0.024,0.047)
Any bleeding	91	1,574	0.058 (0.019,0.097)	644	3,335	0.193 (0.180,0.207)	55	969	0.057 (0.025,0.089)

Abbreviations: AMI, acute myocardial infarction; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; TIA, transient ischaemic attack

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

All analyses were performed using PROC GLIMMIX in SAS (version 9.2). PROC GLIMMIX is a new procedure within SAS that is suitable for NMA and offers an alternative to the traditional WinBUGs software approach.

Model Assumptions

1. The number of patients with presence of the outcome follows a binomial distribution.
2. Response variables are independent between clinical trials.
3. Response variables of patients within a given trial are correlated.
4. The correlation between any two patients from two different treatment arms within a study is lower than the correlation between any two patients from the same treatment arm.

Model Specification

Based on the above assumptions, the following mixed log-binomial model was used:

$$\log(\pi_{ij}) = \alpha_i + \beta X_{ij} + \varepsilon_i \qquad (1)$$

and

$$Y_{ij} \sim \text{Binomial}(n_{ij}, \pi_{ij}) \qquad (2)$$

where

- *i* indexes the clinical trial and j indexes treatment arm
- Y_{ij} is the response variable representing the number of patients with a positive response (presence of outcome event)
- n_{ij} is the number of patients
- π_{ij} is the underlying probability of achieving the positive response in the *i*th clinical trial and *j*th treatment arm
- α_i's are regression coefficients representing the fixed effect of each treatment
- βX_{ij} is a vector of fixed effects that correspond to the included covariates
- ε_i is a trial-specific random effect following a normal distribution with mean 0 and another unknown variance

With a large amount of data for analyses, an additional 'trial by treatment' random effect would be included. However in these analyses, there was not sufficient data to support the addition of this term.

The overall logarithm of the probability of event under treatment A (π_A) is the mean logarithm of the probability of event under treatment A across the trials (i.e., $\log(\pi_A) = \alpha_A + \beta X_{ij}$). Therefore, the

overall relative risk (RR) of treatment A versus treatment B based on overall probability of event was defined by the following equation:

$$\pi_A / \pi_B = \exp(\alpha_A - \alpha_B) \quad (3)$$

PROC GLIMMIX was used to fit the models. For these analyses, we fitted a separate model for each of the outcomes. The programming language used is presented below:

```
proc glimmix data=outcome_data itdetails;
  class treatment study;
  model events/patients = treatment covar / noint link=log solution;
  random intercept / subject=study solution;
  estimate "trt-a vs trt-b" trt 1 -1 0 0 … / exp cl;
run;
```

Covariates

The following covariates were considered for inclusion in each outcome meta-analysis:

- Mean length of follow-up (months)
- Mean age (years)
- Proportion male (range, 0 to 1)
- Mean baseline $CHADS_2$ score (range, 0 to 6); or possibly only a history of stroke or TIA
- Race proportions (range, 0 to 1)—categories to be determined after data collection
- Proportion of patients with prior use of oral anticoagulants (range, 0 to 1)

These covariates were to be included depending on their consistency, quality, and quantity of recording across the trials.

$CHADS_2$, race, and prior use of anticoagulants were not recorded with enough regularity to merit their inclusion in the model. The covariates mean length of follow-up, mean age, and gender were all individually explored for their importance in the meta-analyses for ischaemic stroke, mortality, intracranial haemorrhage, and acute myocardial infarction. Both length of follow-up and age were subsequently deemed appropriate for inclusion in the MTCs as covariates. However, on the initial execution of the primary meta-analyses, it was apparent that the MTCs adversely suffered in their stability due to the inclusion of two covariates. Consequently the project team agreed to include the only covariate deemed important by team consensus. Therefore all MTC models were run using just mean length of follow-up as a covariate.

Individual Treatment Risks

Treatment risks were captured for each outcome for each included trial. Descriptive summaries were produced of these trial level risks for a given treatment/outcome across all trials. The minimum, median, maximum, and the 2.5 and 97.5 percentiles of observed risk for each treatment/outcome were produced. In addition, pooled estimates for the absolute risk of each treatment outcome by summing all numerators and all denominators in the risk estimates were generated. The variance, and therefore 95% confidence interval (CI), was also calculated for these pooled estimates, using cluster sampling methods. The cluster sampling variance is given by the following:

CSvar = ((nT / (nT-1)) * (SN2 + (PR*PR*SD2) - 2*(PR*SND))) / (SD*SD)

where

- CSvar is the cluster sampling variance
- nT is the number of pooled trials
- SN2 is the sum of the squared numerators
- SD2 is the sum of the squared denominators
- PR is the pooled risk
- SD is the sum of the denominators
- SND is the sum of the products of the numerators and denominators

Relative Risks

In order to estimate the RRs from the MTC, the posterior distribution was outputted for all the relevant parameters. The posterior distribution outputs 20,000 log risk (of the outcome) estimates for each treatment separately. For each pairwise comparison, 20,000 RRs were estimated as the exponential of the difference between the two log risks. The median of these 20,000 values was then taken to be the point estimate of the RR, and the 95% CI was estimated by using the 2.5 and 97.5 percentile estimates.

Number Needed to Treat (NNT)

As with the RRs, in order to estimate the NNT from the MTC the posterior distribution for all the relevant parameters was outputted. The posterior distribution outputs 20,000 log risk (of the outcome) estimates for each treatment separately. For each pairwise comparison, 20,000 risk differences were estimated as the difference between the two exponentiated log risks. The inverse of the risk difference was then used for each of the median, 2.5 and 97.5 percentiles in order to obtain the NNT point estimate and 95% CI.

Sensitivity Analyses

Three sensitivity analyses were performed to explore the dependency of the analyses results based on data assumptions:

- Adjusted-dose VKA target INR
- ACTIVE A trial
- Relevant treatment options (RTO)

In the primary analyses, all trials were included that contained adjusted-dose VKA regardless of what the target INR was in those trials. The sensitivity analyses investigated whether including only trials with the recommended therapeutic target INR of 2.0 to 3.0 had any impact on the results.

Also, in the primary analyses trials that only recruited patients who were ineligible for anticoagulation were excluded. One important trial (ACTIVE A), a large trial (over 7,000 patients) studying aspirin plus clopidogrel versus aspirin monotherapy, was excluded for this reason. This sensitivity analysis investigated whether including the ACTIVE A trial had any impact on the results.

Finally, data from large, historically important trials that studied treatments that are not relevant treatment options (RTO) according to current treatment guidelines were included in the primary analysis. As a result, in this RTO sensitivity analysis, the primary analyses were repeated to include only trials that contained at least two of the following treatments: DBG, adjusted-dose VKA, aspirin plus clopidogrel, aspirin monotherapy and placebo.

5.7.6 Please present the results of the analysis.

Due to the vast number of possible pair-wise comparisons, the tables below concentrate on the outcomes and principle treatments of interest. The full set of data tables is presented in Appendix 4.

Table 46 to **Table 48** presents the pair-wise comparisons, by outcome, for each comparator versus DBG 110mg, DBG 150mg and the DBG sequence respectively.

The DBG sequence refers to an analysis utilising the post-hoc analysis of the RE-LY trial introduced in Section 5.5 and presented in **Table 35**, **Table 36, Table 63** and **Table 64**. This analysis is required for the alternative scenario in the economic evaluation and will be explained in full in Section 6.

Table 46 Results of the MTC for DBG 110mg bid

Outcome	RR versus adjusted dose VKA (95% CI)	RR versus aspirin monotherapy (95% CI)	RR versus aspirin plus clopidogrel (95% CI)	RR versus placebo (95% CI)
All stroke	0.92 (0.66 – 1.28)	0.52* (0.28 – 0.96)	0.55 (0.30 – 1.00)	0.35* (0.17 – 0.71)
Ischaemic stroke	1.12 (0.86 – 1.45)	0.69 (0.40 – 1.20)	0.54* (0.33 – 0.87)	0.33* (0.21 – 0.54)
Haemorrhagic stroke	0.32 (0.01 – 15.46)	No data	Unreliable estimates	No data
Fatal or disabling stroke	0.92 (0.68 – 1.26)	0.57* (0.36 – 0.91)	0.63 (0.36 – 1.11)	0.38* (0.20 – 0.72)
Systemic embolism	0.86 (0.41 – 1.79)	0.48 (0.15 – 1.52)	0.24* (0.08 – 0.70)	0.19* (0.06 – 0.57)
Mortality	0.92 (0.79 – 1.06)	0.85 (0.66– 1.10)	0.91 (0.68 – 1.21)	0.66* (0.47 – 0.93)
TIA	0.76 (0.54– 1.08	0.49* (0.25 – 0.97)	No data	0.62 (0.28 – 1.39)
ICH	0.33* (0.15 – 0.72)	0.65 (0.16 – 2.60)	0.62 (0.17 – 2.23)	No data
ECH	0.96 (0.75 – 1.22)	0.84 (0.34 – 2.09)	0.87 (0.52 – 1.44)	1.58 (0.25 – 10.02)
Minor bleeding	0.81* (0.74 – 0.89)	1.30 (0.66 – 2.54)	0.68* (0.56 – 0.83)	1.47^ (1.01 – 2.16)
AMI	1.31 (0.92 – 1.86)	0.93 (0.50 – 1.72)	0.89 (0.45 – 1.73)	0.84 (0.33 – 2.09)
Vascular mortality	0.92 (0.77 – 1.09)	0.90 (0.63 – 1.29)	0.81 (0.57 – 1.14)	1.13 (0.72 – 1.80)
Any bleeding	0.81 (0.76 – 0.86)	1.10 (0.82 – 1.48)	0.69* (0.60 – 0.79)	1.63^ (1.14 – 2.31)

*Denotes statistically significant in favour of DBG

^Denotes statistically significant in favour of comparator

Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; TIA, transient ischaemic attack; VKA, vitamin K antagonist

Table 47 Results of the MTC for DBG 150mg bid

Outcome	RR versus adjusted dose VKA (95% CI)	RR versus aspirin monotherapy (95% CI)	RR versus aspirin plus clopidogrel (95% CI)	RR versus placebo (95% CI)
All stroke	0.65* (0.45 – 0.94)	0.37* (0.20 – 0.69)	0.39* (0.21 – 0.72)	0.25* (0.12 – 0.51)
Ischaemic stroke	0.77 (0.58 – 1.03)	0.48* (0.27 – 0.84)	0.37* (0.23 – 0.61)	0.23* (0.14 – 0.38)
Haemorrhagic stroke	0.27 (0.00 – 16.67)	No data	Unreliable estimates	No data
Fatal or disabling stroke	0.67* (0.48 – 0.95)	0.42* (0.26 – 0.68)	0.46* (0.26 – 0.82)	0.28* (0.14 – 0.54)
Systemic embolism	0.73 (0.34 – 1.59)	0.41 (0.13 – 1.33)	0.21* (0.07 – 0.61)	0.17* (0.05 – 0.50)
Mortality	0.89 (0.77 – 1.03)	0.83 (0.64 – 1.07)	0.88 (0.66 – 1.18)	0.64* (0.45 – 0.91)
TIA	0.89 (0.64 – 1.24)	0.57 (0.29 – 1.12)	No data	0.72 (0.32 – 1.61)
ICH	0.53 (0.27 – 1.03)	1.04 (0.28 – 3.90)	1.00 (0.30 – 3.32)	No data
ECH	1.09 (0.86 – 1.37)	0.96 (0.39 – 2.37)	0.99 (0.60 – 1.63)	1.80 (0.28 – 11.38)
Minor bleeding	0.92 (0.84 – 1.00)	1.47 (0.75 – 2.86)	0.77* (0.63 – 0.94)	1.66^ (1.14 – 2.44)
AMI	1.28 (0.90 – 1.83)	0.91 (0.49 – 1.69)	0.87 (0.44 – 1.70)	0.82 (0.33 – 2.05)
Vascular mortality	0.86 (0.72 – 1.03)	0.85 (0.59– 1.21)	0.76 (0.54 – 1.07)	1.07 (0.67 – 1.69)
Any bleeding	0.91*	1.24	0.78*	1.83^

Outcome	RR versus adjusted dose VKA (95% CI)	RR versus aspirin monotherapy (95% CI)	RR versus aspirin plus clopidogrel (95% CI)	RR versus placebo (95% CI)
	(0.86 – 0.97)	(0.92 – 1.66)	(0.68 – 0.89)	(1.29 – 2.60)

*Denotes statistically significant in favour of DBG
^Denotes statistically significant in favour of comparator
Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; TIA, transient ischaemic attack; VKA, vitamin K antagonist

Table 48 Results of the MTC for DBG Sequence

Outcome	RR versus adjusted dose VKA (95% CI)	RR versus aspirin monotherapy (95% CI)	RR versus aspirin plus clopidogrel (95% CI)	RR versus placebo (95% CI)
All stroke	0.65* (0.45 – 0.94)	0.37* (0.20 – 0.69	0.39* (0.21 – 0.73)	0.25* (0.12 – 0.51)
Ischaemic stroke	0.80 (0.60 – 1.06)	0.49* (0.28 – 0.87)	0.39* (0.23 – 0.63)	0.24* (0.15 – 0.39)
Haemorrhagic stroke	0.23 (0.00 – 19.30)	No data	Unreliable estimates	No data
Fatal or disabling stroke	0.67* (0.48 – 0.95)	0.42* (0.26 – 0.68)	0.46* (0.26 – 0.83)	0.28* (0.14 – 0.54)
Systemic embolism	0.74 (0.34 – 1.61)	0.42 (0.13 – 1.35)	0.21* (0.07 – 0.62)	0.17* (0.05 – 0.51)
Mortality	0.89 (0.77 – 1.03)	0.82 (0.64 – 1.06)	0.88 (0.66 – 1.17)	0.64* (0.45 – 0.90)
TIA	0.82 (0.58 – 1.15)	0.53 (0.27 – 1.04)	No data	0.66 (0.30 – 1.49)
ICH	0.43* (0.21 – 0.88)	0.85 (0.22 – 3.28)	0.82 (0.24 – 2.80)	No data
ECH	1.05 (0.83 – 1.33)	0.92 (0.37 – 2.28)	0.95 (0.57 – 1.57)	1.73 (0.27 – 10.95)
Minor bleeding	0.88* (0.81 – 0.97)	1.41 (0.72 – 2.76)	0.74* (0.61 – 0.91)	1.60^ (1.10 – 2.35)
AMI	1.30 (0.92 – 1.85)	0.92 (0.49 – 1.71)	0.88 (0.45 – 1.72)	0.83 (0.33 – 2.08)
Vascular mortality	0.83* (0.69 – 0.99)	0.82 (0.57 – 1.17)	0.73 (0.51 – 1.03)	1.03 (0.65 – 1.63)
Any bleeding	0.88* (0.83 – 0.94)	1.20 (0.89 – 1.61)	0.75* (0.66 – 0.86)	1.77^ (1.25 – 2.52)

*Denotes statistically significant in favour of DBG
^Denotes statistically significant in favour of comparator
Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; TIA, transient ischaemic attack; VKA, vitamin K antagonist

The results for DBG scenarios versus VKA treatment are presented to facilitate comparison between the MTC and the RE-LY trial. This is discussed in Section 5.7.9. The statistically significant findings from the MTC analyses for each DBG scenario versus aspirin monotherapy are as follows:

- Significant superiority of DBG 110mg bid for all stroke, fatal or disabling stroke and TIA
- Significant superiority of DBG 150mg bid for all stroke, ischaemic stroke and fatal or disabling stroke
- Significant superiority of the DBG sequence for all stroke, ischaemic stroke and fatal or disabling stroke

The statistically significant findings from the MTC analyses for each DBG scenario versus aspirin plus clopidogrel are as follows:

- Significant superiority of DBG 110mg bid for ischaemic stroke, systemic embolism, minor bleeding and any bleeding
- Significant superiority of DBG 150mg and the DBG sequence for all stroke, ischaemic stroke, fatal or disabling stroke, systemic embolism, minor bleeding and any bleeding

The statistically significant findings from the MTC analyses for each DBG scenario versus placebo are as follows:

- Significant superiority of DBG 110mg bid, DBG 150mg bid and the DBG sequence for all stroke, ischaemic stroke, fatal or disabling stroke and mortality
- Significant superiority of placebo for minor bleeding and any bleeding

Potentially important findings (i.e., point estimates imply treatment differences but lack of precision means significance is not reached) from the MTC analyses for each DBG scenario versus aspirin monotherapy are as follows:

- Trend towards benefit of DBG 110mg bid for ischemic stroke, systemic embolism, mortality and intracranial haemorrhage
- Trend towards benefit of DBG 150mg bid and the DBG sequence for systemic embolism , mortality, TIA and vascular mortality
- Trends towards additional risk with all DBG scenarios were seen for minor bleeds

Potentially important findings from the MTC analyses for each DBG scenario versus aspirin plus clopidogrel are as follows:

- Trend towards benefit of DBG 110mg bid for all stroke, fatal or disabling stroke, intracranial haemorrhage and vascular mortality
- Trend towards benefit of DBG 150mg bid and the DBG sequence for mortality and vascular mortality

Potentially important findings from the MTC analyses for each DBG scenario versus placebo are as follows:

- Trend towards benefit of DBG 110mg bid, DBG 150mg bid and the DBG sequence for TIA
- Trend towards benefit of placebo for ECH

The MTC results for DBG versus placebo permit the calculation of numbers needed to treat for benefit or harm (NNT). **Table 49** presents these results, where positive numbers indicate NNT for benefit and negative numbers indicate NNT for harm to prevent/cause one event versus placebo.

Table 49 Results of the NNT analysis for each DBG scenario

Outcome	DBG 110mg bid (NNT and 95% CI)	DBG 150mg bid (NNT and 95% CI)	DBG Sequence (NNT and 95% CI)	Adjusted dose VKA (NNT and 95% CI)
All stroke	18 (11,51)	16 (10,37)	16 (10,37)	19 (11,56)
Ischaemic stroke	21 (14,43)	18 (13,33)	18 (13,33)	20 (14,38)
Fatal or disabling stroke	37 (21,198)	32 (19,111)	32 (19,111)	40 (22,233)
Systemic embolism	116 (62,998)	112 (61,762)	113 (61,778)	121 (63,1363)
Mortality	29 (16,150)	27 (15,117)	27 (15,111)	35 (18,524)
TIA	173 (-264,65)	235 (-183,72)	195 (-221,68)	348 (-155,82)
ECH	-97 (-32,93)	-71 (-28,137)	-78 (-29,119)	-87 (-31,109)
Minor bleeding	-23 (-64,-14)	-16 (-35,-11)	-18 (-41,-11)	-13 (-25,-9)
AMI	324 (-93,59)	294 (-97,58)	314 (-94,59)	147 (-163,51)
Vascular mortality	-219 (-54,105)	-454 (-62,86)	-1,175 (-69,78)	-123 (-47,202)
Any bleeding	-29 (-122,-17)	-22 (-70,-13)	-24 (-79,-14)	-18 (-51,-11)

Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; NNH, number needed to harm; NNT, number need to treat; TIA, transient ischaemic attack; VKA, vitamin K antagonist

The NNT numbers for the most severe endpoints are impressive for DBG and reinforce the important clinical advantages demonstrated in the RE-LY trial. For all stroke and ischaemic stroke, the NNT is 16 and 18 respectively (DBG sequence and 150mg bid) compared to 19 and 20 for WFN. For fatal or disabling stroke, the NNT is 32 for DBG sequence and 150mg bid (37 for DBG 110mg bid), 8 patients fewer than WFN. Similarly, all DBG analyses show lower NNT for mortality than WFN (27 for DBG sequence and 150mg bid, 29 for DBG 110mg bid compared to 35 for WFN).

In summary, there is good evidence to suggest that treatment with DBG offers benefit for stroke (all, ischemic, haemorrhagic and fatal), systemic embolism, mortality and TIA.

The results of the MTC are consistent throughout the primary analysis and the sensitivity analyses (**Table 50**). Given the volume of comparisons possible, the sensitivity results are presented for two comparisons only as an illustration (DBG 110mg bid and DBG 150mg bid versus aspirin monotherapy), alongside the corresponding primary analysis results for ease of comparison. The full set of result tables is available in Appendix 4.

Table 50 Results of the sensitivity analyses for DBG 110mg bid vs aspirin monotherapy

Outcome	Primary analysis (RR and 95% CI)	INR analysis (RR and 95% CI)	ACTIVE-A analysis (RR and 95% CI)	RTO Analysis (RR and 95% CI)
All stroke	0.52* (0.28 – 0.96)	0.52 (0.22 – 1.25)	0.46* (0.30 – 0.71)	0.52* (0.28 – 0.96)
Ischaemic stroke	0.69 (0.40 – 1.20)	0.53 (0.26 – 1.10)	0.48* (0.32 – 0.72)	0.74 (0.39 – 1.39)
Haemorrhagic stroke	No data	No data	Unreliable estimates	No data
Fatal or disabling stroke	0.57* (0.36 – 0.91)	0.42* (0.23 – 0.76)	0.53* (0.35 – 0.81)	0.60* (0.36 – 0.99)
Systemic embolism	0.48 (0.15 – 1.52)	0.46 (0.14 – 1.55)	0.34* (0.14 – 0.79)	0.46 (0.13 – 1.64)
Mortality	0.85 (0.66– 1.10)	0.86 (0.64 – 1.14)	0.86 (0.70 – 1.07)	0.87 (0.67 – 1.14)
TIA	0.49* (0.25 – 0.97)	0.52 (0.24 – 1.14)	0.49* (0.25 – 0.97)	0.52 (0.25 – 1.10)
ICH	0.65 (0.16 – 2.60)	0.41 (0.08 – 2.15)	0.82 (0.29 – 2.30)	0.69 (0.08 – 6.05)
ECH	0.84 (0.34 – 2.09)	0.84 (0.34 – 2.10)	1.15 (0.73 – 1.83)	0.86 (0.02 – 34.23)
Minor bleeding	1.30 (0.66 – 2.54)	1.30 (0.52 – 3.21)	1.54^ (1.17 – 2.02)	1.33 (0.69 – 2.55)
AMI	0.93 (0.50 – 1.72)	0.97 (0.48 – 1.97)	0.84 (0.50 – 1.39)	1.01 (0.49 – 2.08)
Vascular mortality	0.90 (0.63 – 1.29)	0.94 (0.61 – 1.47)	0.84 (0.64 – 1.12)	0.93 (0.64 – 1.34)
Any bleeding	1.10 (0.82 – 1.48)	1.05 (0.74 – 1.50)	1.08 (0.94 – 1.26)	1.10 (0.81 – 1.50)

* Denotes statistically significant in favour of DBG

^ Denotes statistically significant in favour of aspirin monotherapy

Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; TIA, transient ischaemic attack; VKA, vitamin K antagonist

Table 51 Results of the sensitivity analyses for DBG 150mg bid vs aspirin monotherapy

Outcome	Primary analysis (RR and 95% CI)	INR analysis (RR and 95% CI)	ACTIVE-A analysis (RR and 95% CI)	RTO Analysis (RR and 95% CI)
All stroke	0.37* (0.20 – 0.69)	0.37* (0.15 – 0.90)	0.33* (0.21 – 0.51)	0.37* (0.20 – 0.69)
Ischaemic stroke	0.48* (0.27 – 0.84)	0.37* (0.18 – 0.77)	0.33* (0.22 – 0.51)	0.51* (0.27 – 0.98)
Haemorrhagic stroke	No data	No data	Unreliable estimates	No data
Fatal or disabling stroke	0.42* (0.26 – 0.68)	0.30* (0.16 – 0.56)	0.39* (0.25 – 0.60)	0.44* (0.26 – 0.74)
Systemic embolism	0.41 (0.13 – 1.33)	0.40 (0.12 – 1.36)	0.29* (0.12 – 0.70)	0.39 (0.11 – 1.44)
Mortality	0.83 (0.64 – 1.07)	0.83 (0.62 – 1.11)	0.84 (0.84– 1.04)	0.85 (0.65 – 1.11)
TIA	0.57 (0.29 – 1.12)	0.61 (0.28 – 1.32)	0.57 (0.29 – 1.12)	0.61 (0.29 – 1.26)
ICH	1.04 (0.28 – 3.90)	0.66 (0.13 – 3.21)	1.32 (0.51 – 3.42)	1.11 (0.14 – 8.76)
ECH	0.96 (0.39 – 2.37)	0.96 (0.39 – 2.38)	1.31 (0.83 – 2.08)	0.97 (0.02 – 38.57)
Minor bleeding	1.47 (0.75 – 2.86)	1.47 (0.59 – 3.63)	1.74^ (1.32 – 2.28)	1.50 (0.78 – 2.88)
AMI	0.91 (0.49 – 1.69)	0.95 (0.47 – 1.93)	0.82 (0.49 – 1.37)	0.99 (0.48 – 2.04)
Vascular mortality	0.85 (0.59– 1.21)	0.89 (0.57 – 1.38)	0.79 (0.60 – 1.05)	0.87 (0.60 – 1.26)
Any bleeding	1.24 (0.92 – 1.66)	1.18 (0.83 – 1.69)	1.22^ (1.05 – 1.41)	1.24 (0.91 – 1.69)

* Denotes statistically significant in favour of DBG

^ Denotes statistically significant in favour of aspirin monotherapy
Abbreviations: AMI, acute myocardial infarction; DBG, dabigatran etexilate; ECH, extra-cranial haemorrhage; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; TIA, transient ischaemic attack; VKA, vitamin K antagonist

As shown in the tables, there is no great variation in the results across the sensitivity analyses for the major endpoints, indeed improving the results for DBG in most cases. The only change in the opposite direction is seen in non-ICH bleeding endpoints when the ACTIVE-A trial is added. However in that analysis the only endpoint that is statistically significantly in favour of aspirin is minor bleeding (both DBG doses) and any bleeding (DBG 150mg bid). For all othyer endpoints and analyses, the trends demonstrated in the primary analysis are maintained.

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Heterogeneity between trials was not formally assessed in a direct comparison manner due to both the indirect nature of the mixed treatments comparisons (MTC) meta-analyses and also the fact that five of the included treatments— DBG, aspirin plus clopidogrel, idraparinux, indobufen, and triflusal—each contributed data from only one trial. However, the similarity of the trial populations was descriptively assessed and the impact of three trial characteristics used as covariates was statistically measured within the MTC models.

The covariates mean length of follow-up, mean patient age, and gender were all individually explored for their importance in the meta-analyses for four selected analysis outcomes: mortality, ischaemic stroke, acute myocardial infarction, and intracranial haemorrhage. A total of 12 separate exploratory MTC models were fit (that is, one each for each combination of four outcomes by three covariates). **Table 52** presents the p-values derived for each of these models, where a p-value of less than 0.05 would indicate that the covariate included did have an effect on the analysis outcome.

Table 52 Statistical assessment of the effect of specific covariates

Analysis Outcome	Gender	Age	Mean Follow-Up
Mortality	0.187	0.013	0.013
Ischaemic Stroke	0.926	0.780	0.191
Acute MI	0.447	0.076	0.040
ICH	0.845	0.254	0.385

Abbreviations: ICH, intracranial haemorrhage; MI, myocardial infarction

Both length of follow-up and age were subsequently deemed appropriate for inclusion in the MTCs as covariates. However, on the initial execution of the primary meta-analyses, it was apparent that the MTCs adversely suffered in their stability due to the inclusion of two covariates. Consequently, the project team agreed to include the only covariate deemed most clinically relevant by team

consensus. Therefore, all MTC models were run adjusting for the covariate mean length of follow-up (centred about its mean).

The limitations of this work include the following:

- The original data source is a common limitation for meta-analyses. Some good clinical trials were excluded from meta-analyses of a specific outcome because they did not present data for that outcome in their article. Consequently, the underlying population represented by each meta-analysis sample can be different from one another.
- Each clinical trial had inclusion criteria defining the population that each clinical trial sample represents. However, when the clinical trials are combined, it is not clear if the sample should represent the union or the intersection of the populations represented by each trial. For example, if the age requirement in two clinical trials is 45 to 75 years and 35 to 65 years; when the meta-analysis is performed on these two clinical trials, should the meta-analysis sample represent the persons aged 35 to 75 years (union) or those aged 45 to 65 years (intersection)?
- The difference in the data collection methods—e.g., definition of extracranial haemorrhage—between the clinical trials could invalidate the comparisons performed by the meta-analysis. Therefore, the results from this meta-analysis can be used to raise questions and identify trends, but should not be used as confirmatory evidence. However, these results can be used for estimation purposes. This doesn not apply to other endpoints where there is little or no variation in definition (i.e. stroke, death etc).
- From a pure statistical standpoint, the MTC models as used in these analyses are not perfect. To realise (or fit) the model, the Markov Chain Monte Carlo (MCMC) method is needed to obtain the solutions. MCMC is a relatively new and fragile analysis method. For any correctly specified model, MCMC will give many solutions to the estimate of the parameters. As the validity of the solution needs to be verified by users based on the characteristics of the Markov Chain, it is possible to pick up invalid solutions. Additionally, given the properties of MCMC, it is very common for two different researchers to obtain different results even when the data and model are exactly the same.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

An example of the three sensitivity analyses performed has been presented in **Table 50** and discussed in the previous section. The full set of sensitivity analyses is presented in Appendix 4.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

The RE-LY study is an excellent comparison of DBG against the current standard of care (adjusted-dose warfarin) for the important outcomes in this indication. The size, quality and timeliness of the RE-LY study means it should be considered the primary reference with which to draw comparisons between these two treatment options. The requirement for the meta-analyses presented above is driven by other appropriate comparisons not studied in head to head trials, in this case aspirin monotherapy, aspirin plus clopidogrel and placebo.

For completeness, trial data was collected not only on the primary treatments of interest (DBG, adjusted-dose VKA and aspirin monotherapy), but also other treatments which add to the historical landscape of evidence in stroke prevention in AF. Although these additional treatments are not common or current treatment options, they are included to give the meta-analyses a holistic scope, and also to ensure large quantities of data on the treatments of primary interest is not discarded, i.e. all trials included in the meta-analyses include data on at least one of the primary treatments of interest.

Any indirect meta-analysis is likely to be inferior to the alternative of a head to head clinical trial comparing two treatments, however in the absence of such head to head trials, indirect comparisons are an accepted pragmatic solution for comparing two treatments which otherwise could not be objectively contrasted to determine benefits of one over the other. The price paid for making indirect comparisons, via MTC or other indirect comparison methods, is that the precision of the treatment comparison estimates can be quite low, which in turn can mean drawing definitive conclusions or reaching statistical significance can be difficult to achieve. This may be viewed as an advantage in one respect because wider CIs invoke a cautious approach to interpretation of results, which given the limitations of indirect comparisons can be a prudent approach to take. On the other hand, it also means that statistical significance is only reached in those cases where the data exhibit very strong evidence to support a particular conclusion.

In RE-LY, DBG was administered in two separate fixed doses of 110mg and 150mg bid. In these meta-analyses both doses were studied separately, and combined sequentially against the treatments of primary interest. Each of the DBG versus adjusted-dose VKA analyses were cross-checked with the results seen in the RE-LY study. The relative risks observed in the trial analyses and in the MTC were consistent with one another, but as expected the precision was better in the trial analyses and therefore the CIs were narrower.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

As discussed in section 5.2 no relevant non-RCT studies were identified.

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

The studies identified in section 5.2 (RE-LY, PETRO and PETRO-EX) represent the totality of current evidence for DBG in this indication. Therefore a further search for evidence on adverse effects is uneccessary.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

PETRO [67, 70]

Table 53 consolidates the results of the safety analyses from the PETRO study.

Table 53 Safety results from PETRO

Outcome	How defined	Effect size	95% CI	Analysis group and size	Notes, comments and justifications
Exposure					
Total treatment exposure	Subject-years	DBG 50: 23.7 DBG 150: 36.8 DBG 300: 34.1 WFN: 15.8		Number randomised and treated DBG 50: N = 105 DBG 150: N = 166 DBG 300: N = 161 WFN: N = 70	Exposure to study medication was in line with the randomisation schedule.
	Mean days per patient	DBG 50: 83 DBG 150: 81 DBG 300: 77 WFN: 82	Range = 7 - 94 Range = 3 - 93 Range = 1 – 95 Range = 10 - 94		
Bleeding Events					
Major bleeding	Number of events and event rate (%)	DBG 50: 0 DBG 50 + ASA 81: 0 DBG 50 + ASA 325: 0 DBG 150: 0 DBG 150 + ASA 81: 0 DBG 150 + ASA 325: 0 DBG 300: 0 DBG 300 + ASA 81: 1 (2.9%) DBG 300 + ASA 325: 3 (10.0%) WFN: 0	No variance reported	Number treated DBG 50: N = 107 DBG 150: N = 170 DBG 300: N = 169 WFN: N = 70	Major bleeding events were observed only in the DBG 300mg dose group when ASA (81mg or 325mg) was co-administered. No major bleeds were noted in the two lowest DBG dose groups, irrespective of ASA use. Both lower dose DBG groups, with and without ASA administration, and the WFN group all had no major bleeding events reported.
Major and clinically-relevant bleeding	Number of events and event rate (%)	DBG 50: 0 DBG 50 + ASA 81: 1 (4.8%) DBG 50 + ASA 325: 1 (3.7%) DBG 150: 9 (8.9%) DBG 150 + ASA 81: 2 (5.6%) DBG 150 + ASA 325: 2 (6.1%) DBG 300: 6 (5.7%) DBG 300 + ASA 81: 5 (14.7%) DBG 300 + ASA 325: 6 (20.0%) WFN: 4 (5.7%)	No variance reported	Number treated DBG 50: N = 107 DBG 150: N = 170 DBG 300: N = 169 WFN: N = 70	Clinically-relevant bleeding events and the composite endpoint of major and clinically-relevant bleeding showed similar results across all the dose groups, with further evidence that bleeding is increased when DBG 300mg bid is administered concomitantly with ASA at a dose of at least 81mg.

Outcome	How defined	Effect size	95% CI	Analysis group and size	Notes, comments and justifications
Any bleeding	Number of events and event rate (%)	DBG 50: 2 (3.4%) DBG 50 + ASA 81: 2 (9.5%) DBG 50 + ASA 325: 3 (11.1%) DBG 150: 15 (14.9%) DBG 150 + ASA 81: 8 (22.2%) DBG 150 + ASA 325: 7 (21.2%) DBG 300: 14 (13.3%) DBG 300 + ASA 81: 11 (32.4%) DBG 300 + ASA 325: 14 (46.7%) WFN: 12 (17.1%)	No variance reported	Number treated DBG 50: N = 107 DBG 150: N = 170 DBG 300: N = 169 WFN: N = 70	As expected for any anticoagulant, increasing the DBG dose from 50mg bid to 150mg bid and to 300mg bid (with or without ASA) caused increased bleeding. Of interest, there does not appear to be a clinically meaningful difference in bleeding rates between the WFN control group and the 50mg bid and 150mg bid DBG dose groups (with and without ASA) and the DBG 300mg bid (without ASA). The addition of ASA only led to a clinically relevant increase in clinically relevant bleeding in the highest dose group DBG 300mg bid.
Adverse Events					
Any AEs	Number of events (%)	DBG 50: 62 (58%) DBG 150: 111 (65%) DBG 300: 114 (67%) WFN: 35 (50%)	No variance reported	As major bleeding	The majority of all adverse events were of mild intensity, and were considered unrelated to treatment by the investigators. The most frequently reported treatment-related adverse events were contusion (3.2% of all patients), dyspepsia (2.6%), and epistaxis (2.4%). Only 9 Serious AE's were considered causally related to the study drug. Five of the reported serious AEs were related to bleeding events: 4 with major bleeds in the DBG 300mg group and one minor relevant bleed in the WFN group.
Serious AEs	Number of events (%)	DBG 50: 8 (7.5%) DBG 150: 16 (9.4%) DBG 300: 11 (6.5%) WFN: 2 (2.9%)	No variance reported	As major bleeding	
AEs leading to discontinuation	Number of events (%)	DBG 50: 5 (4.7%) DBG 150: 9 (5.3%) DBG 300: 15 (8.9%) WFN: 0	No variance reported	As major bleeding	
Deaths	Number of events (%)	Only one in the DBG 300 group death occurred after the end of the trial	No variance reported	As major bleeding	There were no deaths during the study period, but one patient died 40 days after trial participation.
Liver Function Tests					
ALT > 3x ULN	Number of patients	DBG 150: 1 DBG 150 + ASA 81: 1 DBG 300: 1 DBG 300 + ASA 81: 1	No variance reported	As major bleeding	The liver function test data showed an incidence of elevated ALT > 3x ULN in 4 DBG patients. Furthermore, there were two occurrences of elevated AST and one of elevated AP among the same four patients. There was no occurrence of an elevated ALT or AST in association with a substantially increased bilirubin level. These values show that although elevations of LFT parameters were rare, further examination in larger trials was required.
AST > 3x ULN	Number of patients	DBG 150: 1 DBG 150 + ASA 81: 1	No variance reported	As major bleeding	
AP > 3x ULN	Number of patients	DBG 150 + ASA 81: 1	No variance reported	As major bleeding	
Bilirubin > 3x ULN	Number of patients	Nil	No variance reported	As major bleeding	

Source: [70]. Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; ASA, aspirin; AST, aspartate aminotransferase; DBG, dabigatran etexilate; LFT, liver function tests; ULN, upper limit of normal; WFN, warfarin

Safety Summary

The dose-response for any bleeding events was not uniform for DBG, but dependent on whether ASA was concomitantly given or not. DBG doses up to 150mg bid administered with or without aspirin (ASA) appeared safe and comparable to full dose WFN (INR 2.0-3.0) with regard to the observed incidence of all categories of bleeding. DBG alone at 300mg bid resulted in bleeding rates similar to those seen with 150mg bid alone. DBG dosed at 300mg bid concomitantly with ASA resulted in unacceptable rates of bleeding, and was associated with a risk of major bleeding.

The incidence of elevated transaminases >3xULN was 0.9% in DBG treated patients (4 of 432) and 0% (0 of 70) in WFN treated patients. There were no reported elevations of bilirubin > 3xULN during the study. Long-term data is provided in further details of the open label rollover extension study (PETRO-Ex) in Appendix 14.

No patients had elevated transaminases >3xULN with bilirubin levels > 1.5 or 2x ULN. One patient had an elevated bilirubin level after their transaminases were elevated to >3x ULN. This patient later died of congestive heart failure. The autopsy showed only passive liver congestion consistent with the known diagnosis of congestive heart failure. One other patient had elevated transaminases subsequent to elevated alkaline phosphatase due to obstructive pancreatitis. This patient later was hospitalised with ischaemic bowel and died. Neither case was considered drug-related.

A dose-response was observed for gastrointestinal discomfort/pain (abdominal discomfort, abdominal pain, dyspepsia, gastritis, oesophageal pain) with DBG. In this category, dyspepsia was most frequently observed for higher dosages of DBG, whereas no dyspepsia was reported for WFN. Long-term data is provided by PETRO-Ex (Appendix 14).

The concomitant administration of DBG and ASA appeared to increase all categories of bleeding. The incidence of major bleeding when DBG was given at a dose of 300mg bid concomitantly with ASA was clinically unacceptable. Naturally, this higher dose was not taken forward into phase-III.

DBG administered at any dose studied in this trial without ASA did not appear to result in increased bleeding rates compared to WFN, dosed to an INR of 2.0 to 3.0.

1160.49 [76]

Table 54 consolidates the results of the safety analyses from the PETRO study.

Safety Summary

[redacted]. Major bleeding events occurred [redacted] DBG 150mg bid group and in [redacted] from the WFN group. [redacted].

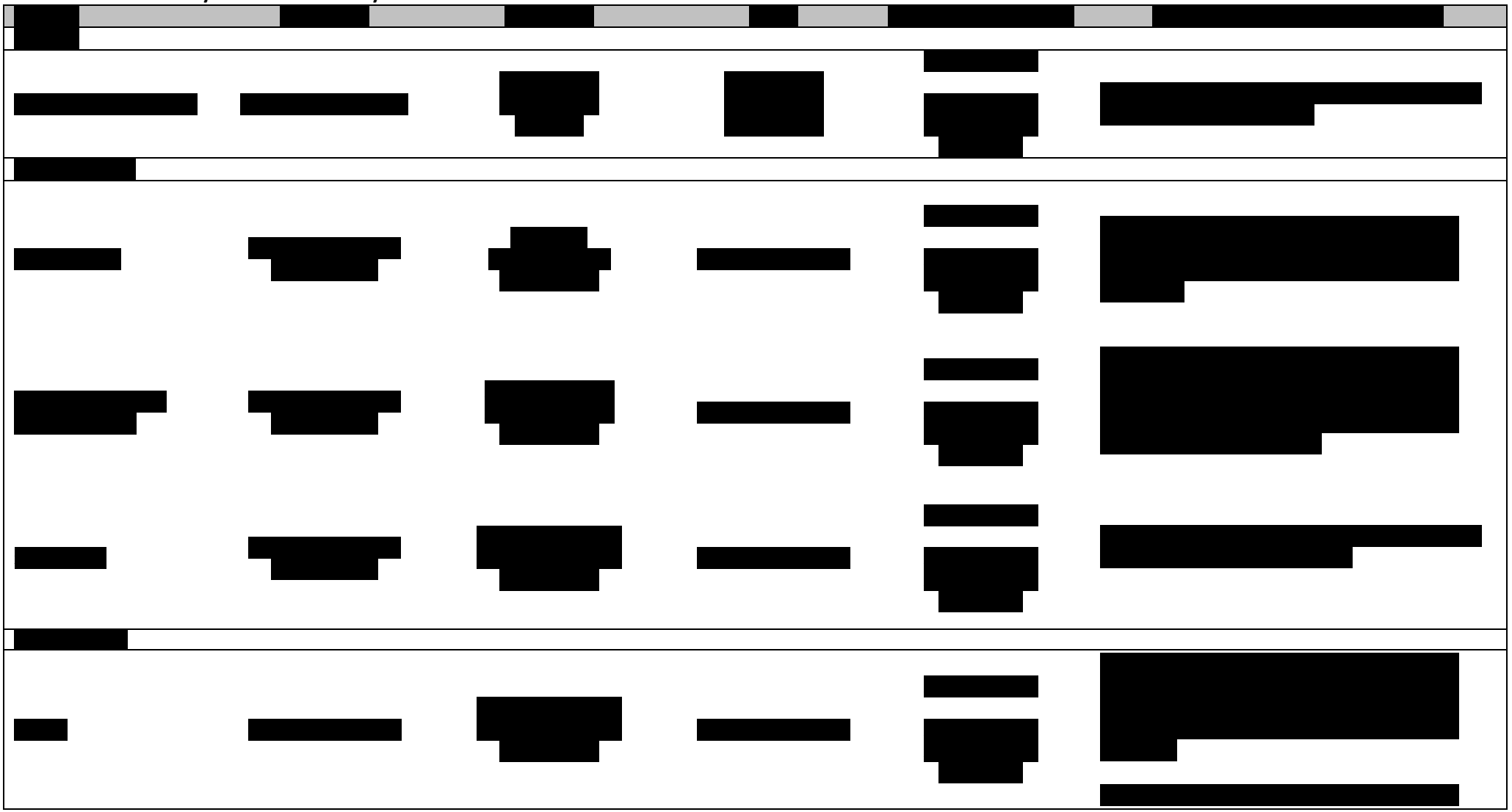
Major or clinically-relevant bleeding events occurred dose-dependently in the DBG groups, the incidence was however lower in both DBG groups compared to the WFN group. Aspirin increased the incidence of major or clinically-relevant bleeding events in all treatment groups including WFN.

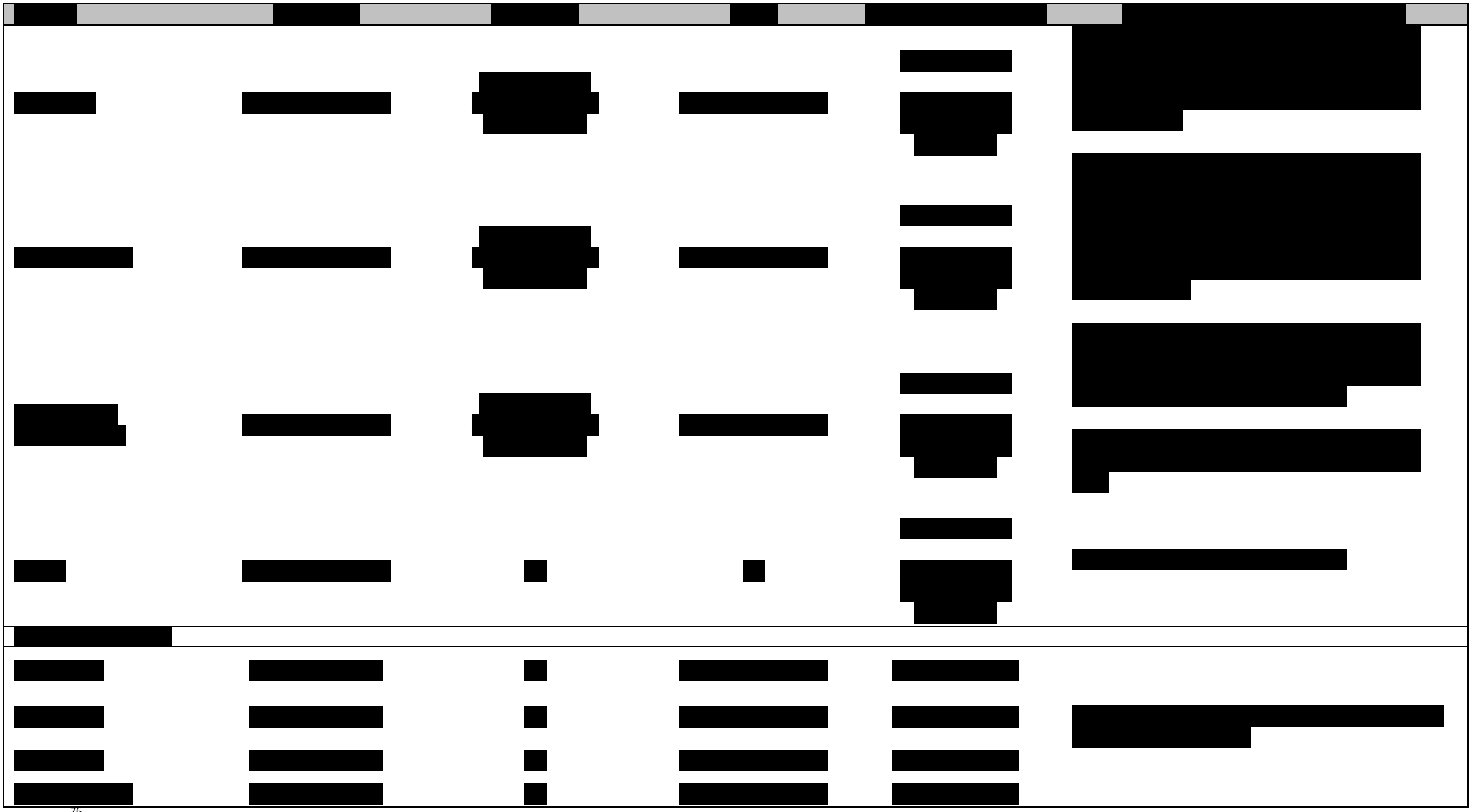
Similarly, any bleeding events occurred dose-dependently in the DBG groups. The incidence in the DBG 110mg bid group was similar to that in the WFN group with the incidence in the DBG 150mg bid group slightly higher.

No patients in the DBG groups had liver function test values that exceeded even *twice* the upper limit of normal range.

No serious adverse events related to the investigational drug occurred in the DBG groups.

Table 54 Safety results from Study 1160.49





Source: [76]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; DBG, dabigatran etexilate; ULN, upper limit of normal; WFN, warfarin

RE-LY [1, 43, 63]

Table 55 to **Table 59** consolidate the results of the safety analyses from RE-LY, with Kaplan-Meier curves for major bleeding and the most important haemorrhagic outcome, intracranial haemorrhage, illustrated in **Figure 15** and **Figure 16**. As outlined in Section 3, it is extremely important to note that the analyses presented are those resulting from the re-evaluation of the RE-LY trial[1] and not those from the original publication[43].

Exposure to study medication was similar across all treatment groups. Overall 52% of the subjects in the study had at least one interruption of study medication, approximately 30% of the subjects had temporary discontinuations for less than 30 days, and 21% permanently discontinued study medication prematurely. More subjects in the WFN group had temporary interruptions between 8 and 30 days (14.6% for WFN vs. 10%-11% for DBG), while interruptions of one day to one week were similar across all treatments.

More subjects in the DBG groups permanently discontinued study medication. The open-label nature of the trial, specifically that subjects and their health care providers knew who was receiving a well-established agent, WFN, or an investigational agent, DBG, may have contributed to this discrepancy. More subjects in the DBG 110mg bid and DBG 150mg bid groups discontinued study medication permanently due to outcome events; however discontinuations due to major bleeds (categorised as an outcome event) were similar across all treatments.

A lower yearly event rate for major bleeds was observed with DBG treatment compared with WFN. Subjects treated with DBG 110mg bid had a significantly lower rate of major bleeds compared with WFN ($p=0.0026$). The rate of major bleeds with DBG 150mg bid compared to WFN was not statistically significantly different ($p=0.3146$). The time from randomisation to the first onset of a major bleed is illustrated in **Figure 15**.

There was a significantly lower rate of life-threatening bleeds, haemorrhagic stroke and ICH for both doses of DBG compared with WFN as follows:

Life threatening bleed

- DBG 110mg bid relative risk of 0.67 compared to WFN ($p=0.0001$)
- DBG 150mg bid relative risk of 0.80 compared to WFN ($p=0.0305$)

ICH (including haemorrhagic stroke)

- DBG 110mg bid relative risk of 0.30 compared to WFN ($p<0.0001$)
- DBG 150mg bid relative risk of 0.41 compared to WFN ($p<0.0001$)

The differences in time to ICH are illustrated in **Figure 16.**

For all critical organs where bleeding events were observed, both DBG groups always had the lower incidence rate compared to WFN, except in one case where the incidence with DBG 150mg bid was equal to WFN (pericardial). However DBG resulted in a higher number of major GI bleeding events compared with WFN. The DBG 150mg bid group also had a significantly higher rate of life-threatening GI bleeds compared with WFN.

Minor bleeding events were reported in a lower number of DBG subjects compared with WFN. The any bleeding events endpoint followed the same pattern.

The incidence of AEs was similar between DBG 110mg bid and DBG 150mg bid. DBG subjects had a higher incidence of AEs considered related to treatment, as well as those resulting in discontinuation. The incidence of serious AEs was similar across treatment groups. However, DBG subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalisation as compared to WFN subjects.

There did not appear to be any strong relationship between the dose of DBG and the overall incidence of AEs or serious AEs. In general, the AE profile was similar for DBG and WFN with the exception of GI AEs, which were reported more frequently with DBG.

Dyspepsia and gastritis was more frequent for DBG compared with WFN. The increased risk for dyspepsia/gastritis with DBG occurred very early on in the first few weeks and remained approximately twice that of WFN. Two clusters were defined separately, “dyspepsia-like symptoms” and “gastritis-like symptoms”. DBG 110mg bid patients tended to have a slightly higher incidence of these clustered symptoms than DBG 150mg bid patients. Gastritis-like symptoms increased the probability of a major GI bleed by 3 to 4-fold and any bleed by 2 to 3 fold for all treatments.

Although discontinuation of treatment due to dyspepsia/gastritis was uncommon, it occurred more frequently in DBG (2.6%, 2.6%, and 0.9% for DBG 110mg bid, DBG 150mg bid, and WFN, respectively). The reporting of dyspepsia or gastritis as a serious AE was infrequent. Use of ASA added slightly to the event rates for both DBG and WFN, but there is no evidence of a synergistic effect

Although WFN subjects had the highest incidence of LFT elevations, there was no significant difference in the risk of ALT/AST elevations of >3, >5xULN, or in association with total bilirubin of >2xULN between DBG and WFN groups. There was no evidence of any liver toxicity issue with either of the DBG doses.

Table 55 Safety analyses relating to treatment exposure reported in RE-LY

Outcome	DBG 110mg bid	DBG 150mg bid	WFN
Mean treatment exposure – months (SD)	20.54 (9.62)	20.32 (9.76)	21.33 (8.80)

Safety analysis set: DBG 110mg bid - N = 5,983, subject years = 10,242; DBG 150mg bid - N = 6,059, subject-years = 10,261; WFN - N = 5,998, subject-years = 10,659
Source: [1]
Abbreviations: DBG, dabigatran etexilate; SD, standard deviation; WFN, warfarin

Table 56 Safety analyses relating to discontinuation reported in RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN	
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate
No treatment interruption	2,910	48.6%	2,881	47.5%	2,878	48.0%
Permanent discontinuation	1,318	22.0%	1,382	22.8%	1,073	17.9%
Reasons for permanent discontinuation – subject refused study drug	424	7.1%	459	7.6%	405	6.8%
Reasons for permanent discontinuation – outcome event	261	4.4%	246	4.1%	177	3.0%
Reasons for permanent discontinuation – minor bleed	67	1.1%	76	1.3%	37	0.6%
Reasons for permanent discontinuation – other	471	7.9%	507	8.4%	372	6.2%

Safety analysis set: DBG 110mg bid - N = 5,983, subject years = 10,242; DBG 150mg bid - N = 6,059, subject-years = 10,261; WFN - N = 5,998, subject-years = 10,659
Source: [1]
Abbreviations: DBG, dabigatran etexilate; WFN, warfarin

Table 57 Safety analyses relating to other adverse events reported in RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN	
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate
Any adverse event	4,703	78.6%	4,746	78.3%	4,551	75.9%
Serious adverse events	1,263	21.1%	1,290	21.3%	1,357	22.6%
Adverse events leading to discontinuation	1,138	19.0%	1,243	20.5%	939	15.7%
Dyspepsia-like symptoms	761	12.7%	738	12.2%	354	5.9%
Gastritis-like symptoms	297	5.0%	257	4.2%	142	2.4%

Safety analysis set: DBG 110mg bid - N = 5,983, subject years = 10,242; DBG 150mg bid - N = 6,059, subject-years = 10,261; WFN - N = 5,998, subject-years = 10,659
Source: [1]
Abbreviations: DBG, dabigatran etexilate; WFN, warfarin

Table 58 Safety analyses relating to haemorrhagic events reported in RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Major bleeding	342	2.87%	399	3.32%	421	3.57%	0.80* (0.70 – 0.93)	0.93 (0.81 – 1.07)
Life threatening major bleeding	147	1.24%	179	1.49%	218	1.85%	0.67* (0.54 – 0.82)	0.80* (0.66 – 0.98)
Intracranial haemorrhage (including haemorrhagic stroke)	27	0.23%	38	0.32%	90	0.76%	0.30* (0.19 – 0.45)	0.41* (0.28 – 0.61)
Intracranial haemorrhage (excluding haemorrhagic stroke)	16	0.13%	26	0.22%	49	0.42%	0.32* (0.18 – 0.57)	0.52* (0.32 – 0.84)
GI major bleeding	134	1.14%	186	1.57%	125	1.07%	1.07 (0.84 – 1.36)	1.47^ (1.17 – 1.85)
GI life-threatening bleeding	67	0.57%	94	0.79%	57	0.49%	1.17 (0.82 – 1.67)	1.62^ (1.17 – 2.26)
Any GI bleeding	600	5.41%	681	6.13%	452	4.02%	1.35^ (1.19 – 1.53)	1.52^ (1.35 – 1.72)
Minor bleeding	1,566	13.16%	1,787	14.85%	1,931	16.37%		
Any bleeding	1,754	14.74%	1,993	16.56%	2,166	18.37%		

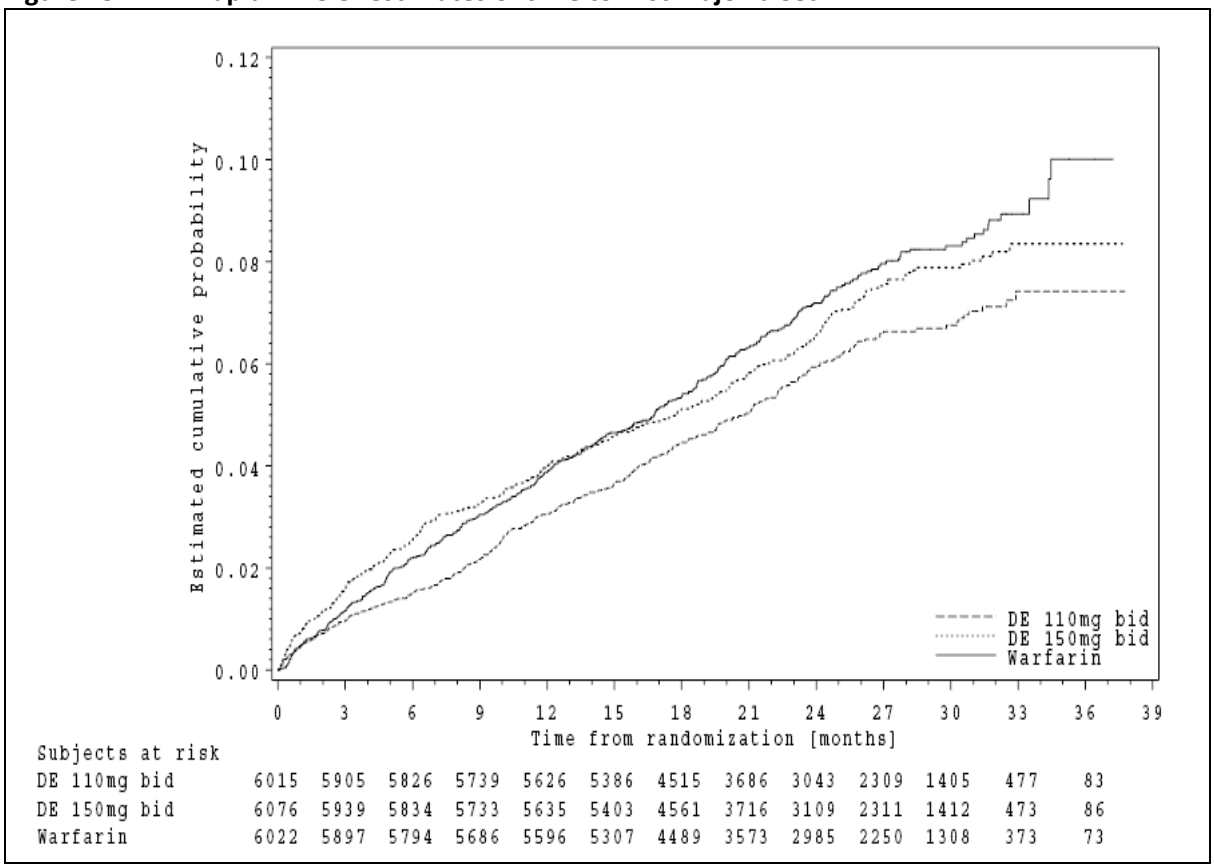
ITT analysis set: DBG 110mg bid - N = 6,015, subject-years = 11,899; DBG 150mg bid - N = 6,076, subject-years = 12,033; WFN - N = 6,022, subject-years = 11,794
* Denotes statistically significant in favour of DBG. ^ Denotes statistically significant in favour of warfarin
Source: [1]
Abbreviations: DBG, dabigatran etexilate; GI, gastrointestinal; WFN, warfarin

Table 59 Safety analyses relating to liver function tests reported in RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
ALT/AST>3xULN	118	2.0%	106	1.7%	125	2.1%	0.98 (0.76 – 1.26)	0.88 (0.68 – 1.14)
ALT/AST>5xULN	36	0.6%	45	0.7%	50	0.8%	0.75 (0.49 – 1.15)	0.93 (0.62 – 1.40)
ALT/AST>3xULN and total bilirubin >2xULN	11	0.2%	14	0.2%	21	0.4%	0.55 (0.26 – 1.13)	0.69 (0.35 – 1.36)

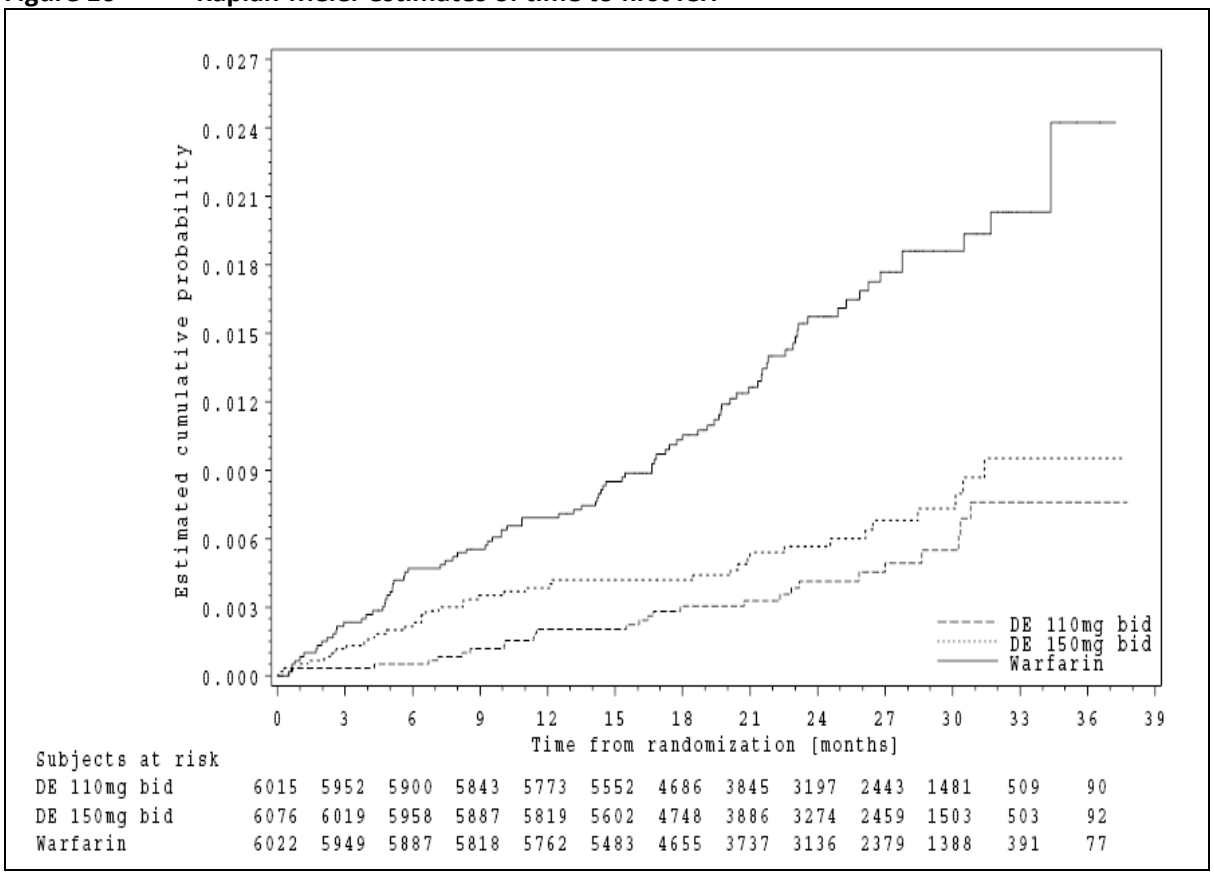
Safety analysis set: DBG 110mg bid - N = 5,983, subject years = 10,242; DBG 150mg bid - N = 6,059, subject-years = 10,261; WFN - N = 5,998, subject-years = 10,659
Source: [1]
Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; DBG, dabigatran etexilate; LFT, liver function test; ULN, upper limit of normal; WFN, warfarin

Figure 15 Kaplan-Meier estimates of time to first major bleed[1]



Abbreviation: DE, dabigatran etexilate

Figure 16 Kaplan-Meier estimates of time to first ICH[1]



Abbreviation: DE, dabigatran etexilate; ICH, intracranial haemorrhage.

Table 60 and **Table 61** detail the analysis of major bleeding for the pre-defined subgroup stratified by WFN experience. The number of VKA experienced and naïve subjects was similar within treatment groups, as well as across treatment groups although exposure was less in VKA naïve subjects. The yearly event rate of major bleeding events was generally similar within treatment groups for VKA naïve and VKA experienced subjects, although VKA experienced subjects treated with DBG 110mg bid had a slightly lower yearly rate of major bleeds compared to VKA naïve subjects.

Table 62 details the results for the primary safety endpoint for selected pre-defined subgroups. These analyses show that the trends demonstrated in the overall results are maintained across a variety of subgroups.

Table 63 and **Table 64** outline the results of the *post-hoc* subgroup analysis using the specified cut-off of age 80 years as required for the economic model.

Table 60 Safety results relating to treatment exposure (mean months per patient) by VKA experience subgroup from RE-LY

Outcome	DBG 110mg bid	DBG 150mg bid	WFN
VKA-naïve (SD)	19.38 (9.08)	19.19 (9.20)	19.72 (8.51)
VKA-experienced (SD)	21.71 (9.99)	21.45 (10.17)	23.02 (8.77)

Safety analysis set (naïve): DBG 110mg bid - N = 2,990, subject years = 4,828; DBG 150mg bid - N = 3,019, subject-years = 4,829; WFN - N = 3,082, subject-years = 5,064
Safety analysis set (experienced): DBG 110mg - N = 2,991, subject years = 5,411; DBG 150mg bid - N = 3,039, subject-years = 5,432; WFN - N = 2,916, subject-years = 5,595
Source: [1]
Abbreviations: DBG, dabigatran etexilate; SD, standard deviation; VKA, vitamin-K antagonist; WFN, warfarin

Table 61 Safety results relating to major bleeding by VKA experience subgroup from RE-LY

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
VKA-naïve	176	3.11%	190	3.33%	205	3.57%	0.87 (0.71 – 1.07)	0.94 (0.77 – 1.14)
VKA-experienced	166	2.66%	209	3.30%	216	3.57%	0.74* (0.60 – 0.91)	0.93 (0.76 – 1.12)
p-value for interaction							0.4705	

ITT analysis set (naïve): DBG 110mg bid - N = 3,005, subject-years = 5,659; DBG 150mg bid - N = 3,028, subject-years = 5,700; WFN - N = 3,093, subject-years = 5,744
ITT analysis set (experienced): DBG 110mg bid - N = 3,008, subject-years = 6,236; DBG 150mg bid - N = 3,047, subject-years = 6,331; WFN - N = 2,929, subject-years = 6,050
* Denotes statistically significant in favour of DBG
Source: [1]
Abbreviations: DBG, dabigatran etexilate; ITT, intention to treat; VKA, vitamin K antagonist; WFN, warfarin

Table 62 Safety results of the primary endpoint for selected pre-defined subgroups

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
Age < 65 years	16	0.81%	18	0.88%	45	2.43%	0.33* (0.19 – 0.59)	0.36* (0.21 – 0.62)
65 < Age < 75	122	2.29%	135	2.60%	170	3.24%	0.70* (0.56 – 0.89)	0.80 (0.64 – 1.00)
Age > 75	204	4.44%	246	5.12%	206	4.39%	1.01 (0.83 – 1.23)	1.18 (0.98 – 1.43)
Male	225	2.92%	258	3.37%	273	3.63%	0.80* (0.67 – 0.96)	0.93 (0.78 – 1.26)
Female	117	2.79%	141	3.23%	87	3.46%	0.80 (0.63 – 1.03)	0.94 (0.74 – 1.18)
BMI < 25	114	3.77%	100	3.33%	130	4.42%	0.75* (0.58 – 0.98)	0.75* (0.58 – 0.98)
25 < BMI < 30	117	2.50%	150	3.10%	157	3.39%	0.91 (0.73 – 1.14)	0.91 (0.73 – 1.14)
30 < BMI < 35	65	2.45%	96	3.52%	86	3.22%	1.11 (0.83 – 1.48)	1.11 (0.83 – 1.48)
BMI > 35	46	3.03%	53	3.66%	48	3.12%	1.18 (0.80 – 1.74)	1.18 (0.80 – 1.74)
Ethnicity class - white	255	3.02%	297	3.48%	275	3.28%	0.92 (0.78 – 1.09)	1.07 (0.91 – 1.26)
Ethnicity class – black	2	2.02%	6	4.99%	10	8.23%	0.23 (0.05 – 1.03)	0.60 (0.22 – 1.65)
Ethnicity class – Asian	41	2.25%	42	2.26%	68	3.80%	0.58* (0.39 – 0.86)	0.59* (0.40 – 0.86)
Ethnicity class – other	44	2.88%	54	3.57%	68	4.52%	0.63* (0.43 – 0.92)	0.79 (0.55 – 1.13)
Hispanic or Latino – No	330	2.95%	382	3.38%	402	3.62%	0.81* (0.70 – 0.94)	0.94 (0.81 – 1.08)
Hispanic or Latino – Yes	12	1.66%	17	2.37%	19	2.75%	0.60 (0.29 – 1.23)	0.86 (0.45 – 1.66)
CrCL (ml/min) < 30	0	0.00%	7	13.31%	0	0.00%	Unreliable result	Unreliable result
30 < CrCL (ml/min) < 50	120	5.65%	116	5.27%	112	5.68%	1.00 (0.77 – 1.29)	0.94 (0.72 – 1.21)
50 < CrCL (ml/min) < 80	154	2.87%	182	3.34%	206	3.78%	0.76* (0.55 – 1.05)	0.89 (0.73 – 1.08)

CrCL (ml/min) > 80	57	1.48%	80	2.09%	94	2.49%	0.97 (0.65 – 1.46)	0.84 (0.62 – 1.13)
Regions – USA, Canada	186	4.19%	217	4.81%	209	4.72%	0.89 (0.73 – 1.08)	1.03 (0.85 – 1.24)
Regions – Central Europe	24	1.74%	25	1.84%	24	1.77%	0.99 (0.56 – 1.74)	1.04 (0.59 – 1.82)
Regions – Western Europe	58	1.87%	73	2.33%	80	2.59%	0.72 (0.51 – 1.01)	0.90 (0.66 – 1.24)
Regions – Latin America	11	2.01%	15	2.72%	17	3.18%	0.63 (0.29 – 1.34)	0.86 (0.43 – 1.72)
Regions – Asia	39	2.22%	39	2.17%	66	3.82%	0.57* (0.39 – 0.85)	0.57* (0.38 – 0.84)
Regions – Other	24	3.60%	30	4.42%	25	3.79%	0.96 (0.55 – 1.67)	1.19 (0.70 – 2.02)

ITT analysis set: Please refer to the clinical trial report[1] for details of the subject-years for each subgroup

* Denotes statistically significant in favour of DBG

Source: [80]

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; DBG, dabigatran etexilate; ITT, intention to treat; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack; WFN, warfarin

Table 63 Safety results for the less than 80 years of age subgroup

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
ICH (excluding haemorrhagic stroke)			17	0.17%	35	0.35%		0.48* (0.27 – 0.85)
ECH			252	2.52%	268	2.71%		0.93 (0.78 – 1.11)
Minor bleeds			1,390	13.88%	1,587	16.06%		0.86* (0.80 – 0.93)

ITT analysis set: DBG 110mg bid - N = 5,044, subject-years = 10,034; DBG 150mg bid - N = 5,019, subject-years = 10,014; WFN - N = 5,034, subject-years = 9,881
* Denotes statistically significant in favour of DBG
Source: [80]
Abbreviations: DBG, dabigatran etexilate; ECH, extracranial haemorrhage; ICH, intracranial haemorrhage; WFN, warfarin.

Table 64 Safety results for the greater than 80 years of age subgroup

Outcome	DBG 110mg bid		DBG 150mg bid		WFN		Hazard Ratio DBG 110mg bid v WFN (95% CI)	Hazard Ratio DBG 150mg bid v WFN (95% CI)
	Number of patients	Annual rate	Number of patients	Annual rate	Number of patients	Annual rate		
ICH (excluding haemorrhagic stroke)	4	0.21%			14	0.73%	0.29* (0.10 – 0.88)	
ECH	93	4.99%			67	3.50%	1.44^ (1.05 – 1.97)	
Minor bleeds	308	16.51%			344	17.98%	0.91 (0.78 – 1.07)	

ITT analysis set: DBG 110mg bid - N = 917, subject-years = 1,866; DBG 150mg bid - N = 1,057, subject-years = 2,019; WFN - N = 988, subject-years = 1,913
* Denotes statistically significant in favour of DBG. ^ Denotes statistically significant in favour of WFN
Source: [80]
Abbreviations: DBG, dabigatran etexilate; ECH, extracranial haemorrhage; ICH, intracranial haemorrhage; WFN, warfarin.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Bleeding

In the RE-LY study DBG resulted in lower rates of major bleeding events compared with WFN, significantly reducing the risk by 20% with DBG 110mg bid (p=0.0026) and 7% with DBG 150mg bid (p=0.3146). Of particular note, both DBG doses resulted in a significantly lower risk of the most serious bleeding events. Life-threatening bleeds were reduced by 33% and 20% for DBG 110mg bid (p = 0.0001) and 150mg bid (p = 0.0305) respectively. The corresponding relative risk reductions for haemorrhagic stroke were marked; 69% (p = 0.001) and 74% (p < 0.0001), with similar marked reductions of 70% and 59% for intracranial haemorrhage (both p < 0.0001).

It is worth noting that fear of major bleeding, particularly intracranial haemorrhage, is a major factor in the decision of whether to treat with WFN (or sub-optimally with aspirin). That the 150mg bid regimen demonstrated improved safety compared to WFN with respect to these most serious of bleeding events whilst also being significantly better than WFN at preventing ischaemic stroke, is a groundbreaking result.

DBG treatment resulted in less than half the incidence of major bleeds in a critical area or organ compared with WFN, including symptomatic intracranial bleeds. However DBG resulted in a higher incidence of major gastrointestinal bleeds compared with WFN. In general, VKA use prior to entering the trial did not appear to influence the time to first major bleed or the yearly event rate across all treatment groups.

Other AEs

Subjects treated with DBG had a slightly higher incidence of AEs compared with WFN. Gastrointestinal adverse events (in particular dyspepsia and gastritis-like symptoms) were reported more frequently with DBG. The risk for dyspepsia/gastritis with DBG generally occurred in the first few weeks of treatment and remained approximately twice that of WFN. However, serious AEs or discontinuations due to dyspepsia/gastritis were infrequent.

Serious AEs were slightly lower for the DBG groups and were consistent with an elderly population with AF receiving anticoagulant therapy.

There was no evidence of a class effect with respect to liver function test (LFT) elevations and direct thrombin inhibition. The risk for LFT elevations was in fact greater for WFN compared with DBG across the spectrum of measurements, from minor elevations (ALT/AST 1 to 3xULN) to the most severe (ALT/AST elevations up to 10xULN or ALT/AST >3xULN associated with total bilirubin >2xULN).

Rates of ALT/AST 3xULN were 2.0%, 1.7% and 2.1% for DBG 110mg, DBG150mg and WFN respectively. The corresponding rates for ALT/AST >3xULN associated with total bilirubin >2xULN were 0.2%, 0.2% and 0.4%.

It can be concluded that the efficacy benefits demonstrated in Section 5.5 are achieved without any significant safety penalty. Indeed in the case of the 150mg bid dose significant efficacy benefits are accompanied by significant improvements in the most serious major bleeding events, which can be considered a groundbreaking result.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

In summary, the main findings of the pivotal RE-LY trial were the following:

<u>DBG 150mg bid</u>

- Demonstrated to be superior to WFN with regards to the primary efficacy endpoint of all stroke and systemic embolism (35% relative risk reduction, $p < 0.0001$)
- Associated with a significantly lower rate of ischaemic stroke compared to WFN (25% relative risk reduction, $p = 0.0296$)
- Non-inferior to WFN with respect to the primary safety endpoint of major bleeding
- Significantly reduced intracranial haemorrhage compared to WFN (59% relative risk reduction, $p < 0.0001$)
- Significantly reduced haemorrhagic stroke compared to WFN (73% relative risk reduction, $p < 0.0001$)
- Significantly reduced life-threatening bleeds compared to WFN (20% relative risk reduction, $p = 0.0305$)
- Associated with a reduction in all-cause mortality approaching statistical significance compared to WFN (12% relative risk reduction, $p = 0.0517$)
- Significantly reduced vascular death compared to WFN (15% relative risk reduction, $p = 0.0430$)
- Associated with higher rates of gastrointestinal major bleeding compared to WFN (47% relative risk increase, $p = 0.0008$)
- The only other adverse event that occurred more frequently with DBG 150mg bid compared to WFN was dyspepsia/gastritis (15.5% compared to 7.8%).
- Higher rate of discontinuation compared to WFN (22.8% compared to 17.9%)

<u>DBG 110mg bid</u>

- Non-inferior to WFN with regards to the primary efficacy endpoint of all stroke and systemic embolism
- No statistically significant difference in ischaemic stroke compared to WFN

- Superior to WFN with respect to the primary safety endpoint of major bleeding (20% relative risk reduction, p = 0.0026)
- Significantly reduced intracranial haemorrhage compared to WFN (70% relative risk reduction, p < 0.0001)
- Significantly reduced haemorrhagic stroke compared to WFN (69% relative risk reduction, p < 0.0001)
- Significantly reduced life-threatening bleeds compared to WFN (33% relative risk reduction, p = 0.0001)
- Reduced all-cause mortality compared to WFN, but difference not statistically significant
- Reduced vascular death compared to WFN, but difference not statistically significant
- Not statistically significantly different to WFN in terms of gastrointestinal major bleeding
- The only other adverse event that occurred more frequently with DBG 110mg bid compared to WFN was dyspepsia/gastritis (16.4% compared to 7.8%).
- Higher rate of discontinuation compared to WFN (22.0% compared to 17.9%)

Overall it can be concluded that DBG offers significant and clinically meaningful efficacy benefits without any significant safety penalty. Indeed in the case of the 150mg dose significant efficacy benefits are accompanied by significant improvements in the most serious major bleeding events, which can be considered a groundbreaking result.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

RE-LY as a groundbreaking trial

The RE-LY trial is the largest ever performed in this therapeutic area, with over 18,000 patients randomised, two years of median follow-up and only 0.5% of patients lost to follow-up. INR control in WFN patients (64% time in therapeutic range) was comparable to other clinical trials, meaning that DBG was compared to what could be considered well-controlled WFN, especially considering the greater proportion of WFN-naïve patients recruited to RE-LY. Such levels of INR control are unlikely to be seen in routine practice.

These factors should all be regarded as indicators of a powerful, well-designed and robustly performed clinical trial. The recent FDA advisory panel decision (9 to 0 in favour of recommending DBG) further demonstrates that the impressive results of the RE-LY trial stand up to intensive scrutiny.

PROBE design of the RE-LY trial

The RE-LY trial employed a Prospective, Randomised, Open-Label, Blinded Endpoint (PROBE) design [63]. This is an obvious departure from the usual gold standard clinical trial design which would blind participants and investigators to treatment allocation. Anticoagulation presents specific challenges

in this regard, particularly in the requirement for regular INR tests for patients receiving WFN. Whilst it is possible to conduct a double-blind, double-dummy trial with the use of matched placebos and sham INR tests (as seen for example in SPORTIF V[84]) this can be complex, troublesome and even undesirable. The PROBE design used for RE-LY remains an attractive, practical and robust option for several reasons:

- More representative of real-life differences in management of DBG and WFN, which would be impossible to recreate in a double-blind, double-dummy study
- Allows anticoagulation–related outcome events to be managed most appropriately according to the treatment received
- Open label design has been used in most placebo-controlled WFN trials, with no apparent difference in effects compared to a double-blind methodology

Since the high subject numbers required for the RE-LY trial necessitated robust recruitment, an open-label design was chosen as the most appropriate design, with the incorporation of extensive measures to minimise bias. These measures included:

- Blinded adjudication of events by at least two independent adjudicators
- Database and data handling assigned to an academic group independent from the sponsor
- Blinding of sponsor and trial management personnel to “by treatment” analyses during trial
- Monitored by DSMB
- CRF construction to elicit events based on investigations and other assessments performed by the site

The following measures were used to minimise reporting bias:

- Objective, clinically relevant outcomes
- Blinded DBG doses
- Categorisation of all hospitalisations
- Patient stroke and bleeding questionnaires at each visit
- Blinded review of TIAs for possible under-reporting of strokes
- Review of adverse events for terms that suggested un-reported stroke or bleed
- Screening of haemoglobin changes in laboratory data for possible under-reporting of major bleeds
- Evaluating reports of anaemia for possible events

In addition, the following procedures were implemented to reduce the potential for bias in the reporting and assessment of the primary and secondary events:

1. Clearly defined objective outcomes: The primary and secondary outcomes of the study were clinically relevant events for which objective documentation was obtained. Standard, widely accepted definitions that relied on objective documentation were used.
2. Blinded adjudication committee(s): All outcome events, including major bleeds, were adjudicated by adjudication experts blinded to the treatments used. Blinding of all event

documentation was performed prior to adjudication. Key documents for major bleeds (not necessarily fatal bleeds) and "other" endpoints, i.e., TIAs, were provided for adjudication. This committee reported to the Steering Committee. Records of all adjudication decisions and of Adjudication Committee meeting minutes were maintained.

3. Blinded DBG doses: Two different doses of DBG were tested. The dose of DBG was blinded by the use of matching capsules.
4. Screening of all hospitalisations: In order to ensure that all stroke, systemic embolism, and other study outcome events were appropriately reported, all hospitalisations were recorded with the reason for admission.
5. Patient Stroke/Bleeding Questionnaire: A questionnaire querying subjects for signs and symptoms of stroke and bleeding was administered at each visit. The goal was to reduce the possibility of the under-reporting of strokes, TIAs, and bleeding events. All symptoms were evaluated, and, if potentially consistent with a study event were referred to the adjudication committee.
6. Review of Transient Ischemic Attack: All reported TIA events were adjudicated for possible upgrade to stroke.
7. Review of data for clinical events: Any adverse event that indicated a potential loss of neurological function, such as unilateral weakness, loss of vision, or sensory disturbance, triggered a request for more information from the centre for event adjudication if potentially consistent with a study event. Any decrease in haemoglobin levels of >2 g/dL was similarly investigated.
8. Data handling and tabulations: During the course of the trial, the Co-ordination Centre (PHRI, McMaster University, Hamilton, Canada) was responsible for the management of the data. By-treatment data tabulations were not done during the course of the trial other than for the DSMB, and that was managed by a statistician removed from the trial team. Key personnel involved with data collection and day-to-day operations did not have access to the randomisation code.

In addition, no member of the Steering Committee, the Operations Committee (which, comprised in the majority by leading academics, also formed part of the Steering Committee), or the sponsor had access to any by-treatment analyses of data during the course of the trial. Individual subject information may have been accessible e.g., when receiving Serious Adverse Events or queries from sites or management of INR control. Separate independent review of the process for managing and maintaining blinding was conducted. This review concluded that the blinding was scrupulous and the emerging trends in the data were unknown to the study leadership or to all personnel involved in the day-to-day operations of the trial at the time of making key decisions.

Importantly, it can be argued that any bias arising from the PROBE design would most likely be against DBG. Investigators and patients are more likely to be sensitive to adverse events occurring with a new, as yet unapproved, study medication, and more comfortable in dealing with familiar issues arising due to WFN use.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Clinical Endpoints

The pivotal RE-LY trial examined each of the outcomes that are clinically relevant within the therapeutic area for stroke prevention in AF. The goal of anticoagulation therapy is to prevent stroke (and systemic embolism); this was the primary outcome measure in RE-LY. The major drawback of anticoagulation therapy is the increased risk of bleeding events; major bleeding was the primary safety endpoint. Each of the primary endpoints was further disaggregated by type/site and severity of stroke and major bleed.

In addition, RE-LY examined a series of secondary endpoints (both efficacy and safety) that should be considered for a patient group that is predominantly elderly and often with several co-morbidities. These include mortality (vascular and all-cause), myocardial infarction, pulmonary embolism and hospitalisation.

Other safety indicators were also closely examined. These include gastrointestinal bleeding and discomfort (dyspepsia and gastritis). In addition, a previous direct thrombin inhibitor, ximelagatran, was withdrawn due to elevated liver toxicity. Liver Function Tests were scrupulously analysed in RE-LY to investigate any potential class effect.

Subgroups

There is a clear dose response relationship between the lower and higher doses of DBG in the RE-LY trial. Whilst both doses were shown to be efficacious and safe compared to well-controlled WFN, as would be expected the higher dose offered increased efficacy whereas the lower dose offered corresponding increased benefits in terms of safety. Subgroup analyses were therefore performed to investigate any potential stratification of patients that may be appropriate for one or other of the doses. This is clearly appropriate given the likely delineation of the doses in the SmPC and therefore routine use in England and Wales.

INR control and setting

The efficacy and safety of WFN depends upon regular monitoring of INR and periodic adjustment of dose to keep the INR in the therapeutic range (INR 2-3). The time in therapeutic range (TTR) summarises the control of WFN over time. In a non-inferiority trial, comparison of a test treatment against well-controlled WFN ensures that a conclusion of efficacy (or safety) similar to standard treatment is not based on a drug that is given sub-optimally. If the TTR is low then efficacy and safety of WFN will decrease. In such a situation, it will be easier for a test agent to do as well as WFN and thus conclude non-inferiority when in fact it may not be as effective or as safe as well-controlled WFN. Therefore it is important that the TTR in RE-LY is reflective of the best quality of WFN control in order that the results of the trial are generalisable.

The mean TTR for WFN in RE-LY was 64.4% (median 67.3%). This is comparable to recent large studies of WFN in AF [84, 85, 89, 91, 106], despite a high proportion of WFN-naïve subjects in RE-LY, which are more difficult to control. In RE-LY the mean TTR was 7.1% to 12.3% less in VKA naïve subjects for the first 9 months of the study, and 5.4% less overall (61.6% TTR vs. 66.9% TTR).

Studies have shown that the consistency of adequate anticoagulation with WFN and other VKAs is lower in the community than in clinical trials. In a systematic review by van Walraven and colleagues, patients managed in the community spent significantly less time within the therapeutic INR range compared with patients within randomised clinical trials (56.7% vs 66.4%; P<0.0001) [107] In the worst performing sub-group (i.e. those treated with VKAs by community physicians without self-monitoring of INR), patients spent half of their time outside the therapeutic range.

However, in the same report many of the study groups that were classified as community-based or clinic-based were from randomised trials, thus potentially underestimating the time spent outside the target INR range in clinical practice. Therefore Dolan *et al*. conducted a systematic review of 22 studies in VKA-treated patients with AF to overcome this limitation[108]. In this analysis, the overall proportion of time spent within the target INR range was 61.3% (95% CI 58.8-63.8; P<0.00001).

Therefore it can be said with some confidence that the level of INR control seen in RE-LY is at least comparable with that likely to be seen in routine clinical practice.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The RE-LY trial compares DBG with the gold standard of care, dose-adjusted WFN. The use of WFN in this indication is based on a risk-benefit decision between the perceived benefit of preventing stroke, compared to the perceived risk of anticoagulation-related bleeding events. In England and Wales, the relevant NICE clinical guideline is guideline number 36[19]. It advocates a stroke risk algorithm (**Figure 2**) with moderate to high risk patients considered for anticoagulation therapy.

Moderate to high risk is defined in patients with a previous stroke or TIA or other stroke risk factors (age over 65 years, hypertension, diabetes, heart failure or left ventricular dysfunction, which loosely follows the recognised $CHADS_2$ risk assessment) [17]. The RE-LY trial inclusion criteria, as outlined in Section 3, match up well with these criteria meaning that the population in RE-LY is of a similar risk profile to English and Welsh patients recommended for WFN treatment.

Another guideline from the European Society of Cardiology[14] (published on 29th August 2010) further advocate the use of stroke risk stratification algorithms that closely reflect that used in the RE-LY trial.

In a recent Scottish audit by QIS [109] it was indicated that approximately 53% of AF patients are receiving WFN. Of the remaining 47% of patients, a significant majority receive aspirin or other antithrombotic therapy (the audit suggests that almost 92% of AF patients receive some form of antithrombotic). Some of these patients will be lower risk patients indicated for aspirin, however a sizeable number are likely to be of sufficiently high stroke risk to warrant treatment with WFN. Patients may refuse WFN due to the lifestyle change necessitated by drug-drug and drug-food interactions and/or continual INR testing and dose adjustment. Others may not be able to be adequately controlled on WFN. It is not unreasonable to assume that this pattern may also be reflected in England and Wales. There are no other therapeutic alternatives to WFN.

Therefore it is clear that clinical guidelines and recent audit data suggest that the design and comparison of the RE-LY trial make it applicable to clinical practice in England and Wales. The patients included in the trial match the risk profile of those indicated for WFN. Further, the RE-LY trial addresses a key unmet need in routine practice (the sub-optimal treatment of patients facing an unnecessarily high stroke risk because they are eligible for WFN but are not willing or able to receive it).

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

Search Strategy

A comprehensive search strategy was designed to retrieve relevant studies from published literature. The following databases were examined from 1990 up to 5th July 2010:

- Embase
- Medline
- Medline ® In-process
- NHS EED
- EconLIT

The search strategies incorporated keyword terms, subject index headings (MESH for terms for Medline ® In-process, NHS EED; EMTREE terms for Embase) and the relationship between the search terms (by using Boolean operators). The study design filter used for Embase/Medline was adapted from SIGN filters and validated in house.

The search was limited to the last 20 years in order to capture the most up to date and therefore the most relevant studies. In addition, the manufacturer's internal literature databases, BILIT and pre-BILIT were searched up to 5th July 2010.

The search strategies used for each database are shown in Appendix 10 along with the following information: database searched, interface, date on which search was conducted, and date span of search.

In addition to the search of literature databases, the following conference proceedings were hand searched:

- ISPOR Annual International Meeting 2008 and 2009
- ISPOR Annual European Congress 2008 and 2009

Eligibility Criteria

To be included in this review, studies were required to meet the eligibility criteria (**Table 65**).

Table 65 Eligibility criteria

Criteria	Rationale
Patient population and intervention	
Disease: atrial fibrillation	As per the decision problem
Gender: male/female	As per the decision problem
Age group: adults (≥ 18 years)	As per the decision problem
Race: any	As per the decision problem
Aim of treatment: Stroke prevention	Only studies examining the prevention of stroke in AF are relevant to the decision problem. Other studies relating to different treatment goals, such as rate or rhythm control, are not relevant to the review.
Intervention: Dabigatran etexilate (primary study question)	Only studies including DBG are relevant to the decision problem.
Study design	
Economic evaluation (cost-effectiveness, cost-utility, cost-benefit and cost-minimisation analyses)	As per the decision problem
Publication timeframe	
1990 onwards for literature searches	Given the changing nature of knowledge and strategies in stroke prevention in AF over the past decades, it is reasonable to restrict the review to studies published over the past 20 years.
Language restrictions	
English only	This is simplifying criteria for the review, however it is not expected that the restriction would limit results substantially.

Abbreviations: AF, atrial fibrillation; DBG, dabigatran etexilate.

First pass of citations

Duplicates of citations (due to overlap in the coverage of the databases) were excluded. The remaining citations were first screened based on the abstract supplied with each citation. Those that did not match the eligibility criteria were excluded at 'first pass'; where unclear, citations were included. First pass involved screening of abstracts in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer.

Full-text copies of all references surviving the first pass were obtained at this stage.

Second pass of citations

The eligibility criteria were applied to the full-text citations in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer. Where appropriate, any included studies were to be categorised by study design during the second pass.

Extraction strategy

Any studies included following 'second pass' were to be extracted to pre-defined data extraction

grids. Data from studies were to be extracted in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer.

If more than one publication was identified describing a single trial, the data were to be compiled into a single entry in the data extraction table to avoid double counting.

Quality assessment

The methodology of included and extracted studies was to be assessed using a format based on Drummond and Jefferson's checklist[110].

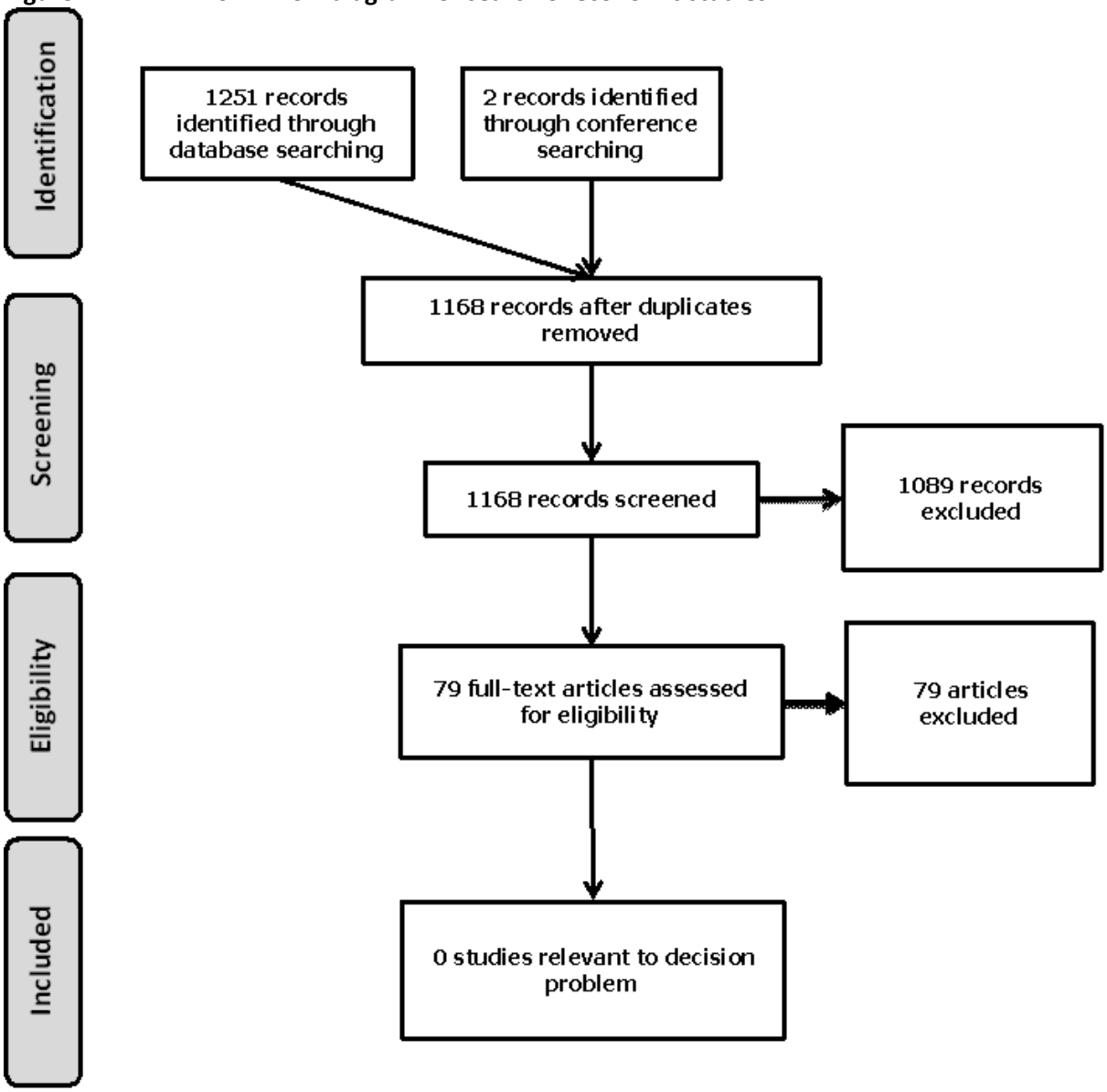
Results

The search of the literature yielded 1,251 citations. Two additional citations were identified through the hand searching of the conferences. De-duplication resulted in the removal of 85 overlapping citations. The titles and abstracts of the remaining 1,168 citations were reviewed for relevance.

Following first pass, 79 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports in the second pass, all the remaining 79 studies were excluded.

The flow of studies in the systematic review is presented in **Figure 17**.

Figure 17 PRISMA flow diagram for search of economic studies



The reasons for exclusion at second pass are detailed in **Table 66**. Many of the studies had multiple reasons for exclusion; only one reason is presented for each in the table.

Table 66 Reasons for exclusion at second pass

Reason	Number of citations
Intervention	**44**
Indication	**15**
Patient population	**13**
Review / editorial	**2**
Study design	**2**
Copy / duplicate	**1**
Disease area (i.e. not AF)	**2**

The full list of studies excluded at second pass is included as a separate file in Appendix 10. As no studies relevant to the decision problem were identified, a *de novo* economic evaluation is required.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Not applicable.

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Not applicable.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient population included in the economic evaluation is adult patients diagnosed with non-valvular AF, at risk of stroke or systemic embolism and eligible for anticoagulation treatment. The population reflects patients eligible for the RE-LY trial [43] and mirrors other stroke risk stratification schema such as $CHADS_2$ [17].

To be eligible for inclusion to the RE-LY trial patients must have had documented AF and at least one of the following stroke risk factors:

- Previous stroke, TIA or systemic embolism
- Left ventricular ejection fraction of less than 40%
- Symptomatic heart failure of New York Heart Association class II or higher within 6 months before screening
- Age of at least 75 years
- Age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease.

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[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Consequently, patients could be enrolled with a $CHADS_2$ score of 0 or 1.

Two doses of dabigatran etexilate (DBG) were studied in the RE-LY trial, 110mg bid and 150mg bid. The economic evaluation examines two different approaches to the use of these doses, as described in **Table 67**.

Table 67 Definitions for DBG interventions used in the economic evaluation

Reference	DBG Regimen
1	DBG 150mg bid for all eligible patients (Denoted as "All RE-LY")
2	DBG 110mg bid for all eligible patients (Denoted as "All RE-LY")
3	Stratified use of the two DBG doses as follows: a) Patients aged less than 80 years at baseline initiated on DBG 150mg bid and switched to DBG 110mg bid at age 80 (Denoted as "DBG Sequence") b) Patients aged at least 80 years at baseline initiated on DBG 110mg bid (Denoted as "DBG ≥80")

Abbreviation: DBG, dabigatran etexilate

Interventions 1 and 2 follow the original design of the RE-LY trial [56] and will provide cost-effectiveness estimates for each DBG dose in a general, eligible AF population. However, given the clear dose-response demonstrated in Sections 3 and 4, it is clear that one or other of the doses may be more appropriate in patients of differing risk profiles. Therefore intervention 3 targets each dose within a specific patient population as per the current proposed SPC, thereby increasing the overall capacity to benefit.

The baseline characteristics of the three populations modelled in the economic evaluation, based on the RE-LY trial, are presented in **Table 68**. As would be expected, the characteristics of the sequence subgroup populations are younger and more male (3a) or older and more female (3b) than the overall population from RE-LY (1 and 2).

Table 68 Baseline characteristics of the modelled populations

Analysis	Gender (% male)	Mean age (years)	$CHADS_2$ breakdown
1 and 2. DBG 150 or DBG 110	63.6%	71.0	0: 2.5% 1: 29.4% 2: 35.6% 3+: 32.5%
3a. DBG Seq <80	65.0%	69.1	0: 3.0% 1: 32.6% 2: 34.4% 3+: 30.0%
3b. DBG Seq ≥80	57.1%	82.9	0: 0% (by rule) 1: 13.5% 2: 41.7% 3+: 44.7%

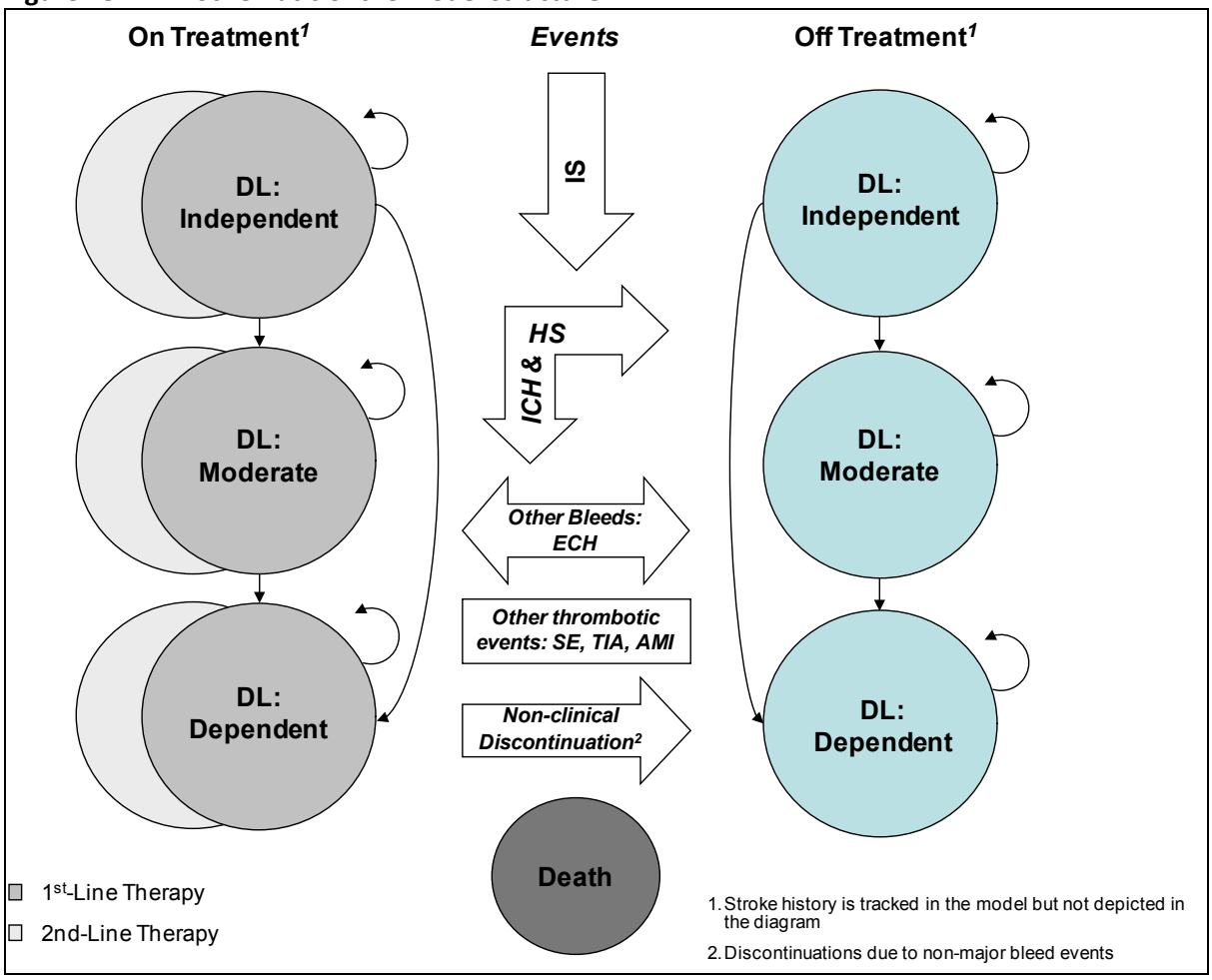
Abbreviation: DBG, dabigatran etexilate; Seq, sequence.
Source: [1, 80]

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

A stylised schematic of the economic model structure is illustrated in **Figure 18**.

Figure 18 Schematic of the model structure*



* Developed from the paper by Sorensen (2009), Figure 1[111].
Abbreviations: AMI, acute myocardial infarction; DL, disability level; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; SE, systemic embolism; TIA, transient ischaemic attack

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

Given the chronic nature of AF and the potential changes in health status over time, it was considered appropriate to employ a Markov cohort simulation model. This was chosen for several reasons. First, it enables transparent representation of the diverse health states relevant to anticoagulation therapy in AF patients and the transitions between them. Second, it is a commonly used approach in this disease area [111, 112]. Third, compared to individual simulation, Markov simulations are easy to use and readily accessible to a wider-range of users. All decision analyses imply some element of time, but decision trees are not well-equipped to model disease processes that are recursive or that occur repeatedly over fixed time intervals. A Markov model is a more flexible approach to model the course of AF from start of treatment through subsequent treatments to a terminal outcome and calculate outcomes such as quality adjusted life years (QALYs).

The model concept followed the recent publication by Sorensen *et al.* [111] and was programmed in MS Excel®. The structure of the model was informed by previous publications and expert clinical

review. A clinical expert panel was assembled to guide the development of the initial model structure developed prior to completion of the RE-LY trial[111]. Specifically this panel provided input on the key clinical events that should be included, typical treatment patterns and important model/assumption validation. As a result of this process, the model considers more clinical events than previous economic evaluations[112].

A further clinician from the UK was recruited to guide the development of a revised model structure based on the initial findings from the RE-LY trial. SE, AMI, and options to switch to second-line treatments were added to the model. Model assumptions were validated with the clinical expert.

6.2.4 Please define what the health states in the model are meant to capture.

The model was designed to follow AF patients through the natural course of disease and Markov health states were stratified by the following factors:

- Treatment status: 1st line, 2nd line or off treatment
- Stroke history: yes or no
- Disability: independent, moderately disabled, dependent or dead

A cohort of 10,000 AF patients enters the model and is distributed by $CHADS_2$ score and previous stroke history. As the model simulates the Markov cycles, patients are at risk of relevant clinical events until the end of their life. These events have varying effects on the transition or otherwise between health states, as described in **Table 69**.

Table 69 Effect of various events on health status

Event	Effect on treatment status	Effect on stroke history	Effect on disability	Additional mortality risk
Ischaemic stroke	If non-fatal, no change	If no previous stroke, switches status from yes to no	Recover to previous disability level or deteriorate to a worse level	Yes
Systemic embolism	If non-fatal, no change	If no previous stroke, switches status from yes to no	If non-fatal, no change	Yes
Haemorrhagic stroke	If non-fatal, permanent discontinuation	If non-fatal, no change	Recover to previous disability level or deteriorate to a worse level	Yes
Intracranial haemorrhage	If non-fatal, permanent discontinuation	If non-fatal, no change	Recover to previous disability level or deteriorate to a worse level	Yes
Extracranial haemorrhage	If non-fatal, no change, temporary or permanent discontinuation	If non-fatal, no change	If non-fatal, no change	Yes
Acute MI	If non-fatal, no change	If non-fatal, no change	If non-fatal, no change	Yes
TIA	No change	If no previous stroke, switches status from yes to no	No change	No
Minor bleed	No change	No change	No change	No
No event	No change, switch to 2nd line or permanent discontinuation	No change	No change	No

Abbreviations: MI, myocardial infarction; TIA, transient ischaemic attack

The various permutations of the possible transitions result in fourteen possible permanent active health states, with a further eight temporary health states which track patients who have an ECH and temporary discontinue therapy for one cycle. The twenty-third and final health state being the absorbing dead state.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The patient cohort starts on one of the comparison treatments. Patients age over time and are also subject to a mortality risk from other causes at every cycle using age and gender adjusted all-cause mortality data. Patients may also switch or discontinue treatment permanently for reasons not related to a clinical event.

As noted in Section 2.1, the main considerations in this indication are the competing risks of embolic and haemorrhagic events. The economic model is designed to capture all relevant events whilst accounting for the varying risks that patients may face across a variety of health states.

The Markov cycle length in the model is 3 months. The cycle length was chosen because it reflected the typical duration of temporary drug discontinuation due to ECH and patients are unlikely to

experience more than one major event during this time. Additionally, stroke disability and survival start to plateau around 90 days [113]. A longer cycle length may mean important events are missed given and a shorter cycle length would not allow disability following an event to be fully established. A half-cycle correction was used in the model.

This economic model represents an advance in the approach to comparing WFN to other treatments by allowing the examination of WFN use in scenarios reflective of real-world clinical conditions. INR control has been shown to have impacts on costs and QALYs[111]. The model tracks patients by disability level following stroke or ICH, which was important given the large costs and health impacts of disability (estimated to account for about 75% of total costs[111]). It also considers the discontinuation of anticoagulation, which is common in clinical care, and has important consequences.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

The key features of the economic model are summarised in **Table 70**.

Table 70 Other features of the analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (up to 100 years)	This is appropriate considering the following factors: • AF is a chronic disease • The disabling consequences of strokes and haemorrhagic events can be life-long The economic model has the flexibility to consider shorter time horizons, which will be explored in sensitivity analysis.
Cycle length	3 months	This assumption is discussed in Section 6.2.5.
Half-cycle correction	Half cycle correction was used at the start of the model	The cycle length is sufficiently long to justify a half-cycle correction in the initial cycle. No half-cycle correction was necessary in the final cycle since the entire cohort is absorbed.
Were health effects measured in QALYs; if not, what was used?	Yes, health effects are measured in QALYs.	None required.
Discount of 3.5% for utilities and costs	Yes, a 3.5% discount rate was applied to both costs and health effects. Other rates are tested in sensitivity analysis.	None required.
Perspective (NHS/PSS)	Yes, the economic evaluation is performed from the NHS & PSS perspective.	None required.

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Please refer to the response to section 6.2.1 regarding the implementation of DBG in the economic model.

The comparators are implemented as follows:

- WFN (primary analysis): Dosing of WFN and frequency of INR testing is patient specific dependent on individual INR results. The economic model implements the relative treatment effects for WFN as per the RE-LY trial, where an INR range of 2.0 – 3.0 is/was targeted (standard practice). The methods for applying the cost of WFN and INR monitoring are explained in Section 6.5.
- Aspirin monotherapy (secondary analysis): It is assumed that aspirin monotherapy is represented in terms of relative treatment effect by the results of the MTC described in Section 5.7. Once-daily aspirin is inexpensive therefore the exact dosing for cost purposes will not be important. This is discussed further in Section 6.5.
- Aspirin plus clopidogrel (secondary analysis): This regimen is not yet licensed for this indication. Therefore the experimental regimen studied in the ACTIVE-A trial[39] is applied to the economic model (clopidogrel 75mg od plus aspirin 75-100mg od). The relative treatment effects for this comparator are also derived from the MTC.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No continuation rules have been assumed.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The responses to Sections 6.3.1 and 6.3.2 are combined below.

Outcome Measures

The decision to initiate a patient on anticoagulation treatment is made in the context of a risk-benefit calculation between perceived benefit from prevention of ischaemic events and perceived risk of harm from haemorrhage. Therefore appropriately the primary clinical outcomes considered by the economic model are the most relevant ischaemic and haemorrhagic events to which AF patients are considered at risk.

Ischaemic events

- Primary and recurrent ischaemic stroke (IS)

The primary goal of anticoagulation in this indication is the prevention of ischaemic stroke. Importantly, IS events in the economic model are assessed by the resultant disability of the patient at 90 days or one Markov cycle following the event, *not* the severity of the initial/infarct event itself, although these are often directly proportional. Resultant disability is classified according to the modified Rankin scale (mRs) as either independent (mRs = 0-2), moderate disability (mRs = 3-4) totally dependant (mRs = 5) or fatal (mRs = 6). Each IS event is associated with a one-shot acute cost and disutility (both stratified by severity), assessed within the cycle in which the event takes place. Further, ischaemic stroke is also associated with ongoing costs and utility levels commensurate with the resultant disability status. These ongoing costs and utilities are assessed in every subsequent model cycle whilst the patient's disability level remains unchanged. Finally, patients may experience recurrent IS in subsequent cycles.

- Systemic embolism (SE)
- Transient ischaemic attack (TIA)
- Acute myocardial infarction (AMI)

SE, TIA and AMI events are all associated with a one-shot acute cost and disutility, assessed within the cycle in which the event takes place. These events do not result in long-term disability meaning no ongoing costs or changes to utility are assumed. SE and AMI can however be immediately fatal.

Haemorrhagic events

- Haemorrhagic stroke (HS)
- Intracranial haemorrhage (ICH)

HS and ICH events, similar to IS, are associated with both one-shot acute cost and disutility, and ongoing costs and utility levels commensurate with the resultant disability status. The resultant disability for HS is assessed using the mRs and for ICH is assessed using the Glasgow Outcomes Scale.

- Extracranial haemorrhage (ECH)

ECH (other non-ICH major bleed) are initially stratified by site as gastrointestinal (GI)/non-GI, then by fatal/non-fatal. It was important to distinguish GI bleeds since they are the most prevalent type of these events (in the RE-LY trial, GI bleeds accounted for approximately 42% of non-ICH major bleeds) and were demonstrated to be higher with DBG compared to WFN[1]. ECH events are all associated with a one-shot acute cost and disutility, assessed within the cycle in which the event takes place. These events do not result in long-term disability meaning no ongoing costs or changes to utility are assumed. ECH can however be immediately fatal.

Each of the events included in the model is clinically-relevant and linked to final outcomes in at least one way, either through mortality risk or change in quality of life (either acute or ongoing). This is non-controversial, however further evidence of these links is provided in the data collection section below.

The economic model reports the absolute number of each event occurring within the patient cohort along with the number of deaths. This information, when combined with the inputted utility scores, can be used to calculate the following final outcomes:

- Total life years (LYs) and mean LYs per patient
- Total QALYs and mean QALYs per patient

The economic model will also accumulate the following costs:

- Cost of antithrombotic treatment, including INR monitoring
- Acute event costs
- Long-term follow-up costs resulting from disability

These cost values will be recorded as both total costs for the cohort and mean cost per patient, both disaggregated for each category and aggregated.

Clinical Data

The clinical data populating the economic model can be stratified into five categories:

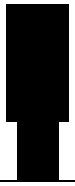
1. Baseline characteristics
2. Baseline risk of treatment-dependent clinical events
3. Relative risk of treatment-dependent clinical events
4. Other treatment-dependent probabilities

5. Other treatment-independent probabilities

1. Baseline characteristics

The initial conditions for the model include the distribution of patients by $CHADS_2$ score and stroke history. These are based on the baseline characteristics of the patients in RE-LY and are shown in **Table 71**.

Table 71 Baseline $CHADS_2$ distribution and proportion with previous stroke history

$CHADS_2$ Score	All RE-LY		Sequence Model < 80		Sequence Model ≥ 80	
	$CHADS_2$ Distribution	% with Previous Stroke	$CHADS_2$ Distribution	% with Previous Stroke	$CHADS_2$ Distribution	% with Previous Stroke
0	2.5%	0.0%		0.0%	0.0%	0.0%
1	29.4%	0.0%		0.0%		0.0%
2	35.6%	6%				0.0%
3	20.2%	37%				
4	8.9%	81%				
5	2.9%	100.0%		100.0%		100.0%
6	0.5%	100.0%		100.0%		100.0%

Source: [1, 80]. Cross-reference: **Table 26**

2. Baseline risk of treatment-dependent clinical events

As the primary comparator for the economic evaluation, and as the pivotal intervention within the network of the MTC, it was necessary to "anchor" all other treatment strategies to a baseline based on WFN. Relative risks for other treatments are then applied to this baseline to assess relative treatment effect. **Table 72** presents the baseline risks for each clinical event derived from the RE-LY trial, stratified by analysis (all RE-LY, <80 years and ≥ 80 years). Of note, the baseline risks for ischaemic stroke in patients with $CHADS_2$ scores of 3 and 4 (similarly for scores of 5 and 6) were pooled due to lack of data. This simplifying assumption is unlikely to have a major impact.

The conversion of baseline risk rates to cycle probabilities is presented in **Table 73**. For the purposes of the PSA, each probability is assumed to have a beta distribution, parameterised as:

- Alpha = number of events
- Beta = Number of person-years – number of events

Table 72 Baseline (warfarin) risks of treatment-dependent clinical events

	All RE-LY analysis (1 and 2)			< 80 years sequence analysis (3a)			≥ 80 years analysis (3b)		
Clinical Event	**Total events***	**Total person-years**	**Rate per 100 person-years**	**Total events**	**Total person-years**	**Rate per 100 person-years**	**Total events**	**Total person-years**	**Rate per 100 person-years**
Ischaemic stroke ($CHADS_2$ Score = 0)	[redacted]	[redacted]	[redacted]	2	322	0.62			
Ischaemic stroke ($CHADS_2$ Score = 1)	[redacted]	[redacted]	[redacted]	25	3,147	0.79	1	236	0.42
Ischaemic stroke ($CHADS_2$ Score = 2)	[redacted]	[redacted]	[redacted]	31	3,512	0.88	13	845	1.54
Ischaemic stroke ($CHADS_2$ Score = 3 and 4)	[redacted]	[redacted]	[redacted]	41	2,646	1.55	18	727	2.48
Ischaemic stroke ($CHADS_2$ Score = 5 and 6)	[redacted]	[redacted]	[redacted]	7	253	2.77	5	106	4.72
Systemic embolism	21	11,794	0.18	15	9,881	0.15	6	1,913	0.31
Haemorrhagic stroke	45	11,794	0.38	33	9,881	0.33	12	1,913	0.63
Intracranial haemorrhage	49	11,794	0.42	35	9,881	0.35	14	1,913	0.73
Extracranial haemorrhage	335	11,794	2.84	268	9,881	2.71	67	1,913	3.50
Acute MI	75	11,794	0.64	58	9,881	0.59	17	1,913	0.89
TIA	99	11,794	0.84	72	9,881	0.73	27	1,913	1.41
Minor bleed	1,931	11,794	16.37	1,587	9,881	16.06	344	1,913	17.98

* The total number of patients with an ischemic or uncertain stroke is 143 for warfarin. In the CTR this number is not given, only the number of patients with an ischemic stroke (=134) and patient with an uncertain stroke (=10) is given - the number of patients with an ischemic or uncertain stroke remains the same (143) as one patient experienced both types of event.
Abbreviations: MI, myocardial infarction; TIA, transient ischaemic attack.
Sources: [1, 80] Cross-reference: **Table 30, Table 31, Table 35, Table 36, Table 58, Table 63, Table 64.**

Table 73 Conversion of rates to probabilities (baseline risk, derived from Table 72)

	All RE-LY analysis (1 and 2)		< 80 years sequence analysis (3a)		≥ 80 years analysis (3b)	
Clinical Event	**Rate**	**Probability**	**Rate**	**Probability**	**Rate**	**Probability**
Ischaemic stroke ($CHADS_2$ Score = 0)	[redacted]	[redacted]	0.62	0.002		
Ischaemic stroke ($CHADS_2$ Score = 1)	[redacted]	[redacted]	0.79	0.002	0.42	0.001
Ischaemic stroke ($CHADS_2$ Score = 2)	[redacted]	[redacted]	0.88	0.002	1.54	0.004
Ischaemic stroke ($CHADS_2$ Score = 3 and 4)	[redacted]	[redacted]	1.55	0.004	2.48	0.006
Ischaemic stroke ($CHADS_2$ Score = 5 and 6)	[redacted]	[redacted]	2.77	0.007	4.72	0.012
Systemic embolism	0.18	<0.001	0.15	<0.001	0.31	0.001
Haemorrhagic stroke	0.38	0.001	0.33	0.001	0.63	0.002
Intracranial haemorrhage	0.42	0.001	0.35	0.001	0.73	0.002
Extracranial haemorrhage	2.84	0.007	2.71	0.007	3.50	0.009
Acute MI	0.64	0.002	0.59	0.001	0.89	0.002
TIA	0.84	0.002	0.73	0.002	1.41	0.004
Minor bleed	16.37	0.040	16.06	0.039	17.98	0.044

Abbreviations: MI, myocardial infarction; TIA, transient ischaemic attack
Notes:

1. Rates are transformed to probabilities per cycle using the following formula: 1 – exp (-(rate / 100) x 0.25)
2. The probabilities apply to each 3-month model cycle

3. Relative risk of treatment-dependent clinical events

The baseline risks presented above apply to the WFN cohort in each analysis. For DBG, aspirin, A+C and "no treatment" relative risks (RR) are applied to each baseline risk to estimate relative treatment effect. The "no treatment" option is included as it is assumed to be the 2nd line treatment when aspirin monotherapy is the 1st line treatment.

Table 74 presents the relative risks for each clinical event derived from the RE-LY trial (DBG) or the MTC (aspirin), stratified by analysis (all RE-LY, <80 years and ≥ 80 years).

The conversion of relative risks to cycle probabilities is calculated by multiplying the baseline probabilities in **Table 73** by the relative risks. These, alongside their standard errors are presented in **Table 75**. For the purposes of the PSA, each probability is assumed to have a log-normal distribution.

Table 74 Relative risks of modelled clinical events (95% CI)

	All RE-LY analysis (1 and 2)		< 80 years analysis (3a)	≥ 80 years analysis (3b)	All models*		
Clinical Event	**DBG 150mg bid**	**DBG 110mg bid**	**DBG 150mg bid**	**DBG 110mg bid**	**Aspirin**	**Aspirin + clopidogrel**	**No Treatment**
Ischaemic stroke	0.76 (0.59 – 0.97)	1.10 (0.88 – 1.37)	0.77 (0.58 – 1.03)	0.82 (0.51 – 1.33)	1.62 (0.99 - 2.65)	2.07 (1.38 - 3.11)	3.35 (2.23 - 5.03)
Systemic embolism	0.61 (0.30 – 1.21)	0.71 (0.37 – 1.38)	0.66 (0.30 – 1.47)	0.51 (0.13 – 2.06)	1.77 (0.66 - 4.77)	3.57 (1.52 - 8.36)	4.44 (1.78 - 11.08)
Haemorrhagic stroke	0.26 (0.14 – 0.49)	0.31 (0.17 – 0.56)	0.21 (0.09 – 0.47)	0.26 (0.07 – 0.91)	0.84	0.84	0.33
Intracranial haemorrhage	0.52 (0.32 – 0.84)	0.32 (0.18 – 0.57)	0.48 (0.27 – 0.85)	0.29 (0.10 – 0.88)	0.51 (0.16 - 1.6)	0.53 (0.19 - 1.45)	0.33
Extracranial haemorrhage	1.07 (0.92 – 1.24)	0.94 (0.81 – 1.10)	0.93 (0.78 – 1.11)	1.44 (1.05 – 1.97)	1.14 (0.47 - 2.73)	1.10 (0.71 – 1.72)	0.61 (0.1 - 3.78)
Acute MI	1.27 (0.94 – 1.71)	1.29 (0.96 – 1.75)	1.26 (0.89 – 1.78)	1.39 (0.74 – 2.60)	1.42 (0.84 - 2.39)	1.48 (0.83 - 2.63)	1.57 (0.67 – 3.69)
TIA	0.86 (0.65 – 1.15)	0.74 (0.55 – 1.00)	0.92 (0.66 – 1.29)	0.45 (0.23 – 0.89)	1.56 (0.86 – 2.83)	1.56 (0.86 – 2.83)	1.23 (0.59 – 2.58)
Minor bleed	0.91 (0.86– 0.97)	0.79 (0.74 – 0.84)	0.86 (0.80– 0.93)	0.91 (0.78 – 1.07)	0.63 (0.32 – 1.22)	1.19 (1.00 – 1.43)	0.55 (0.38 – 0.80)

Abbreviations: DBG, dabigatran etexilate; MI, myocardial infarction; TIA, transient ischaemic attack

Sources: [1, 80]. Cross-reference: **Table 30, Table 31, Table 35, Table 36, Table 46, Table 47, Table 48, Table 58, Table 63, Table 64**

* Note that as a result of the MTC, numbers to more than 2 decimal places may vary for the same parameter across models

Table 75 Probability of modelled events per cycle (derived from Table 73 and Table 74)

	All RE-LY analysis (1 and 2)					< 80 years sequence analysis (3a)				≥ 80 years analysis (3b)			
Clinical Event	**DBG 150mg bid**	**DBG 110mg bid**	**Aspirin**	**Aspirin + clopidogrel**	**No Treatment**	**DBG 150mg bid**	**Aspirin**	**Aspirin + clopidogrel**	**No Treatment**	**DBG 110mg bid**	**Aspirin**	**Aspirin + clopidogrel**	**No Treatment**
Ischaemic stroke ($CHADS_2$ Score = 0)	0.001	0.002	0.003	0.003	0.005	0.001	0.003	0.003	0.005	-	-	-	-
Ischaemic stroke ($CHADS_2$ Score = 1)	0.001	0.002	0.003	0.004	0.006	0.002	0.003	0.004	0.007	0.001	0.002	0.002	0.004
Ischaemic stroke ($CHADS_2$ Score = 2)	0.002	0.003	0.004	0.005	0.008	0.002	0.004	0.005	0.007	0.003	0.006	0.008	0.013
Ischaemic stroke ($CHADS_2$ Score = 3 and 4)	0.003	0.005	0.007	0.009	0.015	0.003	0.006	0.008	0.013	0.005	0.01	0.013	0.021
Ischaemic stroke ($CHADS_2$ Score = 5 and 6)	0.006	0.009	0.013	0.017	0.028	0.005	0.011	0.014	0.023	0.01	0.019	0.024	0.039
Systemic embolism	<0.001	<0.001	0.001	0.002	0.002	<0.001	0.001	0.001	0.002	<0.001	0.001	0.003	0.003
Haemorrhagic stroke	<0.001	<0.001	0.001	0.001	<0.001	<0.001	0.001	0.001	<0.001	<0.001	0.001	0.001	0.001
Intracranial haemorrhage	0.001	<0.001	0.001	0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.001	0.001	0.001	0.001
Extracranial haemorrhage	0.008	0.007	0.008	0.008	0.004	0.006	0.008	0.007	0.004	0.013	0.01	0.01	0.005
Acute MI	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.003	0.003	0.003	0.003
TIA	0.002	0.002	0.003	0.003	0.003	0.002	0.003	0.003	0.002	0.002	0.005	0.005	0.004
Minor bleed	0.036	0.032	0.025	0.048	0.022	0.034	0.025	0.047	0.022	0.04	0.028	0.052	0.024

Abbreviations: DBG, dabigatran etexilate; MI, myocardial infarction; TIA, transient ischaemic attack

4. Other treatment-dependent probabilities

A limited number of other model parameters are assumed to be treatment dependent:

1. Disability and mortality due to IS, HS and ICH

Following an IS or ICH/HS, patients can continue with no change in functional status, have an increased level of disability, or die. Disability levels following an IS or ICH / HS are categorized as independent, moderately dependent and totally dependent.

IS disability and mortality

Data on mortality and disability rates following IS are available from Hylek (2003)[28] (**Table 76**). Patients' severity states are assumed to not change unless they have another event or die. However, mortality rates were adapted when scaling to 90-days to account for higher mortality rates immediately following IS[28].

Disability rates for patients on aspirin were calculated by taking the proportion by disability and multiplying by the derived scaled 90-day survival rate, calculated as:

Scaled 90-day survival rate = $(1 - \text{30-day post-discharge rate})^3$

The overall mortality rate was therefore estimated to be the in-hospital mortality rate plus the scaled 90-day mortality rates across the disability states. This relationship reflects an acute phase of in-hospital mortality, followed by a 90 day period of persistently elevated mortality risk dependent on stroke severity.

The rates for no treatment were calculated similarly to aspirin. The rates for WFN were also calculated in a similar way to aspirin, but were weighted by INR ≥ 2 and INR < 2 using the proportions for WFN from RE-LY (88% and 22% respectively)[1]. In the absence of data, A+C was assumed to have the same end probabilities as WFN.

Table 76 Stroke severity data from Hylek (2003) [28]

Outcomes following stroke by treatment				
	Aspirin	No Treatment	Warfarin with INR ≥ 2	Warfarin with INR <2
In-hospital fatal stroke	6%	14%	1%	9%
Independent	51%	41%	57%	41%
Moderate disability	36%	37%	38%	44%
Totally dependent	7%	8%	4%	6%
30-day mortality by stroke severity after hospital discharge				
Independent	1%			
Moderate Disability	13%			
Totally Dependent	39%			

Abbreviation: INR, International Normalised Ratio

The relative risks for DBG versus WFN were derived from the RE-LY trial[114]. These are shown in **Table 77**. These values are then applied to the rates for WFN.

Table 77 Relative risk of disability by dose and disability level compare to warfarin

	DBG 110 mg bid RR (95% CI)			DBG 150 mg bid RR (95% CI)		
Sequence Model						
Independent		[redacted]			[redacted]	
Moderate Disability						
Mortality						
All RE-LY						
Independent		[redacted]			[redacted]	
Moderate Disability						
Mortality						

Abbreviations: CI, confidence interval; DBG, dabigatran etexilate; RR, relative risk

Note that 'totally dependant' is not shown, as these are used to normalise the total distribution to 1 following the application of the relative risks. The final values are shown in **Table 78**.

Table 78 Probability of disability state by treatment following ischaemic stroke

	WFN/A+C (All RE-LY and <80)	WFN/A+C (≥80)	Aspirin	No Treatment	DBG 150 bid		DBG 110 bid	
					All RE-LY	<80	All RE-LY	≥80
Independent								
Moderate Disability								
Totally Dependent								
90-day Mortality								

Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; WFN, warfarin

ICH/HS disability and mortality

Disability levels and 3-month mortality for ICH were estimated from a study comparing WFN use to no WFN use in patients treated in a tertiary care hospital in the US (**Table 79**). HS is assumed to have the same disability and mortality risks as ICH, as they were grouped together in the source data [115]. The values used in the model are shown in **Table 80**. Probabilities for no treatment and aspirin are assumed the same and based on a weighted average of the rates in **Table 79** of non-WFN outcomes. Probabilities for DBG and WFN are assumed to be the same and based on a weighted average of the rates in **Table 79** of WFN outcomes.

Table 79 Disease states for warfarin/non-warfarin patients by post-event severity[115]

	Warfarin		Non-Warfarin	
	Lobar*	Deep*	Lobar*	Deep*
N	56	45	185	149
Dead	57.6%	44.2%	28.6%	22.5%
Severe Disability	23.7%	41.8%	40.7%	45.3%
Moderate Disability	10.2%	7.0%	12.3%	21.2%
Recovery	8.5%	7.0%	18.4%	11.0%

* Lobar and deep refer to the site of the haemorrhage.

Table 80 Modelled disability and mortality following HS and ICH

	All analyses	
Event result	**WFN and DBG**	**Aspirin and no treatment**
Independent	[redacted]	15.1%
Moderately disabled		16.3%
Dependent		42.8%
Fatal		25.9%

Abbreviations: DBG, dabigatran etexilate; WFN, warfarin

2. The proportion of extracranial haemorrhage (ECH) that are gastrointestinal (GI) bleeds

ECH events are stratified as GI/non-GI because they are the most prevalent ECH and were demonstrated to be higher with DBG compared to WFN[1]. Accordingly, the economic model allows the proportion of ECH that are GI to differ accordingly as presented in **Table 81**.

Table 81 Proportion of ECH events that are GI

Treatment and analysis	**Proportion of ECH events**
DBG 150mg (All RE-LY)	[redacted]
DBG 110mg (All RE-LY)	
Other treatments (All RE-LY)	
DBG 150mg (< 80 years)	
Other treatments (< 80 years sequence)	
DBG 110mg (≥80 years)	
Other treatments (≥ 80 years sequence)	

Abbreviations: DBG, dabigatran etexilate; ECH, extracranial haemorrhage; GI, gastrointestinal
Sources: [1, 80]

3. Treatment discontinuation and switch due to non-clinical events

Patients may discontinue from treatment for non-clinical reasons, e.g. patient choice due to inconvenience, other minor adverse events not considered in the economic model, asymptomatic high INR etc. Each of these factors, whether lifestyle related or otherwise, is likely be dependent on the treatment being received.

To represent this discontinuation rate for first-line treatment, Kaplan-Meier curves from the RE-LY trial were fitted to Weibull distributions for DBG and WFN (**Table 82**). For second-line treatment, constant annual discontinuation rates were used. Discontinuation for aspirin was set based on a study by Mant *et al*. (2007)[97].

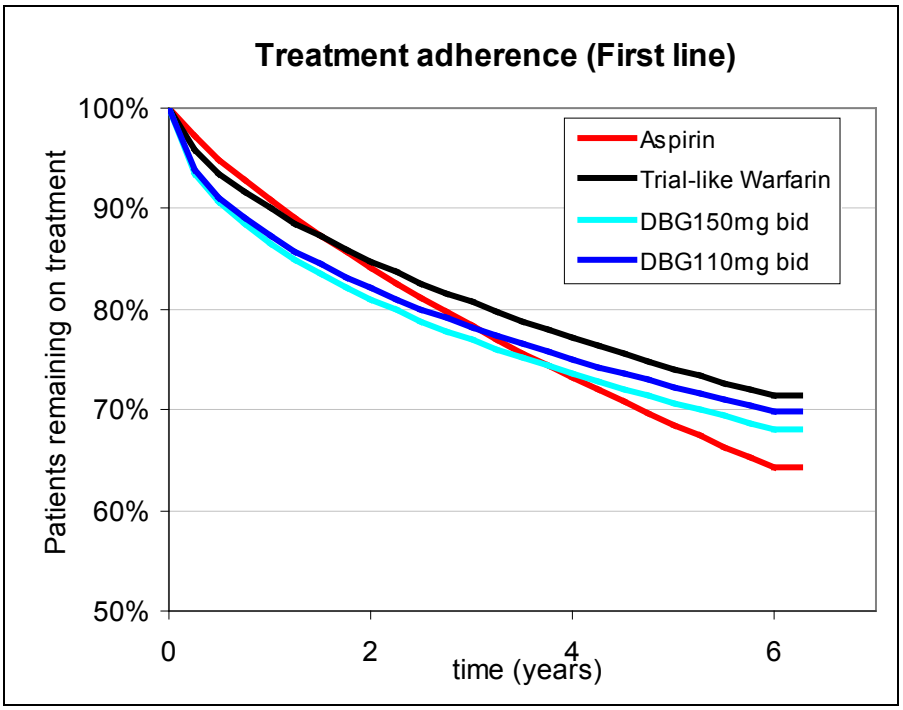
Table 82 Weibull parameters for discontinuation of treatment

Treatment	First-line		Second-line
	Lamda	Gamma	Rate/year
DBG 150mg (All RE-LY)			9.51%
DBG 110mg (All RE-LY)			8.97%
WFN (All RE-LY)			7.61%
DBG 150mg (< 80 years)			9.51%
WFN (< 80 years)			7.61%
DBG110mg (≥ 80 years)			8.97%
WFN (≥ 80 years)			7.61%
Aspirin/Aspirin plus clopidogrel			6.11%

Abbreviations: DBG, dabigatran etexilate; WFN, warfarin
Sources: [1]; [97]; [80]

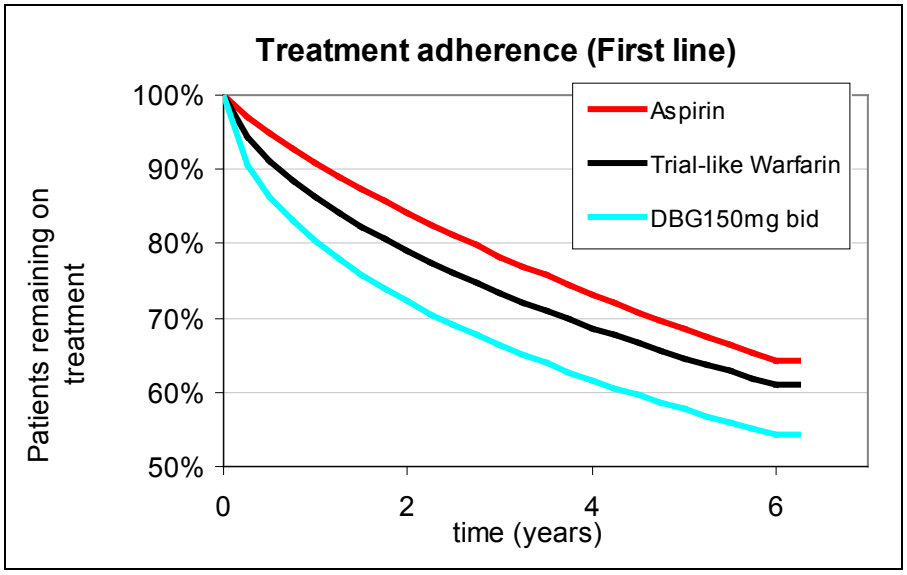
The first-line discontinuation parameters shown above translate into the attrition rates applied to the model as shown in **Figure 19** to **Figure 21**.

Figure 19 First-line treatment adherence (All RE-LY)



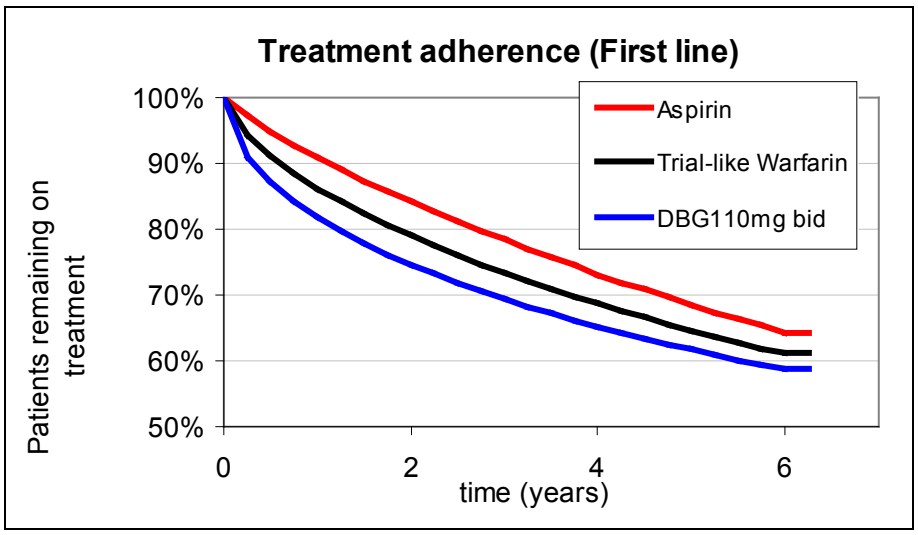
* The curve shown for aspirin also applies to aspirin plus clopidogrel

Figure 20 First-line treatment adherence (< 80 years)



* The curve shown for aspirin also applies to aspirin plus clopidogrel

Figure 21 First-line treatment adherence (> 80 years)



* The curve shown for aspirin also applies to aspirin plus clopidogrel

Following permanent discontinuation of first-line treatment, for any reason other than ICH or HS, some patients switch to a second-line therapy (set at 70% in the base case from DBG and aspirin, 78% from WFN, based on clinical expert guidance).

5. Other treatment-independent probabilities

The final set of clinical variables in the economic model is those that are assumed to be constant irrespective of the treatment being administered. These include mortality rates of non-disabling events, all-cause mortality and age adjustment of bleeding events.

1. Mortality rates of non-disabling events

SE, AMI and ECH are associated with an elevated mortality risk and the economic model applies the same rate to all patients. **Table 83** shows the rates applied to the economic model.

Table 83 Mortality risk of non-disabling events

Event	Proportion fatal
Systemic embolism	0.40% (All RE-LY) 0.46% (Sequence <80) 0.50% (Sequence >80)
Acute MI	1.11%
ECH	0.03%

Abbreviations: ECH, extracranial haemorrhage; MI, myocardial infarction

The rate of fatal SE events was imputed from UK mortality data, as shown in **Table 84** using the following formula:

Fatal SE events = ((ACMM x MSEM x M) + (ACMF x FSEM x (1-M))) x SEE

Table 84 Parameters used to estimate mortality rates for SE

Symbol	Meaning	Value	Source
M	% of baseline cohort that are male	65.0% (Seq <80) 57.1% (Seq >80) 63.6% (All RE-LY)	[1, 80]
ACMM	All cause male mortality	0.027	[116]
ACFM	All cause female mortality	0.017	[116]
MSEM	% of male deaths attributed to SE[a]	0.02%	[117]
FSEM	% of female deaths attributed to SE[a]	0.06%	[117]
SEE	Baseline SE event rate per 100 patient years	0.18 (all RE-LY) 0.15 (Seq Model)	[1, 80]

a. death caused by arterial embolism = SE;
Abbreviation: Seq, sequence.

Other events were assumed to cause no change in disability and to have a mortality risk independent of stroke severity. The model tracks disability levels resulting from clinical events occurring in the brain, and so the model may not capture some permanent disability resulting from SE, however in a study by Andersen *et al*. (2008)[118] SE is more often asymptomatic than embolism to the central nervous system.

The death rate for ECH was based on 5 deaths over 15,300 patient years, giving a mortality rate from ECH of 0.03%[31]. Mortality rates for AMI were derived from 3 fatal events from 270 events in total, leading to a mortality per event of 1.11%[1].

2. All-cause mortality

Age and gender-adjusted, all-cause mortality was obtained from the UK national statistics[116]. Deaths due to IS, SE, AMI, HS, ICH, and ECH were excluded from all cause mortality rates to avoid double counting.

3. Age adjustment of bleeding events

The risk of major bleeding is known to increase with age [119]. To account for this, the All RE-LY analysis allows for an increase in the relative risk of ICH in patients over 80. The relative risk of ICH does not change in the sequence model as this effect is already implicit in the rates of ICH outlined above. Adjustment to both models was made to the relative risk of ECH, which was 0.5 for patients under the age of 70. The values used in the models are shown in **Table 85**.

Table 85 Age-adjustment of bleeding event risk

Event	Age RR (95% CI)
ICH – Age greater than 80	1.80 (1.10 – 3.10)
ECH – Age less than 70	0.50 (0.12 – 0.90)

Abbreviations: CI, confidence interval; ECH, extracranial haemorrhage; ICH, intracranial haemorrhage; RR, relative risk
Source: [31]

4. Discontinuation from ECH

As noted above, based on expert opinion the economic model assumes that 100% of patients permanently discontinue treatment following an HS or ICH. Similarly, also on the basis of expert opinion, it is assumed that 50% of ECH events result in permanent discontinuation.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The RE-LY study represents the largest clinical trial ever performed in this therapeutic area, with over 18,000 patients randomised and a median follow-up of two years. There was no evidence in RE-LY that the treatment effect of DBG would decline over time compared to WFN. The economic model assumes that relative treatment effects remain constant over time and the Kaplan-Meier curves for primary efficacy (**Figure 9** and **Figure 10**) and safety endpoints (**Figure 15** and **Figure 16**) provide some comfort for this assumption. Indeed, far from showing diminishing relative treatment effect over time, it could be argued that the plots indicate the opposite trend.

Further, particular to anticoagulation, treatment effect is expected so long as a therapeutic dose is maintained. There is no observed diminishing effect of anticoagulation over time.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Non-fatal clinical events and their consequences were linked to QALYs by assigning utility scores for each health state and one time decrements for events. Utility values are described in detail in Section 6.4.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The structure and assumptions on which this economic model is based are the subject of a previous publication, Sorensen (2009)[111]. This study was co-authored by Prof. Daniel Singer (Epidemiology, Harvard University) and Prof. Samuel Goldhaber (Medicine, Harvard University), with a further acknowledgement of the involvement of Dr Louis Niessen (Erasmus University) for an independent review of the model and Philip Wolf (Boston University School of Medicine) for clinical guidance on stroke management. The adaptation presented in this submission was developed in collaboration with all of these stakeholders in addition to Prof. Greg Lip (Cardiology, University of Birmingham). This was not a formalised process and should be regarded as personal communication.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

The full list of clinical variables included in the economic model is presented below in **Table 86**.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 86 Clinical variables included in the economic model

Variable	Value (All RE-LY)	Value (Sequence < 80)	Value (Sequence >80)	CI (distribution)	Reference to section in submission
Baseline characteristics					
Age (years)	71.0	69.1	82.9		**Table 68 Table 71**
% male	63.6%	65.0%	57.1%		
% with $CHADS_2$=0	2.5%	[redacted]	0.0%		
% with $CHADS_2$=1	29.4%	[redacted]	[redacted]		
% with $CHADS_2$=2	35.6%	[redacted]	[redacted]		
% with $CHADS_2$=3	20.2%	[redacted]	[redacted]		
% with $CHADS_2$=4	8.9%	[redacted]	[redacted]		
% with $CHADS_2$=5	2.9%	[redacted]	[redacted]		
% with $CHADS_2$=6	0.5%	[redacted]	[redacted]		
$CHADS_2$=0 % with previous stroke history	0.0%	0.0%	0.0%		
$CHADS_2$=1 % with previous stroke history	0.0%	0.0%	0.0%		
$CHADS_2$=2 % with previous stroke history	5.9%	[redacted]	0.0%		
$CHADS_2$=3 % with previous stroke history	37.4%	[redacted]	[redacted]		
$CHADS_2$=4 % with previous stroke history	81.1%	[redacted]	[redacted]		
$CHADS_2$=5 % with previous stroke history	100.0%	100.0%	100.0%		
$CHADS_2$=6 % with previous stroke history	100.0%	100.0%	100.0%		
Baseline risk (WFN) of treatment-dependent events (rate per person years)					
Ischaemic stroke – $CHADS_2$ = 0	[redacted]	0.62		Beta	**Table 72**
Ischaemic stroke – $CHADS_2$ = 1	[redacted]	0.79	0.42	Beta	
Ischaemic stroke – $CHADS_2$ = 2	[redacted]	0.88	1.54	Beta	
Ischaemic stroke – $CHADS_2$ = 3 or 4	[redacted]	1.55	2.48	Beta	
Ischaemic stroke – $CHADS_2$ = 5 or 6	[redacted]	2.77	4.72	Beta	
Systemic embolism	0.18	0.15	0.31	Beta	
Haemorrhagic stroke	0.38	0.33	0.63	Beta	
Intracranial haemorrhage	0.42	0.35	0.73	Beta	
Extracranial haemorrhage	2.84	2.71	3.50	Beta	
Acute MI	0.64	0.59	0.89	Beta	
TIA	0.84	0.73	1.41	Beta	
Minor bleed	16.37	16.06	17.98	Beta	
Relative risk of treatment dependent events					
Ischaemic stroke – DBG 150mg	0.76	0.77		0.59 – 0.97 (LN) 0.58 – 1.03 (LN)	**Table 74**

Ischaemic stroke – DBG 110mg	1.10		0.82	0.88 – 1.37 (LN) 0.51 – 1.33 (LN)	
Ischaemic stroke – Aspirin	1.62			0.99 – 2.65 (LN)	
Ischaemic stroke – A+C	2.07			1.38 - 3.11 (LN)	
Ischaemic stroke – No treatment	3.35			2.23 - 5.03 (LN)	
Systemic Embolism – DBG 150mg	0.61	0.66		0.30 – 1.21 (LN) 0.30 – 1.47 (LN)	
Systemic Embolism – DBG 110mg	0.71		0.51	0.37 – 1.38 (LN) 0.13 – 2.06 (LN)	
Systemic Embolism – Aspirin	1.77			0.66 – 4.77 (LN)	
Systemic Embolism – A+C	3.57			1.52 – 8.36 (LN)	
Systemic Embolism – No treatment	4.44			1.78 – 11.08 (LN)	
Haemorrhagic stroke – DBG 150mg	0.26	0.21		0.14 – 0.49 (LN) 0.09 – 0.47 (LN)	
Haemorrhagic stroke – DBG 110mg	0.31		0.26	0.17 – 0.56 (LN) 0.07 – 0.91 (LN)	
Haemorrhagic stroke – Aspirin	0.84				
Haemorrhagic stroke – A+C	0.84				
Haemorrhagic stroke – No treatment	0.33				
Intracranial haemorrhage – DBG 150mg	0.52	0.48		0.32 – 0.84 (LN) 0.27 – 0.85 (LN)	
Intracranial haemorrhage – DBG 110mg	0.32		0.29	0.18 – 0.57 (LN) 0.10 – 0.88 (LN)	
Intracranial haemorrhage – Aspirin	0.51			0.16 – 1.60 (LN)	
Intracranial haemorrhage – A+C	0.53			0.19 – 1.45 (LN)	
Intracranial haemorrhage – No treatment	0.33				
Extracranial haemorrhage – DBG 150mg	1.07	0.93		0.92 – 1.24 (LN) 0.78 – 1.11 (LN)	
Extracranial haemorrhage – DBG 110mg	0.94		1.44	0.81 – 1.10 (LN) 1.05 – 1.97 (LN)	
Extracranial haemorrhage – Aspirin	1.14			0.47 – 2.73 (LN)	
Extracranial haemorrhage – A+C	1.10			0.71 - 1.72 (LN)	
Extracranial haemorrhage – No treatment	0.61			0.10 – 3.78 (LN)	
Acute MI – DBG 150mg	1.27	1.26		0.94 – 1.71 (LN) 0.89 – 1.78 (LN)	

Acute MI – DBG 110mg	1.29		1.39	0.96 – 1.75 (LN) 0.74 – 2.60 (LN)	
Acute MI – Aspirin	1.42			0.84 – 2.39 (LN)	
Acute MI – A+C	1.48			0.83 – 2.63 (LN)	
Acute MI – No treatment	1.57			0.67 – 3.69 (LN)	
TIA – DBG 150mg	0.86	0.92		0.65 – 1.15 (LN) 0.66 – 1.29 (LN)	
TIA – DBG 110mg	0.74		0.45	0.55 – 1.00 (LN) 0.23 – 0.89 (LN)	
TIA – Aspirin	1.56			0.86 – 2.83 (LN)	
TIA – A+C	1.56			0.86 – 2.83 (LN)	
TIA – No treatment	1.23			0.59 – 2.58 (LN)	
Minor bleed – DBG 150mg	0.91	0.86		0.86 – 0.97 (LN) 0.80 – 0.93 (LN)	
Minor bleed – DBG 110mg	0.79		0.91	0.74 – 0.84 (LN) 0.78 – 1.07 (LN)	
Minor bleed – Aspirin	0.63			0.32 – 1.22 (LN)	
Minor bleed – A+C	1.19			1.00 – 1.43 (LN)	
Minor bleed – No treatment	0.55			0.38 – 0.80 (LN)	
Other treatment dependent probabilities					
IS disability - Independent – WFN/A+C	[redacted]				**Table 78**
IS disability – Moderate disability- WFN/A+C	[redacted]				
IS disability – Totally dependant- WFN/A+C	[redacted]				
IS disability – 90-day mortality- WFN/A+C	[redacted]				
IS disability - Independent - DBG 110mg (RR)	[redacted]		[redacted]	[redacted]	
IS disability – Moderate disability- DBG 110mg (RR)	[redacted]		[redacted]	[redacted]	
IS disability – Totally dependant- DBG 110mg (RR)	[redacted]		[redacted]		
IS disability – 90-day mortality- DBG 110mg (RR)	[redacted]		[redacted]	[redacted]	
IS disability - Independent - DBG 150mg (RR)	[redacted]	[redacted]		[redacted]	
IS disability – Moderate disability- DBG 150mg (RR)	[redacted]	[redacted]		[redacted]	

IS disability – Totally dependant- DBG 150mg (RR)	[redacted]				
IS disability – 90-day mortality- DBG 150mg (RR)	[redacted]			[redacted]	
IS disability - Independent – ASA	[redacted]				
IS disability – Moderate disability- ASA	[redacted]				
IS disability – Totally dependant- ASA	[redacted]				
IS disability – 90-day mortality- ASA	[redacted]				
IS disability - Independent – NT	[redacted]				
IS disability – Moderate disability- NT	[redacted]				
IS disability – Totally dependant- NT	[redacted]				
IS disability – 90-day mortality- NT	[redacted]				
HS/ICH disability - Independent – WFN/DBG150mg/DBG110mg	[redacted]				**Table 80**
HS/ICH disability – Moderate disability- WFN/DBG150mg/DBG110mg	[redacted]				
HS/ICH disability – Totally dependant- WFN/DBG150mg/DBG110mg	[redacted]				
HS/ICH disability – 90-day mortality- WFN/DBG150mg/DBG110mg	[redacted]			[redacted]	
HS/ICH disability - Independent – ASA/A+C/NT	15.1%				
HS/ICH disability – Moderate disability- ASA/A+C/NT	16.3%				
HS/ICH disability – Totally dependant- ASA/A+C/NT	42.8%				
HS/ICH disability – 90-day mortality- ASA/A+C/NT	25.9%				
ECH is GI – DBG 150mg	[redacted]				**Table 81**
ECH is GI – DBG 110mg	[redacted]				
ECH is GI – All other treatments	[redacted]				
Treatment discontinuation due to non-clinical events	Parameterised				**Table 82** **Figure 19** **Figure 20** **Figure 21**
Switch to 2nd-line therapy from DBG/ASA/A+C	70%				Section 6.3.2
Switch to 2nd-line therapy from WFN	78%				
Other non-treatment dependent probabilities					
Systemic embolism mortality risk	0.40%	0.46%	0.50%		**Table 83**
Acute MI mortality risk	1.11%				
ECH mortality risk	0.03%			Beta	
All-cause mortality	Life tables				Section 6.3.2
Age-adjustment of bleeding events – ICH greater than 80 years (RR)	1.80			1.10 – 3.10 (LN)	**Table 85**
Age-adjustment of bleeding events – ECH less than 70 years (RR)	0.50			0.12 – 0.90 (LN)	

Discontinuation following ECH	50%		Section 6.3.2

* For HS/ICH disability, although WFN and DBG are assumed to have the same probability, as are A+C, ASA and NT, for the purposes of PSA a RR of 1 operates for DBG compared to WFN and for A+C and NT compared to ASA. This RR is assumed to have the confidence interval presented in the table.

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; CI, confidence interval; DBG, dabigatran etexilate; ECH, extracranial haemorrhage; GI, gastrointestinal; ICH, intracranial haemorrhage; INR, international normalised ratio; IS, ischaemic stroke; LN, lognormal distribution; MI, myocardial infarction; NT, no treatment; RR, relative risk; TIA, transient ischaemic attack; WFN, warfarin

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Yes, costs and clinical outcomes are extrapolated beyond the follow-up period of the RE-LY trial. There was no evidence in RE-LY that the treatment effect of DBG would decline over time compared to WFN. The economic model assumes that relative treatment effects remain constant over time and the Kaplan-Meier curves for primary efficacy (**Figure 9** and **Figure 10**) and safety endpoints (**Figure 15** and **Figure 16**) provide some comfort for this assumption. Indeed, far from showing diminishing relative treatment effect over time, it could be argued that the plots indicate the opposite trend. Therefore it is a reasonable modelling assumption to assume in the base case that the treatment effect of DBG demonstrated in the trial would remain constant over time. A similar assumption is made regarding the results of the MTC for aspirin and A+C. Shorter model timeframes are considered in sensitivity analysis.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The following is a list of modelling assumptions accompanied by the corresponding justification:

1. Only one clinical event can occur per cycle

Patients are unlikely to experience more than one major event during any 3 month, indeed the overall rate of these events observed in the RE-LY trial is very low (5 to 8 per 100 patient-years, depending on initial $CHADS_2$ score)[43]. Exception: Minor bleeds may occur in any cycle and do not preclude a major clinical event from occurring in the same cycle.

2. Patients can never improve their disability level, but status quo or a worsening is allowed (e.g. moderate to dependent, but not vice versa) following IS/HS/ICH.

While patients receiving rehabilitation may further improve their functional status beyond 30 days, functional improvements may not be as great in AF patients versus non-AF patients[120, 121].

3. Additional mortality risk due to stroke does not differ depending on stroke history.

Mortality due to stroke is strongly correlated with stroke severity rather than a patient's IS history[28].

4. Treatment effect continues beyond the limit of the clinical trial period informing the economic model

In the absence of evidence to the contrary, relative treatment effect was assumed to be continuous over the long-term. The Kaplan-Meier plots from RE-LY for primary efficacy (**Figure 9** and **Figure 10**) and safety (**Figure 15** and **Figure 16**) provide some comfort for this assumption. In fact, far from showing diminishing relative treatment effect over time, it could be argued that the plots indicate the opposite trend.

5. Patients who experience an IS, TIA, or SE have a similar risk of recurrent IS.

In the $CHADS_2$ risk stratification approach, each of these events carries the same weight for overall risk[17, 118]. Any increase in IS risk associated with events not evaluated in the $CHADS_2$ risk scoring algorithm, is not captured in the model and may result in an underestimate of overall stroke rate.

6. Temporary stoppage of treatment for a short period (i.e. 1-2 weeks) following a stroke or during perioperative periods does not significantly impact overall treatment effectiveness or cost.

This is a reasonable assumption based on the findings of Garcia *et al*. which showed that a brief peri-procedural interruption of WFN treatment is associated with a low risk of thromboembolism[122].

7. The risk of events does not change during cycles in which the patient temporarily discontinues anticoagulant treatment following an ECH event.

Baseline events rates were obtained from analysis of the RE-LY trial[1]. In this analysis, events during temporary treatment discontinuations due to ECH were counted in the appropriate treatment arms. Thus the effect of temporary discontinuation of treatment following an ECH is captured in the baseline event rate.

8. The likelihood of an event causing increasing disability is the same regardless of stroke history.

A simplifying assumption based on the available data.

9. After an acute phase of in-hospital mortality risk, mortality past 90 days has the same dependence on stroke severity as mortality past 30 days.

Huybrechts *et al*. show a strong dependence of mortality on stroke severity that persists over 10 years[113]. This assumption was tested by comparing predicted overall 90-day mortality to that observed in the RE-LY trial with good agreement.

10. Systemic embolism does not result in a change in disability level

The model tracks disability levels resulting from clinical events occurring in the brain, and so the model may not capture some permanent disability resulting from SE. However SE is a

rare event and in a study by Andersen *et al*. (2008) SE was shown to be asymptomatic more often than embolism to the central nervous system[118].

11. Patients who experienced a non-HS ICH and patients who experienced an HS have the same risk of residual disability.

The data used on disability levels following intracranial bleeding events pools HS within the more general ICH category and thus the overall rate of disability following ICH or HS is accurately captured by assuming both events carry the same risk of residual disability[115]. No data was identified showing differences in disability post-ICH versus post-HS.

12. Patients who discontinue all antithrombotic treatment due to bleeding are assumed to receive no future clinical benefit and no subsequent treatment.

Regulation of thrombosis and coagulation quickly returns to untreated values. For example, Currie *et al*. showed that patients prescribed WFN, but not receiving WFN within 42 days, have a risk of stroke and bleeding comparable to those who were never prescribed WFN[115].

13. Patients receive a maximum of two lines of different treatment.

Clinical guidelines specify that patients, particularly those at moderate to high risk of stroke as in the model population, should be initiated on anticoagulant treatment and subsequently switch to antiplatelet therapy if necessary[123]. The representation of two lines of treatment in the model reflects this recommendation. The exception to this is the sequential model, where patients may receive DBG 150 mg, DBG 110 mg then aspirin.

14. Patients who discontinue WFN, DBG or A+C can be switched to aspirin. Patients who discontinue aspirin will go to no further treatment.

As above, patients who discontinue anticoagulant therapy can be switched to antiplatelet therapy, per clinical guidelines[12]. In the absence of evidence to the contrary, the same is assumed for A+C. No other effective antithrombotic treatments are available with lower bleeding risk than aspirin, so patients who do not tolerate aspirin discontinue therapy entirely.

15. Pulmonary embolism was not included in the model.

In the RE-LY trial, 0.24% (44 of 18,311) patients experienced a PE event. This was not included in the model because it was a rare event that occurred at similar rates across the treatment arms. Also, data for this endpoint was not reported in other clinical trials making its inclusion problematic for the comparison of DBG with aspirin. Overall, PE was not a primary endpoint of the RE-LY trial or a key event considered essential to the decision problem.

16. Short term treatment discontinuations are not considered where there may be differences between the treatments.

Specifically, the model does not account for the need to temporarily stop WFN and the potential use of bridging therapy when a patient undergoes a procedure carrying a risk of bleeding. This is a conservative assumption against DBG since DBG has a short half-life such that patients do not need to stop treatment until shortly before the procedure.

17. The cost of managing asymptomatic high INR values (defined as INR>8) is not considered.

Again this is a conservative assumption against DBG given that patients experiencing this event may be hospitalised and given fresh frozen plasma and/or vitamin K to reverse the anticoagulation effect.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients with AF may be expected to experience some decrease in quality of life due to the symptoms of AF. These include:

- breathlessness/dyspnoea
- palpitations
- syncope/dizziness
- chest pain
- fatigue
- loss of consciousness (in extreme cases)[4]

However, neither DBG nor the comparators alter the symptoms or severity of AF, therefore the quality of life associated with AF itself is not required in the evaluation.

Treatment with WFN has been shown to decrease quality of life. It is unclear whether this is health-related or due to the inconvenience of taking WFN, which requires frequent monitoring and dose-adjustment, as well as dietary restrictions. In a US study, 19% of patients reported that VKA treatment negatively affected their quality of life.[124] In one study, quality of life relating to stroke prophylaxis with either aspirin or WFN varied among individual patients. Some patients (16%) rated the utility of WFN therapy so low that their quality-adjusted life expectancy would be greater with aspirin. The utility associated with WFN treatment was elicited irrespective of its risk of haemorrhage or effectiveness to prevent stroke; practical considerations included the need to have blood drawn every 4 weeks and avoidance of contact sports and excessive alcohol consumption.[125] This inter-patient variability highlights the importance of patient preference in prophylaxis decision making.

However, the events that can have the most major impact on the quality of life of AF patients are stroke and ICH. These debilitating events can result in severe disability, permanently impacting the quality of life of patients (and carers).

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

In stroke patients, concurrent AF is associated with greater disability, longer in-hospital patient stay and lower rate of discharge to own home. [4]

A study by Gage *et al*. calculated the utility values for three degrees of severity of anticipated stroke (mild, moderate and major) from 70 patients with AF (29% of whom had a history of stroke) using time trade-off and standard gamble methods. Stroke severity was defined according to descriptions of function in multiple domains. Median utilities for mild, moderate and major stroke decreased with increasing severity of stroke ($p<0.001$) and were 0.94, 0.07 and 0.0, respectively. Corresponding mean utility values were 0.76, 0.39 and 0.11 for mild, moderate and major stroke, respectively. However, there was high inter-patient variability, with some patients rating major stroke above 0.5 while the majority (83%) rated it as equal to or worse than death. [125]

A recent study assessed the health-related quality of life (HRQoL) of 59 patients three years after suffering their first ischaemic stroke, measured using the SF-36 health questionnaire. Quality of life was inversely proportional to severity of the functional deficit of surviving stroke patients, defined using the modified Rankin scale, for both the physical and mental component scores ($p<0.001$). In particular, patients surviving extensive strokes (total

anterior circulation infarctions) of cardioembolic origin (i.e. due to AF) reported the greatest negative impact on quality of life ($p<0.05$). [126]

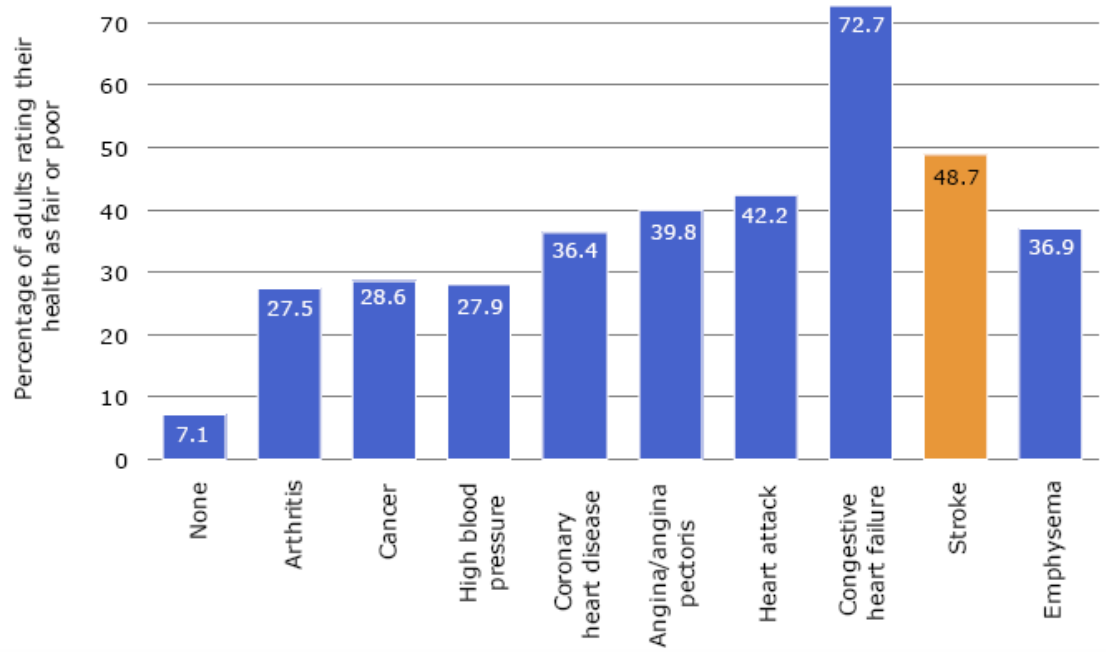
A study of 1,040 non-institutionalised stroke survivors in the United States examined the impact of stroke on HRQoL compared with the non-stroke population (N=38,640) using four measures included in the Medical Expenditure Panel Survey (MEPS):

- 12-item short-form health survey (SF-12)
- Physical component summary (PCS-12)
- Mental component summary (MCS-12)
- EuroQol 5D index (EQ-5D)
- EuroQol visual analogue scale (EQ VAS)

Average scores on all four HRQoL measures were lower among stroke survivors than the non-stroke population. Although differences in HRQoL scores narrowed after adjusting for age, gender, race and geographic region, the association between stroke and reduced quality of life remained statistically significant for each measure ($p<0.01$). [127]

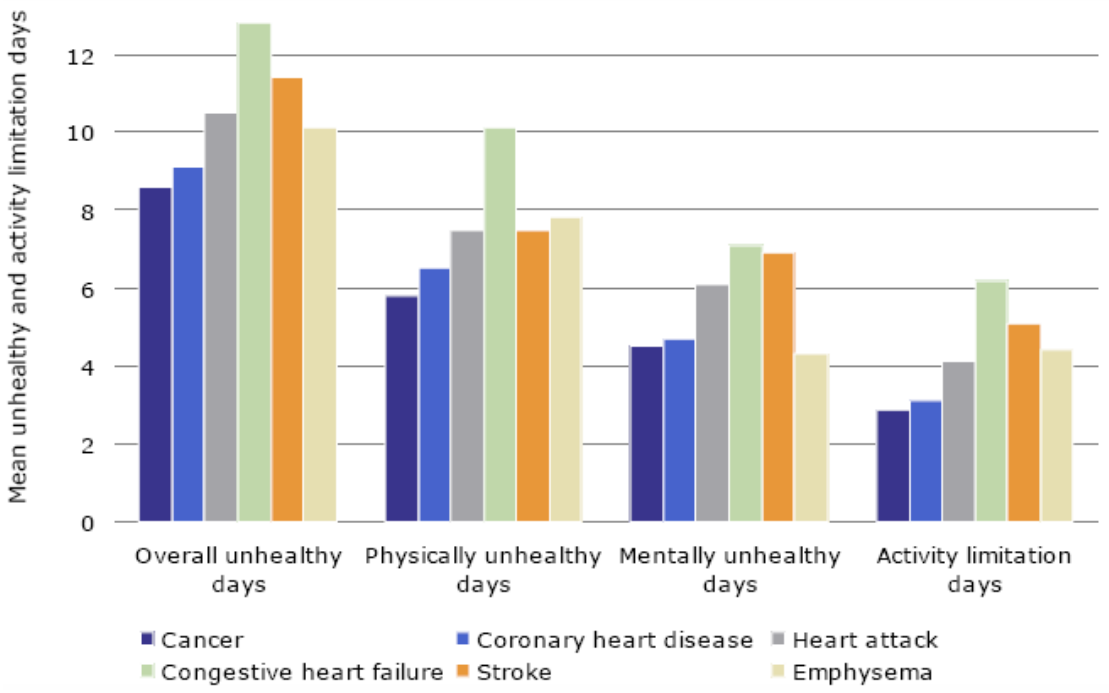
During 2001-2002, NHANES respondents with one or more chronic medical condition reported worse HRQoL than those without such conditions. For example, when patients were asked to rate their general health as excellent, very good, good, fair or poor, only 7.1% of respondents without any chronic medical condition assessed their general health as fair or poor whereas almost half of those who had experienced stroke reported fair or poor health. Only patients with congestive heart failure reported worse HRQoL than those who had experienced stroke (Figure 22).

Figure 22 Percentage of adults who self-rated their health as fair or poor (age-standardised %) with various chronic medical conditions [128]



Respondents who had a history of stroke also reported unhealthier and activity limitation days during the 30 days prior to the survey than those who had ever been diagnosed with a range of other medical conditions (**Figure 23**).

Figure 23 Mean number of unhealthy and activity limitation days reported in a 30-day period by adults with a history of stroke, compared with other chronic medical conditions [128]

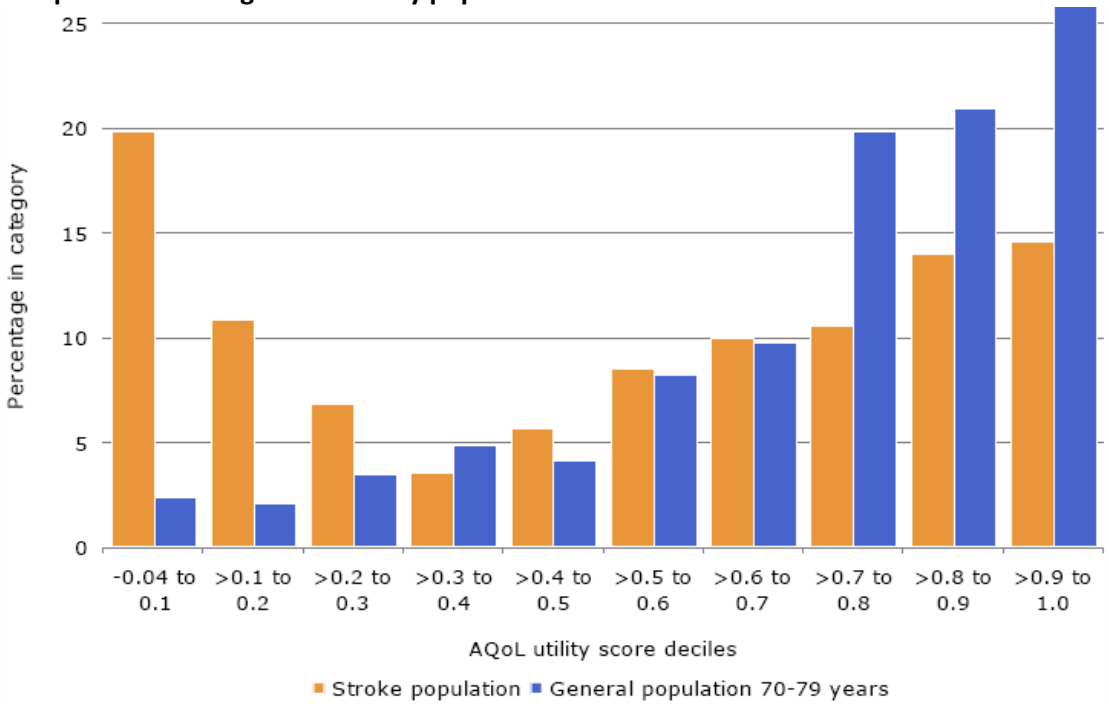


A sub-study of the community-based North East Melbourne Stroke Incidence Study (NEMESIS) assessed quality of life in 225 survivors two years after first-ever stroke using the Assessment of Quality of Life (AQoL) instrument. [129]

At two years post-stroke, the mean utility score for survivors was 0.47, considerably lower than the median score of 0.86 in a corresponding group of healthy elderly people. A substantial proportion of stroke survivors reported very poor quality of life: 8% assessed their quality of life as equivalent to or worse than death and nearly one quarter of all patients had a utility score≤0.1. This distribution of scores provides evidence that HRQoL is impaired to some extent for most survivors two years post-stroke and that, for some patients, the impact of stroke on HRQoL is both severe and long-lasting. Stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS) was significantly associated with worse HRQoL, with those suffering the most severe strokes (NIHSS 11-15 or ≥16) having the lowest mean AQoL scores (0.06 and 0.01, respectively). [129]

The utilities obtained in the NEMESIS study were similar to those reported in a systematic review of the literature, which reported utilities of 0.50-0.70 for minor stroke and ≤0.0 -0.30 for major stroke. [130] Survivors from the NEMESIS study were also interviewed at five years post-stroke. Mean AQoL score at this point in time was 0.50, similar to that at two years post-stroke but considerably lower than that found in a representative sample of the Australian population aged between 70 and 79 years (mean AQoL = 0.75;). [131]

Figure 24 Distribution of AQoL utility scores among survivors 5-years post-stroke compared with the general elderly population [131]



As in the earlier study, a substantial proportion of stroke survivors (20%) were found to have very poor quality of life (AQoL≤0.1) compared with only 3% of the general population. These patients require assistance with activities of daily living and cannot live independently. At this level of disability, patients either require costly nursing home care or considerable help from next of kin to undertake everyday tasks. Stroke survivors with AF reported a lower mean AQoL score than those without AF, although the difference was not statistically significant. [131]

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQL data was collected in a sub-study of the RE-LY trial and this is discussed below.

Representativeness of patients in the RE-LY QoL sub-study

The inclusion of the EQ-5D in the RE-LY study was enacted through a protocol amendment after the study had commenced[132]. The number of participants in the QoL sub-study was far less than that in the overall RE-LY study. Data were available on 18,113 patients in the RE-LY study, whereas only 1,440 patients completed the EQ-5D as part of the QoL sub-study. It is appropriate therefore to assess whether patients for whom the EQ-5D were available are representative of the broader RE-LY population, both in terms of their baseline characteristics (demographic and disease) and the health outcomes observed.

Baseline demographic and disease characteristics for the overall RE-LY patient population and those for whom EQ-5D data were collected are presented in **Table 87**. The substudy population appears to be reasonably representative of the overall RELY population.

Data on the efficacy outcomes observed for the QoL sub-study were available for only 24 patients in whom a main study outcome (non-fatal stroke, systemic embolism, MI, pulmonary embolism or major bleeding, and any bleeding leading to study discontinuation) occurred. There is therefore insufficient information to assess whether the efficacy and safety outcomes observed in the patients included in the QoL sub-study are consistent with

those observed in the overall RE-LY study population. Therefore it is not possible to analyse the EQ-5D data with respect to specific events of interest and the QoL sub-study is unable to provide utility values for use in the economic model with respect to the event driven health states.

However, the information from the QoL sub-study can be used to derive background utility values for patients with AF being treated with WFN and DBG (irrespective of the occurrence of clinical events of interest), as shown in **Table 88**.

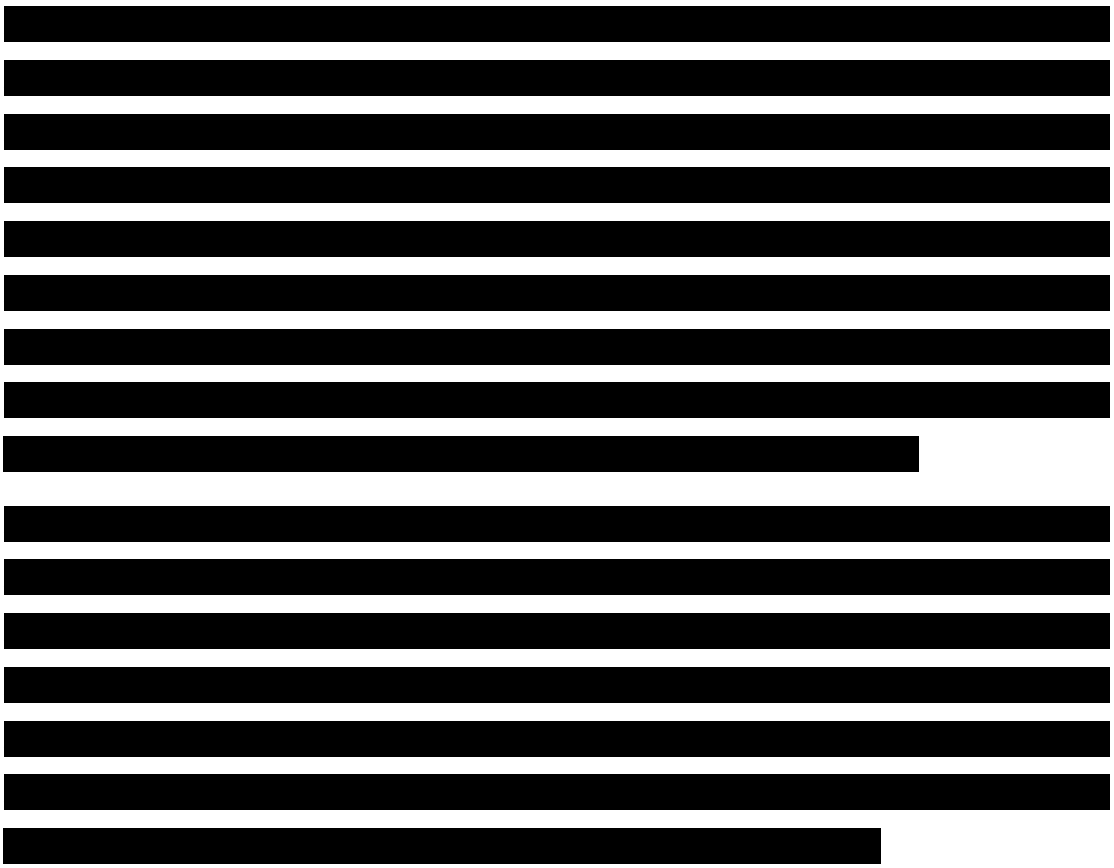


Table 87 Baseline disease and demographic characteristics

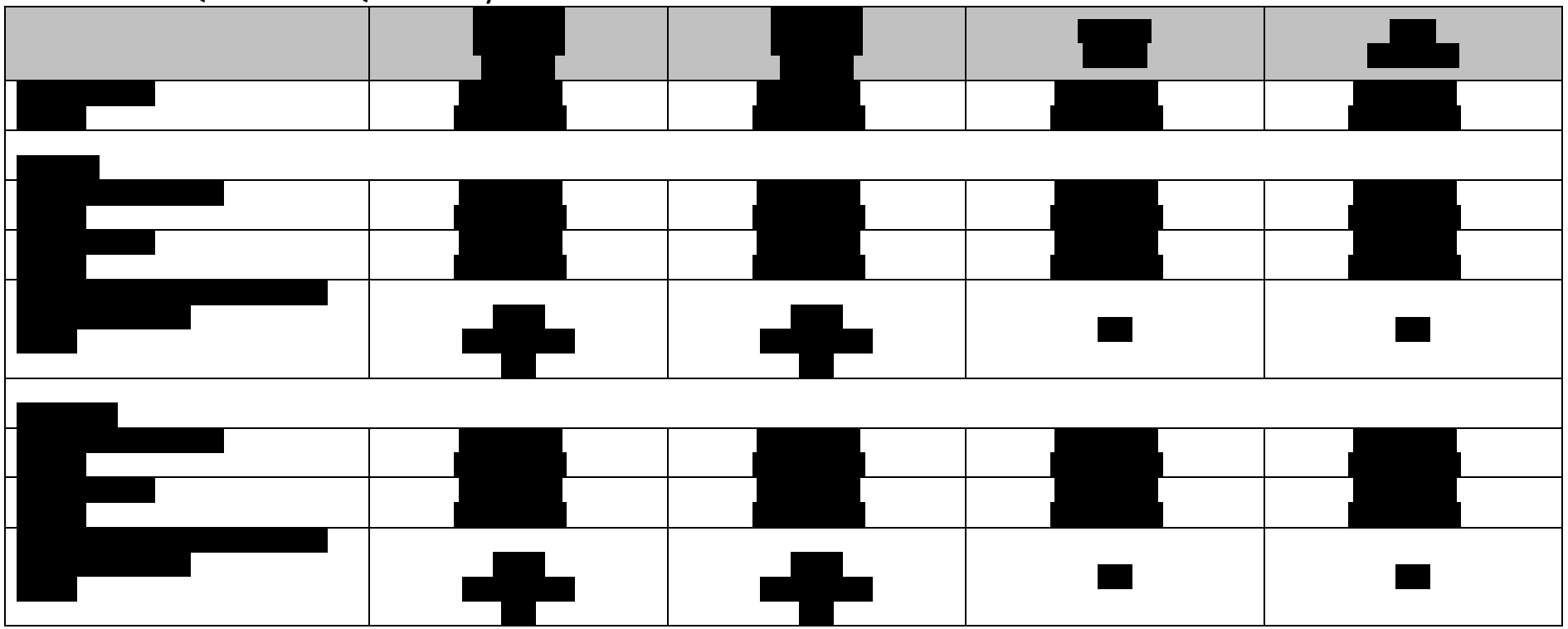
	RE-LY Population			QoL sub-study – EQ-5D only		
	Dabigatran 110mg bid n = 6,015*	**Dabigatran 150mg bid n = 6,076***	**Warfarin n = 6,022***	**Dabigatran 110mg bid n = 498**	**Dabigatran 150mg bid n = 486**	**Warfarin n = 456**
Demographic characteristics						
Age – mean years (s.d.)	71.4 (8.6)	71.5 (8.8)	71.6 (8.6)	71.5 (8.0)	72.1 (7.9)	72.1 (8.6)
Weight – mean kgs (s.d.)	82.9 (19.9)	82.5 (19.4)	82.7 (19.7)	83.7 (19.6)	81.9 (17.4)	83.1 (18.6)
Gender - % female	35.7	36.8	36.7	41.4	41.2	37.1
Disease characteristics						
CHADS2 score n (%)						
0-1	1,958 (32.6)	1,958 (32.2)	1,859 (30.9)	169 (33.9)	160 (32.9)	150 (32.9)
2	2,088 (34.7)	2,137 (35.2)	2,230 (37.0)	177 (35.5)	193 (39.7)	165 (36.2)
3-6	1,968 (32.7)	1,981 (32.6)	1,933 (32.1)	152 (30.5)	133 (27.4)	141 (30.9)
Co-morbidities n (%)						
Prior stroke/TIA	1,195 (19.9)	1,233 (20.3)	1,195 (19.8)	103 (20.7)	98 (20.2)	87 (19.1)
Prior MI	1,008 (16.8)	1,029 (16.9)	968 (16.1)	81 (16.3)	80 (16.5)	66 (14.5)

Abbreviations: MI, myocardial infarction; QoL, quality of life; s.d., standard deviation; TIA, transient ischaemic attack.

* Sample sizes shown are the maximum for each treatment group in RE-LY. Proportions shown may relate to a smaller sample as shown in the RE-LY publication [43].

Sources: [43], [133]

Table 88 EQ-5D values for QoL sub-study



Abbreviations: CI, confidence interval; LS, least squares; n.a., not applicable; s.d., standard deviation.

* Confidence intervals calculated for the purposes of this analysis.

Source: [133]

[redacted]

Table 89 Utility values relevant to warfarin and dabigatran treatment

Health State	Utility value Mean (95% CI)
AF patients without history of stroke	[redacted]

Abbreviations: AF, atrial fibrillation; CI, confidence interval.
Source: [133]

As noted above, the remaining utility values required cannot be sourced from the QoL sub-study.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, Appendix 12.

Based on the clinical data and the structure of the economic model, three sets of utility values are required to apply to the following events or health states:

Set 1: Utility values relating to the general health state and treatment

- AF patient without history of stroke
- WFN treatment (including frequent monitoring to assess compliance with the International Normalisation Ratio (INR)); and
- DBG treatment

Set 2: Post-stroke health state utility values

- Post stroke, remaining independent. This health state consists of patients with a modified Rankin Scales (mRS) of:

mRS 0	No symptoms at all
mRS 1	No significant disability despite symptoms; able to carry out all usual duties and activities
mRS 2	Slight disability; unable to carry out all previous activities, but able to look after their own affairs without assistance

- Post stroke, with moderate dependency. This health state consists of patients with an mRS of:

mRS 3	Moderate disability; requiring some help, but able to walk without assistance
mRS 4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

- Post stroke, totally dependent. This health state consists of patients with an mRS of:

mRS 5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

Set 3: Event specific disutility values

- Stroke
- Systemic embolism
- Transient ischaemic attack (TIA)
- Intra-cranial haemorrhage (ICH)
- Extra-cranial haemorrhage (ECH)
- Minor bleed
- Acute myocardial infarction (AMI)

A systematic review of the literature was conducted to source the required utility values. The search was conducted of the published literature for utility values across four key areas: atrial fibrillation, stroke, myocardial infarction and bleeding/haemorrhage. Accordingly, four separate searches were conducted. The searches were conducted across the Embase, Medline, Cochrane, EconLit and CRD Databases. Searches of the Embase, Medline and Cochrane databases were initially conducted in the week of 13th October 2009. These searches were subsequently updated in the week of 5th July 2010. Updated searches were limited to publications released after 1st September 2009 (providing approximately six weeks of overlap with the initial searches to ensure all possibly relevant citations were identified).

Searches of the EconLit and CRD databases online (including DARE, NHS EED and HTA as required by NICE) were conducted in the week of 5th July 2010 without limits to the date of publication. The results for each specific search were imported into Endnote (with the exclusion of EconLit which could not be imported) for the purposes of review and the removal of duplicate citations. Results of the two stages of the search are presented separately in 6.4.6.

The citations retrieved for each of the four areas were reviewed separately according to the following criteria:

- Not specific to the relevant health state (atrial fibrillation, stroke, myocardial infarction, bleeding/haemorrhage), or was specific to an intervention in those health states not relevant to this analysis, or was not in English.
- Not a QoL paper, or a relevant economic evaluation, or reported values that were sourced from another publication, or was a review/letter/editorial.
- Did not report preference based utility values (that is reported only health related QoL scores, VAS scores, utility values that relied on transformations from an HRQoL instrument, or expert opinion).

The results of the literature search, including the assessment of the retrieved citations against each of these criteria are summarised in **Table 90** and **Table 91**. The annotated citations lists, including the full search strategies, are provided in Appendix 12.

Table 90 Results of initial literature search for utility values

	Therapeutic area				
	Stroke	**AF**	**MI**	**Bleed.**	**Total**
Total retrieved	1,078	352	582	416	2,428
Criteria for exclusion					
A. Not specific to the relevant health state, intervention specific, not in English.	366	63	49	177	655
B. Not QoL, not a relevant economic evaluation, reported values included elsewhere, review/letter/editorial.	454	170	358	202	1,184
C. Not preference based utility values.	227	113	164	31	535
Total excluded	1,047	346	571	410	2,374
Total included from each search	31	6	11	6	54
Citations identified in more than one search	9				
Total included for review	45				

Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; QoL, quality of life.
Searches of the Embase, Medline and Cochrane databases conducted in October 2009.

Table 91 Results of the updated literature search for utility values

	Therapeutic area				
	Stroke	**AF**	**MI**	**Bleed.**	**Total**
Total retrieved	392	97	234	259	982
Criteria for exclusion					
A. Not specific to the relevant health state, intervention specific, not in English.	111	23	81	143	358
B. Not QoL, not a relevant economic evaluation, reported values included elsewhere, review/letter/editorial.	220	49	137	99	505
C. Not preference based utility values.	55	24	15	16	110
Total excluded	386	96	233	258	973
Total included from each search	6	1	1	1	9
Citations identified in more than one search	3				
Total included for review	6				

Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; QoL, quality of life.
Searches of the Embase, Medline, Cochrane, EconLit and CRD databases conducted in July 2010.

Overall, there were 45 citations included from the initial search and six from the updated search. In addition to these 51 citations, one other article was included for review (Sullivan, 2005)[136]. This article was sourced following a manual search and relates to multiple health states. All 52 citations included for review are tabulated in Appendix 12.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.

- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

The 52 articles were assessed with respect to their potential suitability as sources of utility values for use in the economic evaluation. Study suitability was assessed based on the following considerations:

- Study setting:
    - Was the study conducted in the UK, or in a country likely to exhibit similar preferences?
    - Was the study conducted as part of a trial, among patients or among general community members?

Where possible, studies conducted in the UK and/or among general community members were given preference.

- Preference elicitation method:
    - Was the study conducted using a direct preference elicitation method (TTO, SG, DCE) or a MAUI?
    - Where a direct preference elicitation method was used, was there adequate description provided regarding the health states evaluated?
    - What health states were being evaluated?

Studies in which utility values were assessed using the EQ-5D were considered to be of greater relevance than those in which other preference elicitation/valuation methods were used. This criterion reflects NICE's preference for utility values sourced using the EQ-5D. In addition, studies were considered to be more relevant to the economic evaluation if they evaluated more than one of the health states/events occurring within the economic model.

- Presentation of results:
    - Was sufficient detail provided on how results were analysed?
    - Were the utility values reported in a manner that allows them to be used for the purposes of the economic evaluation?

Studies providing more information on the assessment of utility values, and reporting mean utility values (or changes in mean values that could be interpreted as disutilities) were given preference. Note that utility data are typically non-normal in their distribution, such that statistical testing would be non-parametric in nature suggesting that median values are the most relevant. However, the use of mean values is appropriate in the context of an economic evaluation, and therefore papers reporting only medians were not considered relevant for inclusion.

Taking into account these considerations, the 52 studies were reviewed as potential sources of utility data, with an assessment of that relevance provided in Appendix 12. Of those 52 studies, 17 were considered potentially relevant for further review. These studies, including an assessment of their suitability as a source of utility values for the economic evaluation, are summarised in **Table 92**.

Table 92 Summary of potentially relevant sources of utility values

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
Multiple Health States						
Gage (1995)[137]	Seven health states: Well, warfarin therapy, aspirin therapy, mild neurological impairment, moderate to severe neurological impairment, recurrent neurological impairment, haemorrhage.	Part of a cost-utility analysis to assess cost-effectiveness of warfarin/aspirin for stroke prophylaxis. Interviewed 74 patients with AF.	Computer based completion of TTO to elicit utilities for the three types of neurological defects (post stroke) and for daily therapy with aspirin or warfarin. The description for life on warfarin therapy included having blood drawn every 4 weeks and the requirement to avoid contact sports and excessive intake of alcoholic beverages.	74 patients at the VA Health Facility at Palo Alto, or the Stanford University Hospital. Mean age, 70 years, 86% males, 50% of respondents were taking warfarin for AF.	Well No therapy 1.0 (n.r.) Aspirin therapy 0.998 Warfarin therapy: 0.988 (n.r.) Neurological event post stroke with residuals Mild: 0.75 (n.r.) Moderate to severe: 0.39 (n.r.) Recurrent: 0.12 (n.r.) Haemorrhage (not ICH): 0.76 (n.r.)	Relevant for potential inclusion based on elicitation method (TTO), population surveyed, and health states evaluated.
Gage (1996)[125]	Six health states: current health, warfarin therapy, aspirin therapy, mild stroke, moderate stroke, major stroke. Full descriptors of health state vignettes are provided in the paper.	Assessment of stroke utility values in 83 patients with AF at the VA Health Facility at Palo Alto, or the Stanford University Hospital.	TTO and SG – computer based assessment. Stroke health states described as per the mRS. The description for life on warfarin therapy included having blood drawn every 4 weeks and the requirement to avoid contact sports and excessive intake of alcoholic beverages.	70 patients completed the interviews, or were consistent in their understanding of the task. Mean age was 70.1 years, and 86% were male.	TTO utility values Mild stroke: 0.76 (n.r.) Moderate stroke: 0.39 (n.r.) Major stroke: 0.11 (n.r.) Current own health: 0.82 (n.r.) (AF patients) Warfarin therapy: 0.987 (n.r.) Aspirin therapy: 0.998 (n.r.) There was no difference in utility values obtained via TTO and SG (p=0.13).	Relevant for potential inclusion based on elicitation method (TTO), population surveyed, and health states evaluated. Definition of stroke is consistent with that proposed for the health states in the economic evaluation (mRS).
O'Reilly(2009)[138]	No health states specified, but utility values available for MI, stroke, amputation and kidney failure.	Canadian population with type II diabetes. Sought to estimate the impact of diabetes-related complications on utility.	EQ-5D was administered to 1,147 patients with type II diabetes. Both US and UK scoring algorithms were used to	1,143 patients analysed (no other information provided).	UK algorithm: disutility. MI = −0.081 (s.e. 0.026; -0.132, -0.030^) Stroke = −0.067 (s.e. 0.036; -0.138, 0.004^)	Potentially relevant based on the elicitation method (EQ-5D) and the health states for which disutilities are available

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
			estimate respective utility decrements.		US algorithm: disutility. MI = −0.059 (s.e. 0.017; -0.092, -0.026^) Stroke = −0.046 (s.e. 0.023; -0.091, -0.001^)	(MI and stroke). Relevance is diminished to the extent that patients were not from the UK, and only limited information is available (*abstract publication only*).
Robinson (2001)[139]	Five in total: Hospital managed warfarin treatment; GP managed warfarin treatment; mild stroke; severe stroke; major bleed. Health state vignette descriptions are provided.	Assessment of utility values for various health states among patients with AF in the UK.	Face to face SG interviews. Each patient evaluated all five health states.	57 patients with AF completed the interviews – mean age of 73 years, 54% male, 49% on warfarin, 23% with prior stroke.	GP managed warfarin: 0.949 (0.089; 0.925, 0.971^) Hospital managed warfarin: 0.941 (0.101; 0.915, 0.967^) Major bleed: 0.841 (0.172; 0.796, 0.886^) Mild stroke: 0.641 (0.275; 0.570, 0.712^) Severe stroke: 0.189 (0.276; 0.117, 0.261^)	There is sufficient overlap with the proposed health states for inclusion in the economic evaluation. Health states were evaluated using the SG in patients with AF. In addition, patients surveyed were in the UK.
Sullivan (2005)[136]	Multiple health states, including disutilities associated with stroke; systemic embolism; TIA; ICH; ECH; acute MI.	Community based survey in the USA, part of the Medical Expenditure Panel Survey, with data for 2000-2002.	Self administered EQ-5D – collecting values for own health. Reported disutilities are coefficients from EQ-5D regression equations.	Total of 38,678 respondents, mean age of 46 years, and 54% females. Number of participants with: stroke, n = 995 (2.6%); MI, n = 1,211 (3.1%), CHD, n = 1,234 (3.2%), other heart disease, n = 2,272 (5.9%).	<u>Mean:</u> Overall: 0.867 (n.a.) MI: 0.725 (n.a.) Stroke: 0.694 (n.a.) Systemic embolism: n.r. TIA: n.r. ICH: n.r. ECH: n.r. <u>Disutilities:</u> MI: -0.035 (s.e. 0.001; -0.036, -0.033^) Stroke: -0.048 (s.e. 0.001; -0.050, -0.047^) Systemic embolism: -0.033 (s.e. 0.001; -0.035, -0.030^)* TIA: -0.027 (s.e. 0.0004; -0.028, -0.027^)*	Valuations are based on reported own health (using the EQ-5D) among members of the US general public with each condition at the time of completing the survey.

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
					ICH & ECH: -0.035 (s.e. 0.002; -0.039, -0.032^)*	
AF Specific Health State						
Berg (2010)[140]	AF (including stratification by AF type)	The Euro Heart Survey, based on 5,333 patients with AF in 35 European countries.	Self completed EQ-5D (based on UK algorithm).	Baseline: 5,050 respondents. Mean age 66.4 (12.8) years, 58.1% males, and 69.5% with AF symptoms. 1 year follow-up: 3,045 respondents. Mean age 66.6 (12.6) years, 59.8% males, and 40.5% has permanent AF.	Baseline: 0.751 (0.269; 0.744, 0.758^) Follow up: 0.779 (0.253; 0.770, 0.788^) Utilities by AF type were reported graphically.	This is potentially relevant based on the elicitation method (EQ-5D) and the health state assessed. The relevance of the study is diminished insofar as it is not UK specific (the study included only 31 patients from the UK). Nonetheless, the value for AF at baseline could be used within the model.
Stroke Health States						
Barton (2008)[141]	Multiple health states, including stroke.	Cross-sectional survey among UK general practice patients (part of assessing the cost-effectiveness of different interventions for knee pain).	Three HRQoL measures self completed: EuroQoL EQ-5D and VAS, SF-6D.	1,865 patients. Mean age 64.7 years, 55.2% females. Included 62 stroke patients (demographics not provided).	Mean utility estimates for patients with stroke: EQ-5D: 0.612 (0.318) Utility values for overall patient group: EQ-5D: 0.778 (0.239) (VAS and SF-6D values are not shown as these are not directly preference based measures).	Potentially relevant based on the method of elicitation (EQ-5D) and that it is an UK study. However, the value is for a consolidated stroke health state (does not correspond to the three states in the model) and is based on a small sample size. An implied disutility (-0.166) could however be estimated based on the difference between the utility value for the overall patient group (0.778) and that

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
						for the stroke group (0.612).
Dorman (2000)[142]	Three health states relating to post-stroke functioning: dependent, independent, recovered.	Hospital based stroke register, Lothian Stroke Register (LSR) series and patients derived from the International Stroke Trial (IST) with patients with confirmed or suspected ischaemic stroke enrolled between March 1993 and May 1995 in UK.	Interview administered EQ-5D.	LSR: 152 patients with first or recurrent stroke (median of 72 weeks after stroke onset). IST: 1,131 patients.	LSR Dependent: 0.38 (n.r.; 0.29, 0.34) Independent: 0.74 (n.r.; 0.69, 0.79) Recovered: 0.88 (n.r.; 0.80, 0.96) IST Dependent: 0.31 (n.r.; 0.29, 0.34) Independent: 0.71 (n.r.; 0.68, 0.74) Recovered: 0.88 (n.r.; 0.84, 0.92)	Relevant for potential inclusion based on the elicitation method (EQ-5D), it was a UK population and the health states evaluated.
Gore (1995)[143]	Patients without stroke. Patients with stroke, classified according to extent of residual deficit (no, minor, moderate, severe).	QoL sub-study of an RCT assessing four different thrombolytic strategies in patients with acute MI from 1,081 hospitals in 15 countries and assessing the incidence of stroke.	TTO in stroke survivors, conducted by telephone interviews at 30 days, 6 months and 1 year after stroke.	Post-stroke patients in each category according to residual deficit: Severe – n = 51, 7 interviewed. Moderate – n = 67, 32 interviewed. Minor – n = 80, 60 interviewed. None – n = 21, 15 interviewed Remaining patients (non-stroke) – n = 2,957, 2,579 interviewed. Other patient details not provided in publication.	TTO Severe: 0.71 (0.31; 0.480, 0.940^) Moderate: 0.81 (0.24; 0.727, 0.893^) Minor: 0.89 (0.15; 0.852, 0.928^) No: 0.92 (0.17; 0.834, 1.006^) All other patients (no-stroke): 0.87 (0.20; 0.862, 0.878^)	Relevant for potential inclusion based on the elicitation method (TTO) and the health states for which values are provided.
King (2009)[144]	Evaluation of own health plus three post stroke health states: persistent	US community based survey (not patient specific).	Online SG survey.	Total 1,654 respondents, mean age 45.4 years, 51% female.	Own health: 0.82 (0.19; 0.811, 0.829^) Persistent vegetative: 0.39	Relevant for potential inclusion based on the elicitation method (SG),

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
	vegetative, conscious but disabled, disabled but independent. Stroke health states described by GOS (descriptions not shown).				(0.33; 0.374, 0.406^) Conscious but disabled: 0.59 (0.27; 0.577, 0.603^) Disabled but independent: 0.83 (0.17; 0.822, 0.838^) Life with a cerebral aneurysm: 0.79 (0.18; 0.781, 0.799^)	that preferences are community based and the health states evaluated.
Min-Lai and Duncan, (2001)[145]	Evaluation of own health in patients post stroke (those showing improvement) categorised at three months into mRS categories of 0/1, 2 or 3.	Stroke patients in the Kansas City Stroke Study, USA. Applicability of results may be limited insofar as all patients had shown a response to treatment and an improvement in status prior to utility value estimation.	Interviewer based TTO to assess own health state.	459 patients, mean age 70 years, 53% females. Strokes were minor (39%), moderate (50%) and major (11%), with 93.7% being cerebral infarctions and 6.3% intra-cerebral haemorrhages.	Values presented in whole numbers (rescaled to be between 0 and 1 by dividing by 10). mRS 0/1: 0.9 (0.2; 0.848, 0.952^) mRS 2: 0.8 (0.25; 0.747, 0.853^) mRS 3: 0.8 (0.16; 0.724, 0.876^)	Relevant for potential inclusion based on the elicitation method (TTO) and the health states for which values are reported.
Shin (1997)[146]	Evaluation of minor and major stroke (description of health states provided in paper).	Patients at risk of stroke (cerebral vascular malformations) in Canada in 1996.	Interviewer administered SG to assess minor and major stroke.	Total of 31 respondents, mean age 37 years, 45% female.	Major stroke: 0.45 (n.r.; 0.33, 0.56). Minor stroke: 0.81 (n.r.; 0.75, 0.88). No differences in utility observed based on demographic characteristics.	Potentially relevant for inclusion due to the elicitation method (SG), although limited by the small sample size (n=31) and that only two health states were evaluated.
Tavakoli (2009)[147]	Evaluation of stroke according to BI categories: < 40; 40 to 60; 61 to 80; 81 to 100.	Data from PROGRESS study database, primary and secondary care centres in Asia, Australasia and Europe, applied in a Markov decision analytical model	EQ-5D questionnaire was used to assign QoL to health states. This was based on data provided by the Sheffield HE group which related EQ-5D to BI scores. These data were	Data from Sheffield based on a study of 3 residential care homes involving more than 3,000 people.	BI 81-100: 0.74 (0.06#) 61-80: 0.67 (0.12#) 40-60: 0.58 (0.14#) <40: 0.44 (0.19#)	Potentially relevant for inclusion based on the elicitation method (EQ-5D), and that values are presented for different levels of functioning (as assessed by BI). Would

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
		in the treatment of patients presenting with a cerebrovascular event in the UK.	then used to construct beta distributions for each health state as they are bounded on 0-1 interval.			require translation to health states to be used in evaluation (based on mRS).
Van Exel (2004)[148]	Evaluation of own health among stroke survivors at two and six months post stroke. Results reported according to following classifications: independent (BI > 20); mild (BI 15-19); moderate (BI 10-14); severe (BI 5-9); very severe (BI 0-4).	Post stroke services in the Netherlands.	EQ-5D assessed through patient interviews at 2 and 6 months post stroke.	Total of 598 patients, mean age 73.5 years, 46% male. 64% of patients were admitted to hospital with a severe or very severe stroke (BI of 0-9). 364 patients completed EQ-5D at 2 months, and 357 at six months.	Independent: 2 mths: 0.76 (n.r.; 0.72, 0.80); 6 mths: 0.81 (n.r.; 0.78, 0.84); Overall: 0.78 (n.r.; 0.76, 0.81) Mild: 2 mths: 0.61 (n.r.; 0.55, 0.66); 6 mths: 0.56 (n.r.; 0.52, 0.61); Overall: 0.58 (n.r.; 0.55, 0.62) Moderate: 2 mths: 0.41 (n.r.; 0.33, 0.50) 6 mths: 0.33 (n.r.; 0.22, 0.44) Overall: 0.38 (n.r.; 0.31, 0.54) Severe: 2 mths: 0.06 (n.r.; -0.04, 0.17); 6 mths: 0.09 (n.r.; -0.02, 0.20); Overall: 0.08 (n.r.; 0.03, 0.15) Very severe: 2 mths: -0.14 (n.r.; -0.20, -0.08); 6 mths: -0.11 (n.r.; -0.19, -0.02); Overall: -0.12 (n.r.; -0.17, -0.06)	Potentially relevant for inclusion based on the elicitation method (EQ-5D), and that values are presented for different levels of functioning (as assessed by BI). Would require translation to health states to be used in evaluation (based on mRS).
Acute MI						
Oldridge (2008)[149]	Evaluation of own health within six weeks of acute MI, and one year later.	Patients with MI in hospitals in USA randomised to cardiac rehabilitation intervention or to usual care initiated within 6 weeks of the acute MI.	Interviewer administered QWB and TTO on entry into trial, 2 mths (end of intervention), 4,8 and 12 mths.	188 Patients with MI (rehabilitation n=93; usual care n=95). Mean age 53.5 yrs, 89% male in both groups.	<u>Rehab</u> Baseline QWB: 0.61 (0.09; 0.592, 0.628^) TTO: 0.71 (0.19; 0.671, 0.749^) Change to 12 months QWB: + 0.15 (0.21; 0.107,	Potentially relevant based on method of elicitation (TTO) and health states presented.

Study	Health States	Setting	Elicitation method	Respondents	Mean utility values (s.d.; 95% CI)	Inclusion justification
					0.193^) TTO: + 0.13 (0.29; 0.071, 0.189^) <u>Usual care</u> Baseline QWB: 0.63 (0.10; 0.610, 0.650^) TTO: 0.77 (0.25; 0.720, 0.820^) Change to 12 months QWB: + 0.12 (0.21; 0.078, 0.162^) TTO: + 0.07 (0.28; 0.014, 0.126^)	
Rawles (1992)[150]	Evaluation of own health at suspected MI and 100 days later.	Assessed QoL in patients following admission to a teaching hospital in Scotland with suspected MI.	Rosser-Kinder scale. Patients interviewed by a doctor before discharge on their QoL prior to admission. Follow-up was by telephone interview at 1 month and a final interview and examination 3 months after the MI.	206 patients studied (mean age: 63 years; 69% male) of which 160 were assessed as having MI and 46 with no infarction.	<u>Preadmission</u> All MI: 0.977 (0.032; 0.972, 0.982^) Non MI: 0.978 (0.022; 0.972, 0.984^) <u>100 day</u> All MI: 0.844 (0.322; 0.794, 0.894^) Non MI: 0.953 (0.145;0.911, 0.995^)	Potentially relevant based on health state evaluated, that is a Scottish population, but the method of elicitation (Rosser Kind scale) is not preferred.
Winkelmayer (2006)[151]	Evaluation of own health among patients in a clinical trial (pravastatin) and reported for no MI, recent MI, past MI and overall.	PROSPER, clinical trial of pravastatin in patients >70 years (patients originally screened and enrolled in Dec 1997 – May 1999). Study was conducted in Scotland, Ireland and the Netherlands.	HUI3 administered over the phone to all participants alive and active in the study during a regular study visit in the last year of scheduled follow-up (Feb 2001 – April 2002)	3,390 patients with complete responses (mean age: 75.0 ±3.3; 48% male). 2,755 were MI free prior to the HUI assessment, 89 had an MI within the previous 90 days and 546 had an MI>90 days prior to the HUI assessment.	No MI: 0.747 (0.25; 0.738, 0.756^) Past MI: 0.735 (0.26; 0.713, 0.757^) Recent MI: 0.741 (0.25; 0.689, 0.793^) All: 0.745 (0.25; 0.737, 0.753^)	Potentially relevant for inclusion based on the method of elicitation (HUI3) and health states evaluated.

Abbreviations: AF, atrial fibrillation; AQoL, Assessment of Quality of Life; BI, Barthel's Index; ECH, extra cranial haemorrhage; GP, general practice; HUI, health utilities index; ICH, intracranial haemorrhage; MI, myocardial infarction; mRS, modified Rankin Score; n.r., not reported; QoL, quality of life; QWB, quality well being; RCT, randomised controlled trial; SG, standard gamble; TIA, transient ischaemic attack; TTO, time trade off; VAS, visual analogue scale

^ 95% CI were calculated based on the available s.e., or s.d. and sample size.

[#] 95% CI could not be estimated.

* these values were sourced from an online appendix to Sullivan (2005), sourced at http://www.uchsc.edu. The following classifications were applied in this analysis: systemic embolism, ccc116 aortic and peripheral arterial embolism or thrombosis; TIA, ccc112 transient cerebral ischemia; ICH and ECH, ccc115 aortic, peripheral, and visceral artery aneurysms. ICD-9 codes for each event type were matched to those used by Sullivan (2006).

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As can be seen from the summary, of the 52 articles reviewed in depth, 17 contained utility values that are potentially relevant for inclusion in the economic evaluation. No one article contained utility values that could be applied to all the health states (across all three sets) slated for inclusion in the economic evaluation. It is therefore be necessary to source utility values from multiple studies.

The absolute utility (disutility) values for the relevant health states/events were extracted from the studies as appropriate. In each case, justification is provided for why one source for a utility value has been chosen over other potentially relevant sources. Where possible, sources for potentially alternative utility values for use in a sensitivity analysis of the model results to the choice of utility values will be identified. Note that in general it is preferable that when applying utility (or disutility) values obtained in one setting to another setting, they are applied using relative rather than absolute magnitudes. This would allow the utilities associated with a specific health event to be rescaled against the base case of interest, in this case a patient with AF free from specific health events. However, there is insufficient information from the published information to allow such rescaling to be implemented uniformly across all health states, thereby requiring the application of absolute values.

The results of the literature search for Set 1 utilities will be discussed in Section 6.4.7.

Utility values for post-stroke health state (Set 2)

The values reported by many of the stroke specific publications are not for health states as described in Set 2, and would require some degree of transformation (either collapsing them where there are too many states as in Tavakoli (2008)[147] and Van Exel (2004)[148], or translating them where the health state descriptions are not directly applicable as in Barton (2008)[141], Gore (2005)[143], King (2009)[144], Min-Lai and Duncan (2001)[145], O'Reilly (2009)[138], Robinson (2001)[139], and Shin (1997)[146].

This leaves three studies as potential sources of post-stroke utility values: Gage (1995 and 1996)[125, 137] and Dorman (2000)[142]. The Dorman study was based in Scotland and reports values collected using the EQ-5D from 1,131 patients included in the International Stroke Trial for three levels of stroke dependency (recovered, independent, and dependent). However, no values are provided for moderate disability, and we therefore assume that these patients are distributed amongst the independent and dependent patients. As these cannot be disaggregated, it would be inappropriate for this data to be used in the base case.

Gage (1995 and 1996) report values for three states consistent with those required for the economic evaluation (mild stroke being consistent with post-stroke independence (mRs 1 or 2), moderate stroke being consistent with some dependence (mRs 3 or 4), and major stroke being consistent with total dependence (mRs 4 or 5)). Given that appropriate EQ-5D data is unavailable, Gage (1996) appears to be an appropriate alternative source of utility values for the health states for Set 2. The values from Dorman (2000) will be used in the sensitivity analysis with moderate disability represented by the mid-point of the utilities for independent and dependent. Note the values from Gage (1995) are too similar to those from Gage (1996) to serve as alternative parameter values in a sensitivity analysis. A summary of the utility values to be applied to the post-stroke health states in the base case and sensitivity analysis is provided in **Table 93**.

Table 93 Utility values for post-stroke health states

Health state	mRS	Utility value Mean (95% CI)		Source and elicitation method
		Base case	Sensitivity analysis	
Mild stroke (independent)	0 = No symptoms at all 1 = No significant disability despite symptoms; able to carry out all usual duties and activities 2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	0.76 (n.r.)	0.71	Base case: Gage (1996), TTO. [125] Sensitivity analysis: Dorman (2000), EQ-5D. [142]
Moderate stroke (some dependence)	3 = Moderate disability; requiring some help, but able to walk without assistance 4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	0.39 (n.r.)	0.51	
Major stroke (totally dependent)	5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention	0.11 (n.r.)	0.31	

Abbreviations: n.r. not reported; TTO, time trade off.

Disutility values for specific events (Set 3)

As noted previously, it would be preferable if the utility values for the health states within the economic evaluation could all be obtained from within the same study. While it was not possible to obtain all values from the same study, Sullivan (2005)[136] report a set of disutility

values for all bar one (minor bleeding) of the health states within Set 3. The appropriateness of the disutility values reported in Sullivan (2005) for use in the economic evaluations is subject to the following considerations:

- The search of the literature identified another publication by the same authors[152] which purports to use the disutility values in the original publication in a cost-effectiveness analysis. However, the disutility values reported in the 2006 publication do not match those reported in the 2005 publication. An attempt was made to reconcile these data by using the online appendix to the 2005 data (sourced at http://www.uchsc.edu). This did not provide any additional information, so an e-mail was sent to the corresponding author. No reply was received. Thus it is unclear how the disutility values reported in Sullivan (2005) relate to those subsequently used in the economic evaluation (Sullivan (2006)).
- The disutility values were based on a population survey, and therefore reflect QoL effects for a given health outcome of varying duration across individuals. That is, some individuals with a given health outcome may have more recently experienced that outcome than others. Temporal QoL effects for a given health outcome are therefore "averaged" across the respondents with that outcome. The implication is that the resulting disutility values can be applied within the economic evaluation without further amendments for the impact of time in affecting the QoL effects of a health event of interest.
- The survey values are for respondents in the United States. It is possible that these values would be different among UK respondents. Indeed, a study carried out by Johnson (2005), found that valuations of health states using the EQ-5D were on average 0.10 ($p<0.001$) points higher among US respondents than UK respondents[153]. It is unclear how such a difference might translate to estimates of the disutility associated with a health state. That is, while Johnson (2005) shows a difference in valuations for given health states between US and UK populations, they do not compare within sample differences between health states.

An indication of such a difference can be gleaned by reviewing the results reported by O'Reilly (2009)[138]. Within that study, EQ-5D survey responses from Canadian patients with diabetes were valued using both an US and UK based valuation algorithm. As reported in **Table 92**, use of the UK algorithm resulted in disutility values that were numerically larger than those produced using the US algorithm. However, the 95% CI around the point estimates overlapped, suggesting that the values produced using the UK and US algorithms did not differ. On the basis of this comparison, it might be reasonable to assume that use of US based values would not result in outcomes different to those produced if UK based disutility values were available. Nonetheless, the clinical data from the RE-LY study show that the use of DBG 150mg results in statistically significantly fewer occurrences of stroke when compared with WFN. The use of disutility values from Sullivan (2005), US based values which may be lower than UK based values, would therefore bias the analysis against DBG

(since it will reduce the incremental disutility arising from stroke in WFN patients relative to DBG patients).

Finally, the disutility values reported in Sullivan (2005) represent the marginal decrement to utility associated with each of those health states, taking into account patients' age, underlying co-morbidities and demographic characteristics (such as income and education). The authors of that paper recommend against the use of the difference between the mean population utility value and the mean health state specific utility as a disutility value since this difference takes into account many other factors other than the occurrence of that health state alone. For example, as noted above the difference between the overall mean utility (0.867) and the stroke health state (0.694) reported by Sullivan (2005) is 0.173. The reported disutility for that health state is much lower at -0.040, indicating that the presence of co-morbidities in stroke patients contributes to the lower utility value.

Taking these points into consideration, it is proposed that the values from Sullivan (2006) be used as the relevant parameter values within the base case of the economic evaluation, while those from the Sullivan (2005) publication be used to construct the sensitivity analysis. Given that since Sullivan (2006) reports values used within an economic evaluation it is reasonable to assume that the disutility values have been appropriately adjusted from those reported in Sullivan (2005) for that purpose. Moreover, the unadjusted disutility values reported from Sullivan (2005) would appear to be too low given the known severity of the events under consideration. For example, it is likely that a patient experiencing an ischaemic stroke would experience a decrement in their quality of life greater than 0.0483 as suggested by Sullivan (2005). However, insofar as Sullivan (2005) provide disutility values for all the health states of interest it is used as the source of values for the sensitivity analysis in preference to using multiple other studies (which may introduce other biases with respect to study methods and populations). The values for use in the economic evaluation are summarised in **Table 94**.

Table 94 Disutility values for multiple health states

Health state	Base case Mean (95% CI)*	Source and elicitation method	Sensitivity analysis Mean (95% CI)	Source and elicitation method
Stroke	-0.139 (-0.118, -0.160)	Sullivan (2006), EQ-5D[152]	-0.048 (-0.050, -0.047)	Sullivan (2005), EQ-5D[136]
Systemic embolism	-0.120 (-0.102, -0.139)		-0.033 (-0.035, -0.030)	
TIA	-0.103 (-0.088, -0.119)		-0.027 (-0.028, -0.027)	
ICH	-0.181 (-0.155, -0.209)		-0.035 (-0.039, -0.032)	
ECH	-0.181 (-0.155, -0.209)		-0.035 (-0.039, -0.032)	
AMI	-0.125 (-0.106, -0.144)		-0.035 (-0.036, -0.033	

Abbreviations: AMI, acute myocardial infarction; ECH, extra-cranial haemorrhage; ICH intra-cranial haemorrhage; TIA denotes transient ischaemic attack

* reported as the 2.5% and 97.5% limits for use in the probabilistic sensitivity analysis

None of the studies reported a preference based value for minor bleeds. A review of Sullivan (2006) [152] showed that an absolute utility value for minor bleeds was included, but this was based on an author derived utility weight from another published study [112] A search was conducted of the Harvard Online CEA Registry (https://research.tufts-nemc.org/cear/search/search.aspx) using the term "minor bleed". This revealed three publications, one of which was Sullivan (2006), and another which did not contain utility values for minor bleeds [154]. The remaining publication assumed that a minor bleed would result in an additional day of hospitalisation, which would reduce the total QALY estimate by one day (implicitly attaching a utility value of 0 to that day of hospitalisation, or a disutility of -0.0027 for a minor bleed in a given QALY year (calculated as 1/365) [155].

Within the economic evaluation, the definition of minor bleeds is such that patients remain on their existing treatment, they experience no added disability, and there is no impact on mortality. Accordingly, and in the absence of preference based utilities for minor bleeds, it is assumed in the base case of the analysis that there is no disutility associated with the occurrence of a minor bleed. This is varied in a sensitivity analysis in which the absolute utility values reported by Sullivan (2006) are used to construct a disutility value for minor bleeds. Sullivan (2006) report that a patient on ongoing WFN therapy has a utility value of 0.987 (95% interval: 0.967, 0.998), and that a patient with a minor bleed has a utility value of 0.80 (95% intervals: 0.68, 0.92). Subtracting the former from the latter implies an annual disutility associated with minor bleeds of -0.187 (95% intervals: -0.287, -0.078). Assuming that the quality of life decrement associated with a minor bleed applies for only two days, the disutility applicable for each minor bleed event is -0.001 (95% intervals: -0.002, -0.0004).

A summary of the proposed approach to estimating the disutility of a minor bleed is presented in **Table 95**.

Table 95 Disutility values for minor bleeds

Health state	Base case	Source and elicitation method	Sensitivity analysis (95% intervals)	Source and elicitation method
Minor bleed	0	Assumption	-0.001 (-0.002, -0.0004)	Estimation based on Sullivan (2006). [152]

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Adequately measuring health-related quality of life alongside clinical trials remains a challenge in settings such as RE-LY. Given the open design, and the typical patient inclusion criterion that stipulated that patients could not enter into the trial if there was concern that patients may be unreliable concerning "requirements for follow-up during the study and/or compliance with study drug administration", and as patients were informed of the need for regular INR monitoring before enrolment, it can be expected that those patients being unsure about their ability to comply with this, would not have consented. This could introduce a bias in favour of the more complex treatment option, in this case WFN. Additionally, patients in the DBG groups were aware of the investigational nature of the drug whereas the comparator arm constitutes the current standard of care and has been in clinical use for decades. This may have "masked" health-related quality of life changes in both arms. Blinding on the other hand is also not a solution, as with double-dummy technique "sham INR" tests in the DBG arms would not allow a quality of life assessment resembling later routine use either. Hence, such limitations have to be kept in mind when interpreting the findings of the quality of life substudy.

[redacted]. The comparison of these values with those from the literature review is presented below.

Presence of AF without history of stroke

Gage (1996)[125] reports an own current health value for patients with AF of 0.82 (95% CI; n.r.), while Berg (2010)[140] reports a baseline value for patients with AF of 0.751 (95% CI: 0.744, 0.758). [redacted]. It is appropriate therefore that the value from Berg (2010) of 0.751 be used in a sensitivity analysis within the economic evaluation.

WFN treatment (including frequent monitoring of INR)

While the results from RE-LY suggest no change over time in the utility associated with WFN treatment, it is possible that this result is an artefact of the clinical trial rather than a reflection of what is likely to occur in clinical practice. That is, patients in the clinical trial were required to undergo ongoing monitoring (other than for INR levels) that may not otherwise have occurred in clinical practice. The additional impost of INR monitoring is therefore likely to have been diluted in the milieu of other protocol mandated monitoring. This being the case, it is appropriate to consider the potential impact of ongoing INR monitoring.

The literature search identified three studies (Gage (1995, 1996)[125, 137] and Robinson (2001)[139]) which assessed the utility associated with WFN therapy. These studies suggest that there is a measurable disutility directly attributable to the burden of WFN therapy. The results from Gage (1995, 1996) (see **Table 96**) estimated values for WFN therapy to be 0.988 and 0.987, respectively. A set of slightly lower values was reported by Robinson (2001); 0.949 and 0.941 for the GP and hospital based settings, respectively. While it is proposed that a disutility value of 0 be applied within the base case of the economic evaluation, it is pertinent to examine the impact of this assumption. It is proposed that the value from Gage (1996) be used as part of a sensitivity analysis. The relative disutility associated with WFN monitoring is assumed to be given by the difference between the reported mean value and that associated with full health (1.0). Thus, for the value reported by Gage (1996), a mean utility value of 0.987 represents a disutility of 0.013 (1.3%).

Table 96 Disutility attributable to burden of warfarin therapy

Study	Elicitation method	Utility value Mean (95% CI)
Gage (1996)[125]	TTO	0.987 (n.r.)
Gage (1995)[137]	TTO	0.988 (n.r.)
Robinson (2001)[139]	SG	GP setting, 0.949 (0.925, 0.971) Hospital setting, 0.941 (0.915, 0.967)

Abbreviations: GP, general practice; n.r. not reported; SG, standard gamble; TTO, time trade off.

However, for the purposes of the current analysis it is suggested that a conservative approach be adopted in which no disutility is attached to the burden of warfarin therapy.

DBG treatment

As previously noted, [redacted]. Unlike WFN, patients on DBG are not required to undergo anticoagulation monitoring. It is therefore reasonable that no further adjustments, other than those associated with the occurrence of specific health events, be applied to the quality of life of DBG patients. [redacted]

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

The HRQL impact of adverse events (haemorrhagic events) included in the economic model has already been discussed as part of the reporting of Set 2 and 3 utility values in Section 6.4.6. Of other adverse events, only dyspepsia was shown to be statistically significantly different, and only in the short-term. This is discussed above in Section 6.4.7.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The utility values proposed for use in the economic model, including sensitivity analyses, are summarised in **Table 97**.

Table 97 Summary of utility and disutility values

Health state	Base case Mean (95% CI)	Source and elicitation method	Sensitivity analysis Mean (95% CI)	Source and elicitation method
Utility values for general health states (Set 1, from 6.4.3, 6.4.7, and 6.4.8)				
AF patient	[redacted]	RE-LY study, EQ-5D[133]	0.751 (0.744, 0.758)	Berg (2010), EQ-5D.[140]
Warfarin treatment (monitoring)	Not considered		-0.013 (n.r.)	Gage (1996), TTO[125]
DBG treatment (monitoring)	Not considered		-0.027 (n.r.)	RE-LY data, EQ-5D[133]
Utility values for post-stroke health state (Set 2, from 6.4.6)				
Mild stroke: mRS 0-2	0.76 (n.r.)	Gage (1996), TTO[125]	0.71	Dorman (2000), EQ-5D.[142]
Moderate stroke: mRS 3-4	0.39 (n.r.)		0.51	
Major stroke: mRS 5	0.11 (n.r.)		0.31	
Disutility values for event specific (Set 3, from 6.4.6)				
Stroke (severity not specified).	-0.139 (-0.118, -0.160)	Sullivan (2006), EQ-5D[152]	-0.048 (-0.050, -0.047)	Sullivan (2005), EQ-5D[136]
Systemic embolism.	-0.120 (-0.102, -0.139)		-0.033 (-0.035, -0.030)	
TIA	-0.103 (-0.088, -0.119)		-0.027 (-0.028, -0.027)	
ICH	-0.181 (-0.155, -0.209)		-0.035 (-0.039, -0.032)	
ECH	-0.181 (-0.155, -0.209)		-0.035 (-0.039, -0.032)	
Acute MI (severity not specified).	-0.125 (-0.106, -0.144)		-0.035 (-0.036, -0.033	
Minor bleed (not specified).	0	Assumption	-0.001 (-0.002, -0.0004)	Estimation based on Sullivan (2006)[152].

Abbreviations: CI, confidence interval; ECH, extracranial haemorrhage; ICH, intracranial haemorrhage; MI, myocardial infarction; n.r., not reported; TIA, transient ischaemic attack; TTO, time trade off.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical expert opinion was sought regarding the utility values.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Unless an event occurs, the HRQL level of patients remains constant within each health state and from cycle to cycle. Changes in HRQL only occur for three reasons:

1. When a patient has a clinical event, resulting in a one-shot temporary disutility within a single cycle
2. Post stroke/ICH, patient HRQL is modified to reflect their new disability level
3. Death

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

None were identified.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

This has been discussed as part of the reporting of Set 1 utilities in Section 6.4.3 and 6.4.7.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Please see the response to Section 6.4.11.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Treatment costs

Costs for treatments (drug and monitoring) are not available in the PbR tariff.

Cost of events

Events included in the economic evaluation with PbR codes are:

- Ischaemic stroke (by mRs 0-2, 3-4, 5, 6)
    - AA04Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 4
    - AA10Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 3
    - AA16Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 1 or 2
    - AA22Z Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy
- Haemorrhagic stroke and intracranial haemorrhage (by mRs 0-2, 3-4, 5, 6)
    - AA04Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 4
    - AA10Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 3
    - AA16Z Intracranial Procedures Except Trauma with Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy Category 1 or 2
    - AA22Z Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy
    - AA23Z Haemorrhagic Cerebrovascular Disorders
- TIA
    - AA29Z Transient Ischaemic Attack
- AMI (Fatal, non-fatal)
    - EB10Z Actual or suspected myocardial infarction
- ECH (Fatal, non-fatal non-GI, non-fatal GI)

    - LB38A Unspecified Haematuria with Major CC
    - FZ38A Gastrointestinal Bleed with Major CC
- (Clinically relevant) Minor bleeds
    - None available
- Systemic Embolism (Fatal, non-fatal)
    - None available

Cost of post-event disability for IS/HS/ICH

The acute phase of rehabilitation is included under AA22Z (Non-Transient Stroke or Cerebrovascular Accident, Nervous system infections or Encephalopathy). However, long-term stroke rehabilitation costs are not rebundled and no tariffs published. The PbR states that these are to be negotiated locally (code VC04Z)

Other costs

These are:

- costs for other DBG adverse events (dyspepsia)
- discontinuation of treatment without an event to no treatment or another drug
- treatment switch
- death from unrelated cause

These are not included in the PbR codes.

Discussion of codes for IS/HS/ICH

The codes that include IS/HS/ICH refer to a range of outcomes. The codes associated with nervous system infections, or encephalopathy, are clearly inappropriate. Costs for cerbrovascular accident and non-transient stroke may be applicable to HS/ICH and IS. In addition, "Haemorrhagic Cerebrovascular Disorders" may be applicable to HS/ICH. However, these costs should ideally be disaggregated by event type, as event rates vary by event type for patient/treatment groups.

Severity of stroke is based on the post-event mRs. However, these are costed by different categories. Therefore the cost categories could not reliably be mapped onto the mRs.

Stroke in patients with AF is known to be more expensive than stroke in patients without AF. Given that that majority of these strokes are likely to be from non-AF patients, these costs would under-estimate the true costs of strokes in patients with AF.

Discussion of codes for TIA, AMI and ECH

PbR tarriffs were available for TIA (AA29Z), AMI (EB10Z, defined as Actual or suspected myocardial infarction), and non-GI ECH and GI ECH (LB38A and FZ38A, defined as Non-GI ECH - Unspecified Haematuria with Major CC; GI ECH - Gastrointestinal Bleed with Major CC). The PbR tariffs associated with these codes are shown in **Table 98**.

Table 98 PbR Tariffs for TIA, AMI, Non-GI ECH and GI ECH[156]

HRG code	HRG name	Combined Daycase/ Elective tariff (£)	Non-elective spell tariff (£)	Per day long stay payment (for days exceeding trimpoint) (£)	Reduced short stay emergency tariff (£)
AA29Z	TIA	671	1,339	186	603
EB10Z	AMI	1,569	3,872	190	968
LB38A	Non-GI ECH	1,913	2,539	196	635
FZ38A	GI ECH	1,967	2,068	183	517

Abbreviations: AMI - Actual or suspected myocardial infarction; GI ECH - Gastrointestinal Bleed with Major CC; Non-GI ECH - Unspecified Haematuria with Major CC; TIA - Transient Ischaemic Attack

Activity levels for each of the PbR tariffs are shown in **Table 99**. These activity levels are from 2007-08 NHS reference costs[157]. The reason for using this and not the more recent 2008-09 NHS reference costs[158] is due to the PbR tariff costs being based on the 2007-08 NHS reference activity levels and costs[159]. Using activity levels and numbers of excess bed days from the 2007-08 NHS reference costs ensures that the PbR costs which are based on these activity levels (in particular the long-stay trim points), are consistent with the data which was used to derive them.

Table 99 Activity levels for TIA, AMI, Non-GI ECH and GI ECH[157]

HRG Name and Page	Activity	National Average Unit Cost
Transient Ischaemic Attack		
TPCTEI Elective Inpatient HRG Data	164	1,510
TPCTEIXS Elective Inpatient Excess Bed Day HRG Data	129	293
TPCTNEI_L Non-Elective Inpatient (Long Stay) HRG Data	11,662	1,046
TPCTNEI_L_XS Non-Elective Inpatient (Long Stay) Excess Bed Day HRG Data	17,450	191
TPCTNEI_S Non-Elective Inpatient (Short Stay) HRG Data	13,663	338
TPCTDC Day Cases HRG Data	264	510
Actual or suspected myocardial infarction		
TPCTEI Elective Inpatient HRG Data	4,127	1,942
TPCTEIXS Elective Inpatient Excess Bed Day HRG Data	2,283	266
TPCTNEI_L Non-Elective Inpatient (Long Stay) HRG Data	71,704	1,526
TPCTNEI_L_XS Non-Elective Inpatient (Long Stay) Excess Bed Day HRG Data	74,626	193
TPCTNEI_S Non-Elective Inpatient (Short Stay) HRG Data	35,696	381
TPCTDC Day Cases HRG Data	2,580	465
TPCTDCRA Regular Day / Night Admissions	5	638
Gastrointestinal Bleed with Major CC		
TPCTEI Elective Inpatient HRG Data	31	1,654
TPCTEIXS Elective Inpatient Excess Bed Day HRG Data	201	172
TPCTNEI_L Non-Elective Inpatient (Long Stay) HRG Data	922	1,690
TPCTNEI_L_XS Non-Elective Inpatient (Long Stay) Excess Bed Day HRG Data	1,547	205
TPCTNEI_S Non-Elective Inpatient (Short Stay) HRG Data	496	382
TPCTDC Day Cases HRG Data	8	353
Unspecified Haematuria with Major CC		
TPCTEI Elective Inpatient HRG Data	275	1,187
TPCTEIXS Elective Inpatient Excess Bed Day HRG Data	401	198
TPCTNEI_L Non-Elective Inpatient (Long Stay) HRG Data	10,325	1,326
TPCTNEI_L_XS Non-Elective Inpatient (Long Stay) Excess Bed Day HRG Data	18,311	188
TPCTNEI_S Non-Elective Inpatient (Short Stay) HRG Data	7,821	357
TPCTDC Day Cases HRG Data	28	484

Abbreviations: AMI - Actual or suspected myocardial infarction; GI ECH - Gastrointestinal Bleed with Major CC; Non-GI ECH - Unspecified Haematuria with Major CC; TIA - Transient Ischaemic Attack

The average unit cost per event was calculated by first calculating the average cost of an elective stay and a non-elective long-stay. This was derived by calculating the average number of excess days per admission as the number of excess bed days divided by the number of admission, then multiplying this by the cost of an excess bed day then adding to the cost of admission (**Table 100**). Then using these costs along with the tariff costs for non-elective short-stays and day cases, the average costs were calculated weighted by activity. All actual calculations for these are shown in Table 100.

Table 100 Calculation of average cost per patient per event

Event	Types of stay	Calulation	Costs
TIA	Elective	(164/129)*£186+£671	£817
	Non-elective long-stay	(17,450/11,662)*£186+£1,339	£1,617
	Non-elective short-stay	-	£603
	Day cases	-	£671
	Total weighted average	(£817x164 + £1,617x11,662 + £603x13,663 + £671x264)/(164 + 11,662 + 13,663 + 264)	**£1,064**
AMI	Elective	(2,283/4,127)*£190+£1,569	£1,674
	Non-elective long-stay	(74,626/71,704)*£190+£3,872	£4,070
	Non-elective short-stay	-	£968
	Day cases	-	£1,569
	Total weighted average	(£1,674x4,127 + £4,070x71,704 + £968x35,696 + £1,569x2,580)/(4,127 + 71,704 + 35,696 + 2,580)	**£2,956**
Non-GI ECH	Elective	(201/31)*£196+£1,913	£3,184
	Non-elective long-stay	(1,547/922)*£196+£2,539	£2,868
	Non-elective short-stay	-	£635
	Day cases	-	£1,913
	Total weighted average	(£31,84x31 + £2,868x922 + £635x496 + £1,913x8)/(31 + 922 + 496 + 8)	**£2,109**
GI ECH	Elective	(401/275)*£183+£1,967	£2,234
	Non-elective long-stay	(18,311/10,325)*£183+£2,068	£2,393
	Non-elective short-stay	-	£517
	Day cases	-	£1,967
	Total weighted average	(£2,234x275 + £2,393x10,325 + £517x7,821 + £1,967x28)/(275 + 10,325 + 7821 + 28)	**£1,594**

Abbreviations: AMI - Actual or suspected myocardial infarction; GI ECH - Gastrointestinal Bleed with Major CC; Non-GI ECH - Unspecified Haematuria with Major CC; TIA - Transient Ischaemic Attack

The weighted average cost for TIA is estimated at £1,064. It should be noted that this is not necessarily a population of patients with AF, and for this population the cost might differ. The cost of TIA in patients with AF was calculated as part of the OXVASC study (see below for further details) as £[redacted] (SE = £[redacted]) per event (n=[redacted], 2009 cost). This cost is more reflective of the non-elective long stay cost (of £1,617). However, given that we have no clinical justification for using the higher cost, we will conservatively use the weighted average PbR cost of £1,064 per event.

The codes proposed for AMI are for actual or suspected myocardial infarction, and therefore might not necessarily be an AMI. However, this code will not necessarily include the full costs as an additional code is available which related to post-event rehabilitation (VC387). This does not have a mandatory HRG code and is not rebundled (i.e. included in the PbR elsewhere). The PbR advises that these costs should be negotiated locally. Therefore, taking a weighted average based on numbers of admission, which results in an average cost per admission of £2,956, may be an appropriate estimate. The economic evaluation separates events into fatal and non-fatal AMI, and given that the weighting of number of fatal AMIs in the trial is likely to reflect the weighting in clinical practice, these costs are assumed to be the same.

The tariff for unspecified haematuria with major CC was used for for non-GI ECH. Gastrointestinal bleed with major CC was applied for GI ECH. The average cost per patient for each of these was £2,109 and £1,594 per admission. Costs for fatal/non-fatal bleeds are not provided. Whilst the cost for GI bleed appears to be suitable, the code for non-GI ECH may be too narrow for use in the evaluation. These costs and their appropriateness in the model are discussed futher in 6.5.3.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Given that DBG is an oral treatment for a chronic condition, NHS reference costs or PbR tariffs are not appropriate for estimating the cost of the intervention. These sources however may be appropriate for other events included in the economic model as described above.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Systematic reviews were undertaken to estimate the following:

- INR Monitoring costs
- Cost of stoke (IS and HS)
- Cost of bleeds (ICH, ECH)

Systematic review of INR monitoring resource-use and costs

The cost of INR monitoring is likely to be an important consideration in the economic model. No PbR tariffs or NHS reference costs exist for this service. In addition, it is known that practice varies widely both within and across local health economies in England and Wales, as patients may be tested in a variety of settings. This makes the estimation of a national average difficult to estimate.

Details of the methods used in the systematic review are provided in Appendix 13. In total, 17 relevant papers were identified for the UK. Information extracted from these papers is shown in **Table 101**.

Table 101 Data extracted from studies regarding the cost of INR monitoring

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
Abdelhafiz 2001 (Abstract) [160]	Study period 1 year; date unknown; place of monitoring not stated; perspective, cost year, resource year not stated.	Cost of warfarin treatment was £262.6 per patient year (included drug costs, monitoring costs and costs of treating bleeding complications). Cost per stroke prevented was £8,141	Inappropriate for use in economic evaluation as: • monitoring aggregated with costs for bleeding complications • Perspective, cost year and resource year unclear
Abdelhafiz 2003 [160]	Cost year 1999–2000; Mean follow-up period 19 ± 8.1 months (range 1–31 months); date of study unknown; Hospital-based, pharmacist-led, anticoagulation clinic or blood samples taken at home or at GP's office and then monitored at the clinic	Disaggregated costs: • Staff time: Nurse visit £4.90/patient/year or £0.65 (0.18–1.20)/patient/month • Prothrombin test: INR cost £55.60/patient/year or £7.40 (7.00–7.80)/ patient/month • Postage: £2.90/patient/year or £0.39 (0.36–0.41)/patient/month • Transport: £26.10/patient/year for the patient or £3.50 (3.20–3.70)/ patient/ month • £0.90/patient/year or £0.12 (0.01–0.30)/patient/month for work missed Total costs • £90.40/patient/year or £12.06/patient/month	Inappropriate for use in economic evaluation as: • Resources year not provided therefore may not be reflective of current clinical practice • Resource use and unit costs not provided therefore unclear how costs were calculated • Costs per 634 patient years and for 1 patient year differ when normailsed to a single patient year (£161.67 vs £159.40) –unclear if patient years, and costs, are based on patient year costs calculated for patients that have withdrawn from warfarin. • Travel costs are included, but a proportion is funded by the patient and the size of this proportion in not known.
Arya 2005 [161]	Cost year 2004; Based on services provided by six secondary care trusts	Average cost of a monitoring visit £14.58 ± 4.25, of which £6.88 for taking blood, £4.08 for analysis and £3.62 for communicating results and making dose changes. Cost per INR test was lower for Mean for hospital-based care was £13.39; mean for shared secondary and primary care was £23.06. Mean annual cost per patient for INR monitoring was £206.41 ± £63.51	Inappropriate for use in economic evaluation as: • Small sample size limited to secondary care trusts unlikely to reflect current national clinical practice • Resource year not given • Perspective not stated (appears to be NHS)
Bhavnani 2002 [162]	Cost year not reported; Costs are for patient self-monitoring at home	Equipment: Around £400 for a coagulometer; test strips approximately £2.50 each	Inappropriate for use in economic evaluation as: • Self-monitoring not reflective of current clinical practice • Cost and resource year not provided
Connock 2007 [163]	Cost year 2005. Modeled period of 10 years. Patient self-monitoring (PSM) or hospital-based clinic	PSM costs: Staff time: £44.14 (£33.12-£55.20) for two GP consultations; CoaguChek machine £513.56 (£385.17-£641.95); test strips (x26) £71.24 (353.43-£89.05); Internal quality control test (x4) £21.92 (£16.44-£27.40); External quality control test (x1) £26.28 (£19.71-£32.85); Training/education £170.23 (£127.67-	Inappropriate for use in economic evaluation as: • Total cost for PMS not provided, only incremental costs (resources may have derived from Jowett 2006[164] (see below) • Costs for Anticoagulation control cost per year from

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
		£212.67) (success rate 0.6, 0.45-0.75) Anticoagulation control cost (usual care annual costs): £98.47, £73.86-£123.09	Fitzmaurice 2005 [165] However, when this publication was searched, no reference to this or any other cost was found) therefore unclear how costs were derived
Davies 2000 [166]	Cost year 1997; hospital clinic or outreach clinic; Healthcare provider and patient perspective	Annual cost for nursing time £20,150 in a hospital clinic, £14,926 in an outreach clinic; annual cost for doctor's time £1905 and £1280, respectively; Annual fixed costs for hospital and outreach clinic respectively: computer £297 & £344, printer £71 & £83, CDSS £989 & £400, portable test equipment £0 & £593; annual variable costs for clinical equipment: £0 & £240, respectively; Blood test - Annual cost for hospital and outreach clinic respectively: £10,800 & £0; Annual cost for prothrombin test card for hospital and outreach clinic respectively: £0 & £3150; Annual cost for clerical expenses for hospital and outreach clinic respectively: £120 &£0; Annual variable costs for telephone for hospital and outreach clinic respectively: £1350 & £0; annual fixed costs for telephone, transport & education for hospital and outreach clinic respectively: £629 & £826 Annual hospital travel costs for hospital and outreach clinic: £7986 & £0, respectively; Annual overheads on fixed and semi-fixed costs: £4327 & £3750 for hospital and outreach clinic, respectively; annual overheads on variable costs: £3646 & £610, respectively; Average total cost per visit £8.71 for hospital clinic & £21.83 for outreach clinic, giving an overall average cost per visit of £10.90	Inappropriate for use in economic evaluation as: • Resource use may no longer be appropriate – e.g computer costs, printer costs, software costs. • Resource year not given though likely to predate 1997 – therefore would be inappropriate to use as unlikely to reflect current clinical practice.
Fitzmaurice 1996 [167]	Study ran for 12 months from late 1993; Pilot study; Place of monitoring: practice-based clinic.	In-practice use of CDSS: £2.92 per visit for a GP (7 minutes of time); £1.13 per visit for a practice nurse; £1 per visit for consumables (use of CDSS); Capital costs: £2000 for computer software, £1200 for laptop computer; Prothrombin test £5 per visit; Patient transport £5 per visit; Computer maintenance £540 per year; Estimated at 1 hour per patient per visit. For use of CDSS: total cost for first year £6736 (26 patients attended 108 appointments), £3696 for subsequent years. Hospital costs: £6300 per year for first and subsequent years.	Inappropriate for use in economic evaluation as: Resource use may no longer be appropriate as resource use from 1993 and therefore unlikely to reflect current clinical practice.
Fitzmaurice	1 year study from 31 January 1995;	Overheads £500 for 29 patients over 1 year, including CDSS	Inappropriate for use in economic evaluation as:

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
1998 [168]	Place of monitoring: a practice-based nurse-led clinic.	maintenance and quality assurance costs Total costs (for one test): New-patient appointment £7 each; clinic follow-up appointment £3 each; domiciliary follow-up appointment £12 each. Had patients been seen in a local provider unit, the costs would have been £45 per new-patient appointment and £10 for a follow-up appointment. Total costs over the year for the 29 patients were £1751. Had patients been seen in a local provider unit, the corresponding figure would have been £2290	Resource use may no longer be appropriate as resource use from 1995 and therefore unlikely to reflect current clinical practice.
Fitzmaurice 2002 [169]	Study period 6 months; Primary care clinic or self-monitoring at home.	Equipment: £400 per machine; £2.30 per test strip Quality control: £2.30 per assessment for internal quality control; £30.00 per assessment for external quality control Training: £50.46 per patient per training session £425.23 ± 52.65/patient/year (interquartile range £388.23–459.53) for self-management; £89.71 ± 38.58/patient/year (interquartile range £53.04–123.76) for routine clinic care	Only includes patients using Coagucheck patients and therefore unreflective of current clinical practice
Jowett 2006 [164]	Cost year 2003. Study period 1 year. Patient self monitoring (PSM) or hospital- or primary care-based anticoagulation clinic (clinic-based care)	• Direct costs Staff time: PSM: practice nurse salary £23–29 per clinic hour; GP salary £98–116 per clinic hour • Equipment: PSM: machine £468.83; test strip £2.50; lancet £0.03; sharps bin £1.05; box of tissues £0.46; alcowipe £0.02; laminated dosing card £1.00 • Cost per visit: Clinic-based care: GP blood sample, hospital analysis and dosing £9.38 per visit; GP blood sample and dosing, hospital analysis £10.69 per visit • Telephone: PSM: practice nurse phone call £4.83 • Quality control: Internal quality control test £5 • Training: PSM: First training session £42.52 per person; second training session £28.67 per person • Overheads: PSM: £13.16 per hour • Mean costs/year for clinic-based care: £89.89 (95% CI: 83.15–97.32) anticoagulation costs, £32.43 (14.65–55.05) additional	Inappropriate for use in economic evaluation as: • Resource use data was collected as part of a RCT and considered a range of INR monitoring settings (hospital clinics, GP blood sample with hospital analysis and dosing, GP blood sample and dosing with hospital analysis, pharmacist-led practice clinic, practice near-patient testing clinic, MLSO-led practice clinic). The average costs per patient per year were based on sampling these settings, though it is unclear in what proportion. • Resource use from 2001-2002 and therefore less likely than other sources to reflect current clinical practice

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
		(non-anticoagulation) NHS costs, £57.48 (53.65–61.49) patient costs, £179.80 (160.09–202.58) overall societal costs. Mean costs/year for PSM: £381.53 (365.63–397.90) anticoagulation costs, £35.23 (17.35–58.88) additional (non-anticoagulation) NHS costs, £45.97 (42.98–49.31) patient costs, £462.73 (439.28–489.15) overall societal costs	
Lightowlers 1998 [170]	10 year study. Cost year 1997. Retrospective analysis (meta-analysis of 5 trials). Place of monitoring: an anticoagulation clinic.	Total cost of anticoagulation: (drug costs + monitoring) £610.06 per subject per year, amounting to a discounted 10-year cost of £4759.56 per subject Cost of one test: Assuming monitoring every 3 weeks (17 tests per year), the cost of one cycle of anticoagulation (3 weeks of drug costs and one monitoring test) would be £35.86 (cost of one warfarin tablet £0.0125). In the analysis, the unit cost of a visit to the anticoagulation clinic was £35.00	Inappropriate for use in economic evaluation as: • Resource year unclear and likely to predate 1997 and therefore not be reflective of current clinical practice.
McCahon 2007 [171]	1 year study period (1 July 2003 to 30 June 2004). Cost year 2003. Place of monitoring: Self-monitoring at home for PSM patients, hospital or practice-based anticoagulation clinic for controls	Direct costs • Staff time: Unit costs per visit: practice nurse £29 per clinic hour; GP £116 per clinic hour; community pharmacist £83; consultant £109; admin £10.93; GP consultation £15; practice nurse phone call (10 mins) £4.83; GP telephone call (10.8 mins) £21; community pharmacist phone call (10 mins) £13.83; receptionist phone call (10 mins) £1.82 • Equipment: For PSM, machine £468.83; test strip £2.50; lancets £0.03 each; sharps bin £1.05; box of tissues ££0.46 • Cost per visit: For routine care (controls) unit cost per visit £9.38 for GP blood sample, hospital analysis and dosing; £10.69 for GP blood sample and dosing, hospital analysis • Quality control: For PSM, internal quality control test £5 Total costs • Unit cost for routine care (controls) £6.75 for hospital clinic visit, £14.16 for practice-based point-of-care testing. Total	Inappropriate for use in economic evaluation as: • Provides costs for PSM which is not current clinical practice; • Patients were those enrolled in the SMART study and therefore not necessarily representative of current clinical practice. E.g inclusion criteria for the SMART trial included: Patients who had taken warfarin for at least months with a target INR of 2.5 or 3.58; GPs were able to exclude patients from the trial on clinical or social grounds (unclear what this means). However, this may indicate that difficult to manage patients and potentially more costly patients, may have been excluded from the cost analysis. Therefore these patients may not be representative of current clinical practice.

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
		costs to NHS over 12 months £193.01 (bootstrapped 95% CI: 175.44–210.71) per patient for PSM, £117.60 (95.22–139.97) per patient for controls (routine care). • Univariate analysis showed that changing the lifetime of the point-of-care device from 10 years to 3 or 5 years increased the total NHS cost of PSM over 12 months from £193.01 (175.44–210.71) to £303.98 (286.51–323.68) and £240.48 (224.15–260.52), respectively	
Parry 2000 [172]	Study period 1 year. Cost year 1996–7. Place of monitoring: Practice-based, nurse-led clinic or hospital clinic	• Staff time: Mean cost per patient per year for primary care and hospital care, respectively: £4.90 & £8.40 for an initial visit; £21.31 & £13.07 for a follow-up visit; £0 & 12.86 for staff administration; £7.48 & £0 for GP time • Equipment: Mean cost per patient per year for primary care and hospital care, respectively: £38.92 & £0 for software; £23.35 & £1.79 for coagulation machine; £24.59 & £0 for computer maintenance • Prothrombin test consumables: Mean cost per patient per year for primary care and hospital care, respectively: £3.88 & £5.84 • Postage: Mean cost per patient per year for primary care and hospital care, respectively: £0 & £1.36 • Quality control: Mean cost per patient per year for primary care and hospital care, respectively: £14.46 & £0.22 • Training: Mean cost per patient per year for primary care and hospital care, respectively: £5.31 & £0 • Overheads: Mean cost per patient per year for primary care and hospital care, respectively: ££22.28 & £6.66 for overheads; £56.27 & £120.31 for additional costs for home visit • Mean cost per patient per year £169.62 (SE: 10.17, 95% CI: 151–190) for primary care, £69.08 (SE: 5.95, 95% CI: 59–82) for hospital care • Mean cost per patient for primary care and hospital care, respectively: £25.41 (SE 3.13) & £13.89 (0) for first visit,	Inappropriate for use in economic evaluation as: • Resource use may no longer be appropriate as resource use from 1995 and therefore unlikely to reflect current clinical practice.

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
		£20.18 (3.13) & £6.62 (0) for follow-up visit; £22.36 (0.57) & £31.39 (0) for first home visit; £19.21 (0.57) & £24.12 (0) for follow-up home visit	
Parry 2001 [173]	Cost year 1998. Study duration not stated. Survey carried out in Spring 1999. Place of monitoring: primary or secondary care.	Direct costs • Staff costs: £34.65 per patient per year for primary care, £34.33 per patient per year for secondary care. Costs for domicilliary or ambulance £3.38 per patient per year for primary care, £18.87 per patient per year for secondary care • Equipment: costs for software, coagulation machine, maintenance and training £14.46 per patient per year for primary care, £1.80 per patient per year for secondary care. Test consumables £4 per patient per year for primary care, £5.84 per patient per year for secondary care • Overheads + postage: £22.92 and £8.02 per patient per year for primary and secondary care, respectively • Quality control: For primary and secondary care, £17.63 and £0.22 per patient per year, respectively • Mean patient travel costs £1.81 per visit for primary care, £4.67 for secondary care Indirect costs • Mean cost to patient of time for one clinic visit: £4.00 & £8.97 for primary and secondary care, respectively Total costs (for one test) • Mean NHS cost per visit £9.70 for primary care, £9.86 for secondary care. Mean patient cost per visit (travel costs + time costs) £6.78 for primary care, £14.58 for secondary care	Inappropriate for use in economic evaluation as: Resource use may no longer be appropriate as resource use from 1995 and therefore unlikely to reflect current clinical practice.
Taylor 1997 [174]	Two 6-month periods. Cost year 1995. Place of monitoring: hospital-based nursing care or hospital-based consultant care	• Mean cost per patient Group A (newly referred patients) - mean cost per patient over 3 months for nursing and consultant care, respectively: £19.70 (SEM 1.14) & £19.10 (0.84) for clinic visits, £4.40 (1.68) & £0 for home visits, £5.40 (1.04) & £3.30 (0.77) for	Inappropriate for use in economic evaluation as: Resource use may no longer be appropriate as resource use from 1995 and therefore unlikely to reflect current clinical practice.

Reference	Date of study and applicability to current UK clinical practice	Cost valuations used in study	Costs for use in economic analysis (including technology costs)
		related GP visits. • Prothrombin test costs: For group A, mean cost per patient over 3 months for nursing and consultant care, respectively: £0.80 (SEM 0.05) & £0.90 (0.04) for reagents and equipment. For group B, mean cost per patient over 6 months for nursing and consultant care, respectively: £1.03 (0.05) & £1.10 (0.05) for reagents and equipment • Transport: For group A, mean cost per patient over 3 months for nursing and consultant care, respectively: £3.20 (SEM 1.41) & £6.20 (1.76) for transport. For group B, mean cost per patient over 6 months for nursing and consultant care, respectively: £2.20 (1.20) & £4.80 (1.40) • Group A: £45.70 (SEM 2.99) for nursing service excluding hospitalisation costs, £53.10 (8.59) for nursing service including hospitalisation costs, £42.20 (2.27) for consultant service. Group B: total costs of anticoagulation service per patient over 6 months: £47.40 (SEM 2.40) for nursing service excluding hospitalisation costs, £53.40 (7.00) for nursing service including hospitalisation costs, £49.70 (2.80) for consultant service	
Thomson 2000 [175]	Study period 1 year. Place of monitoring not stated.	Annual cost of warfarin treatment £82.88 (not clear whether this is for the drug only or for the drug and monitoring)	Inappropriate for use in economic evaluation as: Year of cost, resource use year unclear; Appears to be based on local cost data derived from a hospital based, pharmacy led anticoagulation service.
NICE 2006 [20]	Cost year 2006/2007; resource use from Estimated average cost per patient in England and Wales	The annual per patient unit cost for anticoagulation services was estimated to be £382.9. This was based on a weighted average that assumed 25% of services were delivered in secondary care and 75% in primary care.	Appropriate for use in economic evaluation as correct patient population is used in the analysis, the analysis includes recent data and therefore is likely to reflect current clinical practice, and the correct cost perspective is applied.

To summarise the studies in **Table 101**, the following were inappropriate for use in the economic evaluation for reasons such as: lack of detail and clarity which meant that it was unclear how the values were derived (Abdelhafiz (2001) and Abdelhafiz (2003)[160, 176]); resource-use was from before 2000 and therefore not reflective of current clinical practice (Davies (2000)[166], Fitzmaurice (1996)[167], Fitzmaurice (1998)[168], Fitzmaurice (2002)[169], Lightowlers (1998)[170], Parry (2000)[172], Parry (2001)[173], Taylor (1997)[174], Thomson (2000)[175]); the methods/resource use used to estimate costs were too narrow to be applicable to the modeled patient population (Arya (2005)[161], Bhavnani (2002)[162], McCahon (2007)[171], Jowett (2006)[164]); costs were based on inappropriate secondary references (Connock (2007)[163]).

The most appropriate value was derived from the NICE costing report[20] for cost year 2006/07, the costing report that accompanies NICE Clinical Guideline number 36 (atrial fibrillation). This was based on a weighted average that assumed 25% of services were delivered in secondary care and 75% in primary care (this assumption is tested in the sensitivity analysis). The value for secondary care was based on an estimated 20 visits per patient per year (adherence data from 2004/2005 reference costs). It should be noted that this is more conservative than other data which estimated the number of visits per patient was 22 visits per year (Jones (2005)[24]). The values from primary care were based on the outlines from INRStar for setting up an anticoagulation clinic (INStar (2006)[177]). Estimated warfarin drug use from Blann (2003)[178], and whilst this estimate is from 1999, this would not be expected to differ between now and then, and in any case is a small component of the total costs.

The cost that will be use in the economic evaluation will be inflated to 2010 prices and is discussed further below.

Systematic review of stroke resource-use and costs, including follow-up

This systematic review was undertaken in two parts, with details of the search strategies in Appendix 13. The data that was sought in this review were:

- stroke type (ischaemic, haemorrhagic)
- severity (mild, moderate, severe, fatal)
- treatment phase (hyper-acute, acute, rehabilitation, long-term care)
- country of origin

This was a systematic review of stroke in all patients with filtering to AF-specific stroke later as appropriate, so as not to overlook any papers that may have relevant cost estimates as a subgroup.

Systematic review of stroke costs – Part 1

Quality Checklist

Quality was assessed using an eight-point checklist. An overall quality assessment was also given to each full paper (abstracts were excluded from the quality assessment); they were assessed as: excellent, good or poor, depending on how well they faired in relation to each criterion and in general with respect the paper as a whole. The criteria are described below.

- Appropriateness of the time horizon: papers may often imply they are estimating the long-term costs of stroke, but actually only consider the hospitalisation costs. This criterion provides a check regarding whether the description of the cost is truly representative of the time horizon described.
- Inclusion of relevant costs: an economic analysis should report the perspective employed (health service, third party payer, patient or societal) and given this, should include all costs relevant to that perspective. This criterion provides an assessment of this and also whether the costing is too narrow given the perspective employed.
- Disaggregation for direct costs: the cost of greatest interest to the decision maker is generally that borne by the health service (or third party payer who is the decision maker in an insurance funded system). This criterion is a check as to whether costs are disaggregated in the paper, or whether they can be disaggregated given the information presented. This is important when making comparisons across studies.
- Appropriate handling of costing issues: a good costing study will need to consider such issues as discounting (to adjust for time preferences), inflation (to adjust for unit costs that are not available in the correct price year) and currency conversions (for multinational studies). There is a generally accepted way of adjusting for each of these and this criterion considers whether a paper has appropriately handled these issues.
- Stochastic or deterministic costs: due to their statistical properties, costs should be estimated in a stochastic fashion; however, papers are often merely descriptive, which is only appropriate if they have undertaken sensitivity analysis.
- Source of resource data: the generalisability of the estimation of cost will be affected by whether the resource data (number of events, length of stay, outpatients visits) has been collected at a hospital level, or from within a registry. These different sources also raise issues regarding whether the cost pertains to incidence or prevalence. This criterion details and provides this information at a quick glance.

- Source of unit cost data: similarly how generalisable a cost estimate is depends on the source of the unit costs. If a primary costing study has been conducted this should be adequately reported.
- Generalisability and comparability with other studies: this is a general comment on whether the authors have considered any limitations in their study and whether they have made comparisons with other studies, essentially whether it was good reflective research.

Results from Part 1

After an initial appraisal 194 full papers and abstracts were considered for data extraction purposes. Of these, 112 papers provided cost estimates relevant to the brief. Data extraction produced 535 cost estimates for the economic burden of stroke. Of these, 56 were for the UK and 6 for England and 15 for Scotland. Cost data was available for the UK from 13 publications, for England from 3 publications, and for Scotland from 3 publications.

Table 102 Assessment of quality of studies identified in part 1

Country	Number of excellent studies	Number of good studies	Number of poor studies	Abstract only
UK	4	8	1	-
England	1	2	-	-
Scotland	-	2	1	-

Two papers were rated poor – these were Wolf (1995)[179] which had a cost year of 1991/92 and Isard (1992)[180] with a cost year of 1988. Both of these are likely to be unreflective of current clinical practice due to the time elapsed since the resouse use for these papers would have been estimated.

Dawson (2007)[181] and Henderson (2001)[182] were rated as good and are both Scottish studies. Dawson estimates costs by mRs and over a 90 day acute period. AF patient sub-groups are not specified though 18.7% had primary intracerebral haemorrhage. However, the objective of the Dawson study was to look at differences between mRs scores rather than estimate absolute costs, and the authors state that total costs will have been underestimated for those who required high dependency or intensive care. It is also possible that the cost of mild stroke was overestimated given that a single unit cost was used for all types of hospital stays. Therefore these costs were considered not suitable for the analysis. Henerson (2001) provides annual costs are are therefore not suitable for the analysis; also costs are 1996/97 therefore the underlying resources use is unlikely to reflect current clinical practice.

Eight studies were rated as good for the UK. However, many of these had resource use pre-dating 2000 and therefore unreflective of current clinical practice (Caro (1999)[183], Caro (2000)[184], Chambers (2002)[185], Beech (1999)[186], Clarke (2003)[187], and Patel (2004a)[188]). Hansson (2002)[189] has a cost year of 2000 for acute cost of stroke but did not differentiate

between different types of strokes or AF patients. Patel (2004b)[190] estimated costs for 2001/02 from a societal perspective over a one year period.

The two papers rated as good for England were McNamee (1998)[191] and Grieve (2000)[192]. Costs from 1995/96 and 1995 and for six month and one-year follow-up costs respectively, with McNamee (1998) having costs based on the Barthel index. However, due to the time elapsed since the studies, the underlying resources use, and costs, are unlikely to reflect current clinical practice.

Five papers were rated as excellent. However, Epstein (2008)[193] estimated costs for females only and is therefore not suitable. Grieve (2001a)[194] and Grieve (2001b)[195] have cost years of 1998 and 1995 respectively and therefore are unlikely to be suitable. This leaves Youman (2003)[196] using cost year of 2001/2002 and Luengo-Fernandez (2006)[197] with cost year of 2004/05.

Costs for stoke calculated by Youman (2003) [196] were stratified by severity according to the Barthel Index. The study included 434 patients with a mean age of 76 and costs were for 2001/2002. The costs were for mild, moderate, severe and fatal stroke. These costs were acute costs calculated for the first three months post-event. However, these costs were inappropriate for use in the economic evaluation for a number of reasons. Patients with mild and very severe stroke were excluded from the analysis and therefore not costed, and the severity classification was not by mRs.

Patients did not necessarily have AF and costs were not stratified by type of stroke. The stated reason for this was that previous studies had showed no significant difference in functional dependence at 1 year between patients surviving a cerebral infarction and those surviving primary intracranial haemorrhage or subarachnoid haemorrhage. However, long-term follow-up costs are available on three monthly intervals by severity which may be used in the model.

The final study by Luengo-Fernandez (2006) [197] was of a particularly high quality and has produced a wealth of data. Luengo-Fernandez (2006) used the Oxford Vascular Study and national sources of unit costs to estimate the acute cost of various subtypes of stroke and for various levels of disability/severity (pre, Rankin score and post, NIHSS score). Notably they also consider a range of baseline characteristics in their cost analysis, including patient history of atrial fibrillation.

Importantly, Luengo-Fernandez (2006) showed that patients with AF had a significantly higher cost of stroke than patients without AF (£9,667 for patients with a history of AF vs

£5,824 for patients without a history of AF (P<0.001)). This study attempted to look at predictors of resource use and acute care costs of stroke using data obtained from the Oxford Vascular study (a population-based cohort of all individuals in nine general practices in Oxfordshire). There were significant differences in rates of hospital admission according to both stroke severity and presence of atrial fibrillation. Patients with a history of atrial fibrillation tended to have higher hospital admission rates than those without (P=0.085). This finding is consistant with the hypothesis that concurrent AF is associated with greater disability, longer in-hospital patient stay, and lower rate of discharge to home[4]. In spite of the wealth of data available provided by Luengo-Fernandez (2006) it is not possible to estimate the costs for use in the evaluation. Whilst costs are provided for different types of stokes, for AF vs non-AF patients, and by severity, costs are not provided for AF patients by stroke type and severity.

Results from Part 2

The second systematic review was undertaken to cover the period 2008 to date. Details of the methods for this systematic review are in Appendix 13. Thirty-three studies were identified that met the inclusion criteria. Of these, the majority (Guilhaume (2010)[198], Bayer (2010)[199], Shaw (2010)[200], Quinn (2009)[201], Jones (2009)[202], Dudley (2009)[203], Latimer (2009)[204], Taylor (2009)[205], Saka (2009)[206], van der Gaag (2008)[207], Sudlow (2009)[208], Kmietowicz (2009)[209], Higgins (2008)[210], Swain (2008)[211], Rudd (2008)[212], Epstein (2008)[193], Schwander (2009)[213], Jenkins (2008)[214]) did not report cost per patient and therefore were unsuitable for the economic evaluation.

Jackson (2009)[215] only reported acute medication and diagnostic costs whereas Luengo-Fernandez (2009)[216] only reported costs for urgent treatment for TIA and minor stroke. Flynn (2008)[217] used secondary sources from Youman (2003)[196]. Therefore each of these was unsuitable.

Acute event stroke costs were availble from a number of sources (Gomes (2010)[218], Wilson (2010)[219], Tavakoli (2009)[147], Luengo-Fernandez (2009)[216], Christensen (2008)[220], Potter (2009)[221]). However, none of these were for AF patients only and none had cost by severity, and only Chritensen (2008) had cost by type of stroke (ICH and HS). Therefore, given that the clinical outcomes in the model requires costs to be stratefied by severity and type, and also the stroke in AF patients is more severe and more costly, none of these are suitable.

The study by Christensen (2008)[220] examined the hospital-based costs for patients with IS and ICH over a 12 month period. This study was based on data collected from 1,016 ICH

patients (mean age = 67.6 years, 49.6% male) and 4,295 IS patients (mean age 70.4, 48.2% male) in Scotland from April 2004 until March 2005. Costs were for 2006 which, when inflated to current prices, were estimated as £13,487 for ICH and £12,672 for IS for the initial hospital stay. The cost of the initial hospital stay for patients that survived for 12 months was estimated to be £20,189 for ICH and £12,636 for IS. Whilst this study is appropriate in terms of setting, with events stratified by stroke type, AF status of patients is unknown and events were not stratified by severity. Therefore this analysis was not appropriate for use in the economic evaluation.

Long-term follow-up costs were available from a number of sources (Lindgren (2009)[222], Saka (2009)[206], French (2008)[223], Elia (2008)[224], Harrington (2010)[225], Forster (2009)[226]). However, acute and long-term costs were aggregated and therefore unsuitable. French (2008) focused on costs likely to be influenced by the intervention and therefore was not total costs. Elia (2008) calculated costs at either a nuring home of at patients home and therefore not representative of patient groups with different levels of severity which are likely to be a mix of the two. Harrington (2010) provided costs for follow-up over six-months but these were only for patients aged at least 50 years at the time of stroke, had returned to living in the community for at least three months, and felt able to participate in group activities. Stroke survivors living in nursing homes were excluded. Forster (2009) estimated costs for patients if they had a new stroke associated with persisting disability (Barthel index score lower than the pre-stroke score) and/or language impairment (failing the Frenchay aphasia screening test) at 4 months post-stroke. Patients whose main clinical problem was vascular dementia, and those considered to have a poor 6 months survival prognosis because of co-morbidity, were excluded. Therefore these patients are unlikely to represent more disabled patients.

Given the paucity of appropriate data, a new study was sponsored by Boehringer Ingelheim to assess the cost of stroke for patients with AF. The study was managed and conducted by the University of Oxford using the Oxford Vascular Study population, independent of the company.

Deatils of the OXVASC study

Patient characteristics for those included in the study are shown in **Table 103**.

Resource-use per event was not provided but was composed of:

- Primary care visits (nurse and GP both at home and at surgery)
- Outpatient care visits
- Inpatient stays (including community hospitals)

- A&E visits
- Emergency services

Precise resource use per event was not available given the low numbers of occurrence of some of the events, and the possibility that patients could be identified from their resource use. Therefore only aggregated costs per event were available. All data supplied with respect to this study is attached in Appendix 13.

Table 103 Patient characteristics for the OXVASC study

Patient characteristics	
Sample size (patients / events)	
Age (mean / SD)	
Gender (males / females)	
History of stroke (yes / no)	
Patient follow-up	
Follow-up in days (mean / SD)	
Reasons for end of follow-up:	
Censored (i.e. patients who did not reach 5-year follow-up and follow-up was stopped on 24/01/10)	
Death	
Reached 5-year follow-up	
Suffered a subsequent stroke/MI	
Number of patients	
number of patients with 1 event	
number of patients with 2 events	
number of patients with 3 events	
number of patients with 4 events	
Total number of events	
Ischaemic stroke	
Haemorrhagic stroke	
Intracranial haemorrhage	
Unknown stroke	
TIA	

Abbreviations: SD, standard deviation; TIA, transient ischaemic attack.

The average cost per ischaemic stroke event is shown in **Table 104**.

Table 104 Cost of ischaemic stroke by severity from OXVASC

Event	**N**	**Mean (2009)**	**Standard Error**	**2010 Mean**	**2010 Standard Error**
Fatal					
Independent					
Moderate Disability					
Totally Dependent					

Compared to the Youman[196] study costs for fatal and independent events are relatively low with moderate disability and totally dependent relatively high. This is not unexpected as mild and very severe strokes were excluded from the Youman analysis. It is unclear why the cost of fatal events in the Youman study is so much higher, though may be related to the

exclusion criteria, in effect excluding patients more likely to die sooner post-event thereby extending length of stay and potentially increasing costs. The costs associated with moderate disability in the Youman paper are inconsistent in that they are improbably lower than the costs for both independent and fatal stroke, which may be due to the poor association between resource use and the Barthel Index[227-229].

The costs from the Christensen (2008)[220] study cannot be compared directly. However, taking a weighted average of the OXVASC data, we find that the average acute costs for all ischaemic strokes is [redacted] and for all strokes excluding fatal strokes is [redacted], which are similar to the costs shown above. This would indicate that, given that AF stokes have been found to costs more, the values in **Table 104** may be conservative.

As for ischaemic stroke, costs for ICH/HS were also required by disease severity as defined by mRs. The literature search failed to identify any suitable values for these costs. As part of the study commissioned by OXVASC, costs for ICH and HS were derived by severity. The results are shown in **Table 105**.

Table 105 Acute care costs for events HS and ICH (cost year = 2009)

Event	N	Mean	SD	SE
Haemorrhagic stroke				
Independent	[redacted]	[redacted]	[redacted]	[redacted]
Moderate disability	[redacted]	[redacted]	[redacted]	[redacted]
Totally dependent	[redacted]	[redacted]		
Fatal	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage				
Independent	[redacted]	[redacted]		
Moderate disability	[redacted]			
Totally dependent	[redacted]			
Fatal	[redacted]	[redacted]		

Abbreviations: SD, standard deviation; SE, standard error

Unfortunately the sample sizes for the costs in **Table 105** are too low to be considered to be reliable estimators of cost by disease severity. The study described above by Christensen (2008)[220] considered acute hospital-based costs for patients with IS and ICH. The study indicated that the acute costs associated with the initial admission for ICH was higher than for IS. In particular, the cost for patients that survived longer was considerably higher. One of the key reasons for this was the greater resource use of high-cost items (e.g. 13% of ICH patients were admitted to neurosurgery departments with an average length-of-stay (LOS) of 16.8 days, whereas 1% of IS were admitted with average LOS of 12.3 days). Comparing the data available for HS/ICH in **Table 105** with the data from IS in **Table 104** would appear to support this. Data from Luengo-Fernandez (2006)[197] also suggested that PICH (primary

intracerebral haemorrhages) and SAH (subarachnoid haemorrhages) are less expensive than partial and total anterior circulation ischaemic stroke but more expensive than lacunar infarct and posterior circulation infarct, though the cost of no stroke type was significantly different from any other type. Whilst the cost of stroke in patients with a history of AF (£9,667, 95%CI £7,145-£13,365)) was more than for PICH (£7041, 95%CI £3,100–£12,736) and SAH (£7,233, 95%CI £4,135–£10,741), it is unclear whether what proportion of PICH and SAH patients had AF. Therefore, given the paucity of data for these costs it will be assumed that the costs for ICH/HS are the same as for IS.

Long-term follow-up costs due to post-stroke/ICH disability

No relevant studies were identified providing costs by disease severity that could be used in the economic evaluation. Therefore, data was used from the OXVASC study described above. In addition to the resources included by OXVASC for the cost of IS (see above), additional resources that were included were:

- Primary care visits (nurse and GP both at home and at surgery)
- Outpatient care visits
- Inpatient stays (including community hospitals)
- A&E visits
- Emergency services
- Nursing care home
- Residential care home
- Sheltered accommodation.

The costs with sample sizes are presented in **Table 106**. The patients are stratified by mRs and have been diagnosed with AF. They were therefore considered ideal and used in the economic evaluation.

Table 106 Stroke 3-month follow-up costs by disability from OXVASC

Event	N	Mean (2009)	Standard Error	2010 Mean	2010 Standard Error
Independent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Systematic review of the cost of major bleeding

Whilst cost data for bleeding events was available from PbR tarfiff, they were not ideal. Therefore a systematic review was undertaken to estimate the costs for:

- ICH by severity
- Non-fatal GI bleeds
- Non-fatal non-GI bleeds
- Fatal bleeds

The systematic review is described in Appendix 13. For the UK, 13 studies were identified. These are discussed below.

Som (2010)[230] estimates the costs of GI bleeds in patients taking warfarin. Thirty patients were included in the study (16 female) with an average age of 80 yrs. 80% were indicated for AF, with the rest for recurrent thrombo-embolic events or metallic valve replacements. Average INR on admission was 5.5, with half exceeding the target upper limit on admission. Thirteen patients required blood transfusion, and 14 required the use of a reversal agent. No patient required surgical intervention or angiography during their acute admission to stop their bleeding. Length of stay ranged from 1-21 days (average 7 days), with all patients initially admitted to the Surgical Assessment Unit at a cost of £325 per day. The cost of a stay in a general ward was £190 per day. The unit cost for 1 unit of blood at the Trust was £139, and the mean number of units of blood used per patient was 3.4. This would result in a cost per hospital stay of £1,465 and cost of blood of £472.60. However, these differ from the values in publication of £1,444 and £430. It is unclear why. Also, these costs do not appear to include other resources used such as diagnostic testing and reversal agent.

Karnon (2006)[231] was a cost-utility analysis of clopidogrel in patients with non-ST-segment-elevation acute coronary syndromes in the UK. Clinical data for the analysis was derived from the CURE trial[232]. Major bleeding was not defined by Karnon (2006), though the definition for bleeding complications from the CURE trial was life-threatening, major (requiring the transfusion of 2 or more units of blood), or minor. It is unclear whether the cost from Karnon (2006) is for life-threatening bleeds, major bleeds, or both. The estimate for this cost was £2,377 (95% CI £1,946-£3,336) per major bleeding event. Costs were for 2002 and based on expert opinion, which suggested average bleed would require two blood count tests, a gastroscopy and a transfusion of two units of blood, leading to a mean cost of £424. This resource use may have been derived from a NICE Technology Appraisal (Palmer 2002)[233], though this is unclear. The resource-use indicates that this might be for GI bleeds only. It is also unclear why this differs from the first cost presented, though the lower costs may not include hospitalisation costs.

A study was undertaken to evaluate the cost-effectiveness of fondaparinux relative to enoxaparin as prophylaxis against venous thromboembolism for patients undergoing total hip replacement, total knee replacement or hip fracture surgery in the UK by Gordois (2003)[234]. Major bleed was defined as bleeding leading to: death; re-operation; critical organ; a bleeding index of 2 or more. The bleeding index was defined as: [number of units of packed red blood cells or whole blood transfused] plus [(prebleeding) minus (postbleeding) haemoglobin values, in grams per decilitre]. It is unclear how exactly the costs for major bleeding were derived, but resource use was based on a survey of six hospitals and the literature, and verified by expert opinion. Unit costs were obtained from national published sources and a survey of 16 hospital trusts. Two costs for major bleeds are provided for 2000/2001. The cost of treating prophylaxis-related major bleeding was calculated from the average cost of each category of major bleeding recorded in the fondaparinux trials, weighted by proportion of patients experiencing each type of bleed (£245-269 per episode), and treatment related major bleed (£730 per episode).

Given these uncertainties, none of these three will be considered for use in the economic evaluation.

The study by Miller (2009)[235] was also identified in the search. However, these provided costs for conditions that were risk factors for ICH, not ICH itself. These were AVM (arteriovenous malformation) and CM (cavernous malformation). A subgroup analysis estimated the difference in median costs between patients presenting with haemorrhagic and non-haemorrhagic AVM and CM. Therefore these costs are inappropriate for the evaluation.

Costs from Offord (2004)[236] report a value for major bleed of £434.30. However, this is a Spanish cost from Nuijten (2003)[237] converted into sterling using the exchange rate of £1=€1.54. The cost of a major bleed of £483.26 for 2001/2002 from Gozzard (2004) is an inflated cost from Lloyd (2001)[238] which in turn was an inflated cost from another study published in 1995, which predates the search criteria. The estimated cost from Bakhai (2003)[239] had a cost year of 1999 and also it was estimated by the authors at £1,500 in order to illustrate in a sensitivity analysis that cost associated with bleeding have little impact on the cost-effectiveness evaluation being undertaken. Abdelhafiz (2003)[176] estimates the costs of warfarin treatment for patients with NVAF. However, the study does not provide cost per event (on total average cost per patient with bleeding event per month). Resourse year was also not provided therefore may predate study exclusion, and a societal perspective is used

(e.g. days of work is included). Therefore these studies are not used as the costs are not sufficiently robust to be used.

The study by Connock (2007)[163] looked at the clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy. As part of this study, an economic evaluation was undertaken where bleeding costs for 2005 were derived. These were based on NHS Reference costs, and as more recent reference costs are available, these will not be considered in the evaluation.

Wolowacz (2009)[240] examined the cost-effectiveness of oral DBG in comparison with subcutaneous low-molecular-weight heparin for the prevention of venous thromboembolism (VTE) after total knee replacement (TKR) and total hip replacement (THR) surgery. Costs were from 2008 and major bleeding was categorised as ICH, GI, Surgical Site or Other, and are shown in **Table 107**.

Table 107 Costs from Wolowacz (2009)[240]

Event	Cost	Source
Intracranial	£7,268	The cost of acute care for ICH was based on a retrospective study involving 38 patients with a major bleeding event associated with warfarin treatment in the UK[33]
Surgical site	£2,355	UK NHS reference costs for inpatients admissions and multiple studies
Gastrointestinal	£2,355	UK NHS reference costs for inpatients admissions and multiple studies
Other	£1,027	UK NHS reference costs for inpatients admissions and multiple studies

The next two studies, McGuire (2007)[241] and Christensen (2008)[220], use data from the Scottish Medical Linkage system held by the Information and Statistics Division of the NHS in Scotland. They both focused on the cost of ICH, and provided costs for 2005 and 2006 respectively. However, the resource-use data from McGuire (2007) is from 1995 to 2005 and therefore include resource-use that predates the inclusion dates for the systematic review; therefore this data is not used. Christernsen (2008) calculated both acute and long-term (12 months) resource-use and costs for ICH patients. This data was from patients between April 2004 and March 2005. Details of the patients, resource-use and estimated costs are shown in **Table 108**.

Table 108 Data on cost of ICH and IS from Christensen (2008)[220]

	ICH	IS
No. of patients	1,016	4,295
Average age	67.6 yrs	70.4 yrs
% Male	49.6%	48.2%
Proportion that died in hospital	45.2%	15.6%
Discharged alive but died with 12 months of stroke onset	7.3%	11.7%
Proportion of death within 12 months of onset	52.5%	27.2%
Adjusted (for age and sex) hazard ratio for death over 12 months	1.00	0.36
Median survival time for first ever event	6.4 months	Not established*
Admitted toward for:		
General medicine (LOS)	80.5% (12.2)	85.1% (12.8)
Geriatric (LOS)	37.7% (45.8)	49.9% (41.1)
Nuerosurgery departments (LOS)	13% (16.8)	1.0% (12.3)
Rehabilitation units (LOS)	<8% (84.3)	<9% (60.3)
ICU	0	0
Average overall length of initial stay	38.4	39.3
Proportion surviving initial stay re-admitted within 12 months for any reason (LOS)	43.6% (10.6)	44.8% (13.2)
Average LOS for ICH having ICH or IS	18.8	17.5
Average LOS for IS having ICH or IS	21.6	31.4
Average cost of initial hospitalisation (SD)	£12,042 (£19,688)	£10,924 (£15,202)
Average cost of hospital readmission (SD)	£1,918 (£7,248)	£3,127 (£8,101)
Average total hospital cost over 12 months (SD)	£13,960 (£21,487)	£14,051 (£17,850)
Average cost of hospital readmission per initial survivor (SD)	£3,495 (£9,507)	£3,702 (£8,693)
Average hospital cost per readmission (SD)	£4,022 (£8,442)	£4,487 (£7,669)
Average initial hospital cost for patients surviving first 12 months	£18,026 (£24,218)	£10,893 (£15,767)
Average total cost for patients surviving first 12 months	£21,493 (£26,222)	£14,263 (£18,736)

Abbreviations: ICH, intracranial haemorrhage; IS, ischaemic stroke

*82.8% were still alive at end of study

Additional information was derived from the OXVASC study on the costs for patients with AF that experienced bleeds. This consisted of data from [redacted] patients, with mean (SD) age of [redacted] of whom [redacted] were male and [redacted] female. Of these patients, [redacted] had minor bleeds, [redacted] major non-GI, [redacted] major GI and [redacted] fatal. The acute costs up to 90 days after bleed event are shown in **Table 109**.

Table 109 Acute costs up to 90 days after bleed event (cost year = 2009)

Event	No.	Mean costs	SD	SE
Minor bleed	[redacted]	[redacted]	[redacted]	[redacted]
Major: non-GI	[redacted]	[redacted]	[redacted]	[redacted]
Major: GI	[redacted]	[redacted]	[redacted]	[redacted]
Fatal	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation; SE, standard error.
Included in these costs are: Inpatient stays (including community hospitals).
Source: OXVASC report, Appendix 13

Additionally, the cost of major bleeds was estimated from the NICE costing report (2006/07 cost year) to be £1,573[20]. Costs for bleeds are summarisd in **Table 110**. The costs from the NICE costing report, PbR and Wolowacz (2009)[240] were similar, reflecting their derivation for

similar data. However, the costs from the OXVASC data are considerably higher, possibly due to the patients having AF and being anticoagulated. However, the sample sizes are small and will therefore not be used. As the costs derived from the PbR are stratified by type of bleed and are the most recent, these will be used in the model.

Table 110 Cost of major bleeds

	ECH			Year
	GI	Non-GI	Fatal	
PbR	£1,594	£2,109		2010/2011
Wolowacz (2009)	£2,355	£1,027		2008
OXVASC	[redacted]	[redacted]	[redacted]	2009
NICE	£1,573			2006/2007

Abbreviations: ECH, extracranial haemorrhage; GI, gastrointestinal

Estimates for fatal bleeds were not found, and were taken as the average of GI and Non-GI bleeds, as £1,852 per event.

ICH has been discussed above, and it is noted that the costs found in this review were similar to the costs derived by Luengo-Fernandez (2006 (see above). Therefore it does not change the rationale for selecting the costs for ICH shown above.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical expert opinion was not sought regarding the choice of cost data.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Costs for the interventions are provided in **Table 111**.

Table 111 Intervention costs

Generic name	Brand name	Daily dose	Unit cost	Cost per day
Aspirin		162.5mg	30 x 162.5mg =£2.70[a]	£0.09
Aspirin + Clopidogrel		162.5mg + 75mg	30 x 162.5mg =£2.70[a] 30 x 75mg =£5.13[a]	£0.26
Dabigatran 150 bid	Pradaxa	2 x 150mg	60 x 150mg = £75.60	£2.52
Dabigatran 110 bid	Pradaxa	2 x 110mg	60 x 110mg = £75.60	£2.52
Warfarin[c]		4.5mg[b]	28 x 0.5 mg =£0.43[a] 28 x 1 mg = £0.31[a] 28 x 3 mg = £0.35[a]	£0.04

Sources: [21], [20]

As stated above, the cost for INR monitoring plus warfarin drug costs from the NICE costing report was £382.9. Inflating to 2009/2010 costs this is £429.50. Subtracting the annual cost of warfarin (£14.60) derived in **Table 111** results in a net annual cost of INR monitoring of £414.90.

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

The health state costs based on the level of disability following IS, HS or ICH are provided in **Table 112**. The rationale for these values has already been provided in Section 6.5.3. The costs presented are the background costs per cycle, other things being equal. These costs will increase at varying levels if the patient is on treatment, and do not include the costs for any acute events that may occur during any given cycle.

Table 112 Background cost per health state

Health state	Cost per patient cycle	Reference
No previous stroke/ICH, independent	£0	Assumption
Previous stroke/ICH, independent	[redacted]	**Table 106**
Previous stroke/ICH, moderate disability	[redacted]	
Previous stroke/ICH, dependent	[redacted]	

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Treatment for dyspepsia for patients on DBG was also included in the evaluation. For the 150mg dose, incidence of dyspepsia was found to be 11.8% and for the 110mg dose was 11.3%. Incidence in the WFN arm was found to be 5.8%[43]. The first line treatment for dyspepsia recommended by NICE is an antacid[242]. The cost of treating dyspepsia was estimated to be £1.12 per patient per quarter, based on the estimated recommended dose of 15ml four times daily from a 500ml bottle of Acidex at £1.70 per bottle and a maximum incremental incidence rate of 6%. An additional management cost of a GP visist was added. A GP vist (2008/09) cost was £35.00, when inflated to 2009/10 was £36.51. For the incidence of 6%, this is £2.19 per patient. This resulted in a total cost per patient of £3.31 per quarter, and is applied to the first cycle. This cost is applied for the duration of treatment as a sensitivity analysis, though is extremely conservative and patients are unlikely to visist their GP for treatment of dyspepsia for the duration of therapy.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Systemic embolism

A literature search, an internet search and a search of the UK Department of Health website failed to produce a unit cost for systemic embolism. Therefore a decision was taken to review the definition of systemic embolism in the RE-LY trial, and base cost on this definition.

Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy. Therefore the cost for a systemic embolism was based on the cost of tests. This was viewed as very conservative since systemic embolism can result in severe complications leading to amputation or loss of organs (embolism to the renal artery or gut artery typically result in irreversible damage and the need to surgically partially or fully remove the affected organ). Diagnosis is typically difficult as symptoms are unspecific and can be delayed. The resources used in the economic model do not include the long-term resources used following complications due to systemic embolism.

The cost of the imaging was assumed to be the weighted average of the 2008-2009 NHS Reference cost codes for Computerised Tomography Scan (RA08Z, RA09Z, RA10Z, RA11Z, RA12Z, RA13Z, RA14Z, RA50Z) weighted by activity level. This resulted on an average cost of £117.22. Inflating to 2009/10 results in a value of £122.28. The cost for surgery was estimated from the PbR 2010-11 tariff for Lower Limb Arterial Surgery without CC (QZ02B) and Extracranial or Upper Limb Arterial Surgery (QZ04Z), and taking the average of the Combined Daycase/Elective tariffs and Non-elective spell tariffs to produce a value of £4,623. No resource-use or cost data was found relating to the cost of an autopsy and this was assumed to be £400. Therefore the cost of a non-fatal SE was assumed to be the average of £122.28 and £4,623 (£2,372 per event) and the cost of fatal SE as £400.

It is recognised that these estimates are not robust, however given the relatively low rate of this event (compared to stroke) and the low difference in event rates for systemic embolism between the treatment arms it is not expected to have a major bearing on the results. It will be explored in sensitivity analysis.

Minor bleeds

Minor bleeding was defined as clinically revelevant but not a major bleed. Therefore costs available which involved hospital admissions were not considered appropriate (e.g. OXVASC study, Appendix 13). In the 2006 NICE costing report[20], minor bleeds were assumed to be treated in Accident and Emergency departments, and based on a weighted average of high-cost attendance, standard attendance and minor A&E/minor injury unit attendance. Therefore a similar approach was taken, using different codes, as the currency codes in the refernce costs have since been updated. The code VB09Z (Category 1 investigation with category 1-2 treatment) for A&E services not leading to an admission was £84. Inflating this to 2009/2010 costs results in a cost of £88 which will be applied to the economic model.

Other costs

No additional costs were assumed to accrue for discontinuation with an event, treatment switch, or death from unrelated cause. Discontinuation without an event was assumed to accrue one GP visit, valued at £36.51 as discussed previously.

Cost inflators

Inflation indices used to inflate non-2010 costs were based on Curtis (2009)[243] and are provided in **Table 113**.

Table 113 Inflation indices[243]

Year	Pay & Prices index (1987/8=100)	Inflation factor (relative to 2009/10)
1999/00	188.6	1.4857
2000/01	196.5	1.4260
2001/02	206.5	1.3569
2002/03	213.7	1.3112
2003/04	224.8	1.2464
2004/05	232.3	1.2062
2005/06	240.9	1.1631
2006/07	249.8	1.1217
2007/08	257.0	1.0903
2008/09	268.6	1.0432
2009/10 [a]	280.2	1.0000

a – based on the assumption that the 2009/10 rate is the same as the 2008/09 rate

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The structure of the model was based on a study by Sorensen (2009)[111]. That study compared 'trial-like' WFN to 'real world' WFN, as it is known that setting is related to the quality of INR control (and therefore outcomes). Given that this analysis is based on the RE-LY trial, alternatives are investigated. These are:

- **"Real-world adjusted-dose WFN"** approximates the proportion of time spent within and outside of INR target range in routine clinical practice. This scenario is based on a retrospective study by Kalra (2000) of patients with AF, treated with warfarin (N=167) and managed in the UK primary care setting[244]. This study estimated that the INRs were within target range 61% of the time, below target range 26% and

above target range 13%. Two approaches were taken in this scenario: to use data from Walker (2008)[245] and weight the WFN arm by INR range (Weighted Warfarin Approach); to use data from Jones (2005)[24] to adjust time out of INR range (Time out of INR Approach).

- **"Real-world prescribing behaviour"** (real-world use of adjusted-dose WFN or aspirin or no treatment for warfarin eligible patients) is a weighted average of real-world WFN, aspirin and no treatment. The data on percentage of WFN eligible patients that are treated with WFN, aspirin, or received no treatment was based on data from study by Dewilde (2006) in the UK setting[36]. Of moderate to high risk patients, 49% received WFN, 35% received aspirin, and 16% received neither.

The cost of INR testing is based on and individual costs per patient per year. However, if DBG is used widely, then the reduction of INR monitoring may lead to greater decommissioning of INR monitoring services. This would lead to to economies of scale, and increased savings per patient. Therefore, as part of the sensitivity analysis, the cost of INR monitoring is increased by 25%. Also, to reflect patients that are well-controlled and do not need to be tested as frequently, the cost of INR testing is reduced by 25%.

Clinical data is extrapolated beyond the duration of the clinical trial to the end of patients' life. In order to investigate cost-effectiveness over shorter periods, the time horizon for the model is varied. Also the clinical data was assumed to remain as effective over the patients' life – this assumption can be crudely tested using the sequence model which provides an indication of the variation in cost-effectiveness that might exist given potential changes in the relative risk of DBG vs WFN beyond the duration of the clinical trial. Efficacy data from the MTC is also available for the DBG vs WFN comparison. This alternative set of efficacy data is also used in the sensitivity analysis.

The structual sensitivity analyses are summarised in **Table 114**. Due to the prohibitive amount of time required to derive probabilistic results, these sentivity analysis are based on the deterministic model. In addition, analyses 1-5 are only applied to the DBG vs WFN comparisons whereas 6-15 are applied to all comparators.

Table 114 Structual sensitivity analysis

No.	Base-case	Vatried to
1	Triallike warfarin	Real-world adjusted-dose warfarin (Weighted Warfarin Approach)
2		Real-world adjusted-dose warfarin (Time out of INR Approach)
3		Real -world prescribing behaviour
4	INR cost	+25%
5	INR cost	-25%
6	Time horizon – life-time	2 years
7	Time horizon – life-time	10 years
8	Time horizon – life-time	15 years
9	Vary effectiveness	Set age to 78, allow full effectiveness of 150 dose, vary effectiveness of 110 dose (RR to WFN) by +/-10%
10		
11	RE-LY clinical data	MTC (SAS) clinical data
12, 13	Vary discount rate for costs	0%, 6%
14, 15	Vary discount rate for health outcomes	0%, 6%

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

An extensive list of model inputs was explored in univariate sensitivity analysis. The analyses performed on baseline characteristics are shown in **Table 115**. Justification for each is provided in the table.

Table 115 Univaraite sensitivity analyses for the baseline characteristics

No.	Description of sensitivity analysis	Original value*	New value	Justification
16,17	Age	Varies	+/-5 years	Indicate variation in cost-effectiveness with age at baseline
18,19	% male	Varies	0%, 100%	Indicate variation in cost-effectiveness with sex
20,21,22, 23, 24	$CHADS_2$ at baseline	Varies	100% for 1, 2, 3, 4 and 5	Potential service implication for treating patients with different $CHAD_2$ scores and stroke history at baseline
25,26	Stroke history at base line	Varies	0% for $CHADS_2$ 2,3,4), 100% ($CHADS_2$ 2,3,4)	

*Varies - varies across models

Univariate sensitivity analyses performed on cost and utility variables are presented in **Table 116**. The sensitivity analyses for utilities (no. 27-29) represent alternative plausible scenarios.

Table 116 Univaraite sensitivity analyses for the costs and utilities

No.	Description of sensitivity analysis	Original value*	New value	Justification
27	Utilities - Change Set 1	**Table 97**	**Table 97**	Only one of the base case utility parameters was derived from the same data as the clinical trial results. Therefore alternative data sets and assumptions were considered in the sensitivity analysis.
28	Utilities - Change Set 2	**Table 97**	**Table 97**	
29	Utilities - Change Set 3	**Table 97**	**Table 97**	
30	Costs - ICH. HS. IS	Various	+50%	Cost of stroke and ICH represent some of the largest costs in the model. Proxy values were also used ICH/HS. These values were varied to assess their impact on the results
31		Various	-50%	
32	SE (non-fatal/fatal)	£2,373/£400	+100%	There was considerable uncertainty over the estimate for this cost. This value was varied to assess its impact on the results.
33		£2,373/£400	-100%	
34	Minor Bleed	£84	-100%	This had a relatively small cost but was a relatively frequent event. Given the uncertainty over its estimation, this was reduced to £0 to assess its impact on the results.
35	AMI	£2,956	+100%	This was derived from the PbR tariffs, and therefore likely to be robust. However, it was varied to assess its impact on the results.
36		£2,956	-100%	
37	MB	Various	+100%	There was uncertainty over the costs for non-fatal GI, non-fatal non-GI, and fatal bleed therefore these were varied to assess their impact on the results.
38		Various	-100%	
39	Dyspepsia	3-months	Treatment duration	Explore alternative managements costs for dyspepsia
40	Follow-up	Various	+50%	Follow-up costs were varied as they are likely to be a major cost-driver in the evaluation
41		Various	-50%	
[redacted]				

Abbreviations: AMI, acute myocardial infarction; HS, haemorrhagic stroke; ICH, intracranial bleed; IS, ischaemic stroke; MB, major bleed; SE, systemic embolism; TIA, transient ischaemic attack.
*Various – various values used within model

Clinical parameters varied in univariate sensitivity analysis are shown in **Table 117.** These are divided into two parts. Analyses 45-58 are based on the confidence intervals of the key clinical parameters and are are used to identify key drivers in the model. Analyses 59-68 are clinical parameters which are not varied in the PSA. Note that the only clinical parameters not varied here or in the PSA are data from standard life tables.

Table 117 Univaraite sensitivity analyses for clinical parameters

No.	Description of sensitivity analysis	Original value*	New value	Justification
45	Risk of IS relative to warfarin	Varies	Lower CI	The relative risks of patients on DBG compared the trial-like warfarin for the major efficacy and safety data was varied between the upper and lower 95% confidence intervals. This was taken to investigate the key clinical drivers in the economic evaluation.
46		Varies	Upper CI	
47	Risk of SE relative to warfarin	Varies	Lower CI	
48		Varies	Upper CI	
49	Risk of TIA relative to warfarin	Varies	Lower CI	
50		Varies	Upper CI	
51	Risk of non-HS ICH relative to warfarin	Varies	Lower CI	
52		Varies	Upper CI	
53	Risk of HS relative to warfarin	Varies	Lower CI	
54		Varies	Upper CI	
55	Risk of ECH relative to warfarin	Varies	Lower CI	
56		Varies	Upper CI	
57	Risk of AMI relative to warfarin	Varies	Lower CI	
58		Varies	Upper CI	
59	RR of HS ASA, A+C, NT, RR of ICH NT	Various	+/-20%	Parameters varied here as they not varied in the PSA.
60,61	%ECH that is GI	Various	0% 100%	
62,63	Discontinuation following ECH	Various	0%, 100%	
64,65	Treatment swirch to 2nd line	Varies	+/-10%	
66	Mortality risk	Varies	SE = 0, AMI = 0, ECH = 0,	
67	Withdrawal	Variiuos	0	
68	Post-event disability	Various	-5% for mild/moderate, +5% totally dependent/death**	

Abbreviations: A+C, aspirin plus clopidogrel, AMI, acute myocardial infarction; DBG, dabigatran etexilate; HS, haemorrhagic stroke; ICH, intracranial bleed; IS, ischaemic stroke; MB, major bleed; SE, systemic embolism; TIA, transient ischaemic attack.

*Varies - varies across models; Various – varies within and between model.

**This has the impact of making disability following stroke/ICH less severe. An analysis examining more severe disability was not undertaken as reducing the rates of these rare events (total dependent/fatal) further would quickly result in negative values.

In the sensitivity analyses, results are deterministic and compared to the deterministic base case ICERs. This approach is a pragmatic step since the time required to run a large number of robust PSAs was prohibitive.

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken to estimate the level of uncertainty in the results and estimate the probability of cost-effectiveness at different willingness-to-pay thresholds. In order to do this, key parameters were chosen for inclusion in the PSA. Where data was available, the variance of each parameter was used within the PSA. If this was not available, conservative assumptions about the variance were made. The parameters considered in the sensitivity analysis are shown from **Table 118** to **Table 128**.

The clinical parameters for ischaemic stroke are shown in **Table 118**. Due to the different data cuts used for different models and subgroups of patients, different mean and error values were required for the same parameter items. In the table, the patient populations are defined by age and model.

The PSA parameters for systemic embolism are shown in **Table 119**, for transient ischaemic attack in **Table 120**, haemorrhagic stroke in **Table 121**, intracranial haemorrhage in **Table 122**, the relative risk of different types of disability (fatal, independent, moderate disability) following ICH or HS in **Table 123**, extracranial haemorrhage in **Table 124,** minor bleed in **Table 125** and acute myocardial infarction in **Table 126**.

Table 118 PSA parameters for Ischaemic Stroke

Item	Sub-item	Age	Model	Mean	Distribution	Error 1	Error 2
Baseline risk of IS on WFN[b]	$CHADS_2$ = 0	<80	Seq	0.62	beta	2	322
	$CHADS_2$= 1	<80	Seq	0.79	beta	25	3147
	$CHADS_2$= 2	<80	Seq	0.88	beta	31	3512
	$CHADS_2$= 3	<80	Seq	1.55	beta	41	2646
	$CHADS_2$= 4	<80	Seq	1.55	beta	41	2646
	$CHADS_2$= 5	<80	Seq	2.77	beta	7	253
	$CHADS_2$= 6	<80	Seq	2.77	beta	7	253
	$CHADS_2$= 1	>80	Seq	0.42	beta	1	236
	$CHADS_2$= 2	>80	Seq	1.54	beta	13	845
	$CHADS_2$= 3	>80	Seq	2.48	beta	18	727
	$CHADS_2$= 4	>80	Seq	2.48	beta	18	727
	$CHADS_2$= 5	>80	Seq	4.72	beta	5	106
	$CHADS_2$= 6	>80	Seq	4.72	beta	5	106
	$CHADS_2$ = 0	All	RCT	[redacted]	beta	[redacted]	[redacted]
	$CHADS_2$= 1	All	RCT	[redacted]	beta	[redacted]	[redacted]
	$CHADS_2$= 2	All	RCT	[redacted]	beta	[redacted]	[redacted]
	$CHADS_2$= 3	All	RCT	[redacted]	beta	[redacted]	[redacted]
	$CHADS_2$= 4	All	RCT	[redacted]	beta	[redacted]	[redacted]
	$CHADS_2$= 5	All	RCT	[redacted]	beta	[redacted]	[redacted]
	$CHADS_2$= 6	All	RCT	[redacted]	beta	[redacted]	[redacted]
Relative risk of IS vs. WFN	No Treatment[c]	All	RCT	3.35	lognormal	2.23	5.03
	A+C	All	RCT	2.07	lognormal	1.38	3.11
	DBG150 bid	All	RCT	0.76	lognormal	0.59	0.97
	DBG110 bid	All	RCT	1.10	lognormal	0.88	1.37
	Aspirin[c]	All	RCT	1.62	lognormal	0.99	2.65
	No Treatment[c]	All	Seq	3.35	lognormal	2.23	5.03
	A+C	All	Seq	2.07	lognormal	1.38	3.11
	DBG150 bid	<80	Seq	0.77	lognormal	0.58	1.03
	DBG110 bid	>80	Seq	0.82	lognormal	0.51	1.33
	Aspirin[c]	All	Seq	1.62	lognormal	0.99	2.65
Relative risk of stroke disability for DBG patients vs. WFN	Independent	<80	Seq	[redacted]	lognormal	[redacted]	[redacted]
	Moderate disability	<80	Seq	[redacted]	lognormal	[redacted]	[redacted]
	Mortality	<80	Seq	[redacted]	lognormal	[redacted]	[redacted]
	Independent	>80	Seq	[redacted]	lognormal	[redacted]	[redacted]
	Moderate disability	>80	Seq	[redacted]	lognormal	[redacted]	[redacted]
	Mortality	>80	Seq	[redacted]	lognormal	[redacted]	[redacted]
	Independent	All	RCT 150 mg	[redacted]	lognormal	[redacted]	[redacted]
	Moderate disability	All	RCT 150 mg	[redacted]	lognormal	[redacted]	[redacted]
	Mortality	All	RCT 150 mg	[redacted]	lognormal	[redacted]	[redacted]
	Independent	All	RCT 110 mg	[redacted]	lognormal	[redacted]	[redacted]
	Moderate disability	All	RCT 110 mg	[redacted]	lognormal	[redacted]	[redacted]
	Mortality	All	RCT 110 mg	[redacted]	lognormal	[redacted]	[redacted]

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; IS, ischaemic stroke; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74**, **Table 77**

Table 119 PSA parameters for Systemic Embolism

Item	Sub-item	Age	Model	Mean	Distribution	Error 1	Error 2
Base line risk of SE on WFN[b]		All	RCT	0.18	beta	21	11,794
RR of SE relative to WFN	No Treatment[c]	All	RCT	4.44	lognormal	1.78	11.08
	A+C	All	RCT	3.57	lognormal	1.52	8.36
	DBG150 bid	All	RCT	0.61	lognormal	0.30	1.21
	DBG110 bid	All	RCT	0.71	lognormal	0.37	1.38
	Aspirin[c]	All	RCT	1.77	lognormal	0.66	4.77
Base line risk of SE on WFN[b]	150mg bid	<80	Seq	0.15	beta	15	9,881
Base line risk of SE on WFN[b]	110mg bid	>80	Seq	0.31	beta	6	1,913
RR of SE relative to WFN	No Treatment[c]	All	Seq	4.44	lognormal	1.78	11.08
	A+C	All	Seq	3.57	lognormal	1.52	8.36
	DBG150 bid	<80	Seq	0.66	lognormal	0.30	1.47
	DBG110 bid	>80	Seq	0.51	lognormal	0.13	2.06
	Aspirin[c]	All	Seq	1.77	lognormal	0.66	4.77

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; SE, systemic embolism; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74**

Table 120 PSA parameters for TIA

Item	Sub-item	Age	Model	Mean	Distribution	Error 1[a]	Error 2[a]
Base line risk of TIA on WFN[b]		All	RCT	0.84	beta	99	11,794
RR of TIA relative to WFN	No Treatment[c]	All	RCT	1.23	lognormal	0.59	2.58
	A+C	All	RCT	1.56	lognormal	0.86	2.83
	DBG150 bid	All	RCT	0.86	lognormal	0.65	1.15
	DBG110 bid	All	RCT	0.74	lognormal	0.55	1.00
	Aspirin[c]	All	RCT	1.56	lognormal	0.86	2.83
Base line risk of TIA on WFN[b]	150mg bid	<80	Seq	0.73	beta	72	9,881
Base line risk of TIA on WFN[b]	110mg bid	>80	Seq	1.41	beta	27	1,913
RR of TIA relative to WFN	No Treatment[c]	All	Seq	1.23	lognormal	0.59	2.58
	A+C	All	Seq	1.56	lognormal	0.86	2.83
	DBG150 bid	<80	Seq	0.92	lognormal	0.66	1.29
	DBG110 bid	>80	Seq	0.45	lognormal	0.23	0.89
	Aspirin[c]	All	Seq	1.56	lognormal	0.86	2.83

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; TIA, transient ischaemic attack; WF, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74**

Table 121 PSA parameters for HS

Item	Sub-item	Age	Model	Mean	Distribution	Error 1 [a]	Error 2 [a]
Base line risk of ICH on WFN[b]		All	RCT	0.38	beta	45	11,794
RR of ICH relative to WFN	DBG150 bid	All	RCT	0.26	lognormal	0.14	0.49
	DBG110 bid	All	RCT	0.31	lognormal	0.17	0.56
Base line risk of ICH on WFN[b]	150mg bid	<80	Seq	0.33	beta	33	9,881
Base line risk of ICH on WFN[b]	110mg bid	>80	Seq	0.63	beta	12	1,913
RR of ICH relative to WFN	DBG150 bid	<80	Seq	0.21	lognormal	0.09	0.47
	DBG110 bid	>80	Seq	0.26	lognormal	0.07	0.91

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years.
Abbreviations: DBG, dabigatran etexilate; HS, haemorrhagic stroke; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74**

Table 122 PSA parameters for ICH

Item	Sub-item	Age	Model	Mean	Distribution	Error 1 [a]	Error 2 [a]
Base line risk of ICH on WFN[b]		All	RCT	0.42	beta	49	11,794
RR of ICH relative to WFN	A+C	All	RCT	0.53	lognormal	0.19	1.45
	DBG150 bid	All	RCT	0.52	lognormal	0.32	0.84
	DBG110 bid	All	RCT	0.32	lognormal	0.18	0.57
	Aspirin [c]	All	RCT	0.51	lognormal	0.16	1.60
Base line risk of ICH on WFN[b]	150mg bid	<80	Seq	0.35	beta	35	9,881
Base line risk of ICH on WFN[b]	110mg bid	>80	Seq	0.73	beta	14	1,913
RR of ICH relative to WFN	A+C	All	Seq	0.53	lognormal	0.19	1.45
	DBG150 bid	<80	Seq	0.48	lognormal	0.27	0.85
	DBG110 bid	>80	Seq	0.29	lognormal	0.10	0.88
	Aspirin [c]	All	Seq	0.51	lognormal	0.16	1.60

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; ICH, intracranial haemorrhage; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74**

Table 123 PSA parameters for post ICH/HS event disability

Item	Sub-item	Age	Model	Mean	Distribution	LCI	UCI	Source	Notes
RR vs Aspirin	No treatment and A+C	all	both	1.00	lognormal	0.80	1.20	assumption	Assume aspirin and no treatment have the same disability distribution after ICH/HS
RR vs WFN	DBG 110 and 150	all	both	1.00	lognormal	0.80	1.20	assumption	Assume DBG and WFN have the same disability distribution after ICH/HS

[a]ICH and HS have the same post-event disability and mortality distribution. LCI = lower 95% confidence interval; UCI = upper 95% confidence interval.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; HS, haemorrhagic stroke, ICH, intracranial haemorrhage; RR, relative risk; WFN, warfarin

Table 124 PSA parameters for ECH

Item	Sub-item	Age	Model	Mean	Distribution	Error 1 [a]	Error 2 [a]
Base line risk of ECH on WFN[b]		All	RCT	2.84	beta	335	11,794
RR of ECH relative to WFN	No Treatment [c]	All	RCT	0.61	lognormal	0.10	3.78
	A+C	All	RCT	1.10	lognormal	0.71	1.72
	DBG150 bid	All	RCT	1.07	lognormal	0.92	1.24
	DBG110 bid	All	RCT	0.94	lognormal	0.81	1.10
	Aspirin [c]	All	RCT	1.14	lognormal	0.47	2.73
Base line risk of ECH on WFN[b]	150mg bid	<80	Seq	2.71	beta	268	9,881
Base line risk of ECH on WFN[b]	110mg bid	>80	Seq	3.50	beta	67	1,913
RR of ECH relative to WFN	No Treatment [c]	All	Seq	0.61	lognormal	0.10	3.78
	A+C	All	Seq	1.10	lognormal	0.71	1.72
	DBG150 bid	<80	Seq	0.93	lognormal	0.78	1.11
	DBG110 bid	>80	Seq	1.44	lognormal	1.05	1.97
	Aspirin [c]	All	Seq	1.14	lognormal	0.47	2.73
Fatal ECH		All	Both	0.03%	beta	5	15300
RR for age		<70	Both	0.50	lognormal	0.12	0.9

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; ECH, extracranial haemorrhage; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74, Table 85**

Table 125 PSA parameters for Minor Bleed

Item	Sub-item	Age	Model	Mean	Distribution	Error 1 [a]	Error 2 [a]
Base line risk of MB on WFN[b]		All	RCT	16.37	beta	1,931	11,794
RR of MB relative to WFN	No Treatment [c]	All	RCT	0.55	lognormal	0.38	0.80
	A+C	All	RCT	1.19	lognormal	1.00	1.43
	DBG150 bid	All	RCT	0.91	lognormal	0.86	0.97
	DBG110 bid	All	RCT	0.79	lognormal	0.74	0.84
	Aspirin [c]	All	RCT	0.63	lognormal	0.32	1.22
Base line risk of MB on WFN[b]	150mg bid	<80	Seq	16.06	beta	1,587	9,881
Base line risk of MB on WFN[b]	110mg bid	>80	Seq	17.98	beta	344	1,913
RR of MB relative to WFN	No Treatment [c]	All	Seq	0.55	lognormal	0.38	0.80
	A+C	All	Seq	1.19	lognormal	1.00	1.43
	DBG150 bid	<80	Seq	0.86	lognormal	0.80	0.93
	DBG110 bid	>80	Seq	0.91	lognormal	0.78	1.07
	Aspirin [c]	All	Seq	0.63	lognormal	0.32	1.22

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; DBG, dabigatran etexilate; MB, minor bleed, MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74**

Table 126 PSA parameters for Acute Myocardial Infarction

Item	Sub-item	Age	Model	Mean	Distribution	Error 1 [a]	Error 2 [a]
Base line risk of MB on WFN[b]		All	RCT	0.64	beta	75	11,794
RR of MB relative to WFN	No Treatment [c]	All	RCT	1.57	lognormal	0.67	3.69
	A+C	All	RCT	1.48	lognormal	0.83	2.63
	DBG150 bid	All	RCT	1.27	lognormal	0.94	1.71
	DBG110 bid	All	RCT	1.29	lognormal	0.96	1.75
	Aspirin [c]	All	RCT	1.42	lognormal	0.84	2.39
Base line risk of MB on WFN[b]	150mg bid	<80	Seq	0.59	beta	58	9,881
Base line risk of MB on WFN[b]	110mg bid	>80	Seq	0.89	beta	17	1,913
RR of MB relative to WFN	No Treatment [c]	All	Seq	1.57	lognormal	0.67	3.69
	A+C	All	Seq	1.48	lognormal	0.83	2.63
	DBG150 bid	<80	Seq	1.26	lognormal	0.89	1.78
	DBG110 bid	>80	Seq	1.39	lognormal	0.74	2.60
	Aspirin [c]	All	Seq	1.42	lognormal	0.84	2.39
Fatal AMI		All	Both	1.11%	beta	3	270

[a] If distribution is beta then Error 1 is Total Events and Error 2 is Total Patient Years. If distribution is lognormal then Error 1 is upper 95% confidence interval and Error 2 is lower 95% confidence interval. [b] Values shown is rate per 100 patient years. [c] Note these differ may differ from each other as they were calculated via a Bayesian process in the MTC - therefore values might be expected to differ slightly between models.
Abbreviations: A+C, aspirin plus clopidogrel; AMI, acute myocardial infarction; DBG dabigatran etexilate; MB, minor bleed; MTC, mixed treatment comparison; RCT, randomised controlled trial; RR, relative risk; Seq, sequence model; WFN, warfarin
Source: [1, 80]. Cross reference: **Table 72**, **Table 74, Table 83**

Table 127 PSA Utilities (beta distribution used for all utility parameters)

	Mean	SE	Source	Notes
Acute Event				
Ischaemic stroke	0.139	0.011	Sullivan 2006[152]	SE derived from 95% confidence intervals in publication
Systemic embolism	0.120	0.009		
Transient ischaemic attack	0.103	0.008		
Intra-cranial haemorrhage	0.181	0.014		
Haemorrhagic stroke	0.139	0.011		
Extra-cranial haemorrhage	0.181	0.014		
Acute myocardial infarction	0.125	0.009		
Post-event disability				
Independent without stroke history	[redacted]	[redacted]	RE-LY data	SE derived from study data
Independent Disability with stroke history	0.76	0.005	Gage 1996[125]	SE unavailable from study and was therefore was estimated and included in the analysis due to the importance of this parameter. It was estimated by assuming the same SD as the 'Independent' value of 0.2 and calculating a SE based on the sample size of 70 provided in the study by Gage 1996.[125]
Moderate Disability	0.39	0.002		
Dependent Disability	0.11	0.001		

Abbreviation: SD, standard deviation; SE, Standard error

The values for the utilities used in the PSA are in **Table 127**. Each value is varied using a beta distribution based on the standard errors shown in the table. The costs that are varied in the PSA are shown in **Table 128**. Values for IS, HS and ICH use the same mean and standard errors but are varied separately to reflect their individual variation. Similarly, although the costs for fatal and non-fatal systemic embolism, and fatal and non-fatal AMI, have the same mean and SEs, these are also varied separately.

Table 128 PSA Costs (gamma distribution used for all cost parameters)

Event	Mean	SE	Source	Notes
IS/HS/ICH - Fatal	[redacted]	[redacted]	OXVASC 2010 (see Appendix 13)	Standard error from study
IS/HS/ICH - Independent	[redacted]	[redacted]		
IS/HS/ICH - Moderate Disability	[redacted]	[redacted]		
IS/HS/ICH - Totally Dependent	[redacted]	[redacted]		
Post-event disability - Independent with stroke history	[redacted]	[redacted]		
Post-event disability - Moderate	[redacted]	[redacted]		
Post-event disability - Dependent	[redacted]	[redacted]		
Systemic Embolism (Non-fatal)	£2,373	£475	Assumption	Assumed to be relatively large at 20% of the mean
Systemic Embolism (Fatal)	£400	£80		
Transient Ischemic Attack	£1,064	£213		
ECH (non-brain), Fatal	£1,852	£370		
ECH (non-brain), Non-fatal, Non-GI	£2,109	£422		
ECH (non-brain), Non-fatal, GI	£1,594	£319		
Minor Bleed	£84	£17		
Acute Myocardial Infarction, (Fatal/Non-fatal)	£2,956	£591		

Abbreviations: ECH, extracranial bleed; HS, haemorrhagic stroke; ICH, intracranial bleed; IS, ischaemic stroke;.

The PSA is extensive and takes into account all the key aspects of the model. Where data does not exist, conservative assumptions have been made. In order to generate robust outcomes for the PSA simulation, each simulation will include 5,000 iterations of the model. In total, twelve PSAs will be undertaken for the base case primary and secondary analyses:

1. DBG 110mg bid vs WFN
2. DBG 150mg bid vs WFN
3. DBG Sequence < 80 years vs WFN
4. DBG sequence ≥ 80 years vs WFN
5. DBG 110mg bid vs aspirin
6. DBG 150mg bid vs aspirin
7. DBG Sequence < 80 years vs aspirin
8. DBG sequence ≥ 80 years vs aspirin
9. DBG 110mg bid vs aspirin plus clopidogrel
10. DBG 150mg bid vs aspirin plus clopidogrel
11. DBG Sequence < 80 years vs aspirin plus clopidogrel
12. DBG sequence ≥ 80 years vs aspirin plus clopidogrel

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 129 compares the outcomes reported in RE-LY with those estimated by the economic model.

Table 129 Outcomes from clinical trial data and the model

	Outcome	All RE-LY			Sequence <80		Sequence ≥80	
		DBG 110mg bid	DBG 150mg bid	WFN	DBG	WFN	DBG	WFN
Clinical data	IS and other	1.34%	0.93%	1.22%	0.83%	1.07%	1.61%	1.93%
	SE	0.13%	0.11%	0.18%	0.10%	0.15%	0.20%	0.19%
	HS+ICH	0.23%	0.32%	0.76%	0.24%	0.68%	0.41%	1.31%
	ECH	2.64%	3.00%	2.81%	2.52%	2.71%	4.99%	3.50%
	AMI	0.73%	0.74%	0.56%	0.74%	0.59%	1.19%	0.90%
Model outcomes	IS and other	1.49%	1.15%	1.35%	0.99%	1.18%	3.22%	3.27%
	SE	0.17%	0.15%	0.20%	0.13%	0.17%	0.44%	0.54%
	HS+ICH	0.26%	0.32%	0.74%	0.25%	0.65%	0.61%	1.67%
	ECH	2.59%	2.91%	2.74%	2.00%	2.13%	6.16%	4.61%
	AMI	0.81%	0.80%	0.65%	0.74%	0.60%	1.67%	1.28%

Abbreviations: DBG, dabigatran etexilate; ECH, extracranial haemorrhage; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; SE, systemic embolism; WFN, warfarin
Cross reference: **Table 32**, **Table 33**, **Table 35**, **Table 36**, **Table 58**, **Table 63**, **Table 64**

All cause mortality rates were not available for the two sub-group analyses and could not be compared to outcomes from the data. There are a number of reasons to explain the difference between the results from the clinical trial and the model:

- The model calculates outcomes as the number of events per patient at baseline per year, and therefore is not adjusted for deaths. This explains the greatest descrepancies occurring in the≥ 80 subgroup (average age = 82.9), and the smallest in the <80 subgroup (average age = 69.1).
- Rates in the clinical trial were based on the ITT population and these were applied in the model in order to be consistant with the trial results and avoid using multiple data sets (i.e. using outcomes derived from the per protocol patients only). This formed a conservative assumption as the model uses the event rates and relative risks per trial arm as estimates of the event rates and relative risks while treatment compliant. This approximation results in an overestimate of ischemic events as patients discontinue therapy in the model and are exposed to the higher risks associated with the less-effective 2nd line therapy (aspirin, in general). Note that because the DBG discontinuation rate is higher than the WFN rate, this is a conservative approach when predicting the cost-effectiveness of DBG.

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces are provided for the different health states. These are:

- Independent Without Stroke History
- Independent Disability
- Moderate Disability
- Dependent Disability
- Death.

A Markov trace is provided for each of the comparators in **Figure 25** to **Figure 31** below.

Figure 25 Markov trace for warfarin

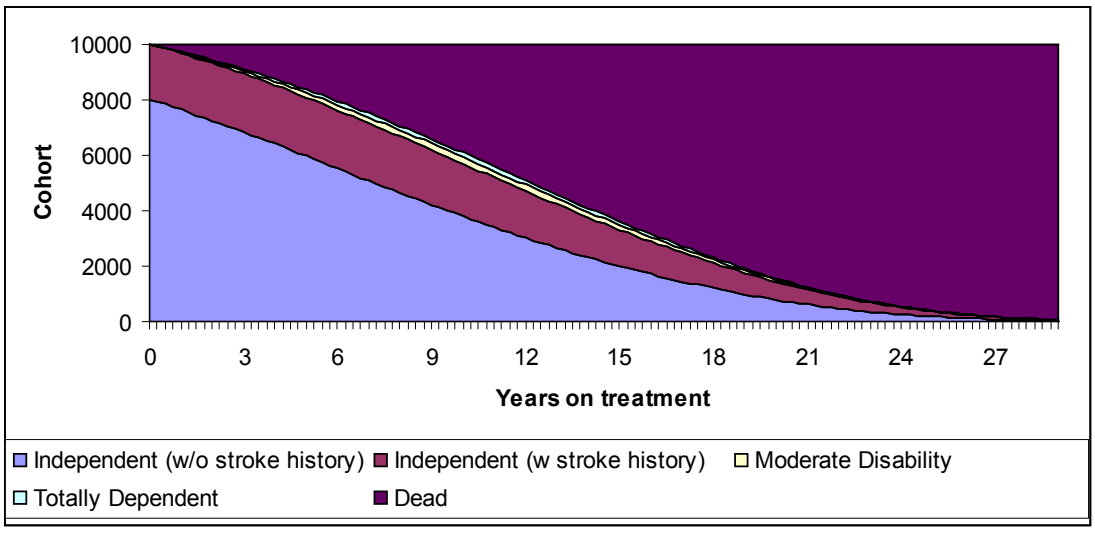


Figure 26 Markov trace for DBG 150mg bid

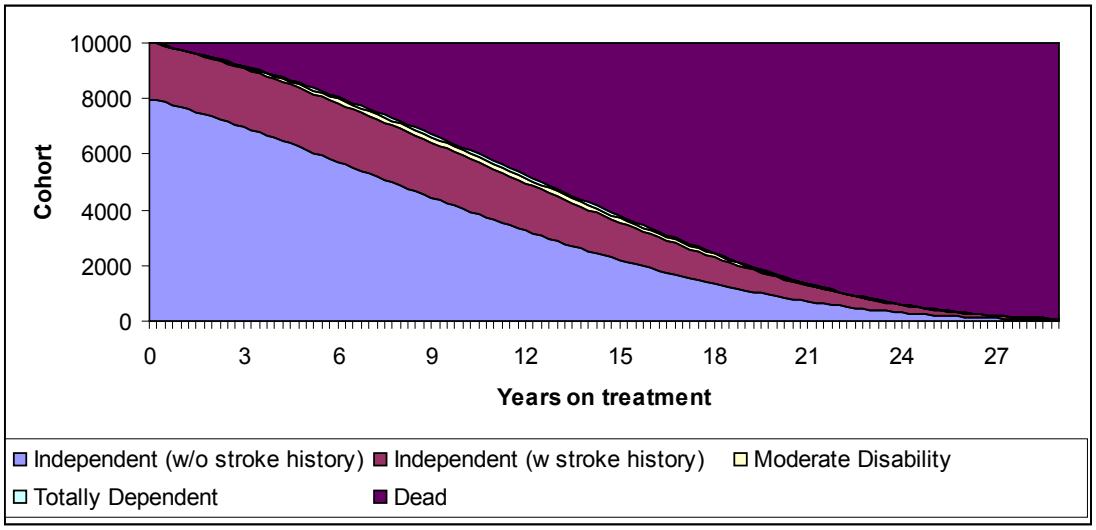


Figure 27 Markov trace for DBG 110mg bid

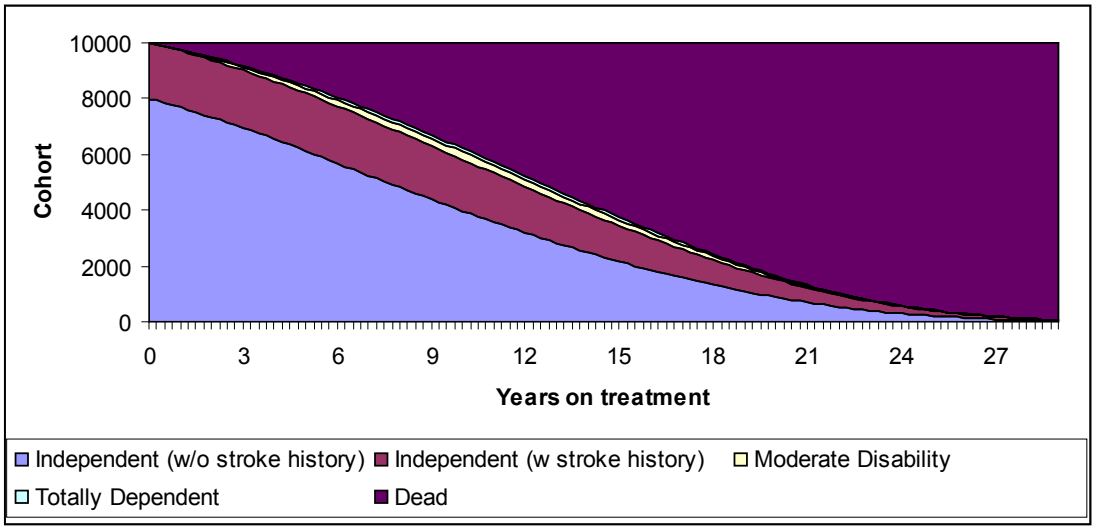


Figure 28 Markov trace for aspirin

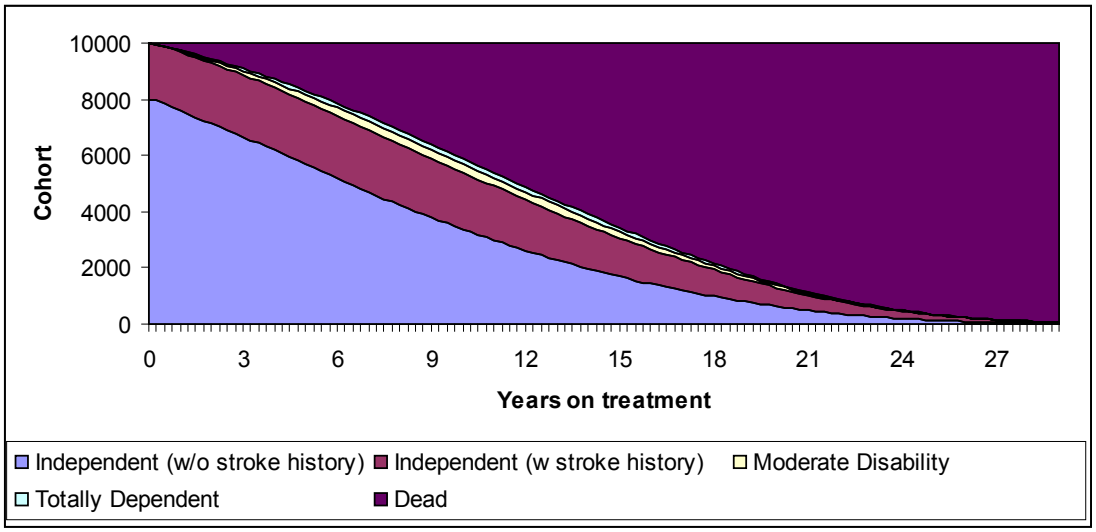


Figure 29 Markov trace for aspirin plus clopidogrel

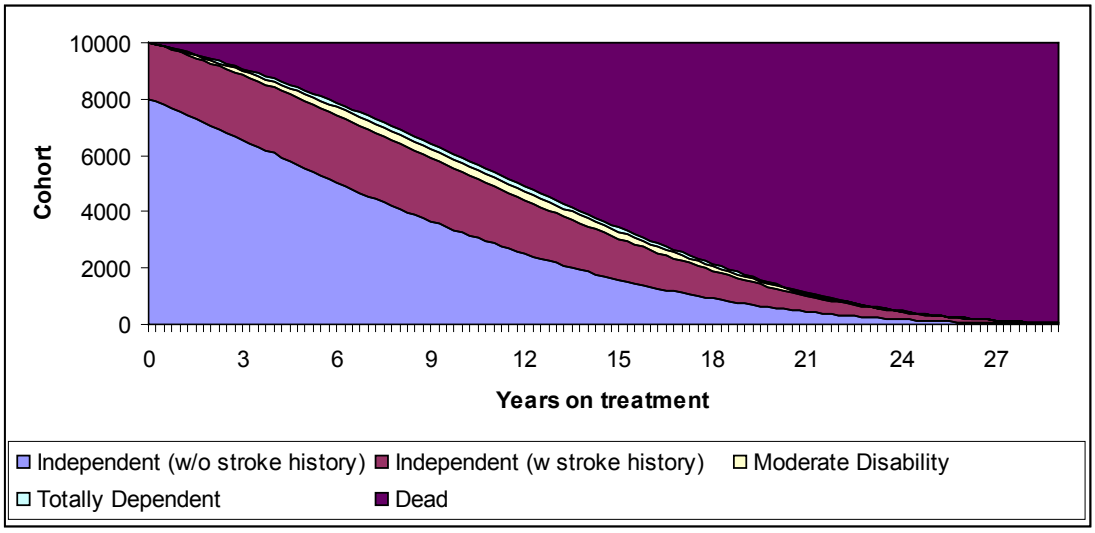


Figure 30 Markov trace for DBG sequence model (< 80 years)

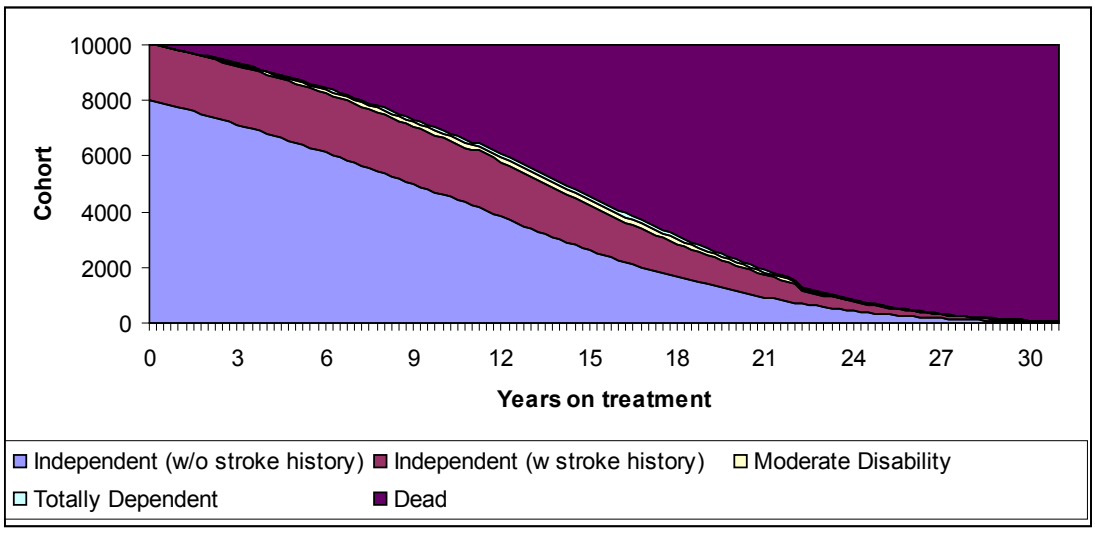
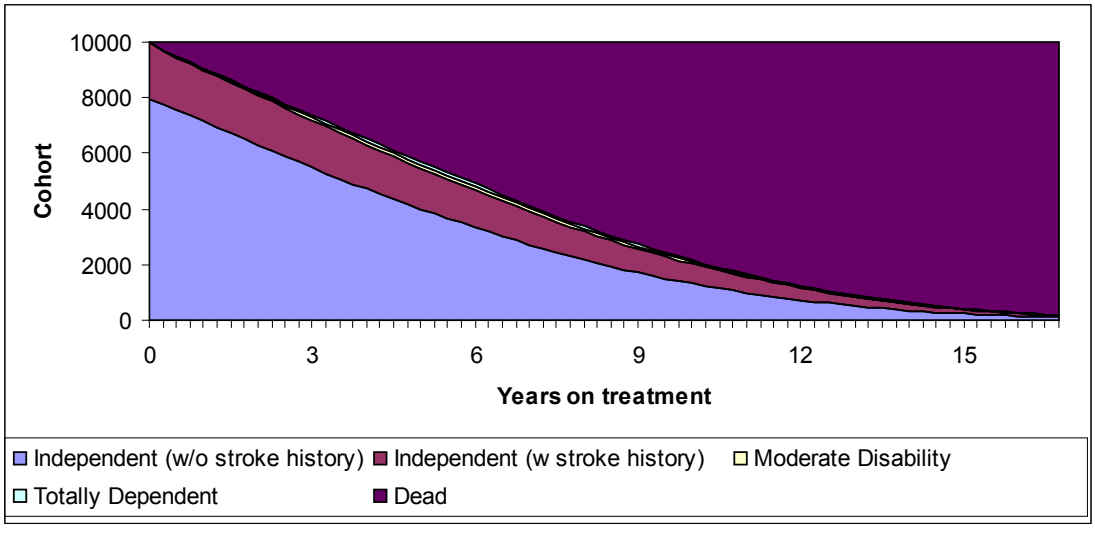


Figure 31 Markov trace for DBG sequence model (≥ 80 years)



The Markov traces in **Figure 25** to **Figure 29** are derived from the single dose model. The Markov traces for WFN, ASA and A+C are not shown for the sequence model as they will only differ as a result of differences in the baseline characteristics (age at baseline, % of cohort that are male, % by $CHADS_2$ score and with previous history of stroke) and small diferences in the clinical parameters that result from their derivation via the MTC.

The Markov traces from the sequence model are shown in **Figure 30** and **Figure 31**.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs are calculated at each timestep for cohorts of patients with different $CHADS_2$ score and previous stroke history at baseline. These are based on the number and type of events per timestep, and the number of patients in each disability state. Changes in quality of life as a result of different therapies are also calulcated at each timestep. QALYs are discounted at each timestep. A weighted average of the QALYs for the population is then caluated as a weighted average based on the proportion of patients in each $CHADS_2$ subgroup and previous stroke history.

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Life years, disaggregated QALYs and disaggregated costs are shown for the single dose model in **Table 130**, for the sequence model in patients under 80 years in **Table 131**, and from the sequence model in patients at least 80 years in **Table 132**.

Table 130 LYs, disaggregated costs and QALYs for the single dose models

	DBG 110mg bid	DBG 150mg bid	WFN	ASA	A+C
Life Years	**9.71**	**9.74**	**9.55**	**9.40**	**9.40**
QALY					
Events					
IS	0.038	0.034	0.036	0.051	0.054
SE	0.003	0.003	0.004	0.005	0.007
TIA	0.008	0.009	0.009	0.012	0.012
ICH and HS	0.005	0.006	0.012	0.007	0.008
ECH	0.045	0.050	0.047	0.047	0.049
AMI	0.011	0.010	0.009	0.011	0.011
Total events	**0.110**	**0.112**	**0.116**	**0.134**	**0.141**
Health State					
Independent w/o stroke history	5.41	5.46	5.24	4.89	4.76
Independent w stroke history	2.03	2.07	2.06	2.19	2.29
Moderate Disability	0.09	0.07	0.08	0.11	0.12
Totally Dependent	0.01	0.01	0.02	0.02	0.02
Total Health states	**7.54**	**7.61**	**7.40**	**7.22**	**7.20**
Total	**7.43**	**7.50**	**7.28**	**7.08**	**7.06**
Costs					
Events					
Ischemic Stroke Fatal	£274	£269	£268	£386	£381
Ischemic Stroke Independent	£389	£370	£385	£532	£601
Ischemic Stroke, Moderate Disability	£1,036	£755	£866	£1,221	£1,360
Ischemic Stroke, Totally Dependent	£520	£354	£427	£728	£604
SE, Fatal	£0	£0	£0	£0	£1
SE, Non-fatal	£10	£10	£12	£18	£24
TIA	£80	£89	£95	£123	£126
ICH, Fatal	£42	£51	£110	£38	£42
ICH, Independent	£11	£13	£22	£24	£25
ICH, Moderate Disability	£66	£77	£132	£138	£149
ICH, Totally Dependent	£288	£337	£619	£507	£548
ECH (non-brain), Fatal	£5	£6	£5	£6	£6
ECH (non-brain), Non-fatal, Non-GI	£414	£441	£441	£442	£459
ECH (non-brain), Non-fatal, GI	£79	£98	£72	£73	£76
Minor Bleed	£95	£106	£113	£76	£125
AMI, Fatal	£3	£3	£2	£3	£3
AMI, Non-fatal	£246	£246	£206	£258	£263
Total event costs	**£3,561**	**£3,224**	**£3,775**	**£4,573**	**£4,792**
Treatment					
First tx	£6,309	£6,144	£2,898	£209	£597
Second tx	£33	£35	£34	£0	£36
Treatment costs	**£6,342**	**£6,179**	**£2,932**	**£209**	**£633**
Follow-up costs					
Independent without stroke history	£0	£0	£0	£0	£0
Independent with stroke history	£4,051	£4,145	£4,111	£4,388	£4,587
Moderate Disability	£2,447	£1,756	£2,172	£2,878	£3,236
Totally Dependent	£1,983	£1,618	£2,593	£3,031	£2,822
Total follow-up	**£8,481**	**£7,519**	**£8,875**	**£10,297**	**£10,645**
Total cost	**£18,385**	**£16,923**	**£15,583**	**£15,080**	**£16,070**

Abbreviations: A+C, aspirin plus clopidogrel; AMI, acute myocardial infarction; ASA, aspirin; DBG, dabigatran etexilate; ECH, extracranial haemorrhage; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; LY, life year; QALY, quality-adjusted life year; SE, systemic embolism; TIA, transient ischaemic attack; tx, treatment; WFN, warfarin

Table 131 LYs, disaggregated costs and QALYs for the sequence model (<80 years)

	Seq < 80	WFN	A+C	ASA
Life Years	**10.48**	**10.26**	**10.08**	**10.09**
QALY				
Events				
IS	0.036	0.038	0.057	0.054
SE	0.004	0.004	0.008	0.006
TIA	0.009	0.011	0.014	0.013
ICH and HS	0.005	0.012	0.008	0.008
ECH	0.053	0.049	0.051	0.049
AMI	0.012	0.010	0.012	0.012
Total events	**0.119**	**0.124**	**0.150**	**0.143**
Health State				
Independent w/o stroke history	5.91	5.65	5.14	5.27
Independent w stroke history	2.18	2.18	2.42	2.32
Moderate Disability	0.07	0.08	0.12	0.11
Totally Dependent	0.01	0.02	0.02	0.03
Total Health states	**8.18**	**7.94**	**7.71**	**7.73**
Total	**8.06**	**7.82**	**7.56**	**7.59**
Costs				
Events				
Ischemic Stroke Fatal	£303	£304	£433	£426
Ischemic Stroke Independent	£336	£372	£578	£514
Ischemic Stroke, Moderate Disability	£832	£824	£1,286	£1,160
Ischemic Stroke, Totally Dependent	£670	£748	£1,025	£1,202
SE, Fatal	£0	£0	£1	£1
SE, Non-fatal	£13	£14	£28	£21
TIA	£95	£109	£142	£139
ICH, Fatal	£43	£111	£42	£39
ICH, Independent	£12	£22	£26	£24
ICH, Moderate Disability	£68	£133	£150	£139
ICH, Totally Dependent	£298	£628	£557	£518
ECH (non-brain), Fatal	£7	£6	£6	£6
ECH (non-brain), Non-fatal, Non-GI	£477	£467	£482	£464
ECH (non-brain), Non-fatal, GI	£99	£75	£77	£74
Minor Bleed	£112	£123	£134	£82
AMI, Fatal	£3	£3	£3	£3
AMI, Non-fatal	£280	£230	£292	£288
Total event costs	**£3,647**	**£4,170**	**£5,264**	**£5,101**
Treatment				
First tx	£6,818	£3,165	£635	£223
Second tx	£34	£34	£39	£0
Treatment costs	**£6,852**	**£3,199**	**£674**	**£223**
Follow-up costs				
Independent without stroke history	£0	£0	£0	£0
Independent with stroke history	£4,358	£4,368	£4,838	£4,646
Moderate Disability	£1,894	£2,163	£3,220	£2,874
Totally Dependent	£2,106	£3,184	£3,578	£3,887
Total follow-up	**£8,357**	**£9,715**	**£11,636**	**£11,408**
Total cost	**£18,856**	**£17,083**	**£17,574**	**£16,732**

Abbreviations: A+C, aspirin plus clopidogrel; AMI, acute myocardial infarction; ASA, aspirin; DBG, dabigatran etexilate; ECH, extracranial haemorrhage; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; LY, life year; QALY, quality-adjusted life year; SE, systemic embolism; Seq, DBG sequence model; TIA, transient ischaemic attack; tx, treatment; WFN, warfarin

Table 132 LYs, disaggregated costs and QALYs for the sequence model (≥80 years)

	DBG 110mg bid	WFN	A+C	ASA
Life Years	**5.38**	**5.27**	**5.19**	**5.23**
QALY				
Events				
IS	0.026	0.025	0.036	0.035
SE	0.003	0.004	0.007	0.005
TIA	0.007	0.009	0.012	0.011
ICH and HS	0.004	0.010	0.007	0.007
ECH	0.042	0.032	0.034	0.033
AMI	0.009	0.007	0.009	0.009
Total events	**0.090**	**0.086**	**0.105**	**0.099**
Health State				
Independent w/o stroke history	3.14	2.97	2.74	2.82
Independent w stroke history	1.02	1.08	1.20	1.15
Moderate Disability	0.04	0.03	0.04	0.04
Totally Dependent	0.01	0.01	0.01	0.02
Total Health states	**4.20**	**4.09**	**4.00**	**4.02**
Total	**4.11**	**4.01**	**3.89**	**3.92**
Costs				
Events				
Ischemic Stroke Fatal	£241	£215	£300	£281
Ischemic Stroke Independent	£189	£223	£343	£300
Ischemic Stroke, Moderate Disability	£635	£465	£709	£631
Ischemic Stroke, Totally Dependent	£591	£634	£833	£1,044
SE, Fatal	£0	£0	£1	£1
SE, Non-fatal	£11	£12	£23	£17
TIA	£68	£91	£119	£117
ICH, Fatal	£32	£89	£36	£34
ICH, Independent	£11	£19	£23	£21
ICH, Moderate Disability	£62	£113	£130	£120
ICH, Totally Dependent	£256	£521	£480	£446
ECH (non-brain), Fatal	£5	£4	£4	£4
ECH (non-brain), Non-fatal, Non-GI	£374	£296	£312	£302
ECH (non-brain), Non-fatal, GI	£79	£58	£61	£59
Minor Bleed	£62	£67	£77	£47
AMI, Fatal	£2	£2	£2	£2
AMI, Non-fatal	£204	£163	£204	£202
Total event costs	**£2,821**	**£2,971**	**£3,657**	**£3,627**
Treatment				
First tx	£2,928	£1,466	£347	£123
Second tx	£32	£29	£21	£0
Treatment costs	**£2,959**	**£1,495**	**£367**	**£123**
Follow-up costs				
Independent w/o stroke history	£0	£0	£0	£0
Independent w stroke history	£2,039	£2,157	£2,404	£2,304
Moderate Disability	**£934**	**£770**	**£1,123**	**£987**
Totally Dependent	**£1,175**	**£1,706**	**£1,928**	**£2,186**
Total follow-up	**£4,148**	**£4,632**	**£5,455**	**£5,477**
Total cost	**£9,929**	**£9,098**	**£9,479**	**£9,227**

Abbreviations: A+C, aspirin plus clopidogrel; AMI, acute myocardial infarction; ASA, aspirin; DBG, dabigatran etexilate; ECH, extracranial haemorrhage; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; LY, life year; QALY, quality-adjusted life year; SE, systemic embolism; TIA, transient ischaemic attack; tx, treatment; WFN, warfarin

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 133 to **Table 135** below present the disaggregated results for costs and outcomes, in the suggested format, for each comparison (see table titles).

Costs are disaggregated into drug (and INR monitoring) costs, acute event and follow-up. Drug costs are consistently higher in the DBG groups, whereas event costs are consistently lower. The lowest event costs are in the DBG Sequence (≥80 years) analysis, which is reflective of the age of the cohort and higher mortality rates. The follow-up costs, which include the long-term care costs for those left disabled by IS, HS and ICH, are consistently the greatest cost element in each of the groups. The follow-up costs are consistently lower for the DBG arms, with the greatest incremental differences being in the analyses using the most efficacious 150mg bid dose.

The most common events are IS, with fewer events when patients receive the DBG 150mg bid dose. The largest difference in events between DBG and WFN are for HS and ICH, with DBG preventing more of these events than WFN. Only in the DBG sequence (≥80 years) analysis did patients on WFN have fewer ECH events.

Table 133 Incremental disagregated QALYs and costs (DBG 110mg bid)

	Intervention - DBG 110mg	Comparator - WFN	Increment	Absolute increment	% Absolute increment
Health states					
Total events	-0.110	-0.116	0.006	0.006	3%
Independent w/o stroke history	5.409	5.242	0.167	0.167	77%
Independent w stroke history	2.026	2.055	-0.030	0.030	14%
Moderate Disability	0.094	0.084	0.011	0.011	5%
Totally Dependent	0.014	0.018	-0.004	0.004	2%
Total	**7.433**	**7.283**	**0.150**	**0.218**	**100%**
Costs					
Total events	£3,561	£3,775	-£214	£214	5%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,051	£4,111	-£59	£59	1%
Moderate Disability	£2,447	£2,172	£275	£275	6%
Totally Dependent	£1,983	£2,593	-£610	£610	13%
Treatment costs	£6,342	£2,932	£3,410	£3,410	75%
Total	**£18,385**	**£15,583**	**£2,802**	£4,568	**100%**
	Intervention - DBG 110mg	**Comparator - A+C**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.110	-0.141	0.032	0.032	3%
Independent w/o stroke history	5.409	4.764	0.645	0.645	66%
Independent w stroke history	2.026	2.293	-0.268	0.268	27%
Moderate Disability	0.094	0.124	-0.030	0.030	3%
Totally Dependent	0.014	0.020	-0.006	0.006	1%
Total	**7.433**	**7.061**	**0.373**	**0.980**	**100%**
Costs					
Total events	£3,561	£4,792	-£1,231	£1,231	14%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,051	£4,587	-£535	£535	6%
Moderate Disability	£2,447	£3,236	-£790	£790	9%
Totally Dependent	£1,983	£2,822	-£839	£839	9%
Treatment costs	£6,342	£633	£5,709	£5,709	63%
Total	**£18,385**	**£16,070**	**£2,315**	£9,104	**100%**
	Intervention - DBG 110mg	**Comparator - ASA**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.110	-0.134	0.024	0.024	3%
Independent w/o stroke history	5.409	4.890	0.520	0.520	71%
Independent w stroke history	2.026	2.194	-0.168	0.168	23%
Moderate Disability	0.094	0.111	-0.017	0.017	2%
Totally Dependent	0.014	0.021	-0.007	0.007	1%
Total	**7.433**	**7.082**	**0.352**	**0.736**	**100%**
Costs					
Total events	£3,561	£4,573	-£1,012	£1,012	11%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,051	£4,388	-£336	£336	4%
Moderate Disability	£2,447	£2,878	-£431	£431	5%
Totally Dependent	£1,983	£3,031	-£1,048	£1,048	12%
Treatment costs	£6,342	£209	£6,133	£6,133	68%
Total	**£18,385**	**£15,080**	**£3,305**	£8,960	**100%**

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 134 Incremental disagregated QALYs and costs (DBG 150mg bid)

	Intervention - DBG 150mg	Comparator - WFN	Increment	Absolute increment	% Absolute increment
Health states					
Total events	-0.112	-0.116	0.004	0.004	1%
Independent w/o stroke history	5.458	5.242	0.215	0.215	83%
Independent w stroke history	2.073	2.055	0.017	0.017	7%
Moderate Disability	0.068	0.084	-0.016	0.016	6%
Totally Dependent	0.011	0.018	-0.007	0.007	3%
Total	**7.497**	**7.283**	**0.214**	**0.259**	**100%**
Costs					
Total events	£3,224	£3,775	-£551	£551	11%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,145	£4,111	£35	£35	1%
Moderate Disability	£1,756	£2,172	-£416	£416	8%
Totally Dependent	£1,618	£2,593	-£975	£975	19%
Treatment costs	£6,179	£2,932	£3,247	£3,247	62%
Total	**£16,923**	**£15,583**	**£1,340**	£5,224	**100%**
	Intervention - DBG 150mg	**Comparator - A+C**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.112	-0.141	0.029	0.029	3%
Independent w/o stroke history	5.458	4.764	0.693	0.693	69%
Independent w stroke history	2.073	2.293	-0.221	0.221	22%
Moderate Disability	0.068	0.124	-0.057	0.057	6%
Totally Dependent	0.011	0.020	-0.008	0.008	1%
Total	**7.497**	**7.061**	**0.437**	1.008	**100%**
Costs					
Total events	£3,224	£4,792	-£1,568	£1,568	15%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,145	£4,587	-£441	£441	4%
Moderate Disability	£1,756	£3,236	-£1,481	£1,481	14%
Totally Dependent	£1,618	£2,822	-£1,203	£1,203	12%
Treatment costs	£6,179	£633	£5,547	£5,547	54%
Total	**£16,923**	**£16,070**	**£853**	£10,240	**100%**
	Intervention - DBG 150mg	**Comparator - ASA**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.112	-0.134	0.022	0.022	3%
Independent w/o stroke history	5.458	4.890	0.568	0.568	74%
Independent w stroke history	2.073	2.194	-0.121	0.121	16%
Moderate Disability	0.068	0.111	-0.043	0.043	6%
Totally Dependent	0.011	0.021	-0.010	0.010	1%
Total	**7.497**	**7.082**	**0.416**	0.764	**100%**
Costs					
Total events	£3,224	£4,573	-£1,349	£1,349	13%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,145	£4,388	-£242	£242	2%
Moderate Disability	£1,756	£2,878	-£1,123	£1,123	11%
Totally Dependent	£1,618	£3,031	-£1,413	£1,413	14%
Treatment costs	£6,179	£209	£5,970	£5,970	59%
Total	**£16,923**	**£15,080**	**£1,843**	£10,097	**100%**

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 135 Incremental disagregated QALYs and costs (sequence model <80 years)

	Intervention - DBG	Comparator - WFN	Increment	Absolute increment	% Absolute increment
Health states					
Total events	-0.119	-0.124	0.005	0.005	2%
Independent w/o stroke history	5.911	5.651	0.261	0.261	91%
Independent w stroke history	2.179	2.184	-0.005	0.005	2%
Moderate Disability	0.073	0.083	-0.010	0.010	4%
Totally Dependent	0.015	0.022	-0.008	0.008	3%
Total	**8.058**	**7.816**	**0.242**	**0.288**	**100%**
Costs					
Total events	£3,647	£4,170	-£523	£523	9%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,358	£4,368	-£10	£10	0%
Moderate Disability	£1,894	£2,163	-£270	£270	5%
Totally Dependent	£2,106	£3,184	-£1,078	£1,078	19%
Treatment costs	£6,852	£3,199	£3,653	£3,653	66%
Total	**£18,856**	**£17,083**	**£1,773**	**£5,533**	**100%**
	Intervention - DBG	**Comparator - A+C**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.119	-0.143	0.023	0.023	3%
Independent w/o stroke history	5.911	5.272	0.639	0.639	75%
Independent w stroke history	2.179	2.323	-0.144	0.144	17%
Moderate Disability	0.073	0.111	-0.038	0.038	4%
Totally Dependent	0.015	0.027	-0.012	0.012	1%
Total	**8.058**	**7.590**	**0.468**	**0.857**	**100%**
Costs					
Total events	£3,647	£5,101	-£1,454	£1,454	13%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,358	£4,646	-£288	£288	3%
Moderate Disability	£1,894	£2,874	-£980	£980	9%
Totally Dependent	£2,106	£3,887	-£1,781	£1,781	16%
Treatment costs	£6,852	£223	£6,629	£6,629	60%
Total	**£18,856**	**£16,732**	**£2,125**	**£11,133**	**100%**
	Intervention - DBG	**Comparator - ASA**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	**-0.119**	**-0.150**	**0.031**	**0.031**	**3%**
Independent w/o stroke history	5.911	5.142	0.769	0.769	70%
Independent w stroke history	2.179	2.419	-0.240	0.240	22%
Moderate Disability	0.073	0.124	-0.051	0.051	5%
Totally Dependent	0.015	0.025	-0.010	0.010	1%
Total	**8.058**	**7.559**	**0.499**	**1.102**	**100%**
Costs					
Total events	£3,647	£5,264	-£1,617	£1,617	15%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£4,358	£4,838	-£480	£480	4%
Moderate Disability	£1,894	£3,220	-£1,326	£1,326	12%
Totally Dependent	£2,106	£3,578	-£1,472	£1,472	13%
Treatment costs	£6,852	£674	£6,178	£6,178	56%
Total	**£18,856**	**£17,574**	**£1,283**	**£11,074**	**100%**

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 136 Incremental disagregated QALYs and costs (sequence model ≥ 80 years)

	Intervention - DBG	Comparator - WFN	Increment	Absolute increment	% Absolute increment
Health states					
Total events	-0.090	-0.086	-0.004	0.004	2%
Independent w/o stroke history	3.138	2.972	0.166	0.166	70%
Independent w stroke history	1.020	1.078	-0.059	0.059	25%
Moderate Disability	0.036	0.030	0.006	0.006	3%
Totally Dependent	0.008	0.012	-0.004	0.004	2%
Total	4.111	4.006	0.106	0.238	100%
Costs					
Total events	£2,821	£2,971	-£149	£149	6%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£2,039	£2,157	-£117	£117	4%
Moderate Disability	£934	£770	£165	£165	6%
Totally Dependent	£1,175	£1,706	-£531	£531	20%
Treatment costs	£2,959	£4,632	-£1,673	£1,673	63%
Total	£9,929	£9,098	£832	£2,635	100%
	Intervention - DBG	**Comparator - A+C**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.090	-0.099	0.009	0.009	2%
Independent w/o stroke history	3.138	2.816	0.322	0.322	68%
Independent w stroke history	1.020	1.152	-0.132	0.132	28%
Moderate Disability	0.036	0.038	-0.002	0.002	0%
Totally Dependent	0.008	0.015	-0.007	0.007	1%
Total	4.111	3.922	0.189	0.472	100%
Costs					
Total events	£2,821	£3,627	-£805	£805	17%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£2,039	£2,304	-£265	£265	6%
Moderate Disability	£934	£987	-£53	£53	1%
Totally Dependent	£1,175	£2,186	-£1,011	£1,011	22%
Treatment costs	£2,959	£5,477	-£2,518	£2,518	54%
Total	£9,929	£9,227	£703	£4,652	100%
	Intervention - DBG	**Comparator - ASA**	**Increment**	**Absolute increment**	**% Absolute increment**
Health states					
Total events	-0.090	-0.105	0.014	0.014	2%
Independent w/o stroke history	3.138	2.736	0.402	0.402	66%
Independent w stroke history	1.020	1.202	-0.183	0.183	30%
Moderate Disability	0.036	0.043	-0.007	0.007	1%
Totally Dependent	0.008	0.013	-0.005	0.005	1%
Total	4.111	3.890	0.221	0.611	100%
Costs					
Total events	£2,821	£367	£2,454	£2,454	39%
Independent w/o stroke history	£0	£0	£0	£0	0%
Independent w stroke history	£2,039	£2,404	-£365	£365	6%
Moderate Disability	£934	£1,123	-£188	£188	3%
Totally Dependent	£1,175	£1,928	-£753	£753	12%
Treatment costs	£2,959	£5,455	-£2,495	£2,495	40%
Total	£9,929	£9,479	£450	£6,256	100%

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

PSA results are shown below in **Table 137** to **Table 140**. In each table the least expensive option is taken as the baseline value for calculation of ICERs. ICERs are then calculated relative to the baseline. In the incremental anlaysis, the ICER is calculated by comparing to the treatment above providing it has not been excluded due to dominance or extended dominance.

The PSAs were based on 5,000 iterations of the model. This meant that the total number of iterations for each dose of DBG (DBG 150, DBG 110, DBG Seq <80, DBG >80) was 15,000, for WFN, ASA and A+C in the single dose model was 10,000 (5,000 from each of the DBG 110 dose and 150 dose models), and in each of the simulations for the sequence model, there were 5,000 iterations for WFN, ASA and A+C (5,000 from the <80 and 5,000 from the >80). Therefore the costs and QALYs in **Table 137** to **Table 140** are based on these corresponding numbers of iterations of the model.

Table 137 Base case PSA of the single dose model for DBG 150mg bid

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,279	7.029	Baseline			
A+C	£15,315	7.014	£36	-0.014	dominated	dominated
WFN	£15,566	7.267	£287	0.238	£1,206	£1,206
DBG 150mg bid	£17,092	7.459	£1,813	0.430	£4,211	£7,940

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 138 Base case PSA of the single dose model for DBG 110mg bid

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,279	7.029	Baseline			
A+C	£15,315	7.014	£36	-0.014	dominated	dominated
WFN	£15,566	7.267	£287	0.238	£1,206	£1,206
DBG 110mg bid	£18,210	7.434	£2,931	0.405	£7,238	£15,867

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 139 Base case PSA of the sequence model for patients under 80 years

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
A+C	£16,696	7.512	Baseline			
ASA	£16,836	7.540	£140	0.028	£5,002	Extended dominance
WFN	£17,057	7.804	£361	0.293	£1,234	£1,234
DBG	£18,820	8.030	£2,125	0.519	£4,097	£7,811

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 140 Base case PSA of the sequence model for patients over 80 years

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
A+C	£8,971	3.868	Baseline			
WFN	£9,092	4.000	£121	0.132	£916	£916
ASA	£9,355	3.899	£384	0.030	£12,597	Extended dominance
DBG	£10,041	4.080	£1,070	0.212	£5,048	£11,912

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Deterministic results are shown below in **Table 141** to **Table 144**.

Table 141 Base case deterministic results for DBG 150mg bid

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,080	7.082	Baseline			
WFN	£15,583	7.283	£503	0.202	£2,493	£2,493
A+C	£16,070	7.061	£990	-0.021	dominated	dominated
DBG 150mg bid	£16,923	7.497	£1,843	0.416	£4,434	£6,264

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 142 Base case deterministic results for DBG 110mg bid

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£15,080	7.082	Baseline			
WFN	£15,583	7.283	£503	0.202	£2,493	£2,493
A+C	£16,070	7.061	£990	-0.021	dominated	dominated
DBG 110mg bid	£18,385	7.433	£3,305	0.352	£9,397	£18,691

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 143 Base case deterministic results for sequence model (<80 years)

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
ASA	£16,732	7.590	Baseline			
WFN	£17,083	7.816	£352	0.226	£1,556	£1,556
A+C	£17,574	7.559	£842	-0.031	dominated	dominated
DBG	£18,856	8.058	£2,125	0.468	£4,536	£7,314

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Table 144 Base case deterministic results for sequence model (≥80 years)

Treatment	Cost	QALY	Inc. Cost	Inc. QALY	ICER vs baseline	Incremental analysis
WFN	£9,098	4.006	Baseline			
ASA	£9,227	3.922	£129	-0.083	dominated	dominated
A+C	£9,479	3.890	£381	-0.115	dominated	dominated
DBG	£9,929	4.111	£832	0.106	£7,873	£7,873

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin

Expanding these results **Table 145** presents the pairwise comparsons with DBG in each analysis.

Table 145 Pair wise comparisons for DBG from the deterministic and probabilistic model

Intervention	Comparator	Analysis	Inc. Cost	Inc. QALY	ICER
DBG 150mg bid	ASA	PSA	£1,813	0.430	£4,211
		Det	£1,843	0.416	£4,434
	WFN	PSA	£1,526	0.192	£7,940
		Det	£1,340	0.214	£6,264
	A+C	PSA	£1,777	0.445	£3,995
		Det	£853	0.437	£1,954
DBG 110mg bid	ASA	PSA	£2,931	0.405	£7,238
		Det	£3,305	0.352	£9,397
	WFN	PSA	£2,644	0.167	£15,867
		Det	£2,802	0.150	£18,691
	A+C	PSA	£2,895	0.419	£6,905
		Det	£2,315	0.373	£6,213
Seq <80	ASA	PSA	£1,984	0.491	£4,045
		Det	£2,125	0.468	£4,536
	WFN	PSA	£1,763	0.226	£7,811
		Det	£1,773	0.242	£7,314
	A+C	PSA	£2,125	0.519	£4,097
		Det	£1,283	0.499	£2,571
Seq > 80	ASA	PSA	£686	0.182	£3,779
		Det	£703	0.189	£3,719
	WFN	PSA	£949	0.080	£11,912
		Det	£832	0.106	£7,873
	A+C	PSA	£1,070	0.212	£5,048
		Det	£450	0.221	£2,038

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; Det, deterministic model; PSA, probabilistic sensitivity analysis; Seq, sequence model; WFN, warfarin

The ICERs indicate that both the evaluations for the proposed use of the two doses and the single dose analyses fall within the thresholds for cost-effectiveness and therefore represent good value-for-money. The ICERs for patients receiving the 150mg bid dose are lower reflecting the significant reduction in IS and the substantial saving that can be made through the reduction in long term disability. The 110mg bid dose had similar IS efficacy to WFN but a better safety profile. Whilst the relative difference in HS and ICH is large, there are relatively few of these events compared to IS. The results of the deterministic and

probabilistic analyses are consistent in all scenarios except for the analysis examining the subgroup aged 80 years and above. This variation is not unexpected given the lower precision in the clinical parameters and the shorter duration of the analysis.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Results from the deterministic sensitivity analyses outlined in section 6.6.2 are shown in **Table 146**. The ICERs from the basecase are provided in the table for comparison.

Table 146 Results from the univariate sensitivity analysis outlined in section 6.6.2.

No	Name	DBG 150mg bid			DBG 110mg bid			Seq <80			Seq >80		
	Comparator	**WFN**	**ASA**	**A+C**	**WFN**	**ASA**	**A+C**	**WFN**	**ASA**	**A+C**	**WFN**	**ASA**	**A+C**
	Base case	**£6,264**	**£4,434**	**£1,954**	**£18,691**	**£9,397**	**£6,213**	**£7,314**	**£4,536**	**£2,571**	**£7,873**	**£3,719**	**£2,038**
16	Decrease average age	£4,852	£3,573	£1,197	£15,795	£8,363	£5,285	£5,955	£4,060	£2,032	£8,699	£4,172	£2,570
17	Increase average age	£8,281	£8,985	£5,229	£16,891	£14,134	£9,420	£8,675	£3,994	£2,372	£10,352	£6,744	£3,989
18	0% male	£5,375	£3,648	£1,298	£17,404	£8,488	£5,478	£6,481	£3,655	£1,884	£7,316	£3,045	£1,588
19	100% male	£6,760	£4,876	£2,318	£19,430	£9,920	£6,632	£7,393	£5,004	£2,935	£8,282	£4,218	£2,369
20	Baseline $CHADS_2 = 1$	£6,770	£7,785	£4,117	£12,763	£11,824	£7,478	£6,912	£6,207	£3,470	£4,409	£11,623	£5,410
21	Baseline $CHADS_2 = 2$	£6,097	£3,714	£1,258	£18,250	£8,320	£5,195	£7,261	£3,972	£2,072	£6,231	£4,072	£1,852
22	Baseline $CHADS_2 = 3$	£5,959	£3,364	£1,173	£23,155	£8,704	£5,754	£7,362	£3,576	£1,962	£9,255	£1,157	£245
23	Baseline $CHADS_2 = 4$	£6,224	£2,970	£1,513	£37,652	£8,991	£7,311	£9,144	£4,004	£2,973	£11,666	£4,352	£3,465
24	Baseline $CHADS_2 = 5$	£5,125	£2,023	£695	£61,552	£8,451	£6,689	£8,094	£2,837	£1,921	£21,129	£1,877	£2,507
25	Low previous stroke history	£5,740	£3,602	£1,097	£18,277	£8,405	£5,166	£6,753	£3,700	£1,724	£6,264	£4,567	£2,068
26	High previous stroke history	£7,693	£7,007	£4,735	£19,957	£12,674	£9,873	£8,733	£6,878	£5,017	£8,606	£8,935	£6,303
25*	Utility Set 1	£6,593	£4,991	£2,232	£19,551	£10,682	£7,181	£7,748	£5,095	£2,920	£8,617	£4,351	£2,392
26*	Utility Set 2	£6,854	£4,696	£2,039	£19,010	£9,597	£6,252	£7,848	£4,788	£2,670	£7,942	£3,815	£2,036
27*	Utility Set 3	£6,335	£4,597	£2,046	£19,273	£9,871	£6,598	£7,402	£4,695	£2,682	£7,622	£3,826	£2,125
30	Stroke/ICH acute cost +50%	£4,853	£2,812	£253	£18,016	£8,050	£4,758	£6,116	£2,978	£1,031	£6,635	£1,442	£143
31	Stroke/ICH acute cost -50%	£7,675	£6,056	£3,655	£19,366	£10,744	£7,668	£8,512	£6,095	£4,110	£9,111	£5,997	£3,934
32	Fatal/non-fatal SE cost +50%	£6,258	£4,416	£1,923	£18,683	£9,376	£6,177	£7,307	£4,518	£2,540	£7,866	£3,687	£1,982
33	Fatal/non-fatal SE cost -50%	£6,270	£4,452	£1,985	£18,699	£9,418	£6,249	£7,320	£4,555	£2,601	£7,879	£3,752	£2,095
34	Minior bleed cost -100%	£6,298	£4,363	£1,998	£18,809	£9,343	£6,292	£7,359	£4,473	£2,615	£7,918	£3,639	£2,108
35	AMI acute cost +100%	£6,453	£4,403	£1,914	£18,966	£9,363	£6,169	£7,521	£4,518	£2,546	£8,263	£3,730	£2,037
36	AMI acute cost -100%	£6,075	£4,465	£1,994	£18,416	£9,431	£6,257	£7,107	£4,554	£2,595	£7,482	£3,709	£2,040
37	ECH acute cost +100%	£6,387	£4,493	£1,964	£18,560	£9,336	£6,102	£7,455	£4,618	£2,604	£8,823	£4,213	£2,407
38	ECH acute cost -100%	£6,141	£4,375	£1,944	£18,822	£9,458	£6,324	£7,173	£4,455	£2,537	£6,922	£3,226	£1,670
39*	Increased dyspepsia cost	£6,662	£4,639	£2,149	£19,275	£9,646	£6,448	£7,705	£4,739	£2,760	£8,245	£3,927	£2,216
40	Disability costs +50%	£3,095	£1,093	dominant	£17,377	£6,815	£3,310	£4,514	£1,280	dominant	£5,583	£203	dominant
41	Disability costs -50%	£9,433	£7,775	£5,533	£20,005	£11,979	£9,116	£10,113	£7,792	£5,856	£10,163	£7,236	£4,995

42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45	DBG vs WFN IS LCI	£4,250	£3,477	£1,260	£10,573	£6,648	£4,061	£4,229	£3,110	£1,466	£3,344	£1,628	£498
46	DBG vs WFN IS UCI	£10,152	£5,896	£2,997	£47,342	£14,378	£10,011	£17,100	£7,496	£4,793	£46,509	£10,680	£6,545
47	DBG vs WFN SE LCI	£6,065	£4,339	£1,874	£18,180	£9,234	£6,077	£7,056	£4,418	£2,469	£7,538	£3,564	£1,916
48	DBG vs WFN SE UCI	£6,658	£4,619	£2,111	£19,737	£9,722	£6,482	£8,031	£4,859	£2,845	£9,297	£4,360	£2,536
49	DBG vs WFN TIA LCI	£5,607	£4,115	£1,680	£17,363	£8,958	£5,843	£6,460	£4,133	£2,222	£6,961	£3,280	£1,688
50	DBG vs WFN TIA UCI	£7,210	£4,880	£2,337	£20,638	£10,010	£6,729	£8,704	£5,167	£3,114	£9,825	£4,618	£2,747
51	DBG vs WFN ICH LCI	£4,654	£3,686	£1,423	£15,373	£8,463	£5,525	£5,736	£3,860	£2,062	£6,066	£2,963	£1,495
52	UDBG vs WFN ICH CI	£10,234	£5,904	£2,986	£28,259	£11,406	£7,677	£12,531	£6,287	£3,868	£18,967	£6,981	£4,255
53	DBG vs WFN HS LCI	£5,446	£4,067	£1,695	£15,995	£8,652	£5,664	£6,296	£4,110	£2,250	£6,314	£3,072	£1,573
54	DBG vs WFN HS UCI	£8,233	£5,219	£2,506	£25,686	£10,941	£7,338	£10,936	£5,819	£3,525	£17,811	£6,725	£4,089
55	DBG vs WFN ECH LCI	£5,575	£4,148	£1,791	£16,702	£8,925	£5,905	£6,195	£4,097	£2,272	£5,931	£2,960	£1,524
56	DBG vs WFN ECH UCI	£7,196	£4,784	£2,152	£21,780	£10,029	£6,622	£9,097	£5,145	£2,980	£11,888	£4,986	£2,864
57	DBG vs WFN AMI LCI	£6,004	£4,311	£1,851	£18,096	£9,211	£6,059	£6,942	£4,366	£2,426	£7,156	£3,378	£1,768
58	DBG vs WFN AMI UCI	£6,622	£4,601	£2,093	£19,558	£9,662	£6,430	£7,934	£4,815	£2,806	£9,323	£4,385	£2,561
57	Increased RR for ASA,A+C, NT	£6,324	£3,832	£1,479	£18,744	£8,430	£5,447	£7,356	£3,939	£2,077	£8,039	£3,001	£1,483
59	0% of ECH GI	£6,303	£4,905	£2,474	£18,756	£10,137	£7,034	£7,393	£4,587	£2,616	£8,024	£3,817	£2,117
60	100% of ECH GI	£6,246	£4,407	£1,932	£18,667	£9,368	£6,188	£7,285	£4,502	£2,543	£7,719	£3,614	£1,954
61	0% disc. following ECH	£6,114	£4,478	£2,011	£19,319	£9,708	£6,431	£7,134	£4,392	£2,491	£7,196	£3,625	£2,034
62	100% disc. following ECH	£6,418	£4,408	£1,909	£18,146	£9,143	£6,027	£7,418	£4,665	£2,638	£8,573	£3,811	£2,041
63	2nd line switch rate +10%	£6,239	£4,189	£1,955	£18,768	£8,983	£6,247	£7,311	£4,425	£2,582	£7,785	£3,410	£1,955
64	2nd line switch rate -10%	£6,278	£4,575	£1,953	£18,646	£9,642	£6,191	£7,317	£4,651	£2,559	£7,962	£4,053	£2,125
65	Mortality risks = 0	£6,220	£4,419	£1,937	£18,659	£9,411	£6,220	£7,276	£4,521	£2,552	£7,745	£3,699	£2,029
66	Withdrawals = 0	£5,582	£6,416	£2,073	£16,553	£13,655	£6,452	£6,692	£6,494	£2,680	£6,828	£5,610	£2,332
67	Disbility - more severe	£5,668	£1,658	£3,962	£17,620	£5,513	£8,567	£6,653	£4,098	£2,245	£7,265	£3,333	£1,722

Abbreviations: A+C, aspirin plus clopidogrel; AMI, acute myocardial infarction; ASA, aspirin; DBG, dabigatran etexilate; Det, deterministic model; ECH, extracranial haemorrhage; GI, gastrointestinal; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; LCI, lower confidence interval; NT, no treatmentl; PSA, probabilistic sensitivity analysis; RR, relative risk; SE, systemic embolism; Seq, sequence model; TIA, transient ischaemic attack; UCI, upper confidence interval; WFN, warfarin

*Can be considered as plausible scenario

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves

The probability of cost effectiveness, at different willingness to pay thresholds for the pairwise comparisons, is shown in **Table 147.**

Table 147 Probability off cost-effectiveness at different willingness to pay thresholds

Intervention	Comparator	£20,000 per QALY	£30,000 per QALY
DBG 150mg bid	ASA	100%	100%
	WFN	93%	98%
	A+C	100%	100%
DBG 110mg bid	ASA	97%	99%
	WFN	67%	84%
	A+C	98%	100%
Seq <80	ASA	100%	100%
	WFN	96%	99%
	A+C	100%	100%
Seq >80	ASA	92%	95%
	WFN	69%	77%
	A+C	92%	96%

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; Seq, sequence model; WFN, warfarin

The various probabilities that DBG is cost-effective at a willingness to pay threshold of £20,000 per QALY gained are impressive. In the primary comparison versus WFN, these probabilities range from a minimum of 67% (DBG 110mg bid) to 96% (sequence <80 years). When the 150mg bid dose is included in the analysis, the probability of cost-effectiveness is markedly increased. For the secondary comparisons versus aspirin and aspirin plus clopidogrel, the cost-effectiveness of DBG is close to certain.

The corresponding cost-effectiveness planes and acceptability curves are in **Figure 32** to **Figure 43**.

Figure 32 Cost-effectiveness plane/acceptability curve for DBG 150mg bid vs WFN

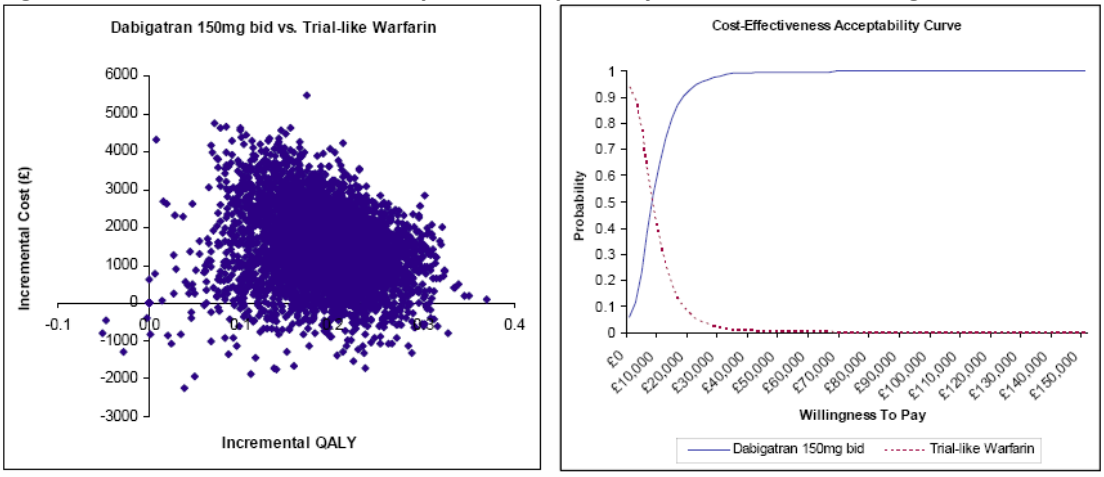


Figure 33 Cost-effectiveness plane/acceptability curve for DBG 150mg bid vs ASA

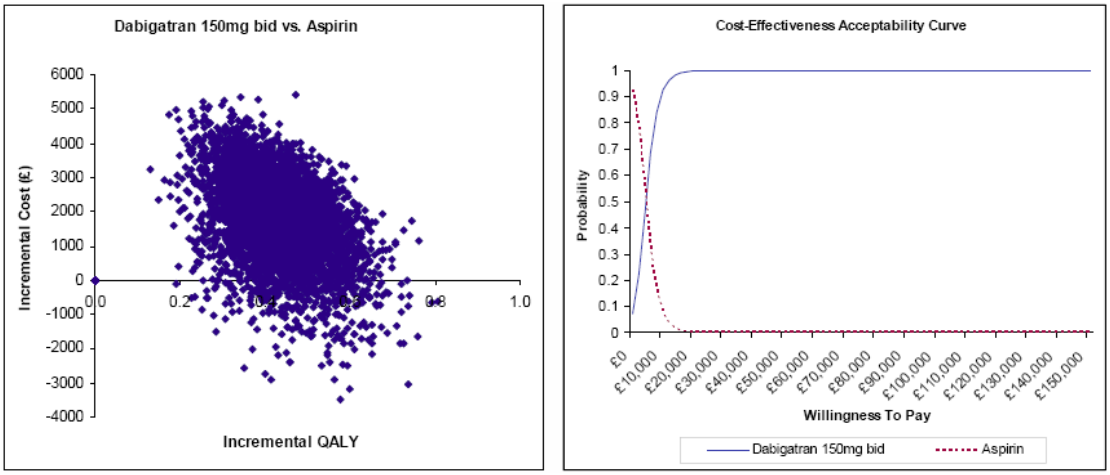


Figure 34 Cost-effectiveness plane/acceptability curve for DBG 150mg bid vs A+C

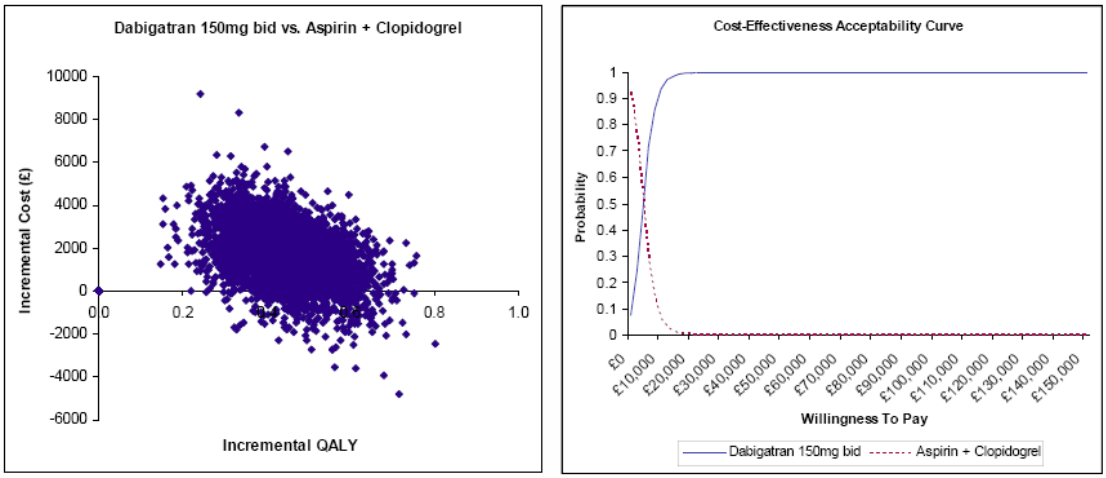


Figure 35 Cost-effectiveness plane/acceptability curve for DBG 110mg bid vs WFN

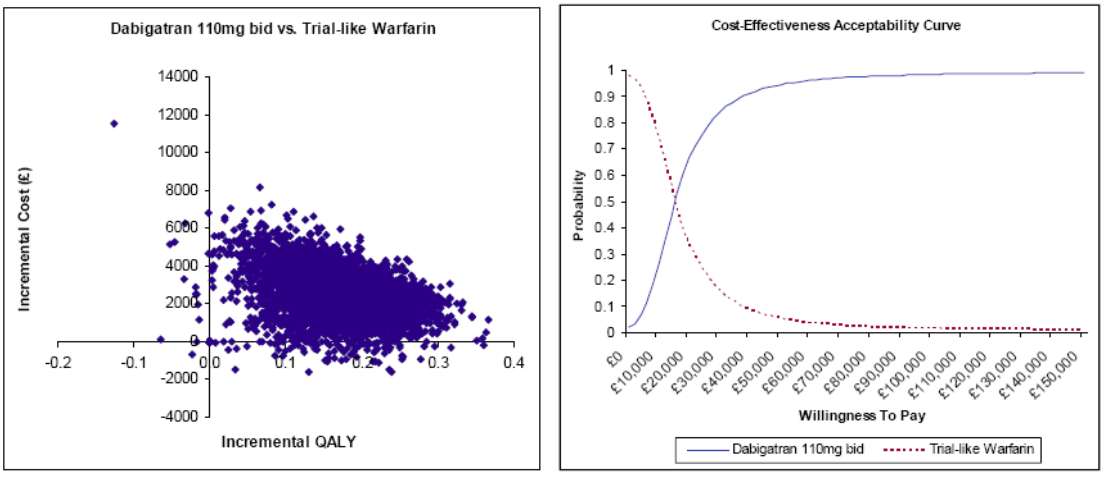
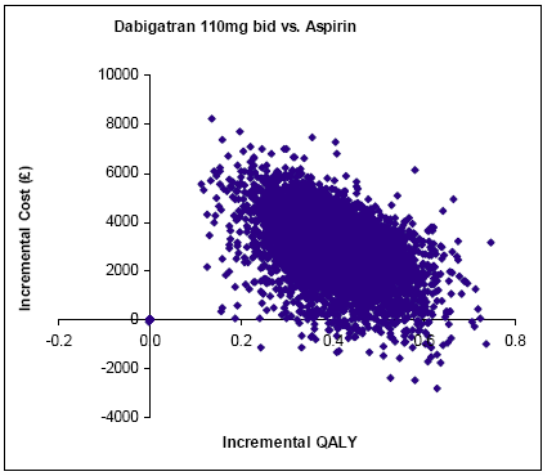


Figure 36 Cost-effectiveness plane/acceptability curve for DBG 110mg bid vs ASA



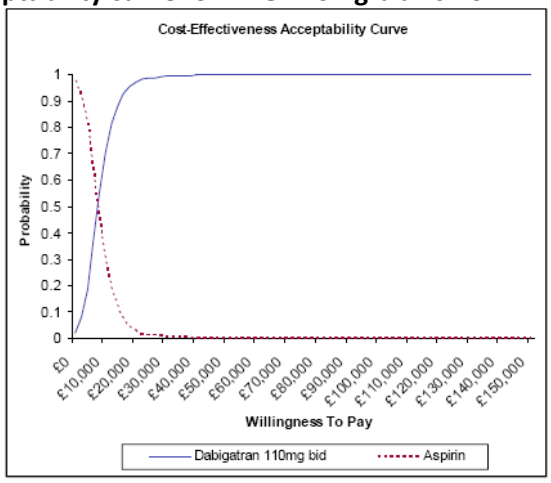
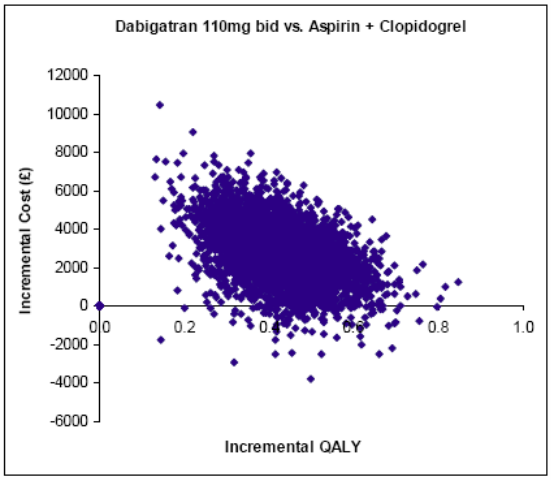


Figure 37 Cost-effectiveness plane/acceptability curve for DBG 110mg bid vs A+C



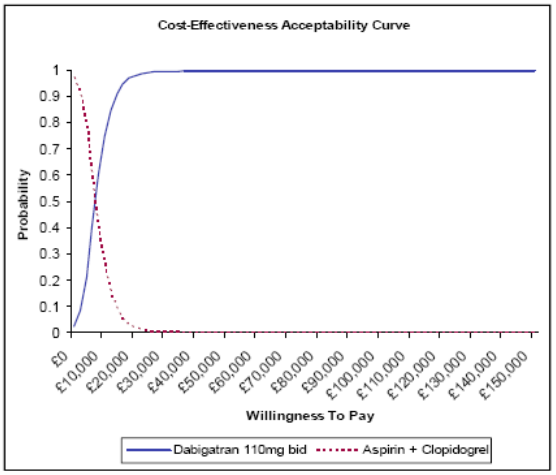
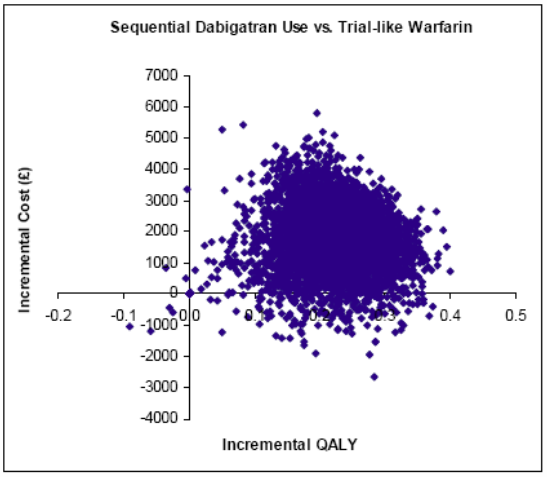


Figure 38 Cost-Effectiveness plane/acceptability curve for DBG Seq <80 vs WFN



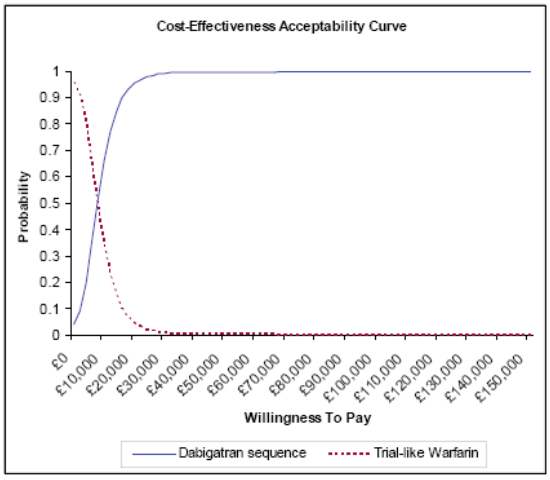


Figure 39 Cost-effectiveness plane/acceptability curve for DBG Seq <80 vs ASA

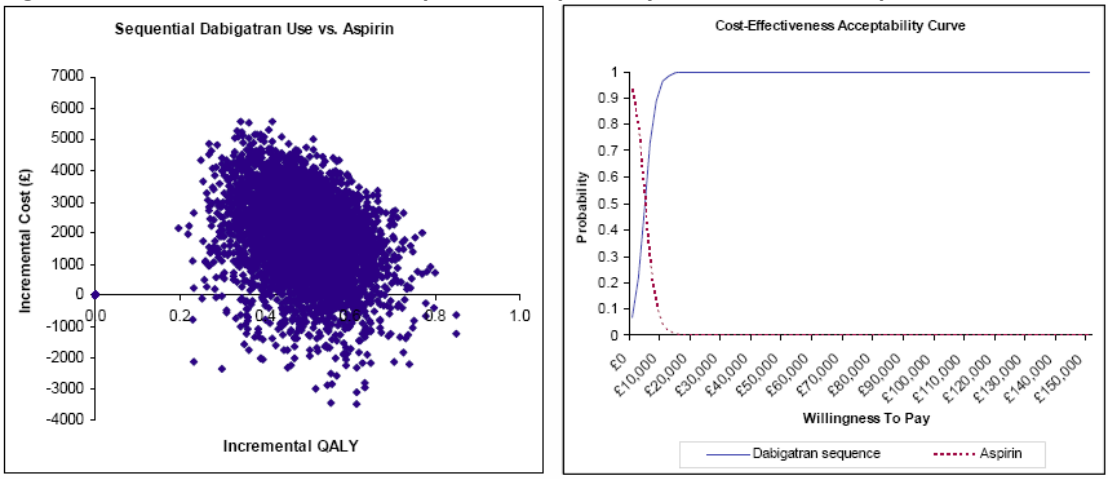


Figure 40 Cost-effectiveness plane/acceptability curve for DBG Seq <80 vs A+C

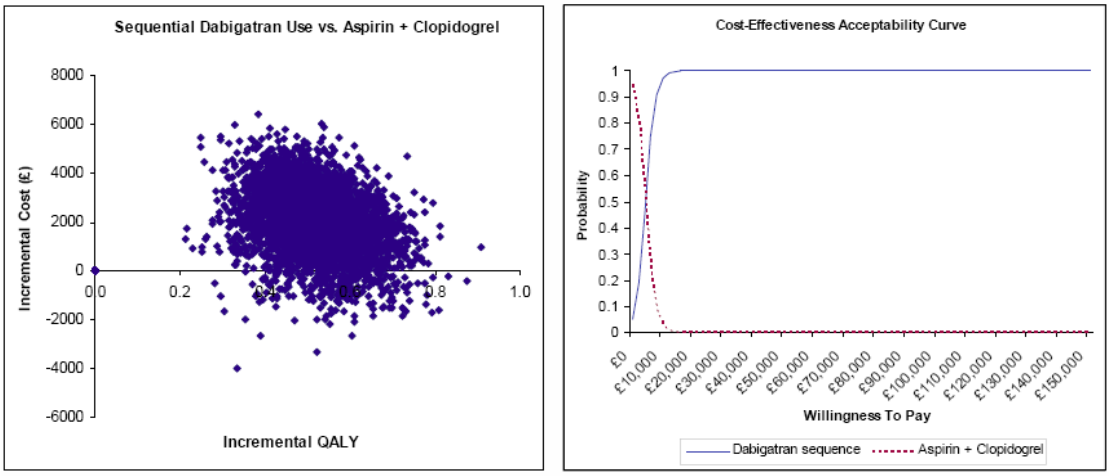


Figure 41 Cost-Effectiveness plane/acceptability curve for DBG Seq >80 vs WFN

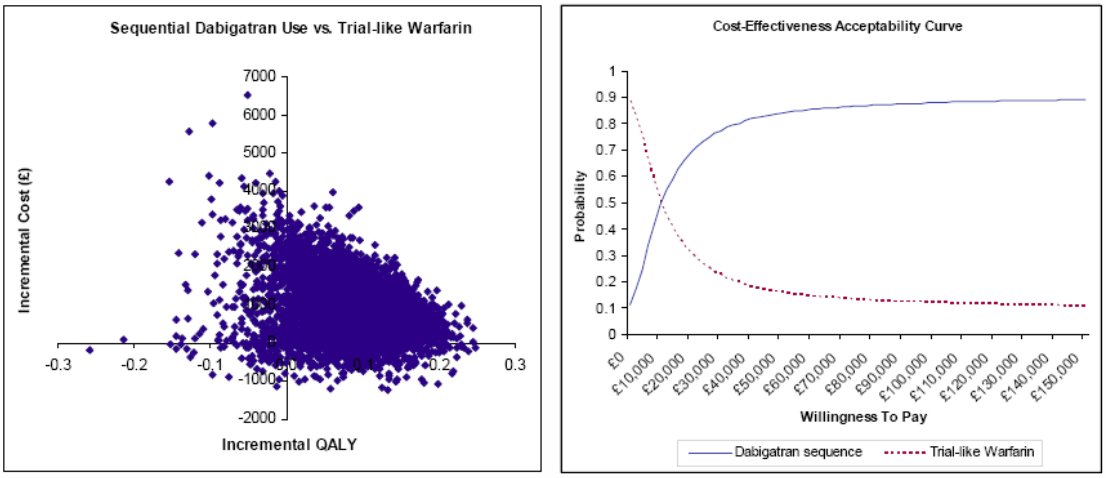


Figure 42 Cost-effectiveness plane/acceptability curve for DBG Seq >80 vs ASA

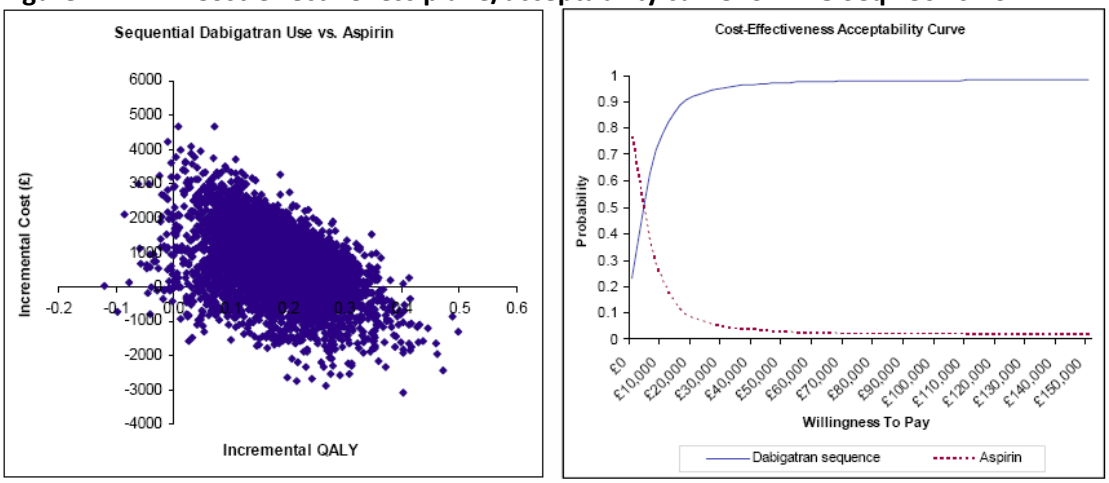
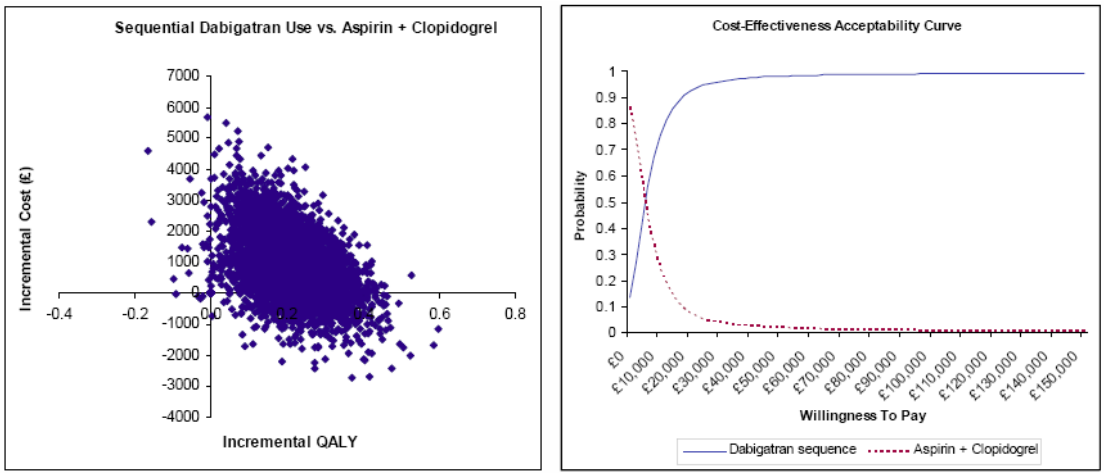


Figure 43 Cost-effectiveness plane/acceptability curve for DBG Seq >80 vs A+C



These graphics show that the vast majority of patients benefit from using DBG as a high proportion of iterations of the model result in a positive incremental QALYs. The DBG sequence (≥80 years) evaluation has the lowest proportion of positive incremental QALYs which is likely to be due to the greater uncertainty discussed above. However, this is still high, with 80% of the iterations resulting in a positive incremental ICER. In addition to the benefits shown in terms of QALYs, a substantial proportion of iterations result in a negative incremental cost.

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Results from the structural sensitivity analyses described in section 6.6.1 are shown in **Table 148**. The base case results are also shown in the table for comparison. Analyses 1, 2, 4 and 5 are only applicable to comparisons with WFN, whereas analysis 3 is applicable to all three comparators simultaneously.

Table 148 Results from the structual sensitivity analysis

No	Name	DBG 150mg bid			DBG 110mg bid			Seq <80			Seq >80		
	Comparator	**WFN**	**ASA**	**A+C**	**WFN**	**ASA**	**A+C**	**WFN**	**ASA**	**A+C**	**WFN**	**ASA**	**A+C**
	Base case	**£6,264**	**£4,434**	**£1,954**	**£18,691**	**£9,397**	**£6,213**	**£7,314**	**£4,536**	**£2,571**	**£7,873**	**£3,719**	**£2,038**
1	Real-world warfarin (WWA)	£5,872	-	-	£17,592	-	-	£6,684			£7,152	-	-
2	Real-world warfarin (TWR)	£5,327	-	-	£16,031	-	-	£6,209			£6,548	-	-
3	Real-world presrcibing	£3,925			£9,576			£4,167			£3,274		
4	INR monitoring cost +25%	£2,997	-	-	£14,029	-	-	£4,165			£4,531	-	-
5	INR monitoring cost -25%	£9,531	-	-	£23,353	-	-	£10,463	-	-	£11,214	-	-
6	Time horizon = 2 years	£75,601	£81,020	£51,900	£108,736	£99,427	£63,687	£75,891	£87,353	£58,336	£23,403	£25,767	£15,720
7	Time horizon = 10 years	£12,696	£10,198	£5,967	£31,318	£17,991	£12,478	£14,778	£13,892	£9,339	£8,700	£4,476	£2,454
8	Time horizon = 15 years	£8,111	£5,839	£2,816	£23,257	£11,861	£8,010	£9,773	£7,242	£4,378	£7,940	£3,759	£2,057
9	Vary effectiveness -10%[a]	-	-	-	-	-	-	£10,139	£7,150	£4,489	-	-	-
10	Vary effectiveness +10%[a]	-	-	-	-	-	-	£6,813	£5,495	£3,321	-	-	-
11	MTC Data	£6,874	£4,698	£2,149	£20,829	£9,963	£6,647	£7,641	£4,664	£2,664	£7,895	£3,912	£2,267
12	Health discount rate = 0%	£4,137	£2,920	£1,289	£12,396	£6,196	£4,106	£4,738	£2,873	£1,624	£9,362	£3,584	£1,917
13	Health discount rate = 6%	£8,146	£5,787	£2,544	£24,220	£12,254	£8,077	£9,622	£6,064	£3,437	£7,273	£3,800	£2,113
14	Cost discount rate = 0%	£7,364	£4,858	£1,644	£23,913	£11,455	£7,319	£8,940	£4,701	£2,323	£7,917	£3,265	£1,554
15	Cost discount rate = 6%	£5,705	£4,205	£2,086	£16,103	£8,364	£5,647	£6,503	£4,387	£2,644	£7,788	£3,932	£2,278

Abbreviations: A+C, aspirin plus clopidogrel; ASA, aspirin; DBG, dabigatran etexilate; INR, international normalised ratio; MTC, mixed treatment analysis; Seq, sequence model; TWR, time in range approach; WFN, warfarin; WWA, weighted warfarin approach.

a – this simulation had patients 78 years at baseline and the efficacy at 80 years was varied by +/-10%. The baseline ICERs for these comparisons are £8,294 vs WFN, £6,272 vs ASA and £3,874 vs A+C.

6.7.10 What were the main findings of each of the sensitivity analyses?

A number of real world examples were examined. As may be expected the real-world WFNanalyses (no. 1,2) were more cost-effective than the base case given that patients have poorer INR control. Similarly, the mixed comparison of real-world prescribing (no. 3) improved the cost-effectiveness.

The cost of INR monitoring is highly variable in clinical practice. Analysis 4 shows that if economies of scale in decommissioning INR monitoring can be achieved, the cost-effectiveness of DBG further improves. Even for exceptionally low cost (well-controlled) WFN patients (no. 5), DBG is cost-effective.

Analyses 9 and 10 attempted to provide an assessment of variation in efficacy over time beyond the course of the clinical trial. This limited analysis shows that as expected, decreases in efficacy lead to poorer cost effectveness, with the 10% decrease in efficacy leading to an approximate £1,000 to £2,000 increase in the ICER.

The MTC data (no. 11) presented an alternative analysis to the RE-LY trial. Reassuringly, the results are similar to the base case results.

Higer discount rates for health and lower rates for costs lead to a decreased ICER, with the converse leading to higher ICERs (no. 12-15). This is expected as health treatment with DBG leads to higher long-term health gains and lower long-term costs.

Increasing the management costs of dyspepsia has little effect on the ICER (no. 39). Also variation in the assumptions around utility (no. 25-27) had little effect on the ICERs.

There was no clear relationship between $CHADS_2$ and cost-effectiveness (no. 20-24) though patients on ASA or A+C tended to be less cost-effecticve in patients with $CHADS_2$=1 and more cost effective in patients with lower $CHADS_2$ on WFN. However, ICERs tended to be lower in populations with a low stroke history compared to populations with a high stroke history (no 25-26). The gender split (no. 18-19) had little impact on the ICERs although variation at baseline of age (no. 16-17) tended to result in better cost-effectiveness for patients treated younger. These analyses indicate that earlier treatment might be preferable, a finding found previously in cost-effectiveness analysis of anticoagulation treatment in elderly patients with AF [246].

Changes in the time horizon had a major effect on cost-effectiveness, which is expected as the key outcomes of stroke and ICH have costs and disabilities associated throughout the patient's lifetime. The effect is more pronounced in the simulations with the younger

baseline ages, as patients on DBG would be expected to live for longer and therefore accrue more benefits and fewer costs.

Sensitivity to cost was considered in analyses 30-38 and 40-44. Analyses 32-38 had little impact on the ICERs. ICERs were sensitive to changes in the cost of stroke (30-31), though less so in the simulations with the DBG 110mg bid dose vs WFN, as expected. Disability costs (40-41) consistently result in relatively large changes in the ICER compared to the other cost sensitivity analyses. [redacted]

Sensitivity to key clinical inputs was examined in analyses 45-58. The majority (47-50 and 55-58) had only little impact, with ICERs tending to be most sensitive to IS (no. 45-46). The ICERs for the simulations inviolving DBG 110mg bid and WFN also being sensitive to ICH and HS (no. 51-54). Reducing withdrawals to zero (no. 66) tended to reduce the ICER vs WFN thougb increased the ICER vs. ASA. Across the simulations, more severe post-event disability rates (no. 67) resulted in lower ICERs.

6.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the results are the parameters associated with long-term disability.

The key cost drivers are the DBG treatment costs, cost of INR monitoring, and the cost of disability follow-up care. The event costs are generally not key drivers in the model. Even though the event costs may be high, they a relatively low compared to a lifetime of care following a disabling event.

The key drivers in the clinical data are the rates of events that cause disabling events. For the simulations involving DBG 150mg bid this is the rate of IS, and for all scenarios the rates of HS/ICH. Also important are the relative disability levels following a disabling event and the rate of withdrawal from treatment.

6.8 Validation

Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The structure and data incorporated in the model was validated at several levels:

- Key opinion leaders reviewed and approved the model structure and data inputs as discussed above
- A modeller not involved in model construction reviewed and validated the mathematical relations

- A modeller not involved in model construction reviewed and validated the numerical inputs

In addition, the outputs of the model were validated for two key outcomes against published data. Specifically, the model predicted rates of overall mortality and IS rate.

In the single dose model, primary comparison, overall survival of patients ranged between 9.74 years (DBG 150mg bid) and 9.55 years (WFN). This survival time falls well below the average life expectancy of the average 71 year old in the general population (16 years for males and 18 years for females)[247]. This difference is in large part attributable to the difference in mortality from IS, which represents 16% of overall mortality in the model, but only 4% in the general population of 70 to 74 year olds. In contrast, the model predicted survival is considerably longer than that reported by Currie (2006)[25] for a an AF patient population in the UK. This studyreport mean survival of 4.3 years for WFN-treated patients with a previous in-patient hospital diagnosis of AF, a somewhat more advanced state of disease progression than that in the RE-LY trial. That the model predicts survival levels between these two estimates seems intuitive and reasonable.

Validation of IS rates was facilitated by the identification of two reports with very similar patient populations to the RE-LY trial. In Rietbrock (2008)[248], IS rates were evaluated in an AF population based on a review of the UK General Practice Research Database. This study found a rate of IS of 3.2 events / 100 patient-years consistent with the rates predicted in the model (3.5 – 3.73 events / 100 patient-years for the example quoted above).

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Subgroup analysis was suggested in the scope for patients who had (not) been previously treated with WFN. Efficacy results from RE-LY for the VKA-naïve and VKA-experienced patients are in **Table 32** and **Table 33**, with safety data in **Table 61**. This data is discussed in section 5.5.3. and 5.9.2. No significant differences or interaction was observed between the VKA-naïve and VKA-experienced groups for either DBG dose, therefore it was unnecessary to perform additional economic analyses for these subgroups.

Subgroup analysis was undertaken by considering treatment stratified by dose and age. Efficacy data from RE-LY for these subgroups are in **Table 35** and **Table 36** and safety data are in **Table 63** and **Table 64**. These are proposed on the basis that they reflect the proposed licensed indication. This subgroup analysis is discussed extensively above and results are included in the base-case.

Therefore to avoid uncessary repetition, no further details of these subgroups are presented here in section 6.9.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

6.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Not applicable.

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

No, please see the response to Section 6.9.1.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

This is the first economic evaluation of DBG in this indication. Therefore there are no published studies with which to draw comparison.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes. The population from which the clinical data was drawn and for which the model was parameterised reflects the patient population in Section 4. In addition, the sequence model reflects the proposed licensed indication which also covers the patient population defined in Section 4.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the economic evaluation is data that underpins it from the RE-LY trial. RE-LY provides a wealth of robust clinical data for the various modelled outcomes for the principle comparison of interest.

The model structure was developed in conjunction with leading clinicians and published in a leading peer-reviewed cardiovascular journal[111], with input on the UK version provided by one of the UK's leading caridologists. This inspires confidence that the model adheres to the clinical course of the disease and is reflective of current clinical practice.

Extensive systematic reviews were undertaken to parameterise the model. The first of these was for utilities values, with the search far exceeding the basic requirements specified by NICE. This review identified a number of studies suitable for use in the model. Using a number of these in the sensitivity showed that the model was robust when alternative plausible utility dataset were included in the model.

Three systematic reviews were undertaken to parameterise the costs. The first for INR monitoring costs only found one suitable study; however, it was directly applicable for the patient population in the model. A systematic review of costs for major bleeds and stroke failed to produce any appropriate studies. However to address this issue the sponsor commissioned an independent study on the cost of stroke, specifically for patients with AF. This had the advantage of being designed specifically for use in this submission and therefore was able to provide excellent data for use in the model.

Weaknesses in the model include a number of parameters where appropriate data was difficult to find, particularly those events that are relatively rare in practice. These include the HS/ICH where an extensive systematic review failed to find any appropriate data. The

OXVASC study also failed to find sufficiently large numbers of appropriate patients to produce robust estimates for costs. However, extensive sensitivity analysis has been undertaken to assess the impact of these uncertainties, and in order to avoid bias in the results, conservative assumptions have been made.

The RE-LY clinical trial provided robust data over two years. However, the data is extrapolated over the patients' lifetime, and beyond the course of the clinical trial. The Kaplan-Meier curves indicate a sustained and potentially increasing relative risk over the course of the trial which provides confidence that the effect may be sustained beyond the course of the clinical trial. In addition, a conservative approach was taken in the implementation of the data into the model, by using the efficacy data from the ITT population rather than the per protocol population. Sensitivity analyses were undertaken to show that variations in the long-term effective would lower the ICERs, though they were likely to remain below the £20,000-£30,000 willingness to pay threshold.

This economic model represents an advance in the approach to comparing WFN to other treatments by allowing the examination of WFN use in scenarios reflective of real-world clinical conditions. The model tracks patients by disability level following stroke or ICH, which was important given the large costs and health impacts of disability (estimated to account for about 75% of total costs[111]). It also considers the discontinuation of anticoagulation, which is common in clinical care, and has important consequences.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The RELY-ABLE study [2] is an ongoing extension of the RE-LY trial. The purpose of RELY-ABLE is to assess the long-term safety (major bleeding is the primary outcome) of DBG 110mg bid and 150mg bid in 6,200 patients who completed the RE-LY trial. The study is due to complete in July 2011. This is likely to provide further evidence of the longer-term effect of the two doses of DBG and would prove useful in this economic model to test the assumption of continued treatment effect.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

7.3 What assumption(s) were made about market share (when relevant)?

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

7.6 Were there any estimates of resource savings? If so, what were they?

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The responses to sections 7.1 to 7.8 are consolidated below.

The estimated epidemiology of AF and treatment rates with current modalities in England and Wales for the years 2011 to 2015 is presented in **Table 149**.

The prevalence of AF is derived from QOF data which estimates the number of people registered with a GP in England and Wales with a confirmed diagnosis of AF as 784,471 (a weighted average prevalence rate of 1.37%; 1.35% in England; 1.65% in Wales)[10, 11]. The annual population growth rate in England and Wales is estimated to be 0.66% per year

based in current trends from national statistics[249]. This results in the estimated total registered population rising from 55.534mio in 2011 to 57.014mio in 2015.

It is estimated that approximately 2.7% of AF patients die each year[250] and that the incidence of AF (as estimated in Renfrew-Paisley project) is approximately 0.05% per year[20]. Applying these two values permits calculation of net inflow, which results in the estimated England and Wales AF population rising from just over 763,000 in 2011, to approximately 792,500 in 2015.

The percentage of patients with AF eligible for antithrombotic therapy is estimated at approximately 90%[20], with 53.3% receiving WFN and the remainder assumed to receive aspirin[109]. A+C is not considered in this analysis as the timeframe for its marketing authorisation in this indication is unknown.

Table 149 Epidemiology of AF in England and Wales (2011-2015)

	Rate	2009	2010	2011	2012	2013	2014	2015	Source
E+W population		54,809,568	55,170,568	55,534,420	55,900,672	56,269,339	56,640,438	57,013,984	[249]
Prevalence of AF	1.37%	748,303							[10, 11]
Mortality	2.70%		20,204	20,403	20,603	20,802	21,000	21,198	[250]
Incidence of AF	0.05%		27,585	27,767	27,950	28,135	28,320	28,507	[20]
Net AF patients			755,684	763,065	770,429	777,776	785,109	792,429	Calculated
Eligible AF patients	90.3%		682,138	688,801	695,448	702,080	708,700	715,307	[20]
Warfarin patients	53.3%		402,780	406,714	410,639	414,555	418,463	422,365	[109]
Aspirin patients	37.0%		279,359	282,087	284,810	287,526	290,237	292,943	Assumption

Abbreviations: AF, atrial fibrillation; E+W, England and Wales.

The estimated take-up of DBG (and substitution of current modalities) based on current expectations is presented in **Table 150**.

Table 150 Take-up of DBG and substitution of current therapy

	2011	2012	2013	2014	2015
Eligible AF patients	688,801	695,448	702,080	708,700	715,307
Estimated DBG take-up *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients receiving DBG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of DBG arrived from warfarin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of DBG arrived from aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Substituted warfarin patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Substituted aspirin patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AF, atrial fibrillation; DBG, dabigatran etexilate

* Based on current forecasting assumptions: 1) March 2011 launch; 2) Positive NICE gudiance; 3) Take-up is of eligible patients.

The daily and annual treatment costs for patients are shown in **Table 151**.

Table 151 Daily and annual treatment costs

Treatment	Daily cost	Annual cost
Dabigatran etexilate	£2.52	£919.80
Warfarin*	£1.18	£429.50
Aspirin	£0.09	£32.85

*Includes cost of INR monitoring.
Source: [21]

These can be used to calculate the annual treatment costs for the total number of patients on each of the therapies. These are shown in **Table 152** for the scenario with and without DBG, and total net treatment costs.

Table 152 Treatment costs with and without DBG from 2011 to 2015 (£'000s)

		2011	2012	2013	2014	2015
Without DBG	DBG	£0	£0	£0	£0	£0
	WFN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With DBG	DBG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WFN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net cost with DBG		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin.

These results indicate that the treatment costs for DBG will rise from [redacted] in 2011 to [redacted] in 2015, and as a result spending on WFN treatment will fall by [redacted] in 2011 and [redacted] by 2015 comapred to the status quo. Spending on aspirin further would be predicted to fall by [redacted] by 2015.

These costs do not include event costs and long-term disability costs prevented in patients receiving DBG. Whilst these differences are substantial, they cannot be calculated directly from the economic model for the purposes of the budget impact analysis. The reason for this is that each treatment arm includes patients that are withdrawn from treatment as well as those that are on treatment. Therefore each arm does not contain only costs and outcomes from a single line of therapy. In addition, the economic model considered a cohort of patients over a predefined time horizon, and is not a dynamic model. This would be required for this analysis, as patients begin treatment at different times.

However, the annual event costs can be estimated for each treatment by setting the time horizon to one year and withdrawal rates to zero. This rate should be a good approximation for up to the first five years on treatment, and any effect of any age-dependant risk factors can be minimised using the sequence models with the costs weighted by the <80:80+ split from the RE-LY trial (where 83% of patients were aged less than 80 years[80]). Thereafter, the only time related variables will be all-cause mortality (which is already accounted for in

changes in total AF patient population in **Table 150**) and the effects of withdrawal due to events.

Table 153 Annual event costs per patient by treatment and age-group

	Patients less than 80 yrs	Patients more than 80 yrs	Weighted (83%:17%)
DBG	£157	£246	£172
WFN	£233	£319	£248
ASA	£283	£408	£304

Abbreviations: ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin.

The event costs per patient by treatment and age-group are shown in **Table 153**. Using the patient numbers in **Table 150** and the weighted costs in **Table 153**, the costs associated with events are shown in **Table 154**.

Table 154 Event costs with and without DBG from 2011 to 2015 (£'000s)

		2011	2012	2013	2014	2015
Without DBG	**DBG**	£0	£0	£0	£0	£0
	WFN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With DBG	**DBG**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WFN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net cost with DBG		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin.

The results in **Table 154** show a net decrease in event costs as expected due the net reduction in events. This net decrease increases over time as more patients are treated with DBG, from £[redacted] in 2011 rising to £[redacted] in savings from acute events alone.

Estimating follow-up costs are more problematic as disability, and therefore follow-up costs, accrue over time. This means that patients who have a disabling event in year 1 will still be incurring costs in year 5. Using year 1 follow-up costs for subsequent years will underestimate any long-term saving through stroke prevention. As a simplifying assumption, the model was run for five years (with withdrawal rates set to zero) and the average follow-up costs used. This will overestimate the follow-up costs earlier in the analysis, and under estimate later in the analysis. Overall, this simplification is conservative with respect to the saving through stroke prevention for patients on DBG, as there are higher numbers of patients on DBG in the later years. These costs are shown in **Table 155** along with the weighted average based on the <80:80+ split from the RE-LY trial described above.

Table 155 Average follow-up costs over five years per patient

	Patients less than 80 yrs	Patients more than 80 yrs	Weighted (83%:17%)
DBG	£352	£332	£348
WFN	£418	£411	£417
ASA	£460	£489	£465

Abbreviations: ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin.

It should be noted that the follow-up costs for patients on DBG and WFN are lower for the over 80s than the under 80s. This is likely to be as a result of significant mortality in the older group over the five years. The follow-up costs shown in **Table 155** were used with the patients numbers in **Table 150** to estimate the follow-up are shown in **Table 156**.

Table 156 Follow-up costs with and without DBG from 2011 to 2015 (£'000s)

		2011	2012	2013	2014	2015
Without DBG	DBG	£0	£0	£0	£0	£0
	WFN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With DBG	DBG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	WFN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total net cost with DBG		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASA, aspirin; DBG, dabigatran etexilate; WFN, warfarin.

As with the event costs, the net saving in follow-up costs increase as uptake of DBG increases. The total net costs are shown in **Table 157**. It is estimated that the introduction of DBG will lead to direct savings in follow-up costs of approximately £[redacted] in 2011, rising to almost £[redacted] in 2015.

Table 157 Disaggregated and total net costs associated with DBG by year (£'000s)

	2011	2012	2013	2014	2015
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Net Cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DBG, dabigatran etexilate.

The net budget impact to the NHS following the introduction of DBG in Engalnd and Wales is estimated to be just over [redacted] in 2011, rising to just over [redacted] in 2015. Due to savings from acute events and follow-up costs, the overall budget impact is [redacted] of the predicted spend on DBG medication depending on the year. Further, as noted above, the savings are likely to be underestimated.

These results re-emphasise the points made earlier in the submission related to the long-term benefits that can be reaped through early investment in DBG. A significant proportion

of the DBG medication spend is predicted to be offset by savings made in acute event costs and disability follow-up costs (over [redacted] by 2015). The simplifying assumption in the analysis means that savings made through disability prevention would be expected to increase, per patient, year-on-year.

Whilst the annual savings that could be made from reduced requirement of INR monitoring are substantial (estimated as [redacted] by 2015), this analysis assumes that anticoagulation services have the flexibility to release the economic cost associated with INR monitoring in substituted patients. In practice, the realisation of efficiencies will not be immediate in all services and the emphasis will be on local health economies to examine their own AF clinical pathway and instigate potential service redesign.

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]					

[redacted]

8 References

Reference List

1. Boehringer Ingelheim International GmbH. RE-LY QC Information Amendment. 14-4-2010.

Ref Type: Generic

2. ClinicalTrials.gov. RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed the RE-LY Trial (NCT00808067). 17-8-2010.

Ref Type: Online Source

3. Boehringer Ingelheim. FDA Committee Unanimously Recommends Approval of Dabigatran Etexilate for Stroke Prevention in Atrial Fibrillation. 20-9-2010.

Ref Type: Online Source

4. The National Collaborating Centre for Chronic Conditions. Atrial Fibrillation: National clinical guideline for management in primary and secondary care. Royal College of Physicians, 2006

5. Ruigomez A, Johansson S, Wallander MA, Garcia Rodriguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. BMC Cardiovasc Disord 2005;5:20.

6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983-988.

7. Singer DE, Albers GW, Dalen JE et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):546S-592S.

8. Carroll K, Majeed A. Trends in mortality and hospital admissions associated with atrial fibrillation in England and Wales. Health Stat Q 2001;9(Spring):37-43.

9. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke 1996;27(10):1765-1769.

10. The Information Centre. Quality and Outcomes Framework (QOF) for April 2008 - March 2009, England. 2009. 26-3-2010.

Ref Type: Online Source

11. Statswales. "Patients recorded on QOF disease registers". Atrial Fibrillation, 2009. 2009. 26-3-0010.

Ref Type: Online Source

12. Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of

Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114(7):e257-e354.

13. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154(13):1449-1457.

14. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Guidelines for the management of atrial fibrillation. Eur Heart J 2010.

15. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Stroke 1999;30(6):1223-1229.

16. van Walraven C, Hart RG, Wells GA et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. Arch Intern Med 2003;163(8):936-943.

17. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285(22):2864-2870.

18. Wang TJ, Massaro JM, Levy D et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290(8):1049-1056.

19. National Institute for Health and Clinical Excellence. Atrial Fibrillation. The management of atrial fibrillation. Clinical Guidleine 36. 2006

20. National Institute for Health and Clinical Excellence. Atrial Fibrillation. The management of atrial fibrillation. Costing report. Implementing NICE guidance in England. 2006

21. MIMS Online. Drug costs from MIMS. 2010.

Ref Type: Online Source

22. British National Formulary. BNF 57. Coumarins: interactions. 2010. 1-4-2009.

Ref Type: Online Source

23. Holbrook AM, Pereira JA, Labiris R et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005;165(10):1095-1106.

24. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart 2005;91(4):472-477.

25. Currie CJ, Jones M, Goodfellow J et al. Evaluation of survival and ischaemic and thromboembolic event rates in patients with non-valvar atrial fibrillation in the general population when treated and untreated with warfarin. Heart 2006;92(2):196-200.

26. Reynolds MW, Fahrbach K, Hauch Oeal. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and meta analysis. Chest 2004;126(6):1938-1945.

27. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;335(8):540-546.

28. Hylek EM, Go AS, Chang Y et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349(11):1019-1026.

29. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):257s-298s.

30. van Walraven C, Oake N, Wells PS, Forster AJ. Burden of potentially avoidable anticoagulant-associated hemorrhagic and thromboembolic events in the elderly. Chest 2007;131(5):1508-1515.

31. Fang MC, Go AS, Chang Y et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120(8):700-705.

32. Fang MC, Chang Y, Hylek EMeal. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med 2004;141(10):745-752.

33. Healthcare costs of treating bleeding and other complications associated with warfarin treatment of atrial fibrillation and venous thromboembolism in the UK.: 2004.

34. Green ES, Bond S, Rhodes S, Taylor M, Emmas C. Bleeding complications of oral anticoagulant therapy in a single centre. Br J Haematol 2005;129(s1):1-83.

35. Pirmohamed M, James S, Meakin Seal. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329(7463):460.

36. DeWilde S, Carey IM, Emmas C, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart 2006;92(8):1064-1070.

37. Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemost 2008;6(9):1500-1506.

38. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-867.

39. ACTIVE Investigators., Connolly SJ, Pogue J et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360(20):2066-2078.

40. National Institute for Health and Clinical Excellence. Atrial fibrillation - clopidogrel (in combination with aspirin). Proposed NICE Single Technology Appraisal. 23-10-2009.

Ref Type: Online Source

41. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost 2009;15 Suppl 1:9S-16S.

42. Cottrell S, LeReun C, Tilden D, Robinson P. Preference and willingness-to-pay study to assess the value of and anticoagulant therapy modelled on dabigatran etexilate using discrete choice analysis: A UK pilot study of warfarin-naive atrial fibrillation patients. Value in Health 2009;12(7):A339.

43. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-1151.

44. Albers GW. Stroke: more protection for patients with atrial fibrillation. Lancet Neurol 2010;9(1):2-4.

45. Savelieva I, Camm J. Atrial fibrillation--all change! Clin Med 2007;7(4):374-379.

46. Stangier J, Rathgen K, Stahle H, Reseski K, Kornicke T, Roth W. Coadministration of dabigatran etexilate and atorvastatin: assessment of potential impact on pharmacokinetics and pharmacodynamics. Am J Cardiovasc Drugs 2009;9(1):59-68.

47. Eikelboom JW, Wallentin L, Yusuf S et al. Does dabigatran improve stroke-prevention in atrial fibrillation? J Thromb Haemost 2010.

48. Stollberger C, Finsterer J. Does dabigatran improve stroke-prevention in atrial fibrillation? J Thromb Haemost 2010.

49. Dabigatran: safer, more effective and easier to use than warfarin. Cardiovasc J Afr 2009;20(5):311-312.

50. Nagarakanti R, Ezekowitz MD, Parcham-Azad K et al. Abstract 4629: Long-Term Open Label Extension of the Prevention of Embolic and Thrombotic Events on Dabigatran in Atrial Fibrillation (PETRO- Ex study). Circulation 118[S-922]. 2008.

Ref Type: Abstract

51. Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. N Engl J Med 2005;353(10):1028-1040.

52. Dabigatran compared to warfarin in patients with atrial fibrillation and prior TIA or stroke: results of RE-LY.: 2010.

53. RE-LY: A randomized trial of dabigatran, a oral direct thrombin inhibitor, compared to warfarin in 18,113 patients with atrial fibrillation at high risk of stroke. European Society of Cardiology; 2009.

54. Schwartz NE, Albers GW. Dabigatran challenges warfarin's superiority for stroke prevention in atrial fibrillation. Stroke 2010;41(6):1307-1309.

55. Boehringer Ingelheim Pharmaceuticals. Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) Comparing the Efficacy and Safety of Two Blinded Doses of Dabigatran Etexilate With Open Label Warfarin for the Prevention of Stroke and Systemic Embolism in Patients With Non-valvular Atrial Fibrillation: Prospective, Multi-centre, Parallel-group, Non-inferiority Trial (RE-LY Study). ClinicalTrials.gov Identifier: NCT00262600.

Ref Type: Generic

56. Ezekowitz MD, Connolly S, Parekh A et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157(5):805-10, 810.

57. Connolly SJ. RELY: Randomized evaluation of long-term anticoagulant therapy. Eur J Heart Fail 2009;11(12):1215.

58. Efficacy and safety of dabigatran compared to warfarin at different levels of INR control for stroke prevention in 18,113 patients with atrial fibrillation in the RE-LY trial.: Circulation; 2009.

59. Rationale and design of the RE-LY trial comparing dabigatran etexilate with warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.: 2009.

60. Dabigatran versus warfarin in atrial fibrillation patients with low, moderate and high CHADS2 score: a RE-LY subgroup analysis.: 2010.

61. Dabigatran versus warfarin in patients with atrial fibrillation – an analysis of patients undergoing cardioversion.: 2010.

62. Effect of age and renal function on the risks of stroke and major bleeding with dabigatran compared to warfarin: an analysis form the RE-LY study.: 2010.

63. Boehringer Ingelheim International GmbH. Randomized Evaluation of Long term anticoagulant therapY (RE-LY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® STUDY). Clinical Trial Report. 2009.

Ref Type: Generic

64. Reduced cerebral bleeding rates with dabigatran compared to warfarin in patients with atrial fibrillation: Results of RE-LY. American Academy of Neurology; 2010.

65. Dabigatran compared to warfarin in patients with atrial fibrillation and prior TIA or stroke: the RE-LY study. 20th Meeting of the European Neurological Society; 2010.

66. Boehringer Ingelheim Pharmaceuticals. RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed the RE-LY Trial and a Cluster Randomised Trial to Assess the Effect of a Knowledge Translation Intervention on Patient Outcomes. ClinicalTrials.gov Identifier: NCT00808067.

Ref Type: Generic

67. Ezekowitz MD, Reilly PA, Nehmiz G et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;100(9):1419-1426.

68. Pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran in a dose finding trial in atrial fibrillation.: 2005.

69. Safety and efficacy of a new oral direct thrombin inhibitor dabigatran in atrial fibrillation - a dose finding trial with comparison to warfarin.: 2005.

70. Boehringer Ingelheim bv. Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation. A Dose Exploration Study of BIBR 1048, an Oral Direct Thrombin Inhibitor, with and without Concomitant Acetylsalicylic Acid, in Comparison to Warfarin (PETRO). Clinical Trial Report. Doc No: U06-1615-02.

Ref Type: Generic

71. Boehringer Ingelheim Pharmaceuticals. Long-term, open-label follow-up treatment of patients with atrial fibrillation who have been previously treated with BIBR 1048 in the PETRO Trial. ClinicalTrials.gov Identifier: NCT00157248.

Ref Type: Generic

72. Long-term open label extension of the prevention of embolic and thrombotic events study in patients with atrial fibrillation randomised to dabigatran (PETRO-EX study). Scientific Sessions of the American Heart Association; 2008.

73. Safety and efficacy of extended exposure to several doses of a new oral direct thrombin inhibitor dabigatran etexilate in atrial fibrillation. Cerebrovasc Dis 2006 21 (Suppl 4) 2; 2006.

74. Boehringer Ingelheim Pharmaceuticals I. Long Term, Open Label Follow Up Treatment of Patients with Atrial Fibrillation Who Have Been Previously Treated with BIBR 1048 in the PETRO trial (Trial 1160.20). (PETRO Extension trial: PETRO-Ex). Interim Report. Doc No: U06-3419-02.

Ref Type: Generic

75. Boehringer Ingelheim Pharmaceuticals I. Long Term, Open Label Follow Up Treatment of Patients with Atrial Fibrillation Who Have Been Previously Treated with BIBR 1048 in the PETRO trial (Trial 1160.20). (PETRO Extension trial: PETRO-Ex). Doc No: U09-3247-01.

Ref Type: Generic

76. Nippon Boehringer Ingelheim Co. L. Open-label, randomised exploratory dose response study in pharmocodynamics and safety of BIBR 1048 (110mg b.i.d and 150mg b.i.d) for 12 weeks in patients with non-valvular atrial fibrillation in comparison to warfarin. Clinical Trial Report. 5-4-2007.

Ref Type: Generic

77. ClinicalTrials.gov. A dose response study of dabigatran etexilate (BIBR 1048) in pharmacodynamics and safety in patients with non-valvular atrial fibrillation in comparison to warfarin. 2-6-2010.

Ref Type: Online Source

78. Connolly SJ, Eikelboom J, O'Donnell M, Pogue J, Yusuf S. Challenges of establishing new antithrombotic therapies in atrial fibrillation. Circulation 2007;116(4):449-455.

79. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briét E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-239.

80. Boehringer Ingelheim International GmbH. Bespoke analysis of the RE-LY trial: Results stratified at age 80. Data on file (commericial-in-confidence). 2010.

Ref Type: Generic

81. Lip GY, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. Thromb Res 2006;118(3):321-333.

82. Aguilar M, Hart R, Pearce L. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database of Systematic Reviews 2007;3.

83. Bristol-Myers Squibb. AVERROES Study of Investigational Agent Apixaban Closes Early Due to Clear Evidence of Efficacy. Press Release. 10-6-2010.

Ref Type: Generic

84. Albers GW, Diener HC, Frison L et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293(6):690-698.

85. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003;362(9397):1691-1698.

86. Hu DY, Zhang HP, Sun YH, Jiang LQ. [The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin]. Zhonghua Xin Xue Guan Bing Za Zhi 2006;34(4):295-298.

87. Lu Y, Zhang J. [Anticoagulant treatment on chronic non-valvular atrial fibrillation in the elderly patients]. Chin J Emergency Med 2006;15(1):54-56.

88. Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation. LASAF Pilot Study Group. Am Heart J 1999;138(1 pt 1):137-143.

89. The Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 2008;371(9609):315-321.

90. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol 1991;18(2):349-355.

91. ACTIVE Writing Group of the ACTIVE Investigators., Connolly S, Pogue J et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367(9526):1903-1912.

92. Ezekowitz MD, Bridgers SL, James KE et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N Engl J Med 1992;327(20):1406-1412.

93. Gulløv AL, Koefoed BG, Petersen P et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second

Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Arch Intern Med 1998;158(14):1513-1521.

94. Hellemons BS, Langenberg M, dder J et al. Primary Prevention of Arterial Thromboembolism in Non-Rheumatic Atrial Fibrillation in Primary Care: randomised controlled trial comparing two intensities of coumarin with aspirin. BMJ 1999;319(7215):958-964.

95. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323(22):1505-1511.

96. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342(8882):1255-1262.

97. Mant J, Hobbs FD, Fletcher K et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370(9586):493-503.

98. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84(2):527-539.

99. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994;343(8899):687-691.

100. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet 1996;348(9028):633-638.

101. Morocutti C, Amabile G, Fattapposta F et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA (Studio Italiano Fibrillazione Atriale) Investigators. Stroke 1997;28(5):1015-1021.

102. Pengo V, Zasso A, Barbero F et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. Am J Cardiol 1998;82(4):433-437.

103. Pérez-Gómez F, Alegría E, Berjón J et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol 2004;44(8):1557-1566.

104. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989;333(8631):175-179.

105. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of Warfarin Versus Aspirin for Stroke Prevention in Octogenarians With Atrial Fibrillation (WASPO). Age Ageing 2007;36(2):151-156.

106. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;437(23):1825-1833.

107. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest 2006;129(5):1155-1166.

108. Dolan G, Smith LA, Collins S, Plumb JM. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. Curr Med Res Opin 2008;24(5):1459-1472.

109. NHS Quality Improvement Scotland. Heart Disease Improvement Programme Interim Audit of First Cycle Results. 2009.

Ref Type: Generic

110. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313(7052):275-283.

111. Sorensen SV, DeWilde S, Singer DE, Goldhaber SZ, Monz BU, Plumb JM. Cost-effectiveness of warfarin: trial versus "real-world" stroke prevention in atrial fibrillation. Am Heart J 2009;157(6):1064-1073.

112. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. JAMA 2005;293(6):699-706.

113. Huybrechts KF, Caro JJ, Xenakis JJ, Vemmos KN. The prognostic value of the modified Rankin Scale score for long-term survival after first-ever stroke. Results from the Athens Stroke Registry. Cerebrovasc Dis 2008;26(4):381-387.

114. Boehringer Ingelheim International GmbH. Long-term disability by severity: Bespoke data analysis from the RE-LY trial. 2010.

Ref Type: Generic

115. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med 2004;164(8):880-884.

116. Office for National Statistics. Interim Life Tables, United Kingdom 2005-2007.

Ref Type: Generic

117. Office for National Statistics. Mortality Statistics Deaths Registered in 2007. 2008.

Ref Type: Generic

118. Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis. Heart 2008;94(12):1607-1613.

119. Fang MC, Go A.S, Hylek EM et al. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. J Am Geriatric Soc 2006;54(8):1231-1236.

120. Ng YS, Stein J, Ning M, Black-Schaffer RM. Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. Stroke 2007;38(8):2309-2314.

121. Lin HJ, Wolf PA, Kelly-Hayes M et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27(10):1760-1764.

122. Garcia DA, Regan S, Henault LE et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med 2008;168(1):63-69.

123. Scottish Intercollegiate Guidelines Network. Antithrombotic Therapy: A National Clinical Guideline. SIGN Publication Number 36, 1999

124. Davis NJ, Billett HH, Cohen HW, Arnsten JH. Impact of adherence, knowledge, and quality of life on anticoagulation control. Ann Pharmacother 2005;39(4):632-636.

125. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med 1996;156(16):1829-1836.

126. Díaz-Tapia V, Gana J, Sobarzo M, Jaramillo-Muñoz A, Illanes-Díez S. Study on the quality of life in patients with ischaemic stroke. Rev Neurol 2008;46(11):652-655.

127. Xie J, Wu EQ, Zheng ZJeal. Impact of stroke on health-related quality of life in the noninstitutionalized population in the United States. Stroke 2006;37(10):2567-2572.

128. Zahran HS, Kobau R, Moriarty DG, Zack MM, Holt J, Donehoo R. Health-related quality of life surveillance – United States, 1993-200. MMWR Surveill Summ 2005;54(4):1-35.

129. Sturm JW, Donnan GA, Dewey HM et al. Quality of life after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2004;35(10):2340-2345.

130. Post PN, Stiggelbout AM, Wakker PP. The utility of health states after stroke: a systematic review of the literature. Stroke 2001;32(6):1425-1429.

131. Paul SL, Sturm JW, Dewey HM, Donnan GA, Macdonell RA, Thrift AG. Long-term outcome in the North East Melbourne Stroke Incidence Study: predictors of quality of life at 5 years after stroke. Stroke 2005;36(10):2082-2086.

132. Boehringer Pharma GmbH & Co.KG. Clinical Trial Protocol Amendment Quality of Life Substudy. 2007

133. Boehringer Ingelheim. QOL Substudy 1160.26. 2010.

Ref Type: Generic

134. Walters S, Brazier J. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Quality of Life Research 2005;14:1523-1532.

135. Ringash J, O'Sullivan B, Bezjak Aeal. Interpreting clinically significant changes in patient reported outcomes. Cancer 2007;110:196-202.

136. Sullivan PW, Lawrence W, Ghuschcyan V. A national catalog of preference-based scores for chronic conditions in the United States. Medical Care 2005;43(7):736-749.

137. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. JAMA 1995;%20;274(23):1839-1845.

138. O'Reilly D, Xie F, Pullenayegum Eeal. Estimation of utility values for diabetes related complications on quality of life for patients with type-2 diabetes in Ontario, Canada. Value in Health 2009;12(3):A17.

139. Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: A standard gamble study. Journal of Health Services Research and Policy 2001;6(2):92-98.

140. Berg J, Lindgren P, Nieuwlaat Real. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. Quality of Life Research 2010;19(3):381-390.

141. Barton GR, Sach TH, Doherty Meal. An assessment of the discriminative ability of the EQ-5D index, SF-6D and EQ-VAS using socio-demographic factors and clinical conditions. European Journal of Health Economics 2008;9(3):237-249.

142. Dorman PJ, Dennis M, Sandercock P. Are the modified 'simple questions' a valid and reliable measure of health related quality of life after stroke? Journal of Neurology Neurosurgery and Psychiatry 2000;69(4):487-493.

143. Gore JM, Granger CB, Simoons ML et al. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. Circulation 1995;92(10):2811-2818.

144. King Jr JT, Brandt CA, Tsevat J, Roberts MS. A national internet-based survey of cerebral aneurysm preference-based quality of life. Neurosurgery 2009;64(2):249-254.

145. Lai SM, Duncan PW. Stroke recovery profile and the modified rankin assessment. Neuroepidemiology 2001;20(1):26-30.

146. Shin AY, Porter PJ, Wallace MC, Naglie G. Quality of life of stroke in younger individuals: Utility assessment in patients with arteriovenous malformations. Stroke 1997;28(12):2395-2399.

147. Tavakoli M, Pumford N, Woodward M et al. An economic evaluation of a perindopril-based blood pressure lowering regimen for patients who have suffered a cerebrovascular event. European Journal of Health Economics 2009;10(1):111-119.

148. Van Exel NJA, Scholte Op Reimer WJM, Koopmanschap MA. Assessment of post-stroke quality of life in cost-effectiveness studies: The usefulness of the Barthel Index and the EuroQoL-5D. Quality of Life Research 2004;13(2):427-433.

149. Oldridge N, Furlong W, Perkins A, Feeney D, Torrance GW. Community or patient preferences for cost-effectiveness of cardiac rehabilitation: does it matter? European journal of cardiovascular prevention and rehabilitation 2008;15(5):608-615.

150. Rawles J, Light J, Watt M. Quality of life in the first 100 days after suspected acute myocardial infarcation - A suitable trial endpoint? Journal of Epidemiology and Community Health 1992;46(6):612-616.

151. Winkelmayer WC, Benner JS, Glynn RJ et al. Assessing health state utilities in elderly patients at cardiovascular risk. Medical Decision Making 2006;26(3):247-254.

152. Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. Pharmacoeconomics 2006;24(10):1021-1033.

153. Johnson J, Luo J, Shaw Peal. Valuations of EQ-5D health states. Are the United States and United Kingdom different? Medical Care 2005;43(3):221-228.

154. Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med 2001;111(2):130-139.

155. Gould MK, Dembitzer AD, Sangers GD, Barosi G. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. Ann Intern Med 1999;130(10):789-799.

156. Department of Health. Payment by Results: 2010-11 Tariff Information. 2010.

Ref Type: Online Source

157. Department of Health. NHS Reference costs 2007-2008. 2009.

Ref Type: Online Source

158. Department of Health. Reference Cost 2008/2009. 23-8-2010. 23-8-2010.

Ref Type: Online Source

159. Department of Health. Payment by Results guidence for 2010-2011. 2010

160. Abdelhafiz AH, Wheeldon NM. Cost of warfarin treatment of atrial fibrillation in clinical practice. Value in Health 4[2], 98-99. 2001.

Ref Type: Abstract

161. Arya R, Green ES, Rose P et al. The cost of anticoagulation monitoring services in the UK National Health Service. Value in Health 2005;8:6870.

162. Bhavnani M, Shiach CR. Patient self-management of oral anticoagulation. Clin Lab Haematol 2002;24(4):253-257.

163. Connock M, Stevens C, Fry-Smith A et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. Health Technol Assess 2007;11(38):iii-66.

164. Jowett S, Bryan S, Murray E et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. British Journal of Haematology 2006;134:632-639.

165. Fitzmaurice DA, Murray E, McCahon D et al. Self management of oral anticoagulation: randomised trial. BMJ 2005;doi:10.1136/bmj.38618.580903.AE (published 10 October 2005).

166. Davies A, Buxton MJ, Patterson DLH, Webster-King J. Anti-coagulantmonitoring service delivery: a comparisonof costs of hospital andcommunity outreach clinics. Clinicaland Laboratory Haematology 2000;22(33):40.

167. Fitzmaurice DA, Hobbs FDR, Murray ET, Bradley CP, Holder R. Evaluation of computerized decision support for oral anticoagulation management based in primary care. Journal of General Practice 1996;46:533-535.

168. Fitzmaurice DA, Hobbs FDR, Murray ET. Primary care anticoagulant clinic management using computerized decision support and near patient international normalized ratio (INR) testing: routine data from a practice nurse-led clinic. Family Practice 1998;15:144-146.

169. Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. J Clin Pathol 2002;55(11):845-849.

170. Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. Stroke 1998;29:1827-1832.

171. McCahon D, Murray ET, Jowett S et al. Patient self management of oral anticoagulation in routine care in the UK. J Clin Pathol 2007;60(11):1263-1267.

172. Parry D, Fitzmaurice D, Raftery J. Anticoagulation management in primary care: a trial-based economic evaluation. British Journal of Haematology 2000;111:530-533.

173. Parry D, Bryan S, Gee K, Murray E, Fitzmaurice AD. Patient costs in anticoagulation management: a comparison of primary and secondary care. British Journal of General Practice 2001;51:972-976.

174. Taylor FC, Gray A, Cohen H, Gaminara L, Ramsay M, Miller D. Costs and effectiveness of a nurse specialist anticoagulant service. J Clin Pathol 1997;50(10):823-828.

175. Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. Lancet 2000;355(9208):956-962.

176. Abdelhafiz AH, Wheeldon NM. Use of resources and cost implications of stroke prophylaxis with warfarin for patients with nonvalvular atrial fibrillation. Am J Geriatr Pharmacother 2003;1(2):53-60.

177. INRStar. Setting up an Anticoagulation Clinic in Primary Care. 19-6-2006.

Ref Type: Online Source

178. Blann AD, Fitzmaurice AD, Lip GYH. ABC of antithrombotic therapy: Anticoagulation in hospitals and general practice. BMJ 2003;326:153-156.

179. Wolf DA, Taub NA, Bryan S, Beech R, Warburton F, Burney PGJ. Variations in the incidence, management and outcome of stroke in residents under the age of 75 in two health districts of southern England. J Public Health Med 1995;17(4):411-418.

180. Isard PA, Forbes JF. The cost of stroke to the National Health Service in Scotland. Cerebrovasc Dis 1992;2(1):47-50.

181. Dawson J, Lees JS, Chang TP et al. Association Between Disability Measures and Healthcare Costs After Initial Treatment for Acute Stroke. Stroke 2007;38:1893-1898.

182. Henderson LR, Scott A. The costs of caring for stroke patients in a GP-led community hospital: an application of programme budgeting and marginal analysis. Health Soc Care Community 2001;9(4):244-254.

183. Caro JJ, Huybrechts KF. Stroke treatment economic model (STEM): predicting long-term costs from functional status. Stroke 1999;30(12):2574-2579.

184. Caro JJ, Huybrechts KF, Duchesne I. Management patterns and costs of acute ischemic stroke: an international study. For the Stroke Economic Analysis Group. Stroke 2000;31(3):582-590.

185. Chambers MG, Koch P, Hutton J. Development of a decision-analytic model of stroke care in the United States and Europe. Value in Health 2002;5(2):82-97.

186. Beech R, Rudd A, Tilling K, Wolf C. Economic consequences of early inpatient discharge to community-based rehabilitation for stroke in an inner-London teaching hospital. Stroke 1999;30(4):729-735.

187. Clarke P, Gray AM, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabet Med 2003;20(6):442-450.

188. Patel A, Knapp M, Perez I, Evans A, Karla L. Alternative strategies for stroke care: cost-effectiveness and cost-utility analyses from a prospective randomized controlled trial. Stroke 2004;35(1):196-203.

189. Hansson LR, Lloyd AC, Anderson P, Kopp Z. Excess morbidity and cost of failure to achieve targets for blood pressure control in Europe. Blood Pressure 2002;11(1):35-45.

190. Patel A, Knapp M, Evans A, Perez I, Karla L. Training care givers of stroke patients: economic evaluation. BMJ 2004;328(7448):1102.

191. McNamee P, Christensen J, Soutter J, Rodgers H, Craig N, Pearson P. Cost analysis of early supported hospital discharge for stroke. Age Ageing 1998;27(3):345-351.

192. Grieve R, Porsdal V, Hutton J, Wolf CDA. A comparison of the cost-effectiveness of stroke care provided in London and Copenhagen. Int J Technol Assess Health Care 2000;16(2):684-695.

193. Epstein D, Mason A, Manca A. The hospital cost of care for stroke in nine European countries. Health economics 2008;17(Supplement 1):S21-S31.

194. Grieve R, Hutton J, Bhalla A, Rastenyte D, Ryglewicz D, Sarti C. A comparison of the costs and survival of hospital-admitted stroke patients across Europe. Stroke 2001;32(7):1684-1691.

195. Grieve R, Dundas R, Beech R, Wolf CDA. The development and use of a method to compare the costs of acute stroke across Europe. Age Ageing 2001;30(1):67-72.

196. Youman P, Wilson K, Harraf F, Karla L. The Economic Burden of Stroke in the United Kingdom. Pharmacoeconomics 2003;21(Suppl. 1):43-50.

197. Luengo-Fernandez R, Gray AM, Rothwell PM. Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom. Stroke 2006;37(10):2579-2587.

198. Guilhaume C, Saragoussi D, Cochran Jeal. Modeling stroke management: a qualitative review of cost-effectiveness analyses. The European journal of health economics : HEPAC : health economics in prevention and care 2010;11(4):419-426.

199. Bayer S, Petsoulas C, Cox B, Honeyman A, Barlow J. Facilitating stroke care planning through simulation modelling. Health informatics journal 2010;16(2):129-143.

200. Shaw L, Rodgers H, Price C et al. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. Health technology assessment (Winchester England) 2010;14(26):1-113.

201. Quinn TJ, Dawson J. Acute 'strokenomics': efficacy and economic analyses of alteplase for acute ischemic stroke. Expert review of pharmacoeconomics & outcomes research 2009;9(6):513-522.

202. Jones M, Holmes M. Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal. Health technology assessment (Winchester England) 2009;13 Suppl 2:15-21.

203. Dudley N. Population of the United Kingdom. Age and ageing 2009;38(5):631-632.

204. Latimer N, Lord J, Grant RL, Mahony R, Dickson J, Conaghan PG. Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. BMJ (Clinical research ed) 2009;339:b2538, ISSN-5833.

205. Taylor J. Stroke care. Fast thinking. The Health service journal 2009;119(6147):18-20.

206. Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. Age and ageing 2009;38(1):27-32.

207. van-der Gaag A, Brooks R. Economic aspects of a therapy and support service for people with long-term stroke and aphasia. International journal of language & communication disorders / Royal College of Speech & Language Therapists 2008;43(3):233-244.

208. Sudlow C, Warlow C. Getting the priorities right for stroke care. BMJ 2009;338(7708):1419-1422.

209. Kmietowicz Z. A quarter of stroke patients are still not treated in a stroke unit. BMJ (Clinical research ed) 2009;338:b1655, eISSN-5833.

210. Higgins P, Ghosh S, Lees K. Improving mortality from stroke disease: Putting the evidence into practice. British Journal of Hospital Medicine 2008;69(12):668-669.

211. Swain S, Turner C, Tyrrell P, Rudd A. Guidelines: Diagnosis and initial management of acute stroke and transient ischaemic attack: Summary of NICE guidance. BMJ 2008;337(7664):291-293.

212. Rudd A, Swain S, Turner C. Recognition and management of transient ischaemic attack. Clinical Medicine 2008;8(4):-363.

213. Schwander B, Gradl B, Zollner Y et al. Cost-utility analysis of eprosartan compared to enalapril in primary prevention and nitrendipine in secondary prevention in Europe: the HEALTH model. Value in Health 2009;12(6):857-871.

214. Jenkins PO, Turner MR, Jenkins PF. What is the place of thrombolysis in acute stroke? A review of the literature and a current perspective. Clinical Medicine 2008;8(3):253-258.

215. Jackson D, Moshinsky J, Begg A. Addressing shortfalls in TIA care in the UK: An economic perspective. Journal of medical economics 2009;12(4):331-338.

216. Luengo-Fernandez R, Gray AM, Rothwell PM. Costs of stroke using patient-level data: a critical review of the literature. Stroke 2009;40(2):e18-e23.

217. Flynn RW, MacWalter RS, Doney AS. The cost of cerebral ischaemia. Neuropharmacology 2008;55(3):250-256.

218. Gomes M, Soares MO, Dumville JC et al. Cost-effectiveness analysis of general anaesthesia versus local anaesthesia for carotid surgery (GALA Trial). The British journal of surgery 2010;97(8):1218-1225.

219. Wilson E, Ford GA, Robinson T, Mistri A, Jagger C, Potter JF. Controlling hypertension immediately post stroke: a cost utility analysis of a pilot randomised controlled trial. Cost effectiveness and resource allocation : C/E 2010;8:3, ISSN-7547.

220. Christensen MC, Munro V. Ischemic Stroke and Intracerebral Hemorrhage: The Latest Evidence on Mortality, Readmissions and Hospital Costs from Scotland. Neuroepidemiology 2008;30:239-246.

221. Potter J, Mistri A, Brodie F et al. Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS): a randomised controlled trial. Health Technology Assessment 2009;13(9):i-xi, 1.

222. Lindgren P, Buxton M, Kahan T et al. The lifetime cost effectiveness of amlodipine-based therapy plus atorvastatin compared with atenolol plus atorvastatin, amlodipine- based therapy alone and atenolol-based therapy alone: results from ASCOT1. Pharmacoeconomics 2009;27(3):221-230.

223. French B, Leathley M, Sutton C et al. A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness. Health technology assessment (Winchester England) 2008;12(30):iii, ix.

224. Elia M, Stratton RJ. A cost-utility analysis in patients receiving enteral tube feeding at home and in nursing homes. Clinical Nutrition 2008;27(3):416-423.

225. Harrington R, Taylor G, Hollinghurst Seal. A community-based exercise and education scheme for stroke survivors: a randomized controlled trial and economic evaluation. Clinical rehabilitation 2010;24(1):3-15.

226. Forster A, Young J, Green Jeal. Structured re-assessment system at 6 months after a disabling stroke: a randomised controlled trial with resource use and cost study. Age and ageing 2009;38(5):576-583.

227. Dodel R, Haake C, Zamzow Keal. Resource utilisation and costs of stroke unit care in Germany. Value in Health 2004;7:144-152.

228. Ward A, Payne KA, Caro JJ, Heuschmann PU, Kolominsky-Rabas PL. Care needs and economic consequence after acute ischaemic stroke: the Erlangen Stroke Project. Eur J Neurol 2005;12:264-267.

229. Asplung K, Ashburner SC, Cargill K, Hux M, Lees KR, Drummond M. Health care resource use and stroke outcome: multinational comparisons within the GAIN trial. Int J Technol Assess Health Care 2003;19:267-277.

230. Som R, Gossage JA, Crane A, Rowe PH. Surgical workload, risk factors and complications in patients on warfarin with gastrointestinal bleeding. Int J Surg 2010;8(1):52-55.

231. Karnon J, Bakhai A, Brennan A et al. A cost-utility analysis of clopidogrel in patients with non-ST-segment-elevation acute coronary syndromes in the UK. Int J Cardiol 2006;109(3):307-316.

232. CURE Study Investigators. The clopidogrel in unstable angina to prevent recurrent events (CURE) trial programme. Eur Heart J 2000;21:2033-2041.

233. Palmer S, Sculpher M, Philips Zeal. A cost-effectiveness model comparing alternative management strategies for the use of glycoproteinIIB/IIIA antagonists in non st-elevation acute coronary syndrome. University of York: Centre for Health Economics, 2002

234. Gordois A, Posnett J, Borris L et al. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. J Thromb Haemost 2003;1(10):2167-2174.

235. Miller CE, Quayyum Z, McNamee P, Al-Shahi SR. Economic burden of intracranial vascular malformations in adults: prospective population-based study. Stroke 2009;40(6):1973-1979.

236. Offord R, Lloyd AC, Anderson P, Bearne A. Economic evaluation of enoxaparin for the prevention of venous thromboembolism in acutely ill medical patients. Pharm World Sci 2004;26(4):214-220.

237. Nuijten MJC, Antoñanzas F, Kosa Jeal. Cost-effectiveness of enoxaparin as thromboprophylaxis in acutely ill medical patients in Spain. Value in Health 2003;6(2):126-136.

238. Lloyd AC, Anderson PM, Quinlan DJeal. Economic evaluation of the use of enoxaparin for thromboprophylaxis in acutely ill medical patients. Journal of medical economics 2001;4:99-113.

239. Bakhai A, Flather MD, Collinson JR et al. National economic impact of tirofiban for unstable angina and myocardial infarction without ST elevation; example from the United Kingdom. Int J Cardiol 2003;91(2-3):163-172.

240. Wolowacz SE, Roskell NS, Maciver F et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism after total knee and hip replacement surgery. Clin Ther 2009;31(1):194-212.

241. McGuire AJ, Raikou M, Whittle I, Christensen MC. Long-term mortality, morbidity and hospital care following intracerebral hemorrhage: an 11-year cohort study. Cerebrovasc Dis 2007;23(2-3):221-228.

242. National Institute for Health and Clinical Excellence. Dyspepsia - management of dyspepsia in adults in primary care. 2004

243. Curtis L. Unit Costs of Health and Social Care 2009. Personal Social Services Research Unit, 2009

244. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. BMJ 2000;320(7244):1236-1239.

245. Walker AM, Bennett D. Epidemiology and outcomes in patients with atrial fibrillation in the United States. Heart Rhythm 2008;5(10):1365-1372.

246. Desbiens NA. Deciding on anticoagulating the oldest old with atrial fibrillation: insights from cost-effectiveness analysis. J Am Geriatr Soc 2002;50(5):863-869.

247. Office for National Statistics. Cohort expectation of life: England and Wales. 2006 projections. 2006

248. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J 2008;156(1):57-64.

249. Office for National Statistics. Mid-2009 population estimates for England and Wales. 2009

250. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Ann Intern Med 1999;131(12):927-934.

9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

A draft SPC is not yet available.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

9.2.2 The date on which the search was conducted.

9.2.3 The date span of the search.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

9.2.6 The inclusion and exclusion criteria.

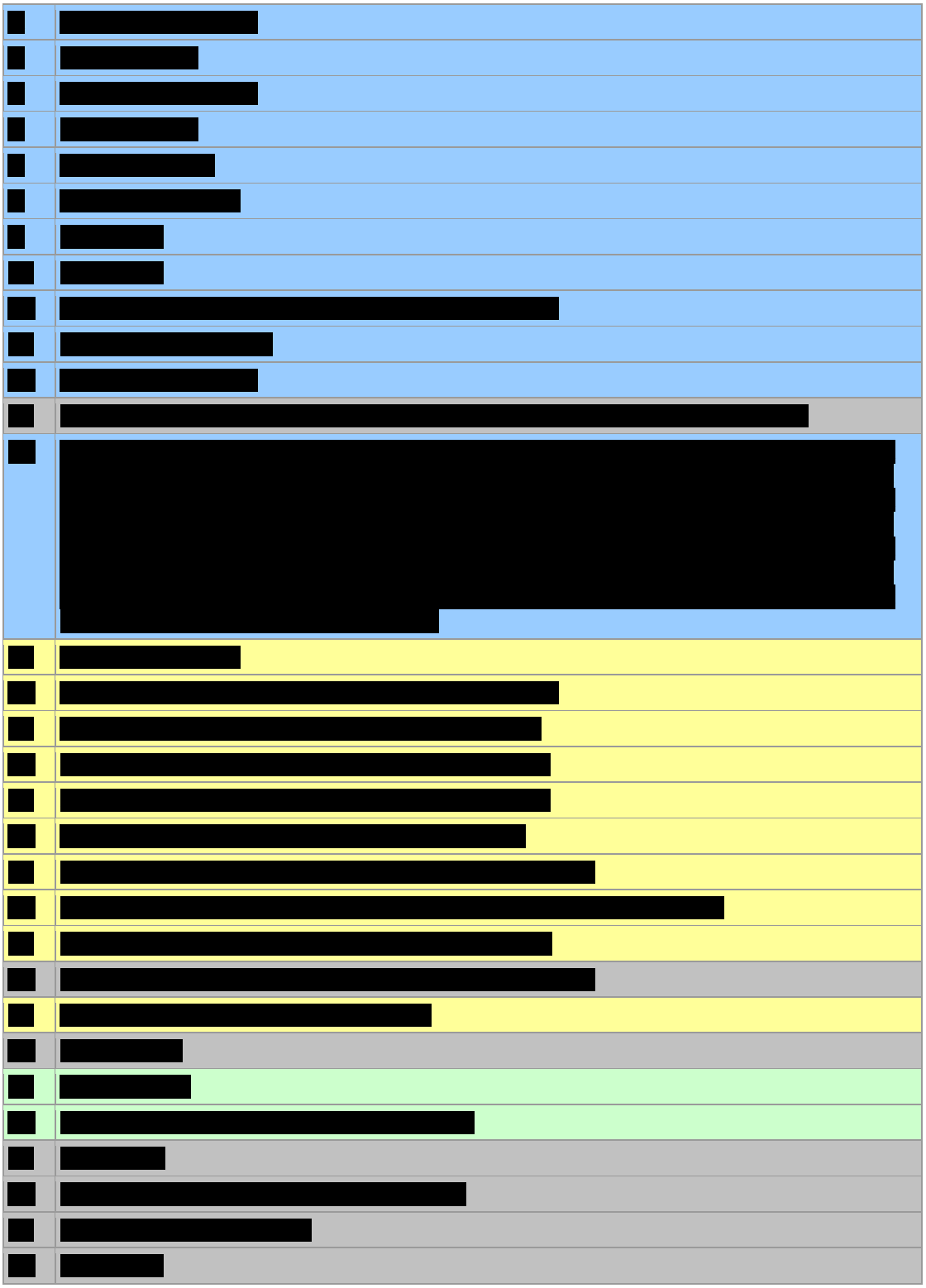
9.2.7 The data abstraction strategy.

Embase and Medline

- Name of the databases searched: Embase, Medline
- Name of the interface: Embase.com
- Date on which search was conducted: 7th July 2010
- Date span of search: No limits

Table 162 Search strategy for Embase/Medline

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



Medline ® In-Process

- Name of the databases searched: Medline ® In-Process
- Name of the interface: Pubmed
- Date on which search was conducted: 7th July 2010
- Date span of search: No limits

Table 163 Search strategy for Medline in process

[redacted]	

Cochrane Clinical Trials Register

- Name of the databases searched: Cochrane Clinical Trials Register
- Name of the interface: Wiley Interscience
- Date on which search was conducted: 7th July 2010
- Date span of search: No limits

Table 164 Search strategy for Cochrane library

[redacted]	

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Other Searches

Abstracts from the following conferences were searched for the years 2007 to 2009:

- European Stroke Conference via the website http://www.esc-archive.eu
- European Society of Cardiology congress via the website http://spo.escardio.org/abstract-book/Default.aspx
- International Stroke Conference via the website http://strokeconference.americanheart.org/portal/strokeconference/sc/
- American College of Cardiology Annual Scientific Session via Abstract book located in British Library
- American Heart Association Scientific Sessions via the website http://circ.ahajournals.org/content/vol116/16_MeetingAbstracts/

The following search key terms were used for searches: dabigatran, pradaxa, bibr 1048, bibr 953.

The ClinicalTrials.gov website was searched for ongoing and completed clinical trials using the search terms dabigatran, pradaxa, bibr 1048, bibr 953.

Boehringer Ingelheim's internal databases BILIT, Pre-BILIT and IDEA were searched for additional abstracts using the following search terms:

BILIT (search performed 21st July 2010)

atrial fibrillation + stroke and (atrial fibrillation and GN=dabigatran and.t CL=major) AND DT=(ABSTRACT or ORIGINAL or THESIS) AND ST=(DRUG THERAPY) AND GN=dabigatran and.t CL=major AND DE=(RCT OR trial OR study).

Pre-BILIT (search performed 21st July 2010)

CL=major AND GN=dabigatran AND (atrial fibrillation + stroke)

IDEA (search performed 5th August 2010)

API = “BIBR 953 ZW” or “dabigatran” or “dabigatran etexilate” or “dabigatran etexilate mesilate”

AND

Document type = “5-3 Clinical Reports”

Inclusion criteria were as follows:

- Studies must be published randomised controlled trials or observational studies
- Studies must be conducted in human adult patients (≥18 years) with Atrial fibrillation
- Studies must contain dabigatran etexilate
- The treatment comparison must be to another biological anticoagulant, a conventional anticoagulant or placebo
- Only English language papers are considered

Exclusion criteria were as follows:

- Non-randomised controlled trials or observational studies
- Studies conducted in human patients (≤18 years), studies in animals or in-vitro, studies in adult patients (≥18 years) without atrial fibrillation
- Studies not investigating dabigatran etexilate
- Non-English language publications

Bibliographic details and abstracts of all citations detected by the literature search were downloaded into an MS Excel database.

First pass of citations

Citations were first screened based on the abstract supplied with each citation. Each abstract was screened by two independent reviewers with any discrepancies resolved by a third reviewer. Those that did not match the eligibility criteria were excluded at this ‘first pass’. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. In instances when it was not possible to include or exclude citations based on the abstract, full-text copies were ordered. Full-text copies of all references that could potentially meet the eligibility criteria were also ordered at this stage.

Second pass of citations

The eligibility criteria were applied to the full-text citations using the same double screening and reconciliation method as described above, and the data presented in the studies still included after this stage were extracted to data extraction grids.

Extraction strategy

Data from trials were extracted independently by two reviewers, with any discrepancies resolved by a third reviewer. Where more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction grid. Each publication was referenced in the grid to recognise that more than one publication may have contributed to the entry.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 165 Quality assessment of PETRO

PETRO study		
	Grade	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	The treatment allocation was determined according to the randomisation code provided the sponsor using ClinPro/LBL version 6.0, release 5 software. Randomisation was stratified by country; each country received a multiple of all treatments, and corresponding treatment assignment envelopes, in the ratio 2:3:3:4. This resulted in a block size that is a multiple of 28 (the actual figure, unknown to the investigators, was 28); the number of treatment kits containing a combination of DBG and ASA was a multiple of 24 (again, the actual figure was 24). Note that these figures were unknown to the investigators in order to make calculations of the block size impossible. Within each country, the allocation of treatments (and envelopes) to the sites was also randomised. Each site received one package (and if necessary, re-supply package(s)) that contained a random selection of 6 out of the DBG/ ASA treatment kits of that country plus 1 warfarin treatment kit. No additional symmetry/balance condition was foreseen for the site-specific random selection from the DBG / ASA treatment kits. This required a random re-shuffling of the DBG / ASA treatment kits within the country-specific blocks, plus a random selection of the position of the warfarin treatment kit between the DBG / ASA treatment kits in each package.
Was the concealment of treatment allocation adequate?	Yes	Randomisation envelopes, with ID number on the outside, were distributed to each site. Each site also received a shipment of DBG medication boxes, as well as ASA and warfarin medications, packaged separately. DBG medication was double blind and was labelled with a medication number. When a new patient was randomised at visit 2, the investigator opened the randomisation envelope with the lowest available ID-number. All investigators were always unaware of the treatment group assignment of the next randomised patient. The unused randomisation envelopes had to be returned unopened as proof that the blind had not been broken.

Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There were no relevant differences between the randomised treatment groups (see **Table 24**).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants (partially). Outcomes assessors (yes).	The study was double-blind for patients allocated to DBG, in that patients and investigators were blinded to dose allocation. Warfarin and aspirin allocation was open label. An experienced and independent central committee of experts blinded to treatment assignments adjudicated all bleeding events, including classification into major bleeding, minor bleeding and clinically relevant bleeds.
Were there any unexpected imbalances in drop-outs between groups?	No	Mean exposure to study drug was similar in all treatment groups (77-83 days). Discontinuation due to adverse events showed a dose-response trend, which was not unexpected.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes planned to be measured in the study protocol appear to be reported in the clinical trial report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All 502 randomised patients who received one dose of study drug were included in the safety analysis. This was appropriate, and only one patient was lost to follow up meaning missing data was not an issue.

Abbreviations: ASA, aspirin; DBG, dabigatran etexilate

Table 166 Quality assessment of study 1160.49

PETRO study		
	Grade	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	The randomisation code was provided by Bell System (a registration centre) with validated software. Randomisation was based on permuted blocks with a block size of six. Eligible patients were randomly assigned in a 1:1:1 ratio to receive DBG 110 mg bid, DBG 150 mg bid or warfarin. After obtaining written consent on Visit 1, the investigator facsimiled a patient registration form to the registration centre, when the patient was eligible. Before Visit 2, the registration centre facsimiled a confirmation form including randomised treatment to the investigator. The investigator dispensed the study drug according to the randomised treatment.
Was the concealment of treatment allocation adequate?	No	This was an open-label study.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There were no relevant differences between the randomised treatment groups (see **Table 25**).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants (no). Outcomes assessors (yes).	The study was open label to patients and investigators. The DSMB adjudicated bleeding events without information on treatment assignment.

Were there any unexpected imbalances in drop-outs between groups?	No	[redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes planned to be measured in the study protocol appear to be reported in the clinical trial report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All 166 randomised patients who received one dose of study drug were included in the safety analysis. This was appropriate, and no patients were lost to follow up meaning missing data was not an issue.

Abbreviations: bid, twice daily dosing; DBG, dabigatran etexilate; DSMB, drug safety monitoring board

Table 167 Quality assessment of RE-LY

PETRO study		
	Grade	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomly allocated to 1 of 3 treatment groups — DBG 110 bid, DBG 150 mg bid, or warfarin, — with equal probability (allocation ratio of 1:1:1). The randomisation was done through an IVRS located at the central coordinating centre. The randomisation was done with a random block size of 3, 6, and 9, and the randomisation schedule was generated by using validated software. The doses of DBG were blinded.
Was the concealment of treatment allocation adequate?	Yes, where blinding was appropriate.	This was an open-label study, where only the dose of DBG was blinded. In that case, DBG 110mg and 150mg capsules were identical in appearance. The blinded treatment code was to be opened only if required by an emergency.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There were no relevant differences between the randomised treatment groups (see **Table 26**).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers and participants (partially). Outcomes assessors (yes).	The study was open label to patients and investigators in terms of treatment allocation, but blinded by DBG dose. Several further measures were put in place to minimise any potential bias arising from the PROBE design. Please see Section 5.10 for more details of these measures and a full justification for the PROBE trial design. All outcome events, including major bleeds, were adjudicated by adjudication experts blinded to the treatments used. Blinding of all event documentation was performed prior to adjudication. Key documents for major bleeds (not necessarily fatal bleeds) and "other" endpoints, i.e., TIAs, were provided for adjudication. This Committee reported to the Steering Committee. Records of all adjudication decisions and of Adjudication Committee meeting minutes were maintained.

Were there any unexpected imbalances in drop-outs between groups?	No	Mean exposure to study drug was similar in the three groups (20.32-21.33 months)). Of the 18,113 randomised patients, only 89 (0.5%) were lost to follow-up. Rates of discontinuation were higher in the two DBG groups (22.0% and 22.8%) compared to warfarin (17.9%), but this is not unexpected given the open-label nature of the trial. The most common reason for permanent discontinuation was "subject didn't want to take study drug".
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes planned to be measured in the study protocol appear to be reported in the clinical trial report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All 18,113 randomised patients were included in the Intention to treat analysis. Several other analysis sets were also defined to deal with missing data and provide the most appropriate analyses for various endpoints (see **Table 27**).

Abbreviations: bid, twice daily dosing; DBG, dabigatran etexilate; PROBE, prospective randomised open-label blinded endpoint.

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

9.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The literature search was performed in the following electronic databases:

- The Cochrane Library, including the following:
  - The Cochrane Database of Systematic Reviews
  - The Cochrane Central Register of Controlled Trials
  - Database of Abstracts of Reviews of Effectiveness
- MEDLINE and MEDLINE In-Process (using PubMed platform)
- EMBASE (using Dialog Platform)
- BIOSIS (using Dialog Platform)

9.4.2 The date on which the search was conducted.

The searches were conducted on 9th July 2009, then reviewed and finalised on 10th August 2009.

9.4.3 The date span of the search.

There was no restriction on publication date.

9.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 168 General search strategy

Term Group	Terms	
Population/Patients	1.	Atrial Fibrillation [MeSH]
	2.	((atrial or atrium or auricular) AND (fibrillat$)).tw.
	3.	or/1-2
	4.	stroke [MeSH] Or stroke* Limit to [titles] OR transient ischaemic attack (TIA)
	5.	#3 AND #4
	6.	non-valvular [All fields] OR 'non valvular' [All fields]
	7.	#5 AND #6
Intervention	8.	dabigatran [MeSH]
	9.	aspirin [MeSH]
	10.	warfarin [MeSH]
	11.	anticoagulants [MeSH]
	12.	antiplatelet therapy [MeSH]
	13.	clopidogrel [MeSH]
	14.	ximelagatran [MeSH]
	15.	'vitamin K antagonists'. tw OR VKA OR dicoumarol OR phenindione OR phenprocoumon OR acenocoumarol OR ethyl biscoumacetate OR clorindione OR diphenadione OR OR tioclomarol
	16.	or/8-15
	17.	#7 AND #16
Study type	18.	" Randomised clinical trial* [pt] OR Randomized clinical trial* [pt] OR 'random allocation'.tw OR (clinical trial* [tw] AND random*)
	19.	#17 AND #18
Limits	Research design: Human	
	Date – No Limits	

MeSH: Medical Subject Heading (Medline medical index term); the asterix sign (*) stands for any character(s); ab = abstract; ti = title; pt = publication type;

Table 169 Medline search strategy and results

Search Number	Search Terms	Returns
#1	"Atrial Fibrillation"[Mesh] -	23300
#2	("atrial"[Text Word] OR "atrium"[Text Word] OR "auricular"[Text Word]) AND fibrillat*[Text Word] -	32888
#3	#1 OR #2	32888
#4	"dabigatran"[Text Word] OR "Aspirin"[Mesh] OR "Warfarin"[Mesh] OR "Anticoagulants"[Mesh] OR "Platelet Aggregation Inhibitors"[Mesh] OR "antiplatelet therapy"[Text Word] OR "clopidogrel"[Substance Name] OR "ximelagatran"[Substance Name] OR "vitamin k antagonist"[Text Word] OR "vitamin k antagonists"[Text Word] OR "VKA"[Text Word] OR "dicoumarol"[Text Word] OR "phenindione"[Text Word] OR "phenprocoumon"[Text Word] OR "acenocoumarol"[Text Word] OR "ethyl biscoumacetate"[Text Word] OR "clorindione"[Text Word] OR "diphenadione"[Text Word] OR "tioclomarol"[Text Word] -	89606
#5	"Randomized Controlled Trial"[Publication Type] OR "random allocation"[Text Word] -	317707
#6	clinical trial*[Text Word] AND random*[Text Word] -	265296
#7	#5 OR #6	355079
#8	#3 AND #4 AND #7	356
#9	"Animals"[Mesh] NOT "Humans"[Mesh] -	3388005
#10	#8 NOT #9	355
#11	#10 NOT ("Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type] OR "overview"[Title] OR "status review"[Title] OR "status reviews"[Title]) -	342

MeSH = Medical Subject Heading (Medline medical index term).

Note: the asterisk (*) stands for any character(s).

Table 170 Cochrane search strategy and results

Search Number	Search Terms	Returns
#1	MeSH descriptor Atrial Fibrillation explode all trees	1710
#2	(atrial OR atrium OR auricular):ti,ab,kw and (fibrillat*):ti,ab,kw	2857
#3	(#1 OR #2)	2857
#4	MeSH descriptor Aspirin explode all trees	3660
#5	MeSH descriptor Warfarin explode all trees	874
#6	MeSH descriptor Anticoagulants explode all trees	6788
#7	#7 MeSH descriptor Platelet Aggregation Inhibitors explode all trees 6783	
#8	(dabigatran OR "antiplatelet therapy" OR clopidogrel OR ximelagatran OR "vitamin K antagonist*" OR VKA OR dicoumarol OR phenindione OR phenprocoumon OR acenocoumarol OR "ethyl biscoumacetate" OR clorindione OR diphenadione OR tioclomarol):ti,ab,kw	1464
#9	(#4 OR #5 OR #6 OR #7 OR #8)	13243
#10	"randomised clinical trial*" OR "randomised controlled trial*" OR "randomized clinical trial*" OR "randomized controlled trial*":pt or "random allocation":ti,ab,kw	264101
#11	"clinical trial*":ti,ab,kw and (random*):ti,ab,kw	36830
#12	(#10 OR #11)	285211
#13	(#3 AND #9 AND #12)	234
#14	(comment* OR letter* OR editorial* OR "case report*" OR "case stud*"):pt or (overview OR "status review*"):ti	5947
#15	(#13 AND NOT #14)	228

MeSH = Medical Subject Heading (Medline medical index term); pt = publication type; ti = title.

Note: the asterisk (*) stands for any character(s).

Table 171 EMBASE search strategy and results

Search Number	Search Terms	Returns
S1	HEART()ATRIUM()FIBRILLATION/DE	29662
S2	(ATRIAL OR ATRIUM OR AURICULAR)/TI,AB,DE AND FIBRILLAT?/TI,AB,DE	34472
S3	S1 OR S2	34472
S4	(DABIGATRAN/DE OR ACETYLSALICYLIC()ACID/DE OR WARFARIN/DE OR ANTICOAGULANT AGENT! OR ANTITHROMBOCYTIC AGENT! OR CLOPIDOGREL/DE OR XIMELAGATRAN/DE)	294409
S5	(ANTIPLATELET()THERAPY OR VITAMIN()K()ANTAGONIST? OR VKA OR DICOUMAROL OR PHENINDIONE OR PHENPROCOUMON OR ACENOCOUMAROL OR ETHYL()BISCOUMACETATE OR CLORINDIONE OR DIPHENADIONE OR TIOCLOMAROL)/TI,AB,DE,TN,ID	11694
S6	S4 OR S5	294858
S7	RANDOMIZED()CONTROLLED()TRIAL/DE OR RANDOM()ALLOCATION/TI,AB,DE	173755
S8	CLINICAL()TRIAL?/TI,AB,DE AND RANDOM?/TI,AB,DE	223613
S9	S7 OR S8	225736
S10	S3 AND S6 AND S9	858
S11	S10/HUMAN	855
S12	RD S11 (unique items)	849
S13	S12 NOT (DT = LETTER OR DT = EDITORIAL OR COMMENT?/TI OR CASE()REPORT/DE OR CASE()STUDY/DE OR OVERVIEW/TI OR STATUS()REVIEW?/TI)	818

DE = descriptor; DT = document type; TI = title.

Symbols: '!' means to 'explode' a descriptor; '?' is a wildcard symbol for plural forms.

Table 172 BIOSIS search strategy and results

Search Number	Search Terms	Returns
S1	ATRIAL()FIBRILLATION/DE	18109
S2	(ATRIAL OR ATRIUM OR AURICULAR)/TI,AB,DE AND FIBRILLAT?/TI,AB,DE	25339
S3	S1 OR S2	25339
S4	(DABIGATRAN OR ASPIRIN OR WARFARIN OR ANTICOAGULANT? OR PLATELET()AGGREGATION()INHIBITOR? OR ANTIPLATELET()THERAPY OR CLOPIDOGREL OR XIMELAGATRAN OR VITAMIN()K()ANTAGONIST? OR VKA OR DICOUMAROL OR PHENINDIONE OR PHENPROCOUMON OR ACENOCOUMAROL OR ETHYL()BISCOUMACETATE OR CLORINDIONE OR DIPHENADIONE OR TIOCLOMAROL)/TI,AB,DE	90818
S5	(RANDOMIZED()CONTROLLED()TRIAL? OR RANDOMISED()CONTROLLED()TRIAL? OR RANDOMIZED()CLINICAL()TRIAL? OR RANDOMISED()CLINICAL()TRIAL?)/DE	3979
S6	RANDOM()ALLOCATION/TI,AB,DE	505
S7	CLINICAL()TRIAL?/TI,AB,DE AND RANDOM?/TI,AB,DE	37246
S8	S5 OR S6 OR S7	39890
S9	S3 AND S4 AND S8	101
S10	S9/HUMAN	99
S11	NOT (DT = LETTER OR DT = EDITORIAL OR COMMENT?/TI OR CASE()REPORT?/DE OR CASE()STUD?/DE OR OVERVIEW/TI OR STATUS()REVIEW/TI OR STATUS()REVIEWS/TI)	98

DE = descriptor; DT = document type; TI = title.

Symbols: '!' means to 'explode' a descriptor; '?' is a wildcard symbol for plural forms.

9.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were performed.

9.4.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria are presented in the main body of the submission in **Table 37** and **Table 38**.

9.4.7 The data abstraction strategy.

The data abstraction strategy is presented in the main body of the submission in Section 5.7.2.

Data tables from the MTC


Separate dose analysis tables.zip


Sequential dose analysis tables.zip


Included/excluded studies and extracted

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

As part of the full text review of studies, each paper was assessed against the Jadad quality criteria. The embedded spreadsheet below presents this assessment for each included study.

Jadad Assessment.xls

Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.5.2 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

9.5.3 The date on which the search was conducted.

9.5.4 The date span of the search.

9.5.5 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

9.5.6 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.5.7 The inclusion and exclusion criteria.

9.5.8 The data abstraction strategy.

The searches outlined in Section 9.2 also encompassed non-RCT evidence from observational studies. No relevant non-RCT studies were identified and therefore no further discussion in this section is required.

9.6 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.6.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.7 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.7.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

9.7.2 The date on which the search was conducted.

9.7.3 The date span of the search.

9.7.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

9.7.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.7.6 The inclusion and exclusion criteria.

9.7.7 The data abstraction strategy.

The results of the searches outlined in Section 9.2 represent the totality of evidence relating to the clinical effectiveness and safety of DBG in this indication. Therefore no further searches were necessary.

9.8 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.8.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.9 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

9.9.2 The date on which the search was conducted.

9.9.3 The date span of the search.

9.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

9.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

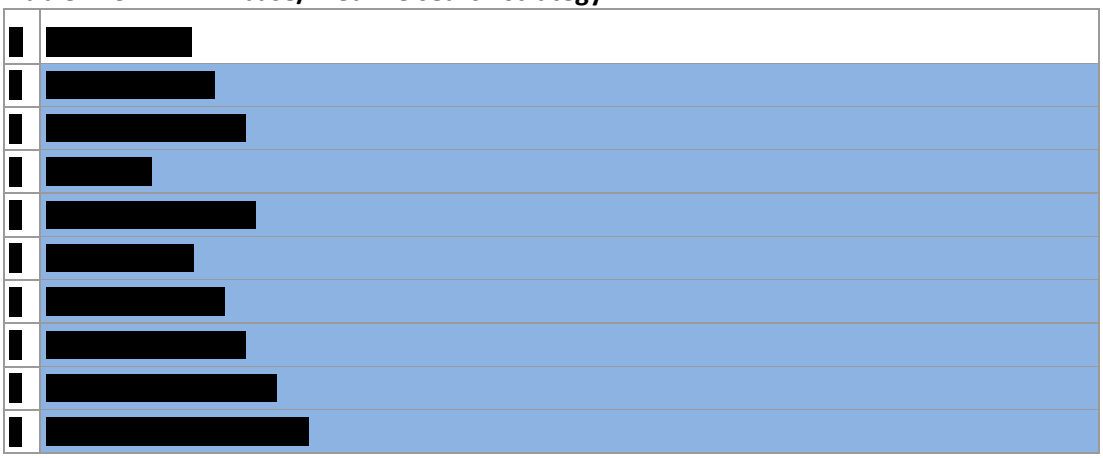
The responses to the above questions are consolidated below.

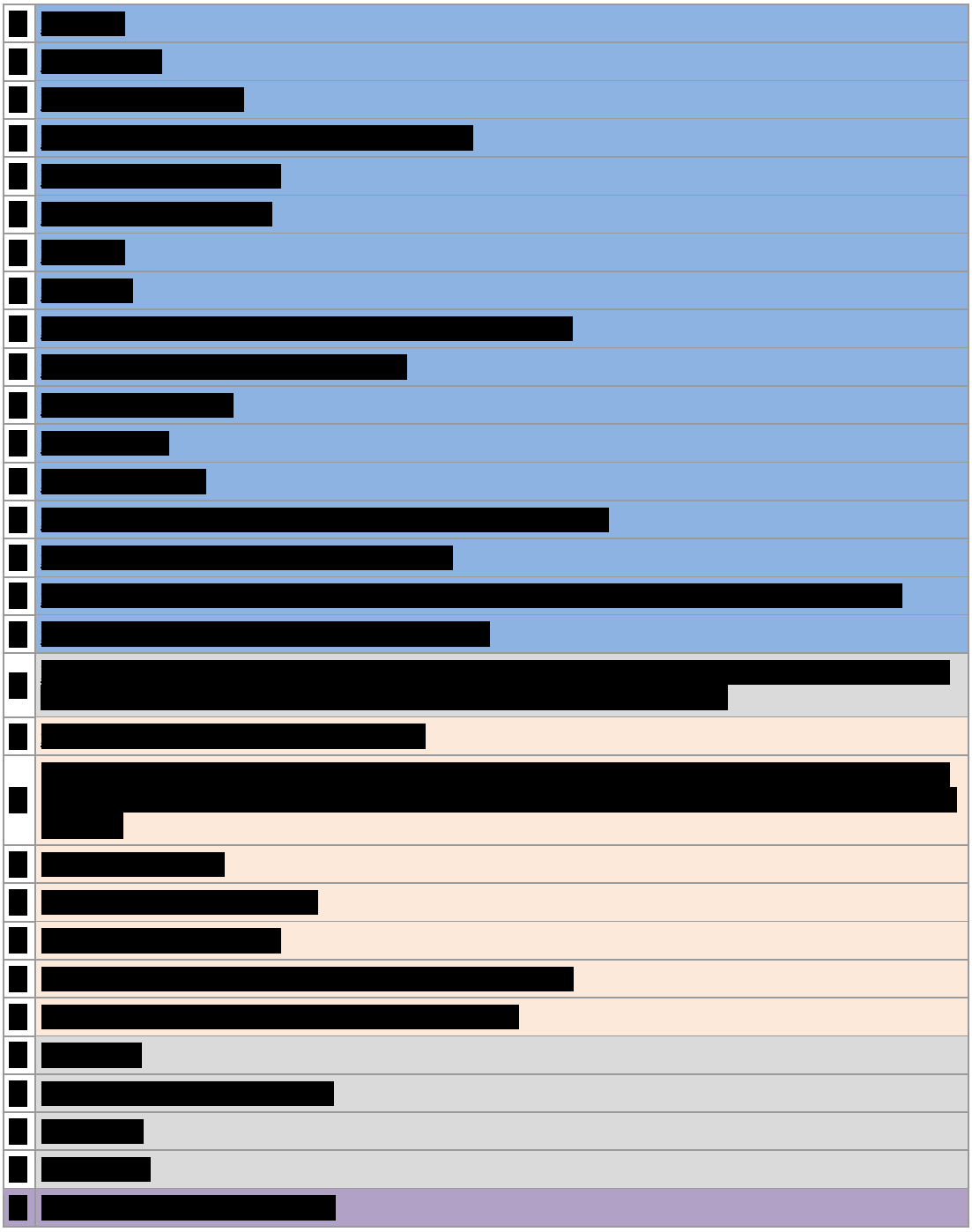
Embase/Medline

- Name of the databases searched: Embase, Medline
- Name of the interface: Embase.com
- Date span of search: 1990-present
- Date on which search was conducted: 05/07/2010

The search strategy for Embase and Medline is presented below in **Table 173**.

Table 173 Embase/Medline search strategy



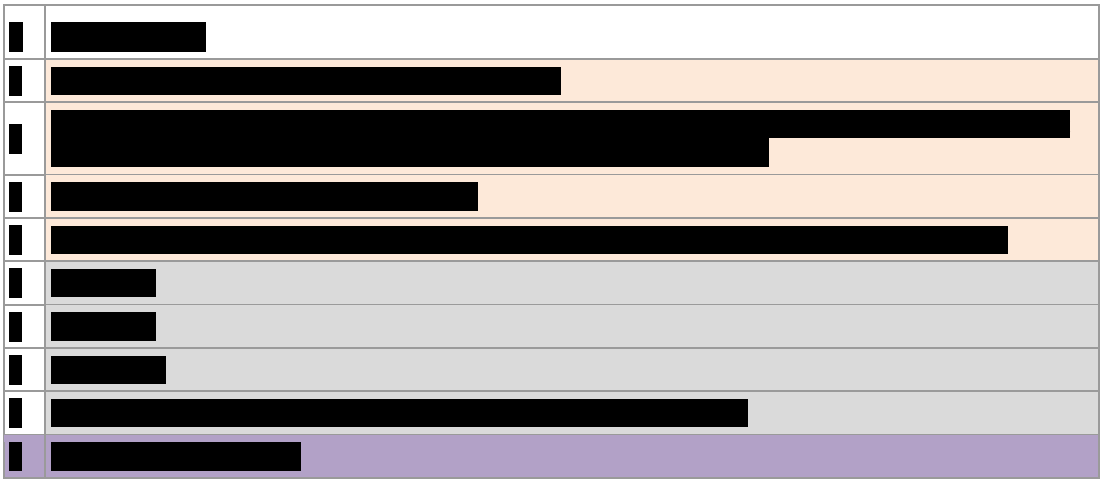


NHS EED

- Name of the databases searched: NHS EED
- Name of the interface: Cochrane library
- Date span of search: 1990-present
- Date on which search was conducted: 05/07/2010

The search strategy for NHS EED is presented below in **Table 174**.

Table 174 NHS EED search strategy



Medline In-Process

- Name of the databases searched: Medline In-Process
- Name of the interface: Pubmed
- Date span of search: Previous year
- Date on which search was conducted: 05/07/2010

The search strategy for Medline In-Process is presented below in **Table 175**.

Table 175 Medline In-Process search strategy

EconLit

- Name of the databases searched: EconLit
- Name of the interface: EBSCOHost

- Date span of search: 1990-present
- Date on which search was conducted: 05/07/2010

The search strategy for EconLit is presented below in **Table 176**.

Table 176 EconLit search strategy

[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

BILIT

- Name of the databases searched: Boehringer Ingelheim Literature database (BILIT)
- Name of the interface: Internal sponsor database
- Date span of search: No limit
- Date on which search was conducted: 05/07/2010

The search strategy for BILIT is presented below in **Table 177**.

Table 177 BILIT search strategy

#	Search History
1	(atrial fibrillation + stroke) AND GN=dabigatran and.t CL=major AND DE=(economics OR economic aspect OR cost OR health care OR fee OR budget OR economic evaluation)

Pre-BILIT

- Name of the databases searched: Boehringer Ingelheim Literature database, pre-publication (Pre-BILIT)
- Name of the interface: Internal sponsor database
- Date span of search: No limit
- Date on which search was conducted: 05/07/2010

The search strategy for Pre-BILIT is presented below in **Table 178**.

Table 178 Pre-BILIT search strategy

#	Search History
1	CL=major AND GN=dabigatran AND (atrial fibrillation + stroke and (economics OR economic aspect OR cost OR health care OR fee OR budget OR economic evaluation))

The full list of studies excluded at second pass is presented in the attached file.

Second pass exclusion.xls

9.10 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

Not applicable.

9.11 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

9.11.2 The date on which the search was conducted.

9.11.3 The date span of the search.

9.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

9.11.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.11.6 The inclusion and exclusion criteria.

9.11.7 The data abstraction strategy.

9.13.1 Databases searched	**Database**	**Service provider**
	Embase, Medline (including In-Process), Cochrane, EconLit and CRD Databases (including DARE, NHS EED and HTA),	Unknown
9.13.2 Date of search	• Searches of the Embase, Medline and Cochrane databases were initially conducted in the week of 13th October 2009 and were subsequently updated in the week of 5th July 2010 • Searches of the EconLit and CRD databases online (including DARE, NHS EED and HTA as required by NICE) were conducted in the week of 5th July 2010.	
9.13.3 Date span of search	No Limits were put on publication dates.	
9.13.4 Search strategies used	See attached files 	

9.13.5 Additional searches	Additional hand searching was conducted
9.13.6 Inclusion and exclusion criteria	• Not specific to the relevant health state (atrial fibrillation, stroke, myocardial infarction, bleeding/haemorrhage), or was specific to an intervention in those health states not relevant to this analysis, or was not in English. • Not a QoL paper, or a relevant economic evaluation, or reported values that were sourced from another publication, or was a review/letter/editorial. • Did not report preference based utility values (that is reported only health related QoL scores, VAS scores, utility values that relied on transformations from an HRQoL instrument, or expert opinion).
9.13.7 Data abstraction strategy	See files attached above plus the additional file below.  Review.doc

9.12 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

9.12.2 The date on which the search was conducted.

9.12.3 The date span of the search.

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

9.12.6 The inclusion and exclusion criteria.

9.12.7 The data abstraction strategy.

Table 179 Details of the systematic review of INR monitoring

9.13.1 Databases searched	**Database**	**Service provider**
	1. MEDLINE 2. Excerpta Medica Database (EMBASE) 3. NHS Economic Evaluation Database (NHSEED)	1. Datastar 2. Datastar 3. NHS National Institute for Health Research – Centre for

	4. Health Technology Assessment (HTA) 5. System for Information on Grey Literature (SIGLE) 6. National Research Registers (NRR) 7. Social Sciences Citation Index (SSCI) 8. Science Citation Index (SCI) 9. MEDLINE In-Process (MEIP) 10. EconLIT	Reviews and Dissemination website 4. NHS National Institute for Health Research – Centre for Reviews and Dissemination website 5. OpenSIGLE website at INIST 6. NHS National Institute for Health Research website – NRR archive 7. Datastar 8. Datastar 9. Datastar 10. Dialog (Thomson Dialog)
9.13.2 Date of search	28 April 2008: Searches from 01 January 1990 to 28 April 2008 were carried out on the following databases: • MEDLINE • EMBASE • NHSEED • HTA • SIGLE • NRR • SSCI • SCI 04 August 2010: Further searches from 01 Jan 2008 to 04 August 2010 were carried out on the above databases. 04 August 2010: Searches from 01 January 1990 to 04 August 2010 were carried out on the following databases: • MEIP • EconLIT	
9.13.3 Date span of search	01 January 1990 to 04 August 2010	
9.13.4 Search strategies used	The comprehensive search strategies (strings) shown below were used in MEDLINE and subsequently translated and adapted for use in the other databases: [redacted] • [redacted]	
9.13.5 Additional searches	The reference lists of relevant studies identified from the database searches were searched manually for further relevant studies, as were the reference lists of reviews identified during preliminary searches of the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). Relevant abstracts from conferences were also identified through searches of the abstract books from the following societies: • American Society of Hematology (ASH) • British Society for Haematology (BSH) • European Hematology Association (EHA) • International Society on Thrombosis and Haemostasis (ISTH) • International Society for Pharmacoeconomic and Outcomes Research (ISPOR). Conference abstracts were evaluated separately from other studies (this was only done for the first search). NICE costing reports were also searched manually.	
9.13.6 Inclusion and	The inclusion criteria were: • Published in or after 1990	

exclusion criteria	• Adult patients (≥18 years of age) receiving oral anticoagulation with warfarin or other vitamin K antagonists for any indication • INR being monitored using any method • Reported data on costs or cost-effectiveness of INR monitoring. Exclusion criteria were • Studies published before 1990 • Letters to the editor • Commentaries (unless they reported the results of a study not reported elsewhere). • The searches had no language restrictions, although only studies with an English abstract were included. Data from foreign language publications that appeared to be relevant were incorporated into the spreadsheet of results as far as possible.
9.13.7 Data abstraction strategy	Data were extracted from relevant publications by the writer into an Excel-based spreadsheet using a predefined set of parameters. The spreadsheet was checked by the reviewer once completed. Disagreements were resolved by discussion, but if the writer and reviewer were unable to come to an agreement, it was discussed with a second reviewer. Studies reported in multiple publications were extracted and reported only once. Standard deviations, 95% confidence intervals and ranges were extracted where available. Data from the NICE was extracted separately.

Table 180 Details of the systematic review of stroke resource-use and costs (Part 1)

9.13.1 Databases searched	**Database and Service provider**
	• EconLit (SilverPlatter) • EMBASE (Ovid) • Health Economics Evaluation Database (HEED) (CD-ROM) • Health Management Information Consortium (HMIC) (HELMIS, DHdata and the King's Fund databases) (SilverPlatter) • Health Technology Assessment Database (HTA) http://agatha.york.ac.uk/welcome.htm • Internet Documents in Economics Access Service (IDEAS) (working papers sections only) • ISI Web of Science Proceedings (WoSP-ISTP) http://wos.mimas.ac.uk/ • LILACS http://www.bireme.br/bvs/E/ebd.htm • MEDLINE (Ovid) • NHS Economic Evaluation Database (NHS EED) http://nhscrd.york.ac.uk/welcome.htm • PREMEDLINE (Ovid) • Science Citation Index (SCI) http://wos.mimas.ac.uk/ • Social Science Citation Index (SSCI) http://wos.mimas.ac.uk/ • System for Information on Grey Literature in Europe (SIGLE) (SilverPlatter) • ZETOC http://zetoc.mimas.ac.uk/
9.13.2 Date of search	1st; 4th-8th and 11th-15th February 2008 inclusive.
9.13.3 Date span of search	1st January 1990 to the 31st January 2008
9.13.4 Search strategies used	[redacted]
9.13.5 Additional searches	**General search terms used:** **Cost(s)** cost analysis/analyses health economics pharmacoeconomics economics

	medical hospital nursing pharmaceutical budget(s) economic models economic evaluation(s) pricing prescription fees expenditure health resources resource utilization/use tariff **<u>Stroke</u>** acute stroke management/care pathway(s) therapy/therapies treatment(s)
9.13.6 Inclusion and exclusion criteria	• Initially abstracts were reviewed and if they included costs associated with stroke treatment, management or rehabilitation the paper was procured for appropriate examination • All papers were reviewed by two separate researchers and any arbitrary papers were examined by an independent health economist. • The primary focus of the search was to identify prospective studies that provided actual costs associated with stroke treatment, management or rehabilitation • Reviewed papers were retained for cross-reference to ensure identification of source reference from original searches; therefore if the study was found to be retrospective, the original prospective study was identified from the references contained within the paper • Abstracts excluded ONLY if clearly not relevant to 'cost of stroke' e.g. 'two-stroke engine' • Non-relevant abstracts were captured and recorded with rationale for exclusion • Full publications obtained for all abstracts identified as potentially relevant
9.13.7 Data abstraction strategy	Data was extracted into a searchable Excel database. The data extracted included: • Source (Author, Date) • Country • Stroke subtype • Severity • Patient/population characteristics • Perspective • Treatment phase • Source of data • Cost description • Cost value • Currency • Price year • Uprated international value - $US PPP (2007) • Indicator of subgroup analysis • Specific cost components estimates (if presented) • Indicator whether resource use is reported • Sponsorship • Overall quality score (excellent, good, poor) • Specific quality criteria

Table 181 Details of the systematic review of stroke resource-use and costs (Part 2)

9.13.1 Databases searched	**Database and Service provider**
	In order to identify publications reporting data pertaining to the costs of stroke in the UK (resource use, unit costs, budgetary impact etc), the following electronic databases were searched via DataStar (http://www.datastarweb.com/):

	• MEDLINE • EMBASE • MEDLINE (R) In-process NHS Economic Evaluations Database (NHS-EED) was searched manually using the Centre for Reviews and Dissemination website (http://www.york.ac.uk/inst/crd/), and Econ Lit was searched for publications via EBSCO (http://www.ebsco.com/).
9.13.2 Date of search	2nd August 2010
9.13.3 Date span of search	January 2008 until date of search
9.13.4 Search strategies used	[redacted]
9.13.5 Additional searches	No additional searches were conducted
9.13.6 Inclusion and exclusion criteria	In order to define the eligible publications for inclusion in the updated systematic review, the **PICO**(S) process was used. • **Patient population** o Only publications presenting data for patients with the following types of event were included: ▪ Ischaemic stroke ▪ Haemorrhagic stroke ▪ Transient ischaemic attack (TIA) Publications presenting data for any other medical condition, or other ischaemic or haemorrhagic events, were excluded. • **Interventions and comparators** Publications presenting cost or resource use data for any therapeutic intervention for patients experiencing the events above were eligible for inclusion in the systematic review. • **Outcome measures** Any costs or resource use attributed to the treatment/management of patients who have experienced a stroke or TIA were considered. Outputs were stratified according to acute (up to 90 days), long-term (longer than 90-days in subsequent 3-month periods), or ongoing (spanning acute and long-term) management of stroke. • **Studies** Any publication that included economic data relating to the cost or use of healthcare resources following stroke was eligible for inclusion in the systematic review.
9.13.7 Data abstraction strategy	A positive exclusion method was employed in the screening of publications, such that only those that did not exhibit one or more of the inclusion criteria were excluded from the review. Publications for which there was insufficient information for exclusion remained in the review until a stage where it could be proven that they did not meet the inclusion criteria. **First-pass screening** First-pass screening of titles and/or abstracts of all publications identified by the systematic literature search was performed by a small team of three experienced researchers using a filtering checklist (Is the publication written in English? Does the publication consider a relevant patient/subject population (e.g. ischaemic or haemorrhagic stroke, TIA)? Are there any resource use or direct cost data of interest (e.g. any UK data)?) A second reviewer independently screened a random selection (approximately 10%) of the titles/abstracts, and the reviewers' decisions were compared. Discrepancies or inconsistencies between reviewers' decisions were identified and a final decision reached by consensus. Full-text copies of publications were retrieved for all citations meeting the first-pass criteria, plus those that could not be positively excluded, and these publications proceeded to the second-pass screening stage. **Second-pass screening** Two reviewers screened the full-texts versions of all published articles proceeding to the second-pass stage using the same filtering checklist (Table 9-4). A randomly generated selection of approximately 10% of the publications identified was then independently reviewed as in the

	first-pass. Publications meeting the inclusion criteria remained in the review and proceeded to the data selection and extraction stage. **Data selection and extraction** Two reviewers independently selected and extracted the data available in 100% of the full-text publications proceeding to data extraction. Extracted data were entered into an Excel spreadsheet.

Table 182 Deatils of the systematic review of major bleeds

9.13.1 Databases searched	**Database and Service provider** • Medline • Embase • Medline in process (access via Embase.com) • Embase (access via Embase.com) • NHS EED (access via Cochrane) • EconLiT (access via AEA)
9.13.2 Date of search	16th June 2010
9.13.3 Date span of search	1st January 2000 to 16th June 2010
9.13.4 Search strategies used	

	[redacted]
9.13.5 Additional searches	None
9.13.6 Inclusion and exclusion criteria	Studies were included if they reported data on the cost or resource use of major bleeds in adult patients in the United Kingdom. Non-English language studies were excluded. The following studies were included: o Cost-effectiveness analyses o Cost-utility analyses o Cost-benefit analyses o Cost-minimisation analyses o Economic evaluation methodology studies o Budget impact models o Cost studies/surveys/analyses o Cost consequence studies o Resource cost surveys/studies o Database studies collecting cost data The following studies were excluded from the review: o Study designs o Randomized controlled trials o Animal or in vitro studies o Clinical studies o Literature reviews
9.13.7 Data abstraction strategy	A conservative search strategy was used to identify studies from the UK as well as studies from other countries that are relevant to the UK in case UK data were unavailable. Abstracts of studies identified by the search strategy were reviewed by two reviewers to determine if they would be passed on to the second screening stage. Discrepancies between the two reviewers were reconciled by a third reviewer. Full text versions of studies included following the first screening stage were ordered. These studies were then reviewed for inclusion in the final review by two reviewers. Discrepancies between the two reviewers were reconciled by a third reviewer. In order to produce model inputs, data were extracted from all UK studies included in this review according to NICE guidelines. Information was extracted from each included study by two reviewers, with the extractions being reconciled by a third reviewer.

OXVASC Study Data Tables

[redacted]

9.13 Appendix 14: PETRO-EX

[redacted]