NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

June 2012

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care 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 10.1 to 10.13) 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’, section 11.

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.

Abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AF	Atrial fibrillation
AIC	Adjusted indirect comparisons
ALT	Aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BD	Twice daily
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRBE	Clinically relevant bleeding
CrCl	Creatinine clearance
CRNMB	Clinically relevant non-major bleeding
CTEPH	Chronic thromboembolic pulmonary hypertension
CUS	Compression ultrasonography
DBG	Dabigatran
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full analysis set
GI	Gastrointestinal
GPRD	General Practice Research Database
HR	Hazard ratio
HRG	Healthcare Resource Groups
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
INR	International normalised ratio
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LFT	Liver function test
LMWH	Low molecular-weight heparin
LY	Life year
MBE	Major bleeding event
MCRB	Major or clinically relevant bleeding
MI	Myocardial infarction
MTC	Mixed treatment comparison
NHS	National Health Service
NHSRC	NHS reference costs
NOAC	Novel oral anticoagulant
NVAF	Non-valvular atrial fibrillation
PE	Pulmonary embolism
P-gp	P-glycoprotein
PKS	Pharmacokinetic set
PPS	Per-protocol set

PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life year
QOF	Quality and Outcomes Framework
RCT	Randomised controlled trial
RR	Relative risk
rVTERD	Symptomatic recurrent VTE and VTE-related death
RVX	Rivaroxaban
SAE	Severe adverse event (including fatal outcomes)
SC	Subcutaneous injection
SD	Standard deviation
SE	Standard error
SG	Standard gamble
SOC	System organ class
SPAF	Stroke patient with atrial fibrillation
SPC	Summary of product characteristics
TA	Technology assessment
TS	Treated set
TTO	Time trade-off
UA	Unstable angina
UFH	Unfractionated heparin
UK	United Kingdom of Great Britain and Northern Ireland
ULN	Upper limit of normal
US	United States of America
VAS	Visual analogue scale
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WFN	Warfarin

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.

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.
- Tabulation of the base-case results as follows:
- When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance.

- Subgroup analyses considered and clinical- and cost-effectiveness results.

Product Details

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

- Formulation: 110mg and 150 mg hard capsules (also available as 75mg hard capsules for another indication)
- Dosing regimen: Either 110mg or 150 mg twice daily
- Course length: 3 or 6 months for the treatment of deep vein thrombosis and pulmonary embolism; or ongoing treatment for the secondary prevention of recurrent deep vein thrombosis and pulmonary embolism
- Pack size: 60 capsule pack for 150 mg; 10 capsule pack and 60 capsule pack for 110 mg (and 75 mg)
- Cost: £65.90 for 60 capsule pack; £10.98 for 10 capsule pack.

Mechanism of Action

The oral pro-drug dabigatran etexilate is rapidly converted to its active form, dabigatran. Dabigatran is an orally available synthetic reversible thrombin inhibitor, which prevents blood clot (thrombus) formation by binding to thrombin with a high affinity and specificity. The pro-drug itself has no anticoagulant activity.

Indication

Treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent DVT and PE in adults.

Marketing Status

Dabigatran etexilate (hereafter dabigatran) holds marketing authorisation in the UK for the use in:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.

Dabigatran does not currently have UK marketing authorisation for the indication detailed in this submission (treatment of DVT and PE, and secondary prevention of recurrent DVT and PE in adults). The dossier for regulatory approval was submitted to the EMEA on 3rd June 2013 and will be considered through the centralised procedure. CHMP positive opinion was adopted on 25th April and marketing authorisation in the European Union is currently expected in June/July 2014.

Comparators

Following acute parenteral treatment with heparin (either low molecular-weight heparin (LMWH) or unfractionated heparin (UFH)), therapy with dose-adjusted warfarin (overlapping

and started as early as possible) is generally recognised as the current gold standard in the acute treatment and secondary prevention of venous thromboembolism (VTE). Therefore, 'LMWH then warfarin' is the primary comparator.

Further relevant comparators for dabigatran in the indication detailed in this submission are:

- Rivaroxaban, a factor Xa inhibitor, which has been recommended as an option for acute treatment of DVT and PE, as well as preventing recurrent DVT and PE in adults (NICE TA261,TA287).
- For patients with active cancer, LMWH has been recognised as the preferred treatment over warfarin for at least the first 3-6 months in patients with cancer-associated VTE. Therefore, LMWH monotherapy in patients with active cancer is a comparator.

Fondaparinux is an alternative to LMWH as UFH, for the initial treatment of DVT. However, it is not approved for long-term prophylaxis of VTE and therefore is not considered a relevant comparator for dabigatran in the indication of treatment and long-term secondary prevention of VTE as detailed in this submission.

Source of clinical evidence

The efficacy and safety of dabigatran in the acute treatment and secondary prevention of VTE have been examined in four phase III studies:

- Completed - RE-COVER (NCT00291330) and RE-COVER II (NCT00680186): duplicate studies designed to compare dabigatran (150 mg BD.) and warfarin (target INR of 2.0-3.0) for 6 months of treatment for acute symptomatic VTE.
- Completed – RE-MEDY (NCT00329238): designed to compare the efficacy and safety of dabigatran (150 mg BD) and warfarin (target INR 2.0-3.0) for the long-term treatment and secondary prevention of symptomatic VTE in patients who had already completed 3 to 12 months of anticoagulation treatment and who were considered to be at risk for recurrent VTE.
- Completed – RE-SONATE (NCT00558259): a placebo-controlled superiority study designed to evaluate whether dabigatran (150 mg BD) was superior to placebo in the prevention of recurrent symptomatic VTE in patients with confirmed symptomatic DVT and/or PE who had previously completed 6 to 18 months of anticoagulation treatment and were considered to be at equipoise for the need for continued anticoagulant therapy.

Summary of clinical evidence

RE-COVER and RE-COVER II

RE-COVER and RE-COVER II demonstrated that dabigatran was non-inferior to warfarin for the treatment of acute symptomatic VTE in terms of the primary endpoint of recurrent symptomatic VTE and VTE-related deaths.

The primary analysis for efficacy was assessed by the hazard ratio calculated with the use of the Cox model and the difference in risk calculated with the use of Kaplan–Meier estimates.[1] Both summary statistics were adjusted for the initial presentation (i.e., PE or DVT) and for the presence or absence of active cancer at baseline (the interaction between active cancer and symptomatic PE was also included in the Cox model).[1]

The secondary efficacy endpoints were the same for both RE-COVER and RE-COVER II and, as in the primary efficacy analyses; the results were divided into the four strata identified by the baseline prevalence of PE and cancer.

A pooled analysis of the pivotal RE-COVER and RE-COVER II studies supported data from the individual trials; with dabigatran 150 mg BD shown to be comparable to warfarin for the primary endpoint (symptomatic recurrent VTE and VTE related death). Pooled event rates for components of the efficacy outcomes are shown in Table 1.[2]

Table 1: Efficacy outcomes in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE[2]

	Dabigatran n = 2,553	Warfarin n = 2,554	Hazard ratio* (95% CI)
Primary endpoint of VTE and VTE related deaths, n (%)			
During 6 months	60 (2.4)	55 (2.2)	1.09 (0.76, 1.57)
During the study period plus an additional 30 day follow up	68 (2.7)	62 (2.4)	1.09 (0.77, 1.54)
Secondary endpoints, n (%)			
Symptomatic DVT[#]	40 (1.6)	34 (1.3)	ND
Symptomatic non-fatal PE[#]	18 (0.7)	18 (0.7)	ND
Death related to PE[#]	2 (0.1)	3 (0.1)	ND
All deaths	46 (1.8)	46 (1.8)	1.0 (0.67, 1.51)

CI, confidence interval; ND, no data. *The hazard ration was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study. [#]These are the events contributing to the primary endpoint. In the case of a patient suffering 2 different events, the first event is counted.

Analyses were conducted for subgroups in which the underlying risks of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ (Table 2).

Table 2: VTE and VTE related deaths for specific subgroups in pooled analysis of RE-COVER and RE-COVER II until the end of post-treatment period[3]

	Dabigatran		Warfarin		
	Total n	Event n (%)	Total n	Event n (%)	Hazard ratio (95% CI)
Total	2553	68	2554	62	-
Symptomatic PE as index event					
No	1758	45 (2.6)	1747	37 (2.1)	1.20 (0.78, 1.86)
Yes	795	23 (2.9)	807	25 (3.1)	0.93 (0.53, 1.64)
Active cancer					
Yes	173	10 (5.8)	162	12 (7.4)	0.76 (0.33, 1.76)
History of bleedings					
Yes	123	6 (4.9)	129	5 (3.9)	1.28 (0.39, 4.21)
Geographical region					
Western Europe	613	13 (2.1)	626	18 (2.9)	0.74 (0.36, 1.50)

An overview of AEs occurring during the studies is provided in Table 3.

Table 3: Summary of adverse events in RE-COVER and RE-COVER II[1;2;4]

Outcome	RE-COVER		RE-COVER II	
	Dabigatran n = 1273	Warfarin n = 1266	Dabigatran n = 1280	Warfarin n = 1288
Patients with any AE – n (%)	844 (66.3)	856 (67.6)	852 (66.6)	916 (71.1)
Patients with severe AEs – n (%)	96 (7.5)	101 (8.0)	156 (12.2)	153 (11.9)
Drug-related AEs* – n (%)	195 (15.3)	229 (18.1)	194 (15.2)	282 (21.9)
AEs leading to discontinuation – n (%)	115 (9.0)	86 (6.8)	100 (7.8)	100 (7.8)

*Relationship as assessed by the investigator
Abbreviations: AE, adverse event.

The timing of the initiation of oral anticoagulation therapy in relation to the parenteral anticoagulant differs between warfarin and dabigatran owing to difference in their onset of action. Therefore, two safety comparisons were made: from the start of any drug (from single-dummy period) and from the start of oral drug only (double-dummy period, after warfarin had reached therapeutic levels).[2]

Regardless of the calculation, pooled data from RE-COVER and RE-COVER II consistently showed a profile of less bleeding with dabigatran than with warfarin, with the exception of major bleeding events (Table 4).[2]

Table 4: Safety outcomes in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE[2]

Outcome	Dabigatran (n = 2,553)	Warfarin (n = 2,554)
From the start of any study drug (single and double-dummy periods)		
MBEs, n (%)	37 (1.4)	51 (2.0)
Hazard ratio (95% CI)*	0.73 (0.48, 1.11)	
Intracranial bleeding	2 (0.1)	5 (0.2)
MBEs or CRBEs, n (%)	136 (5.3)	217 (8.5)
Hazard ratio (95% CI)*	0.62 (0.50, 0.76)	
Any bleeding events, n (%)	411 (16.1)	567 (22.2)
Hazard ratio (95% CI)*	0.70 (0.61, 0.79)	
From the start of the oral drug only (double dummy period only)		
MBEs, n (%)	24 (1.0)	40 (1.6)
Hazard ratio (95% CI)*	0.60 (0.36, 0.99)	
Intracranial bleeding	2 (0.1)	4 (0.2)
MBEs or CRBEs, n (%)	109 (4.4)	189 (7.7)
Hazard ratio (95% CI)*	0.56 (0.45, 0.71)	
Any bleeding events, n (%)	354 (14.4)	503 (20.4)
Hazard ratio (95% CI)*	0.67 (0.59, 0.77)	

*The hazard ratio was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study.
Abbreviations: CRBE, clinically relevant bleeding event; MBE, major bleeding event.

Analyses were conducted for subgroups in which the underlying risks of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ. The incidence of MBE and MBE/CRBE in these subgroups is displayed in Table 5 and Table 6, respectively.

Table 5: Incidence of MBE in specific subgroups for pooled RE-COVER and RE-COVER II analyses from the start of the oral drug only (double dummy period only)[3]

	Dabigatran		Warfarin		
	Total n	Event n (%)	Total n	Event n (%)	Hazard ratio (95% CI)
Total	2456	24	2462	40	-
Symptomatic PE as index event					
No	1697	20 (1.2)	1694	32 (1.9)	0.62 (0.35, 1.08)
Yes	759	4 (0.5)	768	8 (1.0)	0.50 (0.15, 1.67)
Active cancer					
Yes	159	6 (3.8)	152	7 (4.6)	0.78 (0.26, 2.32)
History of bleedings					
Yes	117	1 (0.9)	124	4 (3.2)	0.29 (0.03, 2.61)
Geographical region					
Western Europe	588	8 (1.4)	604	8 (1.3)	1.02 (0.38, 2.71)

Abbreviations: PE, pulmonary embolism.

Table 6: Incidence of MBE or CRBE in specific subgroups for pooled RE-COVER and RE-COVER II analyses from the start of the oral drug only (double dummy period only)[3]

	Dabigatran		Warfarin		
	Total n	Event n (%)	Total n	Event n (%)	Hazard ratio (95% CI)
Symptomatic PE as index event					
No	1697	73 (4.3)	1694	134 (7.9)	0.53 (0.40, 0.70)
Yes	759	36 (4.7)	768	55 (7.2)	0.65 (0.43, 0.99)
Active cancer					
Yes	159	23 (14.5)	152	20 (13.2)	NR
History of bleedings					
Yes	117	13 (11.1)	124	17 (13.7)	NR
Geographical region					
Western Europe	588	30 (5.1)	604	57 (9.4)	NR

Abbreviations: NR, not reported; PE, pulmonary embolism.

RE-MEDY

RE-MEDY demonstrated that dabigatran was non-inferior to well-controlled warfarin, in terms of the primary endpoint of recurrent symptomatic VTE and VTE-related deaths, for the long-term treatment and secondary prevention of symptomatic VTE. The results of RE-MEDY with respect to

the primary endpoint (composite of recurrent symptomatic VTE and death related to VTE within 18 months from randomisation) are presented in Table 7.[5]

For the analyses of the secondary endpoints, results for all three cohorts were pooled. For all secondary endpoints except the composite endpoint of recurrent VTE and all deaths, results from all strata were pooled for the risk difference analysis due to the low number of events.[6]

The incidence of recurrent VTE and all deaths, symptomatic DVT, VTE-related deaths and all deaths was low in both treatment groups (Table 8).There was no statistically significant difference by treatment group in the rate of any of the secondary endpoints.[5]

Table 7: RE-MEDY primary efficacy outcome [5;6]

	Dabigatran n = 1,430	Warfarin n = 1,426
Patients with event, *n* (%)	26 (1.8)	18 (1.3)
Hazard ratio (95% CI)	1.44 (0.78, 2.64)	
p-value for non-inferiority	0.01	
p-value for superiority	0.2424	
Patients with event; VTE, VTE-related and unexplained death, *n* (%)	27 (1.9)	20 (1.4)
Hazard ratio (95% CI)	1.33 (0.74, 2.40)	
p-value for non-inferiority	0.0055	
p-value for superiority	0.3349	
By cohort, *n* (%)		
Cohort 1 (Planned treatment duration 18 months)	18 (2.3)	14 (1.8)
Cohort 2 (Planned treatment duration >18 months)	4 (1.4)	3 (1.1)
Cohort 3 (Planned treatment duration <18 months)	4 (1.1)	1 (0.3)
By stratification factor*, *n* (%)		
Symptomatic PE with cancer	1 (4.0)	0 (0.0)
Symptomatic PE without cancer	13 (2.8)	7 (1.5)
No symptomatic PE with cancer	1 (2.9)	1 (2.8)
No symptomatic PE without cancer	11 (1.2)	10 (1.1)

*Analysis for first adjudicated recurrent VTE or VTE death by baseline strata

Abbreviations: CI, confidence interval. PE, pulmonary embolism.

Table 8: RE-MEDY secondary efficacy outcomes at 18 months [5;6]

	Dabigatran n = 1,430	Warfarin n = 1,426
Recurrent symptomatic VTE and all deaths, *n*	42	36
Hazard ratio (95% CI)	1.18 (0.75, 1.84)	
By stratification factor, *n* (%)		
Symptomatic PE with cancer	4 (16.0)	2 (8.7)
Symptomatic PE without cancer	14 (3.0)	9 (1.9)
No symptomatic PE with cancer	4 (11.4)	3 (8.3)
No symptomatic PE without cancer	14 (1.5)	18 (2.0)
Symptomatic DVT, *n* (%)	17 (1.2)	13 (0.9)
Hazard ratio (95% CI)	1.32 (0.64, 2.71)	
Symptomatic non-fatal PE, *n* (%)	10 (0.7)	5 (0.4)
Hazard ratio (95% CI)	2.04 (0.70, 5.98)	
Deaths related to VTE, *n* (%)	1 (0.1)	1 (0.1)
Hazard ratio (95% CI)	1.01(0.06, 16.22)	
All deaths, *n* (%)	17 (1.2)	19 (1.3)
Hazard ratio (95% CI)	0.90 (0.47, 1.72)	

Analysis was based on data for the planned treatment period, regardless of whether the study drug was discontinued early.

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

The frequency of patients with treatment-emergent MBEs was lower in the dabigatran group (13 patients, 0.9%) than in the warfarin group (25 patients, 1.8%), with a hazard ratio of dabigatran vs. warfarin of 0.52 (95% CI 0.27, 1.02) and a risk difference of −1.29% (95% CI −2.20%, −0.38%). The overall incidence of treatment-emergent AEs was similar in both treatment groups.[6] During the treatment period, 72.0% of patients in the dabigatran group and 70.8% of patients in the warfarin group reported AEs (Table 9). During the post-treatment period, 11.8% of patients in the dabigatran group and 11.6% of patients in the warfarin group reported AEs.[6]

Table 9: Summary of adverse events in RE-MEDY during the treatment period[5;6]

Outcome	Dabigatran n = 1,430	Warfarin n = 1,426
Patients with any AE – n (%)	1,029 (72.0)	1,010 (70.8)
Patients with severe AEs – n (%)	143 (10.0)	151 (10.6)
Drug-related AEs* – n (%)	229 (16.0)	280 (19.6)
AEs leading to discontinuation – n (%)	145 (10.1)	126 (8.8)

* Relationship as assessed by the investigator. AE, adverse event.

The overall hazard ratio for time to first MBE was 0.52 (95% CI 0.27, 1.02) (Table 10).

In both groups, two patients had bleeding at two sites. Major or clinically relevant non-major bleeding occurred in 80 patients (5.6%) in the dabigatran group and 145 patients (10.2%) in the warfarin group (hazard ratio, 0.54; 95% CI 0.41, 0.71; P<0.001). There were no significant differences in the risk of bleeding according to study treatment in predefined subgroups.[5]

Table 10: Bleeding events in RE-MEDY[5]

Outcome	Dabigatran n = 1,430	Warfarin n = 1,426
MBE, n (%)	13 (0.9)	25 (1.8)
Hazard ratio (95% CI)	0.52 (0.27, 1.02)	
MCRB, n (%)	80 (5.6)	145 (10.2)
Hazard ratio (95% CI)	0.54 (0.41, 0.71)	
Fatal event	0	1
Bleeding into critical organ	8	13
Event resulting in fall in Hb level or need for BT	9	18

Abbreviations: BT, blood transfusion; CI, confidence interval; MBE, major bleeding event; MCRB, major or clinically relevant bleeding.

RE-SONATE

RE-SONATE demonstrated that dabigatran was superior to placebo for the prevention of recurrent symptomatic VTE events during the treatment period, providing a 92% reduction in the risk of symptomatic recurrent VTE including unexplained death compared with placebo.

The results of RE-SONATE with respect to the primary endpoint are presented in Table 11.

Table 11: RE-SONATE primary efficacy outcome [5]

	Dabigatran n = 681	Placebo n = 662
Patients with event*, n (%)	3 (0.4)	37 (5.6)
Hazard ratio (95% CI)	0.08 (0.02, 0.25)	
p-value for superiority	<0.001	

*One subject (placebo group) had a symptomatic centrally confirmed DVT and PE on the same day

Abbreviations: CI, confidence interval.

Results for all secondary efficacy endpoints were consistent with the primary endpoint in RE-SONATE (Table 12). For all component events, the frequency was consistently lower in the dabigatran arm than the placebo arm.[7]

Table 12: RE-SONATE secondary efficacy outcomes [5;7]

	Dabigatran n = 681	Placebo n = 662
Recurrent VTE excluding unexplained deaths, n (%)	3 (0.4)	35 (5.3)
Hazard ratio (95% CI)	0.08 (0.03, 0.27)	
Symptomatic DVT, n (%)	2 (0.3)	23 (3.5)
Symptomatic non-fatal PE, n (%)	1 (0.1)	14 (2.1)
Unexplained deaths, n (%)	0 (0.0)	2 (0.3)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

The overall incidence of treatment-emergent AEs (which included bleeding events and efficacy outcome events) was comparable on dabigatran and on placebo.[7] In the dabigatran group, AEs were reported for 50.6% of patients compared with 49.2% of patients in the placebo group (Table 13).[5]

Table 13: Summary of adverse events in RE-SONATE [5]

Outcome	Dabigatran n = 681	Placebo n = 662
Patients with any AE – n (%)	346 (50.6)	324 (49.2)
Patients with serious AEs – n (%)	47 (6.9)	60 (9.1)
AEs leading to discontinuation – n (%)	50 (7.3)	81 (12.3)

Abbreviations: AE, adverse event.

Bleeding events were classified according to three categories as major, clinically relevant, or trivial bleeding events. All bleeding events were adjudicated centrally by an independent committee that was blinded with regard to the treatment allocation of patients.[7] The definitions of MBE and CRBE were consistent with the definitions used in the previous active-controlled trials: RE-COVER, RE-COVER II and RE-MEDY.[8]

There were two patients with major bleeding events, both in the dabigatran group; both events were gastrointestinal bleeding requiring at least two units of blood, but without a fall in the haemoglobin level of 20 g/L or more.[5] The hazard ratio and 95% CI could not be calculated using the Cox proportional hazard model since there were no events on placebo. The Clopper-Pearson method was therefore used (Table 14).[7]

Table 14: Analysis of time to first occurrence of MBE during the treatment period[7;8]

Parameter	Dabigatran n = 684	Placebo n = 659
MBE – n (%)	2 (0.3)	0 (0.0)
Clopper-Pearson/Fisher's exact test		
95% CI	0.04, 1.05	0.00,0.56
p-value	0.4998	
MCRB – n (%)	36 (5.3)	13 (2.0)
Hazard ratio (95% CI)	2.69 (1.43, 5.07)	

Abbreviations: CI, confidence interval; MBE, major bleeding event; MCRB, major or clinically relevant non major bleeding

Economic Evaluation

The patient group in this economic evaluation matches the indication for dabigatran stated in section 1.5 of this submission:

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Cost-effectiveness estimates of dabigatran for the following two treatment options are presented separately:

1) Treatment of DVT and PE

The patient population is adults (≥ 18 years) with acute symptomatic proximal DVT and PE.

In this patient population, analyses are presented for subgroups in which the underlying risk of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ. These subgroups are:

- Type of index event
  - DVT only
  - PE with/without DVT
- Patients with history of bleeding
- Western European patients

2) Treatment followed by prevention of recurrent DVT and PE

The patient population is adults (≥ 18 years) with acute symptomatic proximal DVT and PE who had received treatment with standard doses of an anticoagulant for 6

months and who required anticoagulant therapy beyond 6 months for the long-term treatment and secondary prevention of symptomatic VTE.

The decision to initiate a patient on anticoagulation treatment and to consider extended treatment is made in the context of the risk-benefit ratio between perceived benefit from prevention of recurrent venous thromboembolism and perceived risk of harm from major haemorrhage. Therefore, the economic model is structured around two primary composite endpoints that consolidate the most relevant thromboembolic and haemorrhagic events to which patients with DVT and PE are considered at risk:

1. **Symptomatic recurrent VTE and VTE-related death (rVTERD)**
2. **Major or clinically relevant bleeding (MCRB)**

The model outputs reported in this submission include the absolute number of events in each health state at different time points. An overview of the clinical outcomes presented in the model is shown below.

Table 15: Overview of clinical outcomes

Thromboembolic events	Haemorrhagic events	Additional events[1]
• Pulmonary embolism (PE) • Proximal DVT • Distal DVT • VTE related deaths	• Major bleed event (MBE), incl. ICH • Clinically relevant non-major bleed event (CRNMBE)	• Post-thrombotic syndrome (PTS) • Chronic thromboembolic pulmonary hypertension (CTEPH)

1 Additional clinical events considered appropriate for inclusion in the model, given their relevance to patients receiving anticoagulation treatment for DVT and PE

For the cost-effectiveness analysis the quality-adjusted life year (QALY) is the primary outcome measure.

Incremental results of the economic model for dabigatran versus each comparator are presented in the table below.

Table 16: Base case results - Treatment of DVT and PE (lifetime time horizon) – Mean per patient

Technologies		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Dabigatran	Deterministic	7,503	16.170	12.452	-	-	-	-
	Probabilistic	7,570	16,172	16.172	-	-	-	-
vs LMWH then warfarin	Deterministic	7,482	16.158	12.428	21	0.0121	0.0239	862
	Probabilistic	7,545	16.159	12.431	25	0.0125	0.0241	1,016
vs rivaroxaban	Deterministic	7,523	16.170	12.451	-20	-0.0005	0.0003	Rivaroxaban is dominated by dabigatran
	Probabilistic	7,480	16.168	12.449	-17	-0.0003	0.0003	Rivaroxaban is dominated by dabigatran
vs LMWH monotherapy (in patients with cancer)	Deterministic	5,522	7.491	5.817	-1,370*	-0.0101*	-0.0124*	110,742 (SW)
	Probabilistic	5,496	7.489	5.815	-1,349*	-0.0116*	-0.0144*	93,431 (SW)

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *Incremental comparison with dabigatran cancer subgroup only (data not presented in ths table)

Table 17: Base case results - Treatment followed by secondary prevention of DVT and PE (lifetime time horizon) – Mean per patient

Technologies		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Dabigatran	deterministic	8,319	16.262	12.519	-	-	-	-
	probabilistic	8,305	16.260	12.510	-	-	-	-
vs LMWH then warfarin	deterministic	7,861	16.242	12.464	458	0.0201	0.0551	8,319
	probabilistic	7,839	16.240	12.460	466	0.0200	0.0527	8,848
vs rivaroxaban	deterministic	7,852	16.208	12.478	-67	-0.0022	0.0020	Rivaroxaban is dominated by dabigatran
	probabilistic	7,878	16.19	12.47	-63	0.0100	0.0096	Rivaroxaban is dominated by dabigatran
vs LMWH monotheray (in patients with cancer)	deterministic	11,161	16.194	12.451	-3,340	0.0090	0.0197	LMWH is dominated by dabigatran
	probabilistic	11,118	16.190	12.450	-3,342	0.0200	0.0226	LMWH is dominated by dabigatran

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *Incremental comparison with dabigatran cancer subgroup only (data not presented in ths table)

Comparison with LMWH followed by warfarin

As outlined in section 2, LMWH followed by adjusted-dose warfarin has traditionally been the standard of care for the treatment and secondary prevention of recurrent DVT and PE. The economic analysis presented in this submission suggests that the proposed treatment regimen of LMWH followed by dabigatran is a highly cost-effective alternative to LMWH followed by warfarin. The incremental cost per additional QALY gained with dabigatran over this comparator is less than £10,000 in both deterministic and probabilistic sensitivity analyses. These ICERs are comfortably within the threshold normally considered to represent value-for-money from the perspective of the NHS in England and Wales. The incremental cost per QALY gains remain below £10,000 in the majority of sensitivity scenarios investigated, with the exception of when the warfarin utility decrement is removed during treatment followed by secondary prevention (ICER of £14,947) and when the lifetime horizon for treatment followed by secondary prevention is changed to 1 year (£12,905).

For the sensitivity analysis comparing LMWH followed by dabigatran against LMWH followed by warfarin for treatment of DVT and PE, the base case results remain well below £10,000 per QALY. The base case ICER is £862, and the sensitivity analysis ranging from the lowest ICER of £778 when the time in therapeutic range is adjusted for, to the highest ICER of £5,317 when the time horizon is changed to 6 months. In the same comparison during the treatment and secondary prevention of DVT and PE, the base case ICER is £8,319, and the sensitivity analysis ICERs range from £7,427 (when unexplained deaths are included) to £14,947 (when the utility decrement for warfari is removed).

Comparison with rivaroxaban

A comparative economic analysis has also been presented of LMWH followed by dabigatran versus rivaroxaban. As noted in Section 2 of this submission, NICE have previously issued positive guidance recommending the use of rivaroxaban within its licensed indication for the treatment and long-term secondary prevention of DVT and PE in England and Wales.[9;10] Thus, it was considered informative to conduct and present this comparison. The results of this analysis show that LMWH followed by dabigatran can be considered a dominant alternative to rivaroxaban for the long-term treatment and secondary prevention of recurrent DVT and PE (assuming a lifetime time horizon). When a lifetime (60 years) horizon for this comparison was modelled, dabigatran was dominant over rivaroxaban in both

treatment and treatment followed by secondary prevention, for the deterministic and probabilistic sensitivity analyses. As outlined in Section 2, venous thromboembolism (DVT and PE) is associated with serious long-term complications including post-thrombotic syndrome (PTS), recurrent VTE, pulmonary hypertension, and increased mortality. It is therefore appropriate to primarily consider the results of economic analyses which take these long-term complications (with their resultant impact on patients' HRQL) into account.

When comparing LMWH followed by dabigatran with rivaroxaban in the treatment of DVT and PE, dabigatran is dominant over rivaroxaban in the base case and ICERs in the sensitivity analyses range from dabigatran remaining dominant in a few scenarios (Table 148) to dabigatran being less expensive and less effective (ICER of £48,000) when bleeding events are counted from the double-dummy period. When looking at the same comparison for the treatment and secondary prevention of DVT and PE, dabigatran is dominant over rivaroxaban in the base case, and remains dominant in all sensitivity analyses. When the treatment horizon is shortened from lifetime to 6 months, the ICER for LMWH followed by dabigatran versus rivaroxaban changes from the base case above (dabigatran is dominant) to £46,274. Dabigatran remains dominant versus rivaroxaban in the treatment followed by secondary prevention indication when the lifetime horizon is changed to 1 year (Table 149).

Comparison with LMWH monotherapy (in patients with active cancer)

In recognition of place of LMWH monotherapy as standard of care for the treatment of DVT and PE in patients with active cancer, a further comparative economic analysis of LMWH followed by dabigatran versus LMWH monotherapy has been presented in this submission. In contrast to the two previous comparisons, the clinical efficacy and safety data underpinning this economic analysis has been drawn from subgroups of patients with active cancer who were treated with LMWH followed by dabigatran in pivotal randomised controlled trials (RE-COVER, RE-COVER II and the RE-SONATE trial). Clinical data supporting the use of LMWH monotherapy in this patient group has been derived from 5 trials of LMWH monotherapy in cancer patients. Results of the economic analysis of treatment of DVT and PE indicate that LMWH followed by dabigatran may be considered to be a reasonable alternative to LMWH monotherapy in this patient subgroup, being associated a lower cost, albeit with a slightly lower expected number of QALYs. Assuming a 12 month treatment period and applying a lifetime time horizon for long-term treatment and secondary

prevention of recurrent DVT and PE, results in LMWH followed by dabigatran emerging as a dominant alternative to LMWH monotherapy in this patient subgroup.

LMWH followed by dabigatran compared with LMWH monotherapy in patients with active cancer showed that dabigatran was less expensive and less effective in the base case result for the treatment of DVT and PE, with this result remaining in the sensitivity analyses. For the same comparison in the treatment and secondary prevention of DVT and PE, dabigatran is dominant over LMWH monotherapy in the base case, and remains dominant in all sensitivity analyses.

However, the limitation of this analysis is that the clinical efficacy and safety data supporting the use of LMWH followed by dabigatran in this patient subgroup comes from a relatively small proportion of the overall patient population treated with dabigatran in pivotal studies (approximately 5%). Recognising this, the European Medicines Agency has recommended including a statement in the Summary of Product Characteristics for dabigatran highlighting that the efficacy and safety of dabigatran in patients with cancer has not been established.

In summary, the positive risk benefit balance profile of dabigatran within this indication has been proven across the RE-COVER, RE-COVER II and RE-SONATE trials. The efficacy profile has been demonstrated to be comparable to warfarin and rivaroxaban; whilst having a favourable bleeding profile.

Moreover, the clinical results have translated through into dabigatran being a cost effective treatment option within this indication.

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 10.1, appendix 1).

Please note, commercially confidential information is underlined and highlighted in turquoise. Academic in confidence information is underlined and highlighted in yellow.

1 Description of technology under assessment

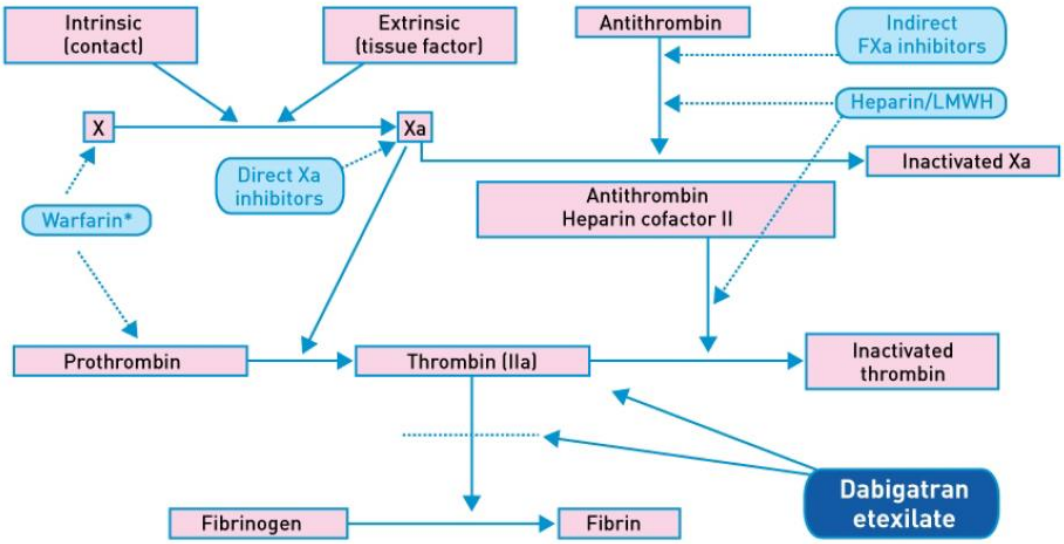
1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

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

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

Dabigatran etexilate (dabigatran hereafter) is an orally available direct thrombin inhibitor which prevents blood clot (thrombus) formation by specifically and reversibly binding thrombin, the central and essential enzyme that enables the conversion of fibrinogen to fibrin (Figure 1).

Figure 1: Coagulation cascade



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).

Dabigatran holds a UK marketing authorisation for the use in:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

Dabigatran was submitted to EMA for regulatory approval for the proposed indication under appraisal on 3 June 2013. CHMP positive opinion was adopted on 25 April 2014[11]. Marketing authorisation in the European Union is currently expected end of June/beginning of July 2014.

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 marketing authorisation).

The benefit of dabigatran in the acute treatment and secondary prevention of VTE indications is considered comparable to that of warfarin, even though it may be marginally less. However, this should be seen in the perspective of the advantages in terms of major bleedings and other bleeding events. The excess of acute coronary syndrome with dabigatran compared to warfarin (but not to placebo) is small and is not considered to outweigh the advantages associated with dabigatran.

Consequently, the benefit-risk balance is considered positive in the acute treatment and secondary prevention of VTE indications.

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

The European Medicines Agency has recently granted positive opinion (CHMP, 25 April 2014)[12] recommending the approval of dabigatran for following the indication detailed in this submission:

> *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.*

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 efficacy and safety of dabigatran in the acute treatment and secondary prevention of VTE have been examined in four phase III studies:

- *Completed*: RE-COVER (NCT00291330) and RE-COVER II (NCT00680186)
  Duplicate studies designed to compare dabigatran (150 mg BD) and warfarin (target INR 2.0 – 3.0) for 6 months of treatment for acute symptomatic VTE.
- *Completed*: RE-MEDY (NCT00329238)
  Designed to compare the efficacy and safety of dabigatran (150 mg BD) and warfarin (target INR 2.0 – 3.0) in patients who had already completed 3 to 12 months of anticoagulation treatment and who were considered to be at risk for recurrent venous thromboembolism.
- *Completed*: RE-SONATE (NCT00558259)

A placebo-controlled superiority study designed to evaluate whether dabigatran (150 mg BD) was superior to placebo in the prevention of recurrent symptomatic VTE in patients with confirmed symptomatic DVT or PE who had previously completed 6 to 18 months of anticoagulation treatment and were considered to be at equipoise for the need for continued anticoagulant therapy.

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

The UK launch of dabigatran in the indication detailed in this submission is planned in June/beginning of July 2014, coinciding with the expected marketing authorisation.

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

Dabigatran has regulatory approval for this indication in Argentina, Chile, Russia, Philippines, Ecuador, Colombia, Mexico, Turkey (acute treatment only), and the USA.

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, Boehringer Ingelheim Ltd intends to make a full submission to the Scottish Medicines Consortium (SMC) for dabigatran in this indication on 2 June 2014. It is expected that SMC issues its advice publicly on 13 October 2014.

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 18: Unit costs of technology being appraised

Pharmaceutical formulation	Hard capsules
Acquisition cost (excluding VAT)	£65.90 per 60 capsule pack (£2.20 per day)
Method of administration	Oral
Doses	150 mg, 110 mg
Dosing frequency	150 mg or 110 mg twice daily
Average length of a course of treatment	6 months for treatment of acute DVT and PE; 12 months (to lifelong) for the prevention of recurrent DVT and PE
Average cost of a course of treatment	Dependent on the patient's risk-benefit profile. A 6 months course of acute treatment would involve the outlay of £401.50 per patient (= (365/2)*£2.20 per day).
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	The standard daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. For the following groups the recommended daily dose of dabigatran is 220 mg taken as one 110 mg capsule twice daily: • Patients aged 80 years or above • Patients who receive concomitant verapamil For the following groups the daily dose of dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding: • Patients between 75-80 years • Patients with moderate renal impairment • Patients with gastritis, esophagitis or gastroesophageal reflux • Other patients at increased risk of bleeding

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.

N/A.

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

The use of dabigatran is not subject to an additional test or administration requirement. This is not true for the comparator medications.

In the case of dabigatran, the summary of product characteristics states that in order to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min; a contraindication), renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with dabigatran.

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?

None.

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.

Venous thromboembolism (VTE), the third most common cardiovascular disorder after coronary artery disease and stroke[13], includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is characterised by the formation of blood clots (thrombi) or emboli (broken-off clots) that block the blood vessels preventing blood flow, which may have serious consequences depending on the vessel involved and how extensive the blockage is.

In cases of DVT, the veins of the legs are blocked by thrombi, often causing pain and swelling of the affected leg. DVT is often described according to the location of the thrombus formation:

- distal – furthest away from the heart i.e. below the knee (in the calf veins)
- proximal – closer to the heart i.e. above the knee (in the femoral veins of the thigh)

The thrombi that form in the legs can extend. Fragments may break off and travel to the pulmonary artery in the lungs and cause PE with symptoms such as shortness of breath and chest pain. The risk of PE is greater with DVT in the large proximal veins than with distal DVT[14].

The current standard treatment for acute VTE is initiation of a vitamin K antagonist (VKA) with rapidly acting parenteral anticoagulation for 5 - 7 days until the international normalised ratio (INR) is stable and within the therapeutic range, followed by at least three months of treatment with a VKA. Treatment with a VKA requires frequent monitoring of INR, and use is complicated by variable patient dose response due to genetic factors and multiple food-drug and drug-drug interactions.

Dabigatran is an orally available, potent, direct inhibitor of thrombin. It is administered in fixed doses without the need for routine coagulation monitoring, is principally excreted by the kidney, and has a half-life of 12 - 14 hours. Dabigatran has similar efficacy and safety to enoxaparin for the prevention of VTE in patients who have had elective total hip or total knee arthroplasty, and is as effective as standard oral anticoagulation with warfarin at preventing stroke or systemic embolism in patients with non-valvular atrial fibrillation. In the RE-LY trial, dabigatran showed similar (110 mg BD) or better efficacy (150 mg BD) than standard treatment with warfarin in preventing stroke or systemic embolism. As such, dabigatran is currently recommended for use within NHS England for the primary prevention of VTE in adults who have undergone elective total hip or total knee replacement surgery (TA157) and for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (TA 249).

A comprehensive clinical trial programme, including four pivotal Phase III trials, was undertaken to establish the efficacy and safety of dabigatran in the treatment of acute VTE and secondary prevention of VTE. Three clinical trials (RE-COVER, RE-COVER II and RE-MEDY) were non-inferiority studies of dabigatran vs adjusted-dose warfarin. In the RE-COVER acute treatment studies, patients were included if 6 months or more anticoagulation was considered appropriate for them. RE-MEDY included patients considered to be at high-risk of recurrent VTE and thus indicated for further anticoagulation following acute VTE, while the remaining clinical trial, RE-SONATE, was a superiority study of dabigatran vs placebo in patients for whom there was considered to be clinical equipoise regarding the need for further anticoagulation.

The evidence from these trials will be presented to support the licence application for the use of dabigatran for the treatment and secondary prevention of VTE.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

It is estimated that there is in the region of 52,320 patients eligible for treatment with anticoagulation under the indication considered in this submission in England and Wales in 2014. This is projected to rise to 56,085 patients in 2018 due to growth and ageing of the

population. These projections are based on the rates of incidence and recurrence of DVT and PE derived from a combined analysis of UK hospital and primary care databases (General Practice Research Database, Hospital Episode Statistics database)[15], which have been applied to the population projections for England and Wales from the Office of National Statistics[16]. For more information on this estimate, please see Section 8.1.

For the second indication of dabigatran, the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF), 849,000 patients with AF have been registered, according to the 2012/13 QOF database.

Finally, approximately 128,000 patients are eligible for dabigatran's third indication in primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery; (based on hip and knee procedures performed in the NHS England and Wales in 2013).[17]

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Patients with venous thrombosis have a four-fold (95% CI 3.7-4.3) increased risk of death and hence a reduced median life expectancy compared with the general population.[18] The risk remains increased after the thrombotic event, even when no additional comorbidities are present.

2.4 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 92: Reducing the risk of venous thromboembolism

NICE clinical guideline 144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

NICE evidence update 55 (April 2014): A summary of selected new evidence relevant to NICE clinical guideline 144

NICE quality standard 29: Quality standard for diagnosis and management of venous thromboembolic diseases

NICE technology appraisal 261: Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

NICE technology appraisal 287: Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism.

NICE pathway: Venous thromboembolism

2.5 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.

NICE clinical guideline 144 depicts the pathway of pharmacological interventions for DVT or PE as follows:

- Offer a choice of LMWH or fondaparinux to patients with confirmed proximal DVT or PE taking into account comorbidities, contraindications and drug costs, with the following exceptions:
    - For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer UFH with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
    - For patients with an increased risk of bleeding consider UFH.
    - For patient with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy.

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the INR is 2 or above for at least 24 hours, whichever is longer.

- Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation.
- Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment.

- Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding.
- Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding.

Dabigatran fits well in the existing clinical pathway as it can displace warfarin (the principal vitamin K antagonist used in the UK[19]) following initial LMWH therapy. It does not require a change of routine practice and existing services/protocols.

Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.[9]

Rivaroxaban is also recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.[10] However, rivaroxaban requires a change in existing patient pathways, as it is licensed for initiation after the index event of DVT / PE (rather than initiation on LMWH – as is the case with warfarin and dabigatran). Uptake of rivaroxaban has been low in NHS England & Wales.[20] Therefore, there is a need for another treatment option.

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

Following acute parenteral treatment with heparin (either LMWH or UFH), therapy with dose-adjusted warfarin (overlapping and started as early as possible) is generally recognised as the current gold standard in the acute treatment and secondary prevention of VTE. Therefore, 'LMWH then warfarin' is a comparator.

Further relevant comparators for dabigatran in the indication detailed in this submission are:

- Rivaroxaban, a factor Xa inhibitor, which has been recommended as an option for acute treatment of DVT and PE, as well as preventing recurrent DVT and PE in adults (NICE TA261, TA287).

- For people with cancer (sub-group analysis): LMWH as it has been recognised as the preferred treatment over warfarin for at least the first 3-6 months in patients with cancer-associated VTE.

Fondaparinux is an alternative to LMWH or UFH for the initial treatment of DVT.[21;22] However, it is not approved for long-term prophylaxis of VTE[23] and therefore is not considered a relevant comparator for dabigatran in its indication for treatment and long-term secondary prevention of VTE detailed in this submission.

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

Dabigatran affects blood clotting, so most adverse reactions are related to bleeding. Clinical protocols exist for the emergency management of major or clinically relevant bleeding events therefore usual treatment measures should be considered. In general, there is no specific medicine that has to be given in conjunction with dabigatran therapy to manage adverse events.

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 the use of dabigatran is its acquisition cost. There are no administration or monitoring costs specifically associated with the use of dabigatran. The unit costs of surgery consultations are taken from PSSRU[24] and of secondary care outpatient consultations from NHS reference costs 2012/2013[25] (inflated to 2014 values).

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

No. In fact, dabigatran does not requiring INR testing. It has the potential to supersede the extensive infrastructure (along with its inherent costs) of hospital and clinical INR monitoring.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Boehringer Ingelheim Ltd is not aware of any equality issues.

3.1.2 How has the analysis addressed these issues?

N/A

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

In the UK, warfarin tablets are available in three different colour-coded dosage strengths: 1mg (brown tablets), 3mg (blue tablets), 5mg (pink tablets). Despite this range of strengths, for some patients, a particular tablet strength might be insufficient, while the next higher tablet strength may be too efficacious, resulting in patients being prescribed a treatment regimen comprising different doses on different days of the week.

This type of regimen is often confusing for the patient and may lead to incorrect dosing or inconvenience if the patient has difficulty identifying the appropriate tablets.

In contrast, dabigatran provides a more convenient alternative to warfarin for the treatment and secondary prevention of DVT and PE, without compromising on efficacy or safety. It has a predictable anticoagulant effect and does not require INR testing. It has thus the potential to supersede the extensive infrastructure (along with its inherent costs) of hospital and clinical INR monitoring. Moreover, dabigatran is prescribed at a fixed dose, eliminating the need for variable dosage regimens and reducing the risk of patients administering incorrect doses.

Routine coagulation monitoring is also unnecessary when treating VTE with rivaroxaban. However, rivaroxaban is administered twice daily for the initial three weeks and then once daily for the remainder of the treatment period, compared to the twice daily administration required for dabigatran for the full treatment period. Moreover, rivaroxaban must be administered with a meal, while dabigatran can be administered with or without food, providing more flexibility.

Furthermore, dabigatran can be used after initial treatment with heparin. Dabigatran is at present the only approved novel oral anticoagulant with evidence on the subsequent treatment after initial therapy with heparin. There is no need to change routine practice and existing services/protocols, as dabigatran can displace warfarin following initial LMWH therapy.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The QALY calculation falls short of taking account of the following concepts:

- Potential convenience benefit due to the non-necessity of regular clinical attendance for coagulation monitoring
- No lifestyle limitations/modifications on account of the absence of significant drug-drug and drug-food interactions
- No re-designing pathway burden for the NHS in England and Wales.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

The submission does not include numerical values on the non-QALY benefits detailed above. Instead, there is some discussion within the submission to explore the extent and impact of these non-QALY benefits.

5 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.

Table 19: Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with deep vein thrombosis and/or pulmonary embolism	People with deep vein thrombosis and/or pulmonary embolism	N/A
Intervention	Dabigatran etexilate	Dabigatran etexilate	N/A
Comparator(s)	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • rivaroxaban For people with cancer: • low molecular weight heparin • rivaroxaban	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • rivaroxaban For people with cancer: • low molecular weight heparin • rivaroxaban	N/A
Outcomes	The outcome measures to be considered include: • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension. • adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • health-related quality of life	The outcome measures to be considered include: • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension. • adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • health-related quality of life	The outcome 'heart failure' was not included in the clinical trials and could thus not be modelled either.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that 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.	Cost utility analysis was performed, using a Markov Model in Microsoft Excel. The time horizon for both the 'treatment phase' and 'treatment + secondary prevention phase' is life time (60 years). The perspective is from an NHS & PSS perspective.	N/A
Subgroups to be considered	If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary	Various subgroup analyses have been conducted: 1. Type of index event:	N/A

	embolism or deep vein thrombosis). The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). Guidance will only be issued in accordance with the marketing authorisation.	• DVT only • PE with/without DVT 2. Patient history of bleeding 3. Active cancer 4. Western European patients
Special considerations, including issues related to equity or equality		N/A

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)		

6 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.

6.1 Identification of studies

6.1.1 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 10.2, appendix 2.

A systematic review was carried out to identify efficacy data relevant to the subject of this submission; dabigatran etexilate for the treatment and secondary prevention of VTE. The interventions of interest were dabigatran, rivaroxaban, edoxaban, apixaban, unfractionated heparin (UFH), low molecular-weight heparin (LMWH) (e.g., enoxaparin, dalteparin, tinzaparin, bemiparin and nadroparin), and fondaparinux.

Registration trials sponsored by manufacturers have compared dabigatran with warfarin for the treatment of VTE, and with warfarin or placebo for the secondary prevention of VTE. So that the review could incorporate all dabigatran trials within an integrated evidence matrix, trials comparing warfarin with placebo in the secondary prevention indication also were included.

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines as specified by NICE in the guidance to manufacturers on systematic reviews, and was performed in accordance with a pre-specified protocol.

An initial systematic review was performed in two phases. Phase 1 aimed to identify studies investigating dabigatran, rivaroxaban, edoxaban, and apixaban. In Phase 2, searches for UFH, LMWH, and fondaparinux were performed.

Searches were carried out on electronic medical databases and the internet (specified websites). The search for relevant studies also included review of bibliographic reference lists of included studies, reviews, meta-analyses, and health technology assessment (HTA) documents.

The Phase 1 searches of electronic databases (for studies of dabigatran, rivaroxaban, edoxaban, and apixaban) were performed on 23 July 2012, using a structured search strategy (see Appendix 2, Section 10.2.4). The following databases were searched, covering the period from 1960 to 23 July 2012: MEDLINE and MEDLINE In-Process (using PubMed platform), Embase (using Dialog Platform), The Cochrane Library (including The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, and Database of Abstracts of Reviews of Effectiveness), and Biosciences Information Service (using the Dialog Platform). The Phase 2 searches (for UFH, LMWH, and fondaparinux) were performed on 1 October 2012, using the same databases as used in the Phase 1 searches.

Additionally, internet searches were conducted and are detailed in **Error! Reference source not found.** and **Error! Reference source not found.**.

No date limitations or language restrictions were applied in the database search strategy. Internet site searches for conference abstracts were limited to those published from January 2010 to 23 July 2012 (for Phase 1) or 13 October 2012 (for Phase 2) (important research presented at conferences prior to January 2010 would be expected to be published at the search date). For any foreign-language sources that appeared relevant at the screening stage, sufficient information was extracted by linguists to determine their eligibility for inclusion.

The systematic review was then updated in 2014 using the same search strategy (see Appendix 2, Section 10.2.4) and methodology. Searches of electronic medical databases were conducted on 28th April 2014 and internet searches were performed between 28th April and 1st May 2014. All searches were limited to data published after 9 July 2012.

6.2 Study selection

6.2.1 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.

The literature review study selection process occurred in the following two phases:

- Level 1 screening: Titles and abstracts of studies identified from the electronic databases and from Internet searches were reviewed for eligibility by one researcher. A second researcher independently screened a random sample of 5% of the records. Any differences were resolved by consensus.

- Level 2 screening: Full texts of studies selected at level 1 were obtained and reviewed for eligibility by one researcher, using the same inclusion and exclusion criteria as used in level 1 screening. A second researcher independently screened a random sample of 5% of the records. Any differences were resolved by consensus. Foreign-language sources were excluded at the level 2 screening stage.

The second researcher also reviewed all studies selected after the level 2 screening to confirm their eligibility.

Table 20 presents the inclusion and exclusion criteria that were used at level 1 and level 2 screening during the systematic review.

Table 20: List of criteria for the inclusion and exclusion of studies during the screening process

Criteria	Included	Excluded
Study Type	• Randomised, controlled prospective clinical trials • Non-randomised, controlled prospective clinical trials • Long-term follow-up studies (e.g., open-label follow-up studies)	• Prospective observational studies (e.g., phase 4 studies) • Preclinical studies • Phase 1 studies • Prognostic studies • Retrospective studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Reviews, systematic reviews, and meta-analyses (however, reference lists were reviewed for any relevant studies)
Patient Populations	• Patients with DVT and/or PE receiving treatment or secondary prevention for recurrent DVT and/or PE	• Patients receiving primary prophylaxis for prevention of a first DVT or PE event
Interventions	• Dabigatran, rivaroxaban, edoxaban, and apixaban • Warfarin (secondary prevention trials only) • UFH or LMWH (all agents, including, but not limited to, enoxaparin, dalteparin, tinzaparin, bemiparin, and	• Studies that do not include any of the interventions in the inclusion criteria list

	nadroparin) given for more than 10 days, i.e., long-term or extended treatment only (trials investigating acute parenteral treatment with heparin, e.g., for 5-10 days followed by a vitamin K antagonist, were not included as heparin trials) • Fondaparinux (given for 7 or more days)	
Outcomes	• Recurrent DVT or PE • Bleeding • Death	• Regression rate of persistent echogenic masses

DVT, deep vein thrombosis; LMWH, low molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin.

6.2.2 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 6.2.4.

Studies were included / excluded on the basis of the criteria described in Section 6.2.1 above. The results of each screening level in terms of articles included and excluded, and reasons for exclusion, for the original systematic review are summarised in Figure 2 and for the update in Figure 3.[26] Details of the excluded studies are available on request.

Figure 2 PRISMA diagram for study inclusion and exclusion: original systematic review

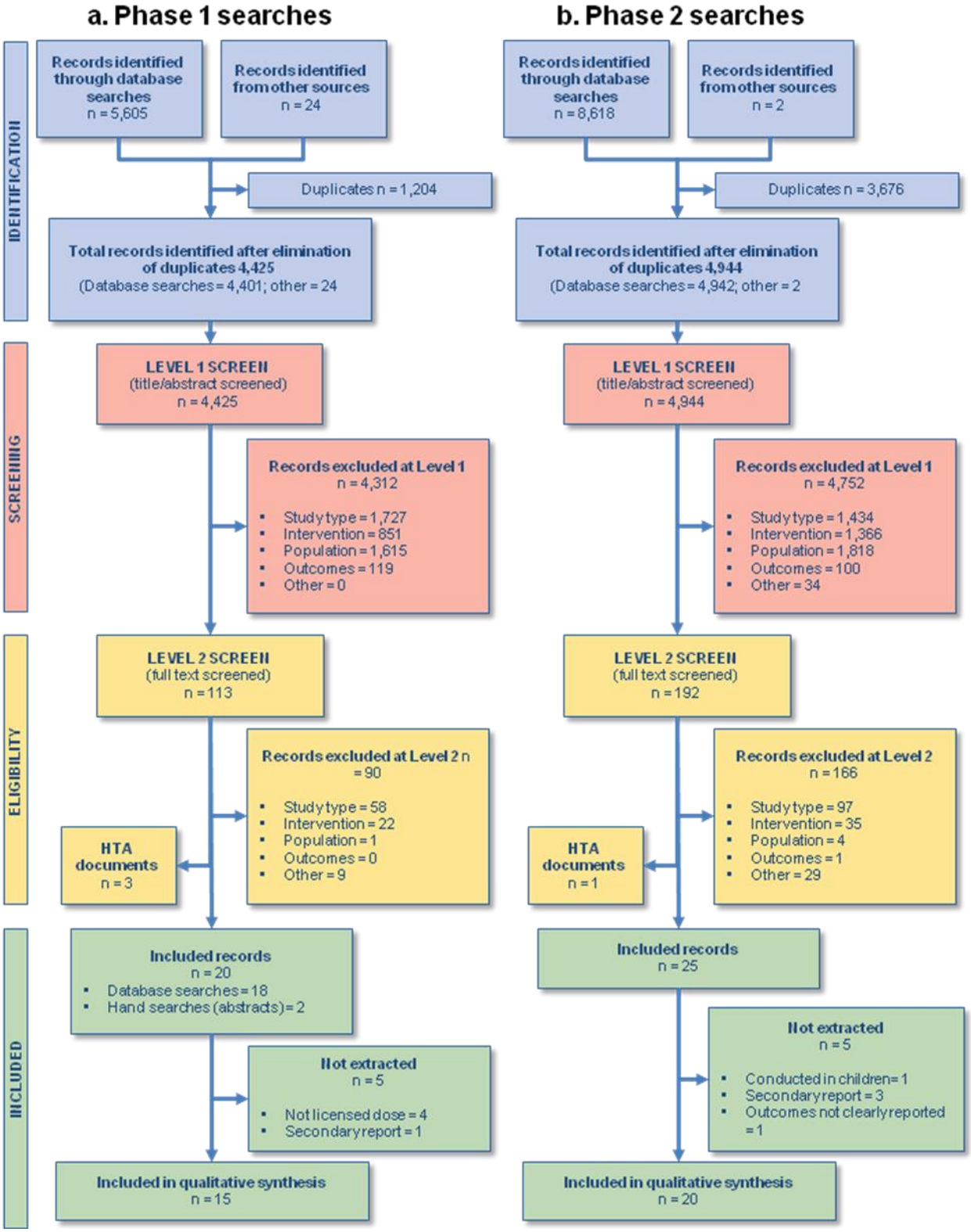
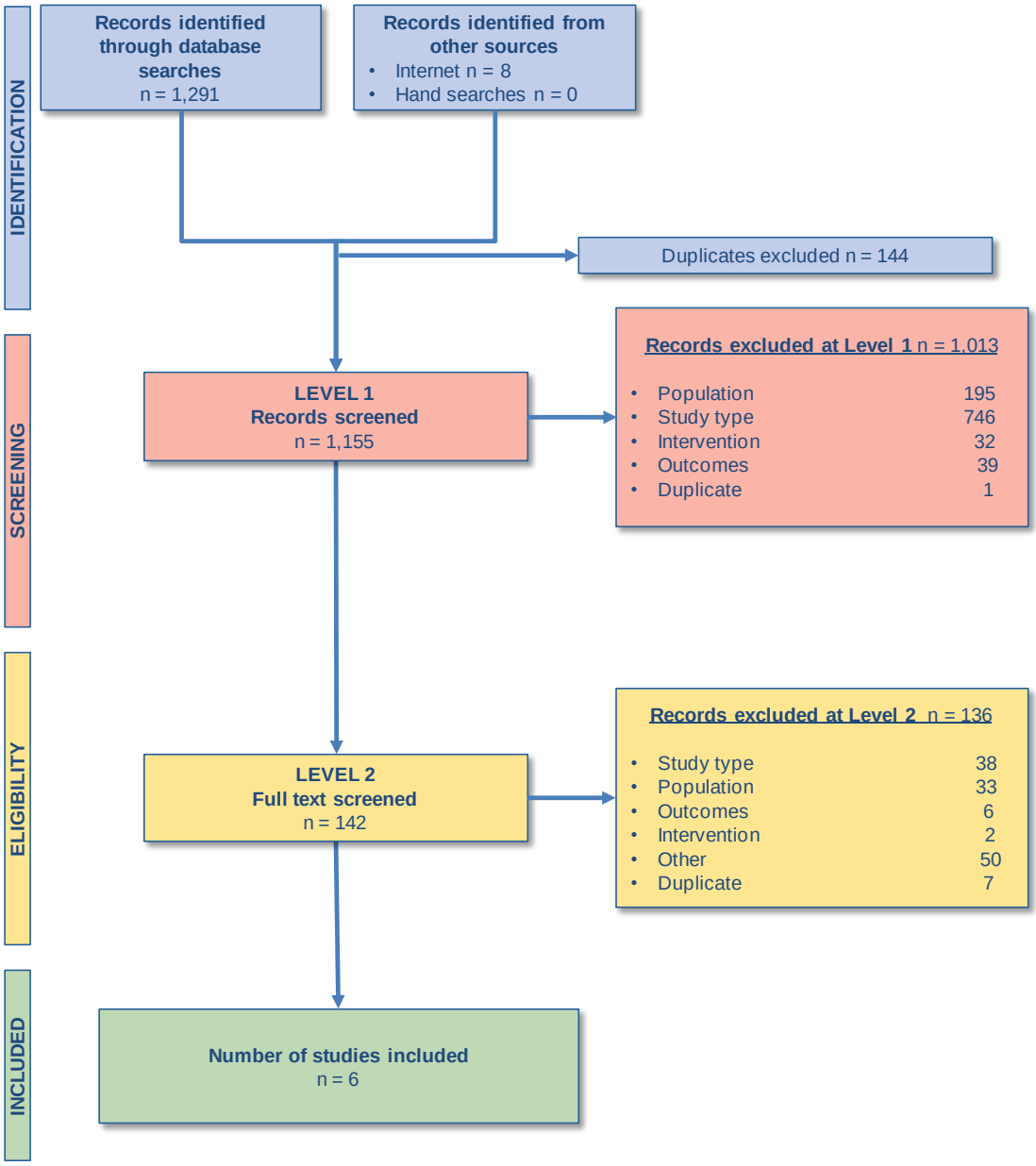


Figure 3 PRISMA diagram for study inclusion and exclusion: systematic review update



Of the 35 identified publications (36 unique studies) identified in the original review that were relevant for data extraction, 23 studies investigated DVT and/or PE treatment and 13 studies investigated secondary prevention.

Of the 23 studies investigating DVT and/or PE treatment, 2 studies investigated dabigatran, two studies investigated rivaroxaban, and 19 studies investigated LMWH, of which two also included UFH. Of the 13 studies investigating secondary prevention of DVT and/or PE, two studies investigated dabigatran, one study investigated rivaroxaban, one study investigated LMWH, eight studies compared warfarin with no treatment or placebo or with alternative

durations of warfarin therapy, and one study compared low-intensity warfarin with conventional-intensity warfarin. No studies investigating edoxaban were identified.

In the update to the systematic review, all of the six studies identified that were relevant for data extraction investigated treatment of DVT and/or PE. Of these studies, two studies compared dabigatran to warfarin therapy or placebo, two studies compared apixaban to warfarin therapy, one study compared edoxaban to warfarin, and one study compared rivaroxaban to warfarin therapy.

6.2.3 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.

The primary resource data resource for all four trials, are their respective peer-reviewed study publications. However, when the clinical trial reports are considered to give further information they have been used to add value and detail to the data presented.

RE-MEDY[5] is an extension trial assessing the efficacy and safety of dabigatran 150 mg against adjusted-dose warfarin therapy in patients with objectively confirmed, symptomatic, proximal DVT or PE that had already been treated with an approved anticoagulant or with dabigatran as part of the duplicate RE-COVER[1] or RE-COVER II[27] trials.

Complete list of relevant RCTs

6.2.4 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 dabigatran for the treatment and secondary prevention of DVT and PE are shown in Table 21. Of these four studies, RE-COVER[1], RE-COVER II[27], and RE-MEDY[5] compare dabigatran directly with warfarin, whilst RE-SONATE[27] compares dabigatran directly with placebo.

Table 21: List of relevant RCTs

Trial	Intervention	Comparator	Population	Primary study ref.
RE-COVER	Oral dabigatran (150 mg BD) + warfarin placebo (n = 1,273)	Warfarin (to obtain a target INR of 2.0-3.0) + dabigatran placebo (n = 1,266)	Adult patients (≥18 years) who had acute, symptomatic, objectively verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered appropriate.	[1]
RE-COVER II	Oral dabigatran (150 mg BD) + warfarin placebo (n = 1,280)	Warfarin (to obtain a target INR of 2.0-3.0) + dabigatran placebo (n = 1,288)	Adult patients (≥18 years) who had acute, symptomatic, objectively verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered appropriate.	[27]
RE-MEDY	Oral dabigatran (150 mg BD) + warfarin placebo (n = 1,430)	Warfarin (to obtain a target INR of 2.0 - 3.0) + dabigatran placebo (n = 1,426)	Adult patients (≥18 years) with objectively confirmed, symptomatic, proximal DVT or PE that had already been treated with an approved anticoagulant or with DBG as part of the RE-COVER or RE-COVER II trials.	[5]
RE-SONATE	Oral dabigatran (150 mg BD) (n = 681)	Oral placebo (BD) (n = 662)	Adult patients (≥18 years) with objectively confirmed, symptomatic, proximal DVT or PE that had already been treated with an approved anticoagulant or if they had received DBG in either RE-COVER or RE-COVER II.	[5]

Abbreviations: BD: twice daily dosing, DVT: deep vein thrombosis, INR: international normalised ratio, PE: pulmonary embolism

6.2.5 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.

RE-COVER[1], RE-COVER II[27], and RE-MEDY[5] compare dabigatran with an intervention relevant to the decision problem. All of these studies are phase III trials and provide meaningful evidence on the clinical effectiveness of dabigatran against warfarin in this indication.

6.2.6 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.

None of the four trials identified above have been excluded from further discussion.

List of relevant non-RCTs

6.2.7 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 6.8 and key details should be presented in a table; the following is a suggested format.

No relevant non-RCT studies were identified through the searches.

6.3 Summary of methodology of relevant RCTs

6.3.1 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 22.

Table 22: Consort 2010 checklist

(i) Section/Topic	(ii) Item number	(iii) Checklist item	v) Reported in section/table
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Section 6.3.2
	2b	Specific objectives or hypotheses	Section 6.3.2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Section 6.3.2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Section 6.3.2/6.3.3
Participants	4a	Eligibility criteria for participants	Section 6.3.3
	4b	Settings and locations where the data were collected	Section 6.3.2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Section 6.3.2
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Section 6.3.5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Section 6.3.2
Sample size	7a	How sample size was determined	Section 6.3.2
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Section 6.3.2
Randomisation	8a	Method used to generate the random allocation sequence	Section 6.3.2
Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Section 6.3.2
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	Section 6.3.2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Section 6.3.2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Section 6.3.2
	11b	If relevant, description of the similarity of interventions	Section 6.3.2
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Section 6.3.6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Section 6.3.7
Results			
Participant flow	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment,	Section 6.3.6/6.3.8

		and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	Section 6.3.8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Section 6.3.2
	14b	Why the trial ended or was stopped	Section 6.3.2

Methods

6.3.2 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.

RE-COVER and RE-COVER II

These studies compared dabigatran 150 mg BD with adjusted-dose warfarin (target INR 2.0-3.0) in patients with confirmed acute symptomatic VTE following initial treatment (for at least 5 days) with a parenteral anticoagulant approved for this indication. The aim of these studies was to demonstrate non-inferiority based on the composite primary endpoint of recurrent symptom

matic VTE and deaths related to VTE within 6 months [1] (Table 23).

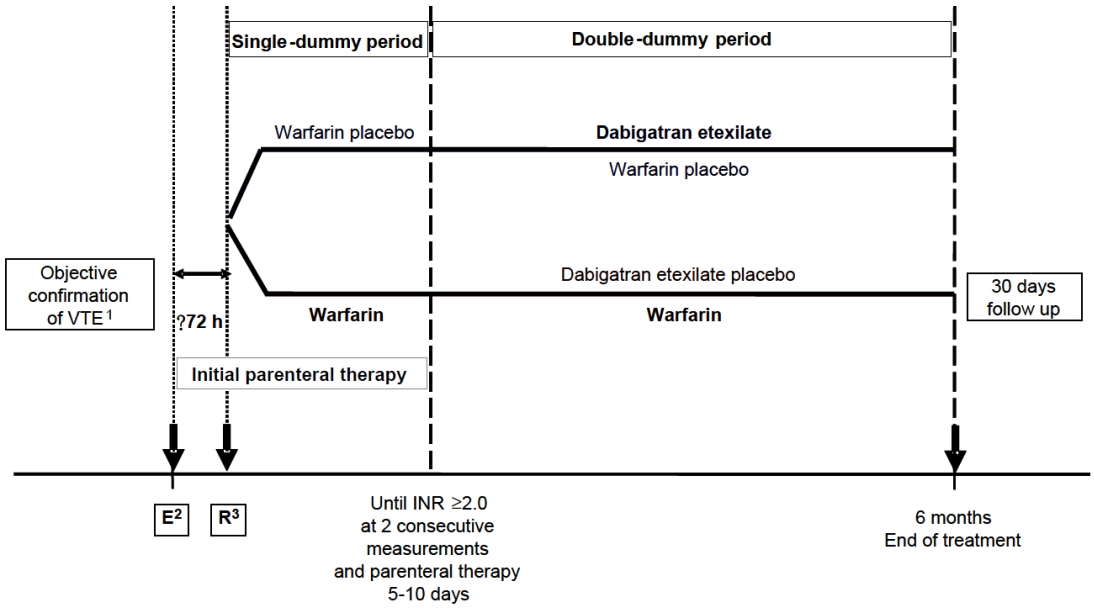
RE-COVER and RE-COVER II are duplicate studies and identical in design [27]. Both trials were Phase III, double-blind, double-dummy, parallel-group, randomised, active controlled trials comparing the clinical safety and clinical efficacy of dabigatran 150 mg BD and adjusted-dose warfarin (target INR of 2.0 - 3.0) in patients with confirmed acute symptomatic VTE following initial treatment (at least 5 days) with a parenteral anticoagulant approved for this indication.[1,27] RE-COVER was conducted across 228 clinical centres in 29 countries,[1] and RE-COVER II was conducted across 208 centres in 31 countries.[27] The design, including endpoints and methodology, were consistent with the guidance of the European Medicines Agency (EMA) on clinical investigation of medicinal products for the treatment of VTE.[28], [4] The aim of both studies was to demonstrate non-inferiority based on the composite primary endpoint of recurrent symptomatic VTE and deaths related to VTE within 6 months. On the basis of the low rate of recurrent VTE observed during recruitment to the first trial (RE-

COVER), we initiated this study (RE-COVER II) to confirm the results and to allow more precise subgroup analyses using pooled data from the 2 trials.

Before randomisation, the diagnosis of VTE was established with the use of compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries.[1] Randomisation was performed by a computer-generated randomisation scheme with variable block sizes, stratified according to presentation (PE or DVT without symptomatic PE) and the presence or absence of active cancer (Table 23).[1] There were four strata: 'active cancer and symptomatic PE', 'active cancer, no symptomatic PE', 'no active cancer, symptomatic PE', 'no active cancer, no symptomatic PE'.[28] Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within five years before enrolment; any treatment for cancer within five years before enrolment; or recurrent or metastatic cancer.[1]

Staff members at the clinical centres called an interactive voice-response system (IVRS) that randomly assigned subjects to one of the supplied medication kits.[1] The treatment-group assignment was concealed from all the investigators and their staff at the coordinating centre and the clinical centres and from the clinical monitors.[1] The study period was 6 months, and included a single-dummy and double-dummy period (Figure 4).[28], [4]

Figure 4: Study flow chart of the RE-COVER trials[28], [4]



Abbreviations: E, enrolment; INR, international normalised ratio; R, randomisation; VTE, venous thromboembolism.

Patients were followed-up seven days after randomisation and then every 30 days for six months.[1] An additional follow-up visit was scheduled for 30 days after completion of the

study, unless the patient had discontinued the study drug before six months, had started open-label anticoagulant therapy, or had been enrolled in another trial.[1]

Table 23: Comparative summary of methodology of RE-COVER and RE-COVER II

Trial	RE-COVER[28]	RE-COVER II[4]
Scientific rationale	Extension of the thrombus, recurrence of VTE, and (fatal) pulmonary embolisation are the most important sequelae for patients that have had a DVT. Current management of patients with acute VTE consists of initial treatment with heparin over at least 5 days followed by long-term oral anticoagulant therapy with vitamin K antagonists (VKAs). Patients with active cancer may also receive long-term (3 or 6 months) treatment with LMWH administered subcutaneously. Treatment with oral VKAs such as warfarin is complicated by several problems, including a delayed onset of antithrombotic action, a narrow therapeutic index, an unpredictable and variable pharmacological response, interactions with drugs and food, and the need for regular laboratory monitoring. Chronic use of injectable anticoagulants is difficult and because of the known problems with the use of oral VKAs, there is a need for new oral anticoagulants. There is an unmet medical need for improved oral anticoagulant agents for the treatment of acute VTE. Desirable characteristics of an oral anticoagulant are a prompt onset of action, a predictable dose response, no need for laboratory monitoring, and limited drug-drug or drug-food interactions. Dabigatran has the potential for fulfil this unmet clinical need.	
Title of study	Dabigatran versus warfarin in the treatment of acute venous thromboembolism.	
Objective	To compare the safety and efficacy of oral dabigatran (150 mg BD) and warfarin (to obtain a target INR of 2.0-3.0) for 6 month treatment of acute symptomatic venous thromboembolism (VTE) following initial treatment (at least 5 days) with a parenteral anticoagulant approved for this indication in patients with acute symptomatic unilateral or bilateral deep vein thrombosis (DVT) of the leg involving proximal veins and/or pulmonary embolism (PE).	
Location of study	Multicentre study (231 enrolling centres, including 288 randomising centres) conducted in 29 countries worldwide (Western Europe: Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom; Central Europe: Czech Republic, Hungary, Russia, Slovak Republic, Turkey, Ukraine; North America: Canada, USA; Latin America: Argentina, Brazil, Mexico; Asia: India; Other: Australia Israel, New Zealand, South Africa).	Multicentre study (208 centres, conducted in 31 countries worldwide) (Western Europe: Denmark, France, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom; Central Europe: Bulgaria, Czech Republic, Hungary, Poland, Russia, Slovakia, Turkey, Ukraine; North America: Canada, USA; Latin America: Brazil; Asia: China, India, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand; Others: Australia, Israel, New Zealand, South Africa)
Study design	Multicentre, Phase III, randomised, double-blind, double-dummy, parallel-group, active controlled trial.	
Duration of study	The treatment period was 6 months and included a single-dummy period (oral and parenteral therapy period) and a double-dummy period (oral only therapy period).	
Method of randomisation	Confirmation of VTE by objective clinical testing was to be obtained prior to randomisation. Patients were to be randomised within 72 hours of enrolment at Visit 2 using an Interactive Voice Response System (IVRS). Randomisation ratio was 1:1 for dabigatran and warfarin. Randomisation was stratified by active cancer and symptomatic PE (4 strata: 'active cancer and symptomatic PE', 'active cancer, no symptomatic PE', 'no active cancer, symptomatic PE', 'no active cancer, no symptomatic PE') and was performed in blocks of 4 to prevent unequal treatment allocation. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment; any treatment for cancer within 5 years before enrolment; or recurrent or metastatic cancer.	
Method of blinding	This study employed a double-blind design; neither the patient not the investigator was informed about the allocated treatment. In addition, the personnel involved in the conduct or assessment of the study were unaware of the treatment allocation for the entire duration of the study until after the final database was locked. Since the two treatments differed in their appearance, blinding was achieved by using a double-dummy design with dabigatran-matching placebo capsules and warfarin-matching placebo tablets. INR values had to be monitored to guide the warfarin therapy; a sham INR procedure was used to prevent unintentional un-blinding. INR measurements were to be	

	performed using a Point of Care (POC) device or alternative that provided an encrypted INR. Note that in cases were the use of a POC device was not feasible for monitoring of INR values, the INR could be measure in a non-blinded manner by pre-specified individuals who then forwarded the non-blinded INR to the IVRS. These individuals were un-blinded, but had no other role during the conduct of the study and did not provide any INR values to personnel involved in the conduct of the study.	
Intervention	Dabigatran etexilate 150 mg BD (dose calculated as free base) taken orally (n = 1,273).	Dabigatran etexilate 150 mg BD (dose calculated as free base) taken orally (n = 1,280).
Comparator	Warfarin as needed to maintain an International Normalised Ratio (INR) of 2.0-3.0 taken orally (n = 1,266).	Warfarin as needed to maintain an International Normalised Ratio (INR) of 2.0-3.0 taken orally (n = 1,288).
Primary outcomes	Composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined as the composite incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography, or spiral [helical] CT).	
Secondary outcomes	Secondary efficacy endpoints (within 6 months): o Composite of recurrent symptomatic VTE and all deaths o Symptomatic DVT o Symptomatic PE o Deaths related to VTE o All deaths All recurrent VTEs required objective verification by definitive diagnostic evaluation. All recurrent VTEs and all deaths were centrally adjudicated by an independent committee that was blinded to treatment allocation. Adjudicated results were used in the analysis.	
Safety outcomes	Safety was assessed based on: o Incidence of bleeding events - Major Bleeding Events (MBEs) - MBEs or Clinically Relevant Bleeding Events (CRBEs) - Any bleeding events (MBEs, CRBEs, and nuisance bleeding events) o Adverse Events (AEs; including findings in the physical examination) o Discontinuation of study treatment due to AEs o Laboratory measures, especially Liver Function Tests (LFTs) o Acute Coronary Syndrome (ACS) o ECG and vital signs All safety endpoints were assessed during treatment and the 6 days following the last intake of study medication. Any bleeding events and all suspected ACS were centrally adjudicated and all potentially liver-related safety issues were centrally reviewed by independent committees that were blinded with regards to the treatment allocation of patients. Adjudicated results were used in the analysis of bleeding events.	
Duration of follow-up	Visit schedule: 1. Screening a. Visit 1 (day -3 to 1) 2. Treatment period: single-dummy a. Visit 2 (day 1): initial parenteral therapy + trial medication (warfarin or warfarin placebo) 3. Treatment period: double-dummy a. Visit 3 (day 3 to 11): 1st oral dose of dabigatran or dabigatran placebo b. Visit 4 (day 30 [25-33]) c. Visit 5 (day 60 [±5])	Visit schedule: 1. Screening a. Visit 1 (day -3 to 1) 2. Treatment period: single-dummy a. Visit 2 (day 1): initial parenteral therapy + trial medication (warfarin or warfarin placebo) 3. Treatment period: double-dummy a. Visit 3 (day 7 [±4]): 1st oral dose of dabigatran or dabigatran placebo b. Visit 4 (day 29 [±4]) c. Visit 5 (day 60 [±5])

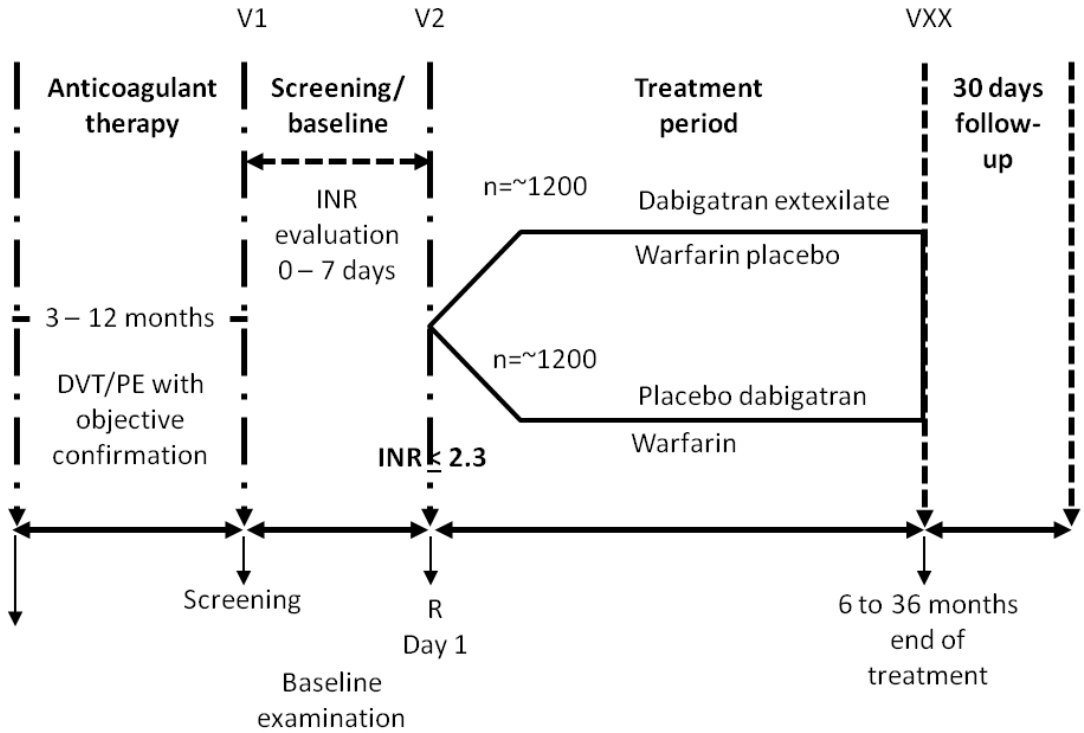
	d. Visit 6 (day 90 [±7]) e. Visit 7 (day 120 [±10]) f. Visit 8 (day 150 [±10]) g. Visit 9 (day 180 [±10]): last oral dose 4. Follow-up a. Visit 10 (day 210 [±14])	d. Visit 6 (day 90 [±7]) e. Visit 7 (day 120 [±10]) f. Visit 8 (day 150 [±10]) g. Visit 9 (day 180 [±10]): last oral dose 4. Follow-up Visit 10 (day 210 [±14])

RE-MEDY

The phase III study RE-MEDY was completed to evaluate the efficacy and safety of dabigatran for long-term prophylaxis after VTE.[5]

RE-MEDY was a randomised, double-blind, warfarin-controlled trial designed to evaluate dabigatran 150 mg BD with adjusted-dose warfarin (target INR 2.0-3.0) in patients who had been successfully treated with standard doses of an approved anticoagulant for 3 to 12 months for confirmed acute symptomatic VTE (Table 24). The aim of this study was to demonstrate non-inferiority based on the composite primary endpoint of recurrent symptomatic VTE and deaths related to VTE within 36 months. Patients were randomised to receive active dabigatran (150 mg BD) and a warfarin-like placebo or active warfarin and a dabigatran-like placebo in a double-dummy design (Figure 5).[5] Prior to randomisation, patients would have received 3 to 12 months of anticoagulant treatment for acute VTE.[5]

Figure 5: Study flow chart of the RE-MEDY trial[6]



Abbreviations: CUS, compression ultrasonography; DVT, deep vein thrombosis; INR, international normalised ratio; PE, pulmonary embolism; R, randomisation.

Patients were assessed at 15 and 30 days after randomisation, then monthly until day 180.[6] After that, patients in RE-MEDY were assessed every 90 days until the end of treatment; INR or sham INR results were obtained at intervals of no longer than four weeks. An additional visit occurred 30 days after the end of treatment.[5] RE-MEDY was initially designed for 18 months of treatment.[5] Because of a lower than projected event rate, the protocol was amended to increase the sample and extend the planned treatment period for patients already enrolled who consented to the extension, with the resulting planned study treatment period ranging from six to 36 months.[5]

As a result of this amendment, three cohorts of patients were included in the study:[6]

1. Patients who had completed the trial prior to implementation of this amendment or those not willing to consent to participate as per this amendment; such patients had a planned treatment duration of 18 months.

2. Patients who had been randomised prior to implementation of this amendment and re-consented to trial participation as per this amendment; such patients had a planned treatment duration of between 18 and 36 months. The actual treatment

period of such patients may have been shorter than 18 to 36 months in case of a primary outcome event or trial discontinuation due to adverse events or other reasons.

3. Patients randomised after implementation of this amendment but enrolled within 18 months of the planned study close-out. These patients had a planned treatment duration of 6 to <18 months.

Table 24: Comparative summary of methodology of RE-MEDY and RE-SONATE

Trial	RE-MEDY[6]	RE-SONATE[7]
Scientific rationale	Current management of patients with acute VTE consists of initial treatment with a parenteral agent such as UFH or LMWH over at least 5 days followed by long-term VKA use. Opinion is divided on the possible risks and benefits of long-term treatment of VKA therapy in patients with a prior PE and/or DVT and the optimal duration of treatment continues to be a subject of debate. Difficulties in keeping patients on VKAs may result in suboptimal treatment of these patients at times due to the discontinuation of VKAs. There is an unmet medical need for improved oral anticoagulant agents for long-term treatment and secondary prevention of VTE. Dabigatran is a suitable candidate to fulfil some of this unmet medical need.	
Title of study	Extended use of dabigatran, warfarin, or placebo in venous thromboembolism.	
Objective	To compare the safety and efficacy of oral dabigatran (150 mg BD) and warfarin (to obtain a target INR of 2.0 to 3.0) for the long-term treatment and secondary prevention of symptomatic venous thromboembolism (VTE) in patients treated with dabigatran or standard doses of anticoagulant for 3 to 12 months for confirmed acute symptomatic VTE.	The primary efficacy objective was to evaluate whether dabigatran was superior to placebo in the long-term prevention of recurrent symptomatic venous thromboembolism (VTE) in patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) who had completed 6 to 18 months of treatment with a vitamin K antagonist (VKA).
Location of study	Multicentre study conducted in 264 centres, in 33 countries worldwide (Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, UK; Eastern Europe: Bulgaria, Czech Republic, Hungary, Poland, Russia, Slovakia, Turkey, Ukraine; North America: Canada, USA; Latin America: Argentina, Brazil, Mexico; Asia: China, India; Others: Australia, Israel, New Zealand, South Africa).	Multicentre study conducted in 147 centres, in 21 countries worldwide (Western Europe: Austria, Belgium, Germany, Italy, Netherlands, Sweden, Switzerland; Eastern Europe: Czech Republic, Estonia, Latvia, Lithuania, Poland, Russia; North America: Canada, USA; Asia: Singapore, South Korea, Thailand; Others: Australia, New Zealand, South Africa).
Study design	Multicentre, Phase III, randomised, double-blind, double-dummy, parallel-group, active-controlled trial.	Multicentre, Phase III, randomised, double-blind, placebo-controlled, event-driven, superiority study.
Duration of study	6 to 36 months, as according to Protocol Amendment 6 (dated 12 December 2008) which extended the treatment duration of ongoing patients who consented to extend study participation to up to 36 months. Original protocol: 18 months.	The intended (planned) treatment period was 6 months. After trial close-out started, the intended treatment period was approximately 3 months for patients who had not already complete their 3-month visit and 6 months for those who has already completed this visit.
Method of randomisation	Randomisation was performed during Visit 2 involving the use of an Interactive Voice Response System (IVRS). The randomisation ratio in this trial was 1:1 and patients had an equal chance of receiving active treatment with either dabigatran or warfarin.	Each eligible patient was randomly assigned to either fixed dose (150 mg BD) dabigatran or to placebo. Assignment of study treatment was via an IVRS with an allocation ratio of 1:1 for dabigatran: placebo. Randomisation was stratified by centre using permuted blocks (block size: 4) to prevent a series of imbalanced treatment allocations and, after the introduction of Protocol Amendment 2, also within centres according to previous participation in RE-COVER.
Method of blinding	This study employed a double-blind design; neither the patient nor the investigators were informed about the allocated treatment. In addition, the personnel involved in the conduct or assessment of	This study employed a double-blind design; neither the patient nor the investigator was informed about the allocated treatment. To ensure appropriate blinding, an IVRS was used for the assignment of patients to

	the study were unaware of the treatment allocation for the entire duration of the study until the final database was locked. Since the 2 treatments differed in their appearance, blinding was achieved by using a double-dummy design with dabigatran-matching placebo capsules and warfarin-matching placebo tablets. INR values had to be monitored to guide the warfarin therapy; a sham INR procedure was used to prevent unintentional un-blinding. INR measurements were to be performed using a POC device or alternative. Moreover, an IVRS was used for the assignment of patients to treatment groups	treatment groups. A randomisation schedule was generated using validated software and verified by a Boehringer Ingelheim statistician who was not involved in the planning or performance of the trial. Individuals involved in the conduct and assessments of the study remained blinded to the randomisation schedule until the database was locked. The access to the randomisation code was supervised by Medical Data Services department's Clinical Trial Support. If needed, the Sponsor's Drug Safety personnel could also un-blind the treatment assignment of individual patients.
Intervention	Dabigatran etexilate 150 mg BD taken orally (dose calculated as free base) (n = 1,430)	Dabigatran etexilate capsules 150 mg BD taken orally (n = 681)
Comparator	Warfarin sodium 1mg, 3mg, and 5 mg tablets taken orally to target an INR of 2.0 to 3.0 (n = 1,426)	Placebo capsules BD taken orally (n = 662)
Primary outcomes	Composite of recurrent symptomatic venous thromboembolism (VTE) and deaths related to VTE during the planned treatment period	The primary efficacy endpoint was symptomatic recurrent VTEs, defined at the composite of symptomatic DVT, non-fatal and fatal PE during the intended treatment period. Deaths that were unexplained were considered as fatal PEs for the evaluation of the primary endpoint. All VTE events and deaths were adjudicated by an independent central adjudication committee.
Secondary outcomes	Secondary efficacy endpoints: ○ Composite of recurrent symptomatic VTE (fatal and non-fatal) and all deaths ○ Symptomatic DVT ○ Symptomatic PE (fatal or non-fatal) ○ Deaths related to VTE (i.e. fatal PE) ○ All deaths All VTEs required objective verification through definitive diagnostic evaluation. All recurrent VTEs and all deaths were centrally adjudicated by an independent committee that was blinded to treatment allocation. Adjudicated results were used in all primary analyses.	Secondary endpoints were the composite of recurrent symptomatic VTE (symptomatic DVT, symptomatic non-fatal PE, and fatal PE, excluding unexplained deaths) and the individual components of the primary efficacy endpoint. All VTE events and deaths were adjudicated by an independent central adjudication committee.
Safety outcomes	Safety was assessed based on: ○ Incidence of bleeding events - Major Bleeding Events (MBEs) - MBEs and Clinically Relevant Bleeding Events (CRBEs) - Any bleeding event (MBEs, CRBEs, and nuisance bleeds) ○ Adverse Events (AEs) ○ Discontinuation of study treatment due to AEs ○ Laboratory measures, especially Liver Function Tests (LFTs) ○ Acute Coronary Syndrome (ACS)	Safety endpoints included: ○ adjudicated bleeding events (major bleeding events [MBEs], clinically relevant bleeding (MBEs and clinically relevant non-major bleeding events [CRBEs]), and all bleeding events (MBEs, CRBEs, and trivial bleeding events) ○ adjudicated cardiovascular events (acute coronary syndrome), ischaemic stroke, non-central nervous system systemic embolism, transient ischaemic attacks [TIAs], and vascular [cardiac] death) ○ adverse events (AEs), coded according to the Medical Dictionary for Regulatory

	○ ECG and vital signs The focus of the safety analysis was on events that occurred during the treatment period including the 6 days following the last intake of study drug. All bleeding events and all suspected ACS events were centrally adjudicated and all potentially liver-related safety issues were centrally reviews by independent committees that were blinded with regard to the treatment allocation of patients.	Activities (MedDRA) version 14.1; during the extended follow-up period only serious AEs (SAEs) were reported ○deaths ○liver function tests (LFTs) and other laboratory parameters
Duration of follow-up	Visit schedule: 1. Screening and baseline period a. Visit 1 (day -7 to 1) 2. Randomisation a. Visit 2 (day 1) 3. Treatment and follow-up a. Visit 3 (day 15 [±3]) b. Visit 4 (day 30 [±7]) c. Visit 5 (day 60 [±7]) d. Visit 6 (day 90 [±7]) e. Visit 7 (day 120 [±7]) f. Visit 8 (day 150 [±7]) g. Visit 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 (day 180, 270, 360, 450, 540, 630, 720, 810, 900, 990 [±14])	Visit schedule: 1. Screening a. Visit 1 2. Randomisation a. Visit 2 (day 1) 3. Study treatment period a. Visit 3 (day 15 [±3]) b. Visit 4 (day 30 [±7]) c. Visit 5 (no longer scheduled as per Protocal Amendment 2) d. Visit 6 (day 90 [±7]) e. Visit 7 ((no longer scheduled as per Protocal Amendment 2) f. Visit 8 (no longer scheduled as per Protocal Amendment 2) g. Visit 9 (day 180 [±7]) 4. Standard follow-up a. Visit 10 (day 210 [±7]) 5. Extended follow-up a. Visit 11 (day 300 [±14]) b. Visit 12 (day 420 [±14]) c. Visit 13 (day 545 [±14])

RE-SONATE

RE-SONATE compared dabigatran 150 mg BD with placebo in patients who had completed 6 to 18 months of treatment with an oral anticoagulant treatment (VKA) for confirmed acute symptomatic VTE (Table 24).[5] The aim of this study was to demonstrate superiority based on the composite primary endpoint or recurrent DVT or fatal or non-fatal PE (including unexplained death) during the treatment period. The planned treatment duration, with either dabigatran or placebo, was 6 months. However, this was an event-driven study (requiring 36 confirmed recurrent VTE events); if the number of events was reached before all patients had completed the intended study duration, either the 3 or 6 month visit would be the final study treatment visit for all patients still treated. Therefore, the last included patients would be treated for at least 3 months.

Patients underwent randomisation by means of an interactive voice-response system. Randomisation was stratified according to the study centre in RE-SONATE.[5] Prior anticoagulant therapy was discontinued, and the study drug was started when the INR was 2.3 or lower. If the patient was recruited from the RE-COVER or RE-COVER II study, a point-of-care coagulometer with encrypted INR results was used to guide the transition so that the patients and investigators would remain unaware of the initial treatment.[5]

Participants

6.3.3 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.

In RE-COVER, patients were recruited from 228 clinical centres in 29 countries while in RE-COVER II, patients were recruited from 208 centres in 31 countries.[1,29] The inclusion criteria were chosen to enter a representative sample of patients in the target indication (Table 25); while the exclusion criteria excluded patients with significant co-morbidities or patients whose participation might have represented a health risk for the patient (Table 26).[28]

Patients for RE-MEDY were recruited from 264 sites in 33 countries and in RE-SONATE they were recruited from 147 sites in 21 countries. Patients were eligible if they were at least 18 years of age and had objectively confirmed, symptomatic, proximal DVT or PE that had already been treated with an approved anticoagulant or if they had received dabigatran in one of two previous clinical trials of short-term treatment of VTE: the RE-COVER and RE-COVER II studies (Table 25).[5] The required duration of initial treatment before trial enrolment was 3 to 12 months for RE-MEDY and 6 to 18 months for RE-SONATE.[5]

Table 25: Inclusion criteria for RE-COVER, RE-COVER II[1;4;28], RE-MEDY and RE-SONATE[5;8]

Trial	Inclusion criteria
RE-COVER and RE-COVER II	Patients could be included in the study if the following criteria were fulfilled: 1. Acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins, and/or PE confirmed by definitive objective clinical test in patients for whom at least 6 months of anticoagulant therapy was considered appropriate by the investigator [proximal veins are: trifurcation area, popliteal, superficial femoral, deep femoral, common femoral, and iliac veins] 2. Male or female, being 18 years of age or older 3. Written informed consent for study participation
RE-MEDY and RE-SONATE	1. Objectively confirmed symptomatic uni- or bilateral DVT of the leg involving proximal veins or PE, treated with approved anticoagulant therapy, or with study drug (in RE-SONATE previous study drug was introduced as an amendment), taken for (RE-MEDY) 3 to 12 months or (RE-SONATE) 6 to 18 months at the time of screening,. 2. Male or female, being 18 years of age or older (the age criterion was turned around as an exclusion criterion in RE-SONATE) 3. Written informed consent for study participation.

Table 26: Exclusion criteria for RE-COVER, RE-COVER II[1;4;28], RE-MEDY and RE-SONATE[5;8]

Trial	Exclusion criteria
RE-COVER and RE-COVER II	If any of the following criteria applied (as defined in the original trial protocol) patients were barred from entering this study: 1. Overt symptoms of VTE for longer than 2 weeks prior to enrolment 2. PE satisfying at least one of the following criteria: – Haemodynamic instability – Embolectomy indicated or performed – Thrombolytic therapy indicated or performed – Suspected source of PE other than the legs 3. Actual or anticipated use of vena cava filter 4. Contraindications to anticoagulant therapy including contraindications to heparins or other alternate approved therapy used for initial treatment, and warfarin 5. Patients who in the investigator's opinion should not be treated with warfarin 6. Allergy to heparins (including history of heparin induced thrombocytopenia) or other alternate approved therapy used for initial treatment, warfarin or dabigatran, or to one of the excipients included in these medications 7. Patients who in the investigator's judgement were perceived as having an excessive risk of bleeding, for example because of: – Haemorrhagic disorder or bleeding diathesis – Trauma or major surgery within the last month or as long as an excessive risk of bleeding persisted after these events, or planned major surgery – Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm – History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intraarticular bleeding – Gastrointestinal haemorrhage within the past 3 months – Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days – Treatment with thrombolytic agents within 14 days before enrolment – Anticipated need of restricted medication during the treatment period – Known thrombocytopenia (platelet count <100·109/L) 8. Known anaemia (haemoglobin <100 g/L)

	9. Need of anticoagulant treatment for disorders other than VTE 10. Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis, or history of myocardial infarction within the last 3 months 11. Elevated AST or ALT >2 x ULN (RE-COVER) or x3 ULN (RE-COVER II) based on the local laboratory results obtained at screening and prior to randomisation (or central screening laboratory results if available on time) 12. Liver disease expected to have any potential impact on survival (e.g. acute hepatitis, possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery) 13. Patients who had developed transaminase elevations upon exposure to ximelagatran (RE-COVER only) 14. Severe renal impairment (estimated creatinine clearance ≤30 ml/min) 15. Women who were pregnant, nursing, or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study (A negative pregnancy test had to be obtained for any woman of childbearing potential prior to entry into the study.) 16. Participation in another clinical trial with an investigational drug during the last 30 days or previous participation in this study 17. Patients considered unsuitable for inclusion by the investigator, e.g. because considered unreliable to comply with the requirements for follow-up during the study and/or compliance with study drug administration, had a life expectancy less than the expected duration of the trial due to concomitant disease, or had any condition which in the opinion of the investigator would not allow safe participation in the study (e.g. drug addiction, alcohol abuse) 18. In case of anticipated study-related diagnostic procedures requiring contrast medium (e.g. contrast venography or pulmonary angiography): – Elevated serum creatinine, which in the investigator's opinion contraindicated these examinations – Known allergy to radio opaque contrast media or iodine, which in the investigator's opinion contraindicated these examinations With Protocol Amendment 2 (dated 11 February 2008) it was added to the exclusion criteria that patients with an anticipated need of quinidine were barred from participation in this trial.
RE-MEDY	1. Symptomatic DVT or PE at screening 2. Patients with primary PE with suspected origin other than leg limbs (e.g. upper limbs, right heart). 3. Actual or anticipated use of vena cava filter 4. Interruption of anticoagulant therapy for 2 or more weeks during the 3-6 months of treatment for the prior VTE (changed from 3 to 6 months to 3 to 12 months treatment following Protocol Amendment 2, dates 15 March 2007) 5. Patients who in the investigator's opinion should not be treated with warfarin 6. Allergy to warfarin or dabigatran, or to one of the excipients included in these medications 7. Patients who in the investigator's judgement are perceived as having an excessive risk of bleeding. a. Haemorrhagic disorder or bleeding diathesis b. Trauma or major surgery within the last month or as long as an excessive risk of bleeding persists after these events, or planned major surgery c. Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm d. History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding e. Gastrointestinal haemorrhage within the past 3 months f. Symptomatic or endoscopically documented gastro-duodenal ulcer disease in the previous 30 days g. Treatment with thrombolytic agents within 14 days before enrolment h. Anticipated need of restricted medication during the treatment period i. Known thrombocytopenia (platelet count <$100*10^9$/L)

	8. Known anaemia (haemoglobin <100 g/L) 9. Need of anticoagulant treatment for disorders other than VTE 10. Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis or history of myocardial infarction within the last 3 months 11. Elevated AST or ALT >2x ULN based on the local lab results obtained at screening and prior to randomisation (or central screening lab if available on time) 12. Liver disease expected to have any potential impact on survival (e.g. acute hepatitis, or possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery) 13. Patients who have developed transaminase elevations upon exposure to ximelagatran 14. Severe renal impairment (estimated creatinine clearance ≤30 ml/min) 15. Women who are pregnant, nursing or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study. 16. Participation in another clinical trial with an investigational drug during the last 30 days, except for the RE-COVER, or previous participation in this study. Following Protocol Amendment 6, dates 12 December 2008, patients who had completed the RE-COVER II trial were allowed to enter into RE-MEDY 17. Patients considered unsuitable for inclusion by the investigator, e.g. because considered unreliable to comply with the requirements for follow-up during the study or compliance with study drug administration, had a life expectancy less than the expected duration of the trial due to concomitant disease, or had any condition which in the opinion of the investigator did not allow safe participation in the study (e.g., drug addiction, alcohol abuse) 18. In case of anticipated study related diagnostic procedures requiring contrast medium (e.g., contrast venography or pulmonary angiography): a. Elevated serum creatinine, which in the investigator's opinion contraindicates these examinations b. Known allergy to radio opaque contrast media or iodine, which in the investigator's opinion contraindicated these examinations Following Protocol Amendment 4, dated 14 February 2008, patients with an anticipated need for quinidine treatment were excluded.
RE-SONATE	1. Younger than 18 years of age 2. Indication for VKA other than DVT and/or PE 3. Patients in whom anticoagulant treatment for their index PE or DVT should be continued 4. Active liver disease or liver disease decreasing survival (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 x ULN 5. Creatinine clearance <30 ml/min 6. Acute bacterial endocarditis 7. Patients who in the investigator's judgement were perceived as having an excessive risk of bleeding, for example because of anticipated need for quinidine or other restricted medication during the treatment period. 8. Uncontrolled hypertension (investigator's judgement) 9. Intake of another experimental drug within the 30 days prior to randomisation into the study, with the exception of patients participating in RE-COVER trials. 10. Life expectancy <6 months 11. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding 12. Patients with known hypersensitivity to dabigatran or any other component of the investigational product or the placebo capsules 13. Patients deemed unsuitable for inclusion by the investigator, because considered unreliable to comply with the requirements of the study and/or compliance with study drug administration, or because having any condition or disease which in the opinion of the investigator would not allow safe participation in the study. 14. Patients with known active cancer

6.3.4 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.

RE-COVER and RE-COVER II

From April 2006 to November 2008, a total of 2,564 patients were randomly assigned to a study group in the RE-COVER study, of which 2,539 received at least one dose of study drug.[1] RE-COVER II was conducted between June 2008 and October 2010 and randomised 2,589 patients, of which 2,568 received at least one dose of study drug.[27] The baseline characteristics of the patients included in the study are provided in Table 27.

In general, there are no significant differences between dabigatran and warfarin treatment groups in the RE-COVER trials in terms of baseline demographics and disease characteristics. In RE-COVER parenteral anticoagulation was given for a mean of 10 days in both treatment groups.[1] Over the 6-month period, patients in the warfarin group had a mean of 16 INR tests, and the INR was in the therapeutic range 59.9% (±22.9%) of the time. Overall, the INR was below the therapeutic range 21% of the time and above the therapeutic range 19% of the time.[1] In RE-COVER II, parenteral anticoagulation was given for a mean of approximately 9 days in both treatment groups. Over the 6-month treatment period, patients in the warfarin group had an INR in the therapeutic range 56.9% (±21.9%) of the time. The INR was below the therapeutic range 24% of the time and above the therapeutic range 19% of the time.

Table 27: Baseline demographics of patients in the RE-COVER trials [1;27]

Characteristic	RE-COVER		RE-COVER II	
	Dabigatran (n = 1,273)	Warfarin (n = 1,266)	Dabigatran (n = 1,280)	Warfarin (n = 1,288)
Age – mean ± SD	55.0 ± 15.8	54.4 ± 16.2	54.7 ± 16.2	55.1 ± 16.3
Female sex – n (%)	535 (42.0)	520 (41.1)	499 (39.0)	512 (39.8)
Race – n (%)				
White	1,212 (95.2)	1,195 (94.4)	993 (77.6)	999 (77.6)
Black	36 (2.8)	31 (2.4)	19 (1.5)	19 (1.5)
Asian	25 (2.0)	40 (3.2)	267 (20.9)	270 (21.0)
BMI – mean ± SD	28.9 ± 5.7	28.4 ± 5.5	28.4 ± 5.8	28.4 ± 5.8
Type of index event				
DVT only	880 (69.1)	869 (68.6)	877 (68.5)	873 (67.8)
PE only	270 (21.2)	271 (21.4)	298 (23.3)	297 (23.1)
DVT and PE	121 (9.5)	124 (9.8)	104 (8.1)	117 (9.1)
Neither DVT or PE	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
Cancer – n (%)	64 (5.0)	57 (4.5)	50 (3.9)	50 (3.9)
Previous VTE – n (%)	327 (25.7)	322 (25.4)	247 (19.3)	203 (15.8)
Parenteral anticoagulation				
Treatment before randomisation (days)				
Median	3.0	3.0	ND	ND
IQR	2.0 - 4.0	2.0 - 4.0		
Treatment after randomisation* (days)				
Median	6.0	6.0	6.8 ± 3.4	7.1 ± 3.7
IQR	5.0 - 8.0	5.0 - 8.0		
Unfractionated heparin – n (%)	144 (11.3)	164 (13.0)	198 (15.5)	207 (16.1)
LMW heparin – n (%)	1,138 (89.4)	1,148 (90.7)	1133 (88.5)	1147 (89.1)
Fondaparinux – n (%)	50 (3.9)	36 (2.8)	32 (2.5)	21 (1.6)

*Treatment after randomisation in the single-dummy phase.

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; LMW, low-molecular-weight; ND, no data; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

RE-MEDY and RE-SONATE

From July 2006 to July 2010, a total of 2,866 patients underwent randomisation in RE-MEDY, and from November 2007 to September 2010, of which 2,856 received at least one dose of study drug. A total of 1,353 patients underwent randomisation in RE-SONATE, of which 1,343 patients received at least one study drug.[5] Baseline demographics of patients included in RE-MEDY and RE-SONATE are provided in Table 28.

There were no significant differences between the treatment groups in either RE-MEDY or the RE-SONATE in terms of baseline demographics and disease characteristics. In RE-MEDY, over the 3-year treatment period, patients in the warfarin group had a mean of 22.9 INR tests, and the INR was in the therapeutic range 61.5% of the time. Overall, the INR was

below the therapeutic range 21.5% of the time and above the therapeutic range 15.2% of the time.

Table 28: Baseline demographics of patients in RE-MEDY and RE-SONATE [5]

Characteristic	RE-MEDY		RE-SONATE	
	Dabigatran (n = 1,430)	Warfarin (n =1,426)	Dabigatran (n = 681)	Warfarin (n = 662)
Age – mean ± SD	55.4 ± 15.0	53.9 ± 15.3	56.1 ± 15.5	55.5 ± 15.1
Female sex – n (%)	559 (39.1)	555 (38.9)	300 (44.1)	298 (45.0)
Race – n (%)				
White	1,288 (90.1)	1,284 (90.0)	610 (89.6)	585 (88.4)
Black	29 (2.0)	28 (2.0)	9 (1.3)	14 (2.1)
Asian	113 (7.9)	114 (8.0)	58 (8.5)	60 (9.1)
American Indian	0	0	4 (0.6)	3 (0.5)
Weight (kg) – mean ± SD	86.1 ± 19.3	86.0 ± 18.9	83.7 ± 18.0	84.0 ± 18.6
Type of index event				
DVT only	938 (65.6)	922 (64.7)	431 (63.3)	441 (66.6)
PE only	324 (22.7)	335 (23.5)	183 (26.9)	178 (26.9)
DVT and PE	167 (11.7)	168 (11.8)	47 (6.9)	35 (5.3)
Neither DVT or PE	1 (0.1)	1 (0.1)	20 (2.9)	8 (1.2)
Cancer – n (%)	60 (4.2)	59 (4.1)	1*	2*
Treatment duration before randomisation – days	198 ± 157	200 ± 117	293 ± 107	299 ± 110
Enrolled from RE-COVER study - n (%)				
Dabigatran group	236 (16.5)	254 (17.8)	7 (1.0)	8 (1.2)
Warfarin group	283 (19.8)	243 (17.0)	8 (1.2)	4 (0.6)
Enrolled from RE-COVER II study - n (%)	70 (4.9)	55 (3.9)	NA	NA
Exposure to study drug – days	473 ± 211	474 ± 206	165 ± 45	162 ± 47

*Active cancer was an exclusion criterion, and the numbers represent protocol violations.

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; SD, standard deviation.

Outcomes

6.3.5 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 (HRQL), 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.

The European Committee for Medicinal Product for Human use (CHMP) recommends a composite primary endpoint consisting of recurrent symptomatic non-fatal DVT and/or PE and mortality. Recurrent DVT and PE should be objectively verified.[12] An analysis of the combined incidence of recurrent VTE and deaths related to VTE is considered most important in trials aiming to document non-inferiority whereas an analysis of the combined incidence of recurrent VTE and all deaths is considered most important in trials aiming to show superiority.

The endpoints used were consistent across the RE-COVER, RE-COVER II and RE-MEDY (non-inferiority) studies. The primary endpoint was a composite of recurrent VTE (objectively confirmed symptomatic DVT and/or PE) and deaths related to VTE. In RE-SONATE (superiority study) the primary endpoint was a composite of objectively confirmed symptomatic recurrent DVT or fatal or non-fatal PE, and this endpoint included unexplained death.

Secondary endpoints in RE-COVER, RE-COVER II and RE-MEDY were (Table 29):

- A composite of recurrent symptomatic VTE and all deaths
- Separate components of the primary efficacy outcome
- All deaths

Secondary endpoints in RE-SONATE were

Table 29):

- Composite of symptomatic recurrent DVT, recurrent non-fatal PE and fatal PE (excluding unexplained death)
- Separate components of the primary efficacy outcome

All venograms, ultrasound images, lung scans, spiral CT images, and other objective tests for suspected VTE were centrally assessed by an external an independent adjudication committee who were blinded to treatment. In addition, all deaths in RE-COVER and RE-COVER II and RE-MEDY were reviewed for evidence of fatal PE or bleeding.

Safety outcomes were focused on bleeding events. However, given the experience with ximelagatran, which was withdrawn from the market due to hepatic safety concerns, special attention was also paid to hepatic and coronary events.

Table 29: Pivotal study endpoints in RE-COVER[28], RE-COVER II[4], RE-MEDY[6] and RE-SONATE[7]

	RE-COVER, RE-COVER II and RE-MEDY	RE-SONATE
Primary endpoint	Composite of recurrent VTE (objectively confirmed symptomatic DVT and/or PE) and deaths related to VTE	Composite of objectively confirmed symptomatic recurrent DVT or fatal or non-fatal PE (including unexplained death)
Secondary endpoints	○ Composite of recurrent symptomatic VTE and all deaths ○ Symptomatic DVT ○ Symptomatic PE ○ Deaths related to VTE ○ All deaths	○ Composite of recurrent DVT, recurrent non-fatal PE and fatal PE (including unexplained death) ○ Separate components of primary efficacy outcome
Safety endpoints	○ Bleeding events - major bleeding events (MBE) - MBE or clinically relevant bleeding events (CRBE) - Any bleeding event (major, clinically relevant and nuisance bleeds) ○ Adverse events (AEs) ○ Discontinuation of study treatment due to AEs ○ Laboratory measures (especially liver function tests) ○ Acute coronary syndrome (ACS) ○ ECG and vital signs	○ Bleeding events - major bleeding events (MBE) - MBE or clinically relevant bleeding events (CRBE) - Any bleeding event (major, clinically relevant and nuisance bleeds) ○ All deaths ○ Cardiovascular events (ACS, ischaemic stroke, transient ischaemic attack, non-CNS systemic embolism, vascular death) ○ AEs ○ Laboratory measures (especially liver function tests)

Confirmation of VTE events

VTE events were confirmed as follows:

- Symptomatic DVT (all studies): confirmed by compression ultrasonography or venography
- Symptomatic PE (all studies): confirmed by spiral CT scan, pulmonary angiogram, ventilation/perfusion lung scan
- Fatal VTE (RE-COVER, RE-COVER II and RE-MEDY): in case of death, VTE should be confirmed by autopsy
- Fatal PE (RE-SONATE): PE confirmed on objective diagnostic testing or autopsy; this outcome could also include unexplained death (for primary endpoint but not secondary endpoint)
- Unexplained death (RE-SONATE): death that was not attributable to a documented cause and for which VTE could not be ruled out.

Assessment of bleeding events

An experienced and independent committee of experts, blinded to all treatment allocations, adjudicated all bleeding events centrally using pre-defined and detailed rules. Bleeds were

classified as major bleeding events (MBE), clinically relevant bleeding events (CRBE) and minor bleeds (Table 30).

Table 30: Definitions of bleeding events in RE-COVER[28], RE-COVER II[4], RE-MEDY[6] and RE-SONATE[7]

	RE-COVER, RE-COVER II and RE-MEDY	RE-SONATE
Major bleeding event	International Society on Thrombosis and Haematosis criteria; i.e. one or more of: ○ fatal bleeding ○ symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome ○ bleeding causing a fall in haemoglobin level of $20gL^{-1}$ ($1.24mmolL^{-1}$) or more, or leading to transfusion of ≥2 units of whole blood or red cells.	
Clinically relevant bleeding event	One or more of: ○ spontaneous skin haematoma $\geq 25cm^2$ ○ 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 and/or requiring surgical treatment ○ bleeding leading to a transfusion of <2 units of whole blood or red cells ○ any other bleeding event considered clinically relevant by the investigator	Overt bleeding not meeting criteria for MBE but associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life. Examples: ○ epistaxis >5 minutes duration or if repetitive or leads to an intervention ○ gingival bleeding if spontaneous or >5 minutes duration ○ macroscopic haematuria, either spontaneous or, if associated with an intervention, lasting more than 24 hours ○ macroscopic gastro-intestinal haemorrhage ○ haemoptysis, if more than a few speckled in the sputum ○ intramuscular haematoma ○ subcutaneous haematoma if $>25cm^2$, or $>100cm^2$ if provoked ○ multiple source bleeding
Other bleeding events	All other bleeding events that did not fulfil the criteria for MBE or CRBE were classified as nuisance bleeds	All other bleeding events that did not fulfil the criteria for MBE or CRBE were classified as trivial bleeds

Statistical analysis and definition of study groups

6.3.6 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.

RE-COVER, RE-COVER II and RE-MEDY

RE-COVER, RE-COVER II and RE-MEDY were designated to determine the efficacy and safety of dabigatran 150 mg BD compared with warfarin in patients with symptomatic VTE, using HRs and risk differences. After achieving non-inferiority, the trials aimed to establish superiority (by means of hierarchical tests) of dabigatran 150 mg BD over adjusted-dose warfarin. The overall significance level was controlled by *a priori* ordering of hypotheses.

> **Hazard ratio (HR):** calculated based on time to first occurrence of any component of the primary endpoint (recurrent symptomatic VTE and deaths related to VTE) using proportional hazard model (Cox regression).
>
> **Risk difference (RD):** calculated using Kaplan-Meier estimates of the cumulative risk of an event at the end of 6 months of treatment (for RE-COVER and RE-COVER II) or 18 months of treatment (for RE-MEDY).

In RE-COVER and RE-COVER II, the non-inferiority margins were defined as 2.75 for the HR and 3.6% for the risk difference at month 6 (i.e. Day 180). By fulfilling both margins simultaneously dabigatran would preserve at least 57% of the warfarin effect vs. placebo in HRs as well as at least 75% risk differences if proven to be non-inferior to warfarin. Both margins were anchored on the lower bound of the 95% confidence intervals (CIs) for the warfarin effect to account for the variability in point estimates.

In RE-MEDY, the non-interiority margins were defined as 2.85 for the HR and 2.8% for the risk difference at month 18. By fulfilling both margins simultaneously dabigatran would preserve at least 70% of the warfarin effect vs. placebo in HRs (based on the point estimates) as well as at least two thirds in risk differences (based on the lower bounds of 95% CI) if proven to be non-inferior to warfarin.

Analyses of the primary and secondary efficacy endpoints were based on the full analysis set (FAS) and followed the intention-to-treat principle, because randomised patients that were not treated were excluded from the analysis. The FAS was composed of all randomised patients who were documented to have taken at least one dose of study drug (Table 31). Patients were assigned to the treatment groups in the FAS as randomised regardless of the actual study drug taken. For the evaluation of the data, 4 analysis sets were used; these were the full analysis set (FAS), the per-protocol set (PPS), the treated set (TS), and the pharmacokinetic set (PKS).

The efficacy analyses for the acute VTE treatment studies included events that occurred between randomisation and the end of the post-treatment period:

- The end of the post-treatment period for roll-over patients was the day after the last intake of the study drug (maximum of last dabigatran/dabigatran-matching placebo intake, last warfarin/warfarin-matching placebo intake).
- For patients who completed treatment (per investigator opinion) and did not roll over to RE-MEDY or RE-SONATE, the date of the last follow-up visit was considered the end of the post-treatment period.
- For patients who terminated treatment prematurely and did not roll over to RE-MEDY or RE-SONATE, the date of the last contact was considered the end of post-treatment period.
    - For RE-COVER, this was the maximum of the latest AE end date, the last know date of intake of treatment, the last date of telephone contact, or the date of last study visit.
    - For RE-COVER II, this was the maximum of the date of last visit, the date of termination from the study, the date of last known intake of study drug, the last AE start/stop date, the last day a patient was known to be alive, or the date of death. The last scheduled contact visit was to be (Day 180 ±10) or the end of follow-up.

Analysis set: RE-COVER

In RE-COVER, all efficacy analyses were based on the FAS, with the exception of the PPS analysis of the primary endpoint. The TS comprised all randomised patients who were documented to have taken at least 1 dose of study drug.

However, patients were assigned to the treatment groups according to the treatment actually received; the first medication kit used by a patient determined their treatment group assignment for the TS. The PPS was a subset of the TS, restricted to patients without important protocol violations. The PKS included all randomised patients who were documented to have taken at least 1 dose of study drug and for whom at least 1 blood sample was available. The allocation of patients to treatment groups was based on the actual treatment. The PKS was employed for the analysis of PK and PD data. Of the total number of 2,630 enrolled patients, 2,564 patients were randomised into the study.

Table 31: Number of patients in analysis sets for RE-COVER[28], RE-COVER II[4] and RE-MEDY[6]

RE-COVER Analysis set	Dabigatran	Warfarin	Total
Randomised patients, n (%)	1,281 (100.0)	1,283 (100.0)	2,564 (100.0)
Full analysis set (FAS), n (%)	1,274 (99.5)	1,265 (98.6)	2,539 (99.0)
Treated patients (TS), n (%)	1,273 (100.0)	1,266 (100.0)	2,539 (100.0)
Per-protocol set (PPS), n (%)	1,222 (96.0)	1,192 (94.2)	2,414 (95.1)
PK set (PKS), n (%)	1,198 (94.1)	1,174 (92.7)	2,372 (93.4)
RE-COVER II Analysis set	**Dabigatran**	**Warfarin**	**Total**
Randomised patients, n (%)	1,293 (100.0)	1,296 (100.0)	2,589 (100.0)
Full analysis set (FAS), n (%)	1,279 (98.9)	1,289 (99.5)	2,568 (99.2)
Treated patients (TS), n (%)	1,280 (100.0)	1,288 (100.0)	2,568 (100.0)
Per-protocol set (PPS), n (%)	1,242 (97.0)	1,256 (97.5)	2,498 (97.3)
RE-MEDY Analysis set	**Dabigatran**	**Warfarin**	**Total**
Randomised set (RS), n (%)	1,435 (100.0)	1,431 (100.0)	2,866 (100.0)
Full analysis set (FAS), n (%)			
as randomised	1,430 (99.7)	1,426 (99.7)	2,856 (99.7)
as treated	1,430 (99.7)	1,426 (99.7)	2,856 (99.7)
Per-protocol set (PPS)	1,400 (97.6)	1,400 (97.8)	2,800 (97.7)

Of these, 2,539 patients (99.0%) were documented to have taken at least 1 dose of study medication. These patients made up both the FAS and the TS. The frequency of patients in the FAS was balanced between the treatment groups (dabigatran: 99.5%, warfarin: 98.6%). The numbers of patients in the treatment groups according to the TS (dabigatran: 1,273 patients, warfarin: 1,266 patients) was virtually the same as for the FAS (Table 31). The differences in patient numbers by treatment arms for the FAS and TS are due to 1 patient who started the study with a different treatment (warfarin) than he had been randomised to (dabigatran). Of the treated patients, 4.9% were excluded from the TS due to important protocol violations. Thus, the PPS included 95.1% of the treated patients (dabigatran: 96.0%, warfarin: 94.2%).

Analysis set: RE-COVER II

Both the FAS and the TS consisted of all randomised patients who were dispensed study drug and were documented to have taken at least 1 dose of study drug. Of the total number of 2,589 randomised patients, 2,568 patients (99.2%) were treated and therefore made up the FAS and the TS (Table 31).

For the FAS, patients were allocated to the randomised treatment groups regardless of the actual medication taken. In this trial, 3 patients (1 in the dabigatran group and 2 in the warfarin group) were dispensed incorrect medication kits at the randomisation visit. These 3 patients are assigned to their randomised treatment groups in the FAS. For the TS, patients were allocated to treatment groups as actually treated (i.e. the first medication kit used by a patient determined their actual treatment group). Accordingly, the 3 patients who received the wrong treatment kit at the randomisation visit are assigned to their received treatment group for the TS, which is different than their assigned treatment group in the FAS.

The PPS was a subset of the TS, restricted to patients without important protocol violations with a possible impact on the analyses of efficacy (study drug assignment as treated). Of the treated patients, 2.7% were excluded from the TS due to important protocol violations. Thus, the PPS included 97.3% of the treated patients.

Analysis set: RE-MEDY

The planned sample size and treatment exposure for patients (at least 1,200 patients per treatment group) was intended to have at least 80% power to claim non-inferiority with one-sided alpha=0.025 (as per Protocol Amendment 6, dated 12 December 2008[6]). The calculation assumed that the observed pooled hazard rates in the strata at the time of the protocol-specified blinded sample size re-assessment were the true rates and stable throughout the trial for the primary endpoint, and that 20% of patients would discontinue from the trial within each 18-month period. According to the original protocol, the planned sample size was 1,000 patients per group for a total of 36 expected events from combined groups, to have at least 85% of power to claim non-inferiority with one-sided alpha=0.025. This calculation assumed an equal hazard rate of 2.0% for both groups for the primary endpoint and a discontinuation rate of 20% over 18 months.

For the primary analysis, the overall hazard ratio (from a Cox model) and the risk difference (from Kaplan-Meier (KM) estimates) were used with events censored at the planned treatment stop date for the hazard ratio and at the minimum of 18 months (540 days) and the planned treatment stop date for the KM estimates.

For the evaluation of the data, 3 analysis sets were used; these were the randomised set (RS), the full analysis set (FAS), and the per-protocol set (PPS). The RS included all randomised patients, whether treated or not. The FAS consisted of all randomised patients who were documented to have taken at least 1 dose of study drug.

The PPS was a subset of the FAS, restricted to patients without important protocol violations. All efficacy analyses were based on the FAS, with the exception of the PPS analysis of the primary endpoint. The primary analysis of the efficacy endpoints was based on a modified intention-to-treat principle, because randomised patients that were not treated were excluded from the analysis. For efficacy analyses, patients were generally allocated to the treatment groups as randomised, regardless of the actual medication taken ('FAS as randomised'). An on-treatment analysis was performed as a sensitivity analysis for the primary endpoint. For this on-treatment analysis, patients were allocated to the treatment groups as treated, i.e. according to the actual medication taken ('FAS as treated'). The first medication kit used by a patient determined their treatment group assignment. For the per-protocol analysis on the PPS, patients were also allocated to treatment groups as treated. The analyses of the secondary efficacy endpoints and the demographic and baseline characteristics were based on the 'FAS as randomised'. The analysis of the safety endpoints was based on the 'FAS as treated'.

Of the total number of 2,866 randomised patients, 2,856 patients (99.7%) were documented to have taken at least 1 dose of study medication (Table 31). The 'FAS as randomised' and the 'FAS as treated' had the same number of patients per treatment group. However, despite being of equal number, they were not composed of precisely the same patients: 1 patient in each treatment group was dispensed an incorrect medication kit (wrong treatment) at the randomisation visit and continued on this treatment throughout the study.

Of the treated patients, 2.0% were excluded from the FAS due to important protocol violations. Thus, the PPS included 97.7% of the treated patients.

RE-SONATE

RE-SONATE was designed to demonstrate superiority of dabigatran 150 mg BD over placebo in patients with symptomatic VTE who had completed 6 to 18 months of treatment with a VKA, using HRs.

Hazard ratio (HR): calculated based on time to first occurrence of any component of the primary endpoint (recurrent DVT or fatal or non-fatal PE, including all unexplained deaths) using a proportional hazard model.

The dabigatran to placebo HR was computed with a 95% CI (two-sided testing). Based on this model, dabigatran would be considered superior to placebo if the incidence of symptomatic recurrent VTE in the dabigatran group was statistically significantly lower than in the placebo group at a significance level of 0.05. If dabigatran was superior to placebo, the time (person-time free from complication) to the principal safety outcome would be compared between treatment groups, using the proportional hazard model.

Superiority of the dabigatran group over placebo was concluded if the upper 95% confidence limit of the HR was less than 1. Kaplan-Meier plots stratified by treatment were produced for efficacy endpoints that occurred during the intended treatment period. Patients who did not experience an event were censored. The log-rank test was performed as a sensitivity analysis. The composite endpoint of recurrent symptomatic VTE without unexplained death was analysed as described for the primary efficacy analysis. The frequencies of the individual components contributing to the primary efficacy endpoint were summarised by treatment group, 95% CIs were calculated using the Clopper- Pearson method, and Fisher's exact test was used to compare the 2 treatment groups.

The cumulative incidence of recurrent symptomatic VTE events (with and without unexplained deaths) from randomisation up to the end of the 12-month extended follow-up period, after the intended treatment period, was determined. Kaplan-Meier plots stratified by treatment were produced, and log rank p-values and HRs were determined. Also, risk differences for recurrent symptomatic VTE events were estimated at 180, 220, 365, and 540 days after randomisation. Kaplan-Meier curves, log rank p-value, and HR were also determined for recurrent symptomatic VTEs including unexplained death and including use of non-study anticoagulant medication during follow-up as an event.

Assuming a 70% risk reduction in the dabigatran group compared to the placebo group, a total of 36 events would give a power of 95% to demonstrate that dabigatran was superior to placebo (two-sided type I error = 0.05). Assuming a 3% frequency for the placebo group, approximately 900 patients per group were needed.

Safety endpoints were summarised using descriptive statistics. Bleeding events were analysed as described for the primary analysis of efficacy. If there were too few events, 95%

confidence intervals were calculated using the Clopper-Pearson method and Fisher's exact test was used to compare the 2 treatment groups. The time to first elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x the upper limit of normal (ULN) or total bilirubin >2 x ULN and the cumulative incidences were determined using the Kaplan-Meier method and compared using the log rank test.

The primary efficacy endpoint was analysed in terms of the time to first occurrence using a Cox proportional hazards model including the main effect of treatment. The dabigatran-to-placebo hazard ratio and its corresponding 2-sided 95% confidence intervals were calculated.

Analysis set: RE-SONATE

The primary analysis was based on the FAS that compared those patients who were randomised and who took at least one dose of study medication (Table 32).

Table 32: Number of patients in analysis sets for RE-SONATE[7]

RE-SONATE Analysis set	Dabigatran	Warfarin	Total
Randomised patients, n (%)	685 (100.0)	668 (100.0)	1,353 (100.0)
Treated patients (TS), n (%)	681 (100.0)	662 (100.0)	1,343 (100.0)
Full analysis set (FAS), n (%)			
as randomised	681 (100.0)	662 (100.0)	1,343 (100.0)
as treated	684 (100.0)	659 (100.0)	1,343 (100.0)
Per-protocol set (PPS), n (%)	603 (88.5)	599 (90.5)	1,202 (89.5)
Extended follow-up, n (%)			
as randomised	672 (98.7)	651 (98.3)	1,323
as treated	675 (98.7)	648 (98.3)	1,323 (98.5)

Table 32 displays the number of patients in each analysis set. The enrolled patients (N=1,366) all provided informed consent. Of these, 1,353 patients were randomised and 1,343 patients were treated with at least 1 dose of study medication. The FAS - as randomised (N=1,343) comprised all patients who were randomised and were documented to have taken at least 1 dose of study medication; patients were assigned to the treatment group to which they were randomised. The FAS - as treated (N=1,343) included patients who

were documented to have taken at least 1 dose of study medication, with patients assigned to the treatment to which they were exposed the longest. The PPS (N=1,202) was a subset of the FAS - as randomised and included patients who did not have a major protocol violation that might confound interpretation of the efficacy results.

All randomised patients who provided informed consent were eligible to continue into the extended follow-up period. In total, 1,330 patients continued into the extended follow-up period. Of these, 1,323 patients (98.5%) were treated during the double-blind phase and were included in the Extended Follow-up - as randomised population (Table 32). For analyses of safety, patients in the extended follow-up period were assigned according to the study medication to which they were exposed the longest (extended follow-up - as treated population).

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

RE-COVER and RE-COVER II

Pre-defined subgroup analyses of the primary endpoint were performed to evaluate the consistency of the treatment effect across a variety of patient groups. Outcomes in each subgroup were summarised by treatment, presenting the number of patients with events and the cumulative risk at 6 months using KM estimates. The proportional hazards model (Cox regression) without adjustment for the stratification factors was used to support the interpretation of data by subgroups in an exploratory manner. The subgroups that were analysed for the primary endpoint are displayed in Table 33.

Table 33: Subgroup analyses for the primary endpoint in RE-COVER[28] and RE-COVER II[4]

Subgroups	Categories
Drug-demographic interactions	Age (years): 18 to <40, 40 to <50, 50 to <65, 65 to <75, ≥ 75
	Sex: male, female
	Race: White, Asian, Black
	Ethnicity: Hispanic, non-Hispanic
	Body weight (kg): <50, 50 to <100, ≥100
	BMI (kg/m^2): <25, 25 to <30, 30 to <35, ≥35
Drug-disease interactions	Creatinine clearance (mL/min): <30, 30 to <50, 50 to <80, ≥80
	Active cancer at any time[1]: yes, no
Extrinsic factors	Geographical region: Western Europe[2], Central Europe[3], North America[4], Latin America[5], Asia[6], Other[7]
	Smoking history: never smoked, ex-smoker, current smoker
Risk factors for VTE	Previous VTE prior to the index event: yes, no
	Thrombophilia: yes, no
	History of venous insufficiency: yes, no
	Prolonged immobilisation: yes, no
	Long distance travel: yes, no
	Surgery/trauma: yes, no
	Recent use of oestrogens systematically[8]: yes, no
	Recent pregnancy[9]: yes, no
	Idiopathic VTE: non-idiopathic VTE, no risk factors identified/idiopathic VTE
Drug-drug interactions	Open-label parenteral therapy for the index event: UFH, LMWH, fondaparinux, any parenteral therapy[10]
	Extent of exposure to open-label parenteral therapy for the index event: ≤9 days, ≥9 days
	Use of concomitant therapies of special interest: platelet inhibitors, other antithrombotic agents, concomitant ASA use (categories: ASA daily dose ≤100 mg, ASA daily dose >100 mg, dose information missing, no ASA), NSAIDs, any anticoagulant

[1] Including active cancer at baseline and active cancer newly diagnosed during the study. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment, any treatment for cancer within 5 years before enrolment, or recurrent or metastatic cancer. Active cancer diagnosed during the study was derived from AEs recorded during the trial (i.e. within 190 days after randomisation) by searching for AEs of the SOC 'neoplasms benign, malignant and unspecified (including cysts and polyps)', but excluding basal-cell or squamous-cell carcinoma of the skin.
[2] Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, UK
[3] Czech Republic, Hungary, Russia, Slovak Republic, Turkey, Ukraine
[4] Canada, USA
[5] Argentina, Brazil, Mexico
[6] India
[7] Australia, Israel, New Zealand, South Africa
[8] Defined as use within the last month
[9] Defined as within the last 3 months
[10] Including any of the following: UFH, LMWH, other heparin, fondaparinux.

RE-MEDY

Subgroup analyses of the primary endpoint were performed to evaluate the consistency of the treatment effect across a variety of patient groups. Subgroup analyses were pre-defined and performed following the modified ITT approach and with the allocation of patients to treatment arms as randomised. Outcomes in each subgroup were summarised by treatment, presenting the numbers of patients with events, and risk differences and hazard ratios for events. The hazard ratio was obtained from the Cox model including the factors treatment, subgroup, and the subgroup-by-treatment interaction. The risk difference at 18 months was calculated using unstratified KM estimates for the pooled cohorts and the pooled strata within each subgroup. Details on subgroups are summarised in Table 34.

Table 34: Subgroup analyses for the primary endpoint in RE-MEDY[6]

Factors	Subgroups (categories)
Demographics	Age (years): 18 to <40, 40 to <50, 50 to <65, 65 to <75, ≥ 75
	Sex: male, female
	Race: White, Asian, Black
	Ethnicity: Hispanic, non-Hispanic
	Body weight (kg): <50, 50 to <100, ≥100
	BMI (kg/m^2): <25, 25 to <30, 30 to <35, ≥35
	Creatinine clearance (mL/min): <30, 30 to <50, 50 to <80, ≥80
	Smoking history: never smoked, ex-smoker, current smoker
	Geographical region: Asia[1], Eastern Europe[2], Latin America[3], North America[4], Western Europe[5], Other[6]

Baseline risk factors for VTE and medical history	More than 1 previous VTE: yes, no
	Symptomatic PE as primary VTE event: yes, no
	Time from the qualifying VTE to randomisation (months): <3, 3 to <6, 6 to <9, 9 to <12, ≥12 months
	Active cancer[7]: yes, no
	History of non-haemorrhagic stroke: yes, no
	History of coronary artery disease: yes, no
	Additional medical history/baseline conditions as recorded on the CRF
Trial conduct	Participation in RE-COVER/RE-COVER II (not rolled over from RE-COVER or RE-COVER II, roll-over patients who took dabigatran in RE-COVER, roll-over patients who took Warfarin in RE-COVER, rolled over from RE-COVER II[8])

[1] China, India
[2] Bulgaria, Czech Republic, Hungary, Poland, Russia, Slovakia, Turkey, Ukraine
[3] Argentina, Brazil, Mexico
[4] Canada, USA
[5] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, UK
[6] Australia, Israel, New Zealand, South Africa
[7] Active cancer was defined as a diagnosis of cancer, other than basal-cell or squamous-cell carcinoma of the skin, within 6 years before the enrolment, any treatment for cancer within 5 years, or recurrent or metastatic cancer.
[8] Treatment allocation for the patients of the double-blind RE-COVER II study was not available because the study was ongoing at the time of report writing for RE-MEDY.

RE-SONATE

Subgroup analyses were performed for the primary endpoint in an exploratory manner based on the following baseline characteristics: previous participation in the RE-COVER study, age, sex, race, ethnicity, geographical region, type of qualifying VTE event, history of multiple VTEs, and creatinine clearance (CrCl) at baseline (Table 35). Some subgroups had very small numbers of patients with events and as such, interpretation of these analyses is limited. This was particularly evident for subgroups of the dabigatran treatment group since the total number of patients with events in this group was very low (only 0.4% of dabigatran patients had recurrent symptomatic VTE events during the intended treatment period).

Table 35: Subgroup analyses for the primary endpoint in RE-SONATE[7]

Subgroups (categories)
Participation in RE-COVER study: yes, no
Age (years): <65, 65 to <75, ≥75
Gender: male, female
Race: American Indian/Alaskan National, Asia, Black/African American, Hawaiian/Pacific Isle, White

Ethnicity: Non-Hispanic/Latino, Hispanic/Latino, Missing
Geographical region: Western Europe, Central Europe, North America, Asia, Other
Qualifying event: confirmed symptomatic DVT only, confirmed symptomatic PE only, confirmed symptomatic DVT and PE, no confirmed symptomatic DVT or PE
History of multiple VTEs: 1, >1
Baseline creatinine clearance (mL/min): <30, 30 to <50, 50 to <80, ≥80, missing

Participant flow

6.3.8 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.

RE-COVER

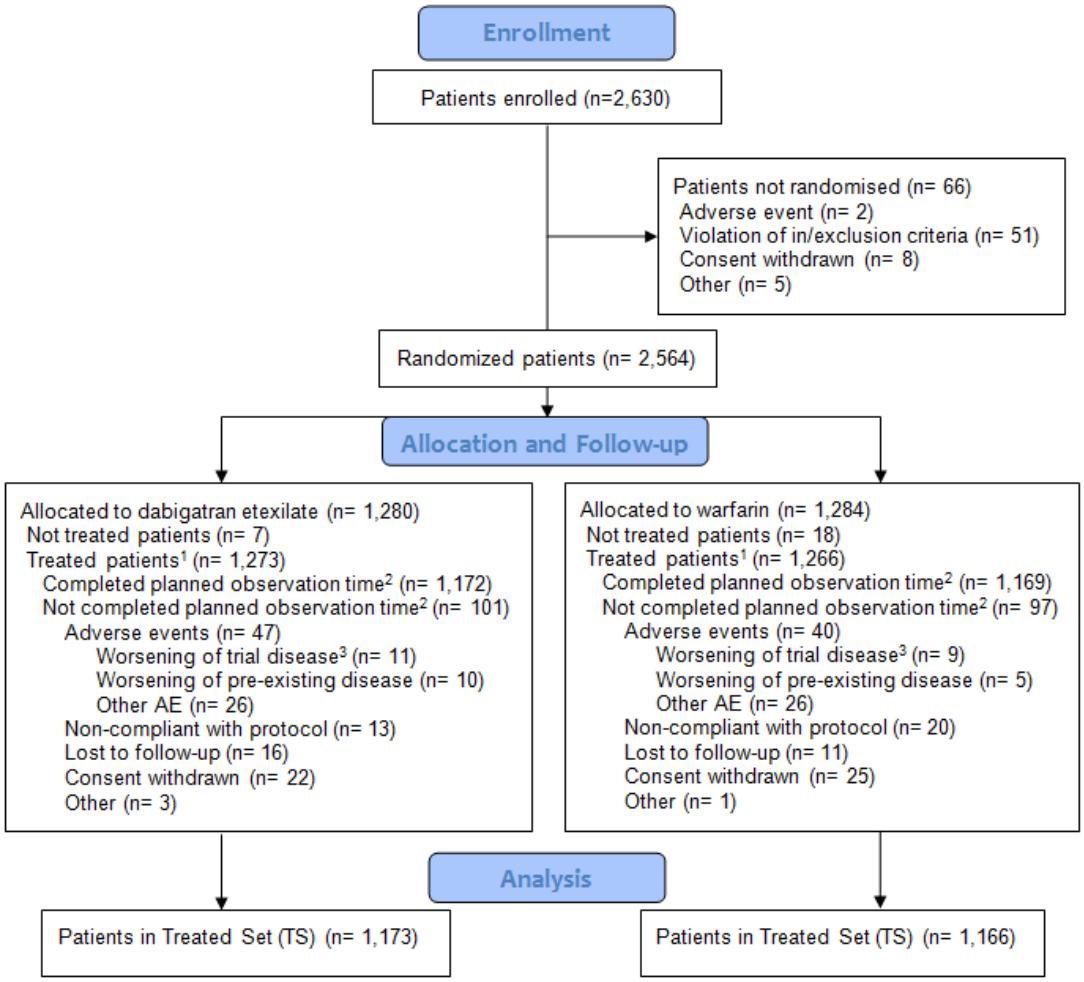
RE-COVER was a multi-centre, multinational study. Overall, 2,630 patients were enrolled in 231 centres in 29 countries worldwide; thereof, 228 centres randomised patients. Initially, there were 213 centres in 27 countries. Due to slow recruitment, 37 centres in 3 countries (India, Israel, and Turkey) were additionally initiated in 2008. Finland did not enrol any patients and stopped participation in this study in January 2008.

The initial parenteral anticoagulant therapy could have been started up to 72 hours prior to randomisation. If not started prior to randomisation, the parenteral therapy was to be started as soon as possible after randomisation. Patients were to be randomised within 72 hours of enrolment provided that they complied with the protocol-specified inclusion and exclusion criteria. Of the 2,630 patients enrolled, 66 patients (2.5%) were not randomised. The most frequent reason for non-randomisation was violation of the inclusion or exclusion criteria (n= 51; 1.9%), followed by withdrawal of consent (n= 8; 0.3%). Two patients (0.1%) were not randomised due to AEs (Figure 6). A total of 2,564 patients were randomised to either dabigatran (1,280 patients) or warfarin (1,284 patients). Of the randomised patients, 25 patients were not treated with study medication (dabigatran: 7, warfarin: 18).

Of the 2,539 treated patients, 92.2% completed the planned observation time, and there were no between group differences for those patients who did not (Figure 6). Of the 47 patients who withdrew their consent and did therefore not complete the planned observation time, most patients (dabigatran: 17 patients, warfarin: 22 patients) had decided that they would no longer take study medication, as expected. The observation time, i.e. the time from randomisation of a patient to the end of study participation, was comparable between the dabigatran and warfarin groups (mean: 191 vs. 189 days, median: 193 vs. 191 days).

Of the 2,539 treated patients, 198 patients (7.8%) prematurely discontinued trial medication, with a slightly higher percentage in the dabigatran treatment group (7.9%) than in the warfarin group (7.6%). Discontinuations of trial medication were due to AEs in 3.8% of patients in the dabigatran group and 3.1% of patients in the warfarin group. At the end of the study, 1,173 and 1,166 patients were in the treated sets for dabigatran and warfarin, respectively.

Figure 6: CONSORT flow chart of participants in RE-COVER[28]



[1] Patients who received at least 1 dose of study medication (active study medication or placebo)
[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

RE-COVER II

RE-COVER II was an international, multi-centre study. Overall, 2,701 patients were enrolled and 2,589 patients were randomised in 208 centres in 31 countries worldwide. The initial parenteral anticoagulant therapy could have been started up to 72 hours prior to randomisation. If not started prior to randomisation, the parenteral therapy was to be started as soon as possible after randomisation. Patients were to be randomised within 72 hours of enrolment provided that they complied with the protocol-specified inclusion and exclusion criteria. Of the 2,701 patients enrolled, 112 patients (4.1%) were not randomised. The most frequent reason for non-randomisation was a violation of the inclusion or

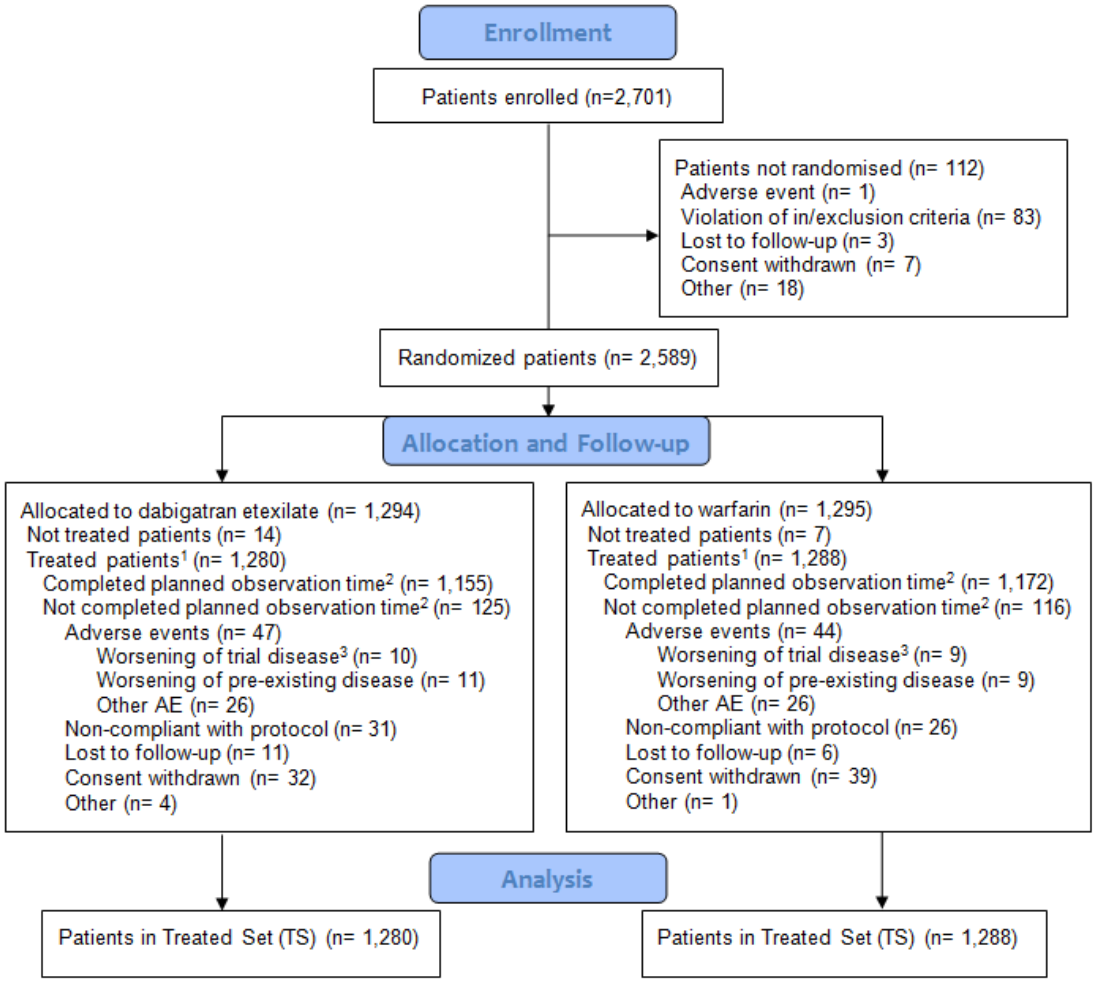
exclusion criteria (3.1%) (Figure 7). After database lock, the sponsor became aware of 1 additional patient that consented to take part in the study in a site in the UK, was subsequently found to be a screening failure, but was by mistake not entered into the database. This patient was not randomised and not treated and is not included in the number of enrolled patients.

A total of 2,589 patients were randomised to either dabigatran (1,294 patients) or warfarin (1,295 patients). Forced randomisation occurred in 18 patients. Of the randomised patients, 21 patients were not treated with study medication (dabigatran: 14, warfarin: 7): 9 of these patients refused to take study medication or withdrew consent; 10 of these patients were non-compliant with the study protocol; 2 of these patients had an AE.

Of the 2,589 randomised patients, 241 patients (9.3%) prematurely discontinued study medication, with a similar proportion in both treatment groups (dabigatran: 9.7%, warfarin: 9.0%). Discontinuations of study medication were due to AEs in 3.6% of patients in the dabigatran group and 3.4% of patients in the warfarin group.

Of the 2,568 treated patients, 90.6% completed the planned observation time, and there were no between-group differences for those patients who did not (Figure 7). Of the 71 patients who withdrew their consent and did therefore not complete the planned observation time, most patients (dabigatran: 18 patients, warfarin: 22 patients) had decided that they would no longer take study medication.

Figure 7: CONSORT flow chart of participants in RE-COVER II[4]



[1] Patients who received at least 1 dose of study medication (active study medication or placebo)
[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

RE-MEDY

RE-MEDY was an international, multi-centre study. Overall, 2,918 patients were enrolled in 261 centres in 33 countries worldwide. The numbers of patients enrolled and randomised by geographical region and overall is shown in Figure 8. The majority of randomised patients came from European countries. Centres in Asian countries joined later in the trial and recruited more patients towards the end of the trial.

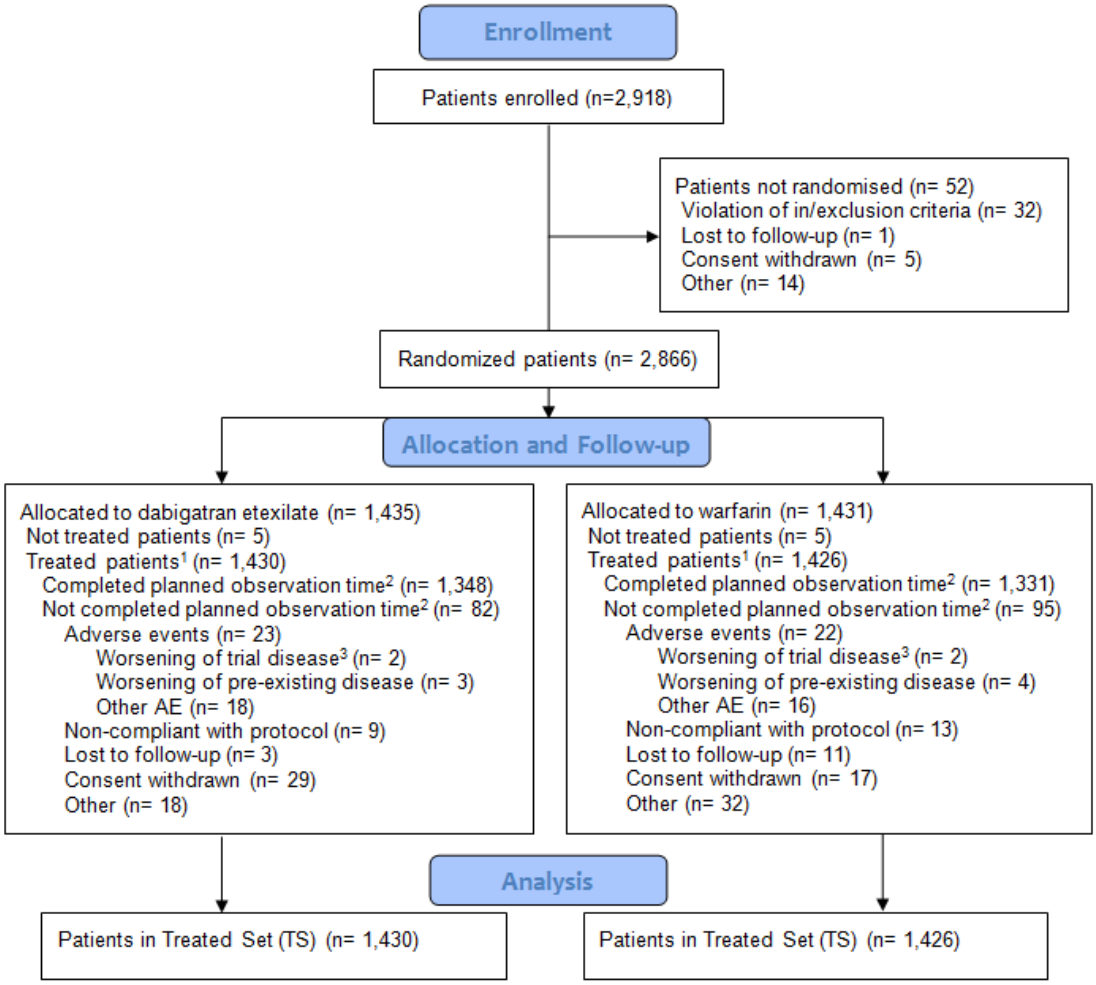
Of the 2,918 patients enrolled, 52 patients (1.8%) were not randomised. The most frequent reason for non-randomisation was a violation of the inclusion or exclusion criteria (1.1%). One patient was recorded as a screening failure, although he had not consented to

participate in the study. This patient was not randomised and not treated and is not included in the number of enrolled patients.

A total of 2,866 patients were randomised to either dabigatran (1,435 patients) or warfarin (1,431 patients). Forced randomisation occurred in 63 patients. Of the randomised patients, 10 patients were not treated with study medication (5 patients of each treatment group): 5 patients refused to take study medication and 1 patient was non-compliant with the study protocol (patient no. 9469 took part in a different clinical trial). Four patients were reported with 'other' reasons. Investigator comments on CRF free-text entry fields indicated that 3 of these 4 patients were not compliant with eligibility criteria and 1 refused to participate in the study.

Of the 2,856 treated patients, 93.8% completed the planned observation time, and there were no between-group differences for those patients who did not (Figure 8). Of the 2,856 treated patients, 177 patients (6.2%) did not complete the planned observation time, with a similar proportion in both treatment groups (dabigatran: 5.7%, warfarin: 6.6%). Discontinuations of study medication were due to AEs in 1.6% of patients in the dabigatran group and 1.5% of patients in the warfarin group.

Figure 8: CONSORT flow chart of participants in RE-MEDY[6]



[1] Patients who received at least 1 dose of study medication (active study medication or placebo)
[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

RE-SONATE

Patients were enrolled in 147 centres in 21 countries. The number of centres within each country ranged from 1 in New Zealand and in Singapore to 21 in the USA. In all countries except Norway, all initiated centres enrolled at least 1 patient. In total, 1,366 patients were enrolled (provided informed consent) and 1,353 were randomised. The numbers of enrolled patients per country ranged from 4 in Singapore to 246 patients in Italy. The numbers of randomised patients per country ranged from 4 in Singapore to 245 patients in Italy. The majority of randomised patients were in Western Europe (741; 55.2%).

In the trial protocol it was planned to randomise 900 patients per group, assuming a mean frequency for the primary outcome of 3% for the placebo group. This number of patients could have been adjusted based on the observed overall incidence of the primary endpoint (symptomatic recurrent VTE events). In accordance with the protocol, after 36 centrally confirmed recurrent symptomatic VTE events had been reached, recruitment into the trial was stopped. Trial close out began on 30 September 2010.

The planned treatment duration was 6 months. Once 36 patients were centrally confirmed as having had a recurrent VTE event during the intended treatment period, all patients completed their participation in the study at their next 3-month visit (Visit 6 or Visit 9; Month 3 or Month 6), so that the last patients randomised (i.e. those who had not had their 3-month visit) were treated for approximately 3 months. Of the 681 patients randomised to and treated with dabigatran, 622 had an intended treatment period of 6 months and 59 had an intended treatment period of 3 months. Of the 662 patients randomised to and treated with placebo, 626 had an intended treatment period of 6 months and 36 had an intended treatment period of 3 months.

In total, 1,366 patients were enrolled and 1,353 were randomised (dabigatran: 685; placebo: 668) (Figure 9). For the 13 patients enrolled but not randomised, the reasons for non-randomisation were predominantly failure to meet inclusion/exclusion criteria (7 patients) or informed consent withdrawn for reasons other than an AE (5 patients) (Figure 9). One further patient (No. 27226) was not randomised due to the late arrival of laboratory results that were to be assessed when evaluating inclusion criteria. This patient returned to the investigational site the following day and was randomised into the study. This patient is counted twice in the total number of patients enrolled (i.e. in the total of 1,366 patients), but only once in the number of randomised patients.

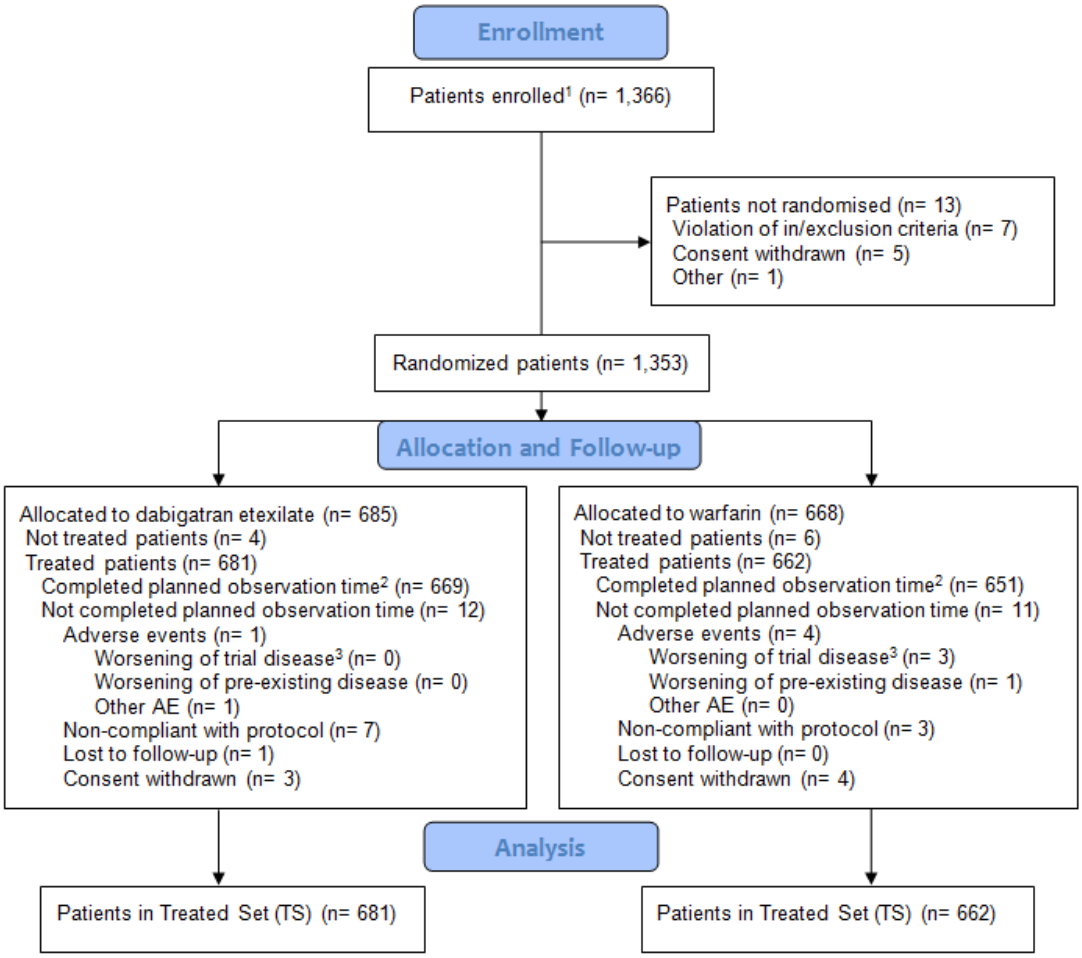
In total, 1,343 of the 1,353 randomised patients were treated (dabigatran: 681; placebo: 662) (Figure 9). Of the 10 patients randomised but not treated, 4 were randomised to dabigatran and 6 to placebo. As per protocol, these patients should have been followed until the end of their intended treatment period and 5 patients were so observed (3 dabigatran and 2 placebo patients). Of the 1,343 patients treated, 1,248 had an intended treatment period of 6 months (622 dabigatran; 626 placebo). The remainder (95 patients) had not completed Visit 6 at the initiation of the trial close out and therefore had an intended treatment period of 3 months (59 dabigatran patients; 36 placebo patients). This slight imbalance between treatment groups in the numbers of patients with an intended

treatment period of 3 months occurred by chance. The block randomisation schedule within centres was followed and no single centre caused the entire imbalance. The randomisation procedure was primarily stratified by centre using a block size of 4. The small number of patients with a 3-month intended treatment period led to the slight treatment imbalance because at trial close out, when recruitment was stopped, some blocks had not been completed.

Patients in this trial were to be followed up until completion of the extended follow-up period, regardless of whether or not they started study treatment and whether or not they completed study treatment or discontinued study treatment prematurely. In total, 1,330 patients (treated and untreated) continued into the extended follow-up period, comprising 1,323 (98.5%) of the 1,343 randomised and treated patients (dabigatran: 98.7%; placebo: 98.3%) and 7 of the 10 patients who were randomised but not treated. In the dabigatran group, there were 675 patients, including 672 patients who were treated and 3 patients who were not treated; in the placebo group, there were 655 patients, including 651 patients who were treated and 4 patients who were not treated.

For the 20 (1.5%) treated patients who did not enter the extended follow-up, the reasons for not doing so were: did not sign Protocol Amendment 2 informed consent (10 patients, 0.7%); consent withdrawn (7 patients, 0.5%); death (3 patients, 0.2%). For the 3 untreated patients who did not enter the extended follow-up, the reasons for not entering was consent withdrawn (2 patients) and Protocol Amendment 2 [7] informed consent not signed (1 patient).

Figure 9: CONSORT flow chart of participants in RE-SONATE[7]



[1] One patient (No. 27906) was randomised without giving written informed consent. Oral confirmation was given (CTMF). The patient was not treated.
[2] The double-blind phase included the treatment period and 30-day follow-up visit (Visit 10, or Visit 9 for patients prematurely withdrawing treatment).
[3] Worsening of disease under study; i.e. symptomatic DVT or PE.

6.4 Critical appraisal of relevant RCTs

6.4.1 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?

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

6.4.3 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 36 summarises the full quality assessment of the four RCTs (RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE) presented in Appendix 3.

Table 36: Quality assessment results for RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE

	RE-COVER	RE-COVER II	RE-MEDY	RE-SONATE
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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 Yes	Yes Yes	Yes Yes

6.5 Results of the relevant RCTs

6.5.1 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.**

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

6.5.3 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.

RE-COVER and RE-COVER II

Primary efficacy endpoint: Composite of recurrent symptomatic VTE and deaths related to VTE

The primary analysis for efficacy was assessed by the hazard ratio calculated with the use of the Cox model and the difference in risk calculated with the use of Kaplan–Meier estimates.[1] Both summary statistics were adjusted for the initial presentation (i.e., PE or DVT) and for the presence or absence of active cancer at baseline (the interaction between active cancer and symptomatic PE was also included in the Cox model).[1]

RE-COVER

The results of RE-COVER with respect to the primary endpoint (6-month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths) are presented in Table 37.[1] Dabigatran 150 mg BD demonstrated non-inferiority to adjusted-dose warfarin (Table 37).

Table 37: RE-COVER primary efficacy outcome [1;28]

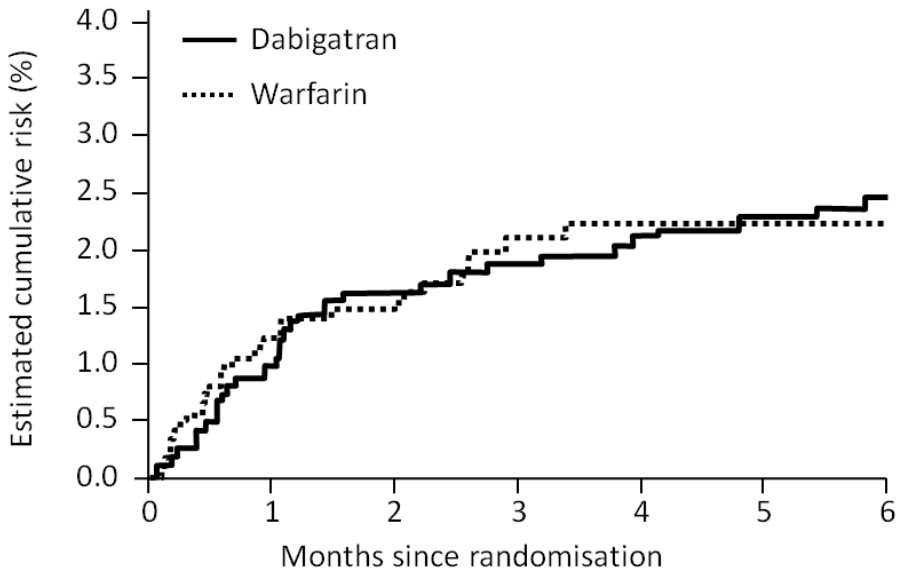
	Dabigatran n = 1,274	Warfarin n = 1,265
Up to the end of the post-treatment period*		
VTE and VTE related deaths, n (%)	34 (2.7)	32 (2.5)
Hazard ratio (95% CI)	1.05 (0.65, 1.70)	
p-value for non-inferiority	<0.0001	
p-value for superiority	0.8508	
By stratification factor, *n* (%)		
Symptomatic PE with cancer	1 (5.9)	1 (6.3)
Symptomatic PE without cancer	10 (2.7)	12 (3.2)
No symptomatic PE with cancer	1 (2.5)	2 (5.1)
No symptomatic PE without cancer	18 (2.2)	12 (1.5)
During treatment period		
VTE and VTE related deaths, *n* (%)	30 (2.4)	27 (2.1)
Hazard ratio (95% CI)	1.10 (0.65, 1.84)	
Risk difference vs. warfarin, % (95% CI)	0.4 (-0.8, 1.5)	
p-value for non-inferiority	<0.0001	

* The extension of the study period was a pre-specified primary end-point. However, this does not reflect the true incidence of the end-point after anticoagulation was discontinued, as more than 500 patients in each group were enrolled in an extended-treatment study with double-blind design, and additional patients received open-label anticoagulants.

After central adjudication, the primary outcome for efficacy was confirmed in 30 patients in the dabigatran group (2.4%) and 27 patients in the warfarin group (2.1%). The difference in risk was 0.4 percentage points (95% confidence interval [CI], −0.8, 1.5; hazard ratio, 1.10; 95% CI, 0.65, 1.84) (

Figure 10).[1;28]

Figure 10: Cumulative risk of recurrent VTE or related death during 6 months of treatment among patients randomly assigned to dabigatran or warfarin [1;28]



No. at Risk							
Dabigatran	1274	1238	1221	1203	1192	1181	1024
Warfarin	1265	1215	1204	1194	1187	1174	998

The cumulative risks and risk differences were also assessed by stratification factor and stratum.[28] As expected, the cumulative risk for the primary endpoint was higher for patients with initial symptomatic PE (dabigatran: 2.9%, warfarin: 3.3%) than for patients without PE (2.2% vs. 1.7%).[28] The hazard ratios for the primary endpoint were 0.94 (95% CI 0.46, 1.95) in patients with initial symptomatic PE and 1.15 (95% CI 0.60, 2.19) in patients without PE. Patients with active cancer at baseline had a higher cumulative risk for the primary endpoint (dabigatran: 3.5%, warfarin: 5.4%) than patients without active cancer at baseline (2.4% vs. 2.0%), which was also as expected.[28] The hazard ratios for the primary endpoint were 0.62 (95% CI 0.10, 3.71) in patients with cancer and 1.09 (95% CI 0.66, 1.80) in patients without cancer at baseline.[28]

Considering the four strata, the cumulative risks were highest in the stratum of patients with initial symptomatic PE and active cancer at baseline, and lowest in patients without PE and cancer, as expected.[28] Within each stratum, there were numerical between-group differences in the numbers of patients with events and in the cumulative risks, likely due to the small numbers of patients per stratum and patients with event.[28] For all 4 strata, the

95% confidence intervals for the hazard ratios included 1, indicating that the observed numerical differences between treatment groups were not statistically significant.[28]

Dabigatran was found to be non-inferior to warfarin in the treatment and secondary prevention of recurrent VTE ($p < 0.001$).[1] Once non-inferiority was established, superiority was tested for, but was not reached.[1]

RE-COVER II

The results of RE-COVER II with respect to the primary endpoint (six month incidence of recurrent symptomatic, objectively confirmed VTE and related deaths) are presented in Table 38.[27] Dabigatran 150 mg BD demonstrated non-inferiority to adjusted-dose warfarin.

Table 38: RE-COVER II primary efficacy outcome[4;27]

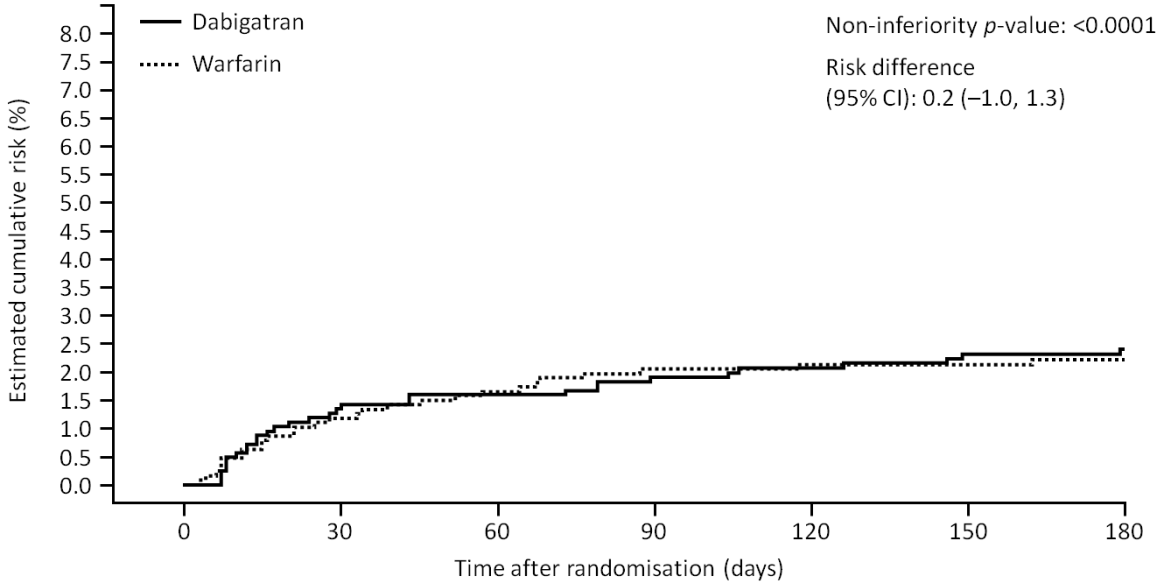
	Dabigatran n = 1,279	Warfarin n = 1,289
Up to the end of the post-treatment period†		
VTE and VTE related deaths, n (%)*	34 (2.7)	30 (2.3)
Hazard ratio (95% CI)	1.13 (0.69, 1.85)	
p-value for non-inferiority	0.0002	
p-value for superiority	0.6159	
By stratification factor		
Symptomatic PE with cancer	0 (0.0)	0 (0.0)
Symptomatic PE without cancer	7 (1.8)	8 (2.0)
No symptomatic PE with cancer	2 (6.7)	2 (5.8)
No symptomatic PE without cancer	21 (2.5)	18 (2.2)
During the treatment period		
VTE and VTE related deaths, n (%)*	30 (2.3)	28 (2.2)
Hazard ratio (95% CI)	1.08 (0.64, 1.80)	
Risk difference vs. warfarin, % (95% CI)	0.2 (-1.0, 1.3)	
p-value for non-inferiority	<0.001	
p-value for superiority	0.7756	

*Patients with at least one event. †Definition of the end of post-treatment period: For patients who completed the trial as planned and did not roll-over to RE-MEDY, the end of the post-treatment period was the date of trial completion collected at the follow-up visit. For patients who rolled over to RE-MEDY the end of the post-treatment period was the day after the last intake of warfarin / warfarin placebo of the RE-COVER II study medication.

The cumulative risk for the primary endpoint at six months was 2.4% in the dabigatran group and 2.2% in the warfarin group

Figure 11).[27] The risk difference for dabigatran vs. warfarin was 0.2 percentage points (95% CI -1.0, 1.3), and the hazard ratio for dabigatran was 1.08 (95% CI 0.64, 1.80).[27]

Figure 11: Time to the composite of recurrent symptomatic VTE and VTE-related death[27]



No. at risk							
Dabigatran	1279	1244	1235	1223	1214	1205	1169
Warfarin	1289	1261	1244	1228	1220	1217	1176

The hazard ratios for dabigatran vs. warfarin for the primary endpoint were 1.25 (95% CI 0.69, 2.25) in patients without initial symptomatic PE and 0.91 (95% CI 0.37, 2.24) in patients with initial PE.[4] The hazard ratios for dabigatran vs. warfarin for the primary endpoint were 0.95 (95% CI 0.13, 6.76) in patients with cancer and 1.15 (95% CI 0.69, 1.91) in patients without cancer at baseline. Patients with active cancer at baseline had a higher cumulative risk for the primary endpoint (dabigatran: 5.2%, warfarin: 4.4%) than patients without active cancer at baseline (2.3% vs. 2.1%).[4]

Considering the four strata, the cumulative risks were highest in the stratum of patients without symptomatic PE but with active cancer at baseline and lowest in patients with PE and cancer. For all four strata, the 95% confidence intervals for the hazard ratios included 1, indicating that the observed numerical differences between treatment groups were not statistically significant.[4]

Dabigatran demonstrated non-inferiority to warfarin in the treatment and secondary prevention of recurrent VTE (p<0.001).[27] Once non-inferiority was established, superiority was tested for, but not reached.[4]

Secondary efficacy outcomes

The secondary efficacy endpoints were the same for both RE-COVER and RE-COVER II and, as in the primary efficacy analyses; the results were divided into the four strata identified by the baseline prevalence of PE and cancer.

RE-COVER

The incidence of recurrent symptomatic VTE and all deaths, symptomatic DVT, symptomatic non-fatal PE, VTE-related deaths and all deaths was low in both treatment groups (Table 39).There was no statistically significant difference by treatment group in the rate of any of the secondary endpoints.[1]

Table 39: RE-COVER secondary efficacy outcomes[28]

	Up to the end of the post-treatment period		Up to Day 180	
	Dabigatran	**Warfarin**	**Dabigatran**	**Warfarin**
Patients, n	1274	1265	1274	1265
Patients with at least 1 event*, n				
VTE and VTE-related deaths	34	32	30	27
Symptomatic DVT	17	22	16	18
Symptomatic PE[‡]	16	7	13	6
VTE-related deaths[#]	1	3	1	3

*Patients who were considered in the primary analysis. [‡]Symptomatic, non-fatal PE. [#]Fatal PE with or without previous symptomatic non-fatal PE. [¥]For patients with 2 events that were centrally confirmed and were components of the primary endpoint, only the first event was used for the time-to-event analysis of the primary endpoint. Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 40: RE-COVER secondary efficacy outcomes by stratification factors[28]

	Dabigatran		Warfarin		
	Total n	**Incidence n (%)**	**Total n**	**Incidence n (%)**	**Risk difference (95% CI)**
Patients, n	1274	30 (2.4)	1265	27 (2.2)	0.4 (-0.7, 1.5)
Initial symptomatic PE					
No	882	19 (2.2)	871	14 (1.7)	0.5 (-0.8, 1.9)
Yes	392	11 (2.9)	394	13 (3.3)	-0.4 (-2.9, 2.0)
Active cancer at baseline					
No	1210	28 (2.4)	1208	24 (2.0)	0.3 (-0.8, 1.5)
Yes	64	2 (3.4)	57	3 (5.4)	-2.0 (-9.5, 5.6)
Sympt. PE with cancer	19	1 (5.9)	16	1 (6.3)	-0.4 (-16.7, 15.9)
Sympt PE, no cancer	373	10 (2.7)	378	12 (3.2)	-0.5 (-2.9, 2.0)
Non sympt. PE with cancer	45	1 (2.4)	41	2 (5.1)	-2.7 (-11.1, 5.7)
Non sympt. PE, no cancer	837	18 (2.2)	830	12 (1.5)	0.7 (-0.6, 2.0)

Abbreviations: PE, pulmonary embolism.

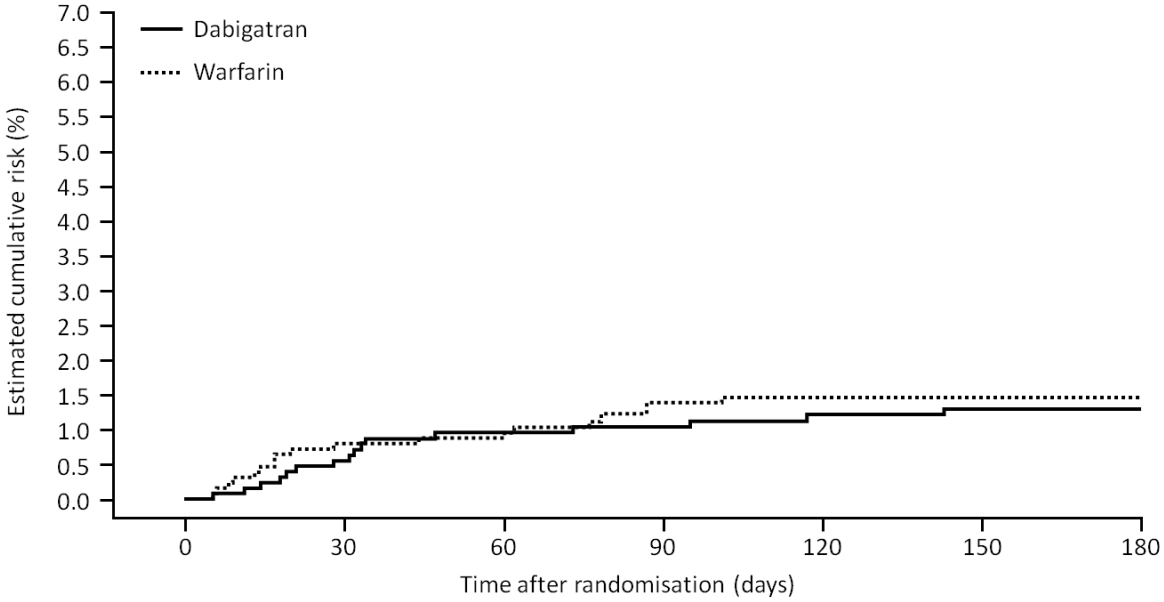
Recurrent VTE and all deaths

The cumulative risks for VTE and all-cause mortality were highest for patients with initial symptomatic PE and active cancer at baseline (dabigatran: 23.5%, warfarin: 6.3%) and for patients with cancer without PE (9.1% vs. 17.5%, respectively).[28] Patients with initial symptomatic PE without cancer at baseline had a lower risk for recurrent VTE and death (4.4% vs. 4.3%, respectively); the lowest risk was associated with patients with neither initial symptomatic PE nor cancer at baseline (2.9% vs. 2.5%, respectively).[28]

Symptomatic DVT

From the initiation of study treatment to the end of the post-treatment period the number of patients with acute symptomatic DVT was lower in the dabigatran group (17 patients) than in the warfarin group (22 patients).[28] At six months, the number of patients with an acute symptomatic DVT was comparable in the two treatment groups (dabigatran: 16 patients, warfarin: 18 patients), resulting in a risk difference of -0.2%. When comparing the four strata defined at randomisation ('active cancer and symptomatic PE', 'active cancer, no symptomatic PE', 'no active cancer, symptomatic PE', 'no active cancer, no symptomatic PE'), the cumulative risks for symptomatic DVT were low and comparable in all four.[28] For patients with initial symptomatic PE and active cancer at baseline, the cumulative risks were 0.0% in both treatment groups.[28] The cumulative risks were 0.5% in the dabigatran group and 1.6% in the warfarin group for patients with initial symptomatic PE without active cancer at baseline; 2.5% (dabigatran) and 5.1% (warfarin) for patients with active cancer at baseline without initial symptomatic PE, and 1.6% (dabigatran) and 1.2% (warfarin) for patients with neither initial symptomatic PE nor active cancer at baseline. No treatment differences were detected within strata.[28] The Kaplan-Meier survival curves for symptomatic DVT together with the number of patients at risk are shown in Figure 12. The majority of events were observed in the first 120 days of the treatment period.[28]

Figure 12: Time to symptomatic DVT[28]



No. at risk							
Dabigatran	1274	1242	1228	1210	1200	1189	1032
Warfarin	1265	1218	1208	1199	1192	1179	1002

Symptomatic non-fatal PE

The number of patients with a symptomatic, non-fatal PE at six months was 16 in the dabigatran group and 8 in the warfarin group. The hazard ratio of dabigatran vs. warfarin was 2.0 (95% CI 0.86, 4.68).[1]

Deaths related to VTE

One patient in the dabigatran group and three patients in the warfarin group died from PE. The hazard ratio of dabigatran vs. warfarin for VTE-related death was 0.33 (95% CI 0.03, 3.15).[1] The cumulative risks at six months were 0.1% and 0.2%, respectively, in the dabigatran group and the warfarin group. The risk difference was -0.3% (95% CI -1.2%, 0.6%).[28]

All deaths

The highest cumulative risks for death were seen in patients with active cancer at baseline and initial symptomatic PE (dabigatran: 18.4%, warfarin: 6.3%) and patients with cancer at baseline without initial symptomatic PE (6.8% vs. 12.7%).[28] The cumulative risks were lower for patients with initial symptomatic PE without cancer (2.2% vs. 1.6%), and lowest for patients with neither of the two risk factors (0.9% vs. 1.1%).[28]

RE-COVER II

The incidence of recurrent symptomatic VTE and all deaths, symptomatic DVT, symptomatic non-fatal PE, VTE-related deaths and all deaths was low in both treatment groups (

Table 41).[28] There was no statistically significant difference by treatment group in the rate of any of the secondary endpoints. There were numerically fewer symptomatic non-fatal PEs but more symptomatic DVTs in the dabigatran group than in the warfarin group.[27]

Table 41: RE-COVER II secondary efficacy outcomes[4;27]

	Up to the end of the post-treatment period		Up to Day 180	
	Dabigatran	**Warfarin**	**Dabigatran**	**Warfarin**
Patients, n	1279	1289	1279	1289
Patients with at least 1 event*, n (%)				
VTE and VTE-related deaths	34	30	30	28
Symptomatic DVT	26	16	24	16
Symptomatic non-fatal PE	7	14	5	12
Fatal PE	1	0	1	0

*Patients who were considered in the primary analysis. ¥For patients with two events that were centrally confirmed, only the first event was used for the time-to-event analysis of the primary endpoint.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 42: RE-COVER II secondary efficacy outcomes by stratification factor[4]

	Dabigatran		Warfarin		
	Total n	**Incidence n (%)**	**Total n**	**Incidence n (%)**	**Risk difference (95% CI)**
Patients, n	1279	30 (2.4)	1289	28 (2.2)	0.2 (-1.0, 1.3)
Initial symptomatic PE					
No	876	23 (2.7)	876	20 (2.3)	0.4 (-1.1, 1.8)
Yes	403	7 (1.8)	413	8 (2.0)	-0.2 (-2.1, 1.7)
Active cancer at baseline					
No	1229	28 (2.3)	1239	26 (2.1)	0.2 (-1.0, 1.4)
Yes	50	2 (5.2)	50	2 (4.4)	0.8 (-8.4, 10.1)
Sympt. PE with cancer	10	0 (0.0)	12	0 (0.0)	-
Sympt. PE, no cancer	393	7 (1.8)	401	8 (2.0)	-0.2 (-2.1, 1.7)
Non sympt. PE with cancer	40	2 (6.7)	38	2 (5.8)	0.9 (-11.0, 12.8)
Non sympt. PE, no cancer	836	21 (2.5)	838	18 (2.2)	0.4 (-1.1, 1.8)

Abbreviations: PE, pulmonary embolism; Sympt., symptomatic

Recurrent VTE and all deaths

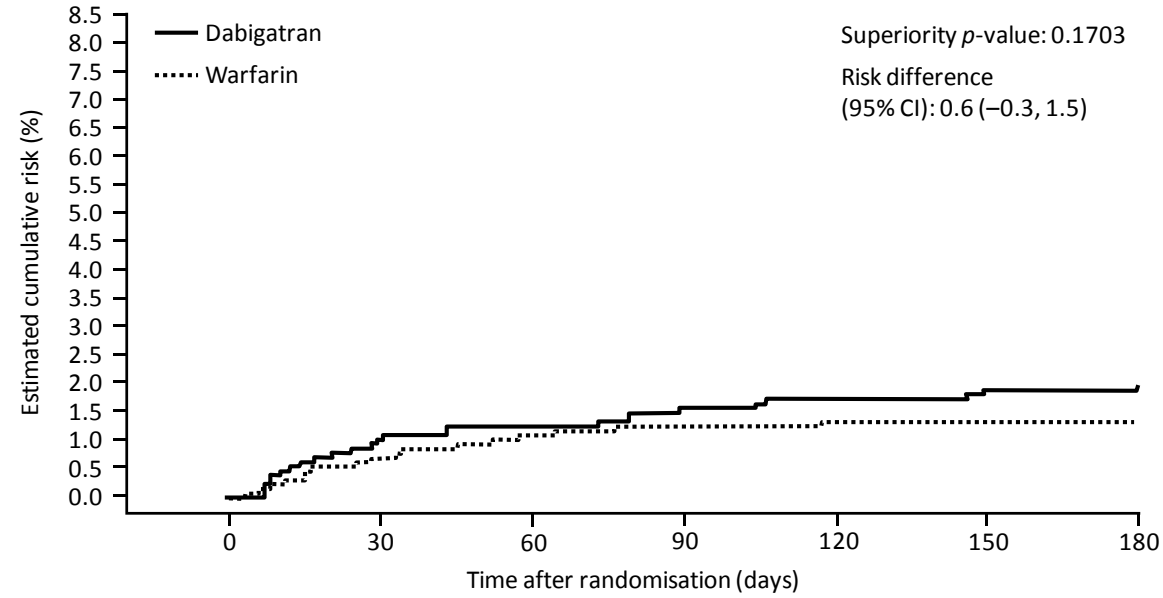
The cumulative risk for the composite of recurrent symptomatic VTE and all death at six months was 4.0% in the dabigatran group and 3.8% in the warfarin group. The risk difference was 0.3% (95% CI -1.1%, 1.6%).[4]

The cumulative risks for VTE and all death were highest for patients with active cancer without initial PE at baseline (dabigatran: 26.1%, warfarin: 27.0%) and for patients with PE and active cancer (20.0% vs. 18.2%).[4] For the remaining two strata, the risk for recurrent VTE and death was lower compared with the overall population (patients with initial symptomatic PE without cancer at baseline: 3.1% in the dabigatran group vs. 3.0% in the warfarin group; patients with neither initial symptomatic PE nor cancer at baseline: 3.3% vs. 2.9%). None of the confidence intervals for the risk differences indicated a statistically significant between-treatment difference within any of the strata.[4]

Events were observed throughout the treatment period, although events seemed to be more frequent early after randomisation and the index VTE, as indicated by steeper slopes of the Kaplan-Meier survival curves (

Figure 13).[4]

Figure 13: Time to symptomatic DVT (RE-COVER II)[4]



No. at risk							
Dabigatran	1279	1246	1237	1225	1216	1208	1172
Warfarin	1289	1267	1251	1238	1230	1227	1187

Symptomatic DVT

The cumulative risks for symptomatic DVT were low in most of the four strata. There were no patients with events in the stratum of patients with initial symptomatic PE and active cancer at baseline.[4] The cumulative risks were 1.0% in the dabigatran group and 0.5% in the warfarin group for patients with initial symptomatic PE without active cancer at baseline; 6.7% and 5.8% for patients with active cancer at baseline without initial symptomatic PE, and 2.3% and 1.6% for patients with neither initial symptomatic PE nor active cancer at baseline. There were no apparent treatment differences between the strata.[4]

Symptomatic non-fatal PE

At six months, the cumulative risks for symptomatic PE were 0.6% in the dabigatran group and 1.0% in the warfarin group. The risk difference was -0.3 (95% CI -1.0, 0.3).[4] Overall, from the initiation of study treatment to the end of the post-treatment period, 10 patients in the dabigatran group and 15 patients in the warfarin group had symptomatic, non-fatal PE or fatal PE. The hazard ratio of dabigatran vs. warfarin was 0.66 (95% CI 0.29, 1.46).[4] The cumulative risks for patients with initial symptomatic PE and active cancer at baseline were 0.0% for both treatment groups, 0.5% (dabigatran) vs. 1.5% (warfarin) for patients with PE without cancer, 3.4% vs. 3.1% for patients with cancer without PE, and 0.5% vs.0.7% for patients with neither of the two risk factors.[4]

Deaths related to VTE

Three patients, all from the dabigatran group, died from PE until the end of the post-treatment period.[4] The cumulative risk at six months was 0.2% in the dabigatran group. The risk difference was 0.2% (95% CI 0.0, 0.5). Two patients had neither symptomatic PE nor active cancer at baseline and one patient had symptomatic PE without cancer at baseline.[4]

All deaths

The number of patients who died until the end of the post-treatment period was comparable between the treatment groups (dabigatran: 29 patients; warfarin: 26 patients). The most frequent cause of death was cancer (15 patients in each treatment group), 10 deaths were categorised as unexplained deaths (five patients in each treatment group) and eight as other (five vs. three patients).[4] Four patients died of a bleeding event (dabigatran: one, warfarin: three patients) and three patients died of a fatal PE (all in the dabigatran group).[4]

The cumulative risks for death at six months were 2.0% in both treatment groups; the resulting risk difference was 0.1% (95% CI -0.7, 1.0).[27] The cumulative risks for death of any cause were highest for patients with active cancer without initial PE at baseline (dabigatran: 20.7%, warfarin: 27.1%) and for patients with PE and active cancer (20.0% vs. 18.2%).[4] For the remaining two strata, the risk for any death was lower compared with the overall population (patients with initial symptomatic PE without cancer at baseline: 1.6% in the dabigatran group vs. 1.0% in the warfarin group; patients with neither initial symptomatic PE nor cancer at baseline: 1.1% in both treatment groups). None of the confidence intervals for the risk differences indicated a statistically significant between-treatment difference within any of the strata.[4]

Pooled RE-COVER and RE-COVER II analyses

A pooled analysis of the pivotal RE-COVER and RE-COVER II studies supported data from the individual trials; with dabigatran 150 mg BD shown to be comparable to warfarin for the primary endpoint (symptomatic recurrent VTE and VTE related death). Pooled event rates for components of the efficacy outcomes are shown in

Table 43.[27]

Table 43: Efficacy outcomes in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE[27]

	Dabigatran n = 2,553	Warfarin n = 2,554	Hazard ratio* (95% CI)
Primary endpoint of VTE and VTE related deaths, n (%)			
During 6 months	60 (2.4)	55 (2.2)	1.09 (0.76, 1.57)
During the study period plus an additional 30 day follow up	68 (2.7)	62 (2.4)	1.09 (0.77, 1.54)
Secondary endpoints, n (%)			
Symptomatic DVT[#]	40 (1.6)	34 (1.3)	ND
Symptomatic non-fatal PE[#]	18 (0.7)	18 (0.7)	ND
Death related to PE[#]	2 (0.1)	3 (0.1)	ND
All deaths	46 (1.8)	46 (1.8)	1.0 (0.67, 1.51)

CI, confidence interval; ND, no data. *The hazard ration was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study. [#]These are the events contributing to the primary endpoint. In the case of a patient suffering 2 different events, the first event is counted.

Analyses were conducted for subgroups in which the underlying risk of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ ().

Table 44).

Table 44: VTE and VTE related deaths for specific subgroups in pooled analysis of RE-COVER and RE-COVER II until the end of post-treatment period[3]

	Dabigatran		Warfarin		
	Total n	Event n (%)	Total n	Event n (%)	Hazard ratio (95% CI)
Total	2553	68	2554	62	-
Symptomatic PE as index event					
No	1758	45 (2.6)	1747	37 (2.1)	1.20 (0.78, 1.86)
Yes	795	23 (2.9)	807	25 (3.1)	0.93 (0.53, 1.63)
Active cancer					
Yes	173	10 (5.8)	162	12 (7.4)	0.76 (0.33, 1.76)
History of bleedings					
Yes	123	6 (4.9)	129	5 (3.9)	1.28 (0.39, 4.21)
Geographical region					
Western Europe	613	13 (2.1)	626	18 (2.9)	0.74 (0.36, 1.50)

RE-MEDY

The primary efficacy endpoint used in RE-MEDY is defined as recurrent symptomatic and objectively verified VTE or death associated with VTE. Clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies.[8]

Primary efficacy endpoint: recurrent VTE and VTE-related death

The results of RE-MEDY with respect to the primary endpoint (composite of recurrent symptomatic VTE and death related to VTE (excluding unexplained death) within 18 months from randomisation) are presented in Table 45.[5] Additional analyses conducted are also presented in Table 45, to show the outcomes for unexplained deaths.[30]

Table 45: RE-MEDY primary efficacy outcome [5;6]

	Dabigatran n = 1,430	Warfarin n = 1,426
Patients with event; VTE and VTE-related death (excl. Unexplained death), *n* (%)	26 (1.8)	18 (1.3)
Hazard ratio (95% CI)	1.44 (0.78, 2.64)	
p-value for non-inferiority	0.01	
p-value for superiority	0.2424	
Patients with event; VTE, VTE-related and unexplained death, *n* (%)[30]	27 (1.9)	20 (1.4)
Hazard ratio (95% CI)	1.33 (0.74, 2.40)	
p-value for non-inferiority	0.0055	
p-value for superiority	0.3349	
By cohort, *n* (%)		
Cohort 1 (Planned treatment duration 18 months)	18 (2.3)	14 (1.8)
Cohort 2 (Planned treatment duration >18 months)	4 (1.4)	3 (1.1)
Cohort 3 (Planned treatment duration <18 months)	4 (1.1)	1 (0.3)
By stratification factor*, *n* (%)		
Symptomatic PE with cancer	1 (4.0)	0 (0.0)
Symptomatic PE without cancer	13 (2.8)	7 (1.5)
No symptomatic PE with cancer	1 (2.9)	1 (2.8)
No symptomatic PE without cancer	11 (1.2)	10 (1.1)

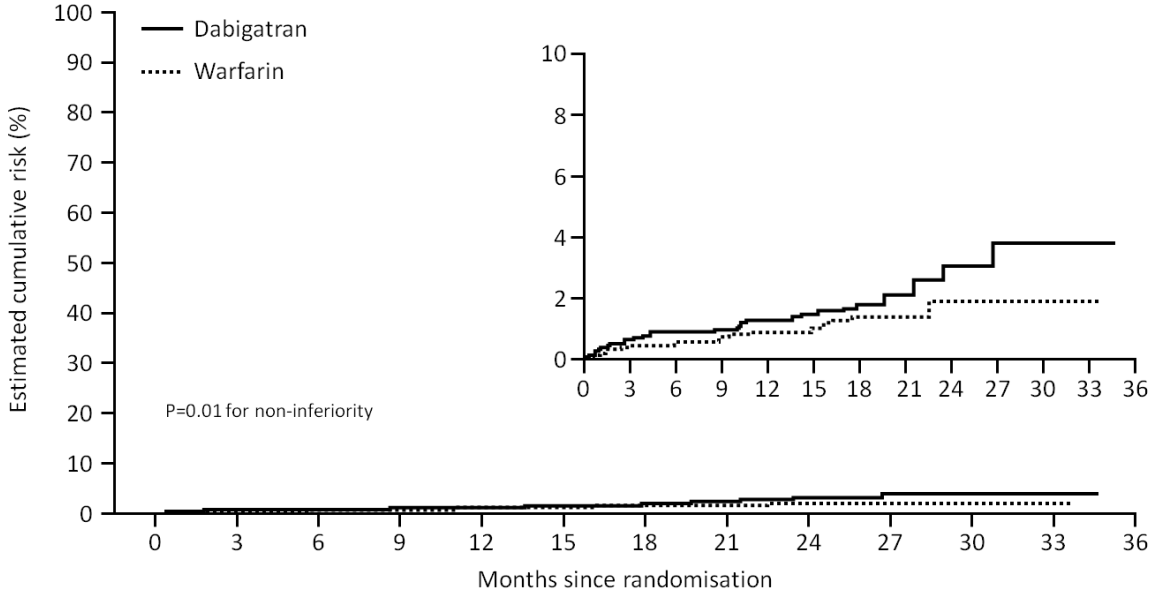
*Analysis for first adjudicated recurrent VTE or VTE death by baseline strata

Abbreviations: CI, confidence interval. PE, pulmonary embolism.

The study was designed so that the risk difference between dabigatran and warfarin would be estimated separately for each stratum. Because of the low number of events, not all strata were evaluable separately.[6] The stratification variable 'active cancer at baseline' would have resulted in strata without events. Therefore only the two strata from the stratification variable 'symptomatic PE as qualifying event' were considered in the analysis. The cumulative risk at 18 months was 1.74% in the dabigatran group and 1.38% in the warfarin group.[6] The risk difference between dabigatran and warfarin was 0.26% (95% CI -0.72, 1.23). The cumulative risks and risk differences by stratum were comparable with the results by stratum for the primary analysis, again with the confidence interval in both strata including 0.0.[6]

Over the study period, dabigatran 150 mg BD demonstrated non-inferiority to warfarin (HR 1.44; 95% CI 0.78, 2.64). The risk difference, calculated at 18 months, was 0.38% (Figure 14) (95% CI –0.50, 1.25; $p < 0.001$ for non-inferiority).[5]

Figure 14: Cumulative risk of recurrent VTE or related deaths in RE-MEDY [5]



No. at risk													
Dabigatran	1430	1409	1389	1259	1087	995	279	233	170	100	49	3	0
Warfarin	1426	1405	1388	1253	1081	997	263	230	168	97	43	5	0

Secondary efficacy outcomes: RE-MEDY

For the analyses of the secondary endpoints, results for all three cohorts were pooled. For all secondary endpoints except the composite endpoint of recurrent VTE and all deaths, results from all strata were pooled for the risk difference analysis due to the low number of events.[6]

The incidence of recurrent VTE and all deaths, symptomatic DVT, VTE-related deaths and all deaths was low in both treatment groups (Table 46).There was no statistically significant difference by treatment group in the rate of any of the secondary endpoints.[5]

Table 46: RE-MEDY secondary efficacy outcomes at 18 months [5;6]

	Dabigatran n = 1,430	Warfarin n = 1,426
Recurrent symptomatic VTE and all deaths, *n*	42	36
Hazard ratio (95% CI)	1.18 (0.75, 1.84)	
By stratification factor, *n* (%)		
Symptomatic PE with cancer	4 (16.0)	2 (8.7)
Symptomatic PE without cancer	14 (3.0)	9 (1.9)
No symptomatic PE with cancer	4 (11.4)	3 (8.3)
No symptomatic PE without cancer	14 (1.5)	18 (2.0)
Symptomatic DVT, *n* (%)	17 (1.2)	13 (0.9)
Hazard ratio (95% CI)	1.32 (0.64, 2.71)	
Symptomatic non-fatal PE, *n* (%)	10 (0.7)	5 (0.4)
Hazard ratio (95% CI)	2.04 (0.70, 5.98)	
Deaths related to VTE, *n* (%)	1 (0.1)	1 (0.1)
Hazard ratio (95% CI)	1.01(0.06, 16.22)	
All deaths, *n* (%)	17 (1.2)	19 (1.3)
Hazard ratio (95% CI)	0.90 (0.47, 1.72)	

Analysis was based on data for the planned treatment period, regardless of whether the study drug was discontinued early.

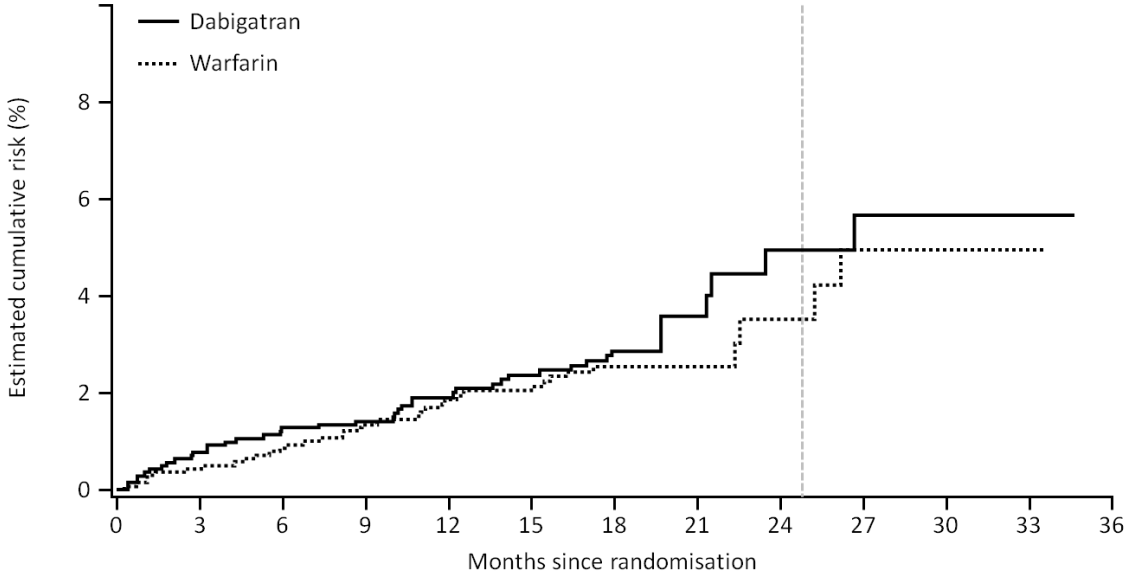
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Recurrent symptomatic VTE and all deaths

The Kaplan-Meier survival curves for the composite of recurrent VTE and all deaths together with the number of patients at risk are shown in Figure 15.[6] The cumulative risk for the composite of recurrent symptomatic VTE and all deaths at 18 months was 2.86% in the dabigatran group and 2.53% in the warfarin group. The risk difference was 0.09% (95% CI -1.11, 1.28). None of the confidence intervals for the risk differences indicated a statistically significant between-treatment difference between any of the strata.[6]

The cumulative risks for the composite of VTE and all deaths were highest for patients with initial symptomatic PE and active cancer at baseline (dabigatran: 18.2%, warfarin: 10.0%) and for patients with active cancer but without PE (11.4% vs. 9.1%).[6] Patients with initial symptomatic PE without cancer at baseline had a lower risk for recurrent VTE and death (3.4% vs. 2.0%); the risk was lowest for patients with neither initial symptomatic PE nor cancer at baseline (1.8% vs. 2.3%).[6]

Figure 15: Time to the composite of recurrent symptomatic VTE and all deaths[6]

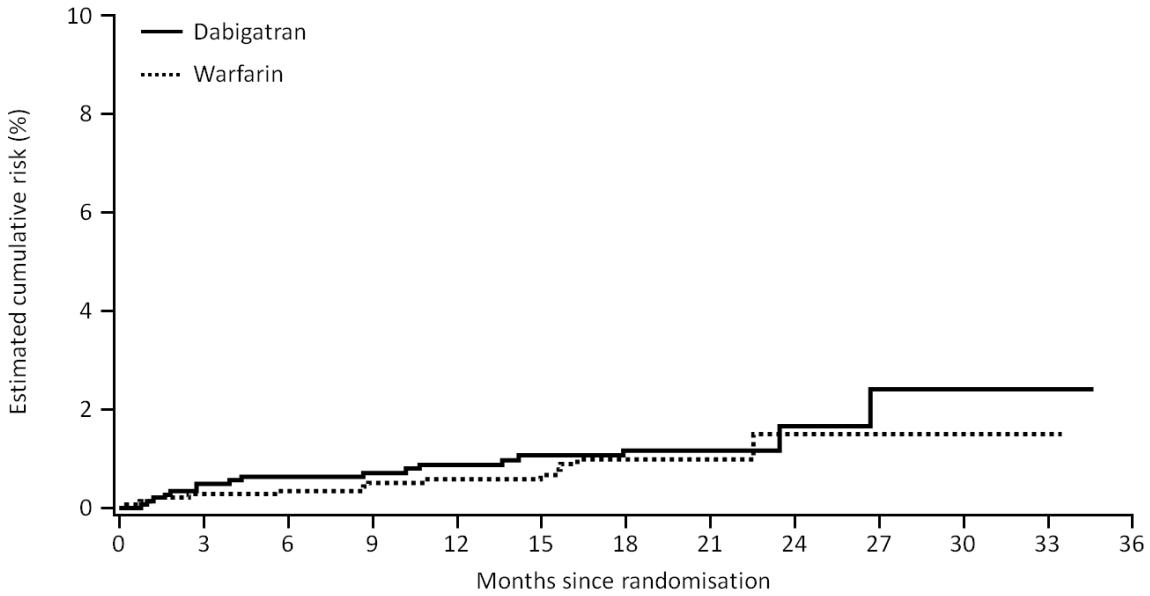


No. at risk													
Dabigatran	1430	1411	1396	1268	1094	1002	279	233	170	100	49	3	0
Warfarin	1426	1410	1394	1257	1083	998	264	230	169	97	43	5	0

Symptomatic DVT

The number of patients with acute symptomatic DVT was 17 patients in the dabigatran group and 13 patients in the warfarin group. The hazard ratio of dabigatran vs. warfarin for symptomatic DVT was 1.32 (95% CI 0.64, 2.71, Figure 16).[5]

Figure 16: Time to DVT[6]



No. at risk													
Dabigatran	1430	1411	1392	1261	1091	998	279	234	172	101	49	3	0
Warfarin	1426	1406	1390	1255	1084	1000	264	231	169	97	43	5	0

Symptomatic non-fatal PE

The number of patients with a symptomatic, fatal or non-fatal PE was 10 in the dabigatran group and five in the warfarin group. The hazard ratio of dabigatran vs. warfarin was 2.04 (95% CI 0.70, 5.98).[5]

Death related to VTE

One patient in the dabigatran group and one patient in the warfarin group died from PE. The hazard ratio of dabigatran vs. warfarin for VTE-related death was 1.01 (95% CI 0.06, 16.22).[5] The cumulative risks at 18 months were 0.08% and 0.07%, respectively, in the dabigatran group and the warfarin group. The risk difference was 0.01% (95% CI -0.20, 0.23).[6]

All deaths

The number of patients who died during the planned treatment period was comparable between the treatment groups (dabigatran: 17 patients; warfarin: 19 patients).[5] The most frequent adjudicated cause of death was cancer for about half of the patients (dabigatran: 7 patients, warfarin: 9 patients).[6] The cumulative risks for death at 18 months were 1.22% in the dabigatran group and 1.24% in the warfarin group; the resulting risk difference was -0.02% (95% CI -0.89, 0.84). [6]

RE-SONATE

The primary efficacy endpoint investigated in RE-SONATE was recurrent symptomatic and objectively verified VTE or death associated with VTE, including unexplained death. Clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies.[8]

Primary efficacy endpoint: recurrent symptomatic, objectively confirmed VTE and death associated with VTE or unexplained death

The results of RE-SONATE with respect to the primary endpoint are presented in Table 47.

Table 47: RE-SONATE primary efficacy outcome [5]

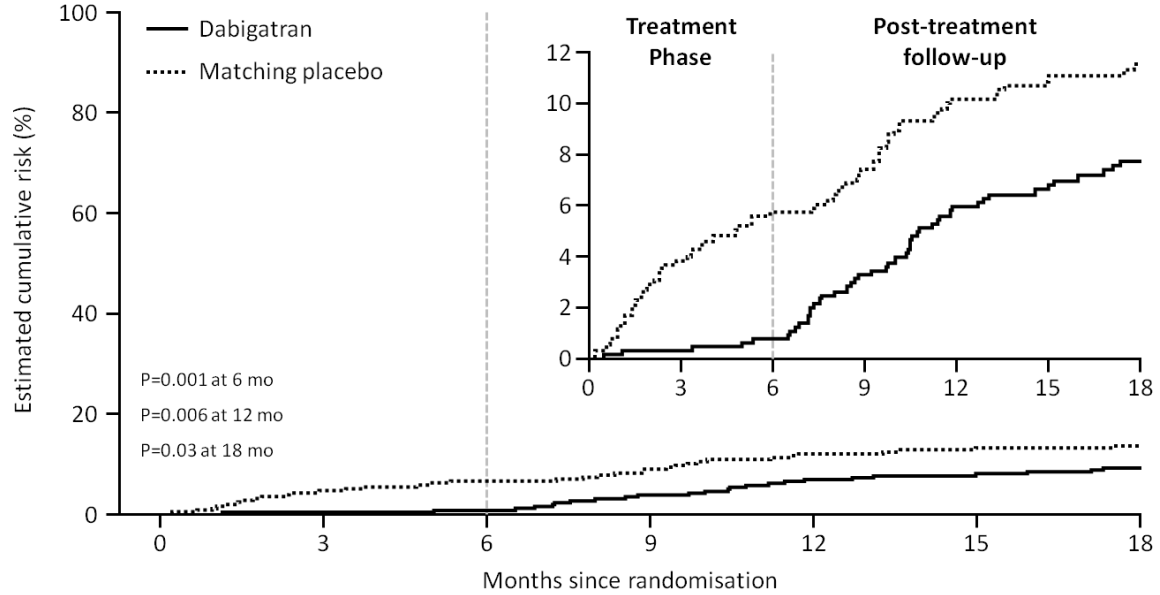
	Dabigatran n = 681	Placebo n = 662
Patients with event*, n (%)	3 (0.4)	37 (5.6)
Hazard ratio (95% CI)	0.08 (0.02, 0.25)	
p-value for superiority	<0.001	

*One subject (placebo group) had a symptomatic centrally confirmed DVT and PE on the same day

Abbreviations: CI, confidence interval.

The hazard ratio with dabigatran for time to the first primary-outcome event was 0.08 (95% CI 0.02, 0.25; P<0.001) (Figure 17). [5]

Figure 17: Cumulative risk of recurrent VTE, related deaths or unexplained deaths in RE-SONATE[5]



No. at risk							
Dabigatran	681	667	651	591	557	503	186
Matching placebo	662	615	586	537	502	461	171

An extended 12 month follow-up was completed for 1323 of the 1343 patients who underwent randomisation and received the study drug (98.5%), at which point the cumulative incidence of the primary efficacy outcome was 6.9% in the dabigatran group as compared with 10.7% in the placebo group (hazard ratio, 0.61; 95% CI, 0.42 to 0.88).[5]

Dabigatran was demonstrated to be a highly efficacious agent for reducing recurrent VTE and unexplained death when used for extended duration prophylaxis after 6 to 18 months of anticoagulation with a VKA, with a 92% reduction in risk compared with placebo.[5;7]

Secondary efficacy endpoints: RE-SONATE

The secondary efficacy endpoints used in RE-SONATE were as follows:[5;7]

- Recurrent VTE excluding unexplained deaths
- Symptomatic DVT
- Symptomatic non-fatal PE
- Unexplained deaths

Results for all secondary efficacy endpoints were consistent with the primary endpoint in RE-SONATE (Table 48). For all component events, the frequency was consistently lower in the dabigatran arm than the placebo arm.[7]

Table 48: RE-SONATE secondary efficacy outcomes [5;7]

	Dabigatran n = 681	Placebo n = 662
Recurrent VTE excluding unexplained deaths, n (%)	3 (0.4)	35 (5.3)
Hazard ratio (95% CI)	0.08 (0.03, 0.27)	
Symptomatic DVT, n (%)	2 (0.3)	23 (3.5)
Symptomatic non-fatal PE, n (%)	1 (0.1)	14 (2.1)
Unexplained deaths, n (%)	0 (0.0)	2 (0.3)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Recurrent VTE excluding unexplained deaths

The incidences of recurrent symptomatic VTE excluding unexplained death were 0.4% in the dabigatran group and 5.3% in the placebo group.[7] The hazard ratio for time to first occurrence of an event for dabigatran versus placebo was 0.08, 95% CI 0.03, 0.27. Superiority was therefore demonstrated for dabigatran versus placebo since the upper 95% confidence limit of the hazard ratio was less than one. Since there were only two unexplained deaths (both in the placebo group), these findings were similar to the primary analysis of efficacy.[7]

Symptomatic DVT

The most frequent component event of the primary endpoint was symptomatic recurrent DVT, and the frequency of events in the dabigatran arm was significantly lower than in the placebo arm (0.3% vs. 3.5%, respectively, $p < 0.0001$).[5;7]

Symptomatic non-fatal PE

The frequency of non-fatal PE was lower in patients receiving dabigatran (0.1%) than in patients receiving placebo (2.1%).[5]

Unexplained deaths

There were two unexplained deaths (0.3%), both in the placebo group.[5]

Consistency of overall efficacy results

The objective of all three warfarin-controlled trials (RE-COVER, RE-COVER II and RE-MEDY) was to show non-inferiority to warfarin in both hazard ratio and risk difference. For the acute VTE treatment studies (RE-COVER and RE-COVER II), based on data from previous published studies in this therapy area, a non-inferiority margin of 2.75 in HR and 3.6% in RD was selected, corresponding to preservation of at least 57% and 75% of the effect of full-dose warfarin, respectively. The individual studies, RE-COVER and RE-COVER II, showed comparable hazard ratios, 1.05 (95% CI 0.65, 1.70) and 1.13 (95% CI 0.69, 1.85) respectively, demonstrating consistent efficacy of dabigatran in two independent studies during the first six months of therapy after an index VTE event. The primary endpoint results of both trials, RE-COVER and RE-COVER II, with regard to the upper limit of the 95% confidence interval of the hazard ratio (1.70 and 1.85, respectively) were well below the pre-specified non-inferiority margin of 2.75 and it is important to note that these results were also below the more restrictive margin of non-inferiority of 2.0, used in the pivotal trials for rivaroxaban, EINSTEIN-DVT [31] and EINSTEIN-PE[32]. The risk differences for both the studies were consistent, and were also well below the pre-specified non-inferiority margin of 3.6%. The risk difference was 0.4% (95% CI -0.7, 1.5) for the RE-COVER study and 0.2% (95% CI -1.0, 1.3) for the RE-COVER II study. The results of the hazard ratios and risk differences from the RE-COVER and RE-COVER II studies indicate a clear relationship between using hazard ratios and risk differences.

In clinical studies with very low incidences of efficacy endpoint events, as observed in the RE-MEDY study, the risk difference is statistically more appropriate than the hazard ratio to measure any difference in the effect size between the treatment groups. For RE-MEDY, a non-inferiority margin of 2.85 in hazard ratio and 2.8% in risk difference was selected, corresponding to preservation of at least 70% and 67% of the effect of full-dose warfarin, respectively. These pre-specified criteria for declaring non-inferiority for the hazard ratio and

risk difference were met in the RE-MEDY study with a hazard ratio of 1.44 (95% CI 0.78, 2.64) and a risk difference of 0.4% (95% CI -0.5, 1.2). Even though the hazard ratio was above 1 in RE-MEDY, the effect of low event rates on the hazard ratio can be seen, as the between-group risk difference was still small and similar to the rate seen in the RE-COVER and RE-COVER II studies. Having a relatively large hazard ratio (upper limit 95% CI was 2.64) while having a small risk difference of 0.4% can be explained by the very low rate of recurrent VTEs and VTE-related deaths in this study (22 VTE events (1.7%) in the dabigatran group, 17 VTE events (1.4%) in the warfarin group). As a result, each incremental event had a significant impact on the hazard ratio, but the event rates and risk differences remained low and indicate both dabigatran and warfarin are very effective.

Based on the yearly event rates calculation, one would expect an excess of 0.4 events (VTE and VTE-related deaths) per 100 patient-years of treatment with dabigatran vs. warfarin in patients treated for secondary VTE prevention, and also 0.4 events (VTE and VTE-related deaths) per 100 patient-years of treatment with dabigatran vs. warfarin in patients treated for acute VTE. This clearly shows the consistency of results between the three warfarin-controlled studies indicating that there is no clinically meaningful difference between the effect of dabigatran in the treatments for both acute VTE treatment and secondary prevention of VTE.

From further analysis of the different components of the primary efficacy endpoint one can expect an excess of 0.35 events (symptomatic DVT) and 0.07 events (fatal and non-fatal PE) per 100 patient-years of treatment with dabigatran vs. warfarin patients treated for acute VTE. For patients treated for secondary VTE prevention on can expect an excess of 0.15 events (symptomatic DVT) and 0.25 events (fatal and non-fatal PE) per 100 patient-years of treatment with dabigatran vs. warfarin (Table 49 and Table 50). This again shows the consistency of results between studies, and confirms that risk differences for more severe events (PE events) are very small in both the acute VTE and secondary VTE prevention studies.

Table 49: Frequency and yearly event rate for components of primary endpoint RE-COVER and RE-COVER II pooled analysis

	Dabigatran		Warfarin	
	N	Time at risk Rate/100pt-yrs	N	Time at risk Rate/100pt-yrs
Number of patients	2,553		2,554	

VTE and VTE-related deaths	68	1,375.0 (4.95)	62	1,368.4 (4.53)
Fatal PE	2	1,375.0 (0.15)	3	1,368.4 (0.22)
Non-fatal PE	23	1,375.0 (1.67)	21	1,368.4 (1.53)
Symptomatic DVT	43	1,375.0 (3.13)	38	1368.4 (2.78)

Table 50: Frequency and yearly event rate for components of primary endpoint RE-MEDY

	Dabigatran		**Warfarin**	
	N	**Time at risk Rate/100pt-yrs**	**N**	**Time at risk Rate/100pt-yrs**
Number of patients	1,430		1,426	
VTE and VTE-related deaths	26	2009.5 (1.29)	18	1990.8 (0.90)
Fatal PE	0	2009.5 (0.00)	0	1990.8 (0.00)
Non-fatal PE	10	2009.5 (0.50)	5	1990.8 (0.25)
Symptomatic DVT	16	2009.5 (0.80)	13	1990.8 (0.65)

In addition, the clinical efficacy of dabigatran in the secondary VTE prevention indication is further supported by the results from the RE-SONATE study, which was a placebo-controlled, secondary VTE prevention study. Dabigatran was clearly shown to be superior compared to placebo in terms of the primary endpoint (VTE, VTE-related and unexplained deaths) with a hazard ratio of 0.08 (95% CI 0.02, 0.25; p<0.001). This result is comparable to the primary efficacy endpoint result from the EINSTEIN-Extension study (HR 0.18; 95% CI 0.09, 0.39). [31]

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Conclusions

Dabigatran demonstrated non-inferiority compared with warfarin and superiority to placebo for acute treatment and secondary prevention of DVT and PE. In RE-COVER and RE-COVER II, dabigatran demonstrated non-inferiority vs. adjusted-dose warfarin in terms of prevention of recurrent symptomatic VTE and VTE-related mortality.[1;27] In patients who had already completed 3 to 12 months of anticoagulation treatment (RE-MEDY),[5] dabigatran was non-inferior to warfarin on the composite primary endpoint of recurrent symptomatic VTE and VTE-related death. In the placebo-controlled RE-SONATE study, dabigatran demonstrated a 92% reduction in risk of symptomatic recurrent VTE including unexplained death compared with placebo in patients who had previously completed 6 to 18 months of anticoagulation treatment.[5]

For patients and health care providers, dabigatran is a more convenient drug than warfarin, since it has no known interactions with foods and fewer interactions with other drugs, compared with VKAs. In addition, dabigatran does not require routine coagulation monitoring or frequent dose adjustment.[1]

6.6 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.

6.6.1 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).

A meta-analysis was performed to provide comparative effectiveness estimates for dabigatran versus rivaroxaban in the treatment and secondary prevention of deep vein thrombosis and pulmonary embolism.[33] The meta-analysis performed will provide relative treatment effect estimates between dabigatran and rivaroxaban for efficacy and safety endpoints. [33]

The trials that comprise the evidence base for the meta-analysis are briefly described below.

Dabigatran trials

Treatment of DVT and PE:

- RE-COVER and RE-COVER II

Secondary prevention of recurrent DVT and PE:

- RE-SONATE
- RE-MEDY

Rivaroxaban trials

Treatment of DVT and PE:

- Einstein-DVT and Einstein-PE were open-label phase III trials that randomised patients to either rivaroxaban (15mg twice daily for the first 3 week, followed by 20mg once daily) or subcutaneous (SC) body-weight-adjusted enoxaparin (1mg/kg twice daily) for at least 5 days plus a VKA, either warfarin or acenocoumarol, for the treatment of either recurrent acute symptomatic DVT or PE. Treatment duration was 3, 6 or 12 months. [31;32]

Secondary prevention of recurrent DVT and PE:

- Einstein-Extension was a phase III, randomised, placebo-controlled, double-blind trial designed to assess the relative efficacy and safety of rivaroxaban 20mg in the prevention of recurrent symptomatic DVT or PE in patients who had completed 6 to 12 months of rivaroxaban or VKA treatment for an acute episode of VTE.[34]

Warfarin trials

Warfarin was the active control for the RE-COVER trials and RE-MEDY. In the Einstein trials the active control arm was a VKA antagonist (either warfarin or acenocoumarol). [27;31;32;34] For the purpose of this analysis, alternative VKAs were assumed to be therapeutically equivalent.

In addition, trials comparing warfarin or another VKA to placebo in the secondary prevention of recurrent DVT and /or PE have been identified by the systematic review in order to link the evidence network, as the RE-MEDY trial compared dabigatran with warfarin, whereas the RE-SONATE and Einstein-Extension studies compared dabigatran and rivaroxaban respectively with placebo.[5;34]

Low Molecular-Weight Heparin trials

Mono-therapy for the treatment of DVT and PE in patients with active caner:

- Adjusted indirect comparisons (AIC) of dabigatran with LMWH monotherapy were performed, using adjusted-dose warfarin as a common comparator for the treatment of DVT and PE. Treatment effect estimates for dabigatran versus adjusted-dose warfarin in patients with active cancer were obtained by meta-analysis of the efficacy and safety data from the subgroups of patients with active cancer in the RE-COVER and RE-COVER II trials. Corresponding treatment effect estimates for LMWH monotherapy versus warfarin were obtained by meta-analysis of 5 trials in which LMWH monotherapy was compared to warfarin in patients with active cancer [35-39].

Mono-therapy for secondary prevention of recurrent VTE in patients with active cancer

- Adjusted indirect comparisons (AIC) of dabigatran with LMWH monotherapy were performed, using placebo as a common comparator, for the secondary prevention of recurrent VTE in patients with active cancer. For the comparison of dabigatran versus placebo, treatment effect estimates were obtained using the efficacy and safety data from the subgroup of patients with active cancer in the RE-SONATE trial. For the comparison of LMWH monotherapy versus placebo in the secondary prevention of recurrent VTE in patients with active cancer, one suitable trial was located (the Cancer DACUS trial).[40]

Treatments and endpoints of interest[33]

The following medications were included in the meta-analyses:

- Dabigatran 150 mg twice daily preceded by acute parenteral treatment
- Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily
- Warfarin dosed to achieve a target INR of 2.0 to 3.0, preceded by acute parenteral treatment

Table 53 summarises the treatments and endpoints of trials that were identified as relevant to the meta-analysis.

Table 53: Summary of trials included in meta-analyses, by treatment

Trial	Treatments of Interest					Endpoints of Interest		
	Dabigatran	Rivaroxaban	Warfarin	Placebo	Low Molecular-Weight Heparin	Recurrent VTE	Clinically Relevant Bleeds	Major Bleeds
VTE Treatment								
RE-COVER	✓		✓			✓	✓	✓
RE-COVER II	✓		✓			✓	✓	✓
EINSTEIN-DVT		✓	✓			✓	✓	✓
EINSTEIN-PE		✓	✓			✓	✓	✓
Deitcher et al. (2006)			✓		✓	✓		✓
Hull et al. (2006)			✓		✓	✓		✓
Lee et al. (2003)			✓		✓	✓		✓
Meyer et al. (2002)			✓		✓	✓		✓
Romera et al. (2009)			✓		✓	✓		✓
VTE Secondary Prevention								
RE-SONATE	✓			✓		✓	✓	✓
RE-MEDY	✓		✓			✓	✓	✓
EINSTEIN-Extension		✓		✓		✓	✓	✓
Cancer DACUS				✓	✓	✓		✓

Endpoints of interest

Review of the evidence base revealed two endpoints suitable to assess efficacy and safety in the treatment and secondary prevention of VTE:

- The primary efficacy endpoint of the trials was recurrent VTE, usually defined as the composite of recurrent VTE and VTE-related mortality.
- The main safety endpoint in the trials was bleeding. Two endpoints were analysed: major bleeding and a composite bleeding endpoint consisting of major or clinically relevant bleeding (MCRB). Bleeding that was not clinically relevant (minor or nuisance bleeds) were not analysed, as these were unlikely to present clinically in routine clinical practice and were therefore excluded from the economic model.

Each endpoint was analysed separately.

Heterogeneity

In all meta-analyses, heterogeneity between the included studies plays a substantial part in the planning and execution of the analyses and the interpretation of results.[33] There is no one method to assess heterogeneity within meta-analysis, but a suite of techniques can be used to explore the heterogeneity of the data and therefore help assess the robustness of the results and highlight the underlying limitations.[33]

Heterogeneity manifests itself in two key aspects in meta-analysis:[33]

- Are the trial populations that we are combining fundamentally similar and hence combinable?
- Are the observed trial results (e.g., treatment effects) consistent across the trials?

We performed the following to assess and account for heterogeneity:[33]

- Compared study design of the trials included in the meta-analyses
- Assessed MTC model fit using the "reduced chi-squared" statistic, i.e., the Pearson chi-square divided by the degrees of freedom. Estimates of the reduced chi-squared statistic close to 1.0 indicate a well-fitting model. Values much greater than 1 indicate persisting heterogeneity within the data. Values considerably less than 1 indicate a saturated model.
- Examined heterogeneity within the direct meta-analysis using the I^2 and chi^2 tests of heterogeneity and by inspection of the Forest plots
- Compared meta-analysis results with results from head-to-head comparison trials.

Interpreting the findings from all these different exploratory techniques required a careful balance of pragmatism with idealism. The challenge was to combine data in a way that was clinically meaningful, representative of the patient population of interest, and fit for the purpose (for example, estimates to be used in an economic model), but that reflected the uncertainties in the observed evidence.

Direct fixed-effects and random-effects meta-analysis[33]

We used RevMan to estimate the pooled fixed-effects and random-effects treatment estimates. Random-effects direct meta-analysis results are seldom different from fixed-effects direct meta-analysis results when fewer than three trials are available. The methods

used in RevMan for fixed effects and random effects are described below. These methods can be applied to any estimate of treatment difference (θ_i) (e.g., binary, continuous) as long as we can assume normality of the estimate.

We assume trials I's treatment estimate to be normally distributed:

$$\theta_i \sim N(\theta_i, w_i^{-1}).$$

The pooled fixed-effects estimate (θ) and standard error (SE) of θ are given by the following equations:

$$\theta = \Sigma(\theta_i\, w_i)/\Sigma(w_i),$$

$$SE\ (\theta) = sqrt[1/\Sigma(w_i)].$$

For random-effects analyses, we assume that the individual study estimates (θ_i) are sampled from a normal distribution with mean θ and variance τ^2, thus:

$$\theta \sim N(\theta_i, w_i^{-1} + \tau^2.$$

Denoting $v_i = 1/\ (w_i^{-1} + \tau^2)$, we have the pooled random-effects estimate (θ) and SE of θ given by the following equations:

$$\theta = \Sigma(\theta_i\, v_i)/\Sigma(v_i),$$

$$SE\ (\theta) = sqrt[1/\Sigma(v_i)].$$

Further details on how to calculate τ^2 are given in Whitehed (2002).

Trial heterogeneity

There were multiple sources of heterogeneity within the evidence bases. The main sources of heterogeneity among the trials for the treatment indication were as follows:[33]

- Type of index VTE (DVT and PE)
- Presence of risk factors for recurrent VTE (e.g., the LMWH trials studies patients with active cancer)
- Duration of treatment and/or follow-up
- Time in the target INR range for the warfarin/VKA arm

The main sources of heterogeneity among the secondary prevention trials were as follows:

- Presence of risk factors for recurrent VTE (e.g., the RE-MEDY trial studied patients at high risk for recurrent VTE, whereas the EINSTEIN-EXT trial included patients for whom the decision to continue therapy was in equipoise)
- Duration of secondary prevention and/or follow-up
- Time in the target INR range for the warfarin arm (relevant only to RE-MEDY and trials comparing warfarin and placebo)

The primary analyses included trials described in the treatment networks without adjustment for between-trial heterogeneity, despite their differences. Adjustment for between-trial heterogeneity using covariates was not the favoured approach for the following reasons:

- Some important sources of heterogeneity could not be reliably represented numerically (e.g., underlying risk).
- Lack of variability within covariates to capture heterogeneity would generate unreliable model estimates (e.g., prior VTE history, proportion of cancer patients).
- Due to paucity of trial data, the model could not support multiple covariates to adjust for multiple sources of heterogeneity.

To explore the impact/importance of trial heterogeneity, sensitivity/subgroup analyses were performed separately to explore each of the areas of heterogeneity outlined above. These analyses are described in more detail in the following sections.

Type of index VTE (treatment indication)

Trials identified for inclusion into the treatment meta-analysis included populations where the incident event was DVT, PE, or both. In addition to analyses based on the intent-to-treat populations, analyses were performed that include trials (or subgroups) in patients with PE (i.e., the Einstein-PE trials and the “PE with or without DVT” subgroup of the RE-COVER and RE-COVER II trials). An equivalent analysis including trials (or subgroups) in patients with DVT (i.e., the Einstein-DVT trial and the “DVT only” subgroup of the RE-COVER and RE-COVER II trials) was performed in an earlier report. Randomisation for the RE-COVER trials was stratified for index VTE.

Cancer patient population (treatment and secondary prevention indications)

The 5 trials highlighted in the NICE rivaroxaban submission comparing LMWH with warfarin in the treatment indication were conducted in patients with active cancer.[35-39] To investigate the importance of heterogeneity with respect to this characteristic AIC was performed comparing the pooled estimate of the "cancer only" subgroup from the RE-COVER trials with the pooled estimate from the LMWH trials (estimates were pooled using standard direct meta-analysis techniques).[27] The randomisation of the RE-COVER trial populations was stratified for cancer; however, the level of inference that could be drawn from this analysis was limited because the number of patients with active cancer in the dabigatran trials was small.

Similarly, the Cancer DACUS trial comparing LMWH with no treatment in the secondary prevention indication also comprised active cancer patients.[40] To investigate the importance of heterogeneity with respect to this characteristic and AIC was performed comparing the pooled estimate of the "cancer only" subgroup from RE-SONATE with Cancer DACUS.[33]

High risk for recurrent VTE (secondary prevention indication)

The inclusion/exclusion criteria of the RE-MEDY[5] trial differed from those of the RE-SONATE and Einstein-Extension trials with respect to the risk of recurrent VTE.[5;34] In other words, the RE-MEDY trial population was a more severely affected patient group than other trial populations within the evidence base. The RE-MEDY trial also violated the consistency assumption required to combine direct and indirect evidence, consequently it was excluded from the analyses.

Duration of treatment and follow-up (treatment and secondary prevention indications)

The duration of therapy differed among the trials included in the treatment meta-analysis. However, since the duration of treatment was the same for both intervention within each trial, and the proportional hazards assumption holds, the HR would be independent of the duration of treatment. For example, the HR observed in a trial comparing 3 months of LMWH with 3 months of warfarin would be expected to be the same as that observed in a trial comparing 6 months of LMWH with 6 months of warfarin. Therefore, no adjustment was made for the duration of therapy in the treatment analyses. This approach was consistent with that taken in the Bayer NICE submission for rivaroxaban.

Two studies on the secondary prevention analyses included a period of active therapy and an extended period of follow-up after therapy was discontinued. These were WODIT and

WODIT-PE trials. The HR observed in a 12-month trial comparing 3 months of warfarin with placebo would be expected to differ from that observed in another 12-month trial comparing 12 months of warfarin with placebo. Consequently, analyses were performed to include and exclude these trials.

Time in the target INR range for the warfarin arm (treatment and secondary prevention indicators)

For the treatment analysis, a sensitivity analysis was performed that adjusts for the effect of time in the target INR range using an analysis of data from the General Practice Research Database (now the Clinical Practice Research Datalink) that estimated the effect of time in the target INR range on the risk of recurrent VTE and bleeding[41]. Unfortunately, this analysis was limited because the majority of trials did not include the time in INR range.

For the secondary prevention analysis, time in the target INR range for the warfarin arm was relevant only to RE-MEDY and trials comparing warfarin and placebo. With respect to the latter, the data were incomplete and of poor quality, which precluded any attempt to adjust for time in the target INR range.

Trial data consistency

The consistency of the trial data was examined using two statistical tests for heterogeneity: the I^2 value and the P value of the chi-squared test. The P value of the chi-squared statistic shows the size of the chi-squared statistic in relation to its degrees of freedom, with a low P value providing evidence of heterogeneity of intervention effects. The I^2 value describes the percentage of variability in effect estimates that is due to trial heterogeneity rather than sampling error, or chance. The Cochrane Handbook (2011) suggests the following thresholds for interpreting I^2:

- 0% to 40%: heterogeneity might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

It is important to note that care should be taken when interpreting these statistics. It is argued that statistical heterogeneity is inevitable in any meta-analysis (Higgins, 2003) and therefore, will be present to some degree whether or not it can be detected. Therefore,

these methods should be used as a guide to help inform discussions of consistency of the data between the trials used in an analysis.

Treatment Analysis

Dabigatran versus Warfarin

The following endpoints were assessed in the meta-analysis of trials comparing dabigatran versus adjusted-dose warfarin for the treatment of DVT and PE (RE-COVER and RE-COVER II trials):

- Recurrent VTE (including VTE-related death)
- Major Bleeding
- Major or clinically-relevant, non-major bleeding

Examination of the heterogeneity p-values and I^2 statistics for each endpoint indicates that there was no evidence of inconsistency between the RE-COVER and RE-COVER II data either for subgroup analyses or analyses including all patient data. The results of the meta-analysis are presented in Table 54. There was no evidence of inconsistency between the RE-COVER and RE-COVER II endpoint data either for subgroup analyses or analyses including all patient data (Table 54).

Rivaroxaban versus Warfarin

The following endpoints were assessed in the meta-analysis of trials comparing rivaroxaban versus adjusted-dose warfarin for the treatment of DVT and PE (EINSTEIN-DVT and EINSTEIN-PE trials):

- Recurrent VTE
- Major Bleeding
- Clinically-relevant Bleedings

There was some indication of recurrent VTE data inconsistency between EINSTEIN-DVT (0.70) and EINSTEIN-PE (1.13). This perhaps was not surprising given the differences in index VTE event and time in INR. Bleeding endpoints were consistent. The results of the meta-analysis are presented in Table 55. There was some indication of recurrent VTE data inconsistency between EINSTEIN-DVT (0.70) and EINSTEIN-PE (1.13). This perhaps was not surprising given the differences in index VTE event and time in INR (Table 55). Bleeding endpoints were consistent.

LMWH versus warfarin

The following endpoints were assessed in the meta-analysis of trials comparing Low Molecular Weight Heparin versus adjusted-dose warfarin for the treatment of DVT and PE:

- Recurrent VTE
- Major Bleeding

The results of the meta-analysis are presented in Table 56 (results of trials in patients with active cancer are highlighted in bold). Examination of the heterogeneity p-values and I2 statistics for each endpoint indicates that there was no evidence of inconsistency in the trial data.

Table 54: Direct meta-analysis random-effects model estimates for dabigatran versus warfarin in treatment analysis[33]

Outcome	Subgroup	Measure	Trials	Dabigatran versus Warfarin				
				Relative Risk/ Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Heterogeneity Test P-Value	I^2 (%)
Recurrent VTE[a]	All patients	Relative Risk	RE-COVER + RE-COVER II	1.10	0.78	1.54	0.82	0
		Hazard Ratio		1.09	0.77	1.54	0.83	0
	Time in INR	Hazard Ratio		1.10	0.78	1.55	0.82	0
	Pulmonary Embolism	Hazard Ratio	RE-COVER (PE subgroup) + RE-COVER II (PE subgroup)	0.93	0.53	1.63	0.96	0
		Relative Risk		0.87	0.47	1.62	0.94	0
	Deep Vein Thrombosis	Hazard Ratio	RE-COVER (DVT subgroup) + RE-COVER II (DVT subgroup)	1.20	0.78	1.86	0.85	0
	Cancer	Hazard Ratio	RE-COVER (cancer subgroup) + RE-COVER II (cancer subgroup)	0.75	0.20	2.86	0.75	0
		Relative Risk		0.75	0.21	2.75	0.69	0
Clinically Relevant Bleeds[b]	All patients	Relative Risk	RE-COVER + RE-COVER II	0.63	0.51	0.78	0.97	0
		Hazard Ratio		0.63	0.51	0.77	0.94	0
	Time in INR	Hazard Ratio		0.63	0.51	0.78	0.97	0
Major Bleeds	All patients	Relative Risk		0.76	0.49	1.18	0.67	0
		Hazard Ratio		0.76	0.49	1.18	0.70	0
	Time in INR	Hazard Ratio		0.77	0.50	1.19	0.71	0
	Cancer	Hazard Ratio	RE-COVER (cancer subgroup) + RE-COVER II (cancer subgroup)	1.64	0.48	5.57	0.87	0
		Relative Risk		1.60	0.48	5.30	0.83	0

[a] Includes VTE-related mortality.
VTE = venous thromboembolism.

Table 55: Direct meta-analysis random-effects model estimates for rivaroxaban versus warfarin in treatment analysis

Outcome	Subgroup	Measure	Trials	Rivaroxaban versus Warfarin				
				Relative Risk/ Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Heterogeneity Test P-Value	I^2 (%)
Recurrent VTE[a]	All patients	Relative Risk	EINSTEIN-DVT + EINSTEIN-PE	0.90	0.56	1.43	0.11	61.9
		Hazard Ratio		0.88	0.54	1.43	0.10	63.7
	Time in INR	Hazard Ratio		0.88	0.55	1.42	0.10	62.2
Clinically Relevant Bleeds[b]	All patients	Relative Risk	EINSTEIN-DVT + EINSTEIN-PE	0.94	0.82	1.07	0.47	0
		Hazard Ratio		0.92	0.80	1.06	0.62	0
	Time in INR	Hazard Ratio		0.93	0.81	1.07	0.55	0
Major Bleeds	All patients	Relative Risk		0.56	0.38	0.82	0.43	0
		Hazard Ratio		0.54	0.36	0.79	0.50	0
	Time in INR	Hazard Ratio		0.54	0.37	0.79	0.48	0

[a] Includes VTE-related mortality.
VTE = venous thromboembolism.

Table 56: Direct meta-analysis random-effects model estimates for LMWH versus warfarin

Outcome	Subgroup	Measure	Trials	LMWH versus Warfarin				
				Relative Risk/ Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Heterogeneity Test (P Value)	I^2 (%)
Recurrent VTE[a]	All patients	Relative Risk	17 trials	0.60	0.47	0.77	0.56	0
		Hazard Ratio	3 trials	0.47	0.32	0.71	0.87	0
	Low risk	Relative Risk	12 trials	0.73	0.52	1.04	0.45	0
	Cancer	**Hazard Ratio**	**3 cancer trials**	**0.47**	**0.32**	**0.71**	**0.87**	**0**
		Relative Risk	**5 cancer trials**	**0.49**	**0.34**	**0.70**	**0.90**	**0**
	Time in INR	Hazard Ratio	2 trials	0.51	0.32	0.80	0.68	0
Major Bleeds	All patients	Relative Risk	14 trials	0.82	0.58	1.17	0.59	0
	All patients	Hazard Ratio	No data					
	Cancer	**Hazard Ratio**						
		Relative Risk	**4 trials**	**1.05**	**0.53**	**2.10**	**0.16**	**42.3**
	Low risk	Relative Risk	10 trials	0.60	0.36	1.01	0.95	0
	Time in INR	Hazard Ratio	2 trials	0.93	0.27	3.16	0.04	75.5

Secondary Prevention Analysis

Dabigatran versus Warfarin

The dabigatran versus warfarin comparison in secondary prevention was the only comparison informed by both direct evidence (RE-MEDY) and indirect evidence (RE-SONATE and the warfarin trials). The principal advantage of the MTC approach is that it allows the simultaneous analysis of direct and indirect evidence.[33] However, it is only valid to combine direct and indirect evidence for the same treatment comparison, if these estimates are consistent. The head-to-head comparison of dabigatran versus warfarin for recurrent VTE RR was 1.44 (95% CI = 0.79, 2.62) whereas the indirect comparison of dabigatran versus warfarin via placebo was 0.65 (95% CI = 0.15, 2.87).

The inconsistency of these results indicated that it was not valid to combine RE-MEDY, RE-SONATE and the warfarin trials in a MTC.[33] Given that the RE-MEDY trial population considered a high risk population and different to the other trial populations, RE-MEDY was excluded from the analysis. However, RE-MEDY remains the best evidence for dabigatran versus warfarin because it is a head-to-head comparison.

Dabigatran versus placebo

One trial was identified in which dabigatran was compared to placebo for the secondary prevention of recurrent VTE (the RE-SONATE trial) and therefore meta-analysis and evaluation of data consistency was not relevant.[33]

Rivaroxaban versus placebo

One trial was identified in which rivaroxaban was compared to placebo for the secondary prevention of recurrent VTE (the EINSTEIN-Ext trial) and therefore meta-analysis and evaluation of data consistency was not relevant.[33]

LMWH versus placebo

One trial was identified in which LWMH was compared to placebo for the secondary prevention of recurrent VTE (the Cancer DACUS trial) and therefore meta-analysis and evaluation of data consistency was not relevant.[33]

Warfarin versus placebo

As mentioned previously, 5 trials were located in which warfarin was compared to placebo for the secondary prevention of VTE in low-risk patients. There was evidence of inconsistency within the warfarin versus placebo trials in the secondary prevention analysis.[33] The heterogeneity test was 0.002 and the I^2 was 76.9%. The two trials that appeared most dissimilar were WODIT (0.99 [0.57, 1.73]) and WODIT-PE (0.81 [0.42, 1.56]). The point estimates of the remaining three trials ranged from 0.06 to 0.14. Once the WODIT trials were excluded, heterogeneity test and I^2 values did not indicate heterogeneity. However, as stated previously, warfarin was not considered to be a relevant comparator for the secondary prevention of DVT and PE in patients considered to be low-risk for recurrent DVT and PE and so, all trials comparing warfarin with placebo were excluded.

6.6.2 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.

N/A.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (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.

None of the trials listed in Section 6.2.4 are excluded from the meta-analysis; RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE are all included in the meta-analysis report.

6.7 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.

6.7.1 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 10.4, appendix 4.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The interventions of interest were dabigatran and rivaroxaban (for secondary prevention only), UFH, LMWH (eg enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin), and fondaparinux.[33] Searches were performed in two phases: Phase 1 aimed to identify studies investigating dabigatran and rivaroxaban; Phase 2 aimed to identify studies of UFH, LMWH, and fondaparinux. Trials comparing warfarin with placebo in the secondary prevention indication also were included.

Eligibility criteria

Table 57 lists the inclusion and exclusion criteria for studies eligible for review, to evaluate dabigatran for the treatment and secondary prevention of DVT and PE.

Table 57: Inclusion and exclusion criteria (PICOS)

	Inclusion	Exclusion
Population	• Patients with DVT and PE receiving treatment or secondary prevention for recurrent DVT and PE	• Patients receiving primary prophylaxis for prevention of a first DVT or PE event
Intervention	• Dabigatran, rivaroxaban • Warfarin (secondary prevention trials only) • UFH or LMWH (all agents, including, but not limited to, enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) given for more than 10 days, i.e., long-term or extended treatment only (trials investigating acute	• Studies that do not include any of the interventions in the inclusion criteria list

	parenteral treatment with heparin, e.g., for 5-10 days followed by a VKA, were not included as heparin trials) • Fondaparinux (given for 7 or more days)	
Comparator	• Dabigatran • Rivaroxaban • Warfarin • UFH • LMWH (including enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) • Fondaparinux	• Other comparators
Outcomes	• Recurrent DVT or PE • Bleeding • Death	• Regression rate of persistent echogenic masses
Study design	• Randomised, controlled prospective clinical trials • Non-randomised, controlled prospective clinical trials • Long-term follow-up studies (e.g., open-label follow-up studies)	• Prospective observational studies (e.g., phase 4 studies) • Preclinical studies • Phase 1 studies • Prognostic studies • Retrospective studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Reviews, systematic reviews, and meta-analyses (however, reference lists were reviewed for any relevant studies)

The following electronic databases were searched: MEDLINE and MEDLINE In-Process, Embase, The Cochrane Library (including The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effectiveness), and Biosciences Information Service. The Phase 1 (dabigatran, rivaroxaban) searches covered the period from 1960 to 23 July 2012; the Phase 2 (UFH, LMWH, and fondaparinux) searches covered the period from 1960 to 1 October 2012.

The search for relevant studies also included review of bibliographic reference lists of included studies, reviews, meta-analyses, and health technology assessment documents. A number of Internet sources also were searched. Reference lists of systematic reviews and meta-analyses meeting the inclusion criteria were reviewed to identify any additional studies. Full details of the search strategy are provided in Appendix 4.

Information sources

Electronic databases

The Phase 1 searches of electronic databases (for studies of dabigatran and rivaroxaban) were performed on 23 July 2012. The following databases were searched, covering the period from 1960 to 23 July 2012:

- MEDLINE and MEDLINE In-Process (using PubMed platform)
- Embase (using Dialog Platform)
- 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
- Biosciences Information Service (using the Dialog Platform)

The Phase 2 searches (for UFH, LMWH, and fondaparinux) were performed on 1 October 2012, using the same databases as used in the Phase 1 searches.

Internet sources

Phase 1 Internet searches were performed on 19 and 20 July 2012. The following Web sites were searched (where possible) for conference abstracts that were published from January 2010 to 19 July 2012:

- International Society on Thrombosis and Haemostasis (http://www.isth.org/default/index.cfm/publications/abstracts/)
- Hematology Association (http://www.ehaweb.org/Congress/Previous-Congresses)

American Society of Hematology (http://www.hematologylibrary.org/) and British Society for Haematology (http://www.b-s-h.org.uk/) conference abstracts are published in the Journal of Blood and British Journal of Haematology, respectively; therefore, any contributions to these conferences would be identified through the electronic database searches. Thus, a separate search of these two Web sites was not conducted.

The ClinicalTrials.gov website also was searched for ongoing trials, while the following internet sites were searched for HTA documentation relating to DVT and PE:

- United Kingdom: National Institute for Health and Care Excellence (http://www.nice.org.uk/)
- Canada: Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/index.php/en/home)
- Germany: German Institute for Quality and Efficiency in Healthcare (http://www.iqwig.de/projects-results.915.en.html)
- Australia: Pharmaceutical Benefits Advisory Committee (http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publicat.htm)
- Scotland: Scottish Medicines Consortium (http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory)

Phase 2 Internet searches were conducted on 11 through 13 October 2012, using the same databases as used in the Phase 1 Internet-based searches.

Time horizon and limitations

No date limitations or language restrictions were applied in the database search strategy. Internet site searches for conference abstracts were limited to those published from January 2010 to 23 July 2012 (for Phase 1) or 13 October 2012 (for Phase 2) (important research presented at conferences prior to January 2010 would be expected to be published at the search date). For any foreign-language sources that appeared relevant at the screening stage, sufficient information was extracted by linguists to determine their eligibility for inclusion.

Searches

Search terms included combinations of free-text and Medical Subject Heading (MESH) terms, grouped into the following categories:

- Health condition of interest (disease): terms for treatment and secondary prevention of DVT and PE
- Interventions: terms for dabigatran, rivaroxaban, warfarin, UFH, LMWH (including enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin), and fondaparinux

[NB: the original search also included the search terms 'edoxaban' and 'apixaban'. However, these have been deleted from this submission as they are outside of the scope].

- Study type: terms for randomised, controlled trials and non-randomised studies
- Exclusionary terms: terms for comments, editorials, letters, case reports, or studies in animals but not humans

Because the literature for LMWH and UFH is large, the search terms for the Phase 2 search (for LMWH, UFH and fondaparinux) were narrowed to identify only randomised, controlled trials, enabling the identification of the most relevant trials.

Study selection

The literature review study selection process was conducted in two phases:

- First pass screening: titles and abstracts of studies identified from the electronic databases and from Internet searches were reviewed for eligibility by one researcher.
- Second pass screening: full texts of studies selected at first pass were obtained and reviewed for eligibility, using the same inclusion and exclusion criteria.

Any uncertainty about the inclusion of studies was checked by a second researcher. The second researcher also reviewed all studies selected after the level 2 screening to confirm their eligibility.

Data extraction and quality assessment

The following data fields were included in the data extraction:

- Trial acronym (if available)
- First author and year of the primary report
- Identity of any linked secondary reports
- Interventions (including dosages, duration of treatment, and type and duration of previous anticoagulation treatment) and associated patient numbers
- Patient population (key disease information, such as whether patients had DVT and PE; cause of DVT and PE; risk factors; time from onset of qualifying events or symptoms; previous DVT and PE; comorbidities; and key demographic information, such as age and percentage of the cohort that was female or male, and creatinine clearance)

- Whether the trial was blinded (single blind, double blind)
- Identification of the primary and key secondary outcome measures that were defined
- Duration of follow-up
- Results for the clinical outcomes of interest (if available), which could include the following:
    - Number of patients with a recurrent DVT and PE
    - Hazard ratio for recurrent DVT and PE
    - Numbers of patients with a major bleed, a clinically relevant non-major bleed, or any bleed
    - Hazard ratio for bleeding
    - Treatment discontinuation due to adverse events
    - Death (DVT- or PE-related and all-cause)
    - Patient-reported outcomes data

The relevant data were extracted into Microsoft Excel worksheets to facilitate validation and planning of the indirect treatment comparisons.

Data were extracted from full-text versions of studies or clinical study reports, where available (i.e. abstracts were not used unless they were the terminal source documents). Resources obtained via the internet were printed to maintain a record of information in case the electronic source changed or was removed.

Quality control

Any uncertainty about the inclusion of studies was checked by a second researcher. The second researcher also checked a random selection (5%) of titles, abstracts, and full texts at each screening level and reviewed all studies selected after the level 2 screening to confirm their eligibility. Quality-control procedures for the data extraction included verification of all extracted data with their original sources by a second researcher.

A quality assessment was performed for all included studies using the following questions:

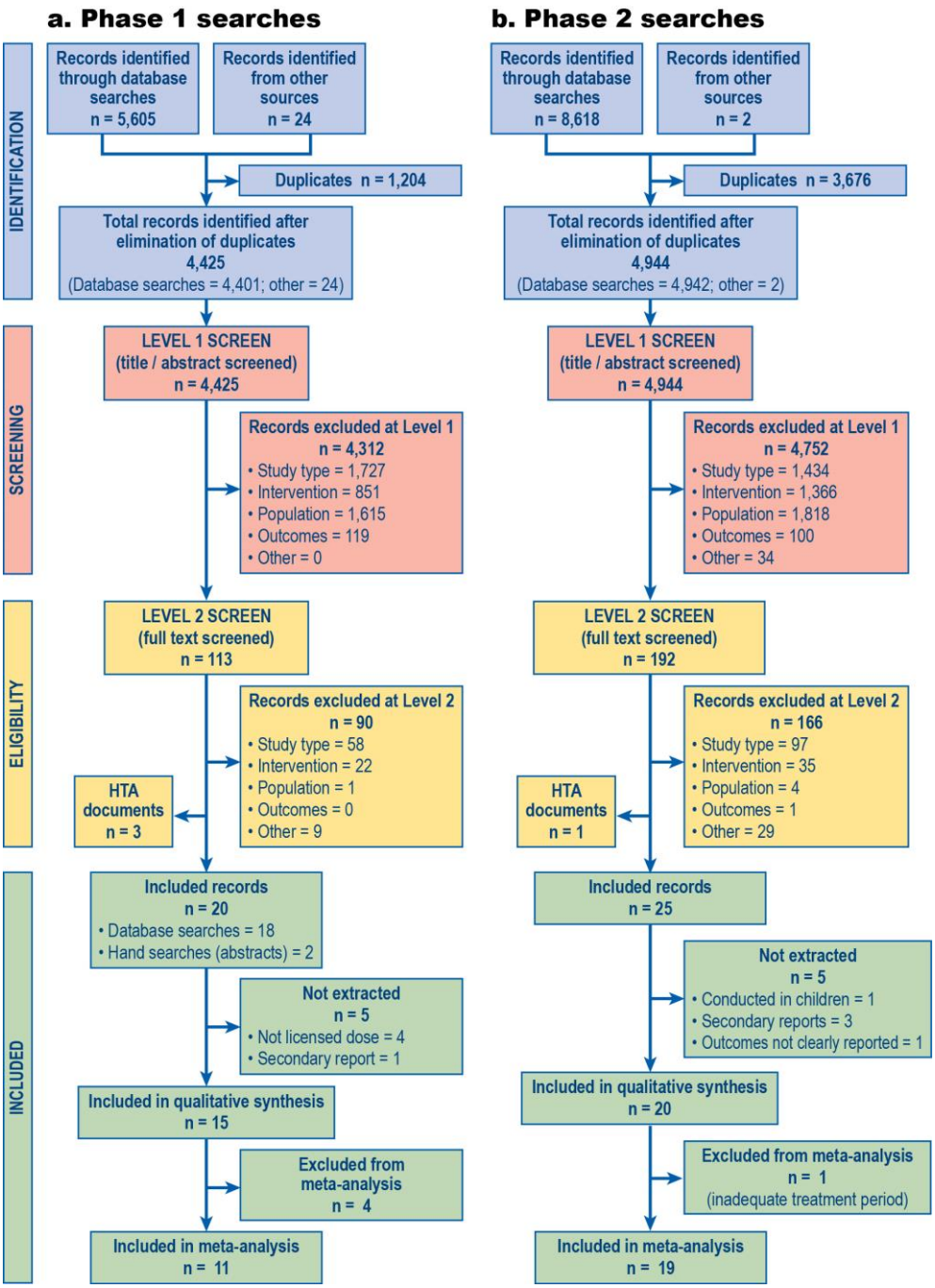
- Was randomisation carried out appropriately?
- Was the concealment of treatment allocation adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors?

- Were the care providers, participants, and outcome assessors blind to treatment allocation?
- Were there any unexpected imbalances in dropouts among groups?
- 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?

Studies identified

A total of 9,369 records were identified for screening. After the initial first pass screening of titles and abstracts, 305 publications (database searches = 281; internet = 19; hand searches = 5) were progressed for second pass screening of full-text articles. At the second pass screening, 45 articles were selected for inclusion in the review (see Figure 18).

Figure 18: **PRISMA flow diagram**



Of these 45 publications, 10 were excluded from further analysis for the following reasons: 4 studies did not investigate the licensed dosage of the study treatment, 4 publications were secondary reports and did not report relevant or additional data, 1 study was conducted in children, and 1 study was excluded because the results were difficult to interpret. The remaining 35 articles were subject to further analysis, and data were extracted from the full

texts where available. Of the 35 publications from which data were extracted, there were 36 unique studies. One publication reported two studies (the EINSTEIN-DVT and EINSTEIN-extension studies).[31]

6.7.3 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.

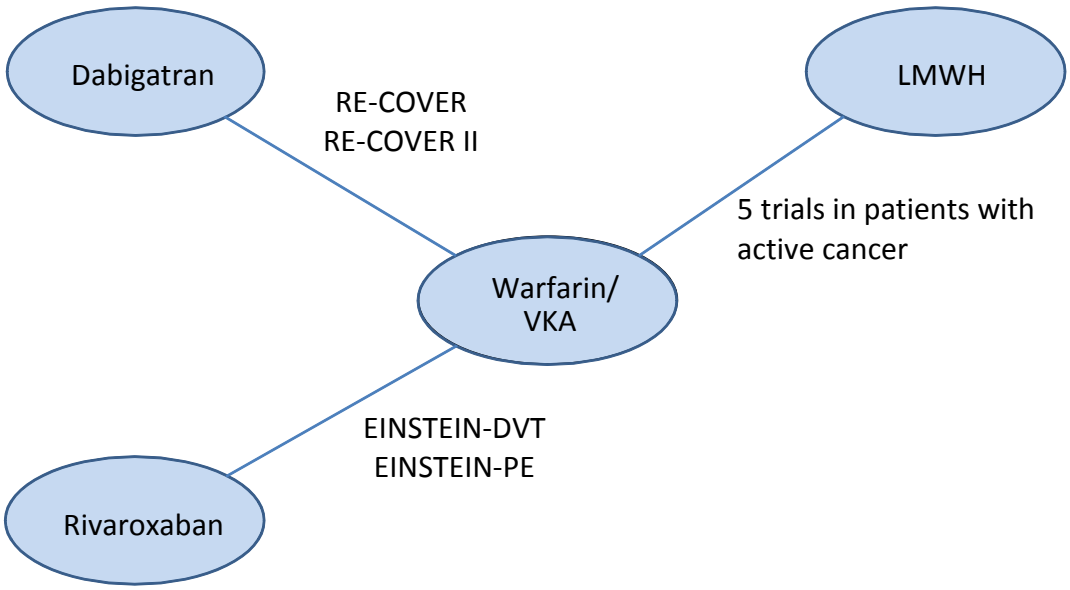
A summary of the trial treatments and endpoints are identified in Table 53 as relevant to the adjusted indirect comparison analysis.

Treatment networks

Treatment of DVT and PE

The network diagram for trials investigating treatment of DVT and PE is presented in Figure 19.

Figure 19: Network diagram: treatment of deep vein thrombosis and pulmonary embolism[33]



LMWH = Low molecular-weight heparin; VKA = vitamin K antagonist
[a] Patients received acute parenteral treatment (e.g., 5-10 days of LMWH or UFH) prior to the named intervention.

The trials that were relevant for this meta-analysis were RE-COVER and RE-COVER II (both of dabigatran), Einstein-DVT and Einstein-PE (both of rivaroxaban) and 5 trials comparing LMWH with warfarin (of VKA). [1;27;31;32;35-39]

All trials were connected by a common comparator, VKA therapy. For the purposes of this analysis, the various VKA agents administered in these trials were considered therapeutically equivalent (although in most cases, patients were treated with warfarin), allowing the comparison of all treatments indirectly via warfarin/VKA.

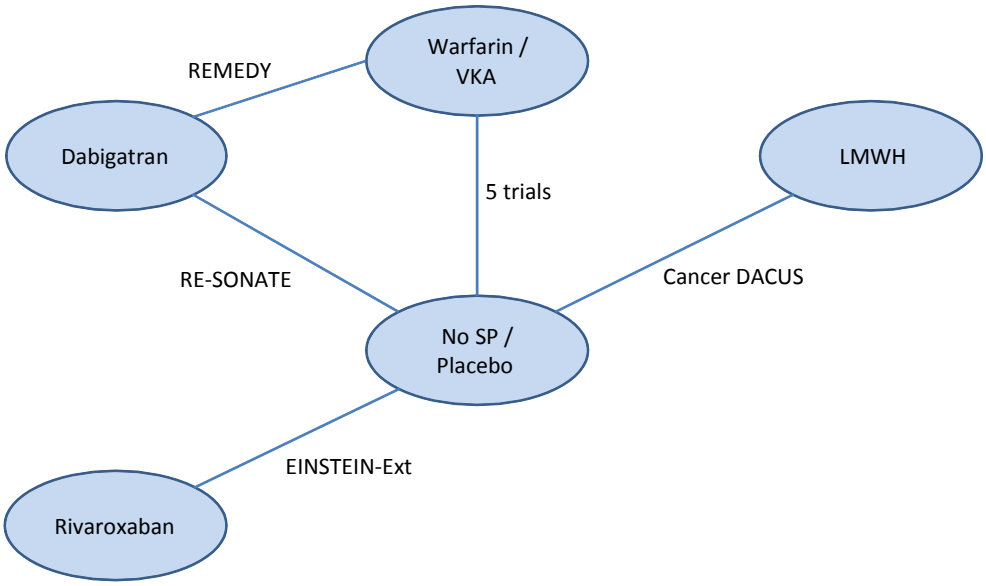
Given the simplicity of this network, dabigatran was compared with all other treatments using AIC. As AIC is a simple approach that cannot handle indirect and direct evidence simultaneously, direct meta-analysis was performed prior to AIC analysis to generate pooled estimates for head-to-head trials comparing the same treatments. For example, RE-COVER and RE-COVER II was directly meta-analysed to provide overall estimates for dabigatran versus warfarin. Similarly, Einstein-DVT and Einstein-PE was pooled to generate an overall estimate of rivaroxaban versus VKA (subgroup analyses were performed to compare individual Einstein trials with PE subgroups of the RE-COVER trials), as were the 17 LMWH-versus-warfarin trials.

In addition to AIC, these treatments were compared using MTC.

Secondary prevention of recurrent DVT and PE

The network diagram for trials investigating secondary prevention of DVT and PE is presented in Figure 20.

Figure 20: Network diagram: secondary prevention of deep vein thrombosis and pulmonary embolism[33]



LMWH = low molecular-weight heparin; SP = secondary prevention; VKA = vitamin K antagonist

The trials that are relevant for this meta-analysis are RE-SONATE, RE-MEDY, EINSTEIN-Extension, Cancer DACUS, and 5 warfarin trials.[5;34-40] No study has been identified that investigates the efficacy and safety of edoxaban in secondary prevention of DVT and PE. All the trials that have been identified for inclusion into this meta-analysis were placebo-compared trials, with the exception of the RE-MEDY trial which compared dabigatran with warfarin. Analyses were performed on both the entire network and subsets of the evidence based for which heterogeneous trials were excluded. Analysis of the entire network had to be performed using MTC given the presence of more than one common comparator. Analysis of subsets for the data where the reduced network only included one common comparator were analysed by both AIC and MTC methods.

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

A summary of the data involved in this MTC is presented in Table 58.

Table 58: Trial data and meta-analysis results used in the AIC

	Treatment	Recurrent VTE		Clinically Relevant Bleeds		Major Bleeds	
Trial	Comparison	Hazard Ratio (95% CI)	Relative Risk (95% CI)	**Hazard Ratio (95% CI)**	**Relative Risk (95% CI)**	**Hazard Ratio (95% CI)**	**Relative Risk (95% CI)**
RE-COVER	Dabigatran vs. Warfarin	1.05 (0.65, 1.70)	1.05 (0.66, 1.70)	0.63 (0.47, 0.84)	0.64 (0.48, 0.85)	0.82 (0.45, 1.48)	0.83 (0.46, 1.49)
RE-COVER II	Dabigatran vs. Warfarin	1.13 (0.69, 1.85)	1.14 (0.70, 1.85)	0.62 (0.45, 0.84)	0.63 (0.47, 0.85)	0.69 (0.36, 1.32)	0.69 (0.36, 1.32)
RE-COVER meta-analysis		1.09 (0.77, 1.54)	1.10 (0.78, 1.54)	0.63 (0.51, 0.77)	0.63 (0.51, 0.78)	0.76 (0.49, 1.18)	0.76 (0.49, 1.18)
Heterogeneity P-value (I^2)		0.83 (0%)	0.82 (0%)	0.94 (0%)	0.97 (0%)	0.70 (0%)	0.67 (0%)
EINSTEIN-DVT	Rivaroxaban vs. Warfarin	0.68 (0.44, 1.04)	0.70 (0.46, 1.07)	0.97 (0.76, 1.22)	1.00 (0.80, 1.26)	0.65 (0.33, 1.30)	0.70 (0.35, 1.38)
EINSTEIN-PE	Rivaroxaban vs. Warfarin	1.12 (0.75, 1.68)	1.13 (0.76, 1.69)	0.9 (0.76, 1.07)	0.91 (0.77, 1.07)	0.49 (0.31, 0.79)	0.50 (0.31, 0.80)
EINSTEIN meta-analysis		0.88 (0.54, 1.43)	0.90 (0.56, 1.43)	0.92 (0.80, 1.06)	0.94 (0.82, 1.07)	0.54 (0.36, 0.79)	0.56 (0.38, 0.82)
Heterogeneity P-value (I^2)		0.10 (63.7%)	0.11 (61.9%)	0.62 (0%)	0.47 (0%)	0.50 (0%)	0.43 (0%)

VTE = venous thromboembolism; Clinically relevant bleeds = major bleeds and non-major clinically-relevant bleeds; CI = Confidence Interval.
If a cell count is 0 (i.e. 0 events), 0.5 is added to both cell counts (outcome risk in a given treatment arm)- this adjustment is only applied to relative risk data.

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

There are several different methods to indirectly meta-analyse trial data. Two commonly used approaches are AIC and MTC.[33] For a more detailed comparison of methods, the Canadian Agency for Drugs and Technologies in Health has published a good review summarising the relative merits of the different available methods for performing indirect treatment comparisons.[42]

For this project, we adopted a frequentist approach using mixed effects regression models developed in SAS to perform the MTC.[33] These models were flexible in the sense that if confronted with insufficient data would fail to estimate the random interaction term and automatically resolve to a fixed effects model. Throughout the rest of this document we will use the terms MTC and regression model/analysis interchangeably to refer to this method.

Another approach that may be used for indirect comparison is meta-regression. Like MTC, this method is able to adjust for covariates.[33] However, unlike MTC, all trials included in the analysis must share the same common comparator.[33] Because MTC includes all of the functionality of meta-regression without any of its limitations, MTC was preferred to meta-regression.

A MTC was performed to provide comparative effectiveness estimates for dabigatran versus rivaroxaban for the treatment, and separately the secondary prevention, of DVT and PE. The MTC provided relative treatment effect estimates for efficacy and safety endpoints pertinent to the economic model. The primary pairwise comparison of interest was dabigatran versus rivaroxaban as the only other factor Xa inhibitor licensed for the same indications as dabigatran.

Adjusted indirect comparison (AIC) methodology

As there were no head-to-head trials comparing dabigatran to rivaroxaban, comparisons were made using indirect meta-analysis techniques, i.e. the adjusted indirect comparison (AIC) methodology. Adjusted indirect comparison [43;44] is a simple and transparent method that requires an identical common comparator across trials to compare the treatments of interest. This method can be used to form indirect comparisons between treatments for different types of effect estimates, for example, RR, HR, and mean difference. The general form for comparing two treatments, for example, *A* and *B*, using only the estimate of each treatment versus a common comparator, say, *P*, is given by the following equation:

$T_{AB} = T_{AP} - T_{BP}$, where

- T_{AP} = the natural logarithm of the HR estimate of A versus P
- T_{BP} = the natural logarithm of the HR estimate of B versus P
- T_{AB} = the natural logarithm of the indirect treatment comparison HR estimate of A versus B

The standard error (SE) for the indirect comparison is given by the following equation:

$SE(T_{AB})^2 = SE(T_{AP})^2 + SE(T_{BP})^2$, where

- $SE(T_{AP})$ = the SE for the natural logarithm of the HR estimate of A versus P
- $SE(T_{BP})$ = the SE for the natural logarithm of the HR estimate of B versus P
- $SE(T_{AB})$ = the SE for the natural logarithm of the indirect treatment comparison HR estimate of A versus B

6.7.6 Please present the results of the analysis.

As an accepted pragmatic solution,[45] the AIC provides an estimate of the relative efficacy and safety of competing interventions that have not been compared directly, whilst preserving randomisation and retaining the strengths of the underlying RCTs. Here the Bucher method[43] was chosen to undertake such AICs. Although the evidence is of lower quality, and the strength of inferences from an AIC is limited, empirical evidence has shown that the results of AIC are generally consistent and not significantly different from those of direct comparisons.[44;46]

Where applicable, a direct meta-analysis was performed prior to AIC analysis to generate pooled estimates for head-to-head trials comparing the same treatments.

Although a mixed-treatment comparison of all trials was performed. However, the results of this approach were not used further since the evidence network did not include mixed evidence from head-to-head trials and indirect evidence and hence did not add additional information.

Dabigatran versus rivaroxaban for the treatment of DVT and PE

The comparison of RE-COVER and RE-COVER II versus EINSTEIN-DVT and EINSTEIN-PE was considered the primary analysis for this treatment comparison and was performed for all endpoints and using both relative risk (RR) and hazard ratios (HR). The following secondary analyses were also performed:

- Time in INR - the warfarin hazard rates were adjusted to account for trial differences with respect to time in INR (all endpoints; HR only)
- PE with or without DVT – this subgroup of patients from the RE-COVER trials was compared to EINSTEIN-PE (recurrent VTE only; RR and HR)
- DVT only - this subgroup of patients from the RE-COVER trials was compared to EINSTEIN-DVT (recurrent VTE only; RR HR only).

The analysis of RR and HR data from the entire patient population of RE-COVER and EINSTEIN trials revealed no significant difference between dabigatran and rivaroxaban for recurrent VTE and major bleeds ([redacted]).

[redacted]

Table 59: [redacted]

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				[redacted]	[redacted]	[redacted]
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Table 60: [redacted]

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[redacted]

Dabigatran versus LMWH monotherapy in patients with active cancer

Results of adjusted indirect comparisons suggest no significant differences in terms of efficacy and safety between dabigatran and LMWH monotherapy in the subgroup of patients with active cancer. As mentioned previously, the number of patients with active cancer at baseline or during follow-up in the RE-COVER and RE-COVER II trials was small (approximately 5% of randomised patients). Thus the relative effectiveness of LMWH followed by dabigatran versus LMWH monotherapy in this patient subgroup is uncertain. Nevertheless, comparative economic analyses have been reported in the submission in order to provide estimates of the cost-effectiveness of LMWH followed by dabigatran in patients with active cancer.

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

As discussed in Section 6.6.1, in all forms of evidence synthesis, heterogeneity between data sources is a key concern and ought to be addressed by thorough investigation and documentation. Please refer to Section 6.6.1 for an in depth discussion of the measures taken to detect trial heterogeneity and inconsistency.

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

N/A.

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

Results from the adjusted indirect comparisons described above have not been used in the economic model described in full in Part 6 of this submission. In the economic model, relative treatment effect estimates for the comparators are derived by application of relevant treatment effects (hazard ratios or risk ratios) from the randomised clinical trials (or meta-analyses of randomised clinical trials) which compared the modelled interventions to a common comparator. For example, the treatment effect of rivaroxaban versus warfarin in the treatment of DVT and PE is derived by application of the hazard/risk ratios obtained by meta-analysis of the EINSTEIN-DVT and PE trials. The corresponding treatment effect of dabigatran is obtained by application of the hazard/risk ratios obtained by meta-analysis of the RE-COVER and RE-COVER II trials.

Adjusted indirect treatment comparisons have been conducted in the interest of completeness and, most importantly, in order to explore the areas of heterogeneity that are present across the respective sets of trials. Therefore, it justifies the use of the approach described above in order to obtain relative treatment effect estimates for use in the economic model. The mean estimates in the model would be identical if the Bucher AIC results versus dabigatran had been used. However, the approach we took avoids using the 95% confidence intervals estimated using the Bucher AIC method, which were calculated using methods which are more open to criticism and are less precise than those estimates from the original trial data.

In addition, the MTC was also performed for comprehensiveness, but in this case, no additional evidence was available for each comparison within the MTC. This is because there are no closed loops in the treatment indication network and all interventions had been compared only with the central common comparator with the exception of RE-MEDY and RE-SONATE. However, both trials were not suitable to include in a single analysis due to the

substantial difference in the underlying risk in the patient populations. Therefore, there was no benefit to performing an MTC in this case.

6.8 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.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 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 10.6 and 10.7, appendices 6 and 7.

As previously discussed in Section 6.2, no relevant non-RCT studies were identified in the searches.

6.9 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.

6.9.1 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 6.1 to 6.5 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 10.8 and 10.9, appendices 8 and 9.

The studies identified in Section 6.2 (RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE) represent the totality of current evidence for dabigatran in this indication. Therefore a further search for evidence on adverse events is unnecessary.

6.9.2 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.

Three active-controlled studies, primarily investigating the efficacy of dabigatran versus warfarin for use in the treatment and secondary prevention of acute VTE, were conducted. Each study collected data on the relative safety of dabigatran, compared to warfarin, and the frequency and severity of adverse events (AEs) associated with dabigatran. Of the three active-controlled studies, RE-COVER and RE-COVER II, which both primarily assessed the efficacy of dabigatran in the 6-month treatment of VTE, were duplicate studies that used the same methodology and endpoints.[1;27] A further study, RE-MEDY, investigated the efficacy of

dabigatran in the long-term prevention of VTE, and therefore provides data on the long-term safety of dabigatran.[5]

Safety outcomes were generally focused on bleeding events. In addition, hepatic function, coronary health and other AEs were routinely assessed.[1;5] All suspected outcome events and death were classified by central adjudication committees, whose members were unaware of treatment assignments.[1;5]

Liver function test (LFT) parameters measured included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and total bilirubin. Increases of possible clinical significance were defined as: ≥3 x upper limit of normal (ULN) (AST, ALT), ≥2 x ULN (AP), and ≥2 mg/dL (total bilirubin).[4;6;28]

In all trials, the analyses of safety parameters focused on treatment-emergent events. These were defined as events with an onset date from the first intake of study drug to the last intake of study drug plus 6 days. In addition, AEs with onset date before the start of study drug but with worsening in intensity during the treatment period were also assigned to the on-treatment period.[4;6;28] The intensity of an AE was judged as 'mild' (i.e., awareness of sign(s) or symptom(s) which is/are easily tolerated), 'moderate' (enough discomfort to cause interference with usual activity), or 'severe' (incapacitating or causing inability to work or to perform usual activities).[4]

Data were stratified according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term system organ class (SOC). A SOC is the highest level of the hierarchy that provides the broadest concept for data retrieval. SOCs comprise groupings by aetiology (e.g., SOC infections and infestations), manifestation site (e.g., SOC gastrointestinal disorders) and purpose (e.g., SOC surgical and medical procedures).[47]

Safety results

RE-COVER and RE-COVER II

RE-COVER and RE-COVER II were duplicate studies assessing dabigatran in the 6 month treatment of adult patients with VTE, compared to warfarin.[1;27] Patients were randomised to receive dabigatran (150 mg BD, taken orally) or warfarin (to obtain a target INR of 2.0-3.0) following initial treatment with a parenteral anticoagulant.[48]

Adverse events

An overview of AEs occurring during the studies is provided in Table 61.

Table 61: Summary of adverse events in RE-COVER and RE-COVER II[1;4;27]

Outcome	RE-COVER		RE-COVER II	
	Dabigatran n = 1273	Warfarin n = 1266	Dabigatran n = 1280	Warfarin n = 1288
Patients with any AE – n (%)	844 (66.3)	856 (67.6)	852 (66.6)	916 (71.1)
Patients with severe AEs – n (%)	96 (7.5)	101 (8.0)	156 (12.2)	153 (11.9)
Drug-related AEs* – n (%)	195 (15.3)	229 (18.1)	194 (15.2)	282 (21.9)
AEs leading to discontinuation – n (%)	115 (9.0)	86 (6.8)	100 (7.8)	100 (7.8)

*Relationship as assessed by the investigator
Abbreviations: AE, adverse event.

In RE-COVER, 115 patients in the dabigatran group (9.0%) had an adverse event that led to treatment discontinuation, compared to 86 patients in the warfarin group (6.8%) (hazard ratio, 1.33; 95% CI 1.01, 1.76; P = 0.05).[1] However, in RE-COVER II, an equal number of patients in each treatment group discontinued treatment due to AEs during the treatment period (100 patients; 7.8% in each group, (Table 61).[27]

The most frequently reported AEs were gastrointestinal disorders. These were more frequent in the dabigatran group (25.1% of patients) than in the warfarin group (19.2%).[1] The difference between gastrointestinal AEs associated with dabigatran and warfarin was not due to the most frequent adverse event in this class, nausea (3.8% vs. 4.6%, respectively), but mostly due to diarrhoea (4.5% vs. 3.0%, respectively) and dyspepsia (3.1% vs. 0.7%, respectively). Respiratory, thoracic, and mediastinal disorders were less frequently reported in the dabigatran group (12.6%) than in the warfarin group (16.5%). This treatment difference can mainly be explained by epistaxis (2.8% dabigatran vs. 6.3% warfarin) and dyspnoea (3.2% dabigatran vs. 4.2% warfarin). AEs following investigations were reported less frequently for dabigatran (4.2%) than for warfarin (6.2%). Of the SOCs with an incidence below 5% per treatment group, cardiac disorders affected 3.5% of dabigatran patients and 3.6% of warfarin patients.[28] There were no significant differences between the two treatment groups in the frequency of any adverse event except for dyspepsia (2.9% in the dabigatran group vs. 0.6% in the warfarin group, P<0.001).[1]

Most of the patients with reported AEs during the treatment period had events of mild (dabigatran: 31.2%, warfarin: 31.1%) or moderate intensity (27.6% vs. 28.5%). AEs classed as severe were reported for 7.5% (dabigatran) and 8.0% (warfarin) of patients. There were no between-group treatment differences. [28]

The AEs most frequently assessed by the investigator as drug-related were epistaxis (dabigatran: 1.7% vs. warfarin: 3.8%), haematuria (1.5% vs. 2.1%), rectal haemorrhage (1.4% vs. 1.2%), contusion (0.9% vs. 1.5%), gingival bleeding (0.7% vs. 1.4%), and headache (1.1%

vs. 1.0%). As might be expected, many of the AEs that were considered to be drug-related by the investigator were bleeding events.[28]

The proportions of patients who discontinued any study drug due to AEs with an onset during the treatment period were 9.0% (dabigatran group) and 6.8% (warfarin group). [1] For the entire treatment period, the most frequent AEs leading to premature discontinuation were PE (dabigatran: 1.2% vs. warfarin: 0.6%) and DVT (1.3% vs. 1.1%). This is consistent with the study protocol, which required patients to discontinue in case of verified recurrent VTE.[28]

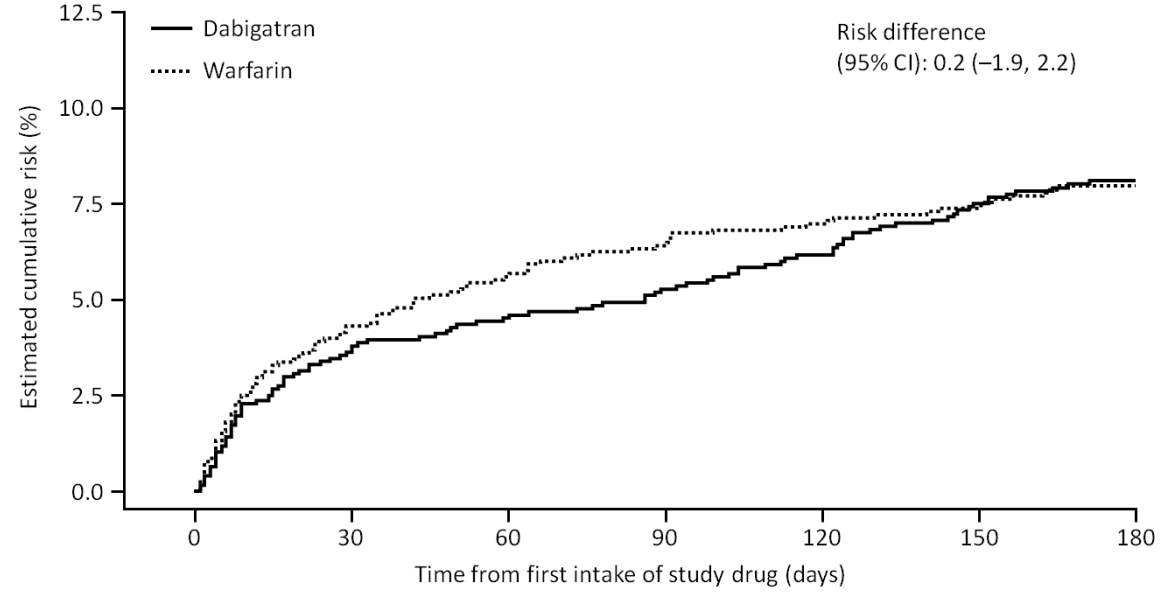
In RE-COVER II, AEs were reported for 66.6% of dabigatran and 71.1% of warfarin patients.[27] The SOC with the most frequent AEs in both treatment groups was 'gastrointestinal disorders' (22.9% and 22.8%) followed by 'infections and infestations' (19.4% vs. 20.3%).[4] There were only two SOCs where a difference between the two groups was reported. The first was 'investigations' which was reported by 11% of the warfarin group and only 7.6% of the dabigatran group.

This was largely accounted for by increased INR reported by 38 patients (3.0%) in the warfarin group and two patients (0.2%) in the dabigatran group. The second difference was in the SOC 'renal and urinary disorders' in which the warfarin group reported 91 patients (7.1%) compared with 55 patients (4.4%) from the dabigatran group. This was largely accounted for by haematuria reported by 50 (3.9%) of warfarin patients and only 16 (1.3%) of dabigatran patients.[4]

Almost all severe AEs were reported in single patients only. The exceptions were: metastatic hepatic cancer, pancreatic cancer, urinary tract infection, cellulitis, and bronchitis, which were all reported as severe in two dabigatran patients, and pneumonia which was reported as severe in five dabigatran patients. Severe sepsis was reported in two dabigatran and four warfarin patients.[4]

The cumulative risk of AEs leading to treatment discontinuation was not significantly different at 0.2 (95% CI -1.9, 2.2). Similarly the hazard ratio of dabigatran versus warfarin was 1.00 (95% CI 0.76, 1.32, Figure 21).[27]

Figure 21: Time to adverse event leading to treatment discontinuation in RE-COVER II[4]



No. at risk							
Dabigatran	1280	1199	1174	1150	1131	1107	998
Warfarin	1288	1201	1174	1152	1136	1124	980

Bleeding events

In RE-COVER, a total of 20 patients in the dabigatran group (1.6%) and 24 patients in the warfarin group (1.9%) had major bleeding events (MBEs) (hazard ratio, 0.82; 95% CI 0.45, 1.48, Table 62). Gastrointestinal and urogenital bleeding was most common in patients treated with dabigatran, while nasal bleeding was most common in the warfarin arm.

A total of 71 patients in the dabigatran group (5.6%), as compared with 111 in the warfarin group (8.8%), had major or clinically relevant non-major bleeding (hazard ratio, 0.63; 95% CI 0.47, 0.84; P = 0.002). The only type of bleeding that showed a trend to higher incidence in the dabigatran group than in the warfarin group was gastrointestinal haemorrhage (53/1274 vs. 35/1265, respectively).[1]

In RE-COVER II, MBE occurred in 15 patients treated with dabigatran and 22 patients treated with warfarin (hazard ratio 0.69; 95% CI 0.36, 1.32) and any bleeding occurred in 200 versus 285 patients, respectively (hazard ratio 0.67, 95% CI 0.56, 0.81). [27] Gastrointestinal bleeding was common in both groups, with more warfarin patients than dabigatran patients experiencing gastrointestinal bleeding (10 patients vs 6 patients, respectively). Fewer dabigatran patients had multiple bleeding events than warfarin patients.[4]

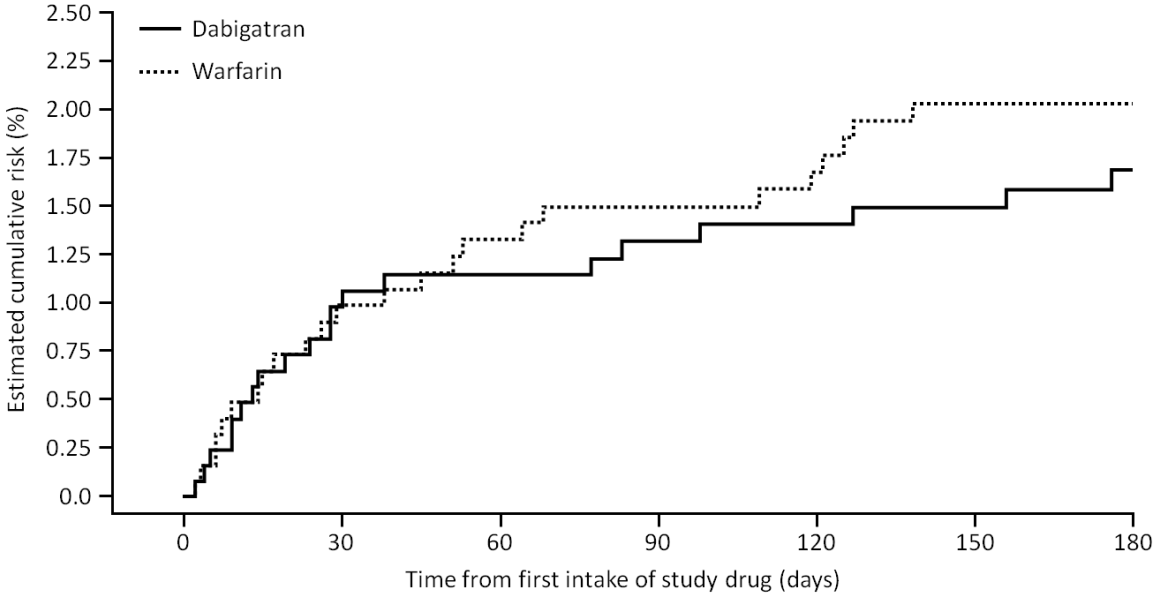
Table 62: Summary of bleeding events in RE-COVER and RE-COVER II[1;27]

Outcome	RE-COVER		RE-COVER II	
	Dabigatran n = 1,274	Warfarin n = 1,265	Dabigatran n = 1,280	Warfarin n = 1,288
MBE – n (%)	20 (1.6)	24 (1.9)	15 (1.2)	22 (1.7)
Hazard ratio (95% CI)	0.82 (0.45, 1.48)		0.69 (0.36, 1.32)	
Fatal event – no. of events	1	1	0	1
Bleeding into critical organ – no. of events	1	9	6	4
Event resulting in fall in Hb level or need for BT* – n (%)	20 (1.6)	18 (1.4)	13	19
MBE or CRBE – n (%)	71 (5.6)	111 (8.8)	64 (5.0)	102 (7.9)
Hazard ratio (95% CI)	0.63 (0.47, 0.84)		0.62 (0.45, 0.84)	
Any bleeding event – n (%)	205 (16.1)	277 (21.9)	200 (15.6)	285 (22.1)
Hazard ratio (95% CI)	0.71 (0.59, 0.85)		0.67 (0.56, 0.81)	
Site of bleeding – no. of events				
Intracranial	0	3	2	6
Intraocular	8	9	5	14
Retroperitoneal	4	1	3	1
Intraarticular/ intramuscular	8	27	9	20
GI	53	35	48	33
Urogenital	53	95	51	75
Nasal	40	107	43	76
Other	137	205	160	255

*Included in this category were patients in whom there was a reduction in haemoglobin level of at least 20 g/L or who required a transfusion of at least 2 units of whole blood or red cells.
Abbreviations: BT, blood transfusion; CRBE, clinically relevant bleeding event; GI, gastrointestinal; Hb, haemoglobin; MBE, major bleeding event.

In RE-COVER, the cumulative risk for MBEs at six months was 1.7% in the dabigatran group and 2.0% in the warfarin group (Figure 22).[28] The risk difference for dabigatran vs. warfarin was −0.4% with a 95% CI of −1.3% to 0.5%. As expected, patients with active cancer at baseline had a substantially higher cumulative bleeding risk than patients without active cancer.[28]

Figure 22: Time to first MBE in RE-COVER[28]



No. at risk							
Dabigatran	1273	1194	1153	1124	1105	1080	884
Warfarin	1266	1178	1146	1128	1110	1093	869

In RE-COVER II, the cumulative risk for MBEs at six months was 1.2% in the dabigatran group for any time during study treatment and 1.8% in the warfarin group.[27] The risk difference for dabigatran versus warfarin was −0.6% (95% CI −1.6%, 0.3%, p-value 0.1946) indicating no significant difference.[4]

Coronary events

In RE-COVER, the number of patients experiencing ACS events did not differ between the two treatment groups (p = 0.73, Table 63).[1] In RE-COVER II, the frequency of reported ACS events was less than 1%, with more cases in the dabigatran treatment group than those treated with warfarin.[27]

Table 63: ACS events in RE-COVER and RE-COVER II[1;27]

Outcome	RE-COVER		RE-COVER II	
	Dabigatran n = 1,274	Warfarin n = 1,265	Dabigatran n = 1,280	Warfarin n = 1,288
ACS – n (%)				
All	5 (0.4)	3 (0.2)	4 (0.3)	2 (0.2)
Myocardial infarction	4 (0.3)	2 (0.2)	4 (0.3)	2 (0.2)

Abbreviations: ACS, Acute coronary syndrome.

Hepatic events

LFTs were closely monitored during all trials in order to record any unusual changes, some of which may be of clinical significance.[4] In RE-COVER, abnormalities of possible clinical significance were most frequently reported for ALT (dabigatran 2.2% and warfarin 3.2%, Table 64), followed by AST (dabigatran 1.7% and warfarin 1.8%). For all four LFTs, numerically higher frequencies were noted in the warfarin group than in the dabigatran group.[28] In RE-COVER II, the most frequent possibly clinically significant abnormalities were an increase in ALT (dabigatran 2.5% and warfarin 3.2%) followed by AST (dabigatran 2.3% and warfarin 2.2%).[4]

Table 64: Patients with possibly clinically significant abnormalities for LFT parameters in RE-COVER and RE-COVER II[4;28]

Parameter	RE-COVER		RE-COVER II	
	Dabigatran n/N* (%)	Warfarin n/N* (%)	Dabigatran n/N* (%)	Warfarin n/N* (%)
ALT	26/1,204 (2.2)	38/1,198 (3.2)	31/1,238 (2.5)	40/1,248 (3.2)
AST	21/1,204 (1.7)	22/1,198 (1.8)	29/1,238 (2.3)	27/1,248 (2.2)
AP	16/1,202 (1.3)	20 (/1,197 (1.7)	8/1,238 (0.6)	6/1,248 (0.5)
Total bilirubin	7/1,204 (0.6)	13/1,198 (1.1)	13/1,238 (1.1)	19/1,248 (1.5)

*n is the number of patients with abnormalities of possible clinical significance, N is the number of patients with at least 1 post-baseline assessment of the respective parameter.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase.

Patients' ALT and AST values were further categorised by multiples of the ULN. In RE-COVER, increases above the reference range were generally infrequent and there was no difference between treatment groups. Extreme LFT values above 20 x ULN occurred only in one patient (warfarin), who had an ALT value >30 x ULN as maximum and last value on treatment (Table 65).[4]

In RE-COVER II, values ≥2 x ULN were infrequent and there was no relevant difference between treatment groups.[4] Extreme ALT values (above 30 x ULN) occurred in one patient in the warfarin group and values between 20 x and 30 x ULN also occurred in one patient in the warfarin group.[4] ALT values between 10 x and 20 x ULN only occurred in two dabigatran

patients and in three warfarin treated patients. Extreme AST values (above 30 x ULN) only occurred in one warfarin patient, there were no values between 20 x and 30 x ULN. AST values between 10 x and 20 x ULN occurred in one warfarin patient.[4]

Table 65: Abnormal LFTs in RE-COVER and RE-COVER II[1;4;27]

Parameter	RE-COVER		RE-COVER II	
	Dabigatran n/N* (%)	Warfarin n/N* (%)	Dabigatran n/N* (%)	Warfarin n/N* (%)
AST >3 x ULN	38/1,220 (3.1)	25/1,199 (2.1)	24/1,238 (1.9)	25/1,248 (2.0)
ALT >3 x ULN	42/1,220 (3.4)	46/1,199 (3.8)	30/1,238 (2.4)	43/1,248 (3.4)
ALT >3 x ULN + bilirubin >2 x ULN	2/1,055 (0.2)	4/1,106 (0.4)	1/1,238 (0.1)	2/1,248 (0.2)

*n is the number of patients with abnormalities of possible clinical significance, N is the number of patients with at least 1 post-baseline assessment of the respective parameter.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ND, no data; ULN, upper limit of normal.

Pooled RE-COVER and RE-COVER II analyses

The timing of the initiation of oral anticoagulation therapy in relation to the parenteral anticoagulant differs between warfarin and dabigatran owing to difference in their onset of action. Therefore, two safety comparisons were made: from the start of any drug (from single-dummy period) and from the start of oral drug only (double-dummy period, after warfarin had reached therapeutic levels).[27]

Regardless of the calculation, pooled data from RE-COVER and RE-COVER II consistently showed a profile of less bleeding with dabigatran than with warfarin, with the exception of major bleeding events (Table 66).[27]

Table 66: Safety outcomes in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE[27]

Outcome	Dabigatran (n = 2,553)	Warfarin (n = 2,554)
From the start of any study drug (single and double-dummy periods)		
MBEs, n (%)	37 (1.4)	51 (2.0)
Hazard ratio (95% CI)*	0.73 (0.48, 1.11)	
Intracranial bleeding	2 (0.1)	5 (0.2)
MBEs or CRBEs, n (%)	136 (5.3)	217 (8.5)
Hazard ratio (95% CI)*	0.62 (0.50, 0.76)	
Any bleeding events, n (%)	411 (16.1)	567 (22.2)
Hazard ratio (95% CI)*	0.70 (0.61, 0.79)	
From the start of the oral drug only (double dummy period only)		
MBEs, n (%)	24 (1.0)	40 (1.6)
Hazard ratio (95% CI)*	0.60 (0.36, 0.99)	
Intracranial bleeding	2 (0.1)	4 (0.2)
MBEs or CRBEs, n (%)	109 (4.4)	189 (7.7)
Hazard ratio (95% CI)*	0.56 (0.45, 0.71)	
Any bleeding events, n (%)	354 (14.4)	503 (20.4)
Hazard ratio (95% CI)*	0.67 (0.59, 0.77)	
Acute coronary syndrome, n (%)		
Any	9 (0.4)	5 (0.2)
Myocardial infarction	8 (0.3)	4 (0.2)

*The hazard ratio was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study.
Abbreviations: CRBE, clinically relevant bleeding event; MBE, major bleeding event.

Analyses were conducted for subgroups in which the underlying risks of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ. The incidence of MBE and MBE/CRBE in these subgroups is displayed in Table 67 and Table 68, respectively.

Table 67: Incidence of MBE in specific subgroups for pooled RE-COVER and RE-COVER II analyses from the start of the oral drug only (double dummy period only)[3]

	Dabigatran		Warfarin		
	Total n	Event n (%)	Total n	Event n (%)	Hazard ratio (95% CI)
Total	2456	24	2462	40	-
Symptomatic PE as index event					
No	1697	20 (1.2)	1694	32 (1.9)	0.62 (0.35, 1.08)
Yes	759	4 (0.5)	768	8 (1.0)	0.50 (0.15, 1.67)
Active cancer					
Yes	159	6 (3.8)	152	7 (4.6)	0.78 (0.26, 2.32)
History of bleedings					
Yes	117	1 (0.9)	124	4 (3.2)	0.29 (0.03, 2.61)
Geographical region					
Western Europe	588	8 (1.4)	604	8 (1.3)	1.02 (0.38, 2.71)

Abbreviations: PE, pulmonary embolism.

Table 68: Incidence of MBE or CRBE in specific subgroups for pooled RE-COVER and RE-COVER II analyses from the start of the oral drug only (double dummy period only)[3]

	Dabigatran		Warfarin		
	Total n	Event n (%)	Total n	Event n (%)	Hazard ratio (95% CI)
Symptomatic PE as index event					
No	1697	73 (4.3)	1694	134 (7.9)	0.53 (0.40, 0.70)
Yes	759	36 (4.7)	768	55 (7.2)	0.65 (0.43, 0.99)
Active cancer					
Yes	159	23 (14.5)	152	20 (13.2)	NR
History of bleedings					
Yes	117	13 (11.1)	124	17 (13.7)	NR
Geographical region					
Western Europe	588	30 (5.1)	604	57 (9.4)	NR

Abbreviations: NR, not reported; PE, pulmonary embolism.

RE-MEDY

RE-MEDY was an active-controlled trial assessing the long-term efficacy and safety of dabigatran versus warfarin for the prevention of recurrent VTE.[5] Patients enrolled in this study had previously been treated with an approved anticoagulant or had received dabigatran in one of two previous clinical trials of short-term treatment of VTE: the RE-COVER and RE-COVER II studies.[5] The required duration of initial treatment before trial

enrolment was three to 12 months for RE-MEDY, and the duration of study treatment was six to 36 months.[5]

Adverse events

The frequency of patients with treatment-emergent MBEs was lower in the dabigatran group (13 patients, 0.9%) than in the warfarin group (25 patients, 1.8%), with a hazard ratio of dabigatran vs. warfarin of 0.52 (95% CI 0.27, 1.02) and a risk difference of −1.29% (95% CI −2.20%, −0.38%). The overall incidence of treatment-emergent AEs was similar in both treatment groups.[6] During the treatment period, 72.0% of patients in the dabigatran group and 70.8% of patients in the warfarin group reported AEs (Table 69). During the post-treatment period, 11.8% of patients in the dabigatran group and 11.6% of patients in the warfarin group reported AEs.[6]

Table 69: Summary of adverse events in RE-MEDY during the treatment period[5;6]

Outcome	Dabigatran	Warfarin
Patients with any AE – n (%)	1,029 (72.0)	1,010 (70.8)
Patients with severe AEs – n (%)	143 (10.0)	151 (10.6)
Drug-related AEs* – n (%)	229 (16.0)	280 (19.6)
AEs leading to discontinuation – n (%)	145 (10.1)	126 (8.8)

* Relationship as assessed by the investigator. AE, adverse event.

The most common AEs at the SOC level were infections and infestations (dabigatran: 29.7%, warfarin: 34.4%), gastrointestinal disorders (26.3% vs. 22.2%), and musculoskeletal and connective tissue disorders (25.7% vs. 26.0%). At the preferred-term level, the most frequent events were nasopharyngitis (7.8% vs. 8.9%), pain in extremity (7.8% in both treatment groups), and headache (6.0% vs. 7.1%). AEs that were assessed by the investigator as drug-related were less frequent in the dabigatran treatment group (16.0%) than the warfarin group (19.6%). The percentage of patients who discontinued study drug due to AEs was 10.1% in the dabigatran group and 8.8% in the warfarin group. The most frequent AEs (preferred term) that led to discontinuation of study drug were DVT (0.8% vs. 1.1%) and haematuria (0.5% in both treatment groups).[6]

During the conduct of this trial, 44 patients were known to have died at any time post randomisation.[6] Of these, 12 patients (0.8%) in the dabigatran group and 18 patients (1.3%) in the warfarin group died after having the onset of the reported AE during the treatment period, while five patients (0.4%) in the dabigatran group and four patients (0.3%) in the

warfarin group had AEs with onset during the post-treatment period and subsequently died. During the post-study period, one patient (0.1%) in the dabigatran group and four patients (0.3%) in the warfarin group had AEs that were subsequently fatal. One patient died due to an AE that the investigator assessed as drug-related (warfarin group).[6]

During the treatment period, serious AEs (SAEs) (including fatal events) were reported for 15.9% of patients in the dabigatran group and 15.7% of patients in the warfarin group. SAEs that caused disability and/or incapacity occurred in 6 dabigatran patients (0.4%) and 5 warfarin patients (0.4%). The most common serious AEs (preferred term) were DVT (0.7% vs. 0.4%), PE (0.6% vs. 0.2%), chest pain (0.3% vs. 0.6%), abdominal pain (0.3% vs. 0.6%), and prostate cancer (0.3% vs. 0.5%).[6]

Bleeding events

The overall hazard ratio for time to first MBE was 0.52 (95% CI 0.27, 1.02) (Table 70). The sites of MBEs are provided in Table 71.

In both groups, two patients had bleeding at two sites. Major or clinically relevant non-major bleeding occurred in 80 patients (5.6%) in the dabigatran group and 145 patients (10.2%) in the warfarin group (hazard ratio, 0.54; 95% CI 0.41, 0.71; P<0.001). There were no significant differences in the risk of bleeding according to study treatment in predefined subgroups.[5]

Table 70: Bleeding events in RE-MEDY[5]

Outcome	Dabigatran n = 1,430	Warfarin n = 1,426
MBE, n (%)	13 (0.9)	25 (1.8)
Hazard ratio (95% CI)	0.52 (0.27, 1.02)	
MCRB, n (%)	80 (5.6)	145 (10.2)
Hazard ratio (95% CI)	0.54 (0.41, 0.71)	
Fatal event	0	1
Bleeding into critical organ	8	13
Event resulting in fall in Hb level or need for BT	9	18

Abbreviations: BT, blood transfusion; CI, confidence interval; MBE, major bleeding event; MCRB, major or clinically relevant bleeding.

Table 71: Sites of MBE in RE-MEDY according to MedDRA preferred term*[8]

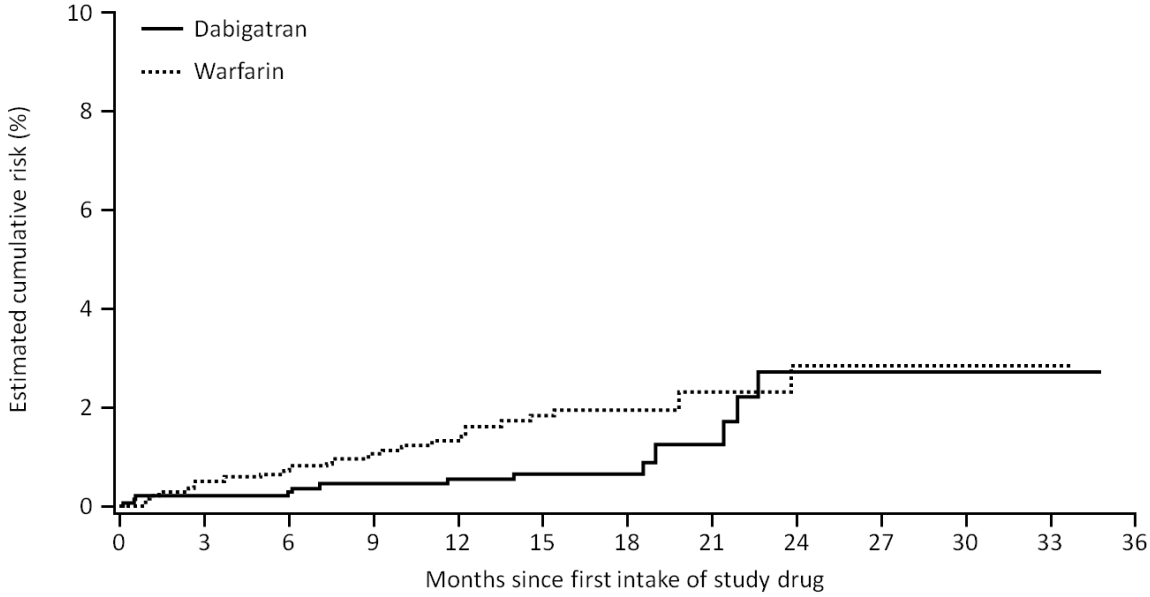
Preferred term	Dabigatran	Warfarin
Intracranial		
Cerebral	2	3
Subdural	0	1
Eye haemorrhage	4	3
Gastrointestinal haemorrhage	5	8
Peritoneal/retroperitoneal hematoma	1	2
Haemarthrosis	0	3
Muscle haematoma	0	3
Other	3	4

*MedDRA – Medical dictionary for regular activities. The MedDRA preferred terms differ in some cases from the reports from the investigators to the sponsors but are more correct since in 7 cases the investigators only described the location as "other".

The cumulative risk for MBEs at 18 months was statistically significantly lower in the dabigatran group (0.65%) than in the warfarin group (1.94%), with a risk difference of −1.29% (95% CI −2.20%, −0.38%). One fatal MBE occurred in a patient in the warfarin group.[6]

The Kaplan-Meier curves for time to the first MBE together with the numbers of patients at risk are shown in Figure 23. The curve for the dabigatran group is positioned below the curve for the warfarin group until month 18, after which the slope of the dabigatran curve increases due to several MBE events occurring between months 18 and 22. As a result, both curves converge at about 22 months.[6]

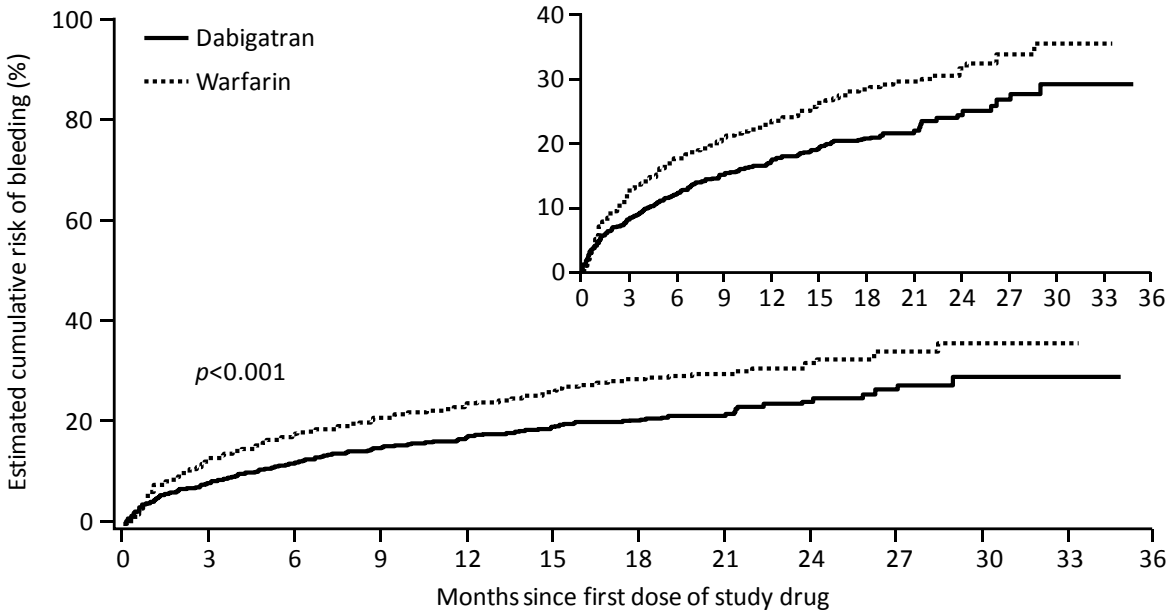
Figure 23: Time to first MBE in RE-MEDY[6]



No. at risk													
Dabigatran	1430	1344	1296	1190	1014	889	705	241	174	106	52	7	0
Warfarin	1426	1351	1303	1198	1017	885	697	234	172	103	50	6	0

All bleeding events after adjudication were reported for 277 patients in the dabigatran group (19.4%) and 373 patients in the warfarin group (26.2%). The hazard ratio for dabigatran vs warfarin was 0.71 (95% CI 0.61, 0.83), with a p-value of <0.001.[5] The cumulative risk of any bleeding is shown in Figure 24.

Figure 24: Cumulative risk of any bleeding in RE-MEDY[5]



No. at risk													
Dabigatran	1430	1241	1152	1026	854	737	575	188	130	75	36	7	0
Warfarin	1426	1192	1089	967	786	661	515	157	115	67	32	4	0

Coronary events

Of the 59 suspected ACS events during the study that triggered central adjudication, 20 were classified as 'definite' ACS events and three as 'likely' events by the ACS adjudication committee.[6] Thirteen patients in the dabigatran group (0.9%) and three patients in the warfarin group (0.2%) were reported with ACS events during the on-treatment period that were adjudicated as definite events, with a hazard ratio for dabigatran vs warfarin of 4.35 (95% CI 1.24, 15.27, Table 72). The most common definite ACS event during treatment was myocardial infarction, with nine events in the dabigatran group and one event in the warfarin group.[5]

Table 72: ACS events occurring during the treatment period [5;6]

Outcome	Dabigatran n = 1,430	Warfarin n = 1,426
ACS		
During treatment – n (%)	13 (0.9)	3 (0.2)
Post-treatment – n	1	5
Cardiac death – n	0	0
Myocardial infarction – n	9	1
Ischaemia/unstable angina – n	3	1

*Includes events that occurred from the day after last intake of study drug until trial termination.
Abbreviations: ACS, acute coronary syndrome.

During the post-treatment period (starting on the day after last intake of study drug), one patient in the dabigatran group and five patients in the warfarin group were reported with ACS events adjudicated as definite, while no likely events occurred. No events were reported for the post-study period (starting on the day after study completion).[6] Of the definite post-treatment events, myocardial infarction was reported for one dabigatran patient (onset of the event was one day after last intake of study drug) and three warfarin patients (all events started more than 14 days after last intake of study drug). Definite ischaemia/unstable angina during the post-treatment period was reported for two patients (both in the warfarin group); the two events started six days and 18 days after last intake of study drug, respectively.[6]

There was a statistically significant difference in the risk of definite ACS events during the on-treatment period, with a hazard ratio of dabigatran/warfarin of 4.35 (95% CI 1.24, 15.27) and a p-value of 0.0217. For the entire study period, there were numerically more patients with definite ACS events in the dabigatran group (13 patients) than in the warfarin group (7 patients), however this difference was not statistically significant, with a hazard ratio for dabigatran vs warfarin of 1.83 (95% CI 0.73, 4.59) and a p-value of 0.1975.[6]

There was a greater baseline prevalence of cardiac risk factors in the dabigatran treatment group than in the warfarin treatment group, with a history of coronary artery disease reported for 8.4% vs. 6.1% of patients, heart failure for 4.0% vs. 2.9% of patients, hypertension for 40.7% vs. 36.5% of patients, and diabetes mellitus for 10.5% vs. 7.6% of patients, respectively.[6]

Hepatic events

Abnormalities of possible clinical significance were most frequently reported for ALT, followed by AST (Table 73). No relevant differences in the frequencies between both treatment groups were observed for any of the four LFTs.[6]

Table 73: Patients with LFT increases of possible clinical significance during treatment in RE-MEDY[6]

Parameter	Dabigatran n/N* (%)	Warfarin n/N* (%)
ALT	26/1,411 (1.8)	30/1,402 (2.1)
AST	23/1,411 (1.6)	23/1,402 (1.6)
AP	9/1,411 (0.6)	14/1,401 (1.0)
Total bilirubin	9/1,411 (0.6)	8/1,402 (0.6)

* n is the number of patients with abnormalities of possible clinical significance, N is the number of patients with at least 1 post-baseline assessment of the respective parameter.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase.

LFT values were further categorised by multiples of the ULN at any point during the study. Increases above the reference range were generally infrequent and there was no relevant difference between treatment groups. Extreme LFT values (above 20 x ULN) occurred only in one patient (dabigatran group).

Table 74: Abnormal LFTs in RE-MEDY[5;6]

Parameter	Dabigatran n (%)	Warfarin n (%)
AST >3 x ULN	15 (1.0)	18 (1.3)
ALT >3 x ULN	24 (1.7)	26 (1.8)
ALT >3 x ULN + total bilirubin >2 x ULN	2 (0.1)	1 (0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

The comparison of the number of patients with an elevation of ALT (or AST) of >3 x ULN did not reveal any treatment difference of statistical significance. Consistent with this, the analysis of the time to the first elevation of ALT (or AST) of >3 x ULN revealed no marked differences between treatment groups.[6]

RE-SONATE

One placebo-controlled study, RE-SONATE, primarily investigating the efficacy of dabigatran was conducted. RE-SONATE was a superiority study which tested the efficacy of dabigatran,

compared to placebo, in the long-term prevention of VTE, and therefore provides data on the long-term safety of dabigatran.[5]

Safety endpoints used in RE-SONATE were:[5]

- Adverse events
- Bleeding events
- Cardiovascular events
- Hepatic events

The intensity of an AE was judged as 'mild' (i.e., awareness of sign(s) or symptom(s) which is/are easily tolerated), 'moderate' (enough discomfort to cause interference with usual activity), or 'severe' (incapacitating or causing inability to work or to perform usual activities).[7]

Adverse events

The overall incidence of treatment-emergent AEs (which included bleeding events and efficacy outcome events) was comparable on dabigatran and on placebo.[7] In the dabigatran group, AEs were reported for 50.6% of patients compared with 49.2% of patients in the placebo group (Table 75).[5]

Table 75: Summary of adverse events in RE-SONATE [5]

Outcome	Dabigatran n = 681	Placebo n = 662
Patients with any AE – n (%)	346 (50.6)	324 (49.2)
Patients with serious AEs – n (%)	47 (6.9)	60 (9.1)
AEs leading to discontinuation – n (%)	50 (7.3)	81 (12.3)

Abbreviations: AE, adverse event.

The most frequently reported AEs for patients in the dabigatran treatment group were gastrointestinal disorders, which were reported by 16.5% of dabigatran patients.[7] Gastrointestinal disorders were less frequent for placebo patients (8.8%). Gastrointestinal AEs with the most marked difference in incidence between groups (i.e., >1%) were dyspepsia and rectal haemorrhage, which were more frequent for dabigatran patients than for placebo patients (dyspepsia: 4.1% for dabigatran vs. 1.2% for placebo; rectal haemorrhage 2.2% vs. 0.3%).[7] The most frequent AEs for patients in the placebo group were infections and infestations (13.2%). The incidence of such events was similar for dabigatran patients

(12.0%). Vascular disorders were less frequently reported by patients on dabigatran (6.4%) than by patients on placebo (11.5%). The difference in incidence was predominantly due to the higher incidence of DVT for patients treated with placebo (5.2%) compared with patients treated with dabigatran (0.4%).[7]

The overall incidences of AEs that led to discontinuation of study medication were lower for patients in the dabigatran treatment group (7.3%) than for patients in the placebo treatment group (12.3%). Similarly, the incidence of SAEs during the treatment period was lower for patients treated with dabigatran (6.9%) than for patients treated with placebo (9.1%).[5] The difference between treatment groups was predominantly due to the lower incidences of DVT and PE leading to discontinuation for patients treated with dabigatran (0.4% and 0.1%, respectively) compared with patients treated with placebo (4.9% and 2.9%, respectively) since, as per protocol, study medication was to be discontinued in cases of locally diagnosed symptomatic recurrent VTEs.[7]

Other than vascular disorders (which included DVT) and respiratory disorders (which included PE), described above, only gastrointestinal disorders leading to discontinuation were reported by ≥1% of patients in either treatment group (dabigatran: 2.8%; placebo: 1.7%).[7]

The most frequently reported SAEs according to SOC were respiratory, thoracic and mediastinal disorders (dabigatran: 1.0%; placebo: 3.5%) and vascular disorders (dabigatran: 0.4%; placebo: 2.6%). In total, SAEs during the treatment period that were considered to be drug-related were reported by two dabigatran patients (a total of four events) and four placebo patients (a total of five events). There were three SAEs with fatal outcomes (one dabigatran; two placebo) with an onset during the treatment period, and there were 12 deaths presumably as a result of AEs with an onset in the post-treatment period (five dabigatran; seven placebo).[7]

Bleeding events

Bleeding events were classified according to three categories as major, clinically relevant, or trivial bleeding events. All bleeding events were adjudicated centrally by an independent committee that was blinded with regard to the treatment allocation of patients.[7] The definitions of MBE and CRBE were consistent with the definitions used in the previous active-controlled trials: RE-COVER, RE-COVER II and RE-MEDY.[8]

There were two patients with major bleeding events, both in the dabigatran group; both events were gastrointestinal bleeding requiring at least two units of blood, but without a fall in the haemoglobin level of 20 g/L or more.[5] The hazard ratio and 95% CI could not be calculated using the Cox proportional hazard model since there were no events on placebo. The Clopper-Pearson method was therefore used (Table 76).[7]

Table 76: Analysis of time to first occurrence of MBE during the treatment period[7;8]

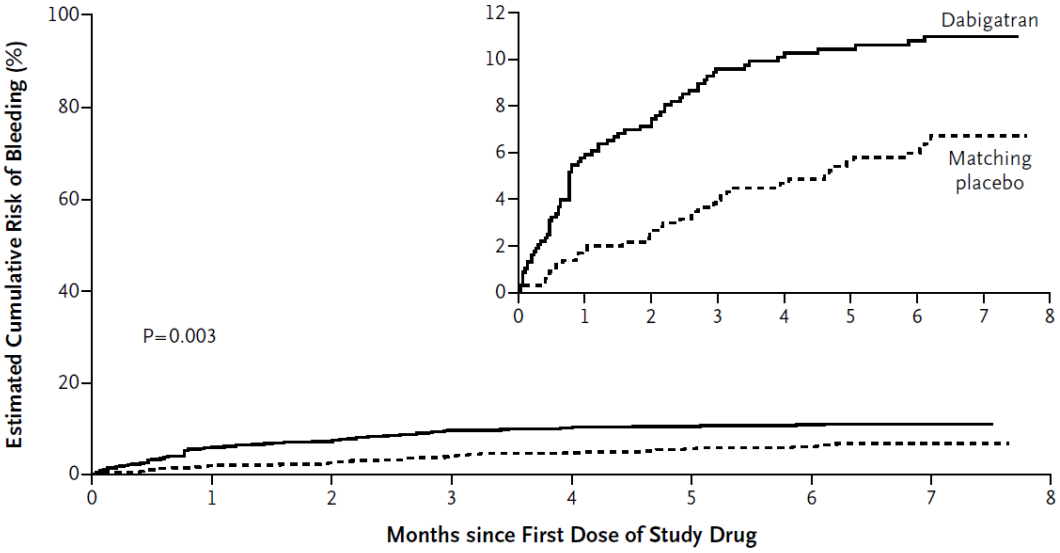
Parameter	Dabigatran n = 684	Placebo n = 659
MBE – n (%)	2 (0.3)	0 (0.0)
Clopper-Pearson/Fisher's exact test		
95% CI	0.04, 1.05	0.00,0.56
p-value	0.4998	
MCRB – n (%)	36 (5.3)	13 (2.0)
Hazard ratio (95% CI)	2.69 (1.43, 5.07)	

Abbreviations: CI, confidence interval; MBE, major bleeding event; MCRB, major or clinically relevant non major bleeding

Major or clinically relevant non major bleeding occurred in 36 patients (5.3%) in the dabigatran group as compared with 12 patients (1.8%) in the placebo group (hazard ratio, 2.92; 95% CI 1.52, 5.60; p = 0.001). [5] In two patients (both in the dabigatran group), the CRBEs led to transfusion of more than two units of packed cells or whole blood.[7]

The Kaplan-Meier curves for the time to any bleeding in the dabigatran and placebo groups diverge immediately after the start of treatment (Figure 1) with the difference between the two groups was maintained until the end of the 180-day treatment period.[7]

Figure 25: Risk of any bleeding in RE-SONATE [5]



No. at Risk								
Dabigatran	684	629	609	579	527	522	489	6
Matching placebo	659	626	598	572	522	508	474	4

The distribution of CRBEs by bleeding sites was comparable within the two groups; but, consistent with the higher incidence of CRBEs overall on active treatment, the incidences were generally higher for the dabigatran group than for the placebo group (Table 77). The most frequently reported CRBEs were rectal bleeds for patients on dabigatran (1.9%). On placebo, the most common bleeding sites were urogenital (0.5%).[7] Rectal bleeding occurred in 19 patients (2.8%) in the dabigatran group and in five patients (0.8%) in the placebo group, whereas the incidence of bleeding at other sites was similar in the two groups.[5]

Table 77: CRBEs during the treatment period in RE-SONATE[7]

Bleeding site	Dabigatran n = 684 n (%)	Placebo n = 659 n (%)
Rectal	13 (1.9)	2 (0.3)
Urogenital	5 (0.7)	3 (0.5)
Gastrointestinal	5 (0.7)	2 (0.3)
Nasal	4 (0.6)	2 (0.3)
Pulmonary	3 (0.4)	2 (0.3)
Gingival	2 (0.3)	0 (0.0)
Uterus	2 (0.3)	1 (0.2)
Skin	2 (0.3)	1 (0.2)
Intramuscular	1 (0.1)	0 (0.0)

The incidence of any bleeding event, which included MBEs, CRBEs and trivial bleeding events, was higher for the active treatment group (dabigatran: 10.5%) than for the placebo treatment group (5.9%). The hazard ratio for time to the first occurrence of any bleeding event was 1.82 (standard error 0.36), indicating an almost two-fold higher risk of an event for patients treated with dabigatran compared with placebo (95% CI 1.23, 2.68; p=0.0027).[7]

Only a small percentage of bleeding events led to discontinuation of study treatment (dabigatran: 1.6%; placebo: 0.6%). [7]

Cardiovascular events

The overall incidence of cardiovascular events during the treatment period was low and comparable for the dabigatran and placebo treatment groups (Table 78). In the dabigatran group, 0.4% of patients had cardiovascular events compared with 0.3% of the placebo-treated patients. One patient in each treatment group had a myocardial infarction (dabigatran: one ST−segment elevation myocardial infarction; placebo: one non ST−segment elevation myocardial infarction), two dabigatran patients had a transient ischaemic attack, and one placebo patient had an ischaemic stroke.[7] There was one ACS event in each group. [5]

Cardiac disorders as reported by investigators (i.e. unadjudicated data) were reported for 1.6% of dabigatran patients and 2.1% of placebo patients. The only event reported by more than two patients in either treatment group by Medical Dictionary for Regular Activities (MedDRA) preferred term was palpitations (0.1% of dabigatran patients; 0.9% of placebo patients).[7]

Table 78: Summary of cardiovascular events during the treatment period[7]

Parameter	Dabigatran n = 684	Placebo n = 659
Patients with CV events – n (%) [number of events]	3 (0.4)	2 (0.3)
NSTEMI	0 (0.0)	1 (0.2)
STEMI	1 (0.1)	0 (0.0)
UA	0 (0.0)	0 (0.0)
TIA	2 (0.3)	0 (0.0)
Ischaemic stroke	0 (0.0)	1 (0.2)
Non-CNS systemic embolism	0 (0.0)	0 (0.0)

Abbreviations: CV, cardiovascular; CNS, central nervous system; NSTEMI: non ST−segment elevation myocardial infarction; STEMI: ST−segment elevation myocardial infarction; UA: unstable angina; TIA: transient ischaemic attack.

Hepatic events

The parameters included in the LFTs were measured at the central laboratory as follows:[7]

- ALT
- AST
- AP
- Bilirubin
- Indirect bilirubin (only if total bilirubin was >1.5 x ULN)

There were no marked differences between the patients treated with dabigatran and those treated with placebo with regard to the incidence of elevated LFT values on treatment (Table 79). For the dabigatran group, the overwhelming majority of patients (95.0%) had no ALT value >2 x ULN during the trial. This was almost identical to the incidence for patients in the placebo group (94.8%). No placebo patient had an ALT value >10 x ULN during the trial.[7]

Table 79: Cumulative incidence of patients categorised by reference range multiples of ALT during the treatment period[7]

Parameter	Dabigatran n = 684 n (%)	Placebo n = 659* n (%)
ALT		
≤ 2 x ULN	650 (95.0)	625 (98.9)
> 2 x ULN	14 (2.0)	5 (0.8)
> 3 x ULN	4 (0.6)	0 (0.0)
AST		
≤ 2 x ULN	657 (96.1)	630 (95.7)
> 2 x ULN	7 (1.0)	6 (0.9)
> 3 x ULN	2 (0.3)	2 (0.3)
Total bilirubin		
≤ 2 x ULN	664 (97.1)	634 (96.5)
> 2 x ULN	1 (0.1)	1 (0.2)
> 3 x ULN	0 (0.0)	0 (0.0)

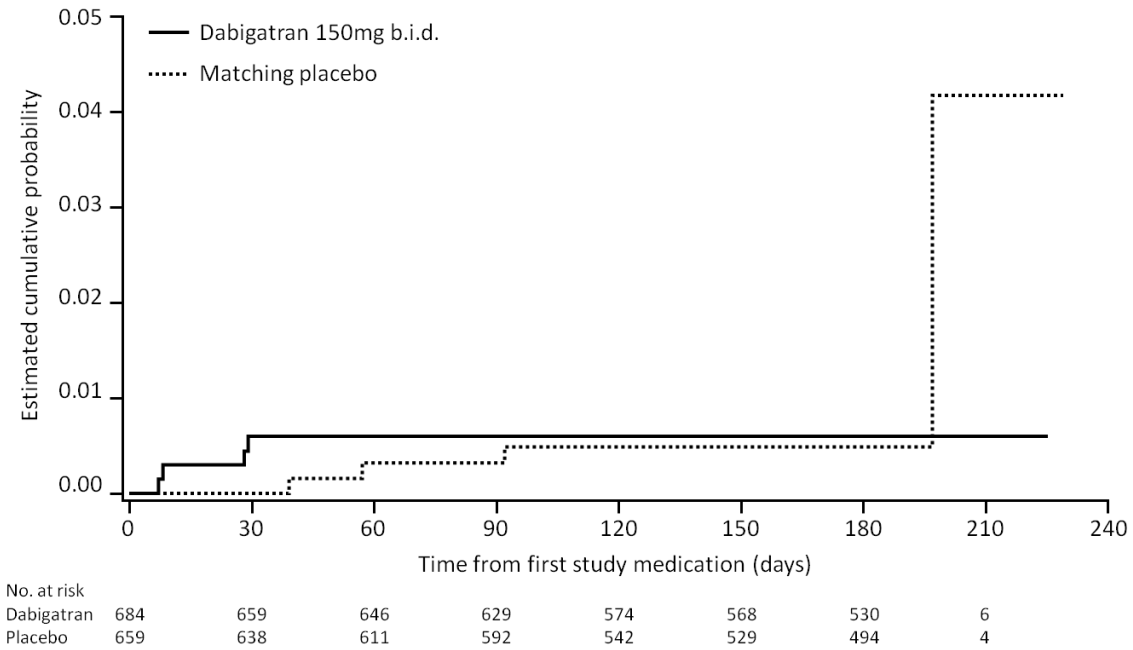
*n = 658 for AST measurements.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

The findings for AST and bilirubin were comparable with those described for ALT, with 96.1% of dabigatran patients and 95.7% of placebo patients having no AST value >2 x ULN at any point during the trial, and 97.1% of dabigatran patients and 96.5% of placebo patients having

no bilirubin value >2 x ULN at any point during the trial. One patient on dabigatran had an ALT value >10 x ULN during the treatment period..[7]For patients who experienced raised ALT levels, 50% of dabigatran patients with a value >3 x ULN had returned to a value <2 x ULN within 30 days compared with 180 days for the placebo group.[7]

Kaplan-Meier estimates of the time to first occurrence of an ALT value >3 x ULN, showed no clinically significant difference between the dabigatran and placebo treatment groups (Figure 26). There were also no significant differences established in the Kaplan-Meier plots of the time to first occurrence of AST value >3 x ULN, or bilirubin >2 x ULN. [7]

Figure 26: Kaplan-Meier estimate of time to first occurrence of ALT > 3 x ULN during the treatment period[7]



Clinical benefit of overall safety results

The incidence of all categories of major bleeding events (consisting of MBEs, adjudicated MBEs with a fatal outcome, major bleeding, and intracranial MBEs) as well as life-threatening bleeding events, MBEs and CRBEs, and any bleeding events (MBEs, CRBEs, and nuisance/trivial bleeding) were lower for dabigatran patients compared to warfarin for both studies of short (6 months in RE-COVER and RE-COVER II) and longer duration (up to 36 months in RE-MEDY). Based on the study results one would expect a reduction of 1.5 events less (MBE) per 100 patient-years of treatment with dabigatran vs. warfarin in patients treated for (acute) VTE, and 0.6 events less (MBE) per 100 patient-years in patients treated

for secondary VTE prevention, and a reduction of 7.7 events less (MBE and CRBE) per 100 patient-years of treatment with dabigatran vs. warfarin in patients treated for (acute) VTE, and 3.8 events less (MBE and CRBE) per 100 patient-years in patients treated for secondary VTE prevention. These bleeding reductions are clinically meaningful, as warfarin therapy is often stopped due to bleeding risks outweighing the risk of recurrent events.

Further analyses were conducted to ascertain the effect of cTTR on the bleeding results (MBE, MBE and CRBE). For both the RE-COVER/RE-COVER II and the RE-MEDY studies, no obvious clear pattern could be observed between the bleeding risk and cTTR quintiles (Table 80 and Table 81 for the MBE analysis and Table 82 and Table 83 for MBE and CRBE). Therefore, it shows that the advantage over warfarin in terms of bleeding does not appear to diminish when compared to warfarin-treated patients who are managed reasonably well.

Table 80: Cox regression factor centre (INR control) for centrally adjudicated MBE for RE-COVER and RE-COVER II

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<47.12	Patients	494 (100)	516 (100)
	MBEs	6 (1.21)	14 (2.71)
	Hazard ratio vs. warfarin (95% CI)	0.438 (0.168, 1.140)	
	Superiority p-value	0.0908	
47.12 - <57.72	Patients	443 (100)	463 (100)
	MBEs	2 (0.45)	5 (1.08)
	Hazard ratio vs. warfarin (95% CI)	0.415 (0.081, 2.140)	
	Superiority p-value	0.2934	
57.72 - <61.91	Patients	535 (100)	517 (100)
	MBEs	5 (0.93)	9 (1.74)
	Hazard ratio vs. warfarin (95% CI)	0.539 (0.181, 1.610)	
	Superiority p-value	0.2684	
61.91 - <67.98	Patients	461 (100)	472 (100)
	MBEs	4 (0.87)	6 (1.27)
	Hazard ratio vs. warfarin (95% CI)	0.682 (0.193, 2.418)	
	Superiority p-value	0.5539	
≥67.98	Patients	476 (100)	492 (100)
	MBEs	7 (1.47)	6 (1.22)
	Hazard ratio vs. warfarin (95% CI)	1.218 (0.409, 3.624)	
	Superiority p-value	0.7231	

Table 81: Cox regression factor centre (INR control) for centrally adjudicated MBE for RE-MEDY

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<49.26	Patients	264 (100)	298 (100)
	MBES	1 (0.38)	8 (2.68)
	Hazard ratio vs. warfarin (95% CI)	0.133 (0.017, 1.063)	
	Superiority p-value	0.0571	
49.26 - <59.28	Patients	284 (100)	291 (100)
	MBEs	3 (1.06)	3 (1.03)
	Hazard ratio vs. warfarin (95% CI)	0.987 (0.199, 4.891)	
	Superiority p-value	0.9872	
59.28 - <66.98	Patients	268 (100)	288 (100)
	MBEs	3 (1.12)	7 (2.43)
	Hazard ratio vs. warfarin (95% CI)	0.443 (0.114, 1.712)	
	Superiority p-value	0.2377	
66.98 - <73.06	Patients	283 (100)	276 (100)
	MBEs	1 (0.35)	4 (1.45)
	Hazard ratio vs. warfarin (95% CI)	0.258 (0.029, 2.306)	
	Superiority p-value	0.2254	
≥73.06	Patients	289 (100)	272 (100)
	MBEs	4 (1.38)	3 (1.10)
	Hazard ratio vs. warfarin (95% CI)	1.353 (0.303, 6.047)	
	Superiority p-value	0.6922	

Table 82: Cox regression with factor centre (INR control) for centrally adjudicated MBE or CRBE for RE-COVER and RE-COVER II

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<47.12	Patients	494 (100)	516 (100)
	MBE or CRBEs	17 (3.44)	57 (11.05)
	Hazard ratio vs. warfarin (95% CI)	0.291 (0.169, 0.500)	
	Superiority p-value	<0.0001	
47.12 - <57.72	Patients	443 (100)	463 (100)
	MBE or CRBEs	16 (3.61)	30 (6.48)
	Hazard ratio vs. warfarin (95% CI)	0.543 (0.269, 0.996)	
	Superiority p-value	0.0484	
57.72 - <61.91	Patients	535 (100)	517 (100)
	MBE or CRBEs	22 (4.11)	32 (6.19)
	Hazard ratio vs. warfarin (95% CI)	0.661 (0.384, 1.138)	
	Superiority p-value	0.1355	
61.91 - <67.98	Patients	461 (100)	472 (100)
	MBE or CRBEs	23 (4.99)	37 (7.84)
	Hazard ratio vs. warfarin (95% CI)	0.623 (0.370, 1.048)	
	Superiority p-value	0.0746	
≥67.98	Patients	476 (100)	492 (100)
	MBE or CRBEs	31 (6.51)	33 (6.71)
	Hazard ratio vs. warfarin (95% CI)	0.977 (0.598, 1.595)	
	Superiority p-value	0.9248	

Table 83: Cox regression with factor centre (INR control) for centrally adjudicated MBE or CRBE for RE-MEDY

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<49.26	Patients	264 (100)	298 (100)
	MBE or CRBEs	11 (4.17)	29 (9.73)
	Hazard ratio vs. warfarin (95% CI)	0.402 (0.201, 0.805)	
	Superiority p-value	0.0101	
49.26 - <59.28	Patients	284 (100)	291 (100)
	MBE or CRBEs	11 (3.87)	29 (9.97)
	Hazard ratio vs. warfarin (95% CI)	0.366 (0.183, 0.733)	
	Superiority p-value	0.0046	
59.28 - <66.98	Patients	268 (100)	288 (100)
	MBE or CRBEs	16 (5.97)	33 (11.46)
	Hazard ratio vs. warfarin (95% CI)	0.503 (0.277, 0.914)	
	Superiority p-value	0.0241	
66.98 - <73.06	Patients	283 (100)	276 (100)
	MBE or CRBEs	20 (7.07)	26 (9.42)
	Hazard ratio vs. warfarin (95% CI)	0.778 (0.434, 1.394)	
	Superiority p-value	0.3984	
≥73.06	Patients	289 (100)	272 (100)
	MBE or CRBEs	19 (6.57)	28 (10.29)
	Hazard ratio vs. warfarin (95% CI)	0.668 (0.373, 1.197)	
	Superiority p-value	0.1753	

Conclusion

Dabigatran is well tolerated for the treatment and secondary prevention of DVT and PE, and is associated with significantly fewer bleeding events than warfarin in phase III studies. For MBE and CRBE, the bleeding risk is significantly lower for dabigatran compared to warfarin in all three active comparator trials.[1;5;27] In the pooled analysis of RE-COVER and RE-COVER II, the risks for all bleeding categories are significantly lower for dabigatran compared with warfarin in the double dummy counting scenario.[27]

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

Dabigatran has a good safety profile in this indication, and is associated with a low rate of adverse events.

Bleeding outcomes

In RE-COVER, the rates of bleeding with dabigatran 150 mg BD were similar to or lower than those with adjusted-dose warfarin. Risk of major bleeding events were similar in both treatment groups (1.6% vs 1.9%; HR 0.82; 95% CI 0.45, 1.48). Risk of major or clinically relevant bleeding events (5.6% vs 8.8%; HR 0.63; 95% CI 0.47, 0.84) and risk of any bleeding (16.3% vs 22.1%; HR 0.71; 95% CI 0.59, 0.85) were significantly lower in the dabigatran group.

In RE-COVER II, numerically fewer patients in the dabigatran group than in the warfarin group had major bleeding events during the treatment period (1.2% vs 1.7%; HR 0.69; 95% CI 0.36, 1.32). Risk of major or clinically relevant bleeding events (5.0% vs 7.9%; HR 0.62; 95% CI 0.45, 0.84) and risk of any bleeding (15.6% vs 22.1%; HR 0.67; 95% CI 0.56, 0.81) were significantly lower in the dabigatran group.

Pooled analysis of RE-COVER and RE-COVER II showed that the dabigatran group reported significantly fewer bleeding events in all categories than in the warfarin group: major bleeding events (1.0% vs. 1.6%; HR 0.60; 95% CI 0.36, 0.99, note; when taking account of the oral treatment period only), clinically relevant bleeding events (4.4% vs 7.7%; HR 0.56; 95% CI 0.45, 0.71), and any bleeding events (14.4% vs 20.4%; HR0.67; 95% CI 0.59, 0.77). Similarly, in RE-MEDY, rates of any bleeding (19.4% vs 26.2%; HR 0.71; 95% CI 0.61, 0.83) and major or clinically relevant bleeding (5.6% vs 10.2%; HR 0.55; 95% CI 0.41, 0.72) were significantly lower in the dabigatran group than in the warfarin group.

In RE-MEDY, the frequency of major bleeding events during the treatment period was numerically lower for the dabigatran group than for the warfarin group (0.9% vs 1.8%; HR 0.54; 95% CI 0.25, 1.16). Rates of any bleeding (19.4% vs 26.2%; HR 0.71; 95% CI 0.61, 0.83) and major or clinically relevant bleeding (5.6% vs 10.2%; HR 0.55; 95% CI 0.41, 0.72) were significantly lower in the dabigatran group than in the warfarin group.

In RE-SONATE, major bleeding events were reported for only 2 patients (0.3%) on dabigatran and none on placebo. There were significantly more major bleeding and clinically relevant bleeding events in the dabigatran group than in the placebo group (5.3% vs 1.8%; HR 2.92; 95% CI 1.52, 5.60). There were more incidences of any bleeding event in the dabigatran group compared with patients in the placebo group (10.5% vs 5.9%; HR 1.82; 95% CI 1.23, 2.68).

Cardiac adverse events

The overall incidence of acute MI in the dabigatran trials for treatment and secondary prevention of DVT and PE was low (≤1%). However, there were numerically more MIs reported in the dabigatran group than in the warfarin treatment group in the warfarin-controlled studies. When viewed within the context of overall CV morbidity and mortality, there were fewer strokes and fewer or similar numbers of all-cause deaths and CV deaths in the dabigatran treatment groups compared with warfarin treatment groups. Furthermore, there were consistently lower rates of bleeding in dabigatran treated patients, compared with those receiving warfarin.

In RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE, the adjudication of ACS events was pre-specified. In these studies, potential ACS events (investigator-reported events of unstable angina, MI, and cardiac death) were adjudicated by a committee that was blinded to individual treatment allocations. In the treatment and prevention of DVT and PE studies, there appear to be fewer ACS events in the warfarin arm compared to with the dabigatran arms. Nevertheless, the overall number of events was small and the incidence was low.

Hepatic safety

In the pooled analysis, there was no evidence of hepatotoxicity with dabigatran 150 mg BD The number of patients with abnormal liver functions tests was comparable across treatment groups.

Clinical benefit of overall safety results

In addition to comparable efficacy to warfarin, the incidence of all categories of major bleeding events was lower for dabigatran patients compared to warfarin for both studies of short (6 months in RE-COVER and RE-COVER II) and longer duration (up to 36 months in RE-MEDY). Based on the study results, one would expect a reduction of 1.5 fewer major bleeding events in 100 patient-years of treatment with dabigatran vs warfarin in patients treated for acute VTE, and 0.6 fewer major bleeding events in 100 patient-years in patients treated for secondary prevention of VTE. To better represent clinical settings, adding clinically relevant bleeding events to major bleeding events demonstrates a reduction of 7.7 fewer events (MBEs and CRBEs) in 100 patient-years of treatment with dabigatran vs warfarin in patients treated for acute VTE, and 3.8 fewer events (MBEs and CRBEs) in 100 patient-years in patients treated for the secondary prevention of VTE. These bleeding

reductions are clinically meaningful, as warfarin therapy is often stopped due to bleeding risks outweighing the risk of recurrent events.

In order to put the rate of ACS events into a broader perspective, a composite net clinical benefit endpoint was applied. The composite endpoint of non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause deaths and major bleeding events was very similar between dabigatran and warfarin for both the pooled RE-COVER and RE-COVER II studies as well as for RE-MEDY, with hazard ratios of 1.02 (95% CI 0.81, 1.27) and 1.05 (95% CI 0.75, 1.46) respectively (Table 84 and Table 86 respectively). Furthermore, when both major bleeding events and clinically relevant non major bleeding events were included into this analysis, a statistically significant benefit for dabigatran over warfarin was shown for both the pooled RE-COVER and RE-COVER II studies as well as for RE-MEDY, with hazard ratios of 0.80 (95% CI 0.68, 0.95) and 0.73 (95% CI 0.59, 0.91) respectively (Table 85 and Table 87).

6.10 Interpretation of clinical evidence

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

In summary, four phase III clinical trials have been conducted to support the regulatory submission for dabigatran in this indication: RE-COVER, RE-COVER II, RE-SONATE, and RE-MEDY. The clinical efficacy and safety outcomes in these trials were the following:

RE-COVER and RE-COVER II

- Dabigatran demonstrated non-inferiority vs. adjusted-dose warfarin in terms of prevention of recurrent VTE and VTE-related mortality. In pooled analysis, the hazard ratio for dabigatran vs. warfarin for this composite endpoint was 1.09 (95% CI 0.77-1.54).
- There was no statistically significant difference between dabigatran and warfarin in the rate of any of the secondary endpoints in these studies (i.e. composite of recurrent symptomatic VTE and all deaths; symptomatic DVT; symptomatic non-fatal PE; death related to VTE; and all deaths).

- Pooled analysis of RE-COVER and RE-COVER II showed that the Pradaxa® group reported significantly fewer bleeding events in all categories than the warfarin group: major bleeding events (1.0% *vs* 1.6%; HR 0.60; 95% CI 0.36-0.99), clinically relevant bleeding events (4.4% vs. 7.7%; HR 0.56; 95% CI 0.45-0.71) and any bleeding events (14.4% *vs* 20.4%; HR 0.67; 95% CI 0.59-0.77).
- There was no evidence of hepatotoxicity with dabigatran, in the incidence of acute coronary syndrome did not differ significantly between treatment groups.
- Both dabigatran and warfarin appeared to be safe and well tolerated in this population; the overall incidence of treatment-emergent reported AEs were similar in the two treatment groups.

RE-MEDY

- Dabigatran was non-inferior to well-controlled warfarin for the long-term treatment and secondary prevention of symptomatic VTE following initial anticoagulant treatment for 3 to 12 months after an index VTE event.
- No statistically significant between-treatment differences were found for the primary endpoint (recurrent VTE or VTE-related death) or any of the secondary endpoints, which included a composite of recurrent symptomatic VTE and all deaths.
- Dabigatran and warfarin were well tolerated. There were significantly fewer occurrences of any bleeding events (19.4% vs. 26.2%; HR 0.71; 95% CI 0.61-0.83), and major or clinically relevant bleeding events (5.6% vs. 10.2%; HR 0.55; 95% CI 0.41-0.72) in the dabigatran group than in the warfarin group. There were numerically fewer major bleeding events in the dabigatran group compared with the warfarin group. More ACS events were reported for dabigatran than for warfarin, however this difference was not statistically significant, with a hazard ratio for dabigatran vs. warfarin of 1.83 (95% CI 0.73, 4.59) and a p-value of 0.1975.

RE-SONATE

- Dabigatran was superior to placebo for the prevention of recurrent symptomatic VTE events including unexplained deaths, with a risk reduction of 92%.
- There were few major bleeding events in either treatment group. Dabigatran resulted in 2 to 3 times as many clinically relevant bleeding events and any bleeding events compared to placebo.
- The safety profile for dabigatran was consistent with the results from other clinical trials. There were fewer severe adverse events and fewer discontinuations due to

adverse events on dabigatran compared with placebo. Furthermore, there was no difference in the number of ACS events reported in the two arms of the study.

Comparison with key competitor products

An adjusted indirect comparison between rivaroxaban and dabigatran for the treatment of acute VTE, did not show superiority of either drug over the other for recurrent VTE, major bleeding or all-cause mortality.[33]

Therefore, it can be concluded that dabigatran offers significant and clinically meaningful benefits without any significant safety concerns.

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

The RCTs that provide the pivotal evidence for dabigatran in the treatment of acute DVT and PE and long-term prevention of recurrent VTE consisted of three active-controlled trials (RE-COVER, RE-COVER II and RE-MEDY) and one placebo-controlled trial (RE-SONATE). All four trials were well designed and adequately powered to detect differences between the treatment arms. Blinding was carried out appropriately using double-dummy concealment, and baseline patient characteristics were well balanced between treatment groups in all trials (Table 27 and Table 28).

The three warfarin-controlled trials compared dabigatran to adjusted-dose warfarin, a VKA. VKAs have been the mainstay of treatment and secondary prevention of VTE for many years, and are recognised by international guidelines as the current standard of care. Warfarin sodium is the most frequently used VKA in the United Kingdom[19;49] and is therefore an appropriate comparator to use for dabigatran in this indication.

These three pivotal studies investigating dabigatran in acute VTE treatment (RE-COVER and RE-COVER II) and in secondary prevention of VTE (RE-MEDY) clearly met the pre-defined non inferiority margins with regard to recurrent VTE for both hazard ratios and risk differences, demonstrating consistent efficacy for both VTE treatment and prevention of recurrent VTE. In addition, a positive net clinical benefit was demonstrated with dabigatran against warfarin, which was not driven by poor levels of INR control in the warfarin patients.

The risk differences for the primary efficacy endpoint of recurrent VTE and VTE-related deaths in RE-COVER, RE-COVER II, and RE-MEDY were comparable at 0.4%, 0.2%, and 0.4%,

respectively. This clearly indicates that there is no clinically meaningful difference in efficacy between treatments for both acute VTE treatment and secondary prevention of VTE. Retrospective calculations showed that the three warfarin-controlled trials independently demonstrated that more than 85% of the warfarin effect was preserved, demonstrating comparability across trial results which is not as clearly observed when comparing hazard ratios alone. The amount of preserved effect is in line with the literature, which recommends 50% preservation of the effect in terms of the confidence interval or 2/3 of the effect.

In the placebo-controlled RE-SONATE trial, dabigatran was demonstrated to be a highly efficacious agent for reducing recurrent VTE and unexplained death when used for extended duration prophylaxis after 6 - 18 months anticoagulation with a VKA, with a 92% reduction in risk relative to placebo.[5;7]

In conclusion, the entirety of the data across the four clinical trials underlines that dabigatran is efficacious and safe, and that dabigatran can serve as a valuable alternative to warfarin for the treatment of acute VTE and the secondary prevention of VTE.

6.10.3 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

For clinical trials of anticoagulants for the treatment of venous thromboembolic disease, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommends a composite primary endpoint consisting of recurrent symptomatic non-fatal DVT/PE and mortality and that recurrent DVT and PE should be objectively verified. An analysis of the combined incidence of recurrent VTE and deaths related to VTE is considered most important in trials aiming to document non-inferiority whereas an analysis of the combined incidence of recurrent VTE and all deaths is considered most important in trials aiming to show superiority.[12] Moreover, it is these endpoints that are most relevant to the patient whose welfare and quality of life may be dependent upon preventing the recurrence of VTE.

In accordance with the CHMP recommendations, consistent endpoints were used across the RE-COVER, RE-COVER II and RE-MEDY (non-inferiority) studies. The primary endpoint was a composite of recurrent VTE (objectively confirmed symptomatic DVT and PE) and deaths related to VTE. In RE-SONATE (superiority study), the primary endpoint was a composite of recurrent symptomatic and objectively verified VTE, death associated with VTE or unexplained death.

Secondary endpoints in RE-COVER, RE-COVER II and RE-MEDY were:

- a composite of recurrent symptomatic VTE and all deaths
- separate components of the primary efficacy outcome
- all deaths

Secondary endpoints in RE-SONATE were:

- composite of recurrent symptomatic DVT, recurrent non-fatal PE and fatal PE (excluding unexplained death)
- separate components of the primary efficacy outcome

In each of the studies, safety outcomes were focused on bleeding events (including major bleeding events, or clinically relevant bleeding event, and any bleeding event [major, clinically relevant and nuisance bleeds]). In addition, hepatic function, coronary health and other AEs were routinely assessed.[1;5]

Subgroup analyses

No interactions were detected between treatment and any of the factors analysed (nominal P-values were all >0.10), except for the items described below. None of these exceptions were considered clinically important, and all but the third item may be chance findings since multiple comparisons have not been made.

- In the pooled analysis of RE-COVER and RE-COVER II, a possible interaction was detected between treatment and age <75 vs. ≥75 years for those who experienced VTE or VTE-related death (p= 0.0517). Among those ≥75 years old, 65/2,265 (2.9%) dabigatran patients and 52/2,239 (2.3%) warfarin patients experienced VTE or VTE-related death. The same interaction was detected for analysis of RE-COVER II (p= 0.1046).

- In the pooled analysis of RE-COVER and RE-COVER II, a possible interaction was detected between treatment and age <80 vs. ≥80 years for those who experienced VTE or VTE-related death (p= 0.0956). Among those ≥80 years old, 67/2,418 (2.8%) dabigatran patients and 57/2,429 (2.3%) warfarin patients experienced VTE or VTE-related deaths. Among those ≤80 years old 1/135 (0.7%) dabigatran patients and 5/125 (4.0%) warfarin patients experiences VTE or VTE-related deaths.
- To confirm that there were no age groups in which the efficacy of warfarin was significantly different from that of dabigatran, age as a continuous variable was also analysed. In RE-COVER, RE-COVER II and RE-MEDY there appeared to be a tendency for dabigatran to have better efficacy at higher ages but it is difficult to draw any definitive conclusions because at all ages the interaction was not statistically significant. In all studies, when age was analysed as a continuous variable, compared with warfarin, the efficacy of dabigatran was somewhat lower in younger patients and higher in older patients, with equal efficacy at about age 60. In RE-MEDY, when age was analysed as a continuous variable, compared with warfarin, the efficacy of dabigatran was somewhat lower at all ages. The 95% CI for the estimates HR was wide. In RE-SONATE, the efficacy of dabigatran was consistent across all ages and was superior to that of placebo at all ages.
- In the pooled analysis of RE-COVER and RE-COVER II, a possible interaction was detected between treatment and history of smoking for VTE and VTE-related death (p= 0.0430; from Wald Chi square test of treatment-by-smoking-status interaction effect). In this pooling the percentages of dabigatran patients who never smoked, were ex-smokers, or current smokers who had bleeding events were 1.9% (26 patients), 3.2% (21 patients), and 3.8% (21 patients), vs. 2.3% (31 patients), 3.4% (23 patients) and 1.4% (8 patients), respectively, for warfarin patients. The finding appears to be driven by the RE-COVER II trial, in which VTE and VTE-related death occurring among current smokers in 4.3% of the dabigatran-treated patients compared to 1.1% of warfarin-treated patients. This finding was not apparent in RE-MEDY or RE-SONATE.

Positive overall benefit-risk balance

The benefit-risk balance of dabigatran compared to warfarin in both the (acute) VTE treatment and the secondary VTE prevention indications can be further explored by evaluating the net clinical benefit. This can be evaluated using two approaches. The first more conservative approach to this composite endpoint includes non-fatal recurrent VTE,

non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death, and MBE. With the second approach, MBE and CRBE are also included, which gives a comprehensive analysis applicable to real-world clinical practice situations.

Net Clinical benefit in RE-COVER, RE-COVER II and RE-MEDY

The first composite net clinical benefit endpoint (non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death, MBE) calculated for the pooled RE-COVER and RE-COVER II studies is shown in Table 84 below (please note that in the tables, the composite net clinical benefit endpoint is presented as "composite cardiovascular endpoint"). With a HR close to 1, the net clinical benefit is similar for dabigatran and warfarin treatment (HR 1.02 (95% CI 0.81-1.27)). However, when MBEs and CRBEs were included in the calculation of the net clinical benefit (endpoint non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death, MBE/CRBE), a statistically significant difference was evident favouring dabigatran over warfarin (HR 0.80 (95% CI 0.68-0.95)) (Table 85).

Table 84: Hazard ratio for composite cardiovascular endpoint incl. MBE and all death for RE-COVER and RE-COVER II

	Dabigatran n	Warfarin n (%)
Number of patients	2,553	2,554
Composite cardiovascular endpoint and MBE (incl. all death)	155 (6.1)	152 (6.0)
Hazard ratio vs. warfarin (95% CI)	1.02 (0.81, 1.27)	

Table 85: Hazard ratio for composite cardiovascular endpoint incl. MBE or CRBE and all death for RE-COVER and RE-COVER II

	Dabigatran n	Warfarin n (%)
Number of patients	2,553	2,554
Composite cardiovascular endpoint and MBE or CRBE (incl. all death)	252 (9.9)	308 (12.1)
Hazard ratio vs. warfarin (95% CI)	0.80 (0.68, 0.95)	

The analyses performed for the RE-COVER studies were also applied to the RE-MEDY study. As with the pooled RE-COVER/RE-COVER II studies, the first composite net clinical benefit endpoint analysis showed similar net clinical benefit between dabigatran and warfarin, with a HR close to 1 (HR 1.05 (95% CI 0.75-1.46)). However, in the second composite net clinical benefit endpoint analysis where MBEs and CRBEs were included, a statistically significant difference was again evident favouring dabigatran over warfarin (HR 0.73 (95% CI 0.59-0.91)) (Table 86 and Table 87 below).

Table 86: Hazard ratio for composite cardiovascular endpoint incl. MBE and all death for RE-MEDY

	Dabigatran n	Warfarin n (%)
Number of patients	1,430	1,426
Composite cardiovascular endpoint and MBE (incl. all death)	72 (5.0)	69 (4.8)
Hazard ratio vs. warfarin (95% CI)	1.05 (0.75, 1.46)	
p-value for superiority	0.7819	

Table 87: Hazard ratio for composite cardiovascular endpoint incl. MBE or CRBE and all death for RE-MEDY

	Dabigatran n (%)	Warfarin n (%)
Number of patients	1,430	1,426
Composite cardiovascular endpoint and MBE or CRBE (incl. all death)	136 (9.5)	183 (12.8)
Hazard ratio vs. warfarin (95% CI)	0.73 (0.59, 0.91)	
p-value for superiority	0.0058	

The results of the net clinical benefit analyses therefore shows that overall, when compared to warfarin, dabigatran has a positive impact to the clinical outcome of the patients treated for acute VTE and also for secondary VTE prevention.

Net Clinical Benefit stratified by cTTR

Table 88 and Table 89 display the first composite net clinical benefit endpoint using only MBEs, and the second composite net clinical benefit endpoint including MBEs and CRBEs respectively, stratified by cTTR quintiles for the pooled RE-COVER and RE-COVER II studies. In both the net clinical benefit endpoint analyses, no clear pattern was obvious between cTTR quintiles and the net clinical benefit, indicating that the positive benefit of dabigatran over warfarin is not dependant on the quality of the INR control in the warfarin patients.

Table 88: Cox regression with factor centre (INR control) for composite cardiovascular endpoint incl. MBE and all death for RE-COVER and RE-COVER II

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<47.12	Patients	516 (100)	531 (100)
	Composite cardiovascular endpoint incl. MBE and all	43 (8.33)	48 (9.04)
	Hazard ratio vs. warfarin (95% CI)	0.920 (0.610,	
	Superiority p-value	0.6911	
47.12 - <57.72	Patients	450 (100)	489 (100)
	Composite cardiovascular endpoint incl. MBE and all	24 (5.33)	21 (4.29)
	Hazard ratio vs. warfarin (95% CI)	1.237 (0.689,	
	Superiority p-value	0.4768	
57.72 - <61.91	Patients	555 (100)	530 (100)
	Composite cardiovascular endpoint incl. MBE and all	23 (4.14)	31 (5.85)
	Hazard ratio vs. warfarin (95% CI)	0.706 (0.412,	
	Superiority p-value	0.2064	
61.91 - <67.98	Patients	481 (100)	492 (100)
	Composite cardiovascular endpoint incl. MBE and all	28 (5.82)	27 (5.49)
	Hazard ratio vs. warfarin (95% CI)	1.049 (0.619,	
	Superiority p-value	0.8580	
≥67.98	Patients	501 (100)	510 (100)
	Composite cardiovascular endpoint incl. MBE and all	35 (6.99)	25 (4.90)
	Hazard ratio vs. warfarin (95% CI)	1.431 (0.856,	
	Superiority p-value	0.1714	

Table 89: Cox regression with factor centre (INR control) for composite cardiovascular endpoint including MBE or CRBE and all death for RE-COVER and RE-COVER II

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<47.12	Patients	516 (100)	531 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	57 (11.05)	86 (16.20)
	Hazard ratio vs. warfarin (95% CI)	0.657 (0.470,	
	Superiority p-value	0.0141	
47.12 - <57.72	Patients	450 (100)	489 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	38 (8.44)	47 (9.61)
	Hazard ratio vs. warfarin (95% CI)	0.856 (0.558,	
	Superiority p-value	0.4759	
57.72 - <61.91	Patients	555 (100)	530 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	47 (8.47)	58 (10.94)
	Hazard ratio vs. warfarin (95% CI)	0.765 (0.520,	
	Superiority p-value	0.1715	
61.91 - <67.98	Patients	481 (100)	492 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	45 (9.36)	66 (13.41)
	Hazard ratio vs. warfarin (95% CI)	0.671 (0.459,	
	Superiority p-value	0.0389	
≥67.98	Patients	501 (100)	510 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	63 (12.57)	51 (10.00)
	Hazard ratio vs. warfarin (95% CI)	1.270 (0.878,	
	Superiority p-value	0.2049	

The same methods as for the pooled RE-COVER studies were applied to RE-MEDY.

Table 90 and Table 91, show the net clinical benefit for RE-MEDY including MBEs and, MBEs and CRBEs, respectively, stratified by cTTR quintiles. These results again show no clear pattern. For the net clinical benefit including MBEs and CRBEs, it is worth noting that for all the cTTR quintiles, all the HRs are below 1, numerically favouring dabigatran over warfarin.

Table 90: Cox regression with factor centre (INR control) for composite cardiovascular endpoint incl. MBE and all death for RE-MEDY

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<49.26	Patients	264 (100)	298 (100)
	Composite cardiovascular endpoint incl. MBE and all	11 (4.17)	22 (7.389)
	Hazard ratio vs. warfarin (95% CI)	0.545 (0.264,	
	Superiority p-value	0.1001	
49.26 - <59.28	Patients	284 (100)	291 (100)
	Composite cardiovascular endpoint incl. MBE and all	14 (4.93)	10 (3.44)
	Hazard ratio vs. warfarin (95% CI)	1.417 (0.629,	
	Superiority p-value	0.4000	
59.28 - <66.98	Patients	268 (100)	288 (100)
	Composite cardiovascular endpoint incl. MBE and all	15 (5.60)	15 (5.21)
	Hazard ratio vs. warfarin (95% CI)	1.038 (0.507,	
	Superiority p-value	0.9189	
66.98 - <73.06	Patients	283 (100)	276 (100)
	Composite cardiovascular endpoint incl. MBE and all	14 (4.95)	12 (4.35)
	Hazard ratio vs. warfarin (95% CI)	1.160 (0.536,	
	Superiority p-value	0.7067	
≥73.06	Patients	289 (100)	272 (100)
	Composite cardiovascular endpoint incl. MBE and all	15 (5.19)	10 (3.68)
	Hazard ratio vs. warfarin (95% CI)	1.495 (0.663,	
	Superiority p-value	0.3407	

Table 91: Cox regression with factor centre (INR control) for composite cardiovascular endpoint incl. MBE or CRBE and all death for RE-MEDY

Centre TTR categorised		Dabigatran n (%)	Warfarin n (%)
<49.26	Patients	264 (100)	298 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	11 (4.17)	22 (7.389)
	Hazard ratio vs. warfarin (95% CI)	0.545 (0.264,	
	Superiority p-value	0.1001	
49.26 - <59.28	Patients	284 (100)	291 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	14 (4.93)	10 (3.44)
	Hazard ratio vs. warfarin (95% CI)	1.417 (0.629,	
	Superiority p-value	0.4000	
59.28 - <66.98	Patients	268 (100)	288 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	15 (5.60)	15 (5.21)
	Hazard ratio vs. warfarin (95% CI)	1.038 (0.507,	
	Superiority p-value	0.9189	
66.98 - <73.06	Patients	283 (100)	276 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	14 (4.95)	12 (4.35)
	Hazard ratio vs. warfarin (95% CI)	1.160 (0.536,	
	Superiority p-value	0.7067	
≥73.06	Patients	289 (100)	272 (100)
	Composite cardiovascular endpoint incl. MBE or CRBE and all death	15 (5.19)	10 (3.68)
	Hazard ratio vs. warfarin (95% CI)	1.495 (0.663,	
	Superiority p-value	0.3407	

The results of the net clinical benefit analyses according to cTTR therefore show that overall, when compared to warfarin, the positive impact of dabigatran to the clinical outcome of the patients treated for acute VTE and also for secondary VTE prevention, is not dependent to the quality of INR control in the warfarin treated patients.

Conclusion

The three active-controlled studies with dabigatran, two of which are in acute VTE treatment (RE-COVER, RE-COVER II) and the third in secondary VTE prevention (RE-MEDY) robustly demonstrated therapeutic equivalence compared to warfarin. No clear dependency between clinical efficacy, clinical safety and net clinical benefit and the cTTR levels was

detected demonstrating that the positive results were not driven by the poorly controlled warfarin patients. Furthermore, dabigatran in the long-term prevention of recurrent VTE (RE-SONATE) was unequivocally superior to placebo in terms of clinical efficacy. The totality of the data demonstrates that dabigatran is safe and efficacious and can serve as a valuable alternative to warfarin for both the (acute) treatment of VTE and secondary VTE prevention.

6.10.4 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?

By their very nature, clinical trials select particular samples from a population. This inherently limits the ability to generalise clinical trial results to a specific population, but does allow a reliable estimate of relative efficacy. Design notwithstanding, efficacy was consistently demonstrated; however, absolute efficacy will need to be established in clinical practice settings.

The majority of patients were white Caucasian (95.2% in RE-COVER, 77.6% in RE-COVER II, 90.1% in RE-MEDY and 89.6% in RE-SONATE).[1;5;27] In RE-COVER, 2,564 patients were randomised 231 centres in 29 countries worldwide. Of these, 29.7% of patients were from Central Europe31.2% from Western Europe and 17.5% from North America.[28] In RE-COVER II, 2,589 patients were randomised in 208 centres in 31 countries worldwide. Of these, 32.8% patients were from Central Europe, 17.4% from Western Europe and 15.7% from North America.[4] In RE-MEDY, 27.5% patients were from Western Europe, 34.1% from Eastern Europe and 11.9% from North America.[6] In RE-SONATE, the majority of patients were from Western or Central Europe (80.2%).[7]

In the pivotal trials, the average age of patients was 55.0 years in RE-COVER, 54.7 years in RE COVER II, 55.4 years in RE-MEDY and 56.1 years in RE-SONATE. There was no significant difference in efficacy in predefined subgroup analyses, including age. Therefore, no age-related difference in clinical effectiveness would be expected when dabigatran is used in patients within the NHS. There were fewer female patients in each of the studies, which may

reflect the increased risk of VTE associated with the male sex. A cohort study in the United States also demonstrated a greater incidence of VTE in men than women.[50]

Two doses, 150 mg BD and 110 mg BD, are recommended by the CHMP as according to the product licence and considered to reflect how the medication would be used in clinical practice. Both doses are also currently accepted for use within the NHS for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation. A lower dose of 220 mg once daily is also accepted for use for the prevention of VTE in adults who have undergone elective total hip or total knee replacement surgery.

Treatment guidelines in the Western world demonstrate general consistency in their treatment algorithms, goals and clinical practice. In all four pivotal Phase III trials, the baseline characteristics were considered to be representative of the population of patients with VTE.

Contraindications and special patient populations

Use of dabigatran is contraindicated in cases of:

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCL < 30 mL/min)
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- Hepatic impairment or liver disease expected to have any impact on survival

- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone
- Prosthetic heart valves requiring anticoagulant treatment.

In all patients:

- Renal function should be assessed by calculating the CrCL prior to initiation of treatment with dabigatran to exclude patients with severe renal impairment (i.e. CrCL <30mL/min). Dabigatran is contraindicated in patients with severe renal impairment
- Renal function should be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products)

No dose adjustment is necessary for patient with renal function over CrCL 30mL/min. In patients with mild to moderate renal impairment and in patients aged over 75 years, renal function should be assessed at least yearly during treatment with dabigatran when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥2 Upper Limit Normal (ULN) were excluded in clinical trials. No treatment experience is available for this subpopulation of patients, and therefore, the use of dabigatran is not recommended in this population.

Dabigatran is under investigation in patients <18 years. The safety and efficacy in children has not yet been established. Treatment of children with dabigatran is therefore not recommended.

Drug-drug and drug-food interactions

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore concomitant use of P-gp transporter inhibitors (amiodarone, verapamil, clarithromycin, quinidine, dronedarone , ticagrelor and ketoconazole) and inducers (rifampicin) had been investigated (see sections 4.2, 4.4 and 4.5).

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

The oral bioavailability may be increased by 75 % compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (HPMC) capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised **not** to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages).

Pharmacokinetic/pharmacodynamic conclusions: no need for coagulation monitoring

Dabigatran had been shown to have a predictable pharmacokinetic and pharmacodynamic profile.

- With an oral bioavailability of ~6.5%, dabigatran has linear pharmacokinetics as demonstrated by a dose-proportional increase in plasma concentrations over a wide range of doses [51;52]
- The pharmacokinetics of dabigatran were not significantly influenced by weight, gender, smoking or alcohol consumption[52;53]
- The maximal effect of dabigatran on clotting parameters occurs simultaneously to maximal dabigatran plasma concentration, with a rapid onset of action[51]
- Offset of dabigatran also occurs in parallel with its elimination[51;54]

Collectively, these data indicate a direct link between thrombin inhibition and dabigatran plasma concentration. [54]

150 mg twice daily dabigatran dose

The clinical data from the 4 pivotal trials are sufficiently supportive for the recommendation that the 150 mg BD dosing is suitable for all patients in the VTE indication. In the overall results, and in most of the subgroups analyses, the incidence of centrally adjudicated MBEs,

MBE or CRBEs, and any bleeding events was lower in dabigatran-treated patients compared with warfarin-treated patients. However it is acknowledged that in certain subgroups, the numbers of events are small and a firm conclusion cannot be made, and therefore the harmonization of the posology in the SPC for the VTE indication and the NVAF indication should be considered.

From the pharmacokinetic and pharmacodynamics analyses of both RE-LY and RE-COVER studies, the pharmacodynamic responses (anticoagulation) as well as therapeutic response (bleeding and antithrombotic efficiency) are closely related to dabigatran exposure. Furthermore, a great consistency could be demonstrated in the pharmacokinetics, and the relation between the exposure and the clinical safety (major bleeding events) between the NVAF and VTE patient population, although no dedicated exposure – efficacy relationship could be demonstrated for the VTE patient population. Therefore, in the sub-populations defined by the current NVAF label (e.g. age > 80 years of age, verapamil co-medication) exposure with 110 mg BD is expected to stay within or even above the average exposure in the majority of VTE patients receiving 150 mg BD. Hence, it can be assumed that most of the anticoagulation efficacy will remain to be preserved when this VTE population with a higher risk of bleeding is treated with dabigatran 110 mg BD.

In conclusion, the existing data on the 110 mg BD dose from RE-LY together with the high consistency between the patient populations in terms of the pharmacokinetics, pharmacodynamics and exposure-response results seen in the RE-LY and RE-COVER studies, is sufficient evidence to consider the 110 mg BD dose for the same sub-populations in VTE as in NVAF, without further need of a dedicated clinical study.

Treatment of VTE in patients with cancer

The percentage of patients with cancer enrolled in warfarin-controlled trials was 4.5% for the pooled RE-COVER trials and 4.2% for RE-MEDY. The data from these patients are displayed in

Table **92**. In all the warfarin-controlled trials, active cancer was defined as a diagnosis of cancer, other than basal-cell or squamous-cell carcinoma of the skin, within five years before the enrolment, any treatment for cancer within five years or recurrent or metastatic cancer.

Table 92: Efficacy and safety endpoints in cancer patients in all 3 active-controlled studies

Cancer at any time during study	VTE or VTE-related death[1] Patients, n/N (%)		MBEs[2] Patients, n/N (%)		MBEs or CRBEs[2.] Patients, n/N (%)		Any Bleeds[2] Patients, n/N (%)	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin
Pooled data from RE-COVER and RE-COVER II								
No	58/2380 (2.4)	50/2392 (2.1)	18/2297 (0.8)	33/2310 (1.4)	86/2297 (3.7)	169/2310 (7.3)	315/2297 (13.7)	468/2310 (20.3)
Yes	10/173 (5.8)	12/162 (7.4)	6/159 (3.8)	7/152 (4.6)	23/159 (14.5)	20/152 (13.2)	39/159 (24.5)	35/152 (23.0)
RE-MEDY data								
No	23/1342 (1.7)	15/132 (1.1)	9/1342 (0.7)	21/1321 (1.6)	68/1342 (5.1)	125/1321 (9.5)	257/1342 (19.2)	332/1321 (25.1)
Yes	3/88 (3.4)	3/105 (2.9)	4/88 (4.5)	4/105 (3.8)	12/88 (13.6)	20/105 (19.0)	21/88 (23.9)	41/105 (39.0)

[1]In RE-COVER and RE-COVER II, measured from randomization (i.e. start of parenteral therapy plus either warfarin or warfarin placebo) up to the end of the prespecified post-treatment follow-up. In RE-MEDY, measured from the randomization to the end of the planned treatment period (6-36 months)

[2]In RE-COVER and RE-COVER II, measured from the start of the double-dummy period (i.e. oral dabigatran or warfarin alone) to the end of the 6-month study period. In RE-MEDY, measured from the first dose of the study drug until 3 days after receipt of the last dose.

The results show that there was a significantly higher frequency of recurrent VTE or VTE-related mortality among patients who had cancer compared to patients who did not have cancer, independently of the anticoagulation treatment received. Amongst the cancer patients, the efficacy of dabigatran was not different from warfarin. In terms of safety, the incidence of bleeding events in cancer patients treated with dabigatran was comparable to those treated with warfarin.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 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 appendix 10.

A comprehensive systematic review of economic studies relevant to the economic evaluation of dabigatran for the treatment and secondary prevention of DVT and PE was performed[55], to identify the following:

- Economic analyses of interventions for the treatment and secondary prevention of DVT and/or PE
- Utility, resource use, and cost estimates relevant to economic models for the treatment and secondary prevention of DVT and/or PE
- Other key model parameters, specifically the following:
    - Mortality rates for myocardial infarction (MI)
    - The impact of age on the risk of recurrent DVT, PE, and bleeding

Comprehensive searches were run across MEDLINE, MEDLINE In-Process, Embase, EconLit, BIOSIS and the Cochrane Library including the NHS EED. The search strategy and terms used are described in Appendix 10. Additionally, internet searches were conducted and are detailed in Appendix 10, **Error! Reference source not found.** and **Error! Reference source not found.**.

Table 93 presents the inclusion and exclusion criteria used to identify relevant studies.

Table 93: List of criteria for the inclusion and exclusion of studies

Criteria	Included	Excluded
Study type	▪ Economic analyses for the treatment or secondary prevention of DVT and/or PE, including economic models and analyses alongside clinical trials ▪ Economic analyses of ximelagatran will be included and reviewed for relevant parameters; no text description or quality assessment will be performed for these studies ▪ Utility studies for DVT, PE, PTS, pulmonary hypertension, or relevant adverse events ▪ Resource use and cost studies relevant to DVT, PE, PTS, pulmonary hypertension, or relevant adverse events, including the following: – Bleeding (including intracranial haemorrhage) – Heparin-induced thrombocytopaenia – MI – Unstable angina – Dyspepsia ▪ National statistics of the mortality rates associated with MI ▪ Studies and reviews reporting the association between age and the risk of recurrent DVT, PE, and bleeding	▪ Reviews, letters, or comment articles that discuss costs but where cost estimates are not evidence-based (reference lists of reviews were searched for relevant studies, but reviews were not be included in their own right)
Population	▪ For economic analyses, patients with DVT and/or PE being treated or receiving secondary prevention for recurrent DVT and/or PE ▪ For utility, resource use, and cost studies, patients with DVT, PE, PTS, pulmonary hypertension or any of the adverse events	▪ Patients receiving primary prophylaxis for prevention of a first DVT and/or PE event
Interventions (applied to economic evaluations only)[a]	▪ Dabigatran ▪ Rivaroxaban ▪ Edoxaban ▪ Apixaban ▪ Warfarin[b] ▪ Low molecular-weight heparin (all agents, including, but not limited to, enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) or unfractionated heparin[b] ▪ Fondaparinux[b] ▪ For studies reporting international normalised rate monitoring: warfarin, phenindione, acenocoumarol, and 4-hydroxycoumarin	▪ Studies that do not include any of the interventions in the inclusion criteria list ▪ Utility, resource use, and cost studies will not be subject to inclusion and exclusion criteria for study interventions

DVT = deep vein thrombosis; LMWH = low molecular-weight heparin; MI = myocardial infarction; PE = pulmonary embolism; PTS = post-thrombotic syndrome; UFH = unfractionated heparin.
[a] Utility, resource use, and cost studies that were relevant to DVT, PE, PTS, pulmonary hypertension, or relevant adverse events were included, regardless of the intervention investigated.
[b] A clarification of the selection criteria was made during the course of the review; economic analyses and cost studies comparing LMWH, UFH, warfarin and fondaparinux that did not evaluate dabigatran, rivaroxaban, edoxaban, or apixaban were identified but not formally included in the review.

Initially, the database searches were limited to retrieval of records published from 1st January 2000 to 22nd January 2013, as detailed in Appendix 10. Conference abstracts were searched from 1st January 2011 to 22nd January 2013, as high-quality studies reported in

abstract form before 2011 were expected to have been published in a peer-reviewed journal. There were no date restrictions on the searches for HTA documentation.

The systematic review was then updated in 2014 using the same search strategy, databases and internet sources, with the exception of the National Health Service's Clinical Knowledge Summaries website, which is now found at http://cks.nice.org.uk. Searches of electronic databases were conducted on 28th April 2014 and internet searches were performed between 28th April and 1st May 2014. All searches in the systematic review update were limited to data published after 22 January 2013.

The study selection process occurred in the following two phases:

- Level 1 screening: Titles and abstracts of studies identified from the electronic databases and from Internet searches were reviewed for eligibility by one researcher. A second researcher independently screened a random sample of 5% of the records. Any differences were resolved by consensus.
- Level 2 screening: Full texts of studies selected at level 1 were obtained and reviewed for eligibility by one researcher, using the same inclusion and exclusion criteria as used in level 1 screening. A second researcher independently screened a random sample of 5% of the records. Any differences were resolved by consensus. Foreign-language sources were excluded at the level 2 screening stage.

The second researcher also reviewed all studies selected after the level 2 screening to confirm their eligibility.

The inclusion and exclusion processes were documented, including completion of a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

Figure 27 for the original review and Figure 28 for the update). The flow charts (adapted from (Moher et al., 2009) detail the volume of articles included and excluded at each screening level, and reasons for exclusion.

Figure 27: PRISMA diagram for study inclusion and exclusion: original systematic review

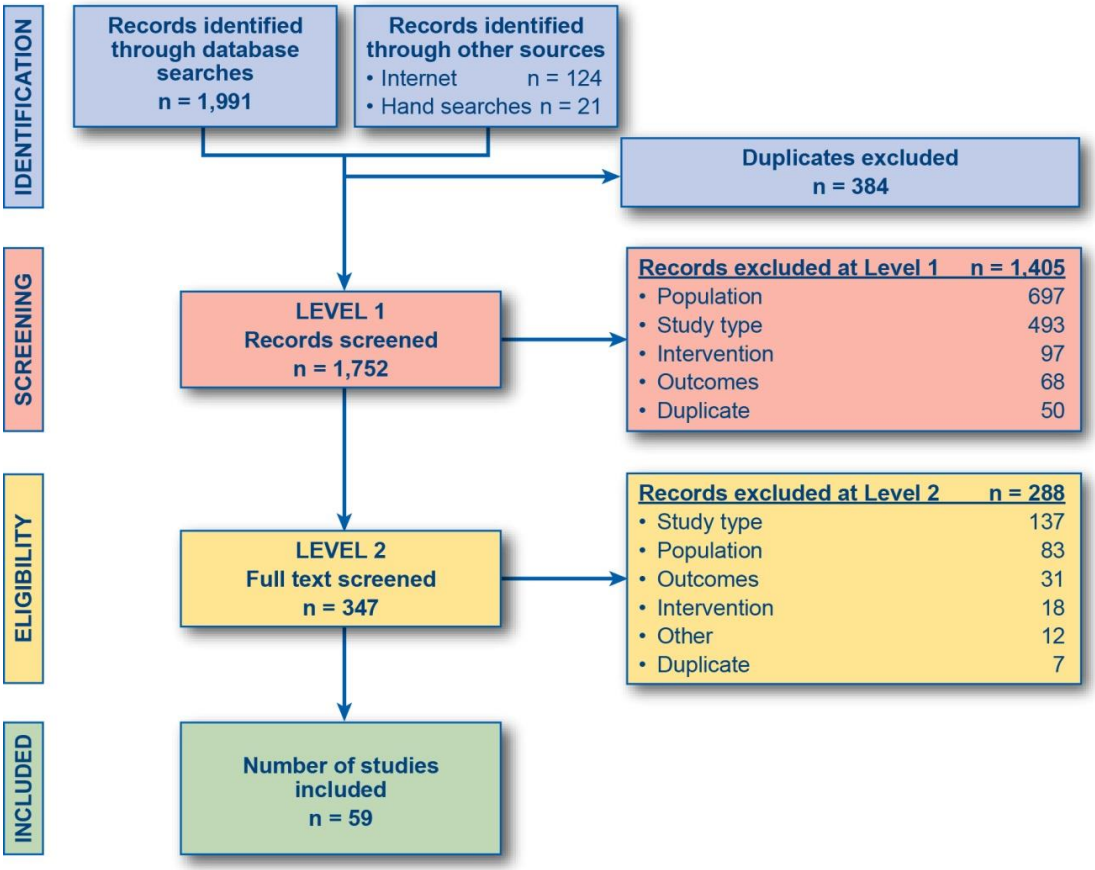
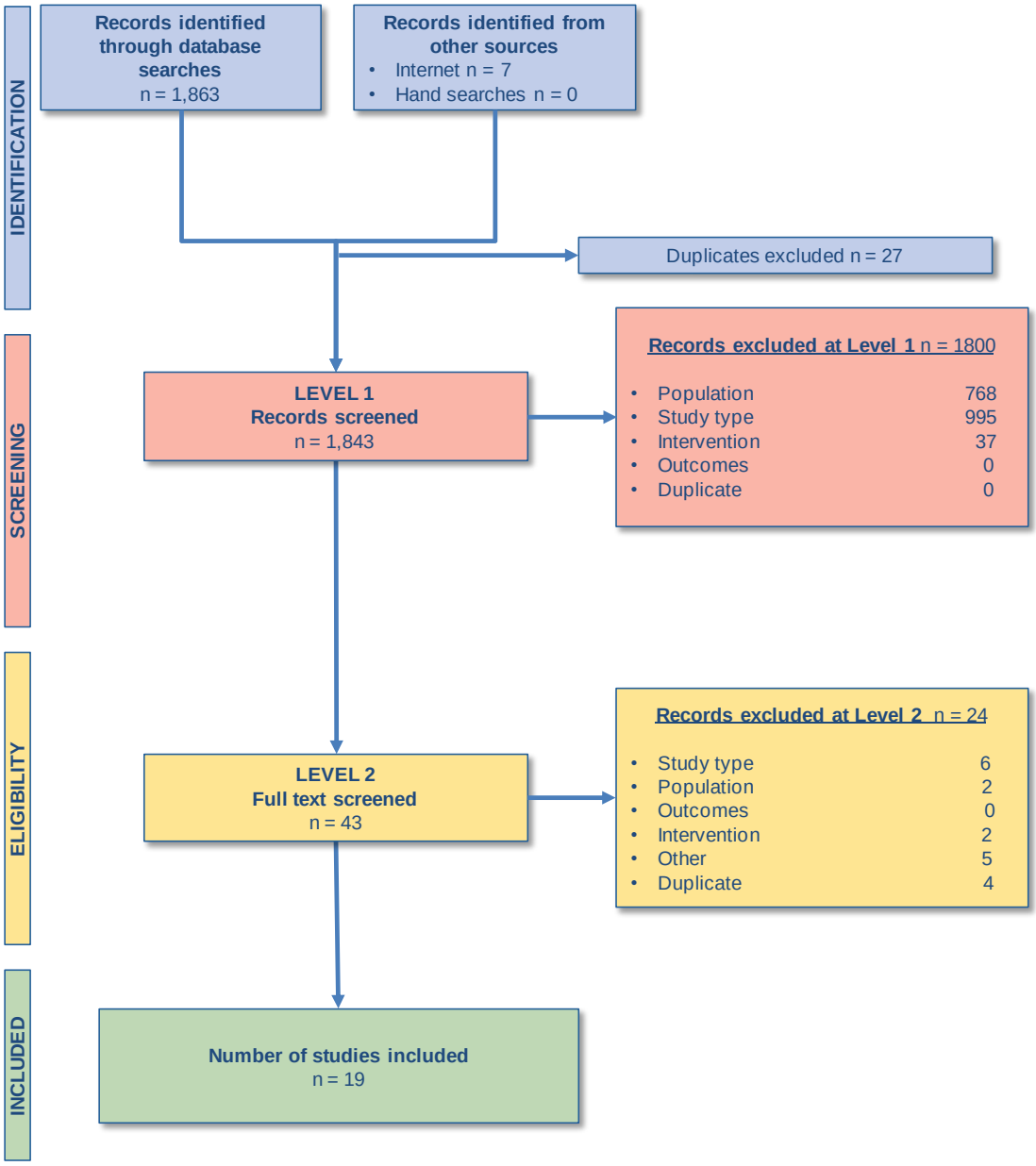


Figure 28: PRISMA diagram for study inclusion and exclusion: systematic review update



In the original review, of the 59 identified studies, five were economic evaluations of the interventions of interest, 27 reported utility-weight estimates, 26 reported resource use and/or cost estimates, one reported the association between age and the risk of VTE, and one reported mortality rates for MI. One study (Braidy et al., 2011)[56] was extracted as both an economic evaluation and as a cost study; it has been reported in the total number of each study type but only once in the total number of included studies.

In the update of the systematic review, of the 19 identified studies, seven were economic evaluations of the interventions of interest, four reported utility-weight estimates and eight reported resource use and/or cost estimates.

Description of identified studies

7.1.2 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.

Table 94 describes the 12 cost-effectiveness evaluations identified in the systematic review update.

Table 94: Overview of cost-effectiveness studies identified by the systematic review

Study	Year	Country	Summary of cost-effectiveness evaluation	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
Bayer plc (2011) (Manufacturer submission to NICE)	2010	UK	Markov state-transition model comprising 11 health and treatment states with a lifetime horizon (assumed to be 40 years) and a 3-month cycle length Discounting was applied at 3.5%	Adults with an acute DVT to match the EINSTEIN-DVT trial population (Bauersachs et al, 2010), which had an average age of 56.1 years	Patients appropriate for 3 months of anticoagulation: 13.348 QALYs (Rivaroxaban) 13.325 QALYs (Dual LMWH/VKA therapy) Patients appropriate for 6 months of anticoagulation: 13.365 QALYs (Rivaroxaban) 13.345 QALYs (Dual LMWH/VKA therapy) Patients appropriate for 12 months of anticoagulation: 13.377 QALYs (Rivaroxaban) 13.356 QALYs (Dual LMWH/VKA therapy)	Patients appropriate for 3 months of anticoagulation: £1,135 (Rivaroxaban) £1,298 (Dual LMWH/VKA therapy) Patients appropriate for 6 months of anticoagulation: £1,318 (Rivaroxaban) £1,442 (Dual LMWH/VKA therapy) Patients appropriate for 12 months of anticoagulation: £1,643 (Rivaroxaban) £1,676 (Dual LMWH/VKA therapy)	Rivaroxaban dominates dual LMWH/VKA therapy at 3, 6 and 12 months of anticoagulation.
Braidy (2011)	2009	Australia	Decision-tree model, cost-minimisation analysis Discounting: NR	NR (mean age of patients incorporated into the model was 81.5 years for VTE)	No QALYs or costs reported. Rivaroxaban (10 mg once daily) was found dominant vs warfarin (5 mg once daily) and enoxaparin (40 mg once daily) Dabigatran (220 mg once daily) was found dominant vs warfarin (5 mg once daily) and enoxaparin (40 mg once daily)		
Kourlaba (2012) (Abstract)	2012	Greece	Markov state-transition model comprising 12 health states with a 6-month time-horizon (acute treatment phase) with 3-month cycles, from a payer perspective	NR	No absolute figures reported. A €170 cost increment and 0.019 QALY increment result into an ICER of €8,795.		

			All costs and outcomes were discounted at 3.5%				
Marchetti (2001)	NR	Italy, US	Decision-tree model Costs and life-years were discounted at a yearly rate of 3%	NR (mean age at baseline was assumed to be 60 years)	Italy: 13.039 QALYs (LMWH) 13.003 QALYs (Warfarin) US: NR	Italy: $904 (LMWH) $667 (Warfarin) US: NR	Italy: $6,583 per QALY US: $28,231 per QALY
Seaman (2012) (Abstract) (note: superseded by Seaman (2013))	2011	US	Markov state-transition model with a 10-year time horizon Discounting: NR	Hypothetical cohort of 60-year-old patients who were diagnosed with their first VTE and received therapy for 6 months	9.30 QALYs (Rivaroxaban) 9.16 QALYs (Warfarin)	$4,057 (Rivaroxaban) $7,004 (Warfarin)	Rivaroxaban dominates warfarin.
Bookhart (2013) (Abstract)	NR	North America	Economic outcomes from EINSTEIN-PE trial	Patients with PE from EINSTEIN-PE trial	NR	Rivaroxaban was associated with $2,040 cost saving compared to LMWH/warfarin therapy as a result of a 1-day shorter length of hospital stay	NR
Seaman (2013) (note: supersedes Seaman (2012))	2011	US	Markov state-transition model with a 10-year time horizon from a societal perspective	Hypothetical cohort of 60-year old patients with VTE, who received secondary prophylaxis with rivaroxaban or warfarin for 3-12 months	9.29 (Rivaroxaban) 9.14 (Warfarin)	$3,195 (Rivaroxaban) $6,188 (Warfarin)	Rivaroxaban dominates warfarin
McLeod (2013) (Abstract)	NR	UK	Markov state-transition model from a UK payer perspective Discounted at 3.5% per year	Patients who had experienced a PE and required 3, 6 or 12 months' treatment (inputs derived from EINSTEIN PE and systematic literature reviews)	Rivaroxaban was associated with the following QALY increases compared to LMWH/VKA therapy, depending on treatment duration: 0.027 (3 months)	Rivaroxaban was associated with the following per-patient cost savings compared to LMWH/VKA therapy, depending on treatment duration: £396 (3 months)	Rivaroxaban dominates LMWH/VKA therapy (£7,072 per QALY)

					0.013 (6 months) 0.019 (12 months)	£213 (6 months) £133 (12 months)	
Parali (2013) (Abstract)	2012	Turkey	Markov state-transition model with a 5-year and lifetime time-horizon from a Turkish payer perspective	Patients from EINSTEIN-DVT trial	5-year time horizon Rivaroxaban increased QALY by 0.005 years compared to warfarin Lifetime time-horizon Rivaroxaban increased QALY by 0.022 years compared to warfarin	5-year time horizon Rivaroxaban cost was $89 higher than warfarin Lifetime time-horizon Rivaroxaban cost was $96 higher than warfarin	5-year time horizon $17,928 Lifetime time-horizon $4,056
Wolowacz (2013) (Conference poster presentation)	2012	UK	Markov state-transition model with a cycle length of 1-month and a time-horizon of up to 60-years from the perspective of the UK NHS Discounted at 3.5% per year	Efficacy and safety data based on the RE-SONATE study	13.088 (Dabigatran) 13.070 (Placebo)	£7,152 (Dabigatran) £7,520 (Placebo)	Dabigatran dominates placebo
Coleman (2014)	2013	US	Markov state-transition model with a 1-month cycle length and a 40-year time-horizon from a Medicare/US payer perspective	Cohort of 58-year old patients, diagnosed with PE or DVT, who had previously received 6-12 months of anticoagulation with rivaroxaban or a VKA	16.167 QALYs (Rivaroxaban) 16.134 QALYs (placebo)	$22,645 (Rivaroxaban) $ 22,083 (placebo)	$17,030 per QALY
Lefebvre (2014)	2012	US	Markov state-transition model with a 3-month cycle length and 5-year time-horizon from a US payer perspective Future costs and effectiveness discounted at 3% per year	Adults with confirmed DVT or PE aged 56 and 58 years, respectively	3.8486 (Rivaroxaban) 3.8427 (Enoxaparin + VKA)	$13,806 (Rivaroxaban) $16,253 (Enoxaparin + VKA)	Rivaroxaban dominates enoxaparin + VKA

DVT, deep vein thrombosis; ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; PE, pulmonary embolism; NHS, National Health Service; NR, not reported; QALY(s), quality-adjusted life year(s); VKA, vitamin K antagonist

7.1.3 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)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Please refer to Section 10.11, Appendix 11 for the suggested quality assessment.

7.2 De novo analysis

Patients

7.2.1 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 1.3 and 6.3.3, 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 group in this economic evaluation matches the indication for dabigatran stated in Section 1.5 of this submission:

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Cost-effectiveness estimates of dabigatran for the following two treatment options are presented separately:

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[1] 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.

[2] 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.

1) Treatment of DVT and PE

The patient population is adults (≥ 18 years) with acute symptomatic proximal DVT and PE.

In this patient population, analyses are presented for subgroups in which the underlying risk of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ. These subgroups are:

- Type of index event
  - DVT only
  - PE with/without DVT
- Patients with history of bleeding
- Western European patients

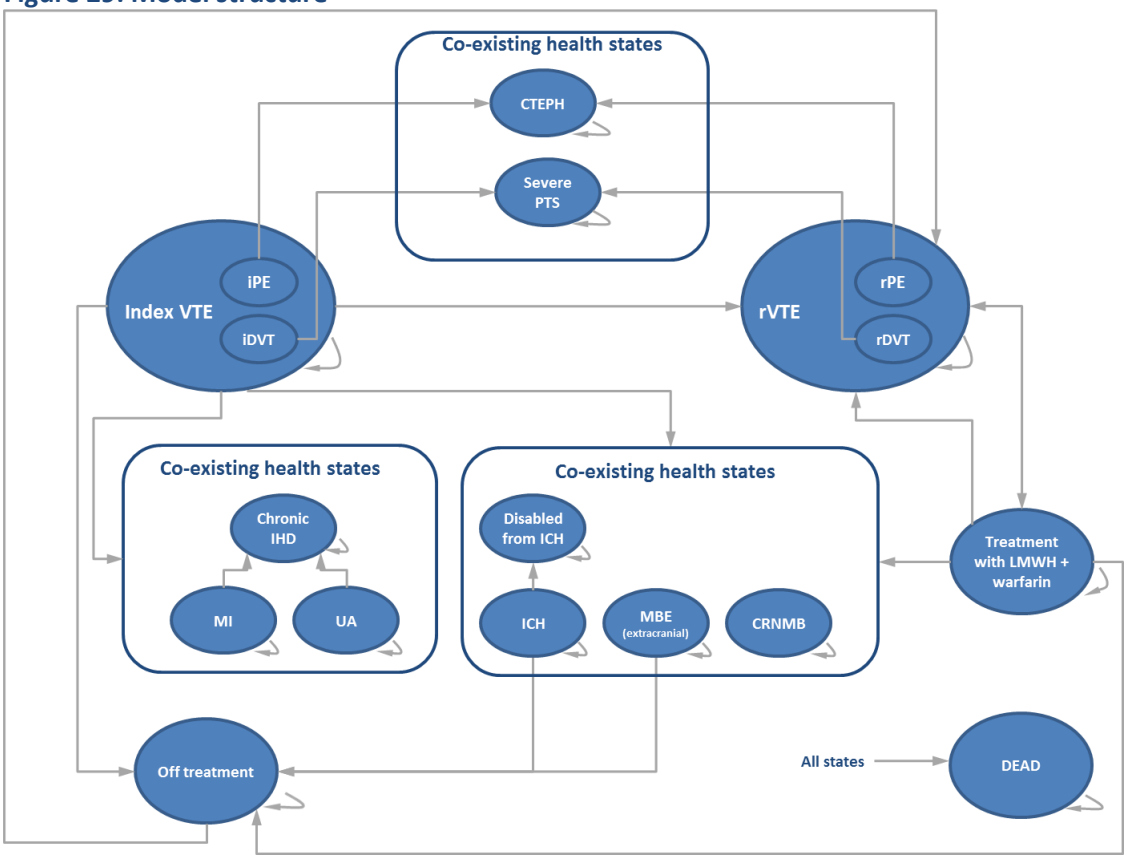
2) Treatment followed by prevention of recurrent DVT and PE

The patient population is adults (≥ 18 years) with acute symptomatic proximal DVT and PE who had received treatment with standard doses of an anticoagulant for 6 months and who required anticoagulant therapy beyond 6 months for the long-term treatment and secondary prevention of symptomatic VTE.

Model structure

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

Figure 29: Model structure



MI = myocardial infarction; UA = unstable angina and IHD = Chronic ischemic heart disease apply to sensitivity analyses only.

Index VTE = index venous thromboembolism; iDVT = index deep vein thrombosis; iPE = index pulmonary embolism; CTEPH = Chronic thromboembolic pulmonary hypertension; PTS = post thrombotic syndrome; rVTE = recurrent venous thromboembolism; rPE = recurrent pulmonary embolism; rDVT = recurrent deep vein thrombosis; MBE = major bleeding events; CRNMB = Clinically relevant non-major bleeds; ICH = intracranial haemorrhage.

Note: The coexisting health states shown within the pale blue panel may occur concurrently with any other health state (they are not mutually exclusive).

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The decision to initiate a patient on anticoagulation treatment and to consider extended treatment is made in the context of the risk-benefit ratio between perceived benefit from prevention of recurrent venous thromboembolism and perceived risk of harm from major haemorrhage. Therefore, the economic model is structured around two primary composite endpoints that consolidate the most relevant thromboembolic and haemorrhagic events to which patients with DVT and PE are considered at risk:

3. **Symptomatic recurrent VTE and VTE-related death (rVTERD)**
4. **Major or clinically relevant bleeding (MCRB)**

The model outputs reported in this submission include the absolute number of events in each health state at different time points. An overview of the clinical outcomes presented in the model is shown below.

Table 95: Overview of clinical outcomes

Thromboembolic events	Haemorrhagic events	Additional events[1]
• Pulmonary embolism (PE) • Proximal DVT • Distal DVT • VTE related deaths	• Major bleed event (MBE), incl. ICH • Clinically relevant non-major bleed event (CRNMB)	• Myocardial infarction (MI) • Unstable angina (UA) • Post-thrombotic syndrome (PTS) • Chronic thromboembolic pulmonary hypertension (CTEPH)

1 Additional clinical events considered appropriate for inclusion in the model, given their relevance to patients receiving anticoagulation treatment for DVT and PE

For the cost-effectiveness analysis the quality-adjusted life year (QALY) is the primary outcome measure.

The pathway of care identified in Section 2.5 is replicated within the economic model. In particular, both the duration of acute parenteral treatment (with LMWH) matches the best practice guidelines and has been analysed in various sensitivity analyses. Treatment with rivaroxaban has been incorporated in the model according to the summary of product characteristics.

Given the long-term impact of VTE and its consequences on healthcare costs and HRQL, and in order to appropriately model the recurrence of VTE, it was considered appropriate to employ a Markov cohort simulation model. This is a flexible approach to modelling the course of anticoagulant therapy and allows to readily analyse cost-effectiveness at different time horizons.

The following Section (7.2.4) expands on health states in the economic models.

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

Table 96: Summary of health states captured in the model

Health state	Description
Index VTE	Patients after acute VTE event who are therefore receiving acute treatment (and ongoing preventive treatment).
Recurrent DVT	Patients who experienced a recurrent DVT. Initial treatment is stopped and a 6 months standard treatment course of LMWH followed by warfarin is initiated (or re-initiated, when warfarin is comparator). The duration of disutility was assumed to be 6 weeks (see Section 7.3.8).
Recurrent PE	Patients who experienced a recurrent PE. Initial treatment is stopped and a 6 months standard treatment course of LMWH followed by warfarin is initiated (or re-initiated, when warfarin is comparator). The duration of disutility was assumed to be 6 weeks (see Section 7.3.8).
ICH	Patients on treatment who are experiencing an intracranial haemorrhage. All treatment is discontinued altogether. A disutility is applied in the month of the event. An additional disutility is applied for the remaining lifetime in patients that are disabled in consequence of the ICH.
MBE	Patients on treatment who are experiencing a (extracranial) major bleeding event. All treatment is discontinued altogether. A disutility is applied in the month of the event.
CRNMB	Patients on treatment who are experiencing a clinically relevant non-major bleeding event. A disutility is applied in the month of the event.
Severe PTS	Patients off treatment who are experiencing a severe post thrombotic syndrome. A disutility is applied for the remaining lifetime.
MI*	Patients off treatment who are experiencing a myocardial infarction. A disutility is applied in the month of the event.
UA*	Patients off treatment who are experiencing an unstable angina. A disutility is applied in the month of the event.
CTEPH	Patients off treatment who are experiencing an acute episode of Chronic thromboembolic pulmonary hypertension. A disutility is applied in the month of the event.
Dyspepsia*	Patients off treatment who are experiencing dyspepsia. The disutility applied is assumed to last for the duration of treatment.
Off treatment	Patients off treatment are assumed to have a zero risk of bleeding but are continuing to be exposed to a risk of recurrent VTE.
Death	Terminal state. Patients may due to modelled events (rVTE, MBE incl. ICH, MI, UA) and other causes.
* Applies to sensitivity analyses only	

Key aspects of the model structure are as follows:

- After an index VTE event, identical hypothetical cohorts of patients enter the model and receive either dabigatran or a comparator.
- The transition to a recurrent VTE event in the model was defined in the same way as the primary endpoint of the trials: *symptomatic recurrent VTE and VTE-related death (rVTERD)*. Patients meeting this endpoint in any model cycle may have a VTE-related death, a non-fatal PE, a proximal DVT (without PE), or a distal DVT (without PE or proximal DVT).
- Patients who experience a first (index) or recurrent PE the model may develop CTEPH.

- Patients who experience a first or recurrent DVT may develop PTS (a literature review found evidence to suggest that mild PTS was of little detrimental effect on quality of life[57]; therefore, the model includes only severe PTS).
- The probability of bleeding in the model is estimated from the combined endpoint, MCRB. Bleeding events that were not MCRB events (i.e. minor bleeds) were assumed to have a negligible impact on costs and HRQL and were thus excluded from the model.
- Patients having an MCRB event in any model cycle may have an ICH, other (extracranial) MBE, or a CRNMB event.
- All modelled patients may discontinue treatment (i) after a recurrent VTE event, (ii) after a MBE or ICH or (iii) due to any reason other than a recurrent VTE or bleeding event.
- ICH may lead to permanent disability (patients enter the "Disabled from ICH" health state in Figure 29), death, or recovery.
- MBEs may lead to death or recovery.
- CRNMB events were assumed to be non-fatal and all patients recovered.
- Patients with an acute coronary syndrome event (MI or unstable angina) may die, experience chronic cardiac ischemic disease, or recover.
- Patients in any of the health states may die of other causes.

Treatment discontinuation

During the treatment and secondary prevention period, all modelled patients may discontinue treatment in the manner described below:

1. *After a recurrent VTE event*, all patients are assumed to stop the initial treatment and initiate (or re-initiate, when warfarin is comparator) a 6 months standard treatment course of LMWH followed by warfarin. During this 6 months standard treatment course, patients continue to be exposed to a risk of recurrent VTE, bleeds and other co-existing health states as observed in the warfarin arm of the pooled RE-COVER trials.

2. *After a MBE or ICH*, all patients are assumed to discontinue treatment altogether having no further risk of bleeding, but continuing to be exposed to a risk of recurrent VTE. In a prospective cohort study, Prandoni et al. (2007)[58] reported a 39.9% cumulative incidence of clinically symptomatic proximal DVT and/or PE after 10

years that was used to estimate the probability of a recurrent VTE (assuming a constant hazard).

3. *Discontinuation due to any reason other than a recurrent VTE or bleeding event* prior to reaching the planned duration of treatment. These may include but are not limited to worsening of other pre-existing diseases, other AEs, non-compliance with trial protocol, loss to follow-up, consent withdrawal. If discontinuation occurs, patients move to no treatment where they continue to experience a risk of recurrent VTE as reported by Prandoni et al. (2007).[58]

All patients, including those who discontinued the study drug due to any reason, can have up to two recurrent VTE events.

7.2.5 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.

As noted in Section 7.2.3, the main considerations relevant to patients and clinicians are the competing risks of thromboembolic and haemorrhagic events. Table 95 describes all events this economic model is designed to capture in detail.

The underlying disease progression is reflected in the model by assigning patients to a risk of recurrent VTE event and MCRB event. The possibility of multiple events in individual patients has also been reflected in the modelling.

The risk of death from other causes is calculated in the model from age and gender-specific mortality rates for the UK. The starting mortality rate in cycle 1 is adjusted to the age and gender-distribution of the model population. An adjustment is made in each model cycle to represent the increased risk of death as patients become older as the model time progresses. This is estimated by fitting an exponential function to the mortality rate in successive age bands.

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

Table 97: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	For both options 'Treatment of DVT and PE' and 'Treatment followed by prevention of recurrent DVT and PE', the time horizon in the base case is 60 years (patients' lifetimes) in order to capture the lifetime of the youngest patients up to 100 years of age (17.6% of people in the UK were expected to reach 100 years of age in 2011).[59] The applied age of the cohort at model start is 54.7 years which equals the average age of the trial population in RE-COVER I.	This time horizon is considered appropriate in order to fully capture the impact of deaths and health-related quality of life (HRQL) impairment from recurrent venous thromboembolism (VTE), bleeding (including permanent disability from intracranial haemorrhage (ICH)), post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH) and acute coronary syndrome events (myocardial infarction (MI) and unstable angina). The economic model has the flexibility to consider shorter time horizons; a 1 year time horizon will be explored in the sensitivity analysis. Treatment effects were not extrapolated beyond the end of follow-up of the pivotal trials.	NICE Reference case/ NICE Guide to the methods of technology appraisal 2013
Cycle length	1 month	A cycle length of 1 month was deemed sufficiently short to reproduce the underlying disease process of DVT and PE.	N/A
Half-cycle correction	Not applied	Given the short cycle length of 1 months, half-cycle correction was not deemed vital to the analysis.	N/A
Were health effects measured in QALYs; if not, what was used?	Yes, the QALY was used as the aggregated outcome measure in the cost-effectiveness analyses.	NICE Reference case	NICE Guide to the methods of technology appraisal 2013
Discount of 3.5% for utilities and costs	Both costs and health effects are discounted to present values at a rate of 3.5% per annum.	NICE Reference case	NICE Guide to the methods of technology appraisal 2013
Perspective (NHS/PSS)	Yes, the perspective is that of the NHS and PSS.	NICE Reference case	NICE Guide to the methods of technology appraisal 2013

NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years

Technology

7.2.7 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?

Dabigatran is modelled in line with its recently adopted indication for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (Section 1.5). The comparators are incorporated into the model as per their marketing authorisation using doses consistent with the respective SPCs.

The expected posology of dabigatran for this indication is as follows (please note that this posology aligns with the approved indication of stroke prevention in patients with non-valvular atrial fibrillation). The draft SPC for dabigatran in DVT/PE prescribes a standard daily dose of 300 mg taken as one 150 mg capsule twice daily and goes on to recommend that the daily dose shall be lowered to 220 mg (taken as one 110 mg capsule twice daily) in:

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups the daily dose of dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

The recommendation to use dabigatran 220 mg (taken as one 110 mg capsule twice daily) in the patient population described above is based on pharmacokinetic and pharmacodynamic analyses only. This strength of dabigatran has not been studied in the clinical development programme and corresponding efficacy and safety data is hence not available. However, the European Medicines Agency has granted positive opinion recommending the approval of

both dabigatran 150 mg BD and dabigatran 110 mg BD for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults.

In this submission it is assumed that the clinical efficacy and safety data that has been presented in Section 6 (and the corresponding clinical event rates used in the economic model described in Section 7) for dabigatran 150 mg BD are equivalent to the expected efficacy and safety data (and clinical event rates) for dabigatran 110 mg BD. Drug costs for the 150 mg and 110 mg capsule are identical in the UK. The different dosing, therefore, does not affect cost-effectiveness modelling.

The efficacy and safety of dabigatran have not been established for DVT/PE patients with active cancer, reflecting the small number of cancer patients in the pivotal trials. However, cancer patients are not contraindicated and cost-effectiveness estimates for this subgroup will be presented nonetheless.

7.2.8 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 clinical continuation rule is assumed. The duration of acute treatment equals the length of treatment in RECOVER I and RECOVER II (6 months).

7.3 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 6). 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.

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

As previously mentioned (Section 7.2.3), the economic model is structured around two primary composite endpoints:

1. Symptomatic recurrent VTE and VTE-related death (rVTERD)
2. Major or clinically relevant bleeding (MCRB)

According to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, an analysis of the combined incidence of recurrent VTE and deaths related to VTE is considered most important in trials aiming to document non-inferiority whereas an analysis of the combined incidence of recurrent VTE and all deaths is considered most important in trials aiming to show superiority[12]. Consistent primary efficacy endpoints were used across the RE-COVER, RE-COVER II and RE-MEDY (pivotal non-inferiority) studies. The primary endpoint was a composite of recurrent VTE (objectively confirmed symptomatic DVT and/or PE) and deaths related to VTE. In RE-SONATE (pivotal superiority study), the primary endpoint was a composite of recurrent symptomatic and objectively verified VTE, death associated with VTE or unexplained death.

The following Table 98 presents the **observed incidence** of rVTERD and MCRB in the warfarin (RE-COVER and RE-MEDY) or placebo arm (RE-SONATE) of the pivotal dabigatran trials. Sub-

group specific risks for rVTERD and MCRB apply when these are selected. **Baseline risks** (assuming a constant hazard) are given in brackets.

Table 98: Incidence of primary composite endpoints in the warfarin or placebo arm

	rVTERD		MCRB		
Trial	**N**	**n (%)**	**N**	**n (%)**	**Source**
Treatment period					
Pooled RE-COVER (warfarin arm)	2554	62[1] (2.43)	2462	217[3] (8.50)	
					Table 43
Secondary prevention (warfarin is comparator)					
RE-MEDY (warfarin arm)	1426	18[2] (1.26)	1426	145[4] (10.17)	Table 45
Secondary prevention (rivaroxaban or LMWH is comparator)					
RE-SONATE (placebo arm)	662	37[2] (5.59)	659	13[2] (1.97)	Table 47

1 Up to end of 30 days follow-period
2 Intended treatment period (ITT)
3 From start of any study drug (single and double-dummy periods)
4 On treatment period

In the probabilistic sensitivity analysis, incidence is sampled from a beta distribution defined by the number of patients with events and the number at risk.

Treatment effects for the primary composite endpoints versus warfarin (or placebo) are presented in Table 99. The HR estimates represent the *first* recurrent VTE or bleed event. In sub-group analyses, sub-group specific probabilities of rVTERD and MCRB apply (not shown).

Table 99: Treatment effects for primary composite endpoints

	rVTERD[1]	MCRB	
	HR (95% CI)	**HR (95% CI)**	**Source**
Dabigatran trials			
Pooled RE-COVER	1.09 (0.77, 1.54)[2]	0.56 (0.45; 0.71)[3,4]	

			Table 43, Table 66
RE-MEDY	1.44 (0.78,2.64)	0.55 (0.41, 0.72)[3]	Table 45, Table 70
RE-SONATE	0.08 (0.02, 0.25)	2.69 (1.43, 5.07)[3]	Table 47, Table 76
Rivaroxaban trials			
EINSTEIN-DVT	0.68 (0.44, 1.04)[5]	0.97 (0.76, 1.22)[6]	[32;60]
EINSTEIN-PE	1.12 (0.75, 1.68)[5]	0.90 (0.76, 1.07)[6]	[32;60]
Pooled EINSTEIN-DVT + PE	0.89 (0.66, 1.19)[5]	0.93 (0.81, 1.06)[6]	[61]
EINSTEIN-EXT	0.18 (0.09, 0.39)[5]	5.19 (2.30, 11.70)[6]	[32;60]
LMWH trials			
LMWH	0.49 (0.34, 0.70)[7]	1.05 (0.53, 2.10)[7,8]	[33]
LMWH SP Cancer	0.63 (0.34, 1.18)	2.58 (0.51, 13.06)[7,8]	[40]

1 ITT population
2 Up to end of 30 days follow-period
3 Treated set
4 From start of any study drug (open label LMWH, followed by single and double-dummy periods)
5 All rivaroxaban trials included unexplained death in the primary composite endpoint rVTERD
6 Safety set
7 RR since no HR available, meta-analysis of 5 LMWH cancer trials (RE)
8 MB instead of MCRB

RRs were applied only if HRs were not available. In the probabilistic sensitivity analysis, HRs and RRs are sampled from normal distributions on the log scale.

For use in the economic model, estimates of **relative treatment effect** for dabigatran, comparators other than warfarin (i.e. rivaroxaban and LMWH) and no treatment are obtained by applying treatment effects (Table 99) versus warfarin (or placebo) to the baseline risk in the warfarin (or placebo) arm of the pivotal dabigatran trials (Table 98). To justify the use of this approach, adjusted indirect comparisons (AIC), accompanied by the imperative assessment of heterogeneity, have been conducted and discussed elsewhere in this submission (see Section 6.6 – 6.7).

Adjustment for time in INR range

The association between time spent within an International Normalised Ratio (INR) range of 2.0 to 3.0 and the incidence of recurrent VTE and bleeding was investigated in an analysis of linked GPRD-HES data.[62]

Table 100 presents the HRs for recurrent VTE and bleeding for a 1% change in the time in INR range estimated from GPRD-HES data.

Table 100: Effect of a 1% Decrease in Time in International Normalised Ratio Range

Endpoint	HR (95% CI)
Recurrent VTE	1.011 (1.003, 1.019)
Bleeding	1.016 (0.999, 1.033)

CI = confidence interval; HR = hazard ratio.
In the probabilistic analysis, HRs are sampled from normal distributions on the log scale defined by the mean and 95% confidence intervals.
Source: [62]

The base case analysis in the economic evaluation assumes an INR control in the WFN arm of 58.4% (in line with that achieved in the RE-COVER and RE-COVER-II trials, where the mean was 58.4% (SD 31.7%)). The effect of adjusting the percentage of time spent in INR range 2.0-3.0 is explored in the sensitivity analysis, using the relationship described in Table 100 above. This has been done for the following reason:

1. To adjust the probabilities of recurrent VTE and bleeding for the WFN cohort to reflect potential differences between outcomes observed in the dabigatran trials and those observed in routine clinical practice due to differences in time in INR range

Intervention-specific discontinuation

The economic model allows for treatment discontinuation prior to reaching the maximum planned duration, in addition to the discontinuation following MBE. Intervention-specific discontinuation rates were applied up to the maximum planned duration of treatment and do encompasses the following reasons:

- AE, worsening of other pre-existing disease
- AE, other than bleeding
- Non-compliant with protocol
- Lost to follow-up
- Patient refused to continue medication
- Other

There were differences in the design of the rivaroxaban comparators trials which needed to be considered and the reasons for discontinuation due to AE were not always reported with the same granularity. In EINSTEIN-PE and EINSTEIN-DVT, it was not possible to isolate discontinuation due to the AE such as bleed from discontinuation due to other AEs. Discontinuation due to disease worsening was not reported specifically. To adjust for this, the rate of first major bleeds was deducted from the total discontinuation rate due to AE. No

data with regards to discontinuation of LMWH was found and as such discontinuation of LMWH was assumed equal to that in the dabigatran arm of the model.

Table 101: Intervention-specific discontinuation rates

Intervention	Rate	Observation period (months)	1-month cycle probability	Maximum treatment duration in model	Source
Dabigatran Treatment					
RE-COVER	12.2%	6.0	2.1%	6.00	[3], Table 1.1.1.2
RE-COVER II	11.6%	6.0	2.0%	6.00	[3], Table 1.1.1.3
RE-COVER I+II	11.9%	6.0	2.1%	6.00	[3], Table 1.1.1.1
Dabigatran Secondary prevention					
RE-MEDY	16.6%	18.0	1.0%	18.00	[3], Table 1.1.1.4
RE-SONATE	8.3%	6.0	1.4%	6	[3], Table 1.1.1.5
Warfarin Treatment					
RE-COVER	10.7%	6.0	1.9%	6.0	[3], Table 1.1.1.2
RE-COVER II	10.9%	6.0	1.9%	6.0	[3], Table 1.1.1.3
RE-COVER I+II	10.9%	6.0	1.9%	6.0	[3], Table 1.1.1.1
Warfarin Secondary prevention					
RE-MEDY	16.1%	18.0	1.0%	18.0	[3], Table 1.1.1.4
Placebo secondary prevention					
RE-SONATE	7.0%	6.0	1.2%	0.0	[3], Table 1.1.1.5
Rivaroxaban treatment					
EINSTEIN-DVT	10.5%	7.2	1.5%	6.0	[31], Table 2
EINSTEIN-PE	9.6%	8.1	1.2%	6.0	[32], Table 2
weighted average PE/DVT	10%	7.5	1.4%	6.0	weighted average PE/DVT
Rivaroxaban secondary prevention					
EINSTEIN-EXT	12.3%	8.4	1.5%	6.0	[31], Table 2

7.3.2 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.

As the economic model assumes a cycle length of one month, event probabilities observed over the duration of the clinical trials had to be converted into monthly transition probabilities.

During the dabigatran clinical development programme, the rates of both primary composite endpoints, rVTERD and MCRB, were observed to be higher in the first months after index

event and gradually declined thereafter. Therefore, the Markov cycle probabilities of rVTERD and MCRB during the *treatment period* were log transformed with respect to time to better reflect the occurrence pattern of these events observed in the dabigatran trials:

$$p_{rVTERD} \text{ per cycle} = \log_{210days^{\wedge}(1/r)} T$$

$$p_{rMCRBE} \text{ per cycle} = \log_{180days^{\wedge}(1/r)} T$$

where *r* denotes the risk. *T* is the number of days at end of cycle.

For the *secondary prevention, post-treatment periods and other probabilities in the model* the incidence do not vary with time (i.e. each month the same risk applies). The Markov cycle probabilities were calculated from the relative treatment effects assuming a constant hazard as follows:

$$p_{cl} = 1 - (1 - r)^{CL/t}$$

where *CL* denotes the cycle length - which is 1 month in this case, *r* is the relative treatment effect (risk), and *t* refers to the follow-up time in months in the respective trial.

Multiple events in individual patients are accounted for by allowing patients to be exposed to a new risk of recurrent VTE or MCRB after initiation of a 6 months standard treatment course of LMWH followed by warfarin and allowing patients to be exposed to a new risk of recurrent VTE after discontinuation to no treatment, thus rates of recurrent VTE and MCRBE applied in the model are reflective of first recurrent event or first MCRBE.

Type of recurrent VTE and bleeding events

To be able to capture the differential costs, HRQL and life expectancy associated with each individual type of event *within* the two composite endpoints (rVTERD and MCRB), conditional probabilities were employed as follows:

- The probability of having a non-fatal PE, proximal DVT, VTE-related death, or distal DVT conditional on having a rVTERD event
- The probability of having an ICH, other MBE (excluding ICH), or CRNMB conditional on having a MCRB.

The probabilities of each type of recurrent VTE event and each type of bleeding event within the composite endpoints rVTERD and MCRB were based on data on number of patients per type of event observed in the pivotal trials (ITT population).

Table 102 shows the event distribution within the two composite endpoints rVTERD and MCRB (excluding unexplained deaths).

Table 102: Treatment-specific distribution by type of event

	Treatment phase			Secondary prevention				After therapy discontinuation
rVTERD	DBG[1]	WFN[2]	RVX[3]	DBG[4]	DBG[5]	WFN[6]	RVX[7]	All[8]
Non-fatal PE	33.8%	33.9%	55.3%	34.6%	33.3%	22.2%	28.6%	23.3%
Proximal DVT (no PE)	63.2%	61.3%	42.1%	61.5%	66.7%	72.2%	71.4%	65.1%
VTE-related death	2.9%	4.8%	2.6%	3.8%	0.0%	5.6%	0.0%	11.5%
Distal DVT only	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
MCRB events	DBG[1]	WFN[2]	RVX[3]	DBG[4]	DBG[5]	WFN[6]	RVX[7]	
ICH	1.8%	2.1%	1.3%	2.5%	0.0%	2.8%	0.0%	
Other MBE (excl. ICH)	20.2%	19.0%	9.0%	13.8%	5.6%	14.5%	11.1%	
Fatal MBE	4.2%	5.0%	7.5%	0.0%	0.0%	4.0%	0.0%	
CRNMB	78.0%	78.8%	89.7%	83.8%	94.4%	82.8%	88.9%	

1 Based on patients with events (ITT set, mixed population) of RE-COVER I+II. Dabigatran arm.
2 Based on patients with events (ITT set, mixed population) of RE-COVER I+II. Warfarin arm.
3 Pooled EINSTEIN-DVT+PE, ITT set (Prins et al.)
4 Based on patients with events (ITT set, mixed population) of RE-MEDY. Dabigatran arm.
5 Based on patients with events (ITT set, mixed population) of RE-SONATE. Dabigatran arm. (Used for comparators other than warfarin.)
6 Based on patients with events (ITT set, mixed population) of RE-MEDY. Warfarin arm.
7 EINSTEIN Investigators, 2010[60]
8 Prandoni, 2007[58]

(i) Type of recurrent VTE events in sub-groups

Number of patients by type of event was not available for sub-groups. Therefore this data needed to be derived. This was done based on:

- The number of events and number of patients with events observed in the ITT population;

- Total rVTE events (fatal and non-fatal) observed in sub-groups and
- Total PE events (fatal and non-fatal) observed in sub-groups.

The derivation was conducted as follows:

Step 1: A ratio of number of patients experiencing PEs (fatal and non-fatal) to total number of PE events (fatal and non-fatal) was calculated in the ITT group. This ratio was then multiplied with the number of PE events in each sub-group and the result was number of patients experiencing PE and VTE-related death, per sub-group. All fatal rVTE events were due to PE.

Step 2: The fraction of VTE-related deaths to total, fatal and non-fatal, PE was calculated for the ITT group, and this was multiplied with the number of patients with VTE events as calculated in step 1; this resulted in number of patients who experience a fatal rVTE.

Step 3: The number of patients with non-fatal PE in each sub-group was calculated as the difference between number of patients with PE and VTE-related death (Step 1) and number of patients who experience a fatal rVTE (Step 2).

Step 4: Finally, number of patients with proximal rDVT was calculated as the difference between number of patients with rVTE and number of patients with fatal and non-fatal rPE (Steps 3 and 3), assuming no distal rDVT.

(ii) Type of bleeding events in sub-groups

In sub-groups, number of patients with ICH was not available, neither was the number of patients with fatal MBE. The number of patients with ICH was calculated as the fraction of ICH to total MBE in the treated set multiplied by total patients with MBE per sub-group. The proportion of fatal major bleeds in sub-groups was calculated as the proportion of fatal MBE to total MBE in the overall treated set, which was then multiplied with the number of patients with MBE per sub-group. Therefore, a measure of case fatality following major bleeds was derived specific for each intervention and each sub-group.

All CRNMB were non-fatal. The number of patients with CRNMB was calculated by simply subtracting the number of MBE (excluding ICH) from the total MCRB.

Probabilities of other model events

The ***probability of recurrent VTE after trial follow-up*** is calculated from the cumulative incidence at 10 years reported by Prandoni et al. (2007)[58], assuming a constant hazard. The risk of bleeding after trial follow-up is assumed to be zero.

Probabilities of cardiovascular outcomes

Please note: The economic model does not assess cardiovascular outcomes in the base case analyses. However, the impact of including these outcomes is explored in sensitivity analyses (Table 123). Probabilities of these events (Table 103 – Table 105) are included in this section for clarity.

Cardiovascular outcomes were excluded from the base case analysis on the grounds that:

- Cardiovascular events were not considered relevant to the disease pathway covered in this submission
- Not including these events is consistent with a previous cost-effectiveness analysis of rivaroxaban for the long-term treatment and secondary prevention of recurrent VTE[9]
- Patients enrolled in the pivotal randomised controlled trials of dabigatran outlined in Sections B of this submission were not stratified according to cardiovascular risk. Thus, interpretation of the cardiovascular outcomes results of these trials is not straightforward.

The probabilities of myocardial infarction (MI), unstable angina (UA) and cardiac death were estimated from the absolute incidences of events in the pivotal trials. In all cases where fatal MIs were reported, these figures were used to estimate the probability of an MI being fatal. This was the case for all dabigatran trials and EINSTEIN PE trial. When fatal MIs were not reported, the number of cardiac deaths was used to estimate probability of MI being fatal in the model.

The probabilities of MI and cardiac deaths as well as UA are presented in Table 103 and Table 104, respectively. In the probabilistic sensitivity analysis, probabilities are sampled from beta distributions. Events were assumed to occur at a constant rate during the trial follow-up. For simplicity, events were assigned to the midpoint, i.e., 3 months (cycle 4).

Table 103: Probabilities MI and cardiac death

Trial	Intervention					Comparator*					Source
	At risk (N)	MI (n)	p	Cardiac deaths (n)	P of MI being fatal†	At risk (N)	MI (n)	p	Cardiac death (n)	P of MI being fatal†	
RE-COVER	1273	4	0.31%	0	0%	1266	2	0.16%	0	0%	Schulman (2009)[1]
RE-COVER II	1280	4	0.31%	0	0%	1288	2	0.16%	0	0%	Schulman (2013)[27]
RE-COVER + RE-COVER II	2553	8	0.31%	0	0%	2554	4	0.16%	0	0%	Schulman (2013)[27]
RE-MEDY	1430	9	0.63%	0	0%	1426	4	0.07%	0	0%	Clemens et al (2013)[63]
RE-SONATE	684	1	0.15%	0	0%	659	1	0.15%	0	0%	Clemens et al (2013)[63]
EINSTEIN-DVT	1718	7	0.35%	1	16.67%	1711	3	0.06%			Bauersachs, 2010[31]
EINSTEIN-PE	2412	8	0.33%	2	25.00%	2405	14	0.46%			ClinicalTrials.gov (NCT00439777), [64]
EINSTEIN-DVT + PE	4130	15	0.34%	3	21.43%	4116	17	0.29%			Sum of EINSTEIN-PE and DVT
EINSTEIN-EXT	598	0	0%	0	0%	590	0	0%			Bauersachs, 2010[31]

* Comparator is warfarin, except in RE-SONATE an d EINSTEIN-EXT where it is placebo
† Calculated as number of cardiac deaths to total number of Mis

Table 104: Probabilities of UA

Trial	Intervention			Comparator*			Source
	N	N	p	n	N	p	
RE-COVER	1	1273	0.08%	1	1266	0.08%	Schulman (2009)[1]
RE-COVER II	0	1280	0.00%	0	1288	0.00%	Schulman (2013)[27]
RE-COVER + RE-COVER II	1	2553	0.04%	1	2554	0.04%	Schulman (2013)[27]
RE-MEDY	3	1430	0.21%	3	1426	0.21%	Clemens et al (2013)[63]
RE-SONATE	0	684	0.00%	0	659	0.00%	Clemens et al (2013)[63]
EINSTEIN-DVT	1	1718	0.06%	1	1711	0.06%	Bauersachs, 2010[31]
EINSTEIN-PE	10	2412	0.41%	6	2405	0.25%	ClinicalTrials.gov (NCT00439777), [64]
EINSTEIN-DVT + PE	11	4130	0.27%	7	4116	0.17%	Sum of EINSTEIN-PE and DVT
EINSTEIN-EXT	3	598	0.50%	1	590	0.17%	Bauersachs, 2010[31]

* Comparator is warfarin, except in RE-SONATE an d EINSTEIN-EXT where it is placebo

The ***probabilities of chronic complications from MI and unstable angina (UA)*** were based on clinical opinion 0.600 (0.500 - 0.700) and were sampled from a square distribution (Table 105).

Table 105: Death and chronic complications from MI and unstable angina (UA)

	Probability	Range	Distribution	Source
Chronic complications from MI	0.6	0.5 – 0.7	Square	Assumption
Chronic complications from UA	0.6	0.5 – 0.7	Square	Assumption

Probability of CTEPH

CTEPH is a complication of PE and is associated with considerable morbidity and mortality.[65] It is relatively rare after a first VTE. However, patients who have experienced a recurrent PE are at a greater risk of developing PH[65;66]. In a prospective, long-term follow-up study Pengo and colleagues (2004)[65] reported a 2-year cumulative incidence of 3.8% after a first PE and 33% after a second PE; no incident cases occurred after 2 years and patients were followed up to 10 years in the study. In the model, all index PE were attributed the 2 year probability of CTEPH at model start.

Subsequently, a probability of PH subsequent to non-fatal PE events, as projected by the model, was applied monthly for 2 years following the PE event; beyond two years the probability was assumed to be zero (note that applying a probability of CTEPH to all index PE and then to all PE events could have overestimated the incidence of PH in those patients who have index PE and subsequently have a recurrent event). Yet, as the same study of Pengo et al noted, the likelihood of developing PE after a recurrent PE can be much higher. In the same way, applying an incidence of PH after a second recurrent event can account for the higher risk.

The 2-year cumulative probability reported by Pengo et al was adjusted to a monthly Markov cycle probability of 0.16%.

Probability of Post-thrombotic Syndrom (PTS)

PTS was not recorded in the trials. In the model, the incidence of PTS is assumed to be the same for all comparators. Published evidence suggests that mild PTS had little detrimental effect on quality of life[67]; therefore, the model includes only severe PTS. The incidence of severe PTS was based on a study by Prandoni and colleagues (1997)[58]. In this study, the cumulative incidence of severe PTS was 8.1% (43/528) after 5 years. All index DVT were attributed the 5 year probability of PTS at model start. Subsequently, a probability of PTS

following non-fatal DVTs events as projected by the model was applied monthly for 5 years after the DVT event (based on the 5-years cumulative incidence reported by Lenert and Soetikno[67]; five years after event, the probability was assumed to be zero. In the probabilistic analysis, the probabilities are sampled from beta distributions.

Probability of dyspepsia

Please note: The inclusion of dyspepsia in the economic model was assessed as a sensitivity analysis only. However, the method of calculating incidence of dyspepsia is included in this section for clarity.

The incidence of dyspepsia in patients receiving dabigatran and warfarin was taken from the RE-COVER and RE-COVER II trials. These incidence rates were converted to monthly Markov cycle probabilities for use in the economic model. Dyspepsia was excluded from the base case economic analysis because the prevalence was low in clinical studies (1-3%) and dyspepsia was felt not to be relevant to the disease pathway considered in the submission.

Probability of death from other causes

The model calculates the probability for death from other causes through age and gender-specific mortality rates for the UK (estimates for 2010, ONS[68]). The starting mortality rate in cycle 1 is adjusted to the age and gender-distribution of the model population. An adjustment is made in each model cycle to represent the increased risk of death as patients become older as the model time progresses. This is estimated by fitting an exponential function to the mortality rate in successive age bands. Mortality rates are adjusted for subgroup analyses as appropriate for age and gender groups. The relative survival was assumed to be 67%, based on SEER Cancer Statistics (5-year survival for all cancer sites diagnosed in 2004).[69]

7.3.3 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.

As described in Section 7.3.2, monthly transition probabilities for the treatment period were log transformed with respect to time to better reflect the occurrence pattern observed

during the pivotal trials. Table 106 exhibits the cumulative probability of rVTE and MCRB applied per cycle (month) over the treatment period. The example is provided for the rVTE and MCRB events observed in the warfarin arms of RE-COVER I and RE-COVER II (pooled).

Table 106: Example log-transformation for cycle probabilities

Cycle in model	Days to end of cycle	Cumulative probability rVTE	Incremental probability applied	Cumulative probability MCRB	Incremental probability applied
1	30	1.54%	1.54%	5.56%	5.56%
2	60	1.86%	0.31%	6.70%	1.13%
3	90	2.04%	0.18%	7.36%	0.66%
4	120	2.17%	0.13%	7.83%	0.47%
5	150	2.27%	0.10%	8.20%	0.37%
6	180	2.36%	0.08%	8.50%	0.30%

For post-acute treatment periods (including post-secondary prevention), the transition probabilities do not vary with time.

7.3.4 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?

Intermediate outcome measures were not used.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- 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 specialist whose opinion was sought

[3] 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.

- 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 experts were only involved in the process of model development to understand patient pathways and the standard of care in the UK. Expert opinion was not sought for clinical parameters derived from trial data of the systematic literature reviews.

Summary of selected values

7.3.6 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.

Table 107: Summary of variables applied in the economic model

Clinical variable	Value	CI (95%)	Distribution	Reference
Incidence of rVTE (baseline risk), treatment	2.43%	-	Beta (α=62, β=2492)	
				Table 43
Incidence of MCRB (baseline risk), treatment	7.68%	-	Beta (α=189, β=2273)	Table 66
Incidence of rVTE (baseline risk), SP	5.59%	-	Beta (α=37, β=625)	Table 47
Incidence of MCRB (baseline risk), SP	1.97%	-	Beta (α=13, β=646)	[70], Table 4.5.5.1.1.5
Treatment effects				
Treatment phase				
rVTE, dabigatran vs warfarin (HR)	1.09	0.77 – 1.54	Normal (log scale)	

				Table 43
rVTE, rivaroxaban vs VKA (HR)	0.89	0.66 – 1.19	Normal (log scale)	[61]
rVTE, LMWH vs VKA (RR)	0.49	0.34 – 0.70	Normal (log scale)	Table 99
MCRB, dabigatran vs warfarin (HR)	0.56	0.45 – 0.71	Normal (log scale)	Table 66
MCRB, rivaroxaban vs VKA (HR)	0.93	0.81 – 1.06	Normal (log scale)	[61]
MCRB, LMWH vs VKA (RR)	1.05	0.53 – 2.10	Normal (log scale)	Table 99
Secondary prevention				
rVTE, dabigatran vs warfarin (HR)	1.44	0.78 – 2.64	Normal (log scale)	Table 45
rVTE, dabigatran vs placebo (HR)	0.08	0.02 – 0.25	Normal (log scale)	Table 47
rVTE, rivaroxaban vs placebo (HR)	0.18	0.09 – 0.39	Normal (log scale)	[31]
rVTE, LMWH vs placebo (HR)	0.63	0.34 – 1.18	Normal (log scale)	[40]
MCRB, dabigatran vs warfarin (HR)	0.55	0.41 – 0.72	Normal (log scale)	Table 66
MCRB, dabigatran vs placebo (HR)	2.69	1.43 – 5.07	Normal (log scale)	[70], Table 4.5.5.1.2.5
MCRB, rivaroxaban vs placebo (HR)	5.19	2.30 – 11.70	Normal (log scale)	[31]
MCRB, LMWH vs placebo (RR)	2.58	0.51 – 13.06	Normal (log scale)	[40]
Type of recurrent VTE events				**Table 102 in this submission**
Treatment phase				
Dabigatran				
Non-fatal PE	33.8%		Beta (α=23, β=45)	[71],Table 2.5.56.1.1
Proximal DVT	63.2%		Beta (α=43, β=25)	[71],Table 2.5.56.1.1
VTE-related death	2.9%		Beta (α=2, β=66)	[71],Table 2.5.56.1.1
Distal DVT	0.0%		n/a	[71],Table 2.5.56.1.1
Warfarin				
Non-fatal PE	33.9%		Beta (α=21, β= 41)	[71],Table 2.5.51.1.1
Proximal DVT	61.3%		Beta (α=38, β=24)	[71],Table 2.5.51.1.1
VTE-related death	4.8%		Beta (α=3, β=59)	[71],Table 2.5.51.1.1
Distal DVT	0.0%		n/a	[71],Table 2.5.51.1.1
Rivaroxaban				
Non-fatal PE	55.3%		Beta (α=42, β= 34)	[61]

Proximal DVT	42.1%	Beta (α=32, β= 44)	[61]
VTE-related death	2.6%	Beta (α=2, β= 74)	[61]
Distal DVT	0.0%	n/a	[61]
LMWH[1]			
Non-fatal PE	42.0%	Beta (α=197, β=274)	Calculated; based on pooled events in all trials
Proximal DVT	54.8%	Beta (α=257, β=214)	Calculated; based on pooled events in all trials
VTE-related death	3.2%	Beta (α=15, β=456)	Calculated; based on pooled events in all trials
Distal DVT	0.0%	n/a	Calculated; based on pooled events in all trials
Secondary prevention			
Dabigatran (RE-MEDY trial)			
Non-fatal PE	34.6%	Beta (α=9, β=17)	[71],Table 2.5.56.1.4
Proximal DVT	61.5%	Beta (α=16, β=10)	[71],Table 2.5.56.1.4
VTE-related death	3.8%	Beta (α=1, β=25)	[71],Table 2.5.56.1.4
Distal DVT	0.0%	n/a	[71],Table 2.5.56.1.4
Dabigatran (RE-SONATE trial)			
Non-fatal PE	33.3%	Beta (α=1, β=2)	[71],Table 2.5.56.1.5
Proximal DVT	66.7%	Beta (α=2, β=1)	[71],Table 2.5.56.1.5
VTE-related death	0.0%	Beta (α=0.5, β=4)	[71],Table 2.5.56.1.5
Distal DVT	0.0%	Fixed	[71],Table 2.5.56.1.5
Warfarin			
Non-fatal PE	22.2%	Beta (α=4, β=14)	[71],Table 2.5.56.1.4
Proximal DVT	72.2%	Beta (α=13, β=5)	[71],Table 2.5.56.1.4
VTE-related death	5.6%	n/a	[71],Table 2.5.56.1.4
Distal DVT	0.0%	Beta (α=1, β=17)	[71],Table 2.5.56.1.4
Rivaroxaban			
Non-fatal PE	28.6%	Beta (α=2, β=5)	[31]
Proximal DVT	71.4%	Beta (α=5, β=2)	[31]
VTE-related death	0.0%	Beta (α=0.5, β=8)	[31]
Distal DVT	0.0%	n/a	[31]

After therapy discontinuation			
Non-fatal PE	23.3%	Beta (α=87, β=286)	[58]
Proximal DVT	65.1%	Beta (α=243, β=130)	[58]
VTE-related death	11.5%	Beta (α=43, β=330)	[58]
Distal DVT	0.0%	n/a	[58]
Type of bleeding events			**Table 102 in this submission**
Treatment phase			
Dabigatran (RE-MEDY)			
ICH	1.8%	Beta (α=2, β=107)	[72]
Other major bleeding event (MBE)	20.2%	Beta (α=22, β=87)	[72]
Fatal MBE	4.2%	Beta (α=1, β=23)	[72]
Clinically relevant non-major bleed (CRNMB)	78.0%	Beta (α=85, β=24)	[72]
Dabigatran (RE-SONATE)			
ICH	0.0%	Fixed	[72]
Other major bleeding event (MBE)	5.6%	Beta (α=2, β=34)	[72]
Fatal MBE	0.0%	Fixed	[72]
Clinically relevant non-major bleed (CRNMB)	94.4%	n/a	[72]
Warfarin			
ICH	2.1%	Beta (α=4, β=185)	[72]
Other major bleeding event (MBE)	19.0%	Beta (α=36, β=153)	[72]
Fatal MBE	5.0%	Beta (α=2, β=38)	[72]
Clinically relevant non-major bleed (CRNMB)	78.8%	Beta (α=149, β=40)	[72]
Rivaroxaban			
ICH	1.3%	Beta (α=5, β= 383)	[61]
Other major bleeding event (MBE)	9.0%	Beta (α=35, β= 353)	[61]
Fatal MBE	7.5%	Beta (α=3, β= 37)	[61]
Clinically relevant non-major bleed (CRNMB)	89.7%	Beta (α=348, β= 40)	[61]
LMWH[1]			

ICH	1.6%		Beta (α=30, β=1853)	Calculated; based on pooled events in all trials
Other major bleeding event (MBE)	12.1%		Beta (α=227, β=1656)	Calculated; based on pooled events in all trials
Fatal MBE	5.4%		Beta (α=14, β=243)	Calculated; based on pooled events in all trials
Clinically relevant non-major bleed (CRNMB)	86.4%		Beta (α=1626, β=257)	Calculated; based on pooled events in all trials
Secondary prevention				
Dabigatran				
ICH	2.5%		Beta (α=2, β=78)	[72]
Other major bleeding event (MBE)	13.8%		Beta (α=11, β=69)	[72]
Fatal MBE	0.0%		Fixed	[72]
Clinically relevant non-major bleed (CRNMB)	83.8%		Beta (α=67, β=13)	[72]
Warfarin				
ICH	2.8%		Beta (α=4, β=141)	[72]
Other major bleeding event (MBE)	14.5%		Beta (α=21, β=124)	[72]
Fatal MBE	4.0%		Beta (α=1, β=24)	[72]
Clinically relevant non-major bleed (CRNMB)	82.8%		Beta (α=120, β=25)	[72]
Rivaroxaban				
ICH	0.0%		Fixed	[60]
Other major bleeding event (MBE)	11.1%		Beta (α=4, β=32)	[60]
Fatal MBE	0.0%		Fixed	[60]
Clinically relevant non-major bleed (CRNMB)	88.9%		Beta (α=32, β=4)	[60]
Other probabilities				
Disabled from intracranial haemorrhage (ICH)	65.3%		Beta (α=90.8, β=48.2)	Rosand (2004)[73]
Cumulative incidence of CTEPH at 2 years in PE patients	3.8%		Beta (α=7, β=184)	Pengo (2004)[65]
Probability of CTEPH (per 1-month cycle)	0.16%			
5 years cumulative incidence of severe PTS	8.1%		Beta (α=43, β=485)	Prandoni (1997)[74]
Probability of severe PTS (per 1-month cycle)	0.14%			
rVTE after therapy discontinuation	39.90%	35.40% - 44.40%	Normal (SE=0.02)	Prandoni et al. (2007)[58]
Discontinuation probabilities (per 1-month cycle)				**Table 101 in this submission**

Treatment phase				
Dabigatran	2.09%			[71], Table 1.1.1.1
Warfarin	1.91%			[71], Table 1.1.1.1
Rivaroxaban	1.44%			Weighted average DVT[60] and PE[32]
Secondary Prevention				
Dabigatran	1.00%			[71], Table 1.1.1.4
Warfarin	0.97%			[71], Table 1.1.1.4
Rivaroxaban	1.55%			[60]

Disutilities				**Table 113 in this submission**
Initial and recurrent DVT	0.25	0.24 – 0.26	Normal (SE=0.0054)	[75]
Initial and recurrent PE	0.25	0.23 – 0.27	Normal (SE=0.0152)	[75]
During active warfarin treatment	0.012	0.008 – 0.016	Gamma (α=28.66, β=0.0004)	[76]
During active LMWH treatment	0.008	0.005 – 0.011	Gamma (α=22.65, β=0.0004)	[76]
Severe PTS	0.07	0.048 – 0.092	Gamma (α=39.22, β=0.002)	[67]
Intracranial haemorrhage (ICH), disabled from	0.5	0.402 – 0.598	Gamma (α=100, β=0.005)	[77]
Major bleeding event (MBE)	0.13	0.105 – 0.155	Gamma (α=100, β=0.001)	[75]
Clinically relevant non-major bleeding (CRNMB)	0.04	0.032 – 0.048	Gamma (α=100, β=0.0004)	[75]
Myocardial infarction (MI)*	0.063	0.050 – 0.075	Gamma (α=22.57, β=0.003)	[78]
Unstable angina (UA)*	0.085	0.069 – 0.102	Gamma (α=40.40, β=0.002)	[78]
CTEPH	0.10	0.080 – 0.120	Gamma (α=100, β=0.001)	[79;80]
Dyspesia*	0.04	0.032 – 0.048	Gamma (α=100, β=0.0004)	[81]

1 Applies to treatment and secondary prevention phase alike
* Applies to sensitivity analyses only

n/a … Not applicable since a calculated residual
fixed … As frequency zero and shape parameter α > 0 (by definition), fall back to deterministic value

7.3.7 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.

Costs and treatment effects were not extrapolated beyond the end of follow-up of the pivotal trials.

7.3.8 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. The duration of acute parenteral treatment was assumed to be 5 days for dabigatran and warfarin, whereas the duration for rivaroxaban in the base case analysis was set to zero. The latter is a conservative assumption as in the EINSTEIN-DVT and EINSTEIN-PE studies, 73% (93%) of DVT (PE) patients received acute parenteral treatment for a duration of 1.1 and 1.4 days, respectively.[82] The former assumption is considered a practical assumption as there is no clinical justification for administering parenteral treatment beyond 5 days if a patient is due to take dabigatran. This assumption was confirmed following a Boehringer Ingelheim advisory board of leading UK clinicians held on Thursday 22nd May 2014.
2. All patients, including those who discontinued the study drug due to any reason, can have multiple recurrent VTE events.

3. The duration for which utility decrements after initial and recurrent VTE should be applied is uncertain. The change from baseline was very similar at 3 months and 6 months (Table 109). Therefore, VTE events appear to impact HRQL for 3 months or less. In the base case analysis, the duration of the disutility is set to conservative 6 weeks which is half of the possible 3 months.
4. As a model simplification, the risk of bleeding after trial follow-up (which equals treatment discontinuation) is assumed to be zero.
5. For assumptions on treatment discontinuation, please refer to Section 7.2.4.
6. The primary endpoint of RE-SONATE included unexplained deaths. There were no fatal PEs in either study arm. In the placebo arm, 2 of the 37 rVTERD events were unexplained death; in the dabigatran arm, 0 of the 3 events were unexplained death. The model assumes that unexplained deaths are not VTE-related deaths.
7. The incidences of PTS and CTEPH are assumed to be the same for all comparators.
8. The relative survival was assumed to be 67%, based on SEER Cancer Statistics[69] (5-year survival for all cancer sites diagnosed in 2004).

For further assumptions relating to model parameters, please refer to Section 7.2.4 and Table 105, Table 106 and Table 113.

7.4 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

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Patients' quality of life is, above all, affected by the experience of an initial and/or recurrent VTE event. Several studies worldwide[83-85] have shown that patients with VTE have impaired HRQL compared with sex- and age-adjusted population norms. In patients with lower limb DVT the physical component score (a subscale of the SF-36) at baseline and 1 month is lower than for patients with other chronic disorders such as lung disease or arthritis.[84] About half of all DVT cases are symptomatic; swelling in the lack can severely affect walking ability and may cause pain and tenderness.[86] Patients with PE most frequently report shortness of breath/difficulty in breathing, fatigue and fear of recurrence after discontinuing anticoagulant treatment.[87] Furthermore, a subgroup of PE patients is more readily emotionally disturbed and experiences more social isolation than prior to the PE.[87]

Long-term complications of VTE may also impact on a patient's quality of life. Chronic thromboembolic pulmonary hypertension (CTEPH), a complication of PE, may manifest as fatigue, limited exercise tolerance or shortness of breath, chest pain.[88;89] Symptoms of severe post thrombotic syndrome (PTS), a complication of DVT, are heaviness, pain, cramps, pruritus and paraesthesia.[90]

The common therapy for VTE (anticoagulation with VKAs) can also have negative effects on patients' perceptions of their HRQL. It necessitates lifestyle modifications and frequent INR monitoring which may be burdensome. It was suggested that patients' utility for warfarin therapy is less than 1.0, although with high inter-patient variability.[76;91]

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

The HRQL of VTE patients, measured by both generic and disease-specific instruments, tends to significantly improve in the course of several months after the initial event.[84] However, patients that experience a recurrent DVT and/or PE event or that develop an intermediate- and long-term complication such as PTS and CTEPH will find their HRQL seriously affected. For instance, self-reported physical quality of life in patients who develop PTS is poor, to a

degree that is comparable to that of patients with chronic diseases such as diabetes, COPD, and congestive heart failure.[83]

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (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.

The impact of initial and recurrent VTE events on HRQL is based on utility weights estimated from EQ-5D data collected within the RE-COVER trials that were deemed appropriate to value health in cost-effectiveness analyses.

The EQ-5D questionnaire, a self-administered utility instrument to assess patients' health status, was administered at visit 2 (day 1), visit 6 (3 months), and visit 9 (6 months). No significant difference was observed between treatment groups in RE-COVER and RE-COVER II. Therefore, utility weights for health states were estimated from pooled results for both treatment groups. Table 108 presents the number of patients with EQ-5D data.

Table 108: Number of patients with EQ-5D data

Trial	Visit	Dabigatran (N)	Warfarin (N)	TOTAL
RE-COVER	Baseline	1263	1248	2511
	Visit 6	1113	1117	2230
	Visit 9	1049	1063	2112
RE-COVER II	Baseline	1264	1270	2534
	Visit 6	1130	1124	2254
	Visit 9	1076	1087	2163

Source: [75]

Analysis set

Analyses were performed on the Full Analysis Set (FAS) of each trial, as defined in the trial SAPs: this patient set includes all randomised patients who were dispensed study drug and who were document to have taken at least one dose of study drug (study drug assignment as randomised). Patients with non-confirmed index events were excluded from the FAS (4 patients in the RE-COVER study, and 2 patients in the RE-COVER II study).

Description of variables

Quantitative variables were described by their frequency, mean, standard deviation (SD), standard error of the mean, median, quartiles 1 and 3, and extreme values (minimum and maximum values).

Qualitative variables were described by the frequency and percentage of each response choice, with missing data included in the calculation of percentages.

Handling of missing data

The EQ-5D items, index score and VAS were not imputed in case of missing data. In particular, no EQ-5D index score was imputed for visits occurring after patients' death.

In the RE-COVER trials, baseline EQ-5D assessments were made for patients entering the trial with a VTE event. This represents a large sample of patients experiencing a VTE (e.g., in the RE-COVER I trial; 1,749 patients entered the trial with a DVT and 786 with PE with or without DVT).[75]

The number of patients with recurrent VTE events was small by comparison (e.g., in RE-COVER I there were 20 recurrent PE events and 34 recurrent DVT events). In addition, EQ-5D assessments may not have coincided with recurrent VTE events, while the baseline assessments (at randomisation) represent the health state immediately after an event. Therefore, the utility decrements for both the initial and recurrent VTE events in the model were estimated using baseline utility data.

The change from baseline was very similar at 3 months and 6 months (Table 109) suggesting that VTE events impact HRQL for 3 months or less. Therefore, the utility decrements for initial and recurrent DVT and PE were estimated from the difference between the mean EQ-5D utility score at baseline and 3 months of patients with an index DVT or index PE event.

Table 109: Change from baseline in EQ-5D (UK) utility values by index VTE event

	DVT [95% CI]	PE [95% CI]

Baseline (day 1)	0.58 [0.56, 0.60]	0.58 [0.55, 0.61]
Change from baseline to 3 months[1]	**0.25 [0.24, 0.26]**	**0.25 [0.23, 0.27]**
Change from baseline to 6 months[1]	0.28 [0.27, 0.28]	0.28 [0.26, 0.29]

[1] Change in mean from baseline
Source: [75]

EQ-5D utility scores were obtained using a value set based on UK general population values elicited via the time trade-off (TTO) methodology. They were, too, derived directly from patients and hence are compatible with the NICE reference case.

In the probabilistic analysis, the utility values at baseline and 3 months are sampled from normal distributions defined by the mean and standard error. The duration for which the disutilities for a DVT or PE event should be applied is uncertain; the default value is assumed to be 1 month which is consistent with the approach taken in the cost-effectiveness model used in NICE CG92.

Mapping

7.4.4 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.

No mapping was undertaken.

HRQL studies

7.4.5 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 10.12, appendix 12.

A search of HRQL data was incorporated into a systematic review conducted to identify economic analyses, utility-weight data, resource use and cost estimates,

and other parameters relevant to economic models for the treatment and secondary prevention of DVT and PE.[55]

Searches encompassed electronic medical databases and pre-specified clinical and economic conference Web sites. Bibliographic reference lists of included studies and systematic reviews also were screened for relevant publications.

Search terms for databases included combinations of free-text and Medical Subject Headings terms, grouped into the following categories:

- Health condition of interest (disease): terms for DVT and PE treatment and secondary prevention
- Study type: terms for economic analyses, utility studies, resource use, and cost studies
- Exclusionary terms: we excluded unwanted publication types using terms for comments, editorials, letters, case reports, or studies in animals but not humans

Table 110 presents the inclusion and exclusion criteria.

Table 110: Inclusion and exclusion criteria

	Inclusion	Exclusion

Study type	• Economic analyses for the treatment or secondary prevention of DVT and PE, including economic models and analyses alongside clinical trials
	• Economic analyses of ximelagatran will be included and reviewed for relevant parameters; no text description or quality assessment will be performed for these studies
	• Utility studies for DVT, PE, PTS, pulmonary hypertension, or relevant adverse events
	• Resource use and cost studies relevant to DVT, PE, PTS, pulmonary hypertension, or relevant adverse events, including the following:
	  ○ Bleeding (including intracranial haemorrhage)
	  ○ Heparin-induced thrombocytopaenia
	  ○ MI
	  ○ Unstable angina
	  ○ Dyspepsia
	• National statistics of the mortality rates associated with MI
	• Studies and reviews reporting the association between age and the risk of recurrent DVT, PE, and bleeding
		• Reviews, letters, or comment articles that discuss costs but where cost estimates are not evidence-based (reference lists of reviews were searched for relevant studies, but reviews were not be included in their own right)

Population	• For economic analyses, patients with DVT and/or PE being treated or receiving secondary prevention for recurrent DVT and PE • For utility, resource use, and cost studies, patients with DVT, PE, PTS, pulmonary hypertension or any of the adverse events	• Patients receiving primary prophylaxis for prevention of a first DVT and/or PE event
Intervention	Utility, resource use, and cost studies that were relevant to DVT, PE, PTS, pulmonary hypertension, or relevant adverse events were included, regardless of the intervention investigated, i.e. the intervention criteria did only apply to economic analyses.	

Full details of the search strategy, including a complete listing of relevant search terms, are provided in Appendix 12.

7.4.6 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.

In the original systematic review, a total of 27 studies were identified that reported utility-weight estimates. A further four studies were identified by the systematic review update. Table 111 presents a summary of the identified studies and utility weight estimates. Table

112 presents a summary of the compliance of the identified utility estimates with the NICE reference case.[92]

Table 111: Summary table for utility-weight estimates, identified in the systematic review

Author (Year)	Study Population	Methods of Elicitation and Valuation	Health-State Description	Utility Estimate
Arnold (2008)	A prospective study was conducted alongside MERLIN-TIMI 36, a randomised, double-blind, placebo-controlled trial of ranolazine in 6,560 patients with non–ST-elevation ACS Patients were stratified by those with a history of prior angina at baseline (n = 3,565) and those with no history of prior angina (n = 2,995) Missing data was calculated at 8% at baseline, 6% at 4 months, 12% at 8 months, and 20% at 12 months	EQ-5D and Physical and Mental component scores of the SF-12 Utilities were determined using the US tariff of the EQ-5D HRQL was evaluated at baseline and 4, 8, and 12 months after index hospitalisation	**Model health state: UA** ***Baseline*** Placebo ACS group with history of prior angina Ranolazine ACS group with history of prior angina Placebo ACS group without history of prior angina Ranolazine ACS group without history of prior angina	**Mean utility score (SD)** 0.67 (0.22) 0.67 (0.21) 0.76 (0.22) 0.76 (0.22) Utility decrement for UA may be calculated by subtracting the mean value for each group with a history of prior angina from the mean value for each group without a history of prior angina EQ-5D showed significant improvement from baseline at each follow-up time point in both treatment arms, with the greatest changes occurring between baseline and the 4-month follow-up time point In general, there were only small differences between treatment arms Evidence of a significant utility benefit of ranolazine among prior angina patients at 12 months

Bach (2011)	Data from a large epidemiological study (DETECT), which drew upon more than 55,000 patients from the German primary care system, was analysed to compare the HRQL of patients (n = 3,109) with MI, stroke, or both to patients with a wide range of other diagnoses	EQ-5D EQ-5D VAS The EQ-5D summary score was calculated according to the corresponding scoring algorithms for the German population	Model health state: MI No MI or stroke MI Also reported Stroke MI and stroke	Mean utility score 0.74 (0.18) 0.66 (0.19) Utility decrement for MI may be calculated by subtracting the MI value from no MI or stroke value 0.62 (0.20) 0.57 (0.20)

Delaney (2008)	Randomised, controlled trial with 699 patients aged 18-65 who presented to their GP in 80 UK practices with epigastric pain, heartburn, or both without "alarm symptoms" for malignancy Patients then were randomised to empirical acid suppression (n = 356) or *Helicobacter pylori* "test and treat" (n = 343)	EQ-5D The practice nurses interviewing the patients completed the baseline EQ-5D Participants saw the practice nurse at 12 months, for completion of the final outcome EQ-5D	**Model health state: dyspepsia** ***Baseline*** Test and treat group (n = 334) Proton pump inhibitor (n = 345) **Also reported** ***12 months*** Test and treat group Proton pump inhibitor	**Mean EQ-5D utility value (SD)** 0.743 (0.229) 0.744 (0.239) Utility decrement for dyspepsia may be calculated by subtracting the mean baseline value for each group from the general population value for the appropriate age 0.834 0.830

Fitzgerald (2011)	The Randomized Assessment of Treatment using Panel Assay of Cardiac markers trial comparing diagnostic assessment using a POC biomarker panel (CK-MB, myoglobin, and troponin, measured at baseline and 90 minutes) to standard care without the POC panel in patients attending 6 EDs with acute chest pain due to suspected MI A total of 2,263 patients were recruited to the trial, of whom 2,243 had analysable data: 63.1% participants returned completed questionnaires at both time points, 22 of the 2,243 (1%) only returned the 1-month questionnaire, 316 (14.1%) only returned the 3-month questionnaire, and 490 of 2,243 (21.8%) returned neither questionnaire	EQ-5D questionnaire was mailed to trial participants at 1 and 3 months Scores range from less than zero (states worse than death), through zero (equivalent to death), to one (perfect health) Missing values for EQ-5D in cases where questionnaire responses were not received at 1 or 3 months using multiple imputation	**Model health state: MI** ***1-month completed case*** Standard care POC	**Mean utility score (SD)** 0.761 (0.267) 0.747 (0.289) Utility decrement for MI may be calculated by subtracting the mean 1-month completed case values for standard care and POC from the general population value for the appropriate age
			Also reported ***1 month imputed analysis*** Standard care POC	0.769 (0.261) 0.753 (0.285)
			3 months imputed analysis Standard care POC	0.772(0.273) 0.764(0.289)
			Completed case Standard care POC	0.759 (0.280) 0.753 (0.290)

Gerson (2005)	Patients with pathologic gastroesophageal reflux disease 249 patients were screened; 167 (67%) entered the study; 158 (63%) completed the study; of these, 118 had reflux alone and 40 had reflux with Barrett's esophagus	TTO SG Patients were interviewed twice: on and off medication	**Model health state: dyspepsia** ***Patients with reflux alone*** *On medication:* TTO SG	 **Mean utility score (SD)** 0.94 (0.09) 0.94 (7.7)[d] Utility decrement for dyspepsia may be calculated by subtracting the mean "on medication" TTO or SG value from the general population value for the appropriate age
			Also reported *Off medication:* TTO SG	 0.90 (0.12) 0.94 (8.9)[d]

Harris (2010) Abstract	Subjects with moderate to severe COPD were evaluated after an enrolment period of 3 months (baseline) Subjects with PH were started on either sildenafil 20 mg 3 times daily or placebo At 3 months, the subjects on placebo were crossed over to sildenafil A total of 5 subjects with PH were included in the final data analysis	EQ-5D Physical functioning score of the SF-36	**Model health state: PH** Baseline **Also reported** ***At 3 months:*** Placebo Sildenafil	**Mean utility (SD)** 68 (27) Utility decrement for PH may be calculated by subtracting the baseline value from the general population value for the appropriate age 60.08 (16.3) 79.00 (21.7) EQ-5D quality-of-life questionnaire scores were significantly higher in patients taking sildenafil than in patients taking placebo

Highland (2003)	A Markov model was constructed to assess a cohort of 100 PAH patients treated for 1 year with bosentan and treprostinil compared with patients treated with epoprostenol, as well as comparing patients treated with bosentan to treprostinil Five Markov states were defined according to functional classification defined by WHO	EQ-5D health states were estimated for each functional state by a group of clinical experts Utilities were determined using the UK tariff from the general population for the EQ-5D An alternative set of utility values were estimated by increasing the State I, estimate by 0.04 and each subsequent estimate by this factor plus 0.02 This allows a minimum value of 0.10 for state IV	**Model health state: PH**	**Baseline utility values**
			Bosentan	
			Functional Class I	0.92
			Functional Class II	0.75
			Functional Class III	0.27
			Functional Class IV	0
			Treprostinil	
			Functional Class I	0.74
			Functional Class II	0.65
			Functional Class III	0.21
			Functional Class IV	0
			Epoprostenol	
			Functional Class I	0.68
			Functional Class II	0.63
			Functional Class III	0.18
			Functional Class IV	0
				Utility decrement for PH may be calculated by subtracting the weighted average of the baseline value for the % in each functional class from the general population value for the appropriate age
				Alternative utility values
				0.96
			Also reported	0.81
			Bosentan	0.35
			Functional Class I	0.10
			Functional Class II	
			Functional Class III	
			Functional Class IV	0.78
				0.71
			Treprostinil	0.29
			Functional Class I	0.10

	Functional Class II	
	Functional Class III	
	Functional Class IV	0.72
		0.69
	Epoprostenol	0.26
	Functional Class I	0.10
	Functional Class II	
	Functional Class III	
	Functional Class IV	

Kuch (2011)	All 75-year-old to 84-year old patients consecutively hospitalised due to an incident AMI in a large community teaching hospital were analysed (N = 235) A variety of treatments were used; the 28-day case fatality rate was 17.4%. Long-term follow up was obtained in 95.9% of all hospital survivors, at a mean of 18.7 ± 6.4 months; during this time, 19.9% of patients died From all surviving patients with long term follow-up (N = 118), HRQL was assessed	Patients were asked to complete the EQ-5D and VAS Utilities were determined using the US tariff of the EQ-5D Scores could range from −0.11, indicating health status worse than death, to 1.0, indicating perfect health	**Model health state: MI** AMI patients with revascularisation in acute AMI phase vs. AMI patients without revascularisation in acute AMI phase	**EQ-5D index score (SD)** 74 (18) vs. 66 (17) Utility decrement for MI may be calculated by dividing the scores by 100 and subtracting the weighted average of the 2 scores from the general population value for the appropriate age
			Also reported AMI patients with PCI as the revascularisation procedure vs. All others	75 (18) vs. 67 (17)

Lenzen (2006)	The Euro Heart Survey on Revascularization assessed pharmacological treatment in patients with proven CAD who were ineligible for revascularisation Patients with ST-elevation MI, and those in whom revascularisation was not indicated were excluded; 4,409 patients remained to be included in secondary analyses and divided in two groups: (1) patients in whom revascularisation was the preferred treatment option (n = 3,777; 86%), and (2) patients who were considered ineligible for revascularisation (n = 632; 14%)	Patients were asked to fill out the EQ-5D questionnaire prior to hospital discharge and at 1-year follow up Utilities were determined using the UK tariff from the general population for the EQ-5D Utility scores range from –0.594 to +1, with scores < 0 being regarded as worse than death and 1 representing full health EQ-VAS	**Model health state: MI** ***Eligible for revascularisation*** Prior to discharge ***Ineligible for revascularisation*** Prior to discharge **Also reported** ***Eligible for revascularisation*** 1-year follow-up ***Ineligible for revascularisation*** 1-year follow-up	**Median (IQR)** (only patients who completed the EQ-5D prior to admission and at 1-year follow up) 0.85 (0.69-1.00) 0.80 (0.62-1.00) Utility decrement for MI may be calculated by subtracting the weighted average for each group prior to discharge from the general population value for the appropriate age; however, results were not disaggregated and included patients with stable angina and and non-ST elevation ACS, which made the utility decrement for MI difficult to extract 1.00 (0.73-1.00) 0.80 (0.66-1.00)
Lindgren (2007)	HRQL data was collected following a non-fatal cardiovascular event in the Swedish part of the Anglo—	EQ-5D and EQ-VAS Utilities were determined using the UK tariff for the EQ-5D	**Model health-state: PH** Mean 1-year utility loss based by type of event	**Mean utility score (SD)**

	Scandinavian cardiac outcomes trial, including patients with mild to moderate hypertension and additional cardiovascular risk factors (n = 60) A control group of randomly selected subjects taking part in the study but who did not experience a cardiovascular event during the trial were invited to participate as a control group (n = 367)	HRQL data was collected prospectively at 3, 6, and 12 months	ACS	0.051 (0.126) 95% CI (–0.003 to 0.103)
			Also reported	
			Baseline (baseline values based on patients' retrospective assessment)	0.82 (0.14) 95% CI (0.80-0.86)
			3 months	0.73 (0.19) 95% CI (0.68-0.78)
			6 months	0.77 (0.17) 95% CI (0.72-0.82)
			12 months	0.74 (0.22) 95% CI (0.68-0.79)
			Control	
			Mean 1-year utility loss based by type of event	0.81 (0.16) 95% CI (0.79-0.83)
			Stroke	0.145 (0.145) 95% CI (0.059-0.249)
			Other	0.040 (0.112) 95% CI (0.012-0.094)
			All	0.075 (0.154) 95% CI (0.038-0.114)

McKenna (2008)	The purpose of the study was to construct a preference-based measure from the 25-item CAMPHOR scale Items were selected that covered major issues covered by the scale These were used to create 36 health states that were valued by 249 people representative of the UK adult population	The main valuation survey was undertaken using the TTO technique, where individuals are asked to undertake conventional TTO valuations for a sample of health states For states better than being dead, they are bounded by 1.0 for perfect health and 0 for states as bad as being dead For states worse than being dead, health state values were calculated to ensure they were bounded by –1.0 EQ-5D and SF-6D also were in the study as a comparison	4 domains were captured using the 6 selected instrument items: social activities, travelling, dependence, and communication **Model health state: PH** ***Association between preference weights and perceived severity of PH*** *PH symptom severity* Mild Moderate Quite severe Very severe **Also reported** ***Association between preference weights and perceived general health*** Very good/good Fair Poor	**Mean utility** 0.90 0.56 0.49 0.31 Utility decrement may be calculated by subtracting the weighted average of the severity groups from the general population value for the appropriate age 0.69 0.49 0.37
Meads (2008)	The aim of the study was to prove the validity and responsiveness of the CAMPHOR index	CAMPHOR scores comprised of separate symptom (25 items), activity limitation (15 items), and QoL (25 items) scales	**Model health state: PH** CTEPH:	**Mean utility (SD):** ***Utility index*** 0.56 (0.29)

	Patients with IPAH (158), CTEPH (308), PH associated with left diseases (59), and PAH associated with CTD (185) attending 3 UK centres at first referral or for periodic assessment, exacerbations, or surgery during the period 2004-2006	Score ranges are 0-25 for the symptom and QoL scales and 0-30 for the activity limitation scale Higher scores indicate greater symptom experience, worse QoL, and greater functional limitation, respectively The Utility Index consists of 6 CAMPHOR QoL items and permits derivation of PH-specific utility scores		Utility decrement for PH may be calculated by subtracting the value for CTEPH from the general population value for the appropriate age
				Utility index
			Also reported	0.54 (0.28)
			IPAH	0.57 (0.31)
			PH associated with left heart diseases	0.48 (0.28)
			PAH associated with CTD	
				Symptoms
			IPAH	11.8 (5.9)
			CTEPH	11.3 (6.7)
			PH associated with left heart diseases	11.9 (6.2)
			PAH associated with CTD	13.5 (6.2)
				Functioning
			IPAH	11.4 (6.7)
			CTEPH	11.2 (6.9)
			PH associated with left heart diseases	10.5 (5.9)
			PAH associated with CTD	13.6 (6.3)
				QoL
			IPAH	10.9 (6.5)
			CTEPH	10.3 (7.0)
			PH associated with left heart diseases	10.3 (7.3)
			PAH associated with CTD	12.1 (6.6)

Mychaskiw (2010) Abstract	274 patients with PAH in a randomised, controlled trial were randomised to receive either sildenafil or placebo for 12 weeks	At each visit (baseline and weeks 1, 4, 8, and 12 of follow-up), patients were administered the SF-36, EQ-5D, and the VAS Patients were pooled across treatment groups, and attention was focused on baseline values	**Model health state: PH** EQ-5D **Also reported** SF-36 EQ-VAS	**Baseline mean utility (95% CI)** 63.2 (60.2-66.3) Utility decrement for PH may be calculated by subtracting the EQ-5D value from the general population value for the appropriate age 71.4 (69.6-73.1) 59.0 (56.9-61.2)
Nowels (2005)	Of the 123 adult, English-speaking individuals who had experienced an MI more than 2 months but less than 25 months previously and who presented to cardiologists' offices during the study period, 111 (90%) appeared for their appointment 20 scheduled patients (18%) refused to consent to the study; therefore, 99 adults participated	Patients were asked while waiting to see the physician to fill in the EQ-5D, EQ-VAS, and SF-36 During the patient visit, cardiologists asked the patients the same EQ-5D questions Utilities were determined using the UK tariff from the general population for the EQ-5D	**Model health state: MI** Mean health state	 0.73 Utility decrement for MI may be calculated by subtracting the value from the general population value for the appropriate age

Pepke-Zaba (2008)	Patients with symptomatic PAH received oral sildenafil (20, 40, or 80 mg 3 times daily) (n = 207) or placebo (n = 70) in a 12-week, double-blind, placebo-controlled study and an open-label extension (24 weeks)	EQ-5D and SF-36 were completed at baseline and after 12 and 24 weeks of therapy Measured on a scale of (1 = perfect health, 0 = dead)	**Model health state:** Sildenafil-treated patients vs. placebo-treated patients from baseline to 12 weeks and 24 weeks	Statistically significant improvements from baseline to 12 weeks were observed for the EQ-5D utility index ($P < 0.01$); these benefits were maintained for 24 weeks Values were not reported; mean changes were presented graphically Utility decrement for PH may be calculated by estimating values from the figure to obtain the baseline values and subtracting the weighted average for all groups from the general population value for the appropriate age

Pepke-Zaba (2009)	The Pulmonary Arterial Hypertension and Response to Tadalafil placebo-controlled 16-week clinical trial examined the efficacy and tolerability of 4 doses of tadalafil in 405 symptomatic PAH patients (≥ 12 years) for the treatment of PAH The impact of tadalafil on HRQL was examined, along with the relationship between HRQL and exercise capacity, measured by the 6-minute walk test	EQ-5D and EQ-VAS EQ-5D index scores were constructed by applying US and UK general population-based preference weights to the health states	**Model health state: PH** ***Mean baseline scores*** Placebo (n = 82) 2.5-mg tadalafil (n = 82) 10-mg tadalafil (n = 80) 20-mg tadalafil (n = 82) 40-mg tadalafil (n = 79)	**UK vs. US** 0.66 vs. 0.75 0.61 vs. 0.71 0.66 vs. 0.75 0.65 vs. 0.74 0.65 vs. 0.74 Utility decrement for PH may be calculated by subtracting the weighted average of the baseline values for all groups from the general population value for the appropriate age All of the tadalafil treatment groups had statistically significant improvements at 16 weeks in both the US and UK population-based EQ-5D index scores, compared with placebo, with the largest improvement seen with the tadalafil 40-mg group Results were displayed graphically The correlations between 6-minute walk test and the EQ-5D were generally poor
Pettersen (2008)	A total of 754 consecutive patients, discharged alive with a diagnosis of acute MI from 15 hospitals during a 3-month period, were included Before discharge, LVEF was measured in 406 (54%) patients Subsequently, a series of questionnaires were sent out and	Patients were asked to complete the EQ-5D and EQ-VAS The UK TTO tariff value set was used Measured on a scale of 1 = perfect health, 0 = dead	**Model health state: MI** All patients with LVEF	**Mean utility score** 0.80 Utility decrement for MI may be calculated by subtracting the value for all patients with LVEF from the general population value for the appropriate age

	256 MI patients who responded to the EQ-5D index and the EQ-VAS, 2.5 years after the index MI were included in the study		**Also reported** ***By LVEF:*** Normal (> 50%) Intermediate (40%-50%) Reduced (< 40%)	0.83 SD (0.18) 0.72 SD (0.27) 0.76 SD (0.14) In multivariable linear regression analysis, female sex, medication for angina pectoris at discharge, and intermediate LVEF were independent determinants a lower EQ-5D index score, while a history of peripheral vascular disease was associated with a higher EQ-5D index score
Robinson (2001)	A total of 57 patients with AF aged over 60 years, mean age of 73 years; 31 were men, 28 were on warfarin, and 13 had had a stroke	Health-state valuations were elicited using the SG technique in patient interviews	**Model health state: major bleed** Major bleed	**Mean (SD)** 0.841 (0.172) Utility decrement for major bleed may be calculated by subtracting the value from the general population value for the appropriate age
			Also reported GP-managed warfarin Hospital-managed warfarin Mild stroke Severe stroke	 0.948 (0.089) 0.941 (0.101) 0.641 (0.275) 0.189 (0.276)

Roman (2010)	A total of 163 adult ambulatory patients with PAH and CTEPH (70.5% women; mean age, 52.2) were recruited in 21 Spanish hospitals NYHA-WHO Functional Class, 6-minute walk test, medical treatment, and HRQL were recorded at baseline and after 6 months	EQ-VAS SF-36 Physical Component Score	**Model health state: PH** ***NYHA-WHO Functional Class*** Functional Class I Functional Class II Functional Class III	**Adjusted mean (SD)** 73.5 (18.4) 62.9 (20.7) 51.3 (16.0) Utility decrement for PH may be calculated by subtracting the weighted average for all functional classes from the general population value for the appropriate age
Sanz (2011)	Adult patients with chronic ITP from 2 international, randomised, placebo-controlled, double-blind, 24-week trials, evaluating the efficacy and safety of romiplostim were evaluated A total of 125 subjects who (83 on romiplostim and 42 on placebo) took part in the studies and were asked to complete the EQ-5D at baseline (week 1) and weeks 5, 13, and 25	Patients were asked to complete the EQ-5D and VAS at baseline (week 1) and weeks 5, 13, and 25 Utilities were determined using the US tariff for the EQ-5D because 83% of the study subjects resided in the US	**Model health-state: bleeding** Mean EQ-5D index scores by study week for both treatment groups were provided **Also reported** Mean changes, adjusted for age, gender, splenectomy status, and baseline score using multiple linear regression models, were analysed	**Baseline mean EQ-5D scores** Romiplostim: 0.8 SD (0.2) Placebo: 0.7 SD (0.2) Utility decrement for bleeding may be calculated by subtracting the mean for each group from the general population value for the appropriate age; however, patients had underlying ITP, which made the utility estimate for bleeding difficult to extract EQ-5D scores are presented only graphically Adjusted mean change scores to the last visit were statistically significant for subjects on romiplostim vs. placebo for the EQ-5D: Romiplostim: 0.05 SD (0.02) Placebo: -0.03 SD (0.02)

					Mean change for subjects with and without bleeding events during the study: No bleeding event: 0.06 SD (0.03) Bleeding event: 0.005 SD (0.02)

Schweikert (2006)	106 consecutive ACS patients starting inpatient rehabilitation after an acute cardiac event were recruited at admission to a rehabilitation hospital in Southern Germany Data were available from 88 patients for whom all 3 surveys (admission, discharge, 3 months' follow-up) were available	EQ-5D EQ-VAS SF-36 Questionnaires were provided at admission, at discharge, and 3 months after inpatient cardiac rehabilitation Utilities were determined using the tariff derived by pooled data from 6 European countries	**Model health state: MI** MI diagnosis	**Mean utility** 77.8 Utility decrement for MI may be calculated by subtracting the MI diagnosis value from the general population value for the appropriate age
			Also reported CABG	64.5
Schweikert (2009)	A follow-up questionnaire of all MI survivors (n = 4,394) included in the MONICA/KORA registry, which is a population-based registry that comprises all hospitalised cases of acute non-fatal MI surviving at least 24 hours and coronary deaths occurring in inhabitants of a defined study region who are aged between 25 and 74 years A total of 2,950 patients returned the questionnaire, yielding a response rate of 67.1%.	The questionnaire included the German version of the EQ-5D and EQ-VAS Utilities were determined using the UK tariff for the EQ-5D	**Model health state: MI**	**EQ-5D index score mean (SD)**
			All	86.5 (15.4)
			Male	87.1 (14.8)
			Female	63.7 (17.0)
			45-54 years	87.7 (15.3)
			All	87.8 (14.5)
			Male	86.9 (21.0)
			Female	
			55-64 years	87.2 (14.4)
			All	86.9 (14.9)
			Male	88.7 (11.7)
			Female	
			65-74 years	87.2 (15.5)
			All	88.3 (14.5)
			Male	83.1 (18.4)
			Female	
			≥ 75 years	84.2 (15.8)
			All	85.3 (15.4)
			Male	80.9 (16.7)

		Female	Utility decrement for MI may be calculated by subtracting each “all patients” value for each age group from the general population value for the appropriate age Main predictors of lower HRQL included older age, diabetes, increasing BMI, current smoking, and experience of re-infarction

Shafazand (2004)	HRQL was assessed in 53 patients with PAH from a tertiary care, university hospital-based pulmonary hypertension clinic	VAS and SG techniques were used to elicit utility values Utility scores, using either technique, ranged from 0 (death) to 1 (ideal health)	**Model health state: PH** All PAH patients	**Mean utility scores** SG: 0.71 95% CI (0.64-0.78) VAS 0.58 95% CI (0.54-0.62) Utility decrement for PH may be calculated by subtracting the SG or VAS value from the general population value for the appropriate
			Also reported Treated with epoprostenol (SG: n = 25; VAS: n = 26)	SG: 0.72 95% CI (0.61-0.82) VAS: 0.60 95% CI (0.54-0.66)
			No epoprostenol treatment (SG: n = 25; VAS: n = 25)	SG: 0.71 95% CI (0.61-0.81) VAS: 0.56 95% CI (0.50-0.62 There was no statistically significant difference between the 2 groups after adjustment for age, duration of disease, NYHA class, and treatment assignment
Shah (2009)	During a 60-month study period, 1,847 consecutive patients with STEMI were admitted to a coronary care unit; 73 (4%) were > 85 years old HRQL was assessed at the time of long-term follow-up, with a median	Patients were asked to complete the EQ-5D and EQ-VAS Utilities were determined using the US tariff of the EQ-5D The scores can range from −0.11, indicating health status worse than death, to 1.0, indicating perfect health	**Model health-state: MI** STEMI survivors ≥ 85 years old	**Mean summary EQ-5D index score** 0.78 SE (0.04) Utility decrement for MI may be calculated by subtracting the value from the general

	of 429 days in the ≥ 85-year age group Results of the EQ-5D instrument were available for 32 patients			population value for the appropriate age
Sitbon (2004)	BREATHE-4, a prospective, non-comparative trial of 16-week duration included 16 patients with PAH associated with HIV infection in stable condition who received bosentan for 16 weeks	EQ-5D, EQ-VAS, and SF-36 at baseline and 16 weeks	**Model health state: PH** Baseline **Also reported** 16 weeks	**Mean utility (SD)** 0.37 (0.43) Utility decrement for PH may be calculated by subtracting the baseline value from the general population value for the appropriate age. However, patients have underlying HIV which makes the utility estimate for PH difficult to extract 0.63 (0.21)
Sullivan (2011) Abstract	Following parenteral treatment of acute VTE, patients were randomised to oral dabigatran etexilate or warfarin for 6 months in a randomised, double-blind phase 3 trial (RE-COVER) At baseline, 1,245 patients were on warfarin and 1,264 on dabigatran with valid EQ-5D scores, and 1,149 and 1150, respectively, at trial end	EQ-5D index scores were constructed by applying the UK general population-based preference weights to the health states Patients completed the EQ-5D questionnaire at baseline, 3 months, and 6 months EQ-5D index scores were regressed on treatment, time since index VTE, age, gender, race, ethnicity, smoking status, body weight, and various clinical characteristics and conditions	**Model health-states: VTE, DVT, PE, and CRNM bleed** After controlling for covariates, the following factors were statistically significant and exhibited the largest magnitude changes in EQ-5D index scores: 6 months post-VTE 3 months post-VTE Recurrent DVT Recurrent pulmonary embolism Clinically relevant bleeding	 (+0.21) (+0.192) (–0.17) (–0.06) (–0.03) Finding that the decrement for recurrent DVT is greater than

		recurrent PE is counterintuitive and is based on a small number of recurrent VTE events Estimates for 3 and 6 months post-VTE were more reliable as they were based on a much larger patient sample; the change from baseline was very similar at 3 and 6 months Therefore, VTE events appear to impact HRQL for 3 months or less; use the change from baseline to 3 months as the decrement for VTE
	Also reported Underweight Female Morbidly obese Heart failure Age > 65 years	(–0.09) (–0.08) (–0.07) (–0.05) (–0.04) There were no statistically significant differences between treatment groups

van Kerkhoven (2006)	Consecutive functional dyspepsia patients referred for endoscopy were included in the study 652 patients were asked to fill in a questionnaire 2 weeks before and 1 month after endoscopy, and 515 were returned Complete responses were available for 420, 42% of whom were found to have an organic abnormality	EQ-5D VAS	**Model health state:** ***Before endoscopy*** Functional dyspepsia ***After endoscopy*** Functional dyspepsia **Also reported** ***Before endoscopy*** Organic abnormalities ***After endoscopy*** Organic abnormalities	**Mean utility (SD)** 0.72 (0.17) 0.72 (0.18) Utility decrement for dyspepsia may be calculated by subtracting the mean for each group from the general population value for the appropriate age 0.74 (0.15) 0.78 (0.12)
Hogg (2013)	Patients diagnosed with either lower extremity DVT or PE were included 215 patients were included	Interviews using the standard gamble technique	54% had prior DVT only 26% had experienced both DVT and PE 20% had prior PE only 23% had cancer-associated thrombosis 42% had >1 episode of thrombosis 87% reported that symptoms from their first episode had lasted <2 months	**Median utility value (IQR)** DVT: 0.81 (0.55-0.94) PE: 0.75 (0.45-0.91) Minor intracranial bleed: 0.75 (0.55-0.92) GI tract bleeding event: (0.65 (0.15-0.86) Major intracranial bleed: (0.15 (0.00-0.65)
Roman (2013)	Outpatients aged ≥18 years old	Short Form 36	Diagnostic categories	**EQ-5D VAS scores**

	with a diagnosis of pulmonary hypertension (pulmonary arterial pressure ≥ 25 mmHg at rest)	EQ-5D 6-Minute Walk Test	**PAH: 139 (89.2%)** iPAH: 76 (48.7%) Hereditary PAH: 5 (3.2%) Drug/toxin-associated PAH: 5 (3.2%) Veno-occlusive disease: 2 (1.2%) Connective tissue disease-associated PAH: 23 (14.7%) Congenital heart disease-associated PAH:8 (5.1%) Portopulmonary hypertension: 9 (5.7%) HIV-associated PAH: 6 (3.8%) **CTEPH: 17 (10.8%)**	Sex Male: 56.0 (21.4) Female: 60.1 (20.3) Age <50 years: 64.4 (17.9) ≥50 years: 54.9 (21.0) EQ-5D, SF-36 and 6MWT scores stratified by NYHA functional class, type of disease, time from initial diagnosis, worsening/no worsening during the first 6 months from baseline, death/transplant during the first 6 months from baseline and pulmonary hypertension treatment at baseline also reported in source.
Tavoly (2013) (Abstract)	Patients surviving acute PE compared to age- and sex-matched controls with no history of VTE, between 2002 and 2011 in Norway 208 patients and 114 controls completed the questionnaire	EQ-5D EQ-VAS	Patients surviving acute PE Age- and sex-matched controls with no history of VTE	**Mean EQ-5D index value (SD)** Patients: 0.81 (0.22) Controls: 0.92 (0.16) **Mean EQ-VAS score (SD)** Patients: 67.2 (21.3) Controls: 81.3 (16.9)
Kumar (2014)	Children between the ages of 0-18 years at the time of DVT diagnosis, during the period 1995-2009, were included in the study. At survery completion, some patients were over 18 years old. 197 patients were asked to fill in a survery, and 73 were returned; 21 participants from the pilot validation study were also included	Self-report and parent-proxy Peds QL 4.0	All diagnosed with DVT Presence of post-thromotic syndrome (PTS) in 65 patients Potential confounders include: inflammatory bowel disease, post-stem cell transplant, post-solid organ transplant, chemotherapy, long-term cancer survivor, neurological condition, congenital	**PedsQL4 scores** No PTS Total: 83.4 (14.0) Psychosocial: 83.8 (13.7) Physical: 82.7 (22.4) Social: 91.1 (11.0) Emotional: 82.5 (17.0) School: 77.7 (20.2) Mild PTS Total: 84.8 (14.2)

	in the overall cohort 4 respondents were excluded for not meeting inclusion criteria; the final study cohort comprised 90 patients, 1 of which did not respond to the Peds QL 4.0 questionnaire 79 patients completed the self-report module, and the parent-proxy module was completed for 34 respondents	cardiac condition, end-stage renal disease, psychiatric condition	Psychosocial: 85.1 (13.6) Physical: 84.2 (18.7) Social: 92.6 (14.1) Emotional: 82.7 (17.8) School: 79.9 (19.9) <u>Moderate/severe PTS</u> Total: 71.3 (13.4) Psychosocial: 74.2 (13.2) Physical: 65.9 (20.3) Social: 77.5 (11.2) Emotional: 69.6 (23.3) School: 75.4 (16.9)

6MWT, 6-minute walk test; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep-vein thrombosis; EQ-5D, EuroQoL-5D; EQ-VAS, EuroQoL visual analogue scale; GP, general practitioner; HIV, human immunodeficiency virus; HRQL, health-related quality of life; iPAH, idiopathic pulmonary hypertension; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PE, pulmonary embolism; POC, point of care; PTS, post-thrombotic syndrome; SD, standard deviation; SF-36, Short Form-36; SF-6D, Short Form-6D; SG, standard gamble; STEMI, ST segment elevation myocardial infarction; TTO, time trade-off; UA, unstable angina; VTE, venous thromboembolism; WHO, World Health Organisation.

Table 112: Compliance of utility estimates with NICE reference case

Author (Year)	Reported Directly From Patients?	Values = Public Preferences Using Choice-Based Method?	EQ-5D?	Utility Scale?
Arnold (2008)	Yes	Yes US general population-based preference weights	Yes	NR; assume 1 = perfect health, 0 = dead
Bach (2011)	Yes	Yes EQ-5D index German general population-based preference weights EQ-5D VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead
Delaney (2008)	Yes	Yes UK general population-based preference weights	Yes	NR; assume 1 = perfect health, 0 = dead
Fitzgerald (2011)	Yes	Yes EQ-5D index Tariff not reported	Yes	Scores ranged from less than zero (states worse than death) through 0 (death) to 1 (perfect health)
Gerson (2005)	Yes	Yes TTO technique was used SG technique was used	No	1 = ideal health (or a state without a particular disease such as heartburn), 0 = dead (or a state equivalent to dead)
Harris (2010) Abstract	Yes	Yes EQ-5D index Tariff not reported Physical functioning score of the SF-36 also reported	Yes	NR; assume 1 = perfect health, 0 = dead
Highland (2003)	No Clinical experts valued the health states by functional class	Yes EQ-5D index UK general population-based preference weights	Yes	NR; assume 1 = perfect health, 0 = dead Alternative health states were valued that allowed the worse health state to be 0.10
Kuch (2011)	Yes	Yes The US general population-based preference weights	Yes	−0.11, indicating health status worse than death, to 1.0 perfect health
Lenzen (2006)	Yes	Yes EQ-5D index UK general population-based preference weights EQ-5D VAS also reported	Yes	Utility scores ranged from –0.594 to +1, with scores < 0 being regarded as worse than death and 1 representing full health
Lindgren (2007)	Yes	Yes EQ-5D index UK general population-based preference weights EQ-5D VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead
McKenna (2008)	Yes	Yes	No	1.0 = perfect health and 0 = states as bad as being dead

		TTO EQ-5D and SF-6D were used for comparison purposes but utilities were NR		For states worse than death, health state values were calculated to ensure they were bounded by –1.0
Meads (2008)	Yes	CAMPHOR scores and Utility Index	No	Score range 0-25 for the symptom and QoL scales and 0-30 for the activity limitation scale Higher scores indicate greater symptom experience, worse QoL, and greater functional limitation, respectively
Mychaskiw (2010) Abstract	Yes	Yes EQ-5D index Tariff not reported EQ-VAS also reported SF-36 also reported	Yes	NR; assume 1 = perfect health, 0 = dead
Nowels (2005)	Yes	Yes EQ-5D index UK general population-based preference weights EQ-5D VAS also reported	Yes	0-1 scale based on the Dolan et al. study
Pepke-Zaba (2008)	Yes	Not reported Source of preference weights not reported	Yes	1 = perfect health, 0 = dead
Pepke-Zaba (2009)	Yes	Yes EQ-5D index UK and US general population-based preference weights EQ-5D VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead Paper stated higher scores represented better HRQL
Pettersen (2008)	Yes	Yes The UK TTO tariff value set was used	Yes	1 = perfect health, 0 = dead
Robinson (2001)	Yes	Yes SG technique was used	No	1 = normal health, 0 = dead
Roman (2010)	Yes	No EQ-VAS but EQ-5D index was not reported Physical functioning score of the SF-36 also reported	Yes	NR; assume 1 = perfect health, 0 = dead
Sanz (2011)	Yes	Yes The US general population-based preference weights	Yes	1 = perfect health, 0 = dead
Schweikert (2006)	Yes	Yes EQ-5D index Utilities were determined using the tariff derived by pooled data from 6 European countries EQ-VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead

Schweikert (2009)	Yes	Yes EQ-5D index UK general population-based preference weights EQ-5D VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead EQ-VAS ranged from 0 (worst imaginable health state) to 100 (best imaginable health state)
Shafazand (2004)	Yes	Yes SG was used which determines the maximum risk a person is willing to accept in order to achieve perfect health VAS also reported	No SG and VAS	Utility scores, using either technique, ranged from 0 (death) to 1 (ideal health)
Shah (2009)	Yes	Yes The US general population-based preference weights	Yes	-0.11, indicating health status worse than death, to 1.0 perfect health
Sitbon (2004)	Yes	Yes EQ-5D index Tariff not reported EQ-5D VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead
Sullivan (2011) Abstract	Yes	Yes EQ-5D index UK general population-based preference weights	Yes	NR; assume 1 = perfect health, 0 = dead
van Kerkhoven (2006)	Yes	Yes EQ-5D index Tariff not reported VAS also reported	Yes	NR; assume 1 = perfect health, 0 = dead
Hogg (2013)	Yes	Yes Standard gamble technique used	No	NR; assume 1 = perfect health, 0 = dead
Tavoly (2013) (Abstract)	Yes	No (EQ-5D reported)	Yes	0-100; 0 = worst health state, 100 = best health state
Roman	Yes	No (SF-36, EQ-5D and 6MWT reported)	Yes	EQ-5D scale 0-100; 0 = worst health state, 100 = best health state
Kumar (2014)	Yes ≥18 years old* Parent-proxy <18 years old*	No (PedsQL4 reported)	No	0-100; higher scores indicate better HRQL

6MWT, 6-minute walk test; EQ-5D, EuroQoL-5D; EQ-VAS, EuroQoL visual analogue scale; HRQL, health-related quality of life; NR, not reported; SF-36, Short Form-36, SG, standard gamble; TTO, time trade-off.

*Age at survey completion. All patients were aged <18 years at DVT diagnosis.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The systematic literature search identified three studies reporting utilities potentially relevant to the modelled health states of index and recurrent DVT/PE. Sullivan (2011)[93] reported a utility decrement for DVT and PE of 0.21 and 0.192, respectively. These disutilities were derived solely from data from RECOVER I clinical trial data; additional information from RECOVER II became available later and was not utilised in this analysis. The mean utility values reported by Hogg (2013)[94], 0.81 (acute DVT) and 0.75 (acute PE), were obtained by interviews using the standard gamble technique within 4 weeks of diagnosis of VTE. The standard gamble, a choice-based method for preference elicitation, is considered merely 'second best' by NICE.

Among patients with objectively verified PE between 2002 and 2011, Tavoly (2013)[95] determined a mean index value of EQ-5D of 0.81 (controls: 0.92). Without pre-specified time of assessment after event, this figure does not provide an appropriate utility estimate specific to the modelled health state of index or recurrent PE. Data collected in the pooled clinical trials (Section 7.4.3) suggest that VTE events impact HRQL for 3 months or less.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Dabigatran is an anticoagulant that affects blood clotting, so most adverse events are related to bleeding. The utility decrement for major bleeding events (MBE) (including ICH) and clinically relevant non-major bleeding events (CRNMB) were taken from an analysis of EQ-5D data collected in the pivotal RE-COVER trials.[75] The disutility value from MBE was assumed to be equal the differences in change in mean EQ-5D index score from baseline to visit 9 between patients with "Index VTE event only" and patients with "Index VTE event and MBE only" =0.16-0.29 = -0.13 and was applied in the month the event occurred. A utility decrement post disabling intracranial haemorrhage was taken from a study by Wolowacz (2009)[77] that used an average of 109 published estimates for stroke and was applied over lifetime. The disutility value from CRNMB was assumed to be equal the differences in change in mean EQ-5D index score from baseline to visit 9 between patients with "Index VTE event only" and patients with "Index VTE event and CRBE only" = 0.25-0.29 = -0.04 and was

applied for the month the event occurred. The values used for calculating the differences in change of mean EQ-5D can be found in the Table 3.4.2 of the Appendix[96] of the MAPI report.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Within the cost-effectiveness analysis all modelled patients are assigned a baseline utility value based on estimates for the general population of the same age and gender; the baseline value decreases over time to model the impact of ageing. Age and gender-specific utility weights for the general population were taken from a national survey in England using the EQ-5D.[79] This study is not specific to VTE and was not within the scope of the systematic review. These estimates form the baseline from which the disutilities associated with VTE and adverse events are subtracted. These values were fixed in the probabilistic analysis to avoid counterintuitive relative values (e.g., random selection of a mean utility for older patients that is higher than the randomly selected value for younger patients).

Table 113 summarises the disutilities for health states and adverse events used in the cost-effectiveness analysis.

Table 113: Summary of utility and disutility values in the cost-effectiveness analysis

Modelled event		Mean disutility [95% CI]	Reference in submission	Source
Initial and recurrent DVT		-0.25[1] [-0.24, -0.26]	Section 7.4.3, Table 59	75
Initial and recurrent PE		-0.25[1] [-0.23, -0.27]	Section 7.4.3, Table 59	75
During active warfarin treatment		-0.012 [-0.008, -0.016]	This section (7.4.9)	76
During active LMWH treatment		-0.008 [-0.005, -0.011]	This section (7.4.9)	76
Severe PTS		-0.07 [-0.048, -0.092]	This section (7.4.9)	67
Major bleed:	ICH, disabled from	-0.5[2] [-0.402, -0.598]	Section 7.4.8	77
	MBE	-0.13[3] [-0.105, -0.155]	Section 7.4.8	75
Non-major bleed:	CRNMB	-0.04[3] [-0.032, -0.048]	Section 7.4.3	75
Myocardial infarction (MI)*		-0.063[3] [-0.050, -0.075]	This section (7.4.9)	78
Unstable angina (UA)*		-0.085[3] [-0.069, -0.102]	This section (7.4.9)	78
CTEPH		-0.12[4]	This section (7.4.9)	79;80

	[-0.080, -0.120]		
Dyspepsia*	-0.04[5] [-0.032, 0.048]	This section (7.4.9)	[81]
For baseline HRQL assessment			
	Males Mean utility [95% CI]	**Females Mean utility [95% CI]**	
Age 25-34 years	0.92 [0.91, 0.93]	0.90 [0.89, 0.91]	Prescott-Clarke, 1998[79]
Age 35-44 years	0.89 [0.88, 0.90]	0.87 [0.86, 0.88]	
Age 45-54 years	0.85 [0.84, 0.86]	0.84 [0.83, 0.85]	
Age 55-64 years	0.80 [0.78, 0.82]	0.78 [0.76, 0.80]	
Age 65-74 years	0.80 [0.78, 0.82]	0.76 [0.74, 0.78]	
Age ≥ 75 years	0.76 [0.74, 0.78]	0.71 [0.69, 0.73]	

[1] Applied for 6 weeks in base case analysis (see 7.3.8 for justification)
[2] Applied for remaining lifetime on patients disabling from ICH
[3] Applied in month of the event
[4] Applied for remaining lifetime on patients developing a CTEPH
[5] Applied during duration of treatment
* Applies to sensitivity analyses only

As described in section 7.4.3, the HRQL data for initial and recurrent DVT and PE events were obtained directly from the patients in the pivotal clinical trials. Based on these data, the disutility values calculated are pursuant to the NICE reference case.

A disutility related to active warfarin and LMWH treatment has been applied in the base case analysis. Marchetti et al. (2001)[76;91] asked 48 patients attending an anticoagulation clinic to trade one year of life on warfarin or LMWH therapy for one year of life reduced by a certain amount of time. Relative disutility is assumed to be given by the difference between the reported mean utility value and that associated with full health (1.0). Thus, patients' mean disutility for warfarin and LMWH therapy was found to be 0.012 and 0.008, respectively.

Utility decrements for severe PTS were searched for in the systematic review. However, only one study (Kumar 2014)[97] was identified reporting HRQL scores in children and young adults (0-18 years). Thus, the study was judged inappropriate and it was resorted to a study outside the time span covered by the literature searches. It estimated the utility of mild-to-moderate and severe PTS, elicited from 30 healthy volunteers and 30 physicians using standard gamble methods.[67] The utility weights were subtracted from perfect health (1.0) to calculate a decrement.

Please refer to Section 7.4.8 where utility decrements applied to major and non-major bleeds have been described at length.

Utility decrements for survivors of MI and UA (sensitivity analysis only) were taken from Sullivan et al. (2011).[78] The authors applied community-based UK preference values to the EQ-5D descriptive questionnaire responses in the US-based Medical Expenditure Panel Survey (MEPS) and derived EQ-5D index scores and disutilities for a variety of conditions.

The disutility of CTEPH was calculated by subtracting the mean utility of functional class I patients reported by Keogh et al. (2007)[80] from the weighted baseline utility weight[79] at model start (mean age = 54.7 years). Therefore, the utility decrement for patients developing a CTEPH was assumed to be 0.12 (=0.85-0.73).

The mean utility decrement for dyspepsia (sensitivity analysis only) was calculated by subtracting the mean utility rating of patients off medication (0.90) from the mean utility rating of patients on medical therapy (0.94) for reflux alone.[81] Utilities used for this calculation were elicited using the time-trade-off technique.

7.4.10 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 specialist 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?)

[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.

- the questions asked
- 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.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQL is constant within each modelled health state and from cycle to cycle. Aspects impacting on a patient's quality of life have been outlined in Section 7.4.1. Disutilities associated with VTE and adverse events are presented in Table 113.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Bleeding events that were neither major nor clinically relevant non-major (i.e. minor bleeds) were assumed to have a negligible impact on costs and HRQL and were excluded from the model.

Patients with a first and/or recurrent DVT may develop PTS. A literature review found evidence to suggest that mild PTS was of little detrimental effect on quality of life[67], therefore, the model only projects severe PTS.

7.4.13 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 in Section 7.4.9.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The utility values were not assumed to change over time.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

There are no such amendments.

7.5 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

7.5.1 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.

Costs for the acute treatment and secondary prevention of VTE are incurred in primary and secondary care NHS settings. Costs of care associated with the technologies under evaluation are, wherever possible, taken from NHS reference costs 2012/2013[25] and PSSRU[24]. Details on the relevant Healthcare Resource Groups (HRG) are expounded it the tables in Section 7.5.5 – 7.5.8.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs are deemed appropriate for costing intervention-associated elements of care as they provide English average unit costs with a high level of granularity. Furthermore, activity data reflect well the patterns of care delivered in the English NHS.

Resource identification, measurement and valuation studies

7.5.3 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 10.13, 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.

A systematic literature review of economic studies relevant to the economic evaluation of dabigatran etexilate for the treatment and secondary prevention of DVT and/or PE was performed. Details of the review methodology and PRISMA diagrams are presented in Section 7.1.1.

Initial systematic searches of electronic databases were performed on 5th February 2013, and an update using the same search strategy was performed on 28th April 2014.

In the original systematic review, a total of 26 resource use and cost studies were identified, including a study reported by Braidy et al. (2011)[56], which was extracted as both an economic evaluation and as a cost study.

Thirteen of the studies were from a US perspective. Resource use and cost estimates reported for VTE included drug costs, bleed costs, total pre-index, medical pharmacy, and index diagnosis costs per patient; intensive care services; and hospitalisation. Resource use and cost estimates reported for DVT included drug, diagnostic tests, total index diagnosis costs per patient and inpatient and outpatient resources. Resource use and cost estimates reported for PE included drug costs, total index diagnosis costs per patient, hospitalisation, and intensive care services.

Seven studies were from a UK NHS perspective and reported estimates that were appropriate for use in the cost-effectiveness model. The Anderson et al. (2002) study reported costs for enoxaparin, unfractionated heparin, administration, inpatient and outpatient visits in the treatment of VTE. The Ara et al. (2012) study reported treatment and monitoring costs using statins for UA and MI. The Bakhai et al. (2012) study reported

resource use and costs for ACS events, including UA and MI, but these were not disaggregated. An estimated cost of intracranial haemorrhage was reported by Youman et al. (2003), an estimated cost of managing dyspepsia in patients taking non-steroidal anti-inflammatory drugs for osteoarthritis was reported by Latimer et al. (2009), and an estimated cost for anticoagulation control was reported by Connock et al. (2007). Goodacre et al. (2006) reported inpatient and outpatient resource use estimates for post-thrombotic syndrome.

Studies conducted in other countries included Belgium, Germany, Spain, Scandinavia, Australia, and Canada. Resource use and cost estimates from these studies included drug, administration, and total annual direct costs for VTE; drug, inpatient and outpatient, laboratory tests, and total annual direct and indirect costs per patient for PE; and hospitalisations for UA and MI.

One study was identified with relevant cost estimates, but a decision was made to exclude it at level 2 screening because it was conducted in Colombia.

In the systematic review update, nine studies reporting resource use and/or cost estimates were identified. One study (Fanikos, 2013) was removed from the results as it had been identified by the original systematic review. Of the eight studies remaining, two studies were from a US perspective, while one study each reported data from EU-27, Spain, China, Japan and Saudi Arabia.

The 35 studies identified by the systematic review are presented in Table 114. Additionally, the costs for bleeds and other adverse events are presented in Table 122, Section 7.5.7.

Table 114: Summary Table for Resource Use and Cost Estimates

Author (Year)	Country, Data-Collection Period	Description of Available Data[a]	Details of Methods[b]
Algahtani (2013)	Saudi Arabia, August 2009 and August 2010	Direct medical costs including the number of days of treatment, number of nursing vists, ultrasound scans, number of physician visits and number of blood tests required Laboratory costs, nursing costs, hospital costs and medicine costs were also reported	Prospective randomised clinical study Patients (≥18 years) symptomatic for acute proximal DVT of the lower limbs were included Patients were randomised to outpatient treatment with LMWH or inpatient treatment with conventional UFH for ≥5-7 days Subjects: 61 Cost-year: NR, Us dollars
Anderson (2002)	UK, Cost collection for the period 2000-2001	Treatment costs of enoxaparin compared with adjusted dose unfractionated heparin for the treatment of VTE for three settings; in-hospital, out-of-hospital (anti-coagulation clinic) or home. Drug costs, administration costs, and costs associated with care both in and out of hospital are reported	Cost-comparison study Perspective: UK National Health Service Treatment: enoxaparin (Clexane) Drug costs from British National Formulary (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2001) and Unit Costs of Health and Social Care (Netten et al., 2000) Cost-year: not reported; UK pounds Unit costs reported by setting for drug costs, administration costs, laboratory costs, and outpatient and inpatient visits

Annemans (2002)	Belgium, 1 January 1998 to 30 June 1998	Resource use: laboratory test for the management of PE Resource use was reported by mean number of each test type for the management of PE Heparin use was reported, but the authors stated this was poorly documented in the charts	Retrospective patient chart review study: randomised selection Subjects: 54, mean age 65.3 years (SE: 2.2), 41% male Perspective: health insurance cost Excluded nurse time and productivity-related resources and direct non-medical resource use, as these are not relevant to the health insurance perspective
Ara (2012)	UK, Data-collection period NR	Health-state costs: UA, MI, stroke, revscularisation at 1 year, CHD, stroke in subsequent years, fatal CHD, and non-coronary vascular events Treatment and monitoring costs also were reported	Cost-effectiveness model Treatment: atorvastatin, rosuvastatin, simvastatin Perspective: UK National Health Service Health state and treatment costs from British National Formulary (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2008) and Ward et al. (2007) Cost-year: 2007; UK pounds
Bakhai (2012)	France, Spain, and the UK, January 2007 to August 2007	Clinical events, resource use, quality of life, and cost estimates were reported for patients with ACS undergoing a percutaneous coronary intervention (PCI) through a follow-up period of 12 months	Antiplatelet Therapy Observational Registry Observational cohort study 1,335 ACS patients undergoing PCI Follow-up period: 12 months Cost-year: not reported; euros and UK pounds Resource use and cost estimates were described but disaggregated values were not reported and methods for cost and resource use estimation were not clearly described

Braidy (2011)	Australia, 29 June 2009 to 13 July 2009	Patients treated with dabigatran, rivaroxaban, or warfarin and enoxaparin Resource use assumptions, drug costs, and unit cost sources were reported Sources of unit cost data and resource use were described, but all the values were not reported in the text Resource use assumed mean duration of prophylaxis for VTE and SPAF under the Australian Therapeutics Guidelines (2009)	Cost-analysis of dabigatran and rivaroxaban compared to warfarin and enoxaparin in treatment of VTE and SPAF Study type: prospective clinical audit; 2 week period to collect data on anti-coagulation management. Subjects: 67 (warfarin = 46, enoxaparin = 21) Mean age: 81.5 for VTE and 83.5 for SPAF Cost-year: 2009; Australian dollars Drug costs: Australian pharmaceutical benefits scheme, 2008 Unit costs for administration were from Australian Public Health 2007-2008 Assumptions used in the analysis were clearly reported
Bullano (2005)	US, 4 years (1 October 1997 to 30 September 2001)	Costs for pre-index period, medical, pharmacy, and index diagnosis costs VTE cost, bleed cost, and VTE + bleed cost Unit costs and resource use were not reported	Retrospective observational cohort study of 2,147 patients (DVT = 1,499; PE = 373; DVT + PE = 275), mean age 61.6 ± (SD) 16 years, 46.3% male Mean follow-up: 21.3 (median: 19.2) months Cost-year: not reported; US dollars Perspective: managed care organisation
Caprini (2003)	US, Model simulation, no data collected	Patients undergoing total hip replacement surgery and complications of a primary DVT and the lifetime cost of treatments (includes PTS) Utility weights stratified by age Costs provided by year and severity Cost split by category: office visits,	Markov Model with probabilistic sensitivity analysis via Monte Carlo simulation Hypothetical cohort analysis Comparison among patients experiencing a DVT and surviving (including costs of treating

		vascular lab tests, medical supplies, medications, vein ligation and stripping, subfascial endoscopic perforator surgery procedure, comprehensive ulcer treatment, and other hospitalisations or procedures	complications) and those not experiencing a DVT Perspective: payers responsible for direct medical costs in both inpatient and outpatient settings Both cohorts age = 72 % female = 65 Cost-year: 2000; US dollars Unit costs and probability of incurring the unit costs were provided, by patient group, year, and severity
Connock (2007)	UK, Data-collection period NR	Annual costs for anticoagulation control, patient self-management, fatal stroke, disabled patients Unit costs for minor and major haemorrhagic, major thrombotic events	NICE HTA systematic review and cost-effectiveness models of managing long-term oral anticoagulation therapy Perspective: UK National Health Service The costs came from a range of data sources identified in the systematic review Cost-year: all costs were updated to 2005; UK pounds
Creekmore (2006)	US, 1 August 2000 to 2 November 2004	Development of HIT, cost of LMWH and UFH to prevent VTE Resource use and cost data provided at an aggregated level as annual costs	Retrospective analysis with a nested case-control Perspective: managed care organisation Cost-year: 2004; US dollars Subjects: patients with HIT Mean age: 57.3, 45.5% female Subjects: 10,121 received either UFH or LMWH to prevent VTE
Elting (2004)	US, 1 January 1994 to 31 December 2000	Resource use data collected: hospital days, clinic visits, blood products, diagnostic tests, and pharmaceuticals associated with DVT treatment in cancer	Retrospective study Cancer patients in whom DVT developed from 1 January 1994 through 31 December 1997 and followed up

		patients Length of stay and actual mean cost figures reported by patient group Unit costs were not reported	through 31 December 2000 Subjects: 529 consecutive patients; 52% female; men aged 55 years (54-57 years) Cost-year: 2002; US dollars The cost but not the charge for each hospitalisation was obtained
Escalante (2000)	US, 1 January 1994 to 31 December 1996	Admissions split by underlying malignancies Resource use costs associated with DVT treatment in cancer patients were reported	Observational study, single site: The University of Texas M.D. Anderson Cancer Centre; all cases of DVT included Perspective: hospital care costs Subjects: 766; 50% male, 50% female Median age: 74 (range: 70-87) years Cost-year: not reported; US dollars Resource use costs were reported by mean cost per age group (< 70, 70-79, and ≥ 80 years) Unit costs were not reported, resource use was not described, and drug costs were not reported
Fanikos (2013)	US, September 2003 to May 2010	Resource use Unit costs (by category) Resource use reported by diagnostic method and total number and proportion across the study population Drug treatment reported by number of patients treated and proportion of the total study population st data reported by category but only at an aggregated level al item costs were not reported	Observational study Subjects: 991; 90-day follow-up period Mean age: 59.4 ± 16.8 years Perspective: hospital care costs Cost-year: not reported; US dollars

Goodacre (2006)	UK, Data-collection period NR	Valuations of health outcomes and health service costs, including costs of diagnostic tests, treatment costs, and resource use PTS was valued as 1 new vascular surgery outpatient visit plus 2 follow-up visits per annum and a further 2 GP consultations per annum	NICE HTA, including systematic reviews and meta-analyses of invasive and non-invasive diagnostic tests, an evaluation of diagnostic algorithms, and a cost-effectiveness analysis for DVT The cost of 1 new vascular surgery outpatient visit plus 2 follow-up visits per annum for PTS was sourced from the NHS reference costs (2003) The cost of the further 2 GP consultations per annum for PTS was sourced from PSSRU (Netten and Curtis, 2003) Cost-year: 2003
James (2009) Abstract	Sweden, Finland, Norway, and Denmark, April 2008 to November 2008	Length of stay, time from admission to PCI, treatment type, and quality-of-life outcomes	Prospective observational study Perspective: not reported Subjects: 56% unstable angina or non-ST-elevation MI, 44% ST-elevation MI; patients were from Sweden (n = 240), Finland (n = 104), Norway (n = 78), and Denmark (n = 74) Median age: 64 years (IQR: 56-72); 75% male
Kroger (2012)	Germany, 2000 to 2006	Cost estimates by cost type: physician outpatient services, drugs, other services, in-hospital treatment, and nursing care Cost per patient and excess cost for each cost category were reported and split by men and women Cost of each PE patient and excess cost were reported No unit costs or resource use data were	Retrospective database study Based on routine health-care data collected by the local statutory health insurance fund (AOK) and the Association of Statutory Health Insurance Physicians of the Federal State of Hesse in Germany Database randomly sampled (18.75% of total sampled) Cost-year: not clearly stated, 2006 was

		reported	implied; in euros
Latimer (2009)	UK, Data-collection period NR	Costs of treating gastrointestinal adverse events in patients taking NSAIDs Includes the cost of managing dyspepsia during the initial 3 months	Cost-effectiveness analysis of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for patients with osteoarthritis Costs of treating gastrointestinal adverse events were calculated using data for the average length of stay (NHS, 2006) and the costs of outpatient appointments (Curtis and Netten, 2006) Cost-year: 2007-2008
Lefebvre (2012)	US, January 2004 to December 2008	All-cause incremental health costs were calculated and reported Costs specifically relating to VTE complications were calculated and reported	Retrospective database study Patients with an index VTE diagnosis, PE, or VTE + PE were matched 1:1 with controls Follow-up ended on the earlier of 1 year follow-up from the date of the index admission date, health plan disenrolment date, or 31 December 2008 Subjects: VTE = 16,969, No-VTE controls = 16,969 Index event reported in DVT = 12,711, PE = 2,473, and DVT + PE = 1,785
Lin (2014)	US, 1 January 2007 to 31 December 2011	Resource use and cost data includes outpatient anticoagulant use, hospitalisations, healthcare payments, LOS, claims data, pharmacy use, outpatient medical costs	Retrospective analysis of patient-level data from the Truven Health Analytics MarketScan Commercial and Medicare databases.

			Patients with ≥1 inpatient claim with a primary or secondary VTE or ≥2 outpatient claims (including emergency room visits) on two separate dates for VTE diagnosis Subjects: 29,275 Cost-year: NR, US dollars
MacDougall (2006)	US, 1 January 1997 to 31 March 2004	Patients split into DVT, PE, and DVT + PE groups Mean age; gender split; pre-index diagnoses of DVT, PE, and DVT + PE; pre-index comorbidities; time to DVT or PE event from prior hospitalisation; and pre-index total health care costs Also included: treatment strategies, length of stay, mean costs, and resource use by cost group The same data items were included for a PTS subanalysis	Retrospective, observational, parallel, comparative cohort study Patients were required to be continuously benefit-eligible for 12 months prior to the index event Patients with prior events were included Patients were excluded if not continuously enrolled in pharmacy and medical benefits or were aged ≥ 65 years with insurance coverage but not Medicare risk (likely to have only supplementary coverage) Costs derived from database analysis that provided health care plan-paid and charged amounts Disease and non–disease-related costs were not separated in this study Perspective: US managed care Cost-year: 2004; US dollars Subjects: DVT = 15,679, PE = 7,653, DVT + PE = 2,932; PTS = 624 Outcomes compared cost differences of care of patients experiencing DVT, PE, or DVT + PE with matched controls

Mahan (2013) (Abstract)	US, Data collection period NR	VTE costs	Literature review to inform decision-trees for PE and DVT outcomes and cost models Cost-year: 2011, US dollars
Mahan (2013) (Abstract)	EU-27, 1994 to September 2012	Annual total, hospital-acquired and preventable VTE costs	Literature review to inform a cost-of-illness model. Costs were input into previously published US decision-analytic models. Subjects: 502.5 million (focus on the 424.11 million ≥15 years old) Cost-year: 2012, Euros
O'Brien (2002)	US, 1997 (whole year)	Cost estimates included initial acute care and that occurred in the following 6 months Costs were reported at an aggregated category level, split into subgroups of patients with DVT: inpatients, home care and outpatient, home care and clinic care	Retrospective database study; DVT discharge data All 1997 payer discharge data from 6 states (California, Florida, Maine, Maryland, Massachusetts, and Washington) Subjects: 1,077; 6-month follow-up Perspective: US health payers Cost-year: 1999; US dollars Drug costs: 1999 Red Book Cost calculation methodologies were clearly stated
Ollendorf (2002)	US, January 1998 to June 1999	Length of hospital stay, use of intensive care services, and costs of inpatient care were compared among patients with and without secondary diagnoses of DVT without PE (DVT only) or PE with or without DVT Mean length of stay and mean costs	Retrospective database study. Clinical Pathways Data Base Patients undergoing knee and hip surgery Perspective: direct hospital treatment costs Subjects: 105,562

		reported by procedure type and diagnosis (no VTE, DVT only, and PE)	Cost-year: not reported; US dollars Authors noted that treatment patterns in the US were different from those in Canada and Europe, due to differences in outpatient management; thus the finding cannot be generalised to these areas
Oster (2004)	US, 1 January 1993 to 31 December 1998 (5 years)	Mean billed index admission costs reported by procedure type and no VTE, in-hospital VTE, and post-discharge VTE Reported data included difference among patients and matched controls, split by surgical outcome for length of stay, visits to the physician's office, emergency department, hospital outpatient clinic, and home health visits	Retrospective (database) study Perspective: managed care 11,960 patients, with each VTE patient matched to 2 patients without VTE on the basis of age and procedure Mean age of cohort: 71.0 ± 13.2 years Mean duration of follow-up: 82 days (range: 2-90 days) Cost-year: 1999; US dollars Resource use and unit costs were not reported at a disaggregated level
Perez-de-Llano (2010)	Spain, April 2005, ended in December 2008	Direct and indirect costs reported Costs presented as total mean cost per patient, split into direct cost categories and indirect costs Resource use and unit cost data were not reported in disaggregated form Methods and sources of data were described	Open-label, randomised trial, comparison of tinzaparin and acenocoumarol Subjects: 102 with acute PE, randomised to tinzaparin monotherapy (52 patients) or tinzaparin followed by chronic acenocoumarol therapy (50 patients); 6 months of follow-up Cost-year: 2008; euros
Shorr (2009) Abstract	US, Data-collection period NR	Total costs were reported for the use of fondaparinux- vs. enoxaparin for the treatment of VTE No unit costs or resource use data reported	Retrospective analysis of discharge records Subjects: 15,40, (fondaparinux = 266, enoxaparin = 14,674). Cost-year: not reported Perspective: unclear

Spyropoulos (2007)	US, 1 February 1998 to 30 June 2004	Costs calculated using the resource utilisation reported in the database Costs reported at an aggregated level Costs were reported at an aggregated level by diagnosis category Reported costs included hospitalisation facility cost, hospitalisation professional cost, outpatient office visit cost, outpatient procedure cost, and outpatient prescription cost	Retrospective analysis using the Integrated Health Care Information Services National Managed Care Database For the cost analysis, patients who had been enrolled in a health care plan for a minimum of 30 days prior to and 365 days following the DVT or PE hospitalisation Subjects: 14,108 Perspective: managed care organisation Cost-year: not reported; US dollars
Tagalakis (2012) Abstract	Canada, 1 January 2000 to 31 December 2009	Total direct cost per year Resource costs included hospitalisations, physician visits, and prescription medications Costs were split by condition (VTE, DVT, and PE)	Retrospective database study Perspective: direct treatment costs Data for the province of Québec, Canada, including the provincial hospitalisation database (MED-ÉCHO) and the health care claims databases of RAMQ, which is a government agency that administers the provincial universal health care programme Cost-year: 2009-2010; Canadian dollars The *Ontario Case Costing Initiative* was used to obtain hospital cost data Costs reported: initial hospitalisation cost, follow-up costs (diagnostic procedures, hospitalisation, treatments, and physician-billed medical acts)
Takai (2013)	Japan, 1 January 2003 to 31 October 2009	90-day cost associated with surgery (composition of costs includes pharmacy, laboratory, medical and room costs), hospital LOS and cumulative costs from 30 days prior to surgery to 6	Retrospective analysis of data from the Medical Data Vision Inc. hospital claims database Included patients underwent major

		months after surgery	orthopaedic surgery and did not have a prior diagnosis of VTE between 8 and 90 days prior to surgery Subjects: 4,650 Cost-year: NR, Japanese yen and US dollars
Vera-Arroyo (2013)	Spain, 1994 and 2009	Cost of diagnostic tests, drugs and hospital stay. Resource use data included use of diagnostic tests, in-patient prescriptions, special treatments, out-patient prescriptions and inpatient LOS	Descriptive, observational study Patients with a diagnosis of DVT in 1994 at a single centre in Spain were included, and compared to a group with the same diagnosis in 2009 Patients with PE, outpatient treatment or superficial thrombophlebitis were excluded Subjects: 110 (1994), 75 (2009) Cost-year: 2009, Euros
Wu (2014)	China, 1 January 2010 to 30 June 2013	Pharmacy and non-pharmacy costs per hospitalisation. Resource use includes hospital LOS, anticoagulant use (including heparin, warfarin and rivaroxaban) and INR monitoring.	Retrospective analysis of a database of electronic medical records, including 1.9 million patients from two tertiary hospitals. Hospitalisations with a diagnosis of VTE were included in the analysis. Subjects: 1,047 Cost-year: 2013, Chinese yuan (also

			coverted to 2013 US dollars)
Youman (2003)	UK, Data-collection period NR	Base-case model considered a hypothetical cohort of 1,000 patients having their first-ever stroke, using data from a 1-year clinical study (Kalra et al., 2000) Presents total cost estimates per patient over a 5-year period and discrete cost results per 3-month model period	Burden-of-illness model using a modified Markov framework to extrapolate data from the 1-year study Perspective: UK National Health Service Per-patient data from Kalra et al. (2000) included hospital, other health services, social services, and informal care resources for stroke over 1 year Other data sources are from published literature Cost-year: 2001/2002

ACS, acute coronary syndrome; AOK, Allgemeine Ortskrankenkasse; CHD, coronary heart disease; COX 2, cyclooxygenase-2; DVT, deep vein thrombosis; GP, general practitioner; HIT, heparin-induced thrombocytopaenia; HTA, health technology assessment; INR, international normalised ratio; IQR, interquartile range; LMWH, low molecular-weight heparin; LOS, length of stay; MI, myocardial infarction; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PSSRU, Personal Social Services Research Unit; PTS, post-thrombotic syndrome; RAMQ, Régie de l'assurance maladie du Québec; SD, standard deviation; SE, standard error; SPAF, stroke patient with atrial fibrillation; UA, unstable angina; UFH, unfractionated heparin; UK, United Kingdom; US, United States; VTE, venous thromboembolism

7.5.4 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 specialist 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 experts were only involved in the process of model development to understand patient pathways and standard of care in the UK. Expert opinion was not sought for cost parameters derived from the systematic literature review.

Intervention and comparators' costs

7.5.5 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 rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

[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.

In this section, unit costs and resource use estimates are outlined separately for the various elements of care.

The economic model accumulates the following costs:

- Acquisition costs of interventional drugs
- Costs of inpatient stay and acute parenteral treatment
- Drug administration and monitoring costs
- Acute event costs
- Follow-up costs after the following events:
    - ICH
    - CTEPH
    - PTS
    - MI / UA (in sensitivity analysis only)
    - Dyspepsia (in sensitivity analysis only)

All unit costs have been inflated to 2014 values using the Hospital and Community Health Services (HCHS) pay & prices index.[24]

In the probabilistic sensitivity analysis, cost parameters are sampled from gamma distributions, subject to availability of data of dispersion. Drug costs were considered fixed.

Table 115 shows the **acquisition costs of interventional drugs** taken from the most recent edition MIMS (March – May 2014).

Table 115: Drug costs (per day)

Treatment	Cost (£)	Source
Dabigatran (150 mg twice daily)	2.20	MIMS (2014)[98]; Section 1.10
Warfarin (generic, 4 mg per day)	0.07	MIMS (2014)[98]
Rivaroxaban		MIMS (2014)[98]
15 mg twice daily (first 21 days of treatment)	4.20	MIMS (2014)[98]
20 mg once daily (remainder of treatment and secondary prevention)	2.10	MIMS (2014)[98]
LMWH		
Enoxaparin (1.5 mg/kg/day sc)	8.33	MIMS (2014)[98]
Dalteparin		
Regimen 1*	11.76	MIMS (2014)[98]
Regimen 2*	11.76	MIMS (2014)[98]
Tinzaparin (175 IU/Kg/day)	6.93	MIMS (2014)[98]
Unfractionated heparin (UFH)		
Regimen 1*	4.67	MIMS (2014)[98]
Regimen 2*	1.76	MIMS (2014)[98]

* Please refer to
Table 116 for details

Patients are assumed to continue treatment up to a maximum duration, which is equal to the planned duration of treatment in dabigatran studies – unless recurrent VTE, or major bleeding event, or discontinuation due to any reason other than a recurrent VTE or bleeding event occurs. Discontinuation rates (Table 101) apply as observed in the clinical trials. For generic drugs, the drug costs reflect the cheapest option available.

Costs of acute parenteral treatment and inpatient stay

According to published guidelines, 5 to 10 days of administration of LMWH or UFH precedes treatment with dabigatran or WFN; in the base case analysis, the duration of acute parenteral treatment is 5 days (an alternative duration of 7.5 days is investigated in sensitivity analyses). By contrast, rivaroxaban patients are assumed to have no prior parenteral treatment in the base case. In the EINSTEIN-DVT and EINSTEIN-PE study, however, 73% (93%) of DVT (PE) patients received acute parenteral treatment, albeit for a much shorter duration (1.1 and 1.4 days, respectively); this was explored in sensitivity analyses. The type of parenteral treatment received is based on local data.[99] These weighting factors were used to calculate the average drug cost over the mean duration of acute parenteral treatment (5 days).

Table 116: Drug costs of acute parenteral treatment

Regimen	Details	% DVT patients[1]	% PE patients[1]
UFH			
Regimen 1	5,000U (IV) followed by 1000-2000 U/hour IV for 5 to 10 days	0.5%	5.0%
Regimen 2	5,000U (IV) followed by 15,000 U twice daily (SC) for 5 to 10 days	0.5%	5.0%
LMWH			
Enoxaparin	1.5 mg/kg (150 IU/kg) per day (SC) for 5 to 10 days	24.75%	90.0%
Dalteparin			
Regimen 1	200 IU/kg body weight (SC), once daily (not exceeding 18,000 IU), for at least 5 days	24.75%	0.0%
Regimen 2	100 IU/kg body weight (SC), twice daily for patients with increased risk for bleeding, for at least 5 days	24.75%	0.0%
Tinzaparin	175 IU/kg body weight once daily, for at least 6 days, and until adequate oral anti-coagulation is established	24.75%	0.0%
Weighted average costs per day		**£9.63**	**£7.81**

[1] Source: UK clinical expert panel [99]

Administration and monitoring costs

The model assumes patients receiving warfarin attend clinic for an initial anticoagulation clinic visit. They then will have a further 4 anticoagulation clinic visits for INR monitoring within the titration period and then once a month for the remainder of the treatment period.[41] Patients receiving dabigatran or rivaroxaban are assumed to have 1 follow-up visit at 5 months. Neither dabigatran nor rivaroxaban require regular INR tests.

The cost of an initial consultant-led anti-coagulation clinic attendance (not admitted, face to face), £62.56, was directly taken from the NHS reference costs 2012/12. The unit costs of anti-coagulation clinic visits (£27.99) during the titration period and the monthly follow up period thereafter were calculated as the weighted average (by activity data) of consultant-led and non-consultant led follow-up anticoagulant service (code 324).

Table 117: Administration and monitoring costs

		Quantities		
Cost element	**Amount (£)**	**Warfarin**	**Others[1]**	**Source**
Initial anti-coagulation clinic visit (consultant-led)	62.56	x1	-	NHSRC 2012/13[25]
Anti-coagulation clinic visits during titration period	27.99	x4	-	NHSRC 2012/13[25]
Anti-coagulation clinic follow-up visits (per month[2])	27.99	x1	-	NHSRC 2012/13[25]
Other follow-up visits	27.99	-	x1	NHSRC 2012/13[25]

[1] Dabigatran or rivaroxaban
[2] Monthly cost accrues up to the end of the planned treatment period, unless the patient discontinues.
Source for quantities: [41]

Cost of inpatient stay

Patients may be treated in an inpatient or an outpatient setting. 52% of acute proximal DVT patients are assumed to receive inpatient care, whereas 90% of PE patients are admitted to hospital. These admission rates are based on hospitalisation records from EINSTEIN trials.[82] The model assumes that the length of stay for admitted patients will be equivalent for rivaroxaban patients (receiving no parenteral treatment) and other comparators (receiving parenteral treatment).

Costs for inpatient stay and mean length of stay were estimated from NHS reference costs 2012/13. For DVT, estimates represent a weighted average of five currency codes (QZ20A, QZ20B, QZ20C, QZ20D, QZ20E) across HRG data of elective inpatients, non-elective inpatients (long stay) and non-elective inpatients (short stay).

Estimates for PE represent a weighted average of five currency codes (DZ09D, DZ09E, DZ09F, DZ09G, DZ09H) across HRG data of elective inpatients, non-elective inpatients (long stay) and non-elective inpatients (short stay).

Please refer to Table 118 for cost estimates used in the model.

Table 118: Cost of inpatient stay

Cost element	Amount (£)	Average LOS (d)	Average cost/day (£)	Source
Inpatient DVT	955.69	5.68	168.28	NHSRC 2012/13[25]
Inpatient PE	1,520,67	6.09	249.69	NHSRC 2012/13[25]

Patients discharged before the completion of their acute parenteral treatment and patients who are not admitted either self-inject LMWH at home (with training in self-administration), receive home nurse visits for LMWH injections, or attend clinic visits each day for LMWH injections. The cost of outpatient administration and monitoring (Table 119) is adjusted to the duration of acute parenteral treatment assumed and includes IV kits, tests, clinic visits for LMWH injections, and physician and nurse time.

Table 119: Outpatient administration and monitoring for LMWH and acute parenteral treatment

Cost element	%	Amount (£)	Source
LMWH at home, self-injection	87%	-	% - Watts (2006)[100]
LMWH at home, nurse injection (per day after discharge)	6%	39.18	% - Assumption; Cost – NHSRC 2012/13[25]
LMWH, administration in clinic (per day after discharge)	7%	27.99[1]	% - Assumption; Cost – NHSRC 2012/13[25]
UFH	0%	-	Assumption: no outpatient administration is received

[1] Equals cost of follow-up anticoagulation clinic visit (Table 117)

Recurrent VTE event costs

Recurrent DVT and PE events are assigned the same costs as the primary events with the addition of diagnosis costs (see Table 120). Patients presenting with DVT symptoms after discharge were assumed to incur an outpatient visit and receive one Doppler ultrasound investigation. Those thought to have PE are assumed to have one outpatient visit (adult follow-up attendance, clinical haematology), where they had a computed tomography, chest x-ray, and an electrocardiogram.

Table 120: Cost of diagnosing recurrent DVT and PE

		Quantities		
Cost element	**Amount (£)**	**DVT**	**PE**	**Source**

Outpatient visit	92.79	x1	x1	NHSRC 2012/13[25]: Non-Admitted Face to Face Attendance, Follow-up, Clinical Haematology
Doppler ultrasound	65.35	x1	-	NHSRC 2012/13[25]: Ultrasound Scan, 20 minutes and over (RA24Z, Diagnostic Imaging)
CT pulmonary angiogram	115.59	-	x1	NHSRC 2012/13[25]: Computerised Tomography Scan, three areas without contrast (RA50Z, Diagnostic Imaging)
Chest x-ray	28.93	-	x1	NHSRC 2012/13[25]: Direct Access Plain Film (DAPF)
Electrocardiogram	54.47	-	x1	NHSRC 2012/13[25]: Electrocardiogram Monitoring and stress testing (EA47Z, DADS)
Source for resource use is NCC-AC, 2007. Appendix, p.445[101]				

Health-state costs

7.5.6 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 7.2.4.

Table 121 shows the costs for the NHS England (primary and secondary care) per modelled event as applied in the economic evaluation.

Table 121: List of health states and associated costs in the economic model

Modelled event	Items	Value [£]	Reference in submission
Index DVT	Hospitalisation	496.96*	Table 118
Recurrent DVT	Diagnosing	158.14	Table 120
	Hospitalisation	496.96	Table 118
	Re-treatment dual LMWH/VKA†	384.67	Table 115, Table 116, Table 119
Index PE	Hospitalisation	1,368.60*	
Recurrent PE	Diagnosing	291.78	Table 120
	Hospitalisation	1,368.60	Table 118
	Re-treatment dual LMWH/VKA†	367.24	Table 115, Table 116, Table 119
ICH	Initial acute management	10,181.54	6.5.7
	Long-term care (per 1-month cycle)	250.94	6.5.7
MBE (extracranial)		2,357.03	6.5.7
CRNMB		395.55	6.5.7
Severe PTS	First month	358.08	6.5.7
	Following 1-month cycles	7.67	6.5.7
MI‡	Acute management	4,724.33	6.5.7
	Long-term care (per 1-month cycle)	33.54	6.5.7
UA‡	Acute management	4,588.20	6.5.7
	Long-term care (per 1-month cycle)	33.54	6.5.7
CTEPH	Pulmonary endarterectomy (cycle 1)	5,112.25	6.5.7
	Ongoing management (per 1-month cycle)	1,364.80	6.5.7
Dyspepsia‡	Management with non-steroidal anti-inflammatory drugs	46.02	6.5.7
Off treatment & death		0	-

* Expected value after admission rates[82] were applied

† After a recurrent VTE event, all patients are assumed to stop the initial treatment and initiate (or re-initiate, when warfarin is comparator) a 6 months standard treatment course of LMWH followed by warfarin. This item contains both drug and administration/monitoring costs.

‡ Applies to sensitivity analysis only

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. 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 7.2.2.

Most adverse events of anticoagulation therapies are related to bleeding. In the economic evaluation, the following three types of bleeding events have been modelled:

- Intracranial haemorrhage (ICH)
- Other major bleeds (excluding ICH)
- Non-major, but clinically relevant bleeds (CRNMB)

The cost of ICH was based on a cost-of-illness study using resource use data collected for 457 stroke patients treated in a UK centre.[102]

The cost of other (extracranial) major bleeds (MBE) was obtained from NHS reference costs 2012/13 for gastrointestinal bleed. A weighted average of the currency codes FZ38G, FZ38H, FZ38J, FZ38K, FZ38L was calculated across HRG data of elective inpatients, non-elective inpatients (long stay) and non-elective inpatients (short stay).

The cost of CRNMB resulting in hospitalisation was determined using the average NHS reference cost for minor lower and upper genital tract procedures (MA22Z, MA23Z, MA25Z, MA26Z).[25] Patients with all other clinically relevant non-major bleeds were assumed to incur the cost of an outpatient visit. Table 122 shows cost summary for major or clinically relevant bleeds and other adverse events.

50.5 % of patients with CTEPH require a pulmonary endarterectomy.[103] The procedure cost used in the model is based on the weighted average of four NHS reference costs (2012/13), DZ02D, DZ02E, DZ02E and DZ02G.

Table 122: Costs for bleeds and other adverse events

Cost element	Amount (£)	Source
MCRB		
ICH		
Initial acute management cost	10,182	[102]
Annual cost of long-term care[1]	3,011	[73;102]
Other major bleed (MBE)	2,357	NHSRC 2012/13[25]
CRNMB		
Hospitalised CRNMB [30%] *assumed*	1,102	NHSRC 2012/13[25]

Outpatient visit[2] [70%]	93	NHSRC 2012/13[25]
Severe post-thrombotic syndrome (PTS)[3]		
Year 1		
1x Vascular surgery, outpatient (first visit)[4]	168	NHSRC 2012/13[25]
2x Vascular surgery, outpatient (follow-up visit)[5]	274	NHSRC 2012/13[25]
Year 2+ (GP appointments, 2x per year)	92	PSSRU[24]
Myocardial infarction (MI)[10]		
Acute management	4,724	[104]
Long-term care [60%][6] (per month)	34	[104]
Unstable angina (UA)[10]		
Acute management	4,588	[104]
Long-term care [60%][6] (per month)	34	[104]
CTEPH		
Pulmonary endarterectomy [50.5%][7,8]	7,447	NHSRC 2012/13[25]
Ongoing management (per month)[9]	1,365	NICE CG92[105]
Dyspepsia[10]		
Management with non-steroidal anti-inflammatory drugs.	46	[106]

1 Average annual cost of long-term care reported by Youman et al. were weighted by disability type (mild, moderate, severe ICH). Weighting factors are taken from Rosand, 2004.[73] Costs defrayed by the patient/family were excluded.
2 Non-Admitted Face to Face Attendance, Follow-up, Clinical Haematology.
3 Quantities are taken from Goodacre et al., 2006.[107]
4 Weighted average of first consultant led outpatient attendances (face to face): WF01B and WF02B
5 Weighted average of follow-up consultant led outpatient attendances (face to face): WF01A and WF02A
6 Only 60% of survivors are assumed to have chronic ischaemic heart disease
7 Only 50.5% of CTEPH patients require a pulmonary endarterectomy[103]
8 Weighted average of the currency codes DZ02D, DZ02E, DZ02F, DZ02G across HRG data of elective inpatients, non-elective inpatients (long stay) and non-elective inpatients (short stay)
9 Based on the estimate of £1,219 per month made for NICE CG92[105] inflated to 2014 values.
10 In sensitivity analysis only

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

7.6 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.

7.6.1 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.

Clinical validity of the model

The economic model as described in Section 7.1 to Section 7.5 has been discussed with a panel of clinical experts in the UK on 30 July 2008. The panel included the following members:

- Dr Roopen Ayra, King's College Hospital, London
- Dr Trevor Baglin, Addenbrooke's Hospital, Cambridge
- Dr Gerry Dolan, Queens Medical Centre, Nottingham
- Dr David Keeling, Oxford Haemophilia and Thrombosis Centre, Oxford

- Dr Patrick Kesteven, Freeman Hospital, Newcastle-upon-Tyne

The members' comments on the model structure, assumptions and techniques were taken into account for the finalisation of the model.

Quality control of the model

Quality-control procedures were performed by staff not involved in the model development according to a prespecified test plan and included verification of all input data with the original source, programming validation by a senior health economist, a series of diagnostic tests to confirm that the model was correctly applying all formulas, and calculation of selected results independent of the model. Model predictions were validated with respect to empirical data.

In addition, an external agency was commissioned to perform a final quality assurance of the model. The quality assurance involved a detailed review of inputs and calculations throughout the entire model.[108] This review found minimal calculation errors which were revised for functional correctness.[108]

7.6.2 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 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Univariate deterministic sensitivity analysis

A series of sensitivity analyses were undertaken in order to test how sensitive the results are to uncertainty in individual parameters. Parameters varied in the sensitivity analysis were chosen on the basis of uncertainty in their estimation or the potential impact that they had on the results. The values varied are shown in Table 123.

Table 123: Description of sensitivity analyses

Sensitivity analysis number	Parameter to be changed	Default parameter value	New parameter value	Justification
1	Adjustment to TTR	As described in below and in Section 7.3.1		Treatment effects may differ depending on differences in TTR.
2	LMWH duration for rivaroxaban regimen	0 days	1.1 for DVT; 1.4 for PE	Rather than assuming no parenteral treatment use, the parenteral use observed in the rivaroxaban pivotal trials will be explored.
3	Utility decrement for WFN	-0.012	0.000	Test the impact of no utility decrement for WFN use
4	Dyspepsia	0.000	3.0% incidence in dabigatran, 1.0% incidence in WFN	Based on AE rate reporting in dabigatran clinical trials programme
5	Time horizon for treatment	Lifetime (60 years)	6 months	To see the results after 6 months have passed
6	Time horizon for treatment	Lifetime (60 years)	1 year	To see the results after 1 year has passed
7	Time horizon for treatment then secondary prevention	Lifetime (60 years)	1 year	To see the results after 1 year has passed
8	Bleeding event counting	Bleeds counted from start of single dummy period (i.e., counted whilst on LMWH for dabigatran or warfarin regimen)	Bleeds counted from double dummy period (i.e., for dabigatran, after 5 days of LMWH)	To estimate the impact across the dabigatran treatment pathway, rather than just the entire treatment pathway.
9	Myocardial infarction and unstable angina (i.e. cardiovascular events	Events excluded in the base case	Included in the scenario analysis	To estimate the effect of including myocardial infarction and unstable angina (i.e. cardiovascular events) in the analysis.
10	Unexplained death	Treatment and secondary prevention indication only: excluded unexplained deaths	Treatment and secondary prevention indication only: to include unexplained deaths	To explore the effects of unexplained deaths on the result
11	Rivaroxaban pre-specified treatment duration	Pooled 3, 6 and 12 month treatment durations	6 month treatment duration only	To compare results from the 6 month treatment period of the rivaroxaban trials with the RE-COVER II trials as the results match more closely.

7.6.3 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 7.3.6, 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).

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to estimate the level of parameter uncertainty in the decision and estimate the probability of cost-effectiveness at commonly applied willingness-to-pay thresholds. In principle, PSA varies all input parameters at the same time, subject to data availability. Where data was available, the variance of each parameter was used within the PSA. If this was not available, conservative assumption over the variance were made. The parameters considered in the sensitivity analysis are shown in Table 150 and Table 151. The PSA is extensive and takes into account all the key aspects of the model. In order to generate robust outcomes for the PSA simulation, each simulation will include 1,000 iterations of the model.

The results from the probabilistic and deterministic sensitivity analyses can be seen in Table 150 and Table 151 in Ssection 7.7.8, it can be seen that they are similar. This indicates that the model is robust to variations in certain parameters which may have an effect on the result.

7.7 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

7.7.1 For the outcomes highlighted in the decision problem (see section 5), 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.

Model predictions were compared with empirical data from the source trials and external sources. The results are presented in Table 124. The model predictions for dabigatran differ slightly from the empirical estimates because the model applies HRs for dabigatran versus warfarin rather than using the observed incidence directly. This approach was adopted so that the same approach could be taken for the indirect comparisons. The results provide confidence that the model is able to reproduce the course of the disease to an acceptable degree of certainty.

Note that the empirical estimates reflect the first event only, while the model allows for multiple events to occur in one patient.

Table 124: Comparison of Model Predictions with Empirical Data

Empirical Data	Empirical Estimate	Model Prediction
RE-COVER I		
Incidence of rVTERD at 7 months, dabigatran (%)	34/1274 (2.67%)[1]	2.70%
Incidence of rVTERD at 7 months, warfarin (%)	32/1265 (2.53%)[1]	2.57%
Incidence of MCRB at 6 months, dabigatran (%)	58/1226 (4.73%)[2]	4.65%
Incidence of MCRB at 6 months, warfarin (%)	99/1214 (8.15%)[2]	8.06%
RE-COVER II		
Incidence of rVTERD at 7 months, dabigatran (%)	34/1279 (2.66%)[3]	2.66%
Incidence of rVTERD at 7 months, warfarin (%)	30/1289 (2.33%)[3]	2.38%
Incidence of MCRB at 6 months, dabigatran (%)	51/1230 (4.15%)[4]	4.00%
Incidence of MCRB at 6 months, warfarin (%)	90/1248 (7.21%)[4]	7.15%
Recurrent VTE after trial follow-up		
Incidence of rVTE at 10 years, warfarin/VKA (%)	39.90% (35.4% to 44.4%)[5]	47.53%

Mean life expectancy for the general population aged 55, years	26 years[6]	26 years
Survival at 5 years for cancer population (%)	Relative survival 67%[7]	Relative survival 61%[8]

1 Including 30 days post treatment. Reference [71]
2 Reference [71]
3 Including 30 days post treatment. Reference [71]
4 Reference [71]
5 Reference [58]
6 Reference [68]
7 5-year survival for all cancer sites diagnosed in 2004. Reference [69]
8 Calculated as the proportion surviving at 5 years for the "active cancer" subgroup divided by the equivalent estimate for the "all patients" population; warfarin cohort, treatment analysis.

7.7.2 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 for dabigatran and the comparators for treatment of DVT and PE are shown in Figure 30 - Figure 33.

Markov traces for dabigatran and the comparators for treatment followed by secondary prevention of recurrent DVT and PE are shown in Figure 34 - Figure 37.

To facilitate the comparison with LMWH monotherapy, which is specific to the cancer patients, Markov traces for dabigatran in patients with active cancer are presented additionally in Figure 38 and Figure 39.

Figure 30: Markov trace for dabigatran for treatment of DVT and PE

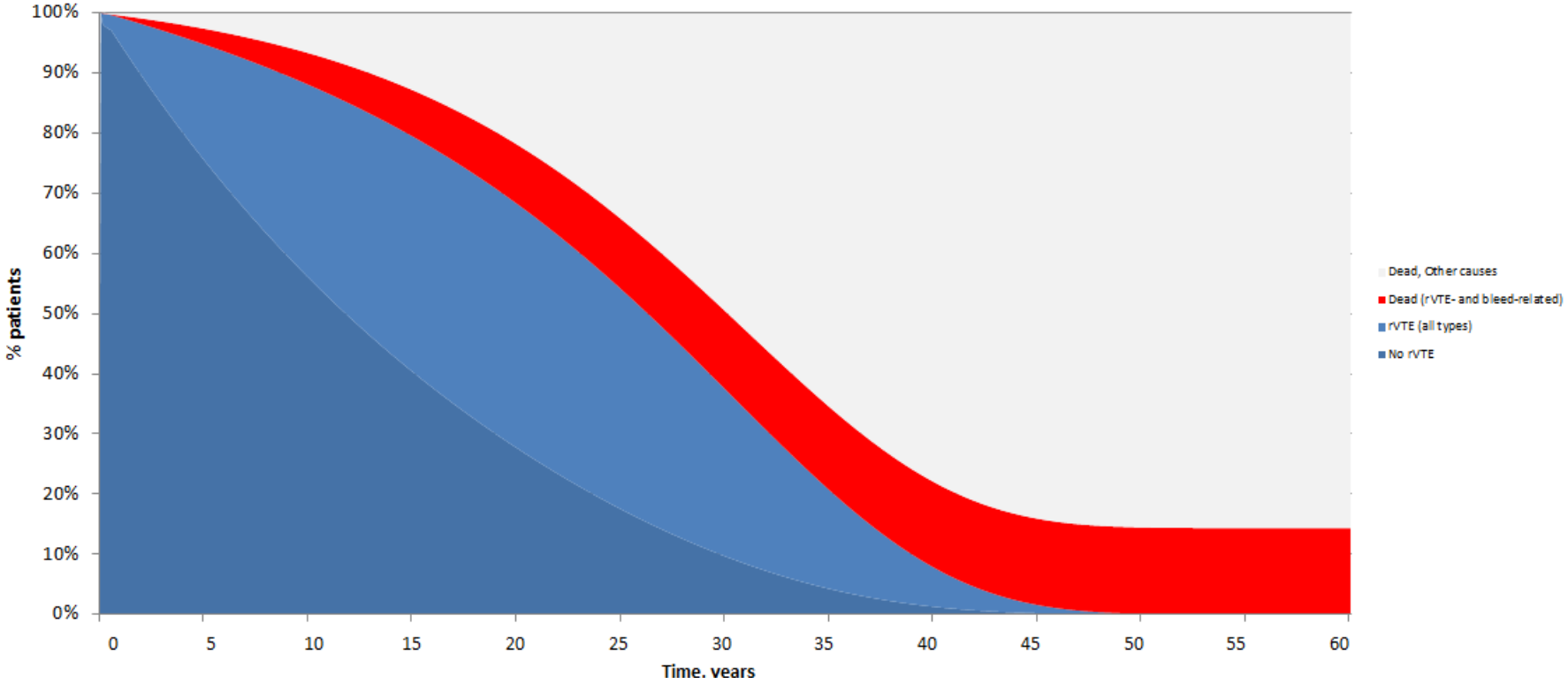


Figure 31: Markov trace for LMWH then warfarin for treatment of DVT and PE

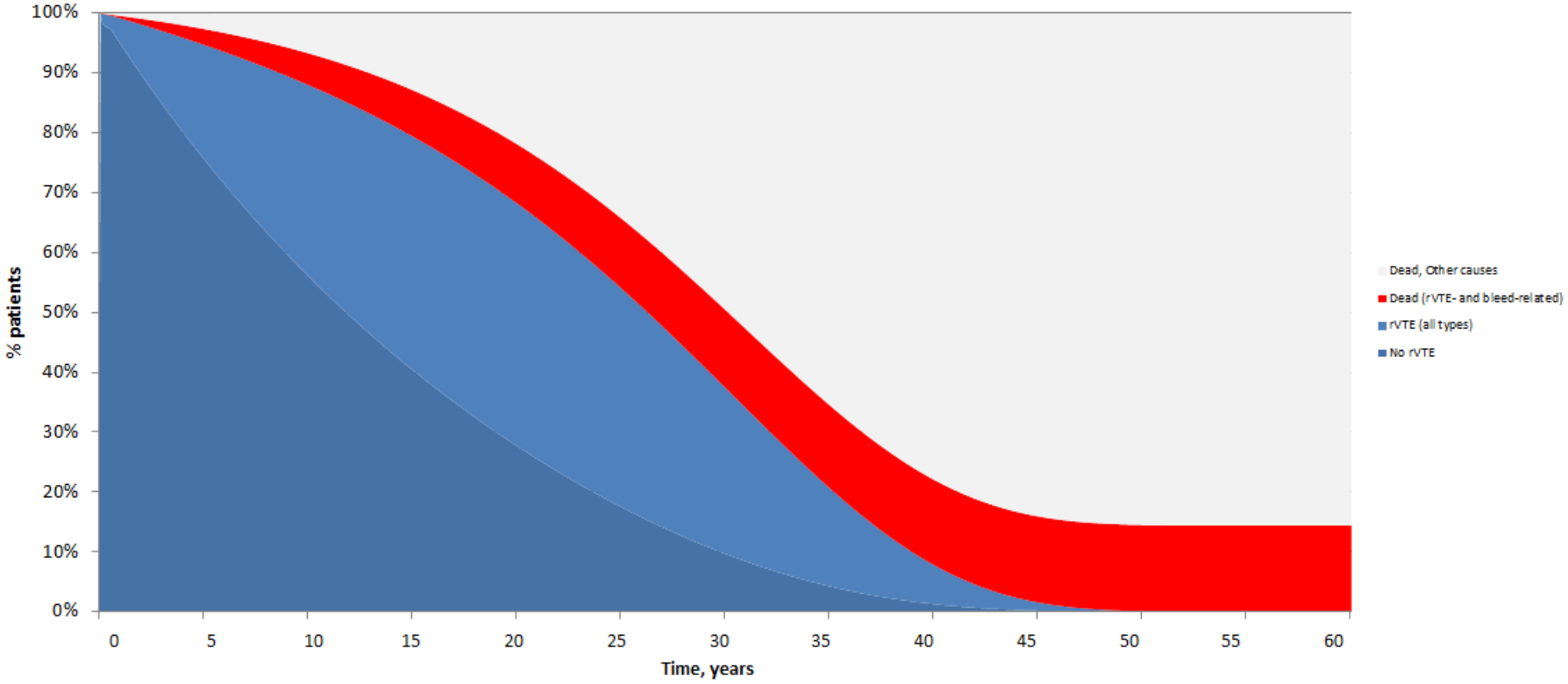


Figure 32: Markov trace for rivaroxaban for treatment of DVT and PE

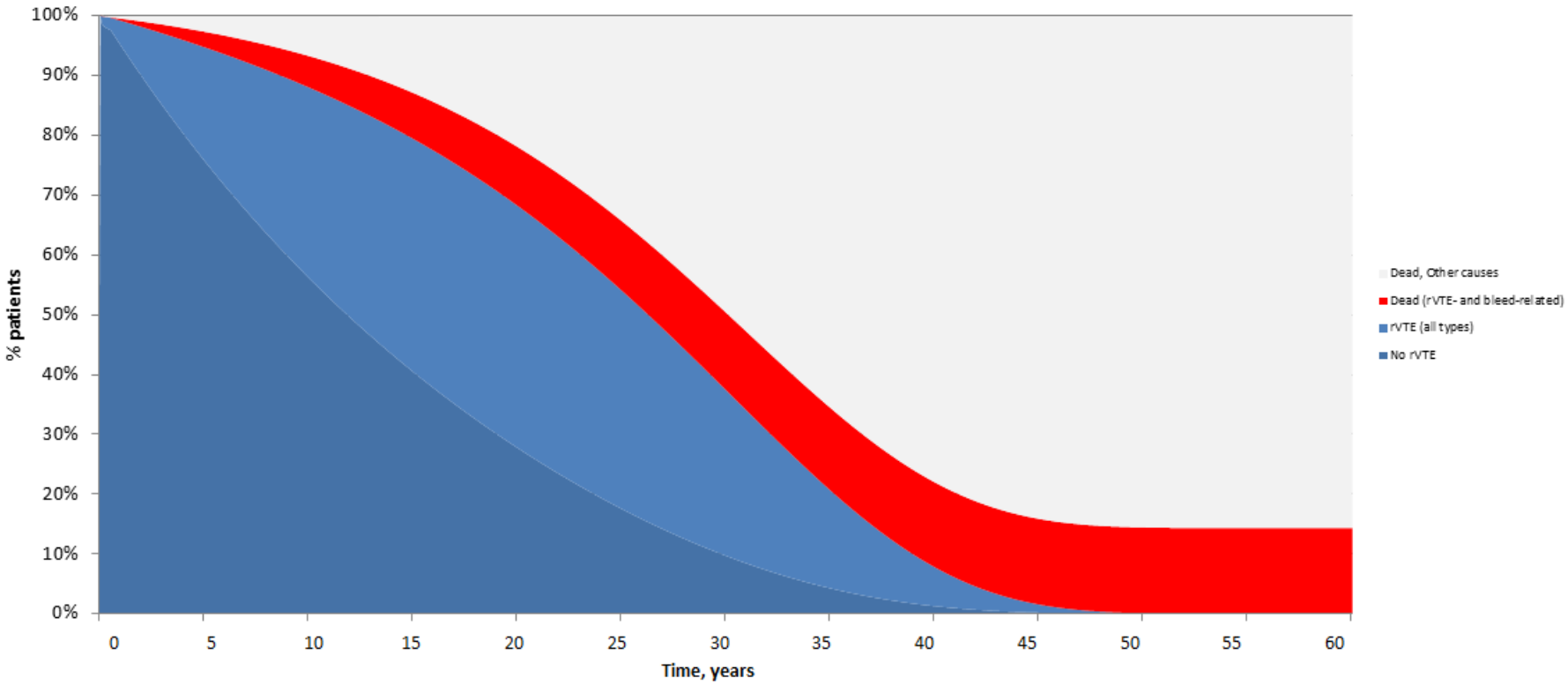


Figure 33: Markov trace for LMWH monotherapy for treatment of DVT and PE (in patients with cancer)

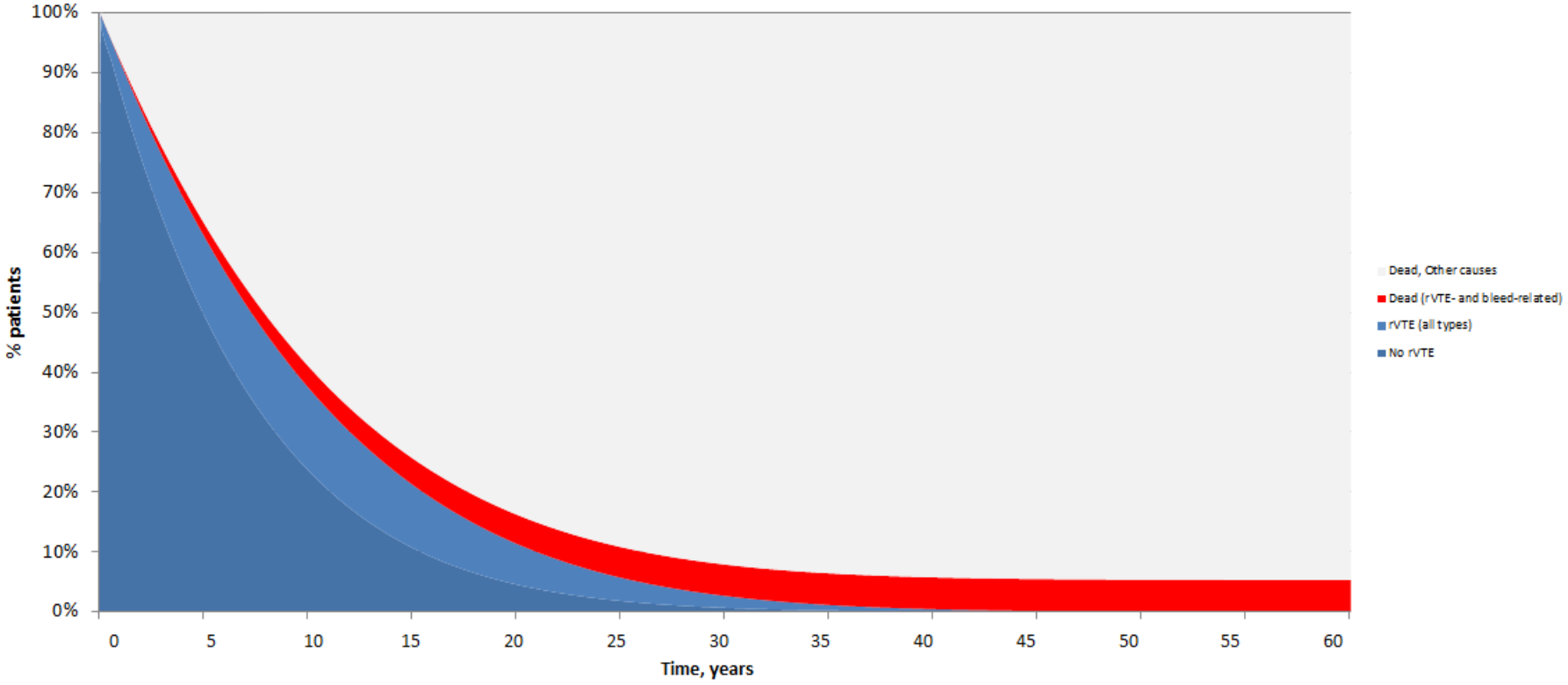


Figure 34: Markov trace for dabigatran for treatment followed by secondary prevention of recurrent DVT and PE

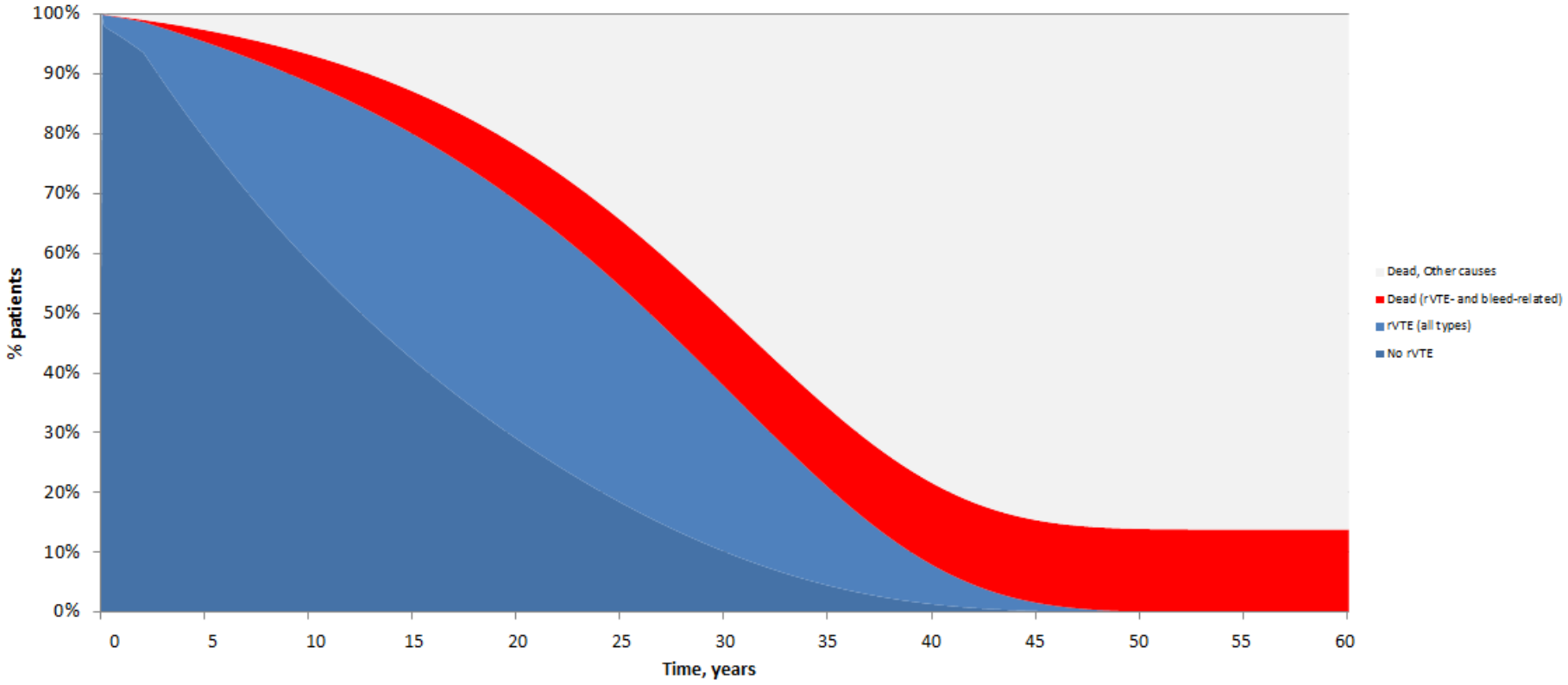


Figure 35: Markov trace for LMWH then warfarin for treatment followed by secondary prevention of recurrent DVT and PE

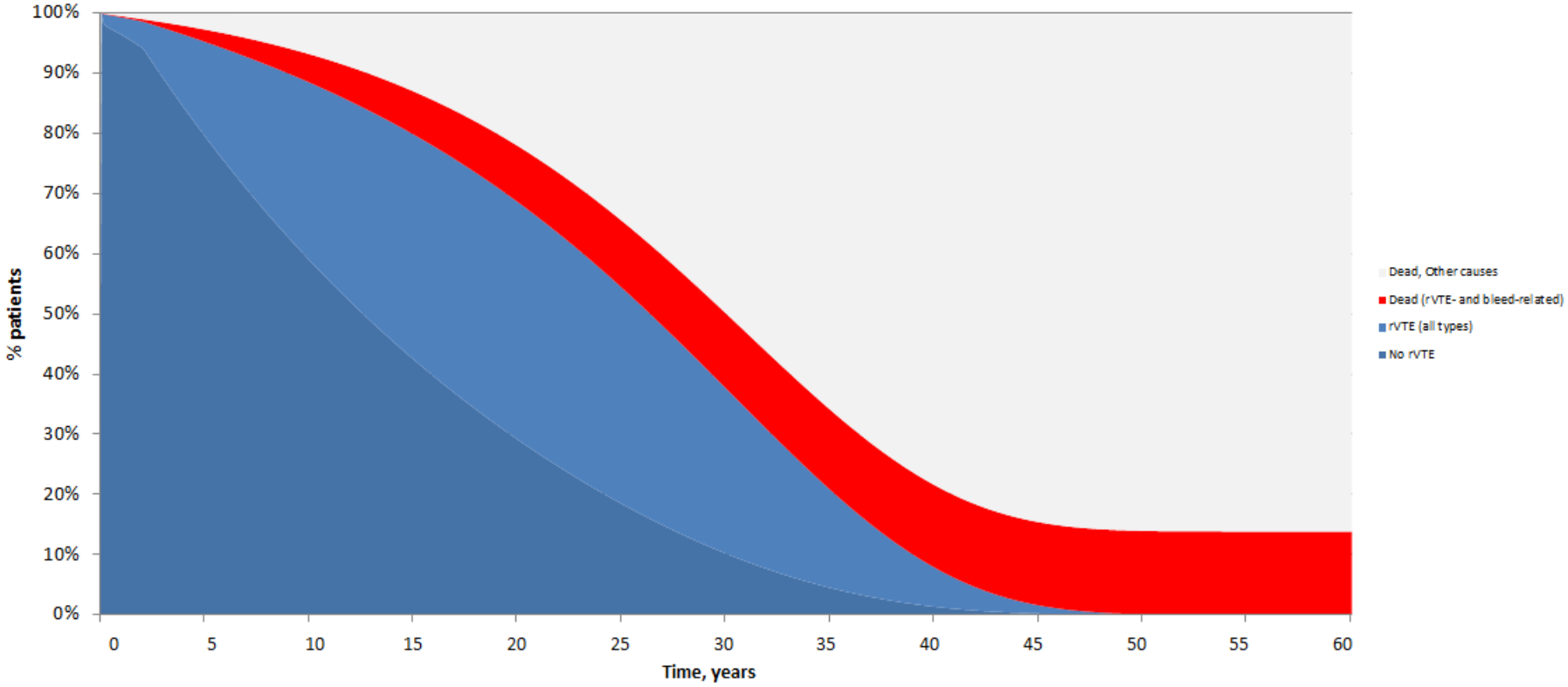


Figure 36: Markov trace for rivaroxaban for treatment followed by secondary prevention of recurrent DVT and PE

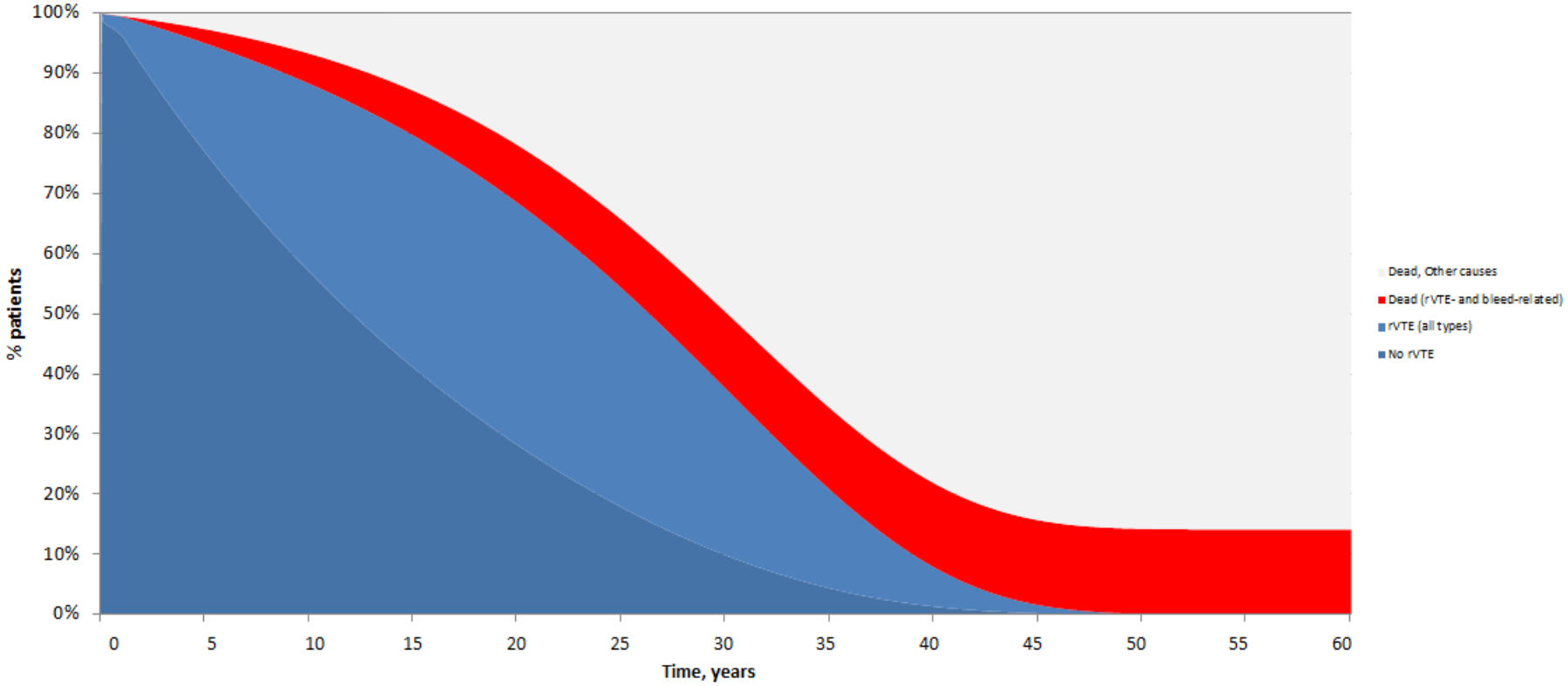


Figure 37: Markov trace for LMWH monotherapy for treatment followed by secondary prevention of recurrent DVT and PE (in patients with cancer)

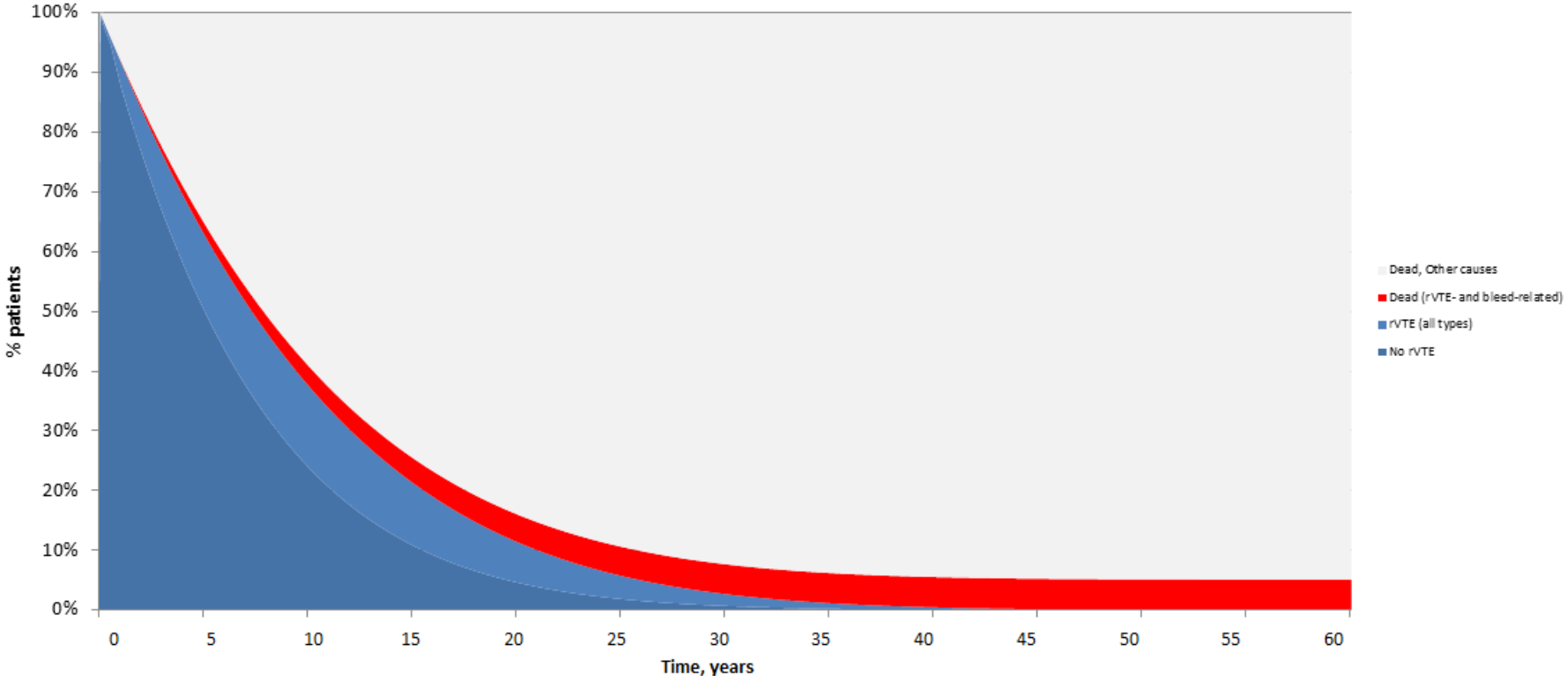


Figure 38: Markov trace for dabigatran for treatment of DVT and PE (in patients with cancer)

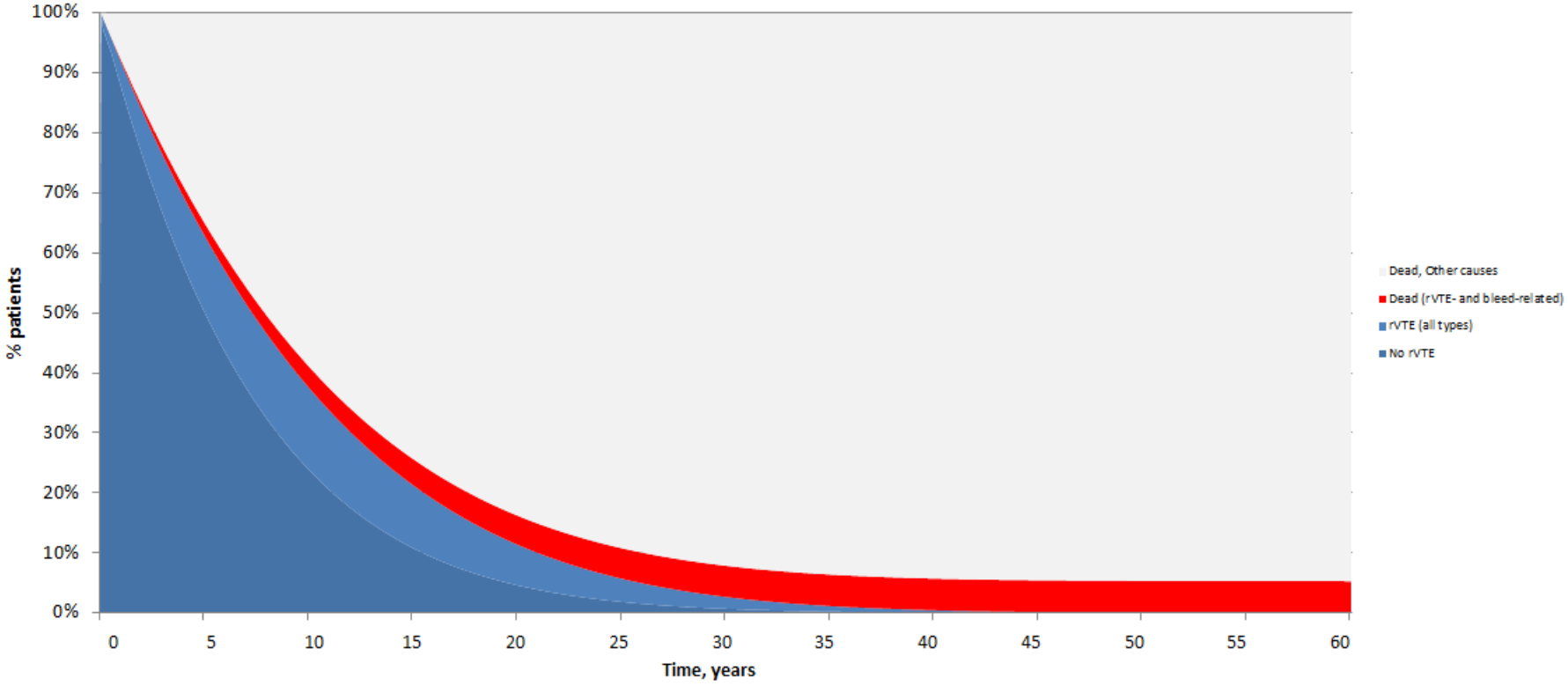
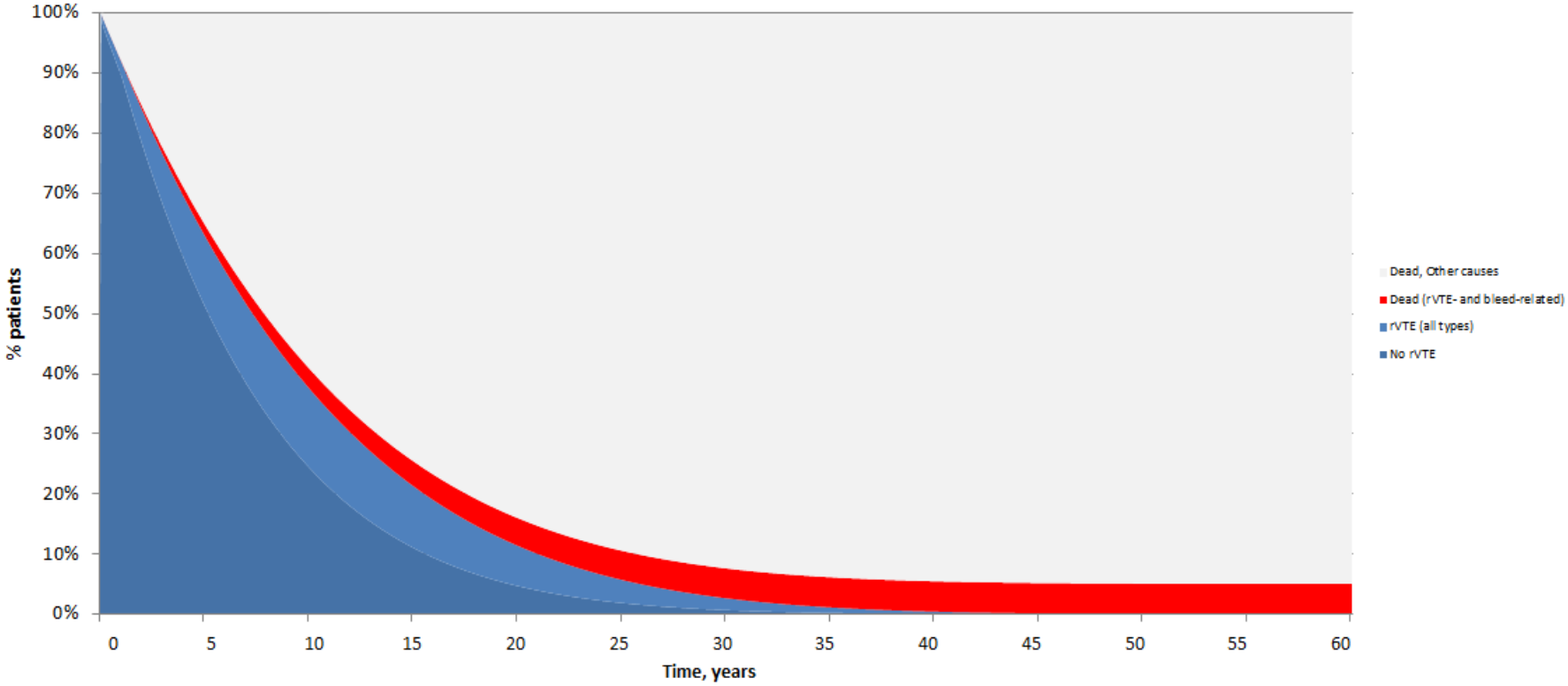


Figure 39: Markov trace for dabigatran for treatment followed by secondary prevention of recurrent DVT and PE (in patients with cancer)



7.7.3 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.

As outlined in 6.4.9, all modelled patients are assigned a baseline utility value based on estimates for the general population of the same age and gender; the baseline value decreases over time to model the impact of ageing. These estimates form the baseline to which the utility reductions (disutilities) due to both VTE and adverse events are applied for the duration described in Table 113. The cycle length in the model is one month, and patients transition between health states (Section 7.2.4) at each cycle. The QALY is thus calculated monthly based on the distribution of the cohort across the health states and the utility associated with being in the health state.

7.7.4 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. For example:

Table 125: Outcomes for the primary analyses for treatment of DVT and PE (10,000 patients over a lifetime horizon)

	LMWH then dabigatran	LMWH then warfarin	***Increment vs LMWH then dabigatran***	Rivaroxaban	***Increment vs LMWH then dabigatran***	LMWH monotherapy†	***Increment vs LMWH then dabigatran†***
Life year (LY)*	16.170	16.158	*0.0121*	16.170	*-0.0005*	7.491	*-0.0101*
QALY*	12.452	12.428	*0.0239*	12.451	*0.0003*	5.817	*-0.0124*
Events per 10,000 patients							
All recurrent VTE	**12,710**	**12,680**	***31***	**12,661**	***49***	**4,999**	***192***
Symptomatic recurrent non-fatal VTE events	11,275	11,242	*33*	11,228	*47*	4,467	*184*
Non-fatal DVT	8,271	8,247	*24*	8,196	*75*	3,223	*155*
Non-fatal PE	3,004	2,995	*9*	3,032	*-28*	1,243	*30*
VTE-related death	1,436	1,438	*-3*	1,433	*3*	532	*8*
All major and clinically relevant bleeds	**1,032**	**1,345**	***-313***	**1,292**	***-261***	**1,872**	***211***
Non-fatal major and clinically relevant bleeds	1,023	1,332	*-309*	1,282	*-259*	1,855	*206*
Intracranial haemorrhage	19	30	*-11*	21	*-2*	33	*13*
Other major bleeds	234	274	*-40*	170	*64*	277	*393*
Clinically relevant non-major bleeds	770	1,029	*-259*	1,091	*-321*	1,546	*-199*
Deaths from bleeding	9	12	*-4*	11	*-2*	17	*5*
Severe PTS	1,253	1,251	*2*	1,247	*6*	827	*13*
CTEPH	236	236	*0*	237	*-1*	168	*1*

* mean per patient
† in patients with cancer

Table 126: Outcomes for the primary analyses for treatment followed by secondary prevention of recurrent DVT and PE (10,000 patients over a lifetime horizon)

	LMWH then dabigatran	LMWH then warfarin	***Increment vs LMWH then dabigatran***	Rivaroxaban	***Increment vs LMWH then dabigatran***	LMWH monotherapy†	***Increment vs LMWH then dabigatran†***
Life year (LY)*	16.262	16.242	*0.0201*	16.208	*-0.0022*	16.194	*0.0119*
QALY*	12.519	12.464	*0.0551*	12.478	*0.0020*	12.451	*0.0282*
Events per 10,000 patients							
All recurrent VTE	**12,347**	**12,262**	***85***	**12,562**	***8***	**12,680**	***-186***
Symptomatic recurrent non-fatal VTE events	10,964	10,878	*86*	11,150	*5*	11,264	*-183*
Non-fatal DVT	8,029	7,982	*47*	8,137	*43*	8,221	*-89*
Non-fatal PE	2,935	2,896	*39*	3,013	*-38*	3,043	*-94*
VTE-related death	1,383	1,384	*-1*	1,412	*3*	1,416	*-3*
All major and clinically relevant bleeds	**1,469**	**2,172**	***-703***	**2,196**	***-728***	**1,902**	***27***
Non-fatal major and clinically relevant bleeds	1,460	2,154	*-693*	2,185	*-725*	1,888	*29*
Intracranial haemorrhage	30	52	*-22*	21	*-2*	33	*-7*
Other major bleeds	294	388	*-95*	270	*-12*	279	*102*
Clinically relevant non-major bleeds (CRNMB)	1,137	1,714	*-577*	1,894	*-711*	1,576	*-67*
Deaths from bleeding	8	18	*-10*	11	*-2*	14	*-2*
Severe PTS	1,233	1,229	*4*	1,242	*4*	1,249	*-7*
CTEPH	233	232	*2*	236	*-1*	237	*-4*

* mean per patient, discounted
† in patients with cancer

7.7.5 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.

All figures in this section are undiscounted and represent the mean per patient. Disaggregated QALYs, costs, and resources consumed are present for:

1) Treatment of DVT and PE (lifetime time horizon)

- LMWH then dabigatran vs LMWH then warfarin - Table 127, Table 130, Table 133
- LMWH then dabigatran vs rivaroxaban - Table 128, Table 131, Table 134
- LMWH then dabigatran vs LMWH (in patients with active cancer) - Table 129, Table 132, Table 135

and

2) Treatment followed by secondary prevention of recurrent DVT and PE (lifetime horizon)

- LMWH then dabigatran vs LMWH then warfarin - Table 136, Table 139, Table 142
- LMWH then dabigatran vs rivaroxaban - Table 137, Table 140, Table 143
- LMWH then dabigatran vs LMWH (in patients with active cancer) - Table 138, Table 141, Table 144

Note that the population definitions for the secondary prevention differ with the comparator chosen. For the comparison of dabigatran vs LMWH then warfarin, it is the population at risk for recurrent venous thromboembolism whereas for the comparison of dabigatran vs rivaroxaban it are the patients considered to be at equipoise for the need for continued anticoagulant therapy. This is down to the distinct definitions in the RE-MEDY and RE-SONATE secondary prevention trials.

Table 127: Summary of QALYs accrued (treatment of DVT and PE, vs LMWH then warfarin)

	LMWH then dabigatran	LMWH then warfarin	Increment	Absolute increment	% absolute increment
No recurrent VTE	10.9300	10.9419	-0.0119	0.0119	0.5041
Recurrent VTE	8.4330	8.4330	0.0000	0.0000	0.0000
QALYs loss from non-fatal events					
MBE (incl ICH)	-0.0033	-0.0039	0.0007	0.0007	0.0279
CRNMB	-0.0031	-0.0041	0.0010	0.0010	0.0437

PTS	-0.1769	-0.1766	-0.0003	0.0003	0.0133
CTEPH	-0.0002	-0.0002	0.0000	0.0000	0.0000
Disabled from ICH	-0.0135	-0.0232	0.0097	0.0097	0.4109
Total QALYs	**19.17**	**19.13**	**0.03**	**0.02**	**1.00**

Table 128: Summary of QALYs accrued (treatment of DVT and PE, vs rivaroxaban)

	LMWH then dabigatran	Rivaroxaban	Increment	Absolute increment	% absolute increment
No recurrent VTE	10.9300	10.9822	-0.0522	0.0522	0.9150
Recurrent VTE	8.4330	8.4330	0.0000	0.0000	0.0000
QALYs loss from non-fatal events					
MBE (incl ICH)	-0.0033	-0.0025	-0.0008	0.0008	0.0141
CRNMB	-0.0031	-0.0044	0.0013	0.0013	0.0225
PTS	-0.1769	-0.1758	-0.0011	0.0011	0.0195
CTEPH	-0.0002	-0.0002	0.0000	0.0000	0.0000
Disabled from ICH	-0.0135	-0.0151	0.0016	0.0016	0.0289
Total QALYs	**19.17**	**19.17**	**0.00**	**0.06**	**1.00**

Table 129: Summary of QALYs accrued (treatment of DVT and PE, vs LMWH monotherapy†)

	LMWH then dabigatran†	LMWH monotherapy†	Increment	Absolute increment	% absolute increment
No recurrent VTE	5.2302	5.3334	-0.1032	0.1032	0.9036
Recurrent VTE	2.1894	2.1894	0.0000	0.0000	0.0000
QALYs loss from non-fatal events					
MBE (incl ICH)	-0.0093	-0.0040	-0.0053	0.0053	0.0461
CRNMB	-0.0054	-0.0062	0.0008	0.0008	0.0070
PTS	-0.0555	-0.0546	-0.0009	0.0009	0.0077
CTEPH	-0.0001	-0.0001	0.0000	0.0000	0.0000
Disabled from ICH	-0.0142	-0.0101	-0.0041	0.0041	0.0356
Total QALYs	**7.34**	**7.35**	**-0.02**	**0.11**	**1.00**
† in patients with cancer					

Table 130: Summary of costs (treatment of DVT and PE, vs LMWH then warfarin)

	LMWH then dabigatran (£)	LMWH then warfarin (£)	Increment	Absolute increment	% absolute increment
VTE events (incl index)	1,812	1,809	3	3	0.03
ICH	101	171	-70	70	0.65
Other major bleeds (excl. ICH)	57	67	-10	10	0.09
CRNMB	30	41	-10	10	0.09
PTS	277	276	0	0	0.00
CTEPH	8,412	8,398	14	14	0.13
Total costs	**10,689**	**10,762**	**-73**	**108**	**1.00**

Table 131: Summary of costs (treatment of DVT and PE, vs rivaroxaban)

	LMWH then dabigatran (£)	Rivaroxaban (£)	Increment	Absolute increment	% absolute increment
VTE events (incl index)	1,812	1,812	0	0	0.00
ICH	101	113	-12	12	0.14
Other major bleeds (excl. ICH)	57	42	15	15	0.17
CRNMB	30	43	-13	13	0.14

PTS	277	275	2	2	0.02
CTEPH	8,412	8,459	-47	47	0.53
Total costs	**10,689**	**10,745**	**-55**	**89**	**1.00**

Table 132: Summary of costs (treatment of DVT and PE, vs LMWH monotherapy†)

	LMWH then dabigatran† (£)	LMWH monotherapy† (£)	Increment	Absolute increment	% absolute increment
VTE events (incl index)	1,204	1,189	15	15	0.09
ICH	133	96	37	37	0.21
Other major bleeds (excl. ICH)	163	69	94	94	0.54
CRNMB	53	61	-8	8	0.05
PTS	102	101	2	2	0.01
CTEPH	2,717	2,698	19	19	0.11
Total costs	**4,372**	**4,213**	**158**	**174**	**1.00**
† in patients with cancer					

Table 133: Summary of resources consumed (treatment of DVT and PE, vs LMWH then warfarin)

	LMWH then dabigatran (£)	LMWH then warfarin (£)	Increment	Absolute increment	% absolute increment
Total Drug Costs	**487**	**143**	**343.75**	**343.75**	**0.28**
Investigational treatment, drug	354	11	343.67	343.67	0.28
Re-treatment with warfarin, drug	17	17	0.02	0.02	0.00
Re-treatment with warfarin, acute parenteral drug	70	70	0.06	0.06	0.00
Total Monitoring (Administration) Costs	**520**	**786**	**-265.88**	**265.88**	**0.22**
Investigational treatment, admin	24	290	-266.31	266.31	0.22
Re-treatment with warfarin, admin	476	476	0.42	0.42	0.00
Re-treatment with warfarin, acute parenteral admin	12	12	0.01	0.01	0.00
Total costs	**1007**	**929**	**155.75**	**1220.12**	**1.00**

Table 134: Summary of resources consumed (treatment of DVT and PE, vs rivaroxaban)

	LMWH then dabigatran (£)	Rivaroxaban (£)	Increment	Absolute increment	% absolute increment
Total Drug Costs	**408**	**1,260**	**-852.44**	**852.44**	**0.27**
Investigational treatment, drug	323	1,222	-899.47	899.47	0.29
Re-treatment with warfarin, drug	8	7	0.13	0.13	0.00
Re-treatment with warfarin, acute parenteral drug	31	31	0.57	0.57	0.00
Total Monitoring (Administration) Costs	**244**	**911**	**-666.48**	**666.48**	**0.21**
Investigational treatment, admin	22	700	-678.06	678.06	0.22
Re-treatment with warfarin, admin	210	206	3.71	3.71	0.00
Re-treatment with warfarin, acute parenteral admin	5	5	0.10	0.10	0.00
Total costs	**652**	**2171**	**-3091.95**	**3100.96**	**1.00**

Table 135: Summary of resources consumed (treatment of DVT and PE, vs LMWH monotherapy†)

	LMWH then dabigatran† (£)	LMWH monotherapy† (£)	Increment	Absolute increment	% absolute increment
Total Drug Costs	**372**	**1,224**	**-852.02**	**852.02**	**0.27**
Investigational treatment, drug	323	1,222	-899.47	899.47	0.29
Re-treatment with warfarin, drug	1	0	0.19	0.19	0.00
Re-treatment with warfarin, acute parenteral drug	2	2	0.93	0.93	0.00
Total Monitoring (Administration) Costs	**45**	**709**	**-664.38**	**664.38**	**0.21**
Investigational treatment, admin	22	700	-678.06	678.06	0.22
Re-treatment with warfarin, admin	15	9	5.76	5.76	0.00
Re-treatment with warfarin, acute parenteral admin	0	0	0.16	0.16	0.00
Total costs	**417**	**1933**	**-3086.89**	**3100.96**	**1.00**
† in patients with cancer					

Table 136: Summary of QALYs accrued (treatment followed by secondary prevention of DVT and PE, vs LMWH then warfarin)

	LMWH then dabigatran	LMWH then warfarin	Increment	Absolute increment	% absolute increment
No recurrent VTE	11.4004	11.4404	-0.0400	0.0400	0.63
Recurrent VTE	8.0779	8.0779	0.0000	0.0000	0.00
QALYs loss from non-fatal events					
MBE (incl ICH)	-0.0042	-0.0057	0.0015	0.0015	0.02
CRNMB	-0.0045	-0.0069	0.0023	0.0023	0.04
PTS	-0.1731	-0.1725	-0.0006	0.0006	0.01
CTEPH	-0.0002	-0.0002	0.0000	0.0000	0.00
Disabled from ICH	-0.0227	-0.0418	0.0191	0.0191	0.30
Total QALYs	**19.27**	**19.20**	**0.07**	**0.06**	**1.00**

Table 137: Summary of QALYs accrued (treatment followed by secondary prevention of DVT and PE, vs rivaroxaban)

	LMWH then dabigatran	Rivaroxaban	Increment	Absolute increment	% absolute increment
No recurrent VTE	11.1134	11.1221	-0.0088	0.0088	0.62
Recurrent VTE	8.2948	8.2948	0.0000	0.0000	0.00
QALYs loss from non-fatal events					
MBE (incl ICH)	-0.0036	-0.0038	0.0002	0.0002	0.01
CRNMB	-0.0047	-0.0076	0.0028	0.0028	0.20
PTS	-0.1754	-0.1748	-0.0007	0.0007	0.05
CTEPH	-0.0002	-0.0002	0.0000	0.0000	0.00
Disabled from ICH	-0.0134	-0.0151	0.0017	0.0017	0.12
Total QALYs	**19.21**	**19.21**	**0.00**	**0.01**	**1.00**

Table 138: Summary of QALYs accrued (treatment followed by secondary prevention of DVT and PE, vs LMWH monotherapy†)

	LMWH then dabigatran†	LMWH monotherapy†	Increment	Absolute increment	% absolute increment
No recurrent VTE	11.1901	10.9715	0.2187	0.2187	0.96
Recurrent VTE	8.2149	8.2149	0.0000	0.0000	0.00
QALYs loss from non-fatal events					

MBE (incl ICH)	-0.0053	-0.0040	-0.0012	0.0012	0.01
CRNMB	-0.0060	-0.0063	0.0003	0.0003	0.00
PTS	-0.1747	-0.1760	0.0013	0.0013	0.01
CTEPH	-0.0002	-0.0002	0.0000	0.0000	0.00
Disabled from ICH	-0.0197	-0.0255	0.0058	0.0058	0.03
Total QALYs	**19.20**	**19.17**	**0.03**	**0.23**	**1.00**

† in patients with cancer

Table 139: Summary of costs (treatment followed by secondary prevention of DVT and PE, vs LMWH then warfarin)

	LMWH then dabigatran (£)	LMWH then warfarin (£)	Increment	Absolute increment	% absolute increment
VTE events (incl index)	1,785	1,775	10	10	0.04
ICH	168	307	-139	139	0.54
Other major bleeds (excl. ICH)	71	95	-24	24	0.09
CRNMB	45	68	-23	23	0.09
PTS	271	270	1	1	0.00
CTEPH	8,288	8,226	62	62	0.24
Total costs	**10,628**	**10,741**	**-114**	**258**	**1.00**

Table 140: Summary of costs (treatment followed by secondary prevention of DVT and PE, vs rivaroxaban)

	LMWH then dabigatran (£)	Rivaroxaban (£)	Increment	Absolute increment	% absolute increment
VTE events (incl index)	1,801	1,805	-4	4	0.03
ICH	100	113	-13	13	0.11
Other major bleeds (excl. ICH)	63	66	-3	3	0.03
CRNMB	47	75	-28	28	0.25
PTS	274	273	1	1	0.01
CTEPH	8,359	8,424	-64	64	0.57
Total costs	**10,645**	**10,755**	**-111**	**113**	**1.00**

Table 141: Summary of costs (treatment followed by secondary prevention of DVT and PE, vs LMWH monotherapy†)

	LMWH then dabigatran† (£)	LMWH monotherapy† (£)	Increment	Absolute increment	% absolute increment
VTE events (incl index)	1,794	1,815	-21	21	0.09
ICH	146	188	-43	43	0.17
Other major bleeds (excl. ICH)	92	69	24	24	0.10
CRNMB	60	62	-3	3	0.01
PTS	273	275	-2	2	0.01
CTEPH	8,316	8,472	-156	156	0.63
Total costs	**10,681**	**10,882**	**-201**	**248**	**1.00**

† in patients with cancer

Table 142: Summary of resources consumed (treatment followed by secondary prevention of DVT and PE, vs LMWH then warfarin)

	LMWH then dabigatran (£)	LMWH then warfarin (£)	Increment	Absolute increment	% absolute increment
Total Drug Costs	**1,379**	**167**	**1211.36**	**1211.36**	**0.33**
Investigational treatment, drug	1,248	37	1211.19	1211.19	0.33

Re-treatment with warfarin, drug	17	17	0.03	0.03	0.00
Re-treatment with warfarin, acute parenteral drug	68	68	0.14	0.14	0.00
Total Monitoring (Administration) Costs	**506**	**1,155**	**-648.62**	**648.62**	**0.17**
Investigational treatment, admin	24	674	-649.55	649.55	0.17
Re-treatment with warfarin, admin	462	461	0.91	0.91	0.00
Re-treatment with warfarin, acute parenteral admin	12	12	0.02	0.02	0.00
Total costs	**1885**	**1322**	**1125.48**	**3721.83**	**1.00**

Table 143: Summary of resources consumed (treatment followed by secondary prevention of DVT and PE, vs rivaroxaban)

	LMWH then dabigatran (£)	Rivaroxaban (£)	Increment	Absolute increment	% absolute increment
Total Drug Costs	**801**	**793**	**8.85**	**8.85**	**0.16**
Investigational treatment, drug	670	706	-36.44	36.44	0.68
Re-treatment with warfarin, drug	17	17	0.01	0.01	0.00
Re-treatment with warfarin, acute parenteral drug	69	69	0.05	0.05	0.00
Total Monitoring (Administration) Costs	**515**	**508**	**6.96**	**6.96**	**0.13**
Investigational treatment, admin	24	25	-1.10	1.10	0.02
Re-treatment with warfarin, admin	472	471	0.36	0.36	0.01
Re-treatment with warfarin, acute parenteral admin	12	12	0.01	0.01	0.00
Total costs	**1317**	**1301**	**-21.29**	**53.79**	**1.00**

Table 144: Summary of resources consumed (treatment followed by secondary prevention of DVT and PE, vs LMWH monotherapy†)

	LMWH then dabigatran† (£)	LMWH monotherapy† (£)	Increment	Absolute increment	% absolute increment
Total Drug Costs	**798**	**2,573**	**-1774.47**	**1774.47**	**0.27**
Investigational treatment, drug	666	2,487	-1821.08	1821.08	0.28
Re-treatment with warfarin, drug	17	17	0.06	0.06	0.00
Re-treatment with warfarin, acute parenteral drug	69	69	0.23	0.23	0.00
Total Monitoring (Administration) Costs	**515**	**1,952**	**-1436.95**	**1436.95**	**0.22**
Investigational treatment, admin	24	1,470	-1446.38	1446.38	0.22
Re-treatment with warfarin, admin	471	470	1.62	1.62	0.00
Re-treatment with warfarin, acute parenteral admin	12	12	0.04	0.04	0.00
Total costs	**1314**	**4525**	**-6476.92**	**6480.83**	**1.00**

† in patients with cancer

7.7.6 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.

Table 145: Base case results - Treatment of DVT and PE (lifetime horizon) – Mean per patient

Technologies		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Dabigatran	Deterministic	7,503	16.170	12.452	-	-	-	-
	Probabilistic	7,570	16,172	16.172	-	-	-	-
vs LMWH then warfarin	Deterministic	7,482	16.158	12.428	21	0.0121	0.0239	862
	Probabilistic	7,545	16.159	12.431	25	0.0125	0.0241	1,016
vs rivaroxaban	Deterministic	7,523	16.170	12.451	-20	-0.0005	0.0003	Rivaroxaban is dominated by dabigatran
	Probabilistic	7,480	16.168	12.449	-17	-0.0003	0.0003	Rivaroxaban is dominated by dabigatran
vs LMWH monotherapy (in patients with cancer)	Deterministic	5,522	7.491	5.817	-1,370*	-0.0101*	-0.0124*	110,742 (SW)
	Probabilistic	5,496	7.489	5.815	-1,349*	-0.0116*	-0.0144*	93,431 (SW)

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *Incremental comparison with dabigatran cancer subgroup only (data not presented in ths table)

Table 146: Base case results - Treatment followed by secondary prevention of DVT and PE (lifetime time horizon) – Mean per patient

Technologies		Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Dabigatran	Deterministic	8,319	16.262	12.519	-	-	-	-
	Probabilistic	8,305	16.260	12.510	-	-	-	-
vs LMWH then warfarin	Deterministic	7,861	16.242	12.464	458	0.0201	0.0551	8,319
	Probabilistic	7,839	16.240	12.460	466	0.0200	0.0500	8,465
vs rivaroxaban	Deterministic	7,852	16.208	12.478	-67	-0.0022	0.0020	Rivaroxaban is dominated by dabigatran
	Probabilistic	7,878	16.19	12.47	-63	0.0100	0.0096	Rivaroxaban is dominated by dabigatran
vs LMWH monotheray (in patients with cancer)	Deterministic	11,161	16.194	12.451	-3,340*	0.0090*	0.0197*	LMWH is dominated by dabigatran
	Probabilistic	11,118	16.190	12.450	-3,342*	0.0200*	0.0226*	LMWH is dominated by dabigatran

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; *Incremental comparison with dabigatran cancer subgroup only (data not presented in ths table)

Table 147: Base case results NMB at £20,000/QALY willingness to pay

	Treatment of DVT and PE	Treatment followed by prevention of DVT and PE
Dabigatran	£24,1537	£242,061
LMWH then warfarin	£24,1078	£241,419

Rivaroxaban	£24,1497	£241,708
LMWH monotherapy	£11,0818	£237,859
Calculated by using deterministic results of Table 145 and Table 146.		

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Results from the sensitivity analysis outlined in Section 7.6.2 are shown in below. The results for the treatment of DVT and PE are shown in Table 148 and for the treatment and secondary prevention of DVT and PE are shown in Table 149. The base case results for each indication are also shown for comparison.

Table 148: Results from the univariate sensitivity analysis for treatment of DVT and PE

Scenario number (as in	Comparator	Incremental costs with LMWH then dabigatran (£)	Incremental QALYs with LMWH then dabigatran	ICER (£/QALY)
		Base case		
	Versus LMWH then WFN	21	0.0239	862
	Versus rivaroxaban	-20	0.0003	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-1,370	-0.0124	DBG is less expensive and less effective
		Sensitivity analysis		
1	Versus LMWH then WFN	19	0.0242	778
	Versus rivaroxaban	-19	0.0001	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-1,370	-0.0123	DBG is less expensive and less effective
2	Versus LMWH then WFN			
	Versus rivaroxaban	-30	0.0003	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)			
3	Versus LMWH then WFN	21	0.0170	1,217
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
4	Versus LMWH then WFN	21	0.0236	911
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
5	Versus LMWH then WFN	48	0.0090	5,317
	Versus rivaroxaban	15	0.0003	46,274

	Versus LMWH mono-therapy (active cancer patients)	-1,401	-0.0012	DBG is less expensive and less effective
6	Versus LMWH then WFN	47	0.0095	4,963
	Versus rivaroxaban	15	0.0003	44,142
	Versus LMWH mono-therapy (active cancer patients)	-1,398	-0.0019	DBG is less expensive and less effective
7	Versus LMWH then WFN			
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
8	Versus LMWH then WFN	32	0.0226	1,435
	Versus rivaroxaban	-24	-0.0005	DBG is less expensive and less effective
	Versus LMWH mono-therapy (active cancer patients)	-1,425	-0.0078	DBG is less expensive and less effective
9	Versus LMWH then WFN	33	0.0239	1,390
	Versus rivaroxaban	-23	0.0067	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-1,364	-0.0124	DBG is less expensive and less effective
10	Versus LMWH then WFN			
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
11	Versus LMWH then WFN			
	Versus rivaroxaban	-40	0.0023	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)			

Cells which are highlighted in grey indicate sensitivity analyses that are not applicable or relevant to the comparison.

Table 149: Results from the univariate sensitivity analysis for treatment and secondary prevention of DVT and PE

Scenario number (as in 7.7.8	Comparator	Incremental costs with LMWH then dabigatran (£)	Incremental QALYs with LMWH then	ICER (£/QALY)
	Base case			
	Versus LMWH then WFN	458	0.0551	8,319
	Versus rivaroxaban	-67	0.0020	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-3,340	0.0197	DBG is dominant
	Sensitivity analysis			
1	Versus LMWH then WFN	454	0.0556	8,160
	Versus rivaroxaban	-66	0.0018	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-3,341	0.0198	DBG is dominant
2	Versus LMWH then WFN			
	Versus rivaroxaban	-76	0.0020	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)			
3	Versus LMWH then WFN	458	0.0306	14,947
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
4	Versus LMWH then WFN	459	0.0536	8,556
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
5	Versus LMWH then WFN			
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			

6	Versus LMWH then WFN			
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
7	Versus LMWH then WFN	209	0.0162	12,905
	Versus rivaroxaban	-22	0.0030	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-3,225	0.0083	DBG is dominant
8	Versus LMWH then WFN	459	0.0550	8,350
	Versus rivaroxaban	-69	0.0013	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-3,362	0.0214	DBG is dominant
9	Versus LMWH then WFN	515	0.0547	9,425
	Versus rivaroxaban	-115	0.0108	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-3,340	0.0197	DBG is dominant
10	Versus LMWH then WFN	459	0.0618	7,427
	Versus rivaroxaban			
	Versus LMWH mono-therapy (active cancer patients)			
11	Versus LMWH then WFN			
	Versus rivaroxaban	-86	0.0041	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)			

Cells which are highlighted in grey indicate sensitivity analyses that are not applicable or relevant to the comparison.

Discussion

For the sensitivity analysis comparing LMWH followed by dabigatran against LMWH followed by warfarin for treatment of DVT and PE, the base case results remain well below £10,000 per QALY. The base case ICER is £862, and the sensitivity analysis ranging from the lowest ICER of £778 when the time in therapeutic range is adjusted for, to the highest ICER of £5,317 when the time horizon is changed to 6 months. In the same comparison during the treatment and secondary prevention of DVT and PE, the base case ICER is £8,319, and the sensitivity analysis ICERs range from £7,427 (when unexplained deaths are included) to £14,947 (when the utility decrement for warfari is removed).

When comparing LMWH followed by dabigatran with rivaroxaban in the treatment of DVT and PE, dabigatran is dominant over rivaroxaban in the base case and ICERs in the sensitivity analyses range from dabigatran remaining dominant in a few scenarios (Table 148) to dabigatran being less expensive and less effective (ICER of £48,000) when bleeding events are counted from the double-dummy period. When looking at the same comparison for the treatment and secondary prevention of DVT and PE, dabigatran is dominant over rivaroxaban in the base case, and remains dominant in all sensitivity analyses.

LMWH followed by dabigatran compared with LMWH monotherapy in patients with active cancer showed that dabigatran was less expensive and less effective in the base case result for the treatment of DVT and PE, with this result remaining in the sensitivity analyses. For the same comparison in the treatment and secondary prevention of DVT and PE, dabigatran is dominant over LMWH monotherapy in the base case, and remains dominant in all sensitivity analyses.

Three variations in time horizon where investigated as part of the sensitivity analysis: shortening the lifetime (60 years) treatment only period to 6 months; shortening the lifetime treatment only period to 21 year and; shortening the lifetime horizon of treatment followed by secondary prevention to 1 year. When shortening the lifetime treatment period to 6 months, this changes the ICER for the comparison against rivaroxaban from dabigatran being dominant to an ICER of £46,274. The ICER fro dabigatran versus rivaroxaban becomes £44,142 when the treatment period is 1 year. However, dabigatran remains dominant versus rivaroxaban in the treatment followed by secondary prevention indication when the lifetime horizon is changed to 1 year (Table 149).

The impact of including the absolute risks of cardiovascular events in the economic model was explored as a sensitivity analysis. The results in Table 148 and Table 149 show that including these events had very little impact on the ICERs and did not change the conclusions of the analysis.

A number of additional univariate sensitivity analyses have been conducted in order to test the robustness of the base case results of the economic model. Regardless of the analysis chosen, the ICER for LMWH followed by dabigatran versus LMWH followed by warfarin (the main comparator) was comfortably within £20,000 per QALY gained.

7.7.11 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The cost effectiveness planes (CEPs) and cost effectiveness acceptability curves (CEACs) for the PSA detailed in Section 7.6.3 are depicted for both of the primary analyses: treatment of DVT and PE (see Table 150, Figure 40, Figure 41, Figure 42, Figure 43, Figure 44 and Figure 45) and treatment and secondary prevention of DVT and PE (see Table 151, Figure 46, Figure 47, Figure 48, Figure 49, Figure 50 and Figure 51).

Treatment of DVT and PE

Table 150: ICERs for the primary analysis for treatment of DVT and PE

	Treatment of DVT and PE with LMWH then dabigatran					
					Willingness to pay threshold (£/QALY)	
	Type	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	£20,000	£30,000
Versus LMWH then warfarin	Deterministic	21	0.0239	862		
	Probabilistic	25	0.0241	1,061	93%	94%
Versus rivaroxaban	Deterministic	-20	0.0003	DBG is dominant		
	Probabilistic	-17	0.0002	DBG is dominant	57%	57%
Versus LMWH mono-therapy (active cancer patients)	Deterministic	-1,370	-0.0124	DBG is less expensive and less effective		
	Probabilistic	-1,349	-0.0116	DBG is less	92%	86%

	expensive and less effective

Figure 40: Cost effectiveness plane for LMWH then dabigatran versus LMWH then warfarin in the treatment of DVT and PE

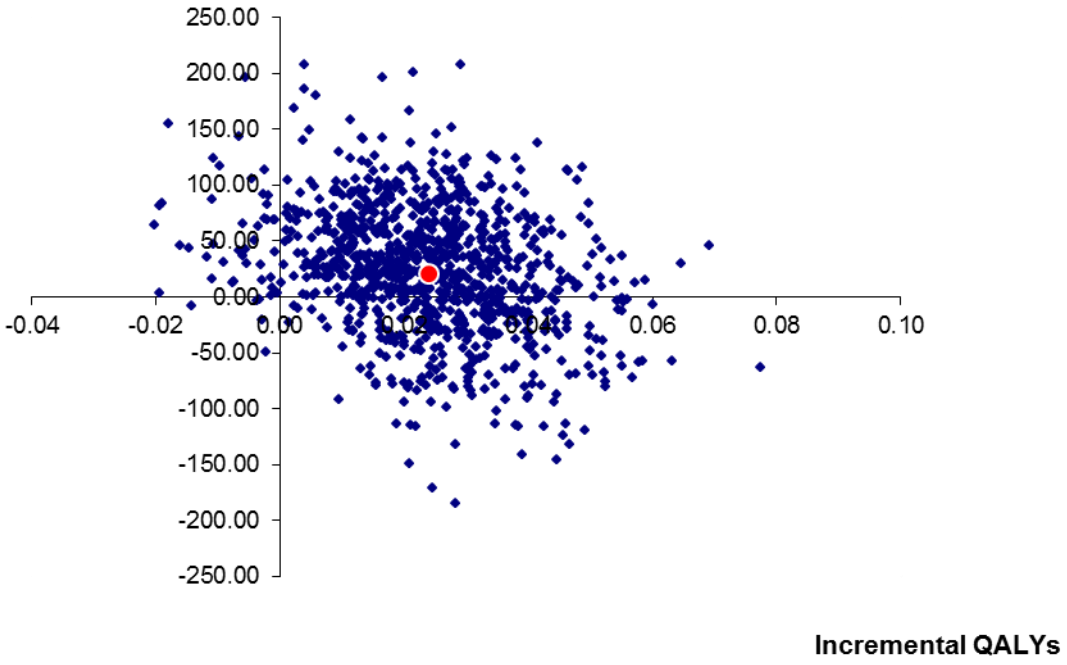


Figure 41: Cost effectiveness acceptability curve for LMWH then dabigatran versus LMWH then warfarin in the treatment of DVT and PE

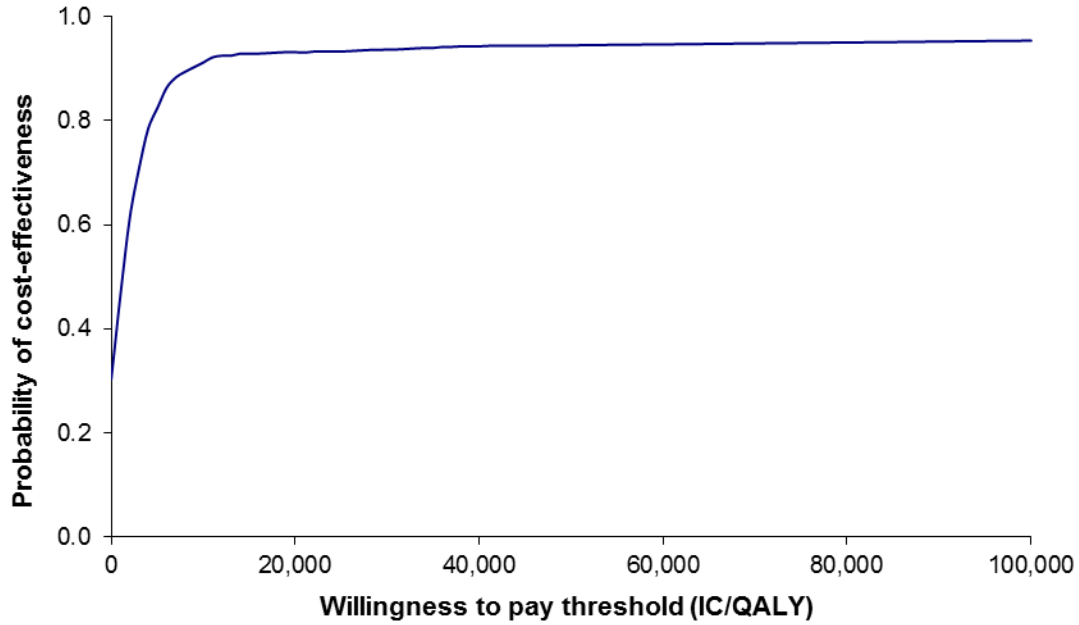


Figure 42: Cost effectiveness plane for LMWH then dabigatran versus rivaroxaban in the treatment of DVT and PE

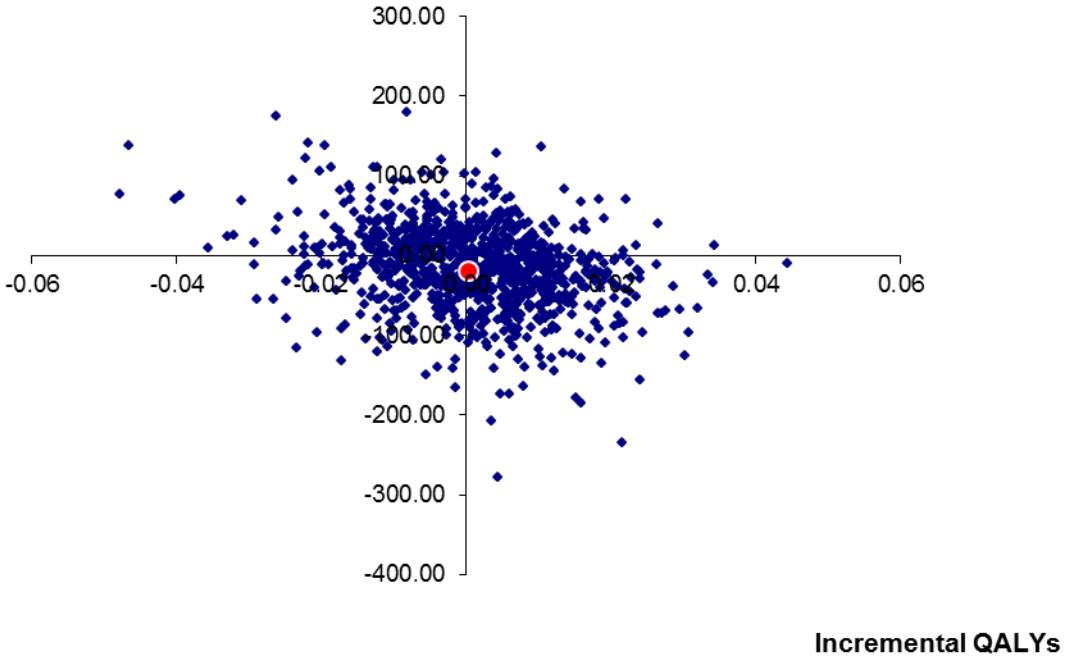


Figure 43: Cost effectiveness acceptability curve for LMWH then dabigatran versus rivaroxaban in the treatment of DVT and PE

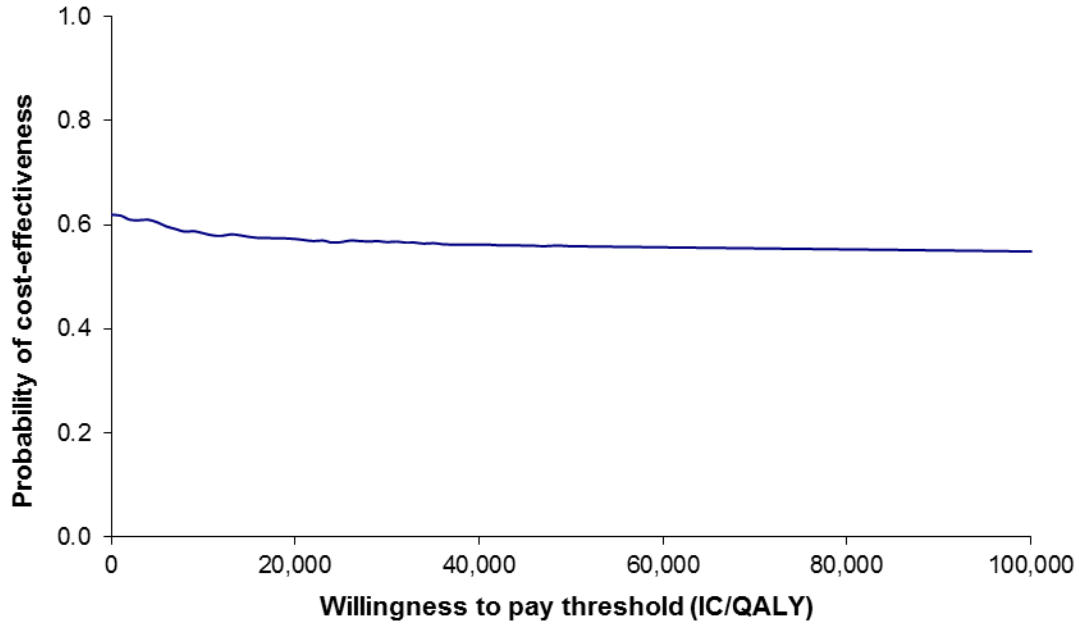


Figure 44: Cost effectiveness plane for LMWH then dabigatran versus LMWH in the treatment of DVT and PE

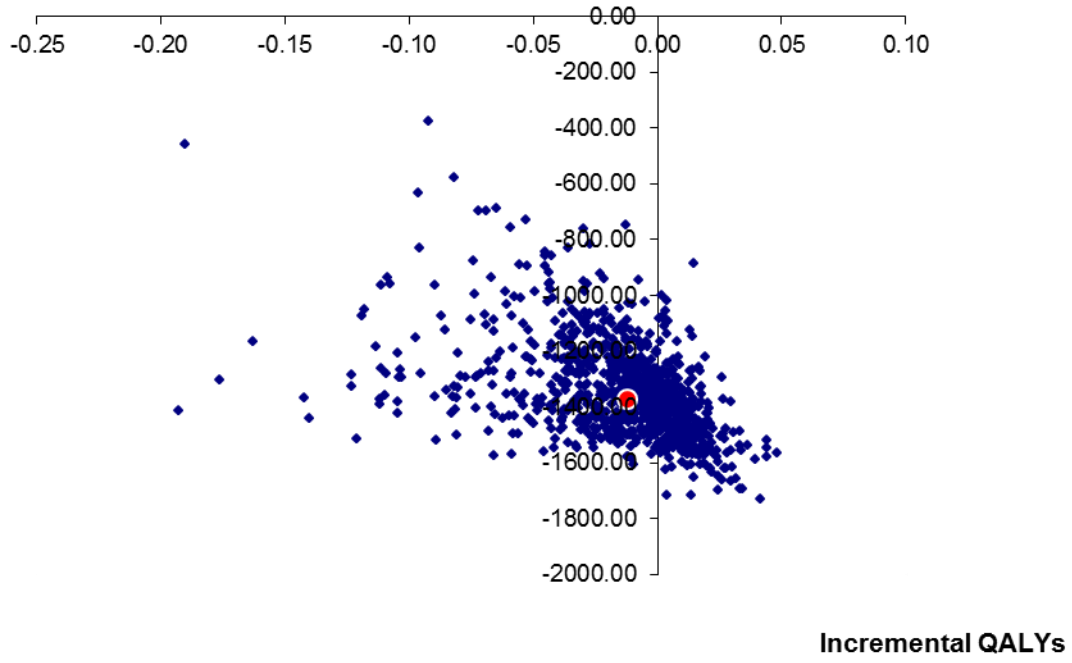
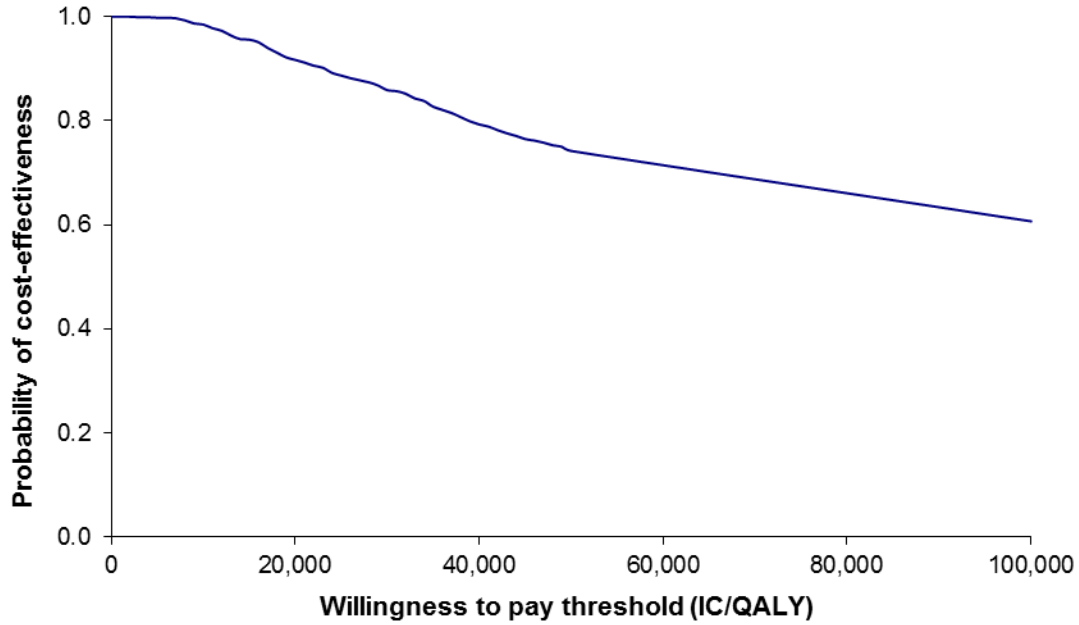


Figure 45: Cost effectiveness acceptability curve for LMWH then dabigatran versus LMWH in the treatment of DVT and PE



Treatment and secondary prevention of DVT and PE

Table 151: ICERs for the primary analysis for treatment and secondary prevention of DVT and PE

	Treatment and secondary prevention of DVT and PE with LMWH then dabigatran					
					Willingness to pay threshold (£/QALY)	
	Type	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	£20,000	£30,000
Versus LMWH then warfarin	Deterministic	458	0.0551	8,319		
	Probabilistic	466	0.0527	8,848	92%	96%
Versus rivaroxaban	Deterministic	-67	0.0020	DBG is dominant		
	Probabilistic	-63	0.0096	DBG is dominant	81%	79%
Versus LMWH mono-therapy (active cancer patients)	Deterministic	-3,340	0.0197	DBG is dominant		
	Probabilistic	-3,342	0.0226	DBG is dominant	100%	100%

Figure 46: Cost effectiveness plane for LMWH then dabigatran versus LMWH then warfarin in the treatment and secondary prevention of DVT and PE

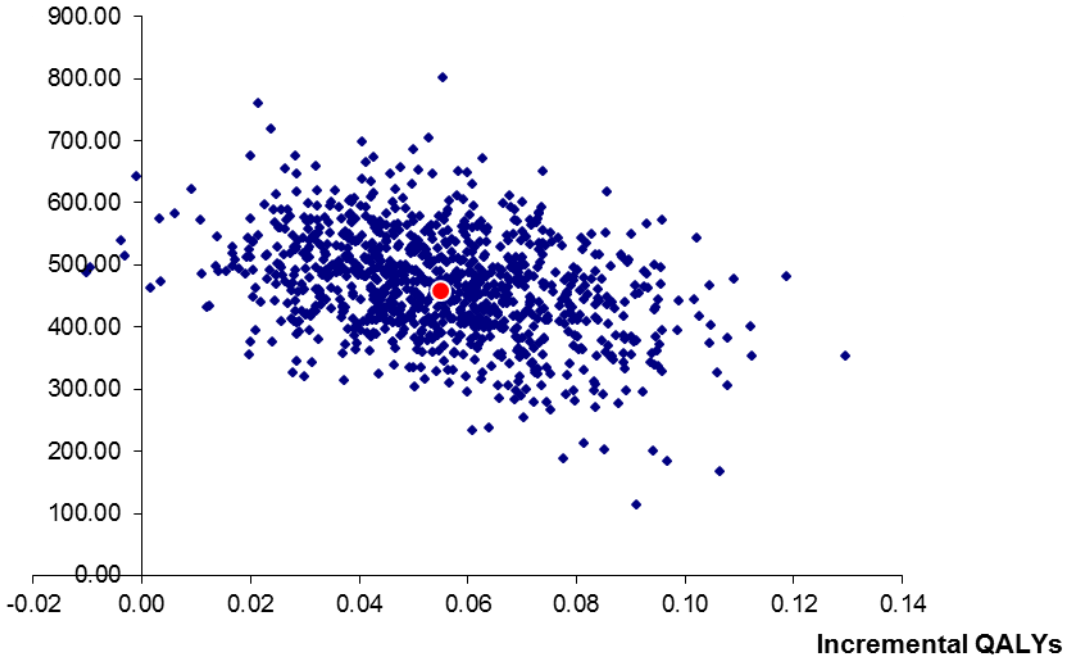


Figure 47: Cost effectiveness acceptability curve for LMWH then dabigatran versus LMWH then warfarin for the treatment and secondary prevention of DVT and PE

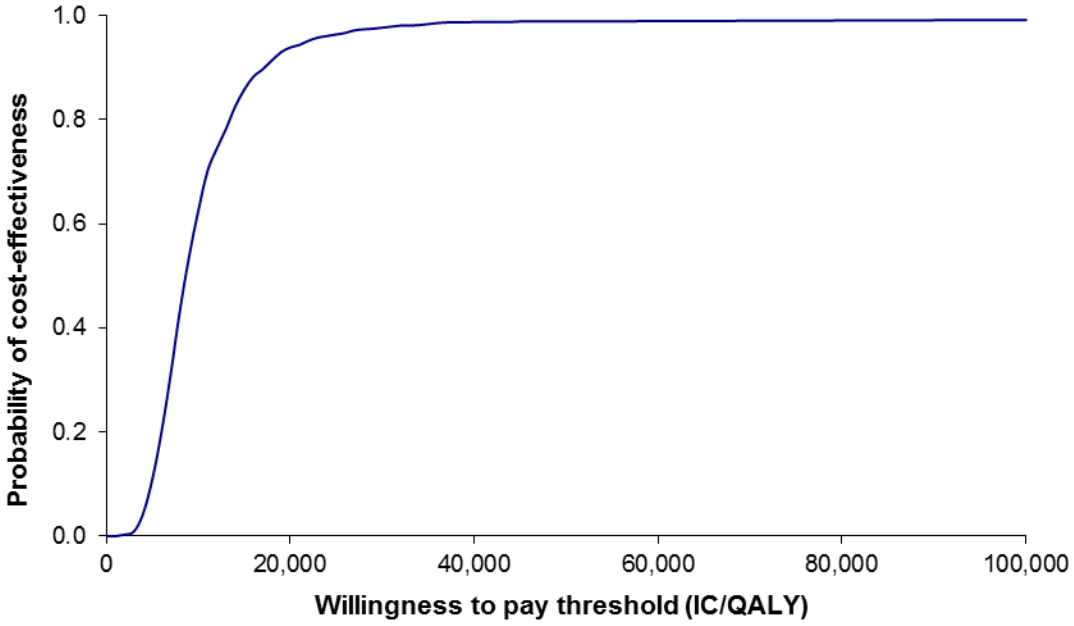


Figure 48: Cost effectiveness plane for LMWH then dabigatran versus rivaroxaban in the treatment and secondary prevention of DVT and PE

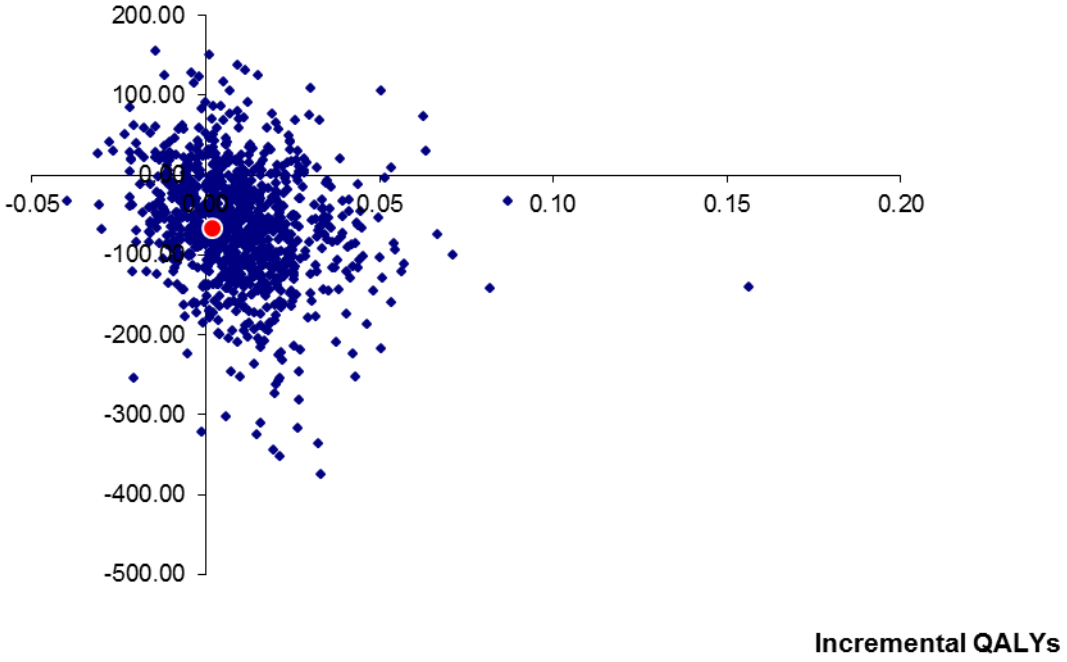


Figure 49: Cost effectiveness acceptability curve for LMWH then dabigatran versus rivaroxaban in the treatment and secondary prevention of DVT and PE

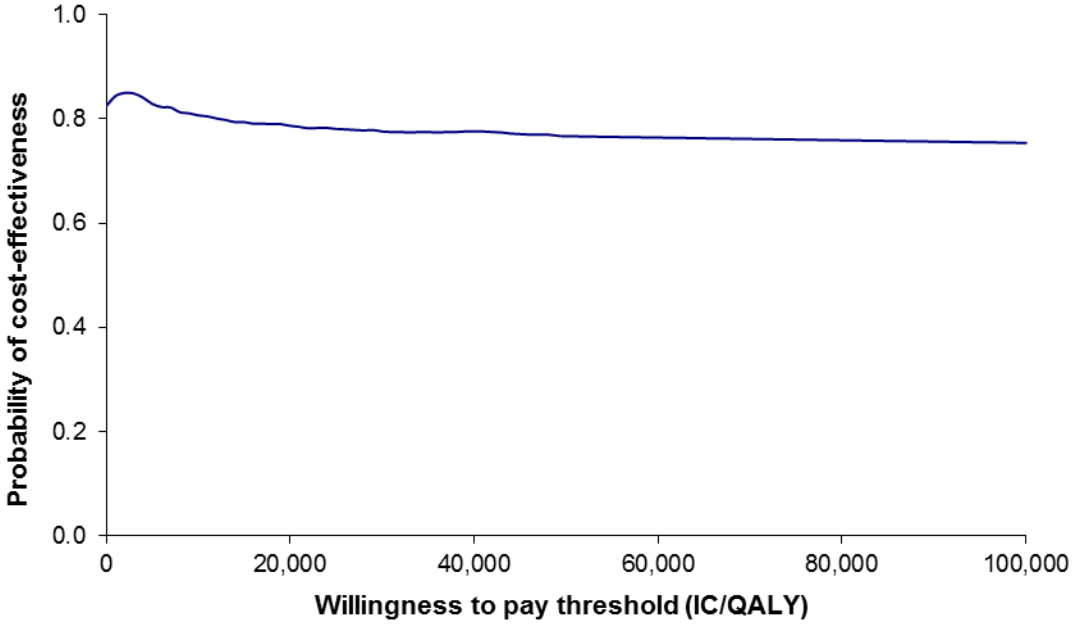


Figure 50: Cost effectiveness plane for LMWH then dabigatran versus LMWH in the treatment and secondary prevention of DVT and PE

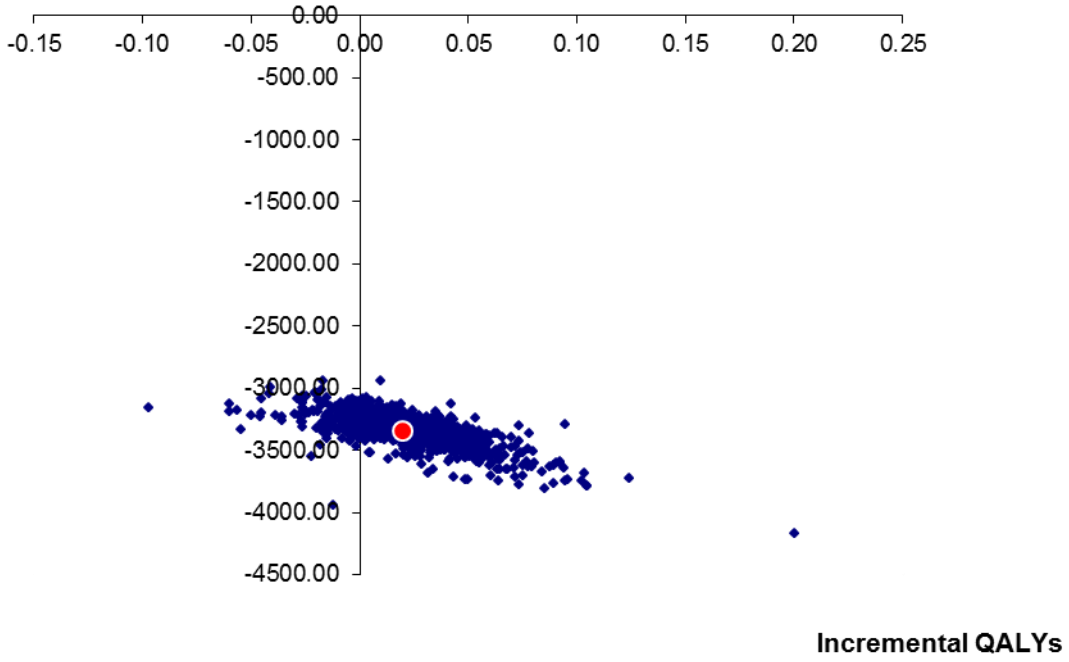
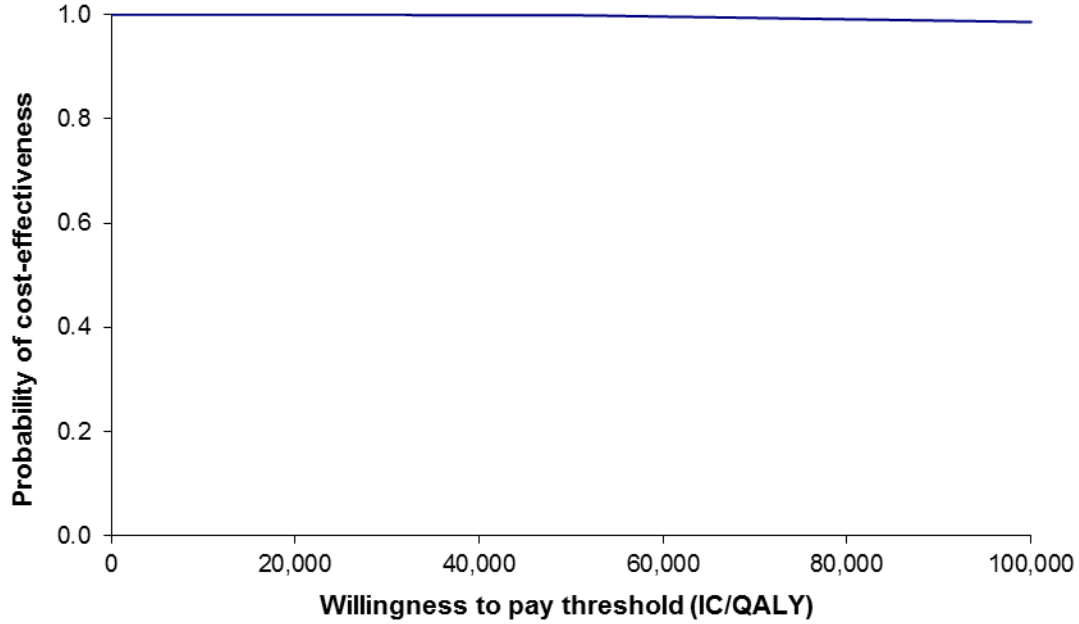


Figure 51: Cost effectiveness acceptability curve for LMWH then dabigatran versus rivaroxaban in the treatment and secondary prevention of DVT and PE



7.7.12 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

As discussed in Section 7.6.1, no scenario analyses were conducted other than those explored in the deterministic univariate sensitivity analysis previously described.

7.7.13 What were the main findings of each of the sensitivity analyses?

Discussion

Comparison with LMWH followed by warfarin

As outlined in section 2, LMWH followed by adjusted-dose warfarin has traditionally been the standard of care for the treatment and secondary prevention of recurrent DVT and PE. The economic analysis presented in this submission suggests that the proposed treatment regimen of LMWH followed by dabigatran is a highly cost-effective alternative to LMWH followed by warfarin. The incremental cost per additional QALY gained with dabigatran over this comparator is less than £10,000 in both deterministic and probabilistic sensitivity analyses. These ICERs are comfortably within the threshold normally considered to represent value-for-money from the perspective of the NHS in England and Wales. The incremental cost per QALY gains remain below £10,000 in the majority of sensitivity scenarios investigated, with the exception of when the warfarin utility decrement is removed during treatment followed by secondary prevention (ICER of £14,947) and when the lifetime horizon for treatment followed by secondary prevention is changed to 1 year (£12,905).

Comparison with rivaroxaban

A comparative economic analysis has also been presented of LMWH followed by dabigatran versus rivaroxaban. As noted in Section 2 of this submission, NICE have previously issued positive advice recommending the use of rivaroxaban within its licensed indication for the treatment and long-term secondary prevention of DVT and PE in England and Wales.[9;10] Thus, it was considered informative to conduct and present this comparison. The results of this analysis show that LMWH followed by dabigatran can be considered a dominant alternative to rivaroxaban for the long-term treatment and secondary prevention of recurrent DVT and PE (assuming a lifetime time horizon). When a lifetime (60 years) horizon for this comparison was modelled, dabigatran was dominant over rivaroxaban in both

treatment and treatment followed by secondary prevention, for the deterministic and probabilistic sensitivity analyses. As outlined in Section 2, venous thromboembolism (DVT and PE) is associated with serious long-term complications including post-thrombotic syndrome (PTS), recurrent VTE, pulmonary hypertension, and increased mortality. It is therefore appropriate to primarily consider the results of economic analyses which take these long-term complications (with their resultant impact on patients' HRQL) into account.

In the sensitivity analyses of LMWH followed by dabigatran versus rivaroxaban, when the treatment horizon is shortened from lifetime to 6 months, the ICER for LMWH followed by dabigatran versus rivaroxaban changes from the base case above (dabigatran is dominant) to £46,274. Dabigatran remains dominant versus rivaroxaban in the treatment followed by secondary prevention indication when the lifetime horizon is changed to 1 year (Table 149).

Comparison with LMWH monotherapy (in patients with active cancer)

In recognition of place of LMWH monotherapy as standard of care for the treatment of DVT and PE in patients with active cancer, a further comparative economic analysis of LMWH followed by dabigatran versus LMWH monotherapy has been presented in this submission. In contrast to the two previous comparisons, the clinical efficacy and safety data underpinning this economic analysis has been drawn from subgroups of patients with active cancer who were treated with LMWH followed by dabigatran in pivotal randomised controlled trials (RE-COVER, RE-COVER II and the RE-SONATE trial). Clinical data supporting the use of LMWH monotherapy in this patient group has been derived from 5 trials of LMWH monotherapy in cancer patients. Results of the economic analysis of treatment of DVT and PE indicate that LMWH followed by dabigatran may be considered to be a reasonable alternative to LMWH monotherapy in this patient subgroup, being associated a lower cost, albeit with a slightly lower expected number of QALYs. Assuming a 12 month treatment period and applying a lifetime time horizon for long-term treatment and secondary prevention of recurrent DVT and PE, results in LMWH followed by dabigatran emerging as a dominant alternative to LMWH monotherapy in this patient subgroup.

However, the limitation of this analysis is that the clinical efficacy and safety data supporting the use of LMWH followed by dabigatran in this patient subgroup comes from a relatively small proportion of the overall patient population treated with dabigatran in pivotal studies (approximately 5%). Recognising

this, the European Medicines Agency has recommended including a statement in the Summary of Product Characteristics for dabigatran highlighting that the efficacy and safety of dabigatran in patients with cancer has not been established.

7.7.14 What are the key drivers of the cost-effectiveness results?

As identified by the analysis, the key inputs driving cost-effectiveness are:

- Relative efficacy parameters, HRs of events including rVTE and VTE related deaths and the corresponding absolute rates for dabigatran and comparators.
- Relative safety parameters, HRs of events including ICH, MBE, CRBE and the corresponding absolute rates for dabigatran and comparators.
- Health Care Resource use associated with routine monitoring of coagulation parameters.

7.8 Validation

7.8.1 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.

As previously described in Section 7.6.1 and Section 7.7.1, the model has undergone rigorous validation and accurately reflects other published studies and clinical practice.

7.9 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).

7.9.1 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 because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

As has already been discussed in the Decision Problem (Section 5) and in Section 7.2.1, cost-effectiveness was assessed separately throughout this submission for two treatment options, both covered by the main indication CHMP adopted a positive opinion for. These are:

- **Treatment of DVT and PE**

  The patient population is adults (≥ 18 years) with acute symptomatic proximal DVT and PE.

  In this patient population, analyses are presented for subgroups in which the underlying risks of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ. These subgroups are:

  1. Type of index event
     a. DVT only
     b. PE with/without DVT

2. Patient history of bleeding
    a. Prior history of bleeding
    b. No prior history of bleeding
3. Western European patients

- **Treatment followed by prevention of recurrent DVT and PE**

  The patient population is adults (≥ 18 years) with acute symptomatic proximal DVT and PE who had received treatment with standard doses of an anticoagulant for 6 months and who required anticoagulant therapy beyond 6 months for the long-term treatment and secondary prevention of symptomatic VTE.

  In this indication, more specific sub-group analyses could not be performed due to data limitations.

Please note that in addition to that, cost-effectiveness results of the comparison 'dabigatran versus LMWH monotherapy' (Table 145 and Table 146) is essentially a sub-group analysis, too. This is due to the fact that 'LMWH monotherapy' in patients with active cancer has been specified as a comparator to 'LMWH followed by dabigatran' in patients with active cancer in this submission.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Patients included in each subgroup were those specified as having the respective characteristic upon enrolment into the relevant trials.

7.9.3 Please describe how the statistical analysis was undertaken.

N/A

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

As per the subgroup analysis listed above in Section 7.9.1, the results of the subgroup analysis are presented in Table 152.

Table 152: Subgroup analyses for the treatment of DVT and PE

Subgroup	Comparator	Incremental costs (£) with LMWH then dabigatran	Incremental QALYs with LMWH then dabigatran	ICER (£/QALY)
		Base case		
	Versus LMWH then WFN	21	0.0239	862
	Versus rivaroxaban	-20	0.0003	DBG is dominant
	Versus LMWH mono-therapy (active cancer patients)	-1,370	-0.0124	DBG is less expensive and less effective
		Sensitivity analysis		
1a	Versus LMWH then warfarin	14	0.0227	614
	Versus rivaroxaban	-15	0.0012	DBG is dominant
1b	Versus LMWH then warfarin	35	0.0270	1,285
	Versus rivaroxaban	-25	0.0079	DBG is dominant
2a	Versus LMWH then warfarin	-124	0.0457	DBG is dominant
2b	Versus LMWH then warfarin	29	0.0227	1,261
3	Versus LMWH then warfarin	-14	0.0275	DBG is dominant
	Versus rivaroxaban	-126	0.0084	DBG is dominant

7.9.5 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 5.

There are no other such subgroups to be considered.

7.10 Interpretation of economic evidence

7.10.1 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 dabigatran for the treatment of DVT and PE, and the treatment and secondary prevention of DVT and PE. Therefore, there is no published economic literature with which to draw comparison.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes. The population from which the clinical data was drawn and for which the model was parameterised reflects the patient population in Section 5. In addition, the sequence of the model also reflects the proposed licenced indication which also reflects the patient population defined in Section 5.

7.10.3 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 lies in the comprehensive model structure fed by a robust clinical trial and extensive research to populate it. During model development a number of weaknesses were identified. Examination of these issues with sensitivity analysis identified that the majority of weaknesses did not substantially influence findings from the model.

A limitation of the base case deterministic analysis, as with any deterministic analysis, is the dependence on point estimates as model inputs. These point estimates may be uncertain, and this uncertainty is not accounted for in a deterministic analysis. However, clinical and economic decision-making are generally recommended to consider confidence/credible intervals over p-values, and PSA has accordingly been developed as a method to illustrate the extent of uncertainty in model outputs due to uncertainty in parameter values used as inputs. The PSA results demonstrate high probability for the cost-effectiveness of dabigatran consistently with the base case deterministic results.

Whilst a lifetime time horizon has been used for analyses of the long-term treatment and secondary prevention of recurrent DVT and PE, clinical efficacy and safety data is only available for a maximum of 24 months. However, the model does not attempt to extrapolate treatment effects beyond two years.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive deterministic and probabilistic sensitivity analyses were carried out in order to test the robustness of the model results. Both short and long-term trials have been conducted to gain insight

into the overall analysis. Nevertheless, further evidence generation programmes may provide additional information to improve the overall robustness of the analyses conducted.

Section C – Implementation

8 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.

8.1 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.

The number of patients eligible for treatment was estimated primarily from a combined analysis of UK hospital and primary care databases (General Practice Research Database, Hospital Episode Statistics database, and Office for National Statistics) for incidence and recurrence of DVT and PE.[15] The incidence rates from this study conducted by Martinez et al. are shown in Table 153. The same study also reported that 18.6% of the total VTEs were active-cancer associated, and that 47.2% of total VTEs as unprovoked cases (i.e. did not have a common risk factor). Together these cancer and unprovoked VTE patients are considered as high risk patients.

Table 153: Age-specific incidence rates of VTE[15]

	Events	Persons-years	IR	95% CI
First VTE				
Age group	**n**		**Per 100,000 PY**	
<18	90	5284814	1.7	(1.4-2.1)
18-29	1266	3883101	32.6	(30.8-34.4)
30-39	2064	3838841	53.8	(51.5-56.1)
40-49	2543	4093014	62.1	(59.7-64.6)
50-59	3569	3585120	99.6	(96.3-102.9)
60-69	5084	2874437	176.9	(172.0-181.8)
70-79	6606	2015974	327.7	(319.8-335.7)

80-89	5980	1100959	543.2	(529.5-557.1)
≥90	1579	221078	714.2	(679.4-750.3)
Total	**28781**	**26897337**	**107.0**	**(105.8-108.2)**

The rates of incidence of VTE were then applied to the age-specific population projections for England and wales for 2014-2018 from the Office of National Statistics shown in Table 154 . The summarised results of the total eligible population are shown in Table 155 for the treatment indication and Table 156 for treatment and secondary prevention.

Table 154: Age-specific population projections for 2014-2018

Year	2014	2015	2016	2017	2018
Population					
20-29	7776224	7783303	7799922	7819608	7798090
30-39	7441436	7520317	7618551	7721534	7839640
40-49	8011887	7877886	7737234	7585408	7458622
50-59	7292545	7472175	7626387	7759074	7855517
60-69	6254984	6278595	6312910	6212229	6197260
70-79	4226875	4336548	4448610	4707896	4894128
≥80	2756703	2824914	2899066	2980130	3069515
Total	43,760,654	44,093,738	44,442,680	44,785,879	45,112,772

Table 155: Estimated population eligible for treatment indication

	Year 1	Year 2	Year 3	Year 4	Year 5
cohort 1	52,320	52,320	52,320	52,320	52,320
cohort 2		53,133	53,133	53,133	53,133
cohort 3			53,985	53,985	53,985
cohort 4				55,065	55,065
cohort 5					56,085

Table 156: Estimated population eligible for treatment and secondary prevention

	2014		2015		2016		2017		2018	
	0-6m	6-12m	0-6m	6-12m	0-6m	6-12m	0-6m	6-12m	0-6m	6-12m
High Risk										
cohort 1	52,320	34,426	34,426		34,426		34,426		34,426	
cohort 2			53,133	34,962	34,962		34,962		34,962	
cohort 3					53,985	35,522	35,522		35,522	
cohort 4							55,065	36,233	36,233	
cohort 5									56,085	36,904
Equipoise										
cohort 1	52,320	17,893	17,893		17,893		17,893		17,893	
cohort 2			53,133	18,172	18,172		18,172		18,172	
cohort 3					53,985	18,463	18,463		18,463	
cohort 4							55,065	18,832	18,832	
cohort 5									56,085	19,181

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact model assumes that new oral anticoagulants (NOACs) will replace a proportion of the existing treatments and that dabigatran will have a share within the NOAC market share. In addition, cancer patients with VTE are expected to be managed with LMWH for 6 months, without any other antigoagulation treatment or monitoring.

8.3 What assumption(s) were made about market share (when relevant)?

An increasing market uptake from NOACs is assumed, up to 52% of the market from start of model until year 5 after dabigatran introduction, as presented in Table 157 and Table 158. Within this share, a proportional uptake for dabigatran is envisaged under two scenarios: a world without dabigatran and a world with dabigatran (in the expected mix of treatments).

Table 157: Market uptake for NOAC: current mix of treatment (world without dabigatran)

	Y1	Y2	Y3	Y4	Y5
New oral share	23.0%	31.0%	43.0%	52.0%	52.0%
Share within NOAC					
dabigatran	0.0%	0.0%	0.0%	0.0%	0.0%
rivaroxaban	100%	100%	100%	100%	100%

Table 158: Market uptake for NOAC: future mix of treatment (world with dabigatran)

	Y1	Y2	Y3	Y4	Y5
New oral share	23.0%	31.0%	43.0%	52.0%	52.0%
Share within NOAC					
Dabigatran	2.0%	5.5%	7.5%	9.5%	11.5%
Rivaroxaban	98.0%	94.5%	92.5%	90.5%	88.5%

NOAC are assumed to replace an equal proportion of current use of VKAs (warfarin) and LMWH in the treatment indication. All patients with active cancer (minus the proportion of those up-taking NOACs) are assumed to receive LMWH. All non-active cancer patients (minus those who uptake NOAC) are assumed to receive warfarin. The market shares for the treatment indication are presented in Table 159 and Table 160.

Table 159: Current mix of treatments: treatment indication

	Y1	Y2	Y3	Y4	Y5
Dabigatran	0%	0%	0%	0%	0%
Warfarin	51.0%	45.7%	37.7%	31.8%	31.8%
Rivaroxaban	23.0%	31.0%	43.0%	52.0%	52.0%
LMWH (patients with active cancer)	14.3%	12.8%	10.6%	8.9%	7.6%
Other treatments	0%	0%	0%	0%	0%

Table 160: Future mix of treatments: treatment indication

	Y1	Y2	Y3	Y4	Y5
Dabigatran	0.5%	1.7%	3.2%	4.9%	6.8%
Warfarin	51.0%	45.7%	37.7%	31.8%	27.1%
Rivaroxaban	22.5%	29.3%	39.8%	47.1%	52.2%
LMWH (patients with active cancer)	14.3%	12.8%	10.6%	8.9%	7.6%
Other treatments	0%	0%	0%	0%	0%

None of the NOACs have been studied for secondary prevention in high risk patients, except for dabigatran. Therefore the current mix of interventions for high risk patients is composed of warfarin, LMWH and in the future, dabigatran as the only NOAC entering this indication. The full NOAC market uptake is attributed to dabigatran.

A separate analysis is programmed to allow comparisons of current vs. future mix of treatments for patients who are equipoise for continued treatment. The clinical safety and efficacy in this patient group has been studied in EINSTEIN Extension and RE-SONATE studies and offers relative efficacy of rivaroxaban, and dabigatran respectively against no treatment. Therefore, in this subgroup, current mix of treatment includes: NOACs – rivaroxaban and dabigatran- and no treatment, while the future mix includes in addition dabigatran as shown in Table 161 and Table 162.

Table 161: Current mix of treatments: secondary prevention indication

	Y1	Y2	Y3	Y4	Y5
High risk					
Dabigatran	0%	0%	0%	0%	0%
Warfarin	40.0%	40.0%	40.0%	40.0%	40.0%
LMWH	60.0%	60.0%	60.0%	60.0%	60.0%
Equipoise					
Dabigatran	0%	0%	0%	0%	0%
No treatment	77.0%	69.0%	57.0%	48.0%	41.0%
Rivaroxaban	23.0%	31.0%	43.0%	52.0%	59.0%
LMWH	0%	0%	0%	0%	0%

Table 162: Future mix of treatments: secondary prevention indication

	Y1	Y2	Y3	Y4	Y5
High risk					
Dabigatran	23.0%	31.0%	43.0%	52.0%	59.0%
Warfarin	30.8%	27.6%	22.8%	19.2%	16.4%
LMWH (with active cancer)	46.2%	41.4%	34.2%	28.8%	24.6%
Equipoise					
Dabigatran	0.5%	1.7%	3.2%	4.9%	46.8%
No treatment	77.0%	69.0%	57.0%	48.0%	41.0%
Rivaroxaban	22.5%	29.3%	39.8%	47.1%	52.2%
LMWH	0.0%	0.0%	0.0%	0.0%	0.0%

For the treatment followed by secondary prevention, the current and future mix of treatments is determined based on market shares for the treatment indication (during first 6 months) and then based on market shares for secondary prevention (high risk and equipoise individual) from 6 months onwards.

8.4 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).

No additional costs are expected.

8.5 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?

The drug, monitoring and event costs in this section are identical to those assumed in the cost-effectiveness evaluation in Section 7.

8.6 Were there any estimates of resource savings? If so, what were they?

Displacement of warfarin by dabigatran will be associated with a reduction in INR monitoring costs in both primary and secondary care. This is discussed in further detail in Section 8.8.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Initial budget impact estimate

A simple budget impact was calculated to illustrate the impact of drug acquisition costs only for 2014-2018. This calculation is shown below in Table 163. A more detailed budget impact analysis is discussed in the following sections, taking into account additional costs such as monitoring costs and events costs.

Table 163: Initial budget impact of net additional medicine costs only

	2014	2015	2016	2017	2018	Source
Number of eligible patients	52,320	53,133	53,985	55,065	56,085	ONS, 2013
% of eligible patients treated with novel anticoagulants	23%	31%	43%	52%	59%	Assumption
Number of eligible patients treated with novel oral anticoagulants	12,034	16,471	23,214	28,634	33,090	Calculation
Pradaxa share of patients treated with novel oral anticoagulants	2.0%	5.5%	7.5%	9.5%	11.5%	Assumption
Number of Pradaxa patients in each year	**241**	**906**	**1741**	**2720**	**3805**	**Calculation**
Medicine acquisition cost per patient per annum	£790.80	£790.80	£790.80	£790.80	£790.80	MIMS March-May 2014 (£65.90x12)
Add: supportive medicines cost per patient per annum	£0	£0	£0	£0	£0	Assumption
Gross additional medicines costs per patient per annum	£790.80	£790.80	£790.80	£790.80	£790.80	Calculation
Less: displaced medicines cost per patient per annum	£11.60	£11.60	£11.60	£11.60	£11.60	MIMS March-May, 2014 £0.89 Per pack of 28 ((£0.89/28)x365)
Net additional medicines (savings)/costs	**£779.20**	**£779.20**	**£779.20**	**£779.20**	**£779.20**	**(£790.80-£779.20)**
Budget impact (new medicine and supportive medicine costs only)	**£187,787.20**	**£705,955.20**	**£1,356,587.20**	**£2,119,424.00**	**£2,964,856.00**	**Calculation**

Treatment indication

Results for treatment indication are based on annual costs of treatment per patient per intervention, weighted by market shares for the current and future mix, and extrapolated to the entire eligible population. Total budget impacts without and with dabigatran and net budget impacts are exhibited in Table 164, Table 165, Table 166 and Figure 52. The introduction of dabigatran was projected to result in cost savings associated with pharmacy drug costs, cost of monitoring, cost of treatment of adverse events (bleedings) and cost of CTEPH (Table 166).

Table 164: Budget impact current mix (world without dabigatran), treatment indication

Treatment costs £	2014	2015	2016	2017	2018	Total
Total drug costs	**16,457,256**	**16,965,588**	**17,481,529**	**18,065,007**	**18,625,897**	**87,595,276**
Investigational treatment, drug	14,683,851	14,912,120	15,151,181	15,454,420	15,740,532	75,942,104
Acute parenteral anticoagulation, index event drug	1,582,888	1,607,495	1,633,265	1,665,954	1,696,796	8,186,398
Re-treatment recurrent event, warfarin drug	33,756	84,877	135,142	184,691	233,535	672,000
Re-treatment recurrent event, acute parenteral anticoagulation drug	156,761	361,096	561,941	759,942	955,033	2,794,774
Total monitoring costs	**16,622,640**	**18,293,070**	**19,950,776**	**21,656,689**	**23,324,364**	**99,847,539**
Investigational treatment	15,337,752	15,576,187	15,825,894	16,142,636	16,441,490	79,323,961
Acute parenteral anticoagulation, index event	267,271	271,425	275,777	281,296	286,504	1,382,273
Re-treatment recurrent event, warfarin	990,530	2,382,828	3,751,535	5,100,732	6,430,384	18,656,010
Re-treatment recurrent event, acute parenteral anticoagulation	27,087	62,628	97,570	132,024	165,985	485,295
Total events costs	**61,733,567**	**76,058,737**	**90,962,554**	**106,677,381**	**122,907,564**	**458,339,802**
Embolic events (index event)	40,359,831	40,987,250	41,644,329	42,477,807	43,264,213	208,733,431
Embolic events (recurrent)	2,249,405	4,417,121	6,596,781	8,796,850	11,012,728	33,072,885
Bleeding costs	4,273,515	4,690,360	5,102,444	5,527,862	5,951,690	25,545,871
Other AE	0	0	0	0	0	0
PTS	1,312,040	1,615,384	1,937,670	2,286,409	2,658,281	9,809,784
CTEPH	13,538,775	24,348,622	35,681,331	47,588,452	60,020,652	181,177,832
Total costs	**94,813,463**	**111,317,394**	**128,394,860**	**146,399,076**	**164,857,825**	**645,782,618**

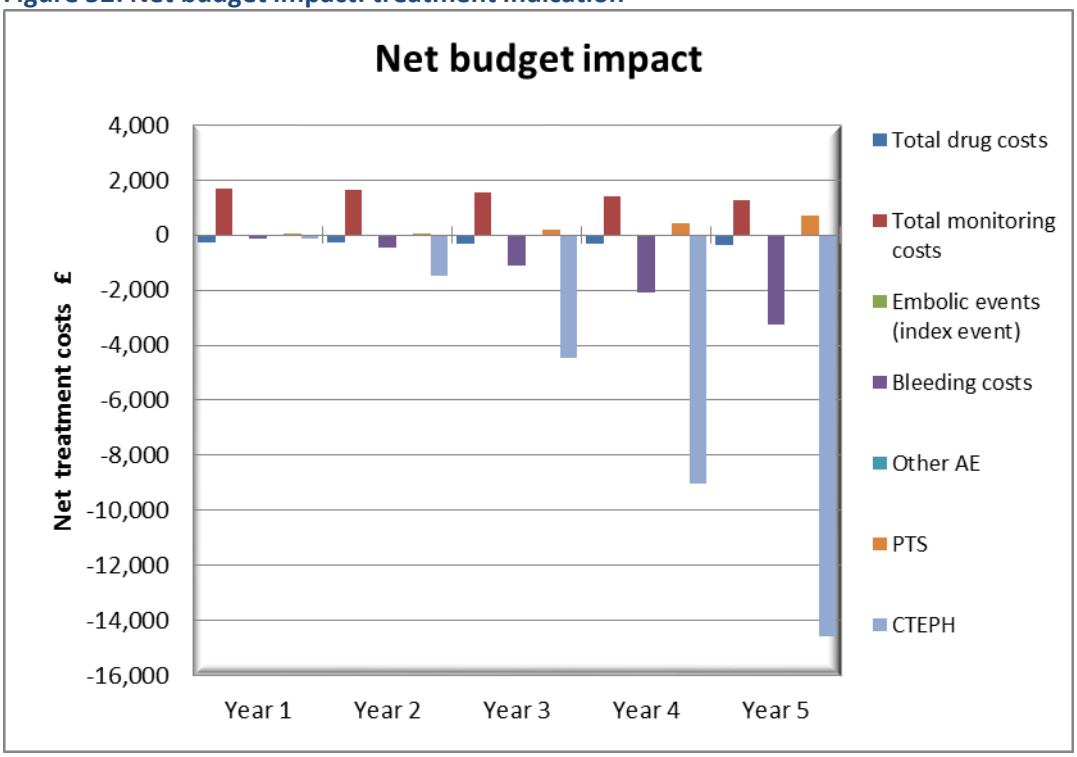
Table 165: Budget impact future mix (world with dabigatran), treatment indication

Treatment costs £	2014	2015	2016	2017	2018	Total
Total drug costs	**16,456,992**	**16,965,310**	**17,481,228**	**18,064,669**	**18,625,519**	**87,593,718**
Investigational treatment, drug	14,674,624	14,902,750	15,141,661	15,444,709	15,730,642	75,894,386
Acute parenteral anticoagulation, index event drug	1,591,782	1,616,527	1,642,442	1,675,314	1,706,330	8,232,395
Re-treatment recurrent event, warfarin drug	33,769	84,888	135,150	184,693	233,531	672,032
Re-treatment recurrent event, acute parenteral anticoagulation drug	156,817	361,144	561,975	759,953	955,016	2,794,905
Total monitoring costs	**16,624,311**	**18,294,708**	**19,952,331**	**21,658,112**	**23,325,618**	**99,855,080**
Investigational treatment	15,337,488	15,575,919	15,825,621	16,142,358	16,441,207	79,322,595
Acute parenteral anticoagulation, index event	268,818	272,997	277,373	282,924	288,162	1,390,274
Re-treatment recurrent event, warfarin	990,908	2,383,155	3,751,761	5,100,803	6,430,266	18,656,894
Re-treatment recurrent event, acute parenteral anticoagulation	27,097	62,637	97,576	132,026	165,982	485,318
Total events costs	**61,733,374**	**76,056,920**	**90,957,242**	**106,666,751**	**122,890,501**	**458,304,788**
Embolic events (index event)	40,359,831	40,987,250	41,644,329	42,477,807	43,264,213	208,733,431
Embolic events (recurrent)	2,249,478	4,417,194	6,596,853	8,796,920	11,012,796	33,073,240
Bleeding costs	4,273,388	4,689,897	5,101,347	5,525,794	5,948,441	25,538,868
Other AE	0	0	0	0	0	0
PTS	1,312,051	1,615,450	1,937,860	2,286,821	2,658,999	9,811,182
CTEPH	13,538,626	24,347,128	35,676,852	47,579,409	60,006,052	181,148,068
Total costs	**94,814,677**	**111,316,938**	**128,390,801**	**146,389,532**	**164,841,638**	**645,753,586**

Table 166: Net budget impact treatment, treatment indication

Net treatment costs £	2014	2015	2016	2017	2018	Total
Total drug costs	**-263**	**-278**	**-302**	**-337**	**-378**	**-1,558**
Investigational treatment, drug	-9,227	-9,370	-9,520	-9,711	-9,891	-47,718
Acute parenteral anticoagulation, index event drug	8,894	9,032	9,177	9,361	9,534	45,997
Re-treatment recurrent event, warfarin drug	14	12	8	3	-4	32
Re-treatment recurrent event, acute parenteral anticoagulation drug	56	48	33	10	-17	131
Total monitoring costs	**1,671**	**1,638**	**1,555**	**1,423**	**1,254**	**7,541**
Investigational treatment	-264	-268	-273	-278	-283	-1,366
Acute parenteral anticoagulation, index event	1,547	1,571	1,596	1,628	1,658	8,001
Re-treatment recurrent event, warfarin	378	327	226	71	-118	884
Re-treatment recurrent event, acute parenteral anticoagulation	10	8	6	2	-3	22
Total events costs	**-193**	**-1,817**	**-5,313**	**-10,629**	**-17,063**	**-35,014**
Embolic events (index event)	0	0	0	0	0	0
Embolic events (recurrent)	73	73	72	70	67	355
Bleeding costs	-128	-463	-1,096	-2,068	-3,249	-7,003
Other AE	0	0	0	0	0	0
PTS	11	66	190	412	718	1,398
CTEPH	-149	-1,493	-4,479	-9,043	-14,599	-29,764
Total costs	**1,215**	**-456**	**-4,059**	**-9,544**	**-16,187**	**-29,031**

Figure 52: Net budget impact: treatment indication



Treatment followed by secondary prevention

The weighted costs per patient per year for world with and world without dabigatran in first 6 months of treatment are equal to all patients in the eligible cohort, and represent the costs of 6 months acute treatment; beyond 6 months, the costs per patient per year pertain to the 2 sub-groups considered, equipoise and high risk, and respective market shares.

The introduction of dabigatran for treatment and secondary prevention in all patients was projected to result in cost savings over the first year after the introduction of dabigatran on the market. Cost saving were mainly associated with reduction of drug acquisition costs and monitoring costs in high risk patients in the first year after introduction, where dabigatran is expected to partially substitute the use of LMWH in cancer patients. In subsequent years, an increase in net pharmacy costs are projected with introduction of dabigatran for the high risk group, as patients continue to use up to 24 months treatment followed by secondary prevention dabigatran (or warfarin), while cancer patients on LMWH will only receive 6 months treatment plus 6 month secondary prevention according to current model settings. Nonetheless, the model continues to project some savings each year after introduction, with

savings resulting from reductions in monitoring costs, avoidance of bleedings and recurrent VTE. Total and net costs in this indication are exhibited in Table 167, Table 168, Table 169 and Figure 53.

Table 167: Budget impact current mix (world without dabigatran), treatment followed by secondary prevention

Treatment costs £	2014	2015	2016	2017	2018	Total
Total drug costs	**29,688,776**	**30,745,414**	**31,483,544**	**32,348,687**	**33,177,293**	**157,443,714**
Investigational treatment, drug	27,967,420	28,825,835	29,287,745	29,872,202	30,425,892	146,379,092
Acute parenteral anticoagulation, index event drug	1,582,888	1,607,495	1,633,265	1,665,954	1,696,796	8,186,398
Re-treatment recurrent event, warfarin drug	22,879	58,788	107,783	157,408	206,272	553,129
Re-treatment recurrent event, acute parenteral anticoagulation drug	115,590	253,296	454,751	653,124	848,334	2,325,094
Total monitoring costs	**26,865,389**	**34,336,484**	**36,244,181**	**38,269,143**	**40,268,486**	**175,983,682**
Investigational treatment	25,875,848	32,359,487	32,875,298	33,508,672	34,138,447	158,757,753
Acute parenteral anticoagulation, index event	267,271	271,425	275,777	281,296	286,504	1,382,273
Re-treatment recurrent event, warfarin	702,508	1,661,845	3,014,312	4,365,837	5,696,193	15,440,695
Re-treatment recurrent event, acute parenteral anticoagulation	19,762	43,727	78,794	113,337	147,342	402,962
Total events costs	**63,340,323**	**78,365,262**	**93,353,949**	**109,124,419**	**125,410,742**	**469,594,696**
Embolic events (index event)	40,359,831	40,987,250	41,644,329	42,477,807	43,264,213	208,733,431
Embolic events (recurrent)	2,439,027	3,991,550	6,172,661	8,374,415	10,589,091	31,566,744
Bleeding costs	5,688,680	7,424,404	7,986,776	8,594,328	9,205,578	38,899,767
Other AE	0	0	0	0	0	0
PTS	1,312,115	1,613,520	1,931,535	2,274,827	2,640,314	9,772,311
CTEPH	13,540,670	24,348,538	35,618,648	47,403,042	59,711,546	180,622,443
Total costs	**119,894,488**	**143,447,160**	**161,081,674**	**179,742,249**	**198,856,521**	**803,022,092**

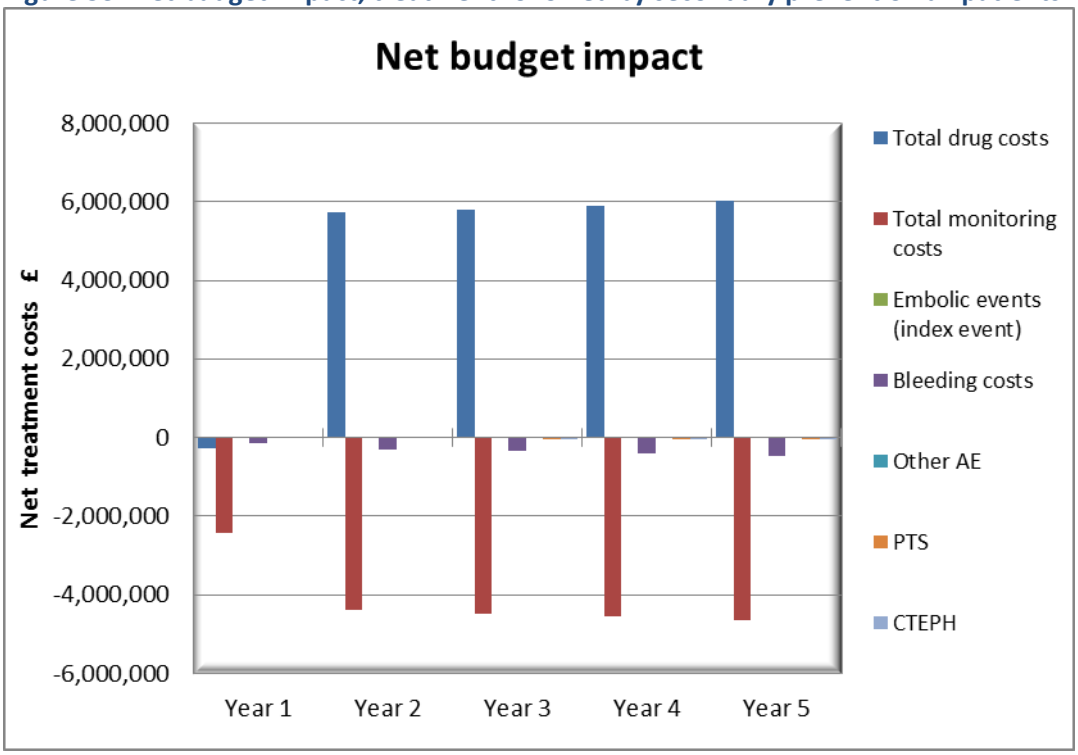
Table 168: Budget impact future mix (world with dabigatran), treatment followed by secondary prevention

Treatment costs £	2014	2015	2016	2017	2018	Total
Total drug costs	**29,425,445**	**36,467,917**	**37,295,075**	**38,252,690**	**39,200,252**	**180,641,379**
Investigational treatment, drug	27,697,034	34,549,444	35,100,198	35,776,725	36,449,016	169,572,417
Acute parenteral anticoagulation, index event drug	1,591,782	1,616,527	1,642,442	1,675,314	1,706,330	8,232,395
Re-treatment recurrent event, warfarin drug	22,748	56,846	105,733	155,402	204,301	545,030
Re-treatment recurrent event, acute parenteral anticoagulation drug	113,882	245,099	446,702	645,249	840,605	2,291,537
Total monitoring costs	**24,435,189**	**29,935,370**	**31,773,249**	**33,718,679**	**35,632,859**	**155,495,346**
Investigational treatment	23,451,822	28,012,549	28,459,589	29,012,212	29,555,823	138,491,995
Acute parenteral anticoagulation, index event	268,818	272,997	277,373	282,924	288,162	1,390,274
Re-treatment recurrent event, warfarin	695,081	1,607,546	2,958,943	4,311,660	5,642,993	15,216,223
Re-treatment recurrent event, acute parenteral anticoagulation	19,468	42,279	77,344	111,883	145,881	396,854
Total events costs	**63,143,485**	**77,980,978**	**92,907,520**	**108,602,197**	**124,811,133**	**467,445,313**
Embolic events (index event)	40,359,831	40,987,250	41,644,329	42,477,807	43,264,213	208,733,431
Embolic events (recurrent)	2,389,648	3,906,797	6,087,897	8,289,669	10,504,275	31,178,285
Bleeding costs	5,539,967	7,123,044	7,631,362	8,175,206	8,721,617	37,191,195
Other AE	0	0	0	0	0	0
PTS	1,312,185	1,613,525	1,931,220	2,274,041	2,638,975	9,769,945
CTEPH	13,541,854	24,350,362	35,612,712	47,385,475	59,682,054	180,572,457
Total costs	**117,004,118**	**144,384,265**	**161,975,844**	**180,573,567**	**199,644,244**	**803,582,038**

Table 169: Net budget impact treatment, treatment followed by secondary prevention

Net treatment costs £	2014	2015	2016	2017	2018	Total
Total drug costs	**-263,331**	**5,722,503**	**5,811,531**	**5,904,003**	**6,022,959**	**23,197,666**
Investigational treatment, drug	-270,386	5,723,610	5,812,453	5,904,523	6,023,125	23,193,325
Acute parenteral anticoagulation, index event drug	8,894	9,032	9,177	9,361	9,534	45,997
Re-treatment recurrent event, warfarin drug	-131	-1,942	-2,050	-2,006	-1,971	-8,099
Re-treatment recurrent event, acute parenteral anticoagulation drug	-1,708	-8,197	-8,049	-7,875	-7,729	-33,557
Total monitoring costs	**-2,430,200**	**-4,401,113**	**-4,470,932**	**-4,550,463**	**-4,635,628**	**-20,488,337**
Investigational treatment	-2,424,026	-4,346,938	-4,415,709	-4,496,461	-4,582,625	-20,265,758
Acute parenteral anticoagulation, index event	1,547	1,571	1,596	1,628	1,658	8,001
Re-treatment recurrent event, warfarin	-7,428	-54,299	-55,368	-54,177	-53,200	-224,472
Re-treatment recurrent event, acute parenteral anticoagulation	-293	-1,448	-1,451	-1,454	-1,461	-6,108
Total events costs	**-196,838**	**-384,284**	**-446,430**	**-522,222**	**-599,609**	**-2,149,383**
Embolic events (index event)	0	0	0	0	0	0
Embolic events (recurrent)	-49,379	-84,753	-84,765	-84,747	-84,816	-388,459
Bleeding costs	-148,714	-301,361	-355,414	-419,122	-483,961	-1,708,571
Other AE	0	0	0	0	0	0
PTS	70	5	-315	-786	-1,339	-2,366
CTEPH	1,184	1,825	-5,936	-17,567	-29,493	-49,987
Total costs	**-2,890,370**	**937,105**	**894,170**	**831,318**	**787,722**	**559,946**

Figure 53: Net budget impact, treatment followed by secondary prevention all patients



8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As mentioned elsewhere in this submission (Sections 2.5 and 4.1.1-4.1.2), dabigatran is at present the only approved novel oral anticoagulant with evidence on the subsequent treatment after initial therapy with heparin. Thus it does not require a change of routine practice and existing services/protocols of which the likely expenditure for is unknown.

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