NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Edoxaban

For the treatment and secondary prevention of deep vein thrombosis and /or pulmonary embolism

Submitted by

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Abbreviations

AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
CAT	Computer Axial Tomography
CHMP	Committee for Medicinal Products
CrCl	Creatinine Clearance
CrI	Credibility Interval
CRNM	Clinically Relevant Non-Major
CT	Computed Tomography
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EQ-5D	EuroQoL-5-Dimensions
ESC	European Society of Cardiology
FXa	Factor Xa
HIT	Heparin-Induced Thrombocytopenia
HR	Hazard Ratio
INR	International Normalised Ratio
LMWH	Low Molecular Weight Heparin
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
NVAF	Nonvalvular Atrial Fibrillation
mITT	Modified Intention To Treat
NHS	National Health System
NMA	Network Meta-Analysis
NOAC	Non-VKA Oral Anticoagulants
NT-proBNP	N-terminal pro Brain Natriuretic Peptide
NVAF	Nonvalvular Atrial Fibrillation
OD	Once Daily
OR	Odds Ratio
P-gp	P-glycoprotein
PD	Pharmacodynamic
PE	Pulmonary Embolism

PICOS	Population/patients, Intervention, Comparison, Outcomes and Study design
PK	Pharmacokinetic
PP	Per Protocol
PSS	Personal Social Services
PT	Prothrombin Time
PTS	Post-Thrombotic Syndrome
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
r-FVIIa	Recombinant Factor VIIa
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TTO	Time Trade-Off
TTR	Time in Therapeutic Range
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
4F-PCC	4- Factor Prothrombin Complex Concentrate

Executive summary

Background

Venous thromboembolism (VTE) is a severe disease characterised by the formation and embolisation of a blood clot in a vein. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two clinical manifestations of VTE: DVT is the formation of a thrombus in the deep veins of the extremities; PE is an obstruction of a pulmonary artery, caused by a deep vein thrombus that breaks off, migrates to the pulmonary arterial system and occludes a pulmonary artery.

VTE is the third most common cardiovascular disease worldwide after acute ischaemic syndromes and stroke. There are around 1.5 million VTE events in Europe each year, of which approximately one third are fatal. The estimated incidence of VTE varies between 100 and 200 per 100,000 person-years; translated to the England and Wales population, this suggests that between 56,000 and 112,000 people suffer from VTE each year. VTE may be provoked (most common risk factors are older age, cancer, surgery, pregnancy) or unprovoked (idiopathic).The incidence of first VTE event increases with age and cancer. About 30% of patients without transient risk factors have a recurrent VTE event within 10 years. The risk of VTE recurrence is increased in patients with cancer and those with an idiopathic first event.

Treatment of VTE is divided into two phases: (1) the initial phase, which aims to prevent further extension or embolisation of the thrombus; and (2) long-term secondary prevention, with the objective to complete treatment of the acute episode of VTE, and to prevent recurrence of the disease. Anticoagulant pharmacotherapy forms the basis of VTE treatment. The duration of treatment will vary for each individual. By their very nature, all anticoagulants are associated with a risk of bleeding. Anticoagulant treatment should be continued until the benefits no longer outweigh the risk of bleeding.

Patients with VTE are generally treated for at least 5 days with parenteral anticoagulants (Unfractionated Heparin (UFH) or subcutaneous Low Molecular Weight Heparin (LMWH)), followed by at least 3 months of Vitamin K Antagonist (VKA) treatment. Non-VKA Oral Anticoagulants (NOACs) are also available to treat VTE and to prevent recurrence; like the standard of care, edoxaban and dabigatran are administered after initiation of treatment with parenteral anticoagulation, while rivaroxaban and apixaban do not require a heparin lead-in. The 2014 European Society of Cardiology (ESC) guidelines recommend NOACs as alternatives to LMWH/VKA therapy in acute PE. NICE guidance similarly recommends dabigatran and rivaroxaban as options for the treatment and secondary prevention of VTE.

VKAs have many well-documented limitations: slow onset of action; drug-food and drug-drug interactions; narrow therapeutic windows requiring frequent monitoring; and variability in dose response. By contrast, NOACs offer the advantages of rapid onset of action, a short half-life, no need for routine coagulation monitoring, and few drug-drug or drug-food interactions. Patients receiving NOACs report greater

treatment satisfaction and fewer issues with managing treatment compared with those on VKAs.

Clinical evidence for edoxaban

Hokusai-VTE was a phase III, event-driven, randomised, double-blind, double-dummy, parallel-group, multi-centre, multi-national non-inferiority study designed to evaluate the benefits and risks of edoxaban in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE. It compared initial heparin followed by edoxaban versus initial heparin overlapping with warfarin, followed by warfarin only with respect to efficacy and safety in patients with DVT, PE, or both. A total of 8292 patients were enrolled across 37 countries in 439 centres (including 111 randomised UK patients), and across a broad spectrum of VTE manifestations, ranging from limited proximal DVT to severe PE. The baseline characteristics of the patients were similar in the two study groups.

All patients received initial therapy with open-label enoxaparin or UFH for at least 5 days, or until target International Normalized Ratio (INR) (2.0-3.0) had been achieved. Edoxaban (or placebo) was started after discontinuation of initial heparin. Edoxaban was administered at a dose of 60 mg orally once daily, taken with or without food, or at a dose of 30 mg once daily in patients in whom any of the following criteria were met: creatinine clearance (CrCl) of 30 to 50 mL/min; body weight ≤60 kg; patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors.

The primary efficacy outcome was the incidence of adjudicated symptomatic recurrent VTE (defined as a composite of DVT or nonfatal or fatal PE). Edoxaban was non-inferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.70 to 1.13; P<0.001 for non-inferiority), when considering the overall study period (mITT analysis set). Similar results were found when considering the on-treatment period (HR, 0.82; 95% CI, 0.60 to 1.14; mITT analysis set).

The principal safety outcome was the incidence of adjudicated clinically relevant bleeding, which was defined as a composite of Major and/or Clinically Relevant Non-Major (CRNM) bleeding. Edoxaban demonstrated a superior reduction in this endpoint, compared to warfarin. Adjudicated clinically relevant bleeding occurred in 349 of 4118 patients (8.5%) in the edoxaban group and in 423 of 4122 patients (10.3%) in the warfarin group (HR, 0.81; 95% CI, 0.71 to 0.94; p=0.004 for superiority). Moreover, there were fewer fatal and intracranial bleeds in the edoxaban group compared with warfarin.

Indirect comparisons of NOACs for VTE

As there are no head-to-head studies, comparisons of the relative efficacy and safety in the NOAC class are difficult. The difficulty is compounded by a number of important differences in the design and patient populations among the VTE pivotal trials in this class. For example, Hokusai-VTE had flexible and risk-adapted treatment duration, compared with the fixed duration of the other studies. Hokusai-VTE had the

longest median follow up of the pivotal studies, and collected data for all patients for 12 months, including those who had already completed their treatment, as part of the primary efficacy analysis. Hokusai-VTE also included a high proportion of patients with more extensive disease, including severe PE patients. By contrast, EINSTEIN-DVT and EINSTEIN-PE had open-label designs; in AMPLIFY and the EINSTEIN studies, patients received apixaban and rivaroxaban, respectively, without a heparin lead-in. Furthermore, there were key differences between the studies with respect to the risk profile and demographics of the randomised populations. These factors mean that indirect comparisons must be interpreted with caution.

A network meta-analysis was conducted to estimate relative effects of edoxaban, warfarin, dabigatran and rivaroxaban, for the purposes of a cost-effectiveness analysis. This analysis indicates that edoxaban is associated with comparable risk of VTE recurrence and major and clinically relevant non-major bleeding, compared with warfarin, dabigatran and rivaroxaban, in all patients with VTE. Among comparable patients with PE from the included studies, edoxaban had a favourable efficacy profile versus comparators, and a similar risk of bleeding.

Economic analysis

A cost-effectiveness analysis was conducted for edoxaban in the treatment and prevention of recurrent VTE. A Markov model was developed to consider the effect of introduction of edoxaban within the current clinical pathway for the treatment of VTE and prevention of recurrence in England. Analysis of the results of the model indicate that the predicted event rates for edoxaban and the included comparators are similar to those reported from pivotal randomised controlled trials.

In the base-case cost-effectiveness analysis, treatment of patients with VTE with edoxaban for 12 months is dominant compared with warfarin (with 0.018 additional QALY and £1 less in cost) and dabigatran (with 0.004 additional QALY and £37 less in cost), and is dominated by rivaroxaban (with 0.008 fewer QALY and £45 more in cost) over a lifetime horizon. The results of the deterministic and probabilistic sensitivity analyses support the robustness of these conclusions.

Cost-effectiveness results from sub-group analyses in the PE population are consistent with those of the base case (evidence did not allow for sub-group analyses in the DVT population). These results are insensitive to changes in the assumed treatment duration.

Summary

The positive risk-benefit profile of edoxaban within this indication has been proven in the Hokusai-VTE trial, an innovative study that sought to mirror clinical practice and demonstrated the safety and efficacy of edoxaban among representative patients with VTE. Moreover, indirect treatment comparisons confirm that edoxaban has a favourable efficacy profile compared with other NOACs while maintaining safety, and can be an alternative treatment option. The analyses presented in this submission suggest that edoxaban can be a cost-effective treatment option within this indication.

In conclusion, the use of edoxaban in accordance with its licensed indication is a clinically effective and cost-effective allocation of healthcare resources in the National Health Service in England and Wales.

Section A – Decision problem

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: Lixiana ®

Approved name: Edoxaban tosylate

Therapeutic class: Oral anticoagulant (B01A – antithrombotic agent)

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

Factor Xa is a serine protease that converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and thus plays a central role in formation of a cross-linked thrombus.(1-3) Factor Xa is the primary site of amplification as one molecule of Factor Xa catalyses the formation of ~1000 thrombin molecules.(2) Factor Xa has been shown to activate clotting over a much wider concentration range than thrombin in preclinical studies, suggesting that Factor Xa inhibitors may have a wider therapeutic window than thrombin inhibitors.(2)

Edoxaban tosylate (henceforth edoxaban) is an oral, highly selective, rapidly-acting, potent, competitively reversible, direct inhibitor of Factor Xa that can inhibit thrombin generation, and produces sustained inhibition of anticoagulation for up to 24 h.(4)

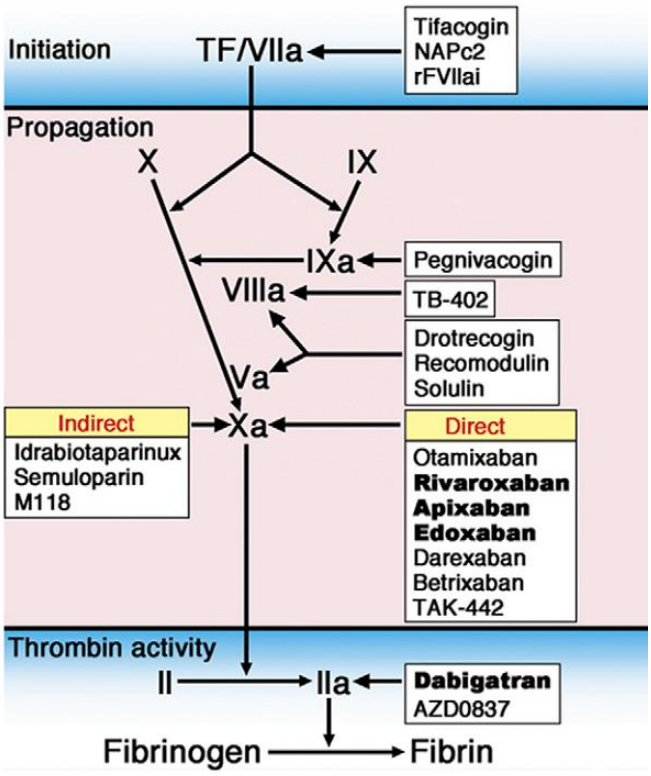
Edoxaban produces rapid onset of pharmacodynamic (PD) effects within 1 - 2 hours, which corresponds with peak edoxaban exposure (Cmax). The PD effects measured by anti-factor Xa assay are predictable and correlate with the dose and the concentration of edoxaban. As a result of FXa inhibition, edoxaban also prolongs clotting time in tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests are expected at the therapeutic dose; however, these changes are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of edoxaban.(5)

Approximately 40–59% of edoxaban is bound to plasma proteins (4) and it is a substrate for the P-glycoprotein (P-gp) transporter;(6) however, a very limited proportion of edoxaban (<4%) is metabolised by the cytochrome P450 system.(7)

Clinical pharmacology studies of edoxaban have shown it has a predictable and consistent pharmacokinetic (PK) profile. The elimination half-life of edoxaban is approximately 10-14 h in healthy subjects, with an absolute bioavailability of approximately 63%.(8) Approximately 50% of the absorbed edoxaban dose undergoes renal elimination (9), meaning around 35% is eliminated in the urine.(8)

Figure A 1, taken from De Caterina 2012 (10) represents the coagulation pathway and the different targets for several oral and parenteral anticoagulants (licenced or in development), including edoxaban.

Figure A 1. Targets for new anticoagulants in the coagulation pathway, adapted from De Caterina 2012 (10)



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).

Edoxaban tosylate does not currently have a UK marketing authorisation for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults. European Medicines Agency (EMA) filing occurred on [redacted]. Positive Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in [redacted] and EMA marketing authorisation in [redacted].

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).

Discussions with the regulator are ongoing. [redacted]

As Daiichi Sankyo does not have access to the draft EPAR, we are unable to provide a copy at this time. A version will be provided when available.

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

Edoxaban is anticipated to be indicated for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults.

It is also expected to be indicated for the prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

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 tolerability of edoxaban in its approved indication were evaluated in one phase III randomised clinical trial (RCT) sponsored by Daiichi Sankyo: Hokusai-VTE. Table A 1 presents a summary of this phase 3 study investigating edoxaban in adults with documented acute symptomatic DVT and/or PE, to evaluate whether initial (LMW) heparin followed by edoxaban only is non-inferior to initial heparin overlapping with warfarin, followed by warfarin only during the 12-month study period.

With respect to ongoing studies, Daiichi Sankyo is not currently conducting any study for the indication being appraised.

Table A 1. List of completed trials of edoxaban for the treatment of VTE and prevention of recurrent VTE

Trial acronym (NCT number and phase)	Hokusai-VTE (NCT00986154) Phase 3
Trial design	Randomised Double-Blind Double-Dummy Parallel-Group Multi-Centre Multi-National
Interventions	<u>Heparin/edoxaban group:</u> • Initial heparin plus placebo warfarin • Then heparin stopped, subject started edoxaban (60 mg OD*) and continued placebo warfarin. <u>Heparin/warfarin group:</u> • Initial heparin plus warfarin • Then heparin stopped, subject started placebo edoxaban (60

	mg OD*) and continued warfarin.
Population	Adults with documented acute symptomatic DVT and/or PE
Primary outcome measures	Efficacy • Symptomatic recurrent VTE, defined as the composite of DVT, non-fatal PE, and fatal PE Safety • Adjudicated clinically relevant bleeding, defined as a composite of major or CRNM bleeding
Secondary outcome measures	Efficacy • Composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE and all-cause mortality Safety • All bleeding.
Reference	Methodology • Raskob et al. 2013(11) Results : • Hokusai-VTE investigators et al. 2013(12)

* Reduced to 30mg if patients had one or more of the factors associated with edoxaban overexposure, including
- Body weight ≤ 60 kg
- CrCl between 30 mL/min and 50 mL/min
- Concomitant use of the P-glycoprotein inhibitors verapamil, dronedarone, or quinidine

** CRNM=Clinically Relevant Non-major, defined as overt bleeding that did not meet the criteria for major bleeding (if it was overt and was associated with a decrease in haemoglobin of 2 g per deciliter or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death) but was associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life

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

Daiichi Sankyo intends to launch edoxaban shortly after UK marketing authorisation is granted. We anticipate edoxaban will be available in the UK from [redacted].

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

Approval was obtained in Japan in September 2014 for the prevention of stroke and systemic embolism in patients with NVAF and for the treatment and recurrence prevention of VTE (DVT and PE).

Edoxaban was approved in Japan in April 2011, for the prevention of VTE after major orthopaedic surgery and was launched in July 2011 under the name LIXIANA™.

In January 2015, the US FDA approved edoxaban for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant.

In January 2015, the US FDA also approved edoxaban to reduce the risk of stroke and systemic embolism in patients with Nonvalvular atrial fibrillation (NVAF), with the following limitation of use in this indication: edoxaban should not be used in patients with CrCL > 95 mL/min because of increased risk of ischaemic stroke compared to warfarin at the highest dose studied (60 mg).

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?

In January 2015, Daiichi Sankyo submitted data to NICE for the appraisal of edoxaban for the prevention of stroke and systemic embolism in adults with NVAF. Guidance on this indication is expected in September 2015.

Daiichi Sankyo also plans to submit edoxaban for appraisal by the Scottish Medicines Consortium (SMC) in [redacted].

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 A 2. Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated (15 mg, 30mg and 60mg tablets)
Acquisition cost (excluding VAT)	[redacted]
Method of administration	Oral
Doses	The recommended dose is 60 mg Lixiana once daily, or 30 mg in specific patient groups (See Dose adjustments) [redacted]
Dosing frequency	Once daily
Average length of a course of treatment	Dependent on patient's risk-benefit profile. Treatment guidelines recommend a minimum of 3 months.
Average cost of a course of treatment	[redacted]
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	The standard daily dose of edoxaban is 60 mg taken once daily. For the following groups, the recommended daily dose of edoxaban is 30mg: • Moderate or severe renal impairment (CrCl 15-50 mL/min) • Low body weight ≤60 kg • Concomitant use of the following P-glycoprotein (P-gp) inhibitors: cyclosporine, dronedarone, erythromycin or ketoconazole.

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

Not applicable.

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

The use of edoxaban is not subject to any additional tests or investigations for patient selection compared to routine clinical practice as, prior to starting NOACs, renal function and liver function tests must be checked.

However treatment with edoxaban requires the lower (30mg) dose in patients with moderate to severe renal failure (CrCL 15-50 mL/min). As a result, the assessment of renal function may be required; however these tests are not above and beyond what would normally be assessed for these patients.

No additional monitoring is therefore required because of edoxaban.

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

There is no general need for monitoring of patients on edoxaban over and above usual clinical practice, as recommended by NICE with regard to the use of currently available NOACs.(13) It is anticipated there will be a reduction in the need for anticoagulation monitoring compared to warfarin.

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?

There is no requirement to administer other therapies at the same time as edoxaban.

It is noteworthy to mention that heparin lead-in is part of the recommended usage, but no concomitant administration is necessary.

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.

Natural history of VTE

VTE is a vascular disease characterised by the formation of a blood clot (thrombus) in a vein. VTE consists of two clinical entities: DVT and PE. DVT is the formation of a thrombus in the deep veins of the extremities. PE is an obstruction of a pulmonary artery, caused by a deep vein thrombus that breaks off, migrates to the pulmonary arterial system and occludes a pulmonary artery by a blood clot that has formed in the venous system of the extremities and migrated to the lungs.(14;15)

Clinical manifestations

DVTs are asymptomatic for more than 50% of patients.(16) In symptomatic DVTs, the symptoms are non-specific as they overlap with other conditions (i.e., muscle strain or skin infection) (14) and include swelling, erythema, tenderness, soreness, and pain in the affected leg.

The clinical presentation of PE is mostly non-specific and heterogeneous, ranging from asymptomatic to acute presentation with obstructive shock, dyspnoea, syncope or death.

Epidemiology

Because VTE is usually asymptomatic, the exact number of people affected each year by VTE is difficult to determine. Nevertheless it is widely accepted that VTE is the third most frequent cardiovascular disease after acute coronary syndromes and stroke with an overall annual incidence of 100-200 per 100 000 inhabitants.(17;18) Translated to the England and Wales population, between 56,000 and 112,000 people would suffer from VTE each year.

Table A 3 presents incidence rates of VTE, DVT and PE as reported in UK studies.

Table A 3. Studies on incidence of a first event of VTE

Country/region (Reference)	Patient characteristics	Type of study (Period of follow-up)	Incidence rate per 100,000 person-years		
			VTE	DVT	PE
UK Huerta 2007 (19)	General population N=1,814,669	Prospective GPRD analysis (1994-2000)	74.5	40.3	34.2
UK Martinez 2011 (20)	General population N=2,000,000	Prospective GPRD analysis (2001-2008)	164	87	77

Overall, approximately one third of VTE cases on a yearly basis are fatal; an epidemiological modelling study conducted in 2004 showed that the number of casualties in Europe annually due to VTE is double that of people who die of breast cancer, prostate cancer, AIDS and traffic accidents combined.(18)

VTE risk factors

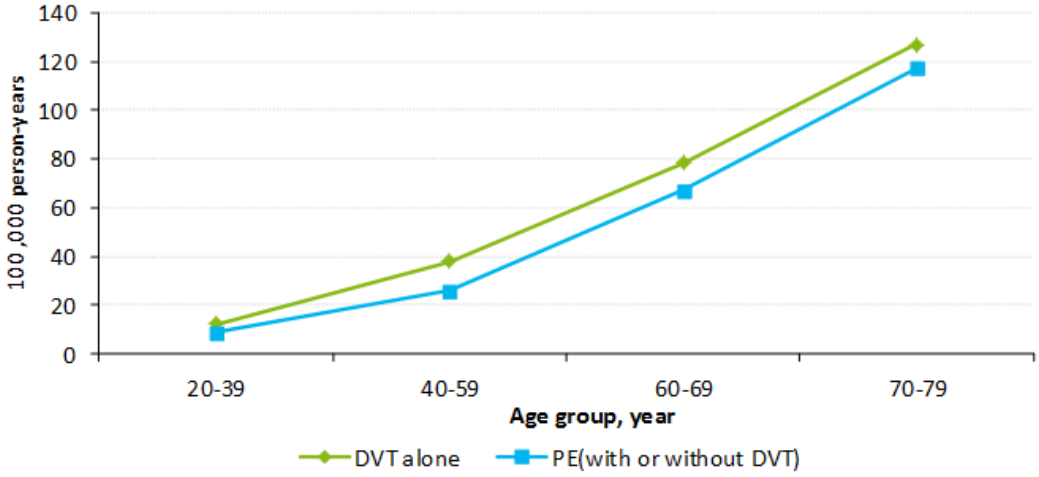
VTE can arise spontaneously (i.e. idiopathic or unprovoked), but in 50 to 70% of cases VTE is associated with acquired or inherent risk factors (i.e. provoked).(21;22) PE and DVT share the same risk factors.(15;22)

VTE is considered to be 'provoked' in the presence of a temporary or reversible risk factor within the last 6 weeks to 3 months before diagnosis, and 'unprovoked' in the absence thereof (23) :

- Reversible risk factors include surgery (the risk being highest during the first two post-operative weeks, but remaining elevated for two to three months), trauma, immobilisation, pregnancy, oral contraceptive use or hormone replacement therapy.(23)
- Other main factors include age over 60 years, overweight, active cancer or cancer treatment (with varying risks for different types of cancer), inflammatory bowel disease, hip fractures, fractures of the lower extremities and proximal femur.(19;23)

Age has been identified as a strong risk factor for first VTE in several epidemiological studies.(19;24;25) For instance, a UK retrospective study reported that the incidence rate for first VTE events rises exponentially with age (Figure A 2).(19) This could be explained by both the accumulation of risk factors and the biology of ageing.(17)

Figure A 2. Incidence rate of first DVT and first PE stratified by age group based on a UK primary care study (19)



Therefore it is anticipated that the number of cases of DVT and PE will increase as a result of the ageing of the population, increased exposure to surgery, oral contraceptives, long distance travel, and increasing levels of obesity.

VTE recurrence

There is a high rate of recurrence after a first VTE event. The risk of recurrence varies with time, with the highest risk occurring within the first year after the index event.

During the early period, active cancer and failure to rapidly achieve therapeutic levels of anticoagulation appear to independently predict an increased risk of recurrence.(26;27)

Based on historical data, the recent ESC guidelines (23) indicate the cumulative proportion of patients with early recurrence of VTE (on anticoagulant treatment) amounts to 2.0% at 2 weeks, 6.4% at 3 months and 8% at 6 months.

The cumulative proportion of patients with late recurrence of VTE (after 6 months, and in most cases after discontinuation of anticoagulation) has been reported to reach 13% at 1 year, 23% at 5 years, and 30% at 10 years.(27)

VTE complications

In addition to recurrence, VTE is associated with complications, including post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).(14)

- **PTS** is a chronic complication of DVT, and affects 20% to 50% of patients within 2 years of the first DVT event.(28) It is caused by venous hypertension, resulting either in a residual venous obstruction or valvular reflux. PTS is characterised by persistent or intermittent pain, swelling, itching, tingling or cramping in the limb and skin ulceration. PTS is severe in 5% to 10% of cases, and often manifests as venous ulceration.(29) Moreover, recurrent DVT in the same leg is a strong risk factor for development of PTS (HR 6.4; 95% CI 3.1 to 13.3).(30)

- **CTEPH** is a serious long-term complication of PE. It is characterised by an increase of blood pressure in the pulmonary artery, and can cause right ventricular heart failure. Several studies produced estimates of the proportion of patients with PE affected by CTEPH ranging from 0.4% to 8.8%.(31-37) The most recent one estimated a rate of 5.4%.(37)

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.

The manufacturer has estimated that the following numbers of patients are covered by the indication described in section 1.1 and would be potentially eligible for treatment with edoxaban according to its SmPC.

- Year 1 60,453 patients

- Year 2 61,410 patients
- Year 3 62,624 patients
- Year 4 63,764 patients
- Year 5 64,844 patients

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.(38)

The rates of incidence of VTE were then applied to the age-specific population projections for England and Wales for 2015-2019 from the Office of National Statistics.(39)

Further details are provided in section 8.1.

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.

VTE is associated with substantial mortality. In EU-25, around 543,000 deaths each year are attributed to VTE.(18)

The life expectancy of people with VTE and the mortality rates strongly depend on the disease severity at the time of diagnosis, treatments, and long term complications, such as PTS, major bleeding and CTEPH. This may explain the variability of mortality rates found in literature.

Recent England and Wales specific rates could not be retrieved. A prospective cohort (1994-2000) using the General Practice Research Database showed that the 1-month fatality rate was 1.4% after an episode of DVT and 22.6% after PE (with or without DVT).(19)

It is assumed that life expectancy in England and Wales would be consistent with the following rates:

- European and American registries and hospital discharge datasets of unselected patients with VTE yielded 30-day all-cause mortality rates between 9% and 11%, and 3-month mortality ranging between 8.6% and 17%.(40-42)
- Long-term mortality in a large cohort of Dutch patients with VTE was 22.7 per 1,000 person-years (95% CI 21.0-24.6), with a 4.0-fold (95% CI 3.7-4.3) increased risk of death compared with controls.(43) The risk remained increased up to 8 years after the thrombotic event, even when no additional comorbidities were 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.

Table A 4 summarises all guidance on VTE issued by NICE and the subgroups considered.

Table A 4. Guidance of VTE issued by NICE and the subgroups addressed

Guideline	Label	Issue date
NICE CG92	Reducing the risk of VTE	January 2010
NICE CG144	The management of VTE diseases and the role of thrombophilia testing	June 2012
NICE evidence update 55	A summary of selected new evidence relevant to NICE clinical guideline 144	April 2014
NICE QS29	Quality standard for diagnosis and management of VTE diseases	March 2013
NICE technology appraisal 261	Rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE	July 2012
NICE technology appraisal 287	Rivaroxaban for treating PE and preventing recurrent VTE	June 2013
NICE pathway	VTE	June 2014

CG = Clinical Guidelines; QS = Quality Standard

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.

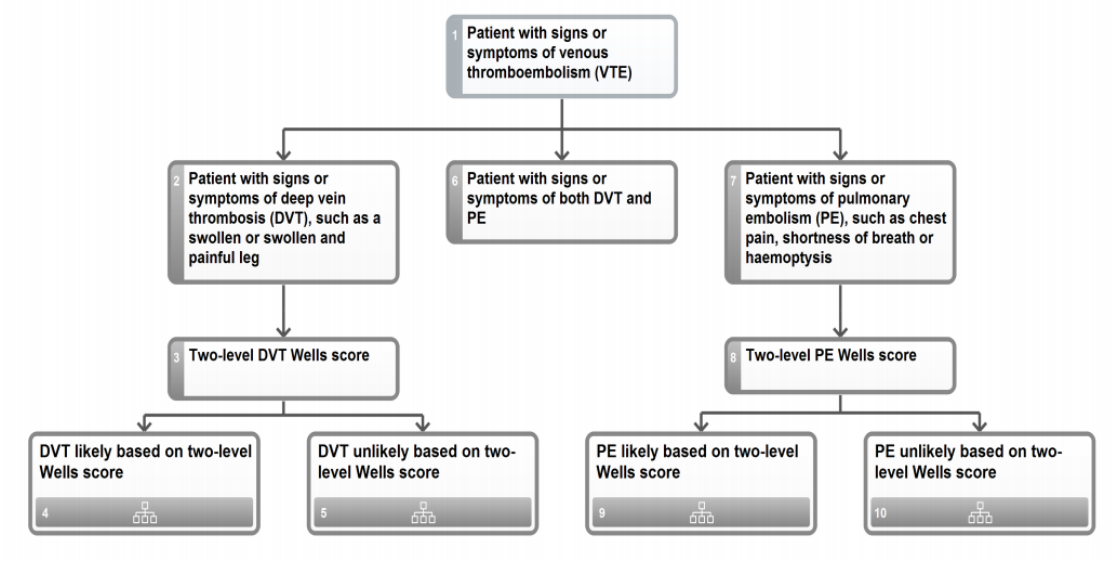
Diagnosis

Because symptoms are mostly non-specific, and DVT and PE are often asymptomatic (50-80% of cases), diagnosis is usually challenging and cannot be based only upon clinical examination.(14;44) Patients with signs or symptoms of VTE are screened for signs or symptoms of DVT and/or PE. When signs of DVT and/or PE are found, an assessment of the patient's general medical history and a physical examination are carried out, to exclude other causes. Then a clinical and risk factors standardised assessment is used to determine the need for further diagnostic testing (23;45;46):

- If DVT is suspected, the two-level DVT Wells score should be used to estimate the clinical probability of DVT (2 points or more indicates the DVT is likely), and an interim therapeutic dose of anticoagulation therapy for suspected DVT is given.
- If PE is suspected, the two-level PE Wells score is used to estimate the clinical probability of PE (more than 4 points indicated the PE is likely), and an interim therapeutic dose of anticoagulation therapy for suspected PE is given.

Diagnosis pathway for VTE in primary, secondary and tertiary, as provided by NICE guidance, is shown in Figure A 3.

Figure A 3. NICE pathway for VTE in primary, secondary and tertiary care (47)



Anticoagulant pharmacotherapy

Anticoagulant pharmacotherapy forms the basis of VTE treatment, and is central to the prevention of recurrence.(23;48;49) It includes parenteral and oral therapies, as shown in Table A 5.

Table A 5. Current anticoagulant pharmacotherapy for treatment of VTE and prevention of recurrent VTE in UK

Type of therapy	Pharmaceutical class	Name
Parenteral therapies	Heparin group	Unfractionated heparin (UFH) (eg, calciparin)
		Low-molecular-weight heparin (LMWH) (eg, enoxaparin)
	Factor Xa inhibitors	Fondaparinux
Oral therapies	Vitamin K antagonists (VKA)	Warfarin, acenocoumarol, phanocoumarol and fluindione
	Non VKA oral anticoagulants (NOACs)	Direct thrombin inhibitors (dabigatran)
		Direct factor Xa inhibitors (rivaroxaban)

The standard treatment consists of LMWH followed by VKA.(50)

LMWH, fondaparinux and UFH

According to NICE guidelines (51), patients with confirmed proximal DVT or PE should be treated with LMWH or fondaparinux, according to comorbidities, contraindications and drug costs, with the following exceptions:

- Patients with severe renal impairment or established renal failure should be treated with UFH with dose adjustments based on the aPTT or LMWH with dose adjustments based on an anti-Xa assay.
- Patients with an increased risk of bleeding should be treated with UFH.

- Patients with PE and haemodynamic instability should be treated with UFH and/or thrombolytic therapy.

The parenteral anticoagulant should be started as soon as possible and continued for at least 5 days or until the INR is 2 or above for at least 24 hours, whichever is longer.(51)

Patients with active cancer and confirmed proximal DVT or PE should be treated with LMWH for at least 6 months. At 6 months, the risks and benefits of continuing anticoagulation should be assessed.(51)

VKA

VKA are offered to patients with confirmed proximal DVT or PE within 24 hours of diagnosis. (51) This treatment should continue for 3 months, after what the risks and benefits of continuing VKA treatment is to be assessed:

- Patients with an unprovoked PE may continue the VKA treatment, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding.

- Patients with unprovoked proximal DVT may continue the VKA treatment if their risk of VTE recurrence is high and there is no additional risk of major bleeding.

VKAs are highly effective at treating VTE and preventing recurrence, however their use can be very challenging in clinical practice (52): slow onset of action, drug-food and drug-drug interactions, narrow therapeutic window requiring frequent monitoring, and variability in dose response.

NOACs

VTE treatment approach has been evolving in recent years with the entry of NOACs. NOACs have proven efficacy and safety in large clinical trials and are indicated for use in VTE. Their advantages include rapid onset of action, a short half-life, no need for routine anticoagulation monitoring, and few drug-drug or drug-food interactions.

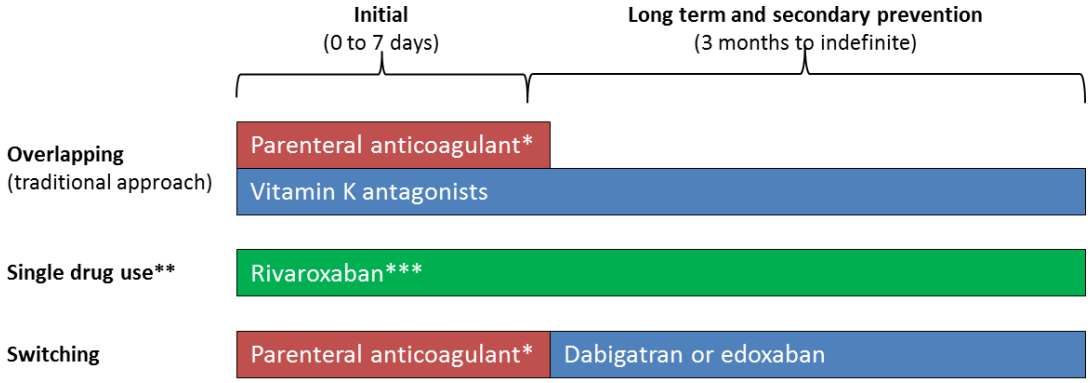
- Alternatively to VKAs, dabigatran and edoxaban can be started after the acute phase of parenteral anticoagulation.(23;53;54)

- Rivaroxaban represents an alternative to the combination treatment of parenteral and VKA anticoagulation.(23)

Summary of anticoagulation treatment approach

Figure A 4 summarises the anticoagulation treatment approach.

Figure A 4. Anticoagulation approach (54)



* UFH, LMWH, fondaparinux
** No NICE guidance on apixaban at the time of submission
*** Initiation dose different to maintenance dose

ESC also provides recommendations about NOACs (23), for acute phase treatment of pulmonary embolism. As alternatives to the combination of parenteral anticoagulation with a VKA, the following are recommended:

- rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily)
- apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily)

In addition, as an alternative to VKA treatment, the following are recommended:

- dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) following acute phase parenteral anticoagulation
- edoxaban[1] following acute-phase parenteral anticoagulation

In the ESC guidelines (23), NOACs (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).

Need for another treatment option

Although VKA treatment efficacy is acknowledged, VKAs have several limitations (for example narrow therapeutic range, unpredictable dose response, drug and food interactions). Despite multiple recently introduced NOACs, recurrence and bleeding risk remain a threat for patients with VTE, leading to severe clinical consequences and resultant resource utilisation, as well as direct and indirect costs to the economy.

NICE guidance recommends rivaroxaban as an option for treating DVT and preventing recurrent DVT and PE after a diagnosis of acute DVT in adults.(51) Rivaroxaban is also recommended as an option for treating PE and preventing recurrent DVT and PE in adults.(51) However, rivaroxaban requires a change in

[1] Not approved for use at the time of guideline publication

existing patient pathways, as it is licensed for initiation after the index event of DVT / PE (rather than initiation after a 5 day course of LMWH).

NICE has also recently recommended dabigatran as an option for treating and preventing recurrent DVT and PE in adults.(51) Nevertheless dabigatran is associated with several limitations: it is to be taken twice daily (once daily for edoxaban), it is associated with dyspepsia and tablets are not stable outside of their blister pack, so they cannot be added to any Dosette box, which is often done by pharmacists for patients with multiple medications to help patients remember to take them on the right day and at the right time.

These NOACs have complicated dosing schedules in patients with VTE:

- Patients initiated on rivaroxaban receive 15mg twice daily for the first 21 days, followed by 20mg once daily thereafter.(55)
- Patients on dabigatran receive 150 mg twice daily.(56)
- Those receiving apixaban for VTE receive a dose of 10 mg for 7 days, followed by 5 mg for up to 6 months thereafter. For prevention of recurrent VTE following completion of 6 months of treatment, the dose is 2.5 mg once daily.(57) Please note the apixaban was not yet appraised by NICE at the time of submission.

The guidance becomes more complicated in patients with renal impairment.

For **rivaroxaban**, among patients with moderate or severe renal impairment (55):

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, patients should be treated with 15 mg BD for the first 3 weeks. Thereafter, the recommended dose is 20 mg OD. A reduction of the dose from 20 mg OD to 15 mg OD should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE.

For **dabigatran**, among patients aged 80 years or above, or those who receive concomitant verapamil (56):

- Recommended dose is 110 mg BD.

Therefore, there is an unmet need for oral anticoagulant option with clear and simple dosing guidance, which reduces the incidence of VTE recurrences without compromising safety. Edoxaban represents a new and valuable alternative for VTE patients who need an effective and well-tolerated treatment following initial parenteral heparin therapy including those with increased risk of bleeding.

The dosing guidance for edoxaban is clear: it is always 60 mg OD, reduced to 30 mg in patients with moderate or severe renal impairment, body weight ≤ 60 kg, or concomitant use of selected P-gp inhibitors.

In the pivotal Hokusai-VTE study, edoxaban was non-inferior to warfarin for the treatment and secondary prevention of symptomatic recurrent VTE, and

demonstrated broadly consistent efficacy across a broad range of patients and in-pre-specified high-risk subgroups, such as fragile patients and those with severe PE.

Furthermore, edoxaban has a favourable tolerability profile, and significantly reduced the risk of clinically relevant bleeding (composite of major and clinically relevant non-major bleeding) vs. warfarin in Hokusai-VTE, which was the primary safety endpoint of the trial.

Edoxaban can benefit patients and clinicians due to its once-daily dosing regimen and unique dosing across VTE indications, which is likely to increase compliance.

Moreover, edoxaban fits well in the existing clinical pathway as it can displace warfarin or dabigatran following initial LMWH therapy. It does not require any change of routine practice and existing services/protocols.

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

Unmet needs

A number of unmet needs remain in the treatment of VTE (including DVT and PE) and prevention of recurrent VTE with regard to available treatments.

Data from PREFER in VTE provide accurate data on treatment patterns in 7 European countries.(58) This multi-national, multi-centre, prospective observational disease registry was performed by 380 participating sites (70% hospitals and 30% office-based physicians) in seven European countries, starting from January 2013. Overall, 3546 patients were documented across the seven participating countries at the time of the data snapshot (May 2014).(134)

Data from PREFER in VTE indicate that patient risk profiles influence treatment decisions in VTE. Compared with VKAs, NOACs are more often used in younger patients.(58) Furthermore, NOACs are prescribed to less severe patients in other categories, including those with body weight >60 kg, patients without renal disease or diabetes, and those with low HAS-BLED or high EQ-5D scores at baseline.(58)

Heparin was the most frequent concurrent medical treatment of acute VTE: the majority of patients were treated with low-molecular-weight heparin compared to unfractionated heparin.(134) NOACs were more frequently prescribed for acute VTE, younger VTE patients, patients with higher body weight.(58)

Compared with patients on VKAs, patients receiving NOACs in PREFER in VTE were less likely to report that treatment is difficult; that they were bothered by treatment; that dose adjustment is difficult; that managing food interactions or concomitant medications was difficult; or that they were bothered by medical follow up. Furthermore, the overall treatment convenience score on the PACTQ2 instrument was lower for patients receiving VKAs compared with those on NOACs.(135)

VKAs are associated with numerous challenges: narrow therapeutic window, requirement for routine monitoring and dose adjustments, unpredictable dose response, slow onset of action and associated with a risk of bleeding.(59)

Although NOACs have several advantages compared to VKA – including a rapid onset of action, short half-life, fixed dosing, no need for routine anticoagulation monitoring, few drug-drug or drug-food interactions – there are still issues associated with anticoagulant therapies that are available to treat patients with VTE.(59)

Existing VTE treatments are associated with several challenges

Even with anticoagulation therapy, the risk of recurrence remains. VTE recurrence continues to be a risk, even years after the conclusion of anticoagulation therapy. This has severe consequences for patients as it can be potentially life threatening.(98)

High rates of bleeding events remain a major issue in the management of patients with VTE, resulting in increased risk of mortality, hospitalisation, and recurrence. Elderly patients and those with cancer are at the highest risk of bleeding.

VTE treatment regimens are complicated; suboptimal treatment adherence can lead to recurrence, bleeding events or hospitalisation.

In conclusion, VTE treatment is associated with several unmet needs

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

The main comparators and their rationale for inclusion are presented in Table A 6.

Table A 6. Comparators

Comparators listed in the final scope issued by NICE	Consideration in this submission	Rationale if not considered
Initial treatment with a LMWH or fondaparinux and continued VKA	Yes (Initial treatment with a LMWH or fondaparinux and continued VKA for 3, 6 or 12 months)	
Rivaroxaban	Yes	Not applicable
Dabigatran	Yes	Not applicable
LMWH or fondaparinux alone, for people for whom a VKA is unsuitable	No	LMWH alone has not been included in the submission because it is typically used in patients with active cancer, which is not part of the expected indication for edoxaban
Rivaroxaban, for people for whom a VKA is unsuitable	No	There is no evidence available for edoxaban in patients for whom VKA is unsuitable
Dabigatran, for people for whom a VKA is unsuitable	No	There is no evidence available for edoxaban in patients for whom VKA is unsuitable

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

As there is no specific antidote for bleeds while on any of the non-VKA oral anticoagulants, the edoxaban SmPC recommends in case of bleeding to promptly evaluate any signs or symptoms of blood loss and discontinue edoxaban in patients with clinically significant active bleeding.

A number of reversal agents are currently under development. These include the 4-factor prothrombin complex concentrate (4F-PCC) which has been investigated recently in a phase I trial. The study demonstrated that, for life-threatening bleedings that cannot be controlled, the administration of a 4F-PCC at 50 iU/kg reverses the effects of edoxaban 30 minutes after completing the infusion.(60)

[redacted].

[redacted].

2.9 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 to the NHS associated with edoxaban is the acquisition cost of the drug. No additional costs are anticipated to arise based on location of care, staff usage, administration costs, monitoring or tests. As INR monitoring is unnecessary with edoxaban, a reduction in INR monitoring required with warfarin treatment is expected. No additional laboratory testing is expected to be recommended compared to other NOACs.

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

Edoxaban does not require additional infrastructure to be put in place.

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.

There are no equality issues surrounding the use of edoxaban.

3.1.2 **How has the analysis addressed these issues?**

Not applicable.

4 Innovation

4.1 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.

Warfarin has been established as the standard of care for treatment of VTE and prevention of recurrence, but it is associated with several limitations, including the following (61): unpredictable pharmacokinetics (PK) and pharmacodynamics (PD); numerous drug and dietary interactions; genetic variability in metabolism response; and a narrow therapeutic window requiring frequent monitoring and dose adjustments to maintain a therapeutic level of anticoagulation.

By contrast, the currently NICE-recommended NOACs have predictable PK/PD, have minimal interactions with other drugs compared to VKAs, and do not require INR monitoring. However, rivaroxaban is associated with several limitations, including: the need to be administered with a meal, and the use of an initiation dose which differs from its maintenance dose (55), as stated in section 2.5. Similarly, dabigatran is limited by its need to be taken twice daily; its association with dyspepsia; and that the tablets are not stable outside of their blister pack, so they cannot be added to any pill organiser, which is often done by pharmacists for patients with multiple medications to help patients remember to take them on the right day and at the right time.(56)

Edoxaban may provide a convenient alternative to comparators without compromising efficacy or safety. Like the other NOACs, edoxaban does not require any INR monitoring; it has predictable PK/PD, and has minimal interactions with other drugs. In addition, it can be taken with or without food, is once-daily and is stable outside its blister pack. Furthermore, the dose of edoxaban can be halved in specific patient groups anticipated to be at increased risk of edoxaban overexposure (i.e. patients with moderate or severe renal impairment, low body weight ≤ 60 kg or concomitant use of P-gp inhibitors), thus providing a very simple dosing regimen both for the physician and the patient.

Lastly, as described above in section 2.8, [redacted].

4.2 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 use of edoxaban may result in potential convenience benefit due to the absence of lifestyle limitations/modifications on account of the absence of significant drug-drug or drug-food interactions and the ease of use (edoxaban is to be taken once daily, and doesn't need to be taken with food).

These convenience benefits are not captured within the QALY calculation.

4.3 Please identify the data you have used to make these judgments, 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.

A large European registry (PREFER in VTE) provide insights into the real-world patterns of treatment of patients with VTE across seven countries.(58) Preliminary findings were that compared with patients on VKAs, patients receiving NOACs were less likely to report that managing food interactions or concomitant medications was difficult. This is not accounted for in QALY calculations.

5 Statement of the decision problem

Table A 7. Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with DVT and/or PE	As per NICE scope	Not applicable
Intervention	Edoxaban tosylate	As per NICE scope	Not applicable
Comparator(s)	- Initial treatment with a LMWH or fondaparinux and continued VKA - Rivaroxaban - Dabigatran - For people for whom a VKA is unsuitable: o LMWH or fondaparinux alone o Rivaroxaban o Dabigatran	As per NICE scope Note: no evidence available for edoxaban in patients for whom VKA is unsuitable	Not applicable
Outcomes	The outcome measures to be considered include: - Mortality - VTE recurrence - Complications following DVT or PE, 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	As per NICE scope	Not applicable
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.	As per NICE scope	Not applicable

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Subgroups to be considered	If evidence allows, subgroups will be considered by type of VTE (PE or DVT). 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). If evidence allows, the analysis should also consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. If the evidence allows, the analysis should consider separately people with active cancer and include any effect on the person's cancer or cancer treatment.	As per NICE scope Notes: - duration of anticoagulation can be varied in the model but no specific subgroups were aligned with different treatment durations - patients for whom need for long-term anticoagulation is uncertain: no evidence available - active cancer: no evidence available from our pivotal trial	Not applicable
Special considerations, including issues related to equity or equality	Not applicable	Not applicable	Not applicable

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.**

Two systematic reviews were conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of edoxaban and relevant comparators as outlined in the scope:

- RCT evidence on the efficacy and safety of edoxaban and relevant comparators for the treatment and secondary prevention of DVT and/or PE.
- Non-RCT evidence on the efficacy and safety of edoxaban for the treatment and secondary prevention of DVT and/or PE.

The searches were performed using Medline, Embase and The Cochrane Central Register of Controlled Trials (CENTRAL) databases.

Searches were performed on December 1st, 2014, without any time span.

Keywords used in the search strategy were defined according to the decision problem with a wide scope, to ensure that the maximum amount of relevant articles was detected in the search. MeSH terms related to the relevant comparators, as well as filters for study type and human were applied.

The population of interest was adults with VTE (including DVT and PE).

A complete list of the literature search strategy including search terms and filters employed are provided in section 9.2, Appendix 2.

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.**

Table B 1 presents the PICOS (population/patients, intervention, comparison, outcomes and study design) inclusion and exclusion criteria used for the systematic review.

Table B 1. Eligibility criteria used in search strategy

	Description	Justification
Inclusion criteria		
Population (P)	Adults (≥18 years) with DVT or PE	Consistent with scope
Interventions (I)	• NOACs: direct thrombin inhibitors i.e. dabigatran • NOACs: Factor Xa inhibitors i.e. apixaban, rivaroxaban, edoxaban • Coumarins/ VKA i.e. warfarin	Consistent with scope
Comparators (C)	All the interventions listed above	Consistent with scope
Outcomes (O)	• Mortality • Recurrent VTE • Complications following DVT or PE, including post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension • Adverse effects of treatment including bleeding events, intracranial and gastrointestinal bleeding	Consistent with scope

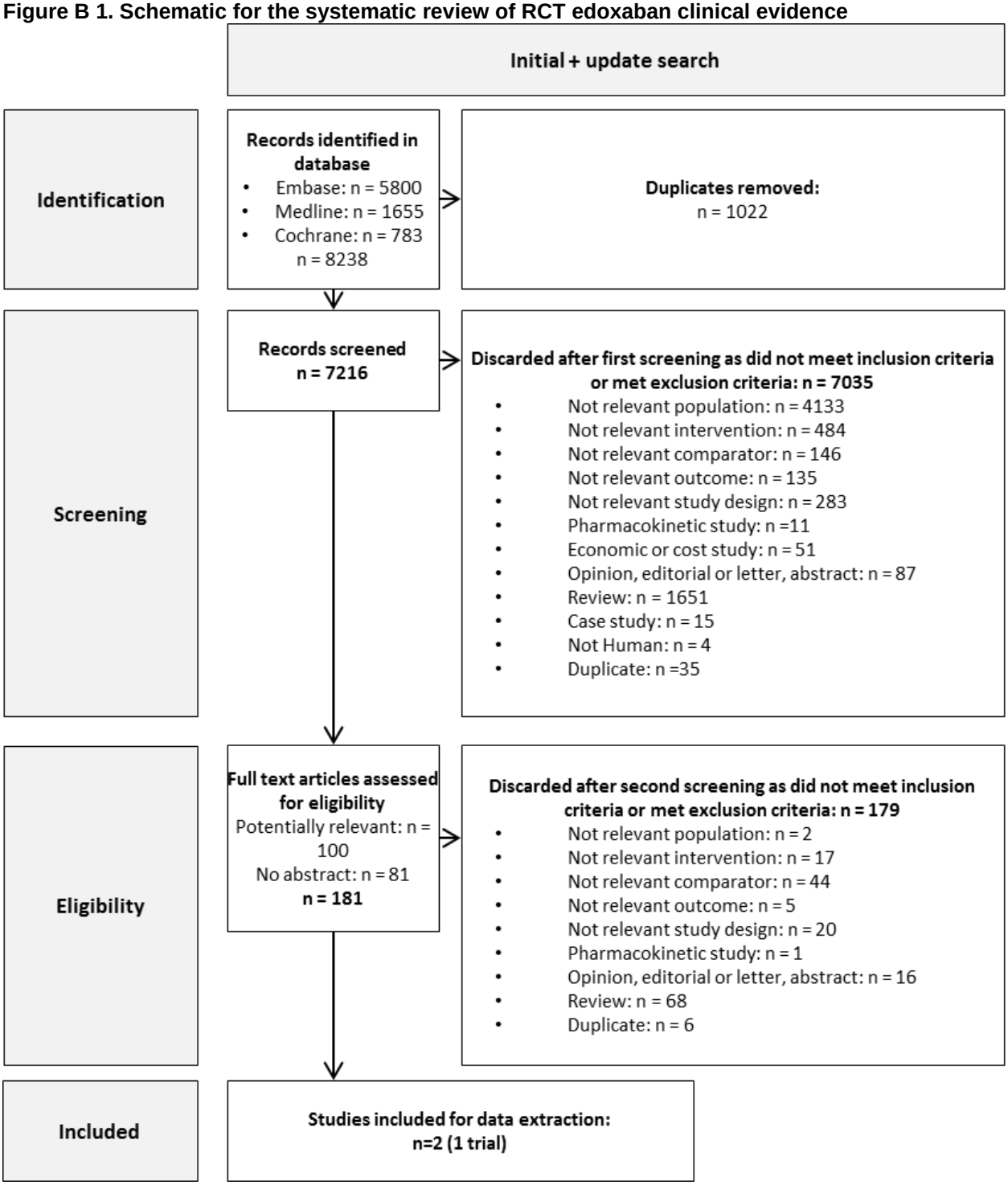
Study design (S)	• For RCT studies
	  ○ RCTs
	  ○ Systematic review of clinical trials
	  ○ Meta-analyses
	• For non-RCT studies
	  ○ Non-RCTs
		Consistent with scope

Exclusion criteria		
Population (P)	Subjects <18 y and subjects at risk of VTE after surgery	Consistent with scope
Interventions (I)	Studies not investigating edoxaban or relevant comparator	Consistent with scope
Comparators (C)	Studies not investigating edoxaban or relevant comparator	Consistent with scope
Outcomes (O)	Studies not reporting the outcomes listed in the scope	Consistent with scope
Study design (S)	Designs not listed in inclusion criteria	Consistent with scope

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.

The article selection process is summed up in Figure B 1.

Figure B 1. Schematic for the systematic review of RCT edoxaban clinical evidence



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.

Not applicable.

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.

The only source for the edoxaban phase 3 trial is its peer-reviewed publication. As per the flow diagram presented in section 0, one publication for edoxaban was retrieved:

- Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013 Oct 10;369(15):1406-15.

It is noteworthy to mention that a minor error was corrected in this article. In Table 2 (page 1411), in the edoxaban column, the denominator for the outcome "Patients with index DVT" should have been 4118 rather than 4188. The PDF was updated online.

Main characteristics of this RCT are shown in Table B 2.

Table B 2. List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Hokusai-VTE	Heparin/edoxaban • Initial heparin plus placebo warfarin • Heparin stopped once target INR reached, subject started edoxaban (60 mg OD*) and continued placebo warfarin.	Heparin/warfarin • Initial heparin plus warfarin • Heparin stopped once target INR reached, subject started placebo edoxaban (60 mg OD*) and continued warfarin	Adults aged ≥18 years with either • Objectively diagnosed, acute, symptomatic DVT involving the popliteal, femoral, or iliac veins • Objectively diagnosed, acute, symptomatic PE (with or without DVT)	• Hokusai-VTE investigators et al. 2013 (12)

* Reduced to 30mg if patients had one or more of the factors associated with edoxaban overexposure, including

- Body weight ≤ 60 kg
- CrCl between 30 mL/min and 50 mL/min
- Concomitant use of the P-glycoprotein inhibitors (verapamil, dronedarone, or quinidine

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.**

One primary Phase III study compares the intervention with one of the named comparators in the decision problem:

- Hokusai-VTE compared initial (LMW) heparin, followed by edoxaban only ([LMW] heparin/edoxaban) with initial (LMW) heparin overlapping with warfarin, followed by warfarin only ([LMW] heparin/warfarin)

In this study the dose of edoxaban was halved (from 60 mg OD to 30 mg OD) if any of the following characteristics were present at the time of randomisation or during the study: estimated CrCl of 30 to 50 ml per minute, a body weight of 60 kg or less, or the concomitant use of verapamil, quinidine or dronedarone.

The Phase III Hokusai-VTE study is reported in full in this submission.

This study provides meaningful evidence on the clinical efficacy and safety of edoxaban against warfarin in this indication. There are no other direct comparisons available for edoxaban versus any of the other named comparators. Therefore a network meta-analysis was conducted to estimate the relative efficacy and safety of these agents and was used in the cost-effectiveness analysis provided in this submission (see section 6.7 for details).

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.**

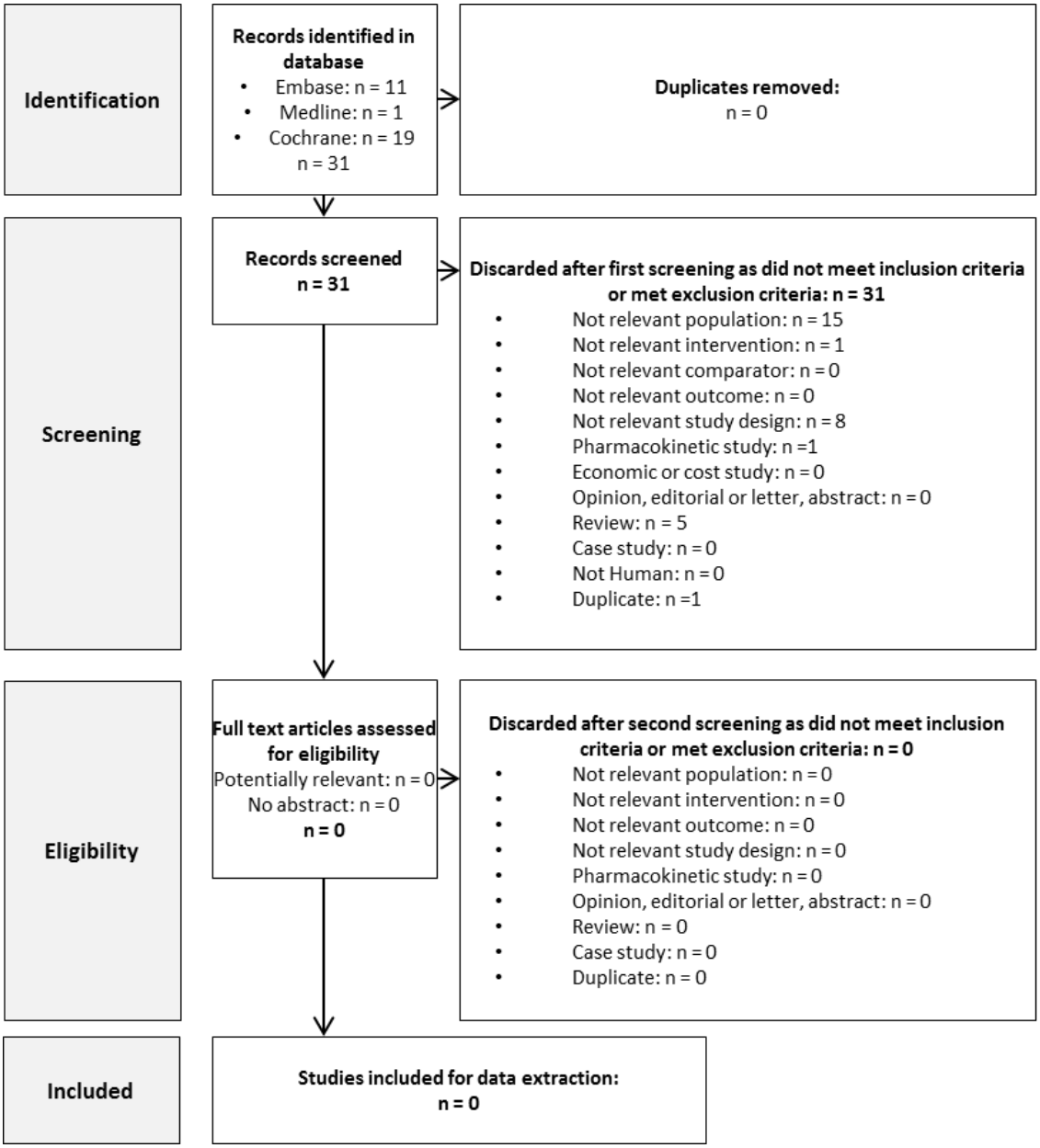
No studies have been excluded.

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-RCTs study was identified from the systematic review, as shown in Figure B 2.

Figure B 2. Schematic for the systematic review of non-RCT edoxaban clinical evidence



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.**

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.

Design

Hokusai-VTE was a phase III, event-driven, randomised, double-blind, double-dummy, parallel-group, multi-centre, multi-national non-inferiority study designed to evaluate the benefits and risks of edoxaban in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE.

The primary objective of Hokusai-VTE was to evaluate whether initial (LMW) heparin followed by edoxaban only ([LMW] heparin/edoxaban) is non-inferior to initial (LMW) heparin overlapping with warfarin, followed by warfarin only ([LMW] heparin/warfarin) in the treatment of subjects with acute symptomatic VTE for the prevention of symptomatic recurrent VTE during the 12-month study period.

Secondary objectives were to compare (LMW) heparin/edoxaban to (LMW) heparin/warfarin with regard to clinically relevant bleeding (i.e., Major or Clinically Relevant Non-Major [CRNM] bleeding) occurring during treatment or within 3 days of interrupting or stopping study drug, and to compare (LMW) heparin/edoxaban to (LMW) heparin/warfarin with regard to net clinical outcome defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality during the 12-month study period.

Eligible patients were stratified by presenting diagnosis (PE with or without DVT and DVT only), baseline risk factors (temporary risk factors only, such as trauma, surgery, immobilisation, oestrogen therapy, etc., versus all others), and need for dose reduction (see criteria below). After stratification, patients were randomly assigned (in a 1:1 ratio) to one of the following treatment groups:

- **Edoxaban group:** Initial open-label heparin (LMWH or UFH) plus placebo warfarin for ≥5 days until the sham international normalised ratio (INR) was ≥2.0 on two separate measurements at least one calendar day apart, or a single supratherapeutic sham INR measurement ≥3.0 was achieved (with the reasonable assumption that a therapeutic INR, ie, ≥2 had been achieved for at least 24 hours). Then heparin was stopped, and the patient started on edoxaban (60 mg OD, or 30 mg OD for those requiring dose reduction) and continued placebo warfarin (adjusted to maintain a sham INR between 2.0 and 3.0, inclusive).

- **Warfarin group:** Initial open-label heparin (LMWH or UFH) plus warfarin for ≥5 days until the INR was ≥2.0 on two separate measurements at least one calendar day apart or after a single supratherapeutic INR measurement ≥3.0 was achieved (with the reasonable assumption that a therapeutic INR, ie, ≥2 had been achieved for at least 24 hours). Then heparin was stopped, and the

patient started on placebo edoxaban (60 mg OD or 30 mg OD) and continued warfarin (adjusted to maintain an INR between 2.0 and 3.0, inclusive).

Heparins permitted for the initial heparin treatment were subcutaneous enoxaparin 1 mg/kg BD, subcutaneous enoxaparin 1.5 mg/kg OD, and intravenous UFH (started with 5000 IU bolus and 1300 IU/h infusion, activated partial thromboplastin time adjusted).

Edoxaban was taken orally, once daily. The standard dose used was 60 mg. The dose of edoxaban was halved (to 30 mg) for patients perceived to be at higher risk for overexposure (and therefore increased risk of bleeding). Dose adjustment occurred at randomisation and at any point during the study; dose adjustment after randomisation was a unique feature of Hokusai-VTE compared with studies of other non-VKA oral anticoagulants in VTE. The presence of one or more of the following criteria was required for dose adjustment (Table B 3):

Table B 3. Criteria for dose adjustment in Hokusai-VTE

At randomisation	During study
- Moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min as calculated using the Cockroft-Gault formula) - Low body weight (≤60 kg) - Concomitant potent P-glycoprotein (P-gp) inhibitor use (quinidine, verapamil)*	- Moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min as calculated using the Cockroft-Gault formula) and >20% drop from baseline - Low body weight (≤60 kg) and >10% drop from baseline - Concomitant potent P-gp inhibitor use (verapamil, dronedarone, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole)*

*The edoxaban dose was to be returned to 60 mg OD at any time the patient was not taking the concomitant medication (provided no other criteria for dose reduction were met).

All patients were to receive a minimum of 3 months treatment, consistent with clinical guidelines; after 3 months, the remaining duration of treatment was at the physician's discretion, up to a maximum of 12 months. Regardless of the total duration of treatment actually received, efficacy and safety data were collected on all patients during the entire 12-month period following randomisation.

This flexibility in treatment duration is uncommon in clinical trials, and potentially empowers the trial to reflect clinical practice more than do other studies of VTE treatment and secondary prevention.

A summary of the design of Hokusai-VTE is described in

Figure B 3. More details are provided in Figure B 4.

Figure B 3. Hokusai-VTE design

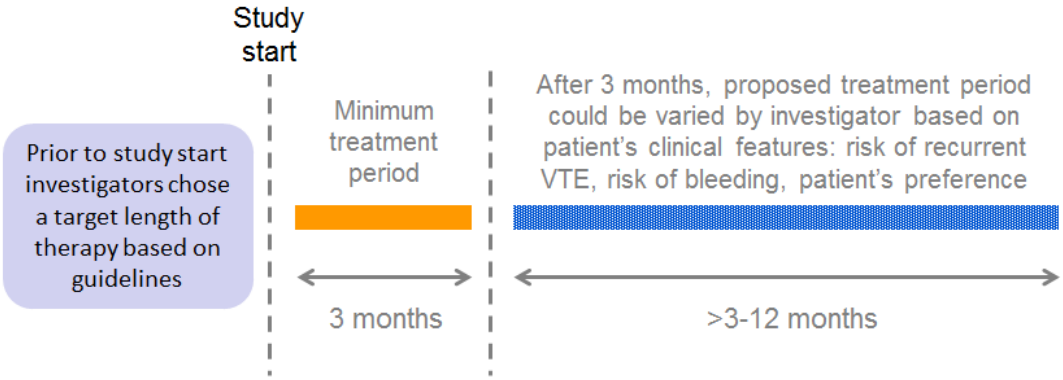
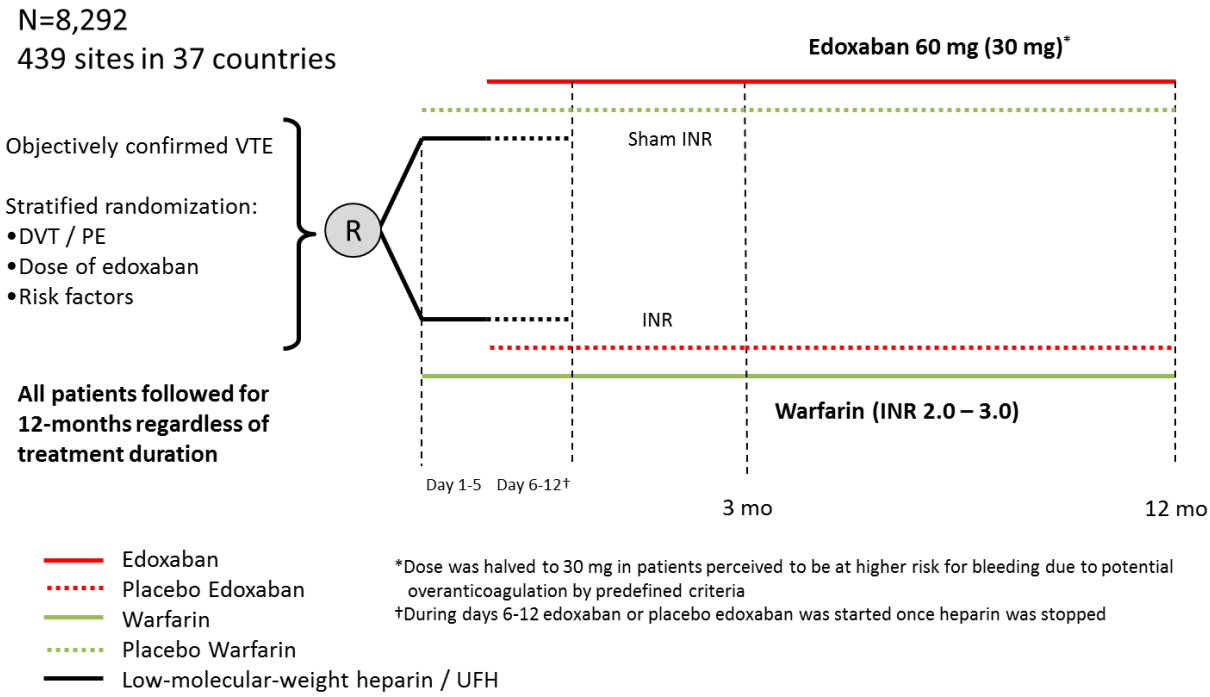


Figure B 4. Detailed Hokusai-VTE design



The design aimed to broaden the applicability of edoxaban to the real-world treatment of VTE via:

- enrolment of a broad range of patients, including those with extensive disease
- use of initial heparin as recommended by clinical guidelines
- dose adjustment of edoxaban (50% reduction i.e. from 60mg to 30 mg) for patients perceived to be at increased risk of bleeding due to edoxaban overexposure, at randomisation or during the study, to reflect clinical practice
- flexible treatment duration (minimum 3 months, maximum 12 months), based on evolving evidence or clinician discretion

Analysis Sets

From January 2010 through October 2012, a total of 8292 patients were enrolled at 439 centres in 37 countries.(12) Several analysis sets from within this patient population were considered for outcome assessment:

- **Modified Intent-to-Treat (mITT) Set:** All randomised subjects who received at least 1 dose of study drug. Analyses were based on the randomised treatment even if a subject inadvertently received the incorrect study drug.
- **Per Protocol (PP) Analysis Set:** All randomised subjects who received at least 1 dose of study drug, who did not have treatment misallocation, and for whom the index DVT or PE event at baseline was confirmed by the Clinical Events Committee (CEC). Treatment misallocation was defined as a subject taking incorrect treatment during the entire study period.
- **Safety Analysis Set:** All randomised subjects who received at least 1 dose of study drug. Analyses were based on the randomised treatment, unless a subject inadvertently received the incorrect drug during the entire study, in which case, the subject was grouped according the treatment actually received.

In addition to these analysis sets, two study periods were considered:

- **Overall Study Period:** The time from the reference date (randomisation date/initial dose of study drug date) to the last study follow-up visit.
- **On-Treatment Period:** The time period the subject was taking study drug up to 3 days after their last dose for that time period. A subject may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study.

Regarding outcome assessments, the primary efficacy analysis was performed in the mITT Analysis Set for the Overall Study Period (all events occurring during the Overall Study Period are included regardless of study drug administration status). Summary statistics for the primary efficacy endpoint were also prepared using an “On-Treatment” approach. Subjects were censored 3 days after any study drug interruption and 3 days after the day of permanent study medication discontinuation.

Regarding the different study periods, the duration of anticoagulation in Hokusai-VTE could be chosen to be between 3 and 12 months, based on the physician’s assessment of the patient’s risk profile. Thus, patients who received treatment beyond 3 months were those that physicians identified as having higher risk of recurrence; therefore the study population was enriched in higher-risk patients as the duration of treatment increased. The study design meant that patients who received shorter periods of anticoagulation were followed up after completing treatment; analyses of the overall study period captured events experienced by all patients, through 12 months of the study, regardless of whether patients were receiving therapy.

As set out in the Statistical Analysis Plan, when non-inferiority in the primary endpoint was established, superiority was also tested in the mITT Analysis Set for the Overall Study Period. The analysis of the primary safety endpoint is based on an “On-Treatment” approach. By way of comparison, the ‘on treatment’ study period most closely reflects the treatment periods analysed in the trials of the other NOACs.

The primary efficacy endpoint was the incidence of adjudicated symptomatic recurrent VTE in the mITT “Overall Study Population” analysis set (composite of recurrent DVT, new non-fatal symptomatic PE, or fatal PE during the 12-month study period). The principal safety endpoint was the incidence of adjudicated clinically relevant bleeding, defined as the composite of major or CRNM bleeding, in the Safety Analysis Set.

The data for the Overall Study and On-Treatment populations in the mITT analysis set, as well as the Safety Analysis Set are provided in the sections below. Data from the Per Protocol Analysis Set is provided in section **Error! Reference source not found.**, Appendix 14.

Table B 4. Summary of methodology of the RCT (12)

Topic	Hokusai-VTE
Location	Austria, Belarus, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Israel, Italy, Netherlands, Norway, Poland, Russia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom, India, China, Korea, Japan, Australia, New Zealand, Taiwan, Thailand, Philippines, Singapore, Canada, USA, Argentina, Brazil, Mexico
Design	Phase III, event-driven, randomised, double-blind, double-dummy, parallel-group, multi-centre, multi-national, non-inferiority study*
Duration of study	Study enrolment started in January 2010 and stopped in October 2012. The maximum possible treatment period for any individual subject after randomisation was 12 months. All subjects were to receive a minimum of 3 months treatment.
Method of randomisation	Patients were randomly assigned in a 1:1 ratio to one of the two groups (i.e., intervention or comparator)
Method of blinding (care provider, patient and outcome assessor)	- Edoxaban (30 mg) and matching placebo were supplied as yellow film-coated tablets in blister packs. To maintain blinding, yellow film-coated placebo tablets identical in appearance and packaging to that of edoxaban, but not containing any active drug substance, were used. Placebo for edoxaban was required to maintain the blind for warfarin vs. edoxaban. - Warfarin 1 mg (brown), 2.5 mg (green), and 5 mg (pink) tablets and matching placebo were supplied in blister packs by the Sponsor (global supply by a commercially available EU approved generic-single vendor). For China, Japan, South Korea, and Taiwan, warfarin 0.5 mg (white) and matching placebo were also supplied. The warfarin 5 mg strength was removed from the study to minimise the potential for warfarin dosing errors. To maintain blinding, placebo tablets identical in appearance and packaging to that of all strengths of warfarin, but not containing any active drug substance, were used. Placebo for warfarin was required to maintain the blind for edoxaban vs. warfarin.
Intervention(s) (n =) and comparator(s) (n =)	- Edoxaban 60 mg / 30 mg DR, N=4118 - Warfarin (INR 2.0-3.0), N=4122
Primary outcomes (including scoring methods and timings of assessments)	**Efficacy** - Incidence of symptomatic recurrent VTE (composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period. The primary efficacy analysis was performed in the mITT analysis set for the Overall Study Period. **Safety** - Incidence of adjudicated clinically relevant bleeding, which was defined as a composite of major or CRNM bleeding. The primary safety analysis was performed in the safety analysis set for the On-Treatment Period.
Secondary outcomes (including scoring methods and timings of assessments)	**Efficacy** - Composite clinical outcome of symptomatic recurrent DVT including non-fatal symptomatic recurrent PE and all-cause mortality during the 12-month study period **Safety** - All bleeding

Topic	Hokusai-VTE
	- Cases with pre-defined criteria suggesting hepatic dysfunction were evaluated and adjudicated by hepatic specialists in a blinded manner - All bleeding, clinical laboratory assessments, vital signs, physical examinations, AEs, SAEs, deaths, and other cardiovascular events **Other** - Net clinical outcome, defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality - Net clinical benefit, defined as the composite of symptomatic recurrent VTE or major bleeding - Health-related quality of life - Treatment duration - Permanent discontinuation
Duration of follow-up	Treatment with edoxaban or warfarin was to be continued for at least 3 months in all patients and for a maximum of 12 months. The duration was determined by the treating physician on the basis of the patient's clinical features and patient preference.

* Efficacy testing for non-inferiority and superiority utilised the followed test plan to control for study-wise type I error: All tests were two-sided:

- Step 1: Test the primary efficacy endpoint for non-inferiority mITT set at α=0.05. If the upper limit of the two-sided 95% CI of the hazard ratio was below 1.5, then non-inferiority to Warfarin group was considered
- Step 2: If non-inferiority was achieved in step 1, then test the secondary efficacy endpoint for superiority mITT set at α=0.01.

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.

The inclusion criteria were chosen to provide a representative sample of patients in the indication described in section 1.5.

Study population included adults presenting with acute, symptomatic DVT involving the popliteal, femoral or iliac veins, or PE requiring anticoagulant therapy were eligible for the study. Approximately 7,500 subjects were to be randomised targeting at least 40% of subjects presenting with PE (with or without DVT).

Symptoms of DVT include erythema, warmth, pain, swelling, tenderness, and pain upon dorsiflexion of the foot. Diagnosis for the index DVT event required one of the following:

- a non-compressible vein on ultrasonography
- an intraluminal filling defect on venography
- an intraluminal filling defect on spiral/contrast computed tomography (CT) of the legs

Symptoms of PE include sudden onset dyspnoea, tachypnoea, tachycardia, syncope, hypotension, and hypoxemia. Palpitations, cough, anxiety, and light-headedness may also be present. Diagnosis for the index PE event required one of the following:

- an intraluminal filling defect on spiral CT or pulmonary angiography
- cut-off of contrast material in a vessel more than 2.5 mm in diameter on pulmonary angiography
- a perfusion defect involving at least 75% of a defect, with corresponding normal ventilation
- a non-diagnostic lung scan accompanied by documentation of new DVT by ultrasonography or venography

All specific inclusion and exclusion criteria are presented in Table B 5.

Table B 5. Eligibility criteria of participants

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Hokusai-VTE	- Aged ≥18 years - Objectively diagnosed, acute, symptomatic DVT involving the popliteal, femoral, or iliac veins requiring anticoagulant therapy - Acute, symptomatic PE (with or without DVT) requiring anticoagulant therapy - Able to provide written informed consent	- Any contraindications listed in local labelling of LMWH, UFH, or warfarin - Thrombectomy, insertion of a caval filter or use of a fibrinolytic agent to treat the current episode of DVT and/or PE - Indication for warfarin other than DVT and/or PE - >48 h pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, UFH, and fondaparinux per local labelling) or more than a single dose of a VKA prior to randomisation to treat the current episode or treatment with any investigational drug within 30 days of randomisation - CrCl <30 mL/min (calculated by the Cockcroft and Gault method) - Significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or alanine transaminase ≥2 times the upper limit of normal (ULN), or total bilirubin ≥1.5 times the ULN - Patients with active cancer for whom long-term treatment with LMWH was anticipated - Life expectancy <3 months - Active bleeding or high risk for bleeding contraindicating treatment with LMWH or warfarin - Uncontrolled hypertension as judged by investigator (e.g. systolic blood pressure >170 mmHg or diastolic blood pressure >100 mmHg despite antihypertensives) - Known history of positive hepatitis B antigen or hepatitis C antibody - Women of childbearing potential without proper contraceptive measures and women who are pregnant or breastfeeding - Patients with any condition that, as judged by the investigator, would place the patient at increased risk of harm if they participated in the study - Chronic treatment with non-steroidal anti-inflammatory drugs including both COX-1 and COX-2 inhibitors for ≥4 days/week anticipated to continue during the study - Treatment with aspirin >100 mg/day or dual antiplatelet therapy (any two antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study - Treatment with potent P-glycoprotein (P-gp) inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study - Systemic use of the strong P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin, or clarithromycin at the time of randomisation (subsequent use was permitted)

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.

A total of 8292 subjects were randomised and assigned to the edoxaban (N=4143) or warfarin (N=4149) treatment groups, and a total of 8240 subjects were treated with edoxaban (N=4118) or warfarin (N=4122). A total of 67 patients (1.6%) and 44 (1.1%) in the warfarin and edoxaban arms, respectively, were from the UK. The 8240 subjects treated comprise the mITT Analysis Set (described in section 6.3.2).

Baseline demographics

Demographic and baseline characteristics were comparable between the treatment groups including age, gender, race, presenting diagnosis, and risk factors (Table B 6):

- the mean age was 56 years, and approximately 13% of patients were aged ≥75 years
- the majority of patients were male (57%) and approximately 70% were Caucasian
- approximately 17% of patients in the mITT analysis set were recruited in Western Europe, 14% in Southern Europe, and 11% to 12% in Eastern and in Central Europe
- low body weight (≤60 kg) was recorded for ~13% of patients, and ~7% had CrCl ≥30 to ≤50 mL/min

Approximately 18% of patients in the mITT analysis set had their (edoxaban or placebo) dose reduced at randomisation, in accordance with the protocol. Patients' disease characteristics, other medical history and prior/concomitant treatments were generally comparable across the treatment groups and typical for the population under study.

Patients were also categorised into two groups based on baseline VTE representation (as confirmed by investigators): those with DVT without PE, and those with PE with/without DVT. A total of 4921 patients presented with DVT, and 3319 with PE. While the recurrent VTE risk profile of patients with DVT is considered homogenous, that of patients with PE may vary depending on the disease severity. In the Hokusai-VTE study, there were no specific clinical exclusion criteria related to PE severity other than excluding patients who were haemodynamically unstable (and which represents only a small proportion of all PE patients). Moreover, haemodynamically stable, normotensive patients can also be at high risk for recurrence and/or complications and those patients were included in Hokusai-VTE. Therefore the severity of PE was assessed at the time of entry into the study to enable patients with PE to be profiled and ensure that results obtained in the analysis were of value. Three different methods for assessing PE risk were used, as follows:

- anatomical extent of the PE (assessed at the time of the index PE), evaluated using Computer Axial Tomography (CAT) scan or perfusion scan, classified as ‘Limited’ (≤25% vasculature of a single lobe), ‘Intermediate’ (>25% vasculature of a single lobe or multiple lobes with ≤25% of entire vasculature), or ‘Extensive’ (multiple lobes with ≥25% of entire vasculature)

- biomarkers (serum N-terminal pro Brain Natriuretic Peptide [NT-proBNP]) measured in all index PE patients at baseline (morning sample) in a core laboratory (right ventricular dysfunction was defined as an NT-proBNP level ≥500 pg/mL)

- right ventricular dilatation using spiral CAT scan in a random sample of 1002 patients with index PE (right ventricular dysfunction was defined as the ratio of right ventricular diameter to left ventricular diameter ≥0.9)

Table B 6. Baseline characteristics in Hokusai-VTE, overall study group and patients according to index diagnosis (mITT analysis set)

Characteristic	Warfarin (N=4122)	Edoxaban (N=4118)	DVT only		PE ± DVT	
			Warfarin (N=2453)	Edoxaban (N=2468)	Warfarin (N=1669)	Edoxaban (N=1650)
Mean age (years±SD)	55.9±16.2	55.7±16.3	54.9±15.9	54.7±16.0	57.4±16.5	57.1±16.6
Age ≥75 years, n (%)	544 (13.2)	560 (13.6)	273 (11.1)	282 (11.4)	271 (16.2)	278 (16.8)
Male sex, n (%)	2356 (57.2)	2360 (57.3)	1481 (60.4)	1497 (60.7)	875 (52.4)	863 (52.3)
Weight, n (%)						
≤60 kg	519 (12.6)	524 (12.7)	304 (12.4)	320 (13.0)	215 (12.9)	204 (12.4)
>100 kg	654 (15.9)	611 (14.8)	379 (15.5)	360 (14.6)	275 (16.5)	251 (15.2)
Creatinine clearance, n (%), 30–50 mL/min	273 (6.6)	268 (6.5)	153 (6.2)	152 (6.2)	120 (7.2)	116 (7.0)
Patients dosed with 30 mg edoxaban (or placebo) at randomization, n (%)	719 (17.4)	733 (17.8)	411 (16.8)	425 (17.2)	308 (18.5)	308 (18.7)
Race, n (%)*						
Caucasian	2895 (70.2)	2867 (69.6)	1727 (70.4)	1695 (68.7)	1168 (70.0)	1172 (71.0)
Asian	861 (20.9)	866 (21.0)	544 (22.2)	561 (22.7)	317 (19.0)	305 (18.5)
Black or African-American	144 (3.5)	156 (3.8)	84 (3.4)	99 (4.0)	60 (3.6)	57 (3.5)
Other	215 (5.2)	220 (5.3)	97 (4.0)	109 (4.4)	118 (7.1)	111 (6.7)
Country, n (%)						
United Kingdom	67 (1.6)	44 (1.1)	-	-	-	-
Causes of DVT or PE, n (%)						
Unprovoked	2697 (65.4)	2713 (65.9)	1655 (67.5)	1666 (67.5)	1042 (62.4)	1047 (63.5)
Temporary risk factor†	1140 (27.7)	1132 (27.5)	655 (26.7)	655 (26.5)	485 (29.1)	477 (28.9)
History of cancer	393 (9.5)	378 (9.2)	205 (8.4)	209 (8.5)	188 (11.3)	169 (10.2)
Active cancer	99 (2.4)	109 (2.6)	-	-	-	-
Previous VTE	736 (17.9)	784 (19.0)	414 (16.9)	416 (16.9)	322 (19.3)	368 (22.3)
Anatomical extent of qualifying event‡, n (%)						
Limited	-	-	596 (24.3)	603 (24.4)	123 (7.4)	128 (7.8)
Intermediate	-	-	773 (31.5)	795 (32.2)	682 (40.9)	679 (41.2)
Extensive	-	-	1049 (42.8)	1035 (41.9)	778 (46.6)	743 (45.0)
Not assessable	-	-	35 (1.4)	35 (1.4)	86 (5.2)	100 (6.1)
Baseline NT pro-BNP, n (%)	-	-	-	-	1505 (90.2)	1484 (89.9)
≥500 pg/ml	-	-	-	-	484 (29.0)	454 (27.5)
Right ventricular dysfunction§, n/N (%)	-	-	-	-	179/504 (35.5)	172/498 (34.5)
Concomitant DVT, n (%)	-	-	-	-	404 (24.2)	410 (24.8)

Characteristic	Warfarin (N=4122)	Edoxaban (N=4118)	DVT only		PE ± DVT	
			Warfarin (N=2453)	Edoxaban (N=2468)	Warfarin (N=1669)	Edoxaban (N=1650)
Actual duration of treatment with study drug, n (%)						
3 months	528 (12.8)	485 (11.8)	306 (12.5)	299 (12.1)	222 (13.3)	186 (11.3)
>3 to ≤6 months	1084 (26.3)	1076 (26.1)	602 (24.5)	600 (24.3)	482 (28.9)	476 (28.9)
>6 months	2510 (60.9)	2557 (62.1)	1545 (63.0)	1569 (63.6)	965 (57.8)	988 (59.9)
12 months	1659 (40.2)	1661 (40.3)	1048 (42.7)	1054 (42.7)	611 (36.6)	607 (36.8)
Duration of study drug, mean days±SD /median	248.4±112.6 / 261	250.3±111.8 / 265	254.3±111.9 / 282	253.9±112.9 / 278	239.8±113.2 / 214	244.9±109.8 / 236
Total patient-years on study drug	2804	2822	1708	1716	1096	1107
Total patient-years of follow-up off study drug	994	970	559	565	436	405

* Not reported in 9 and 7 patients respectively

† Temporary risk factors include: recent surgery, trauma, immobilisation or oestrogen use

‡ Definitions of anatomical extent: DVT alone, defined by most proximal site: Limited – popliteal vein; Intermediate – superficial femoral vein; Extensive – common femoral or iliac vein. For patients with PE: Limited – ≤25% vasculature of a single lobe; Intermediate – >25% vasculature of a single lobe or multiple lobes with ≤25% of entire vasculature; Extensive – multiple lobes with ≥25% of entire vasculature.

§ Substudy of random sample of 1002 PE patients

Medical history

The baseline medical history was generally comparable between the edoxaban and warfarin treatment groups (Table B 7).

Table B 7. Summary of Medical History (mITT Analysis Set)

Characteristic n (%)	Edoxaban N=4118	Warfarin N=4122
History of Bleeding	25 (0.6)	37 (0.9)
Active or High Risk of Bleeding	10 (0.2)	17 (0.4)
Hypertension	1590 (38.6)	1672 (40.6)
Diabetes	422 (10.3)	442 (10.7)
Dyslipidaemia	908 (22.1)	909 (22.1)
Cardiovascular Disease	546 (13.3	576 (14.0)
Valvular Disease	133 (3.2)	147 (3.6)
Heart Rhythm Disorder	284 (6.9)	255 (6.2)
Cerebrovascular Disease	178 (4.3)	146 (3.5)
Renal Disease	291 (7.1)	303 (7.4)
Hepatic Disease	427 (10.4)	412 (10.0)
Pulmonary Disease	672 (16.3)	683 (16.6)
Rheumatoid Arthritis	87 (2.1)	100 (2.4)
Cancer	378 (9.2)	393 (9.5)
Cancer Active at Baseline	109 (2.6)	99 (2.4)
Osteoporosis	204 (5.0)	180 (4.4)
Prior Fracture	688 (16.7)	677 (16.4)
Current Alcohol Use	1391 (33.9)	1389 (33.7)
History of Smoking/Tobacco Use	1650 (40.1)	1659 (40.3)

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 primary analysis set presented in this submission is the mITT analysis set, considered for the overall period.

The **primary efficacy outcome** was incidence of symptomatic recurrent VTE (composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period.

The **primary safety outcome** was clinically relevant bleeding (i.e., composite of major bleeding or CRNM bleeding) which occurred during treatment or within 3 days after interrupting or stopping study drug. All bleeding events were adjudicated by the Clinical Events Committee.

- **Major bleeding**: overt bleeding (with one or more of a fall in haemoglobin ≥2 g/dL; leading to a transfusion of ≥2 units of packed red blood cells or whole blood; occurring in a critical site [intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal]; contributing to death

- **CRNM bleeding**: overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with any other discomfort such as pain, or impairment of activities of daily life)

The **secondary efficacy endpoint** was the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

The **secondary safety endpoint** was cases with pre-defined criteria suggesting hepatic dysfunction were evaluated and adjudicated by hepatic specialists in a blinded manner.

Other safety assessments included all bleeding, clinical laboratory assessments, vital signs, physical examinations, AEs, SAEs, deaths, and other cardiovascular events.

Additional endpoints included net clinical outcome (defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality) and net clinical benefit (defined as the composite of symptomatic recurrent VTE or major bleeding).

All efficacy and safety endpoints were suitable for evaluating a treatment in this indication, recommended by relevant and authoritative bodies, measured in appropriate ways so as to assure internal validity and remove potential for bias.

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.**

Primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses

The primary hypothesis was that heparin/edoxaban is non-inferior to heparin/warfarin in preventing recurrence of acute, symptomatic VTE following an initial index event.

Heparin/edoxaban was considered non-inferior to the standard therapy (heparin/warfarin) if the upper limit of the two-sided 95% confidence interval for the Hazard Ratio (heparin/edoxaban to standard therapy) was less than 1.5. If non-inferiority was achieved, then secondary efficacy endpoint were tested for superiority mITT set at α=0.01.

For the primary efficacy variable, the time to first event was analysed using the Cox proportional hazards model with model terms for treatment group and the following randomisation stratification factors:

- Presenting diagnosis (PE with or without DVT; DVT only)
- Baseline risk factors (temporary factors [e.g., trauma, surgery, immobilisation, oestrogen therapy, etc.]; all others)
- Need for 30 mg edoxaban/edoxaban placebo dose at randomisation (Yes, No)

Secondary efficacy and key safety endpoints were analysed using the same covariates as used in the primary Cox proportional hazards model for the primary endpoint.

Details of the power of the study and a description of sample size calculation

The study was designed to accumulate approximately 220 overall primary efficacy events in the mITT Analysis Set. The analysis sets and treatment populations are described in Section 6.3.2. Assuming equal efficacy (Hazard Ratio = 1.00), a total of 220 events gave a power of 85% to demonstrate that (LMW) heparin/edoxaban was non-inferior to the comparator, considering a relative non-inferiority margin of 1.5 (two-sided α=0.05). Based on recently completed trials, an incidence of recurrent VTE of 3.0% was expected during the study period. With these estimates 7,500 subjects were planned to be randomised to study treatment in order to accrue 220 overall primary efficacy events in the mITT Analysis Set in this event driven trial. Based on projections of the blinded, aggregate accumulated events, and through a protocol amendment, the total number of subjects ultimately randomised to treatment was 8,292 to ensure accumulation of 220 primary endpoint events in the mITT Analysis Set, Overall Study Period.

The sample size in the original protocol powered the study for both the primary efficacy analysis (mITT Analysis Set with overall events: > 90% of power) and the sensitivity analysis (PP Analysis Set with On-Treatment events: 90% of power) and was based on the expected incidence of recurrent VTE from published trials available at time. Since then several trials have been completed and the incidences of recurrent VTE were much lower. Because of this, the protocol was amended and the study was powered for the primary efficacy (non-inferiority) analysis only. Keeping the original non-inferiority margin of 1.5 and α=0.05 with 220 overall events in the mITT Analysis Set, the power of the primary efficacy (non-inferiority) analysis was lowered but was still at a reasonable level (85%).

Handling of Dropouts or Missing Data

All analyses including the primary analyses were performed on observed data only. Missing data were imputed only for sensitivity analyses as described in the analysis sections. Right censoring was applied for all time to event analyses.

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.

Pre-specified subgroup analyses were performed for the primary efficacy endpoint with the mITT population for the overall study period. Subgroups were based on characteristics including, but not limited to:

- Presenting diagnosis: PE with/without DVT, DVT only
- Age: <75 years, ≥75 years
- Gender: male, female
- Baseline risk factor: temporary, other
- Need for edoxaban 30 mg at randomisation: yes, no
- Body weight at randomisation: ≤60 kg, >60 kg; ≤100 kg, >100 kg
- CrCl at randomisation: 30–50 mL/min, >50 mL/min
- Fragile population at randomisation: age ≥75 years and/or body weight ≤50 kg and/or CrCl 30–50 mL/min
- Region and/or specific countries
- Race
- Medical history/active cancer at randomisation: yes, no
- Centre level INR percent time in therapeutic range (TTR): <60%, ≥60%; by TTR quartiles
- Initial heparin treatment duration: 0–5, 6, 7, 8–9, ≥10 days; <median (7 days), ≥median (7 days)
- Initial type of heparin treatment received: enoxaparin, UFH
- Concomitant aspirin use

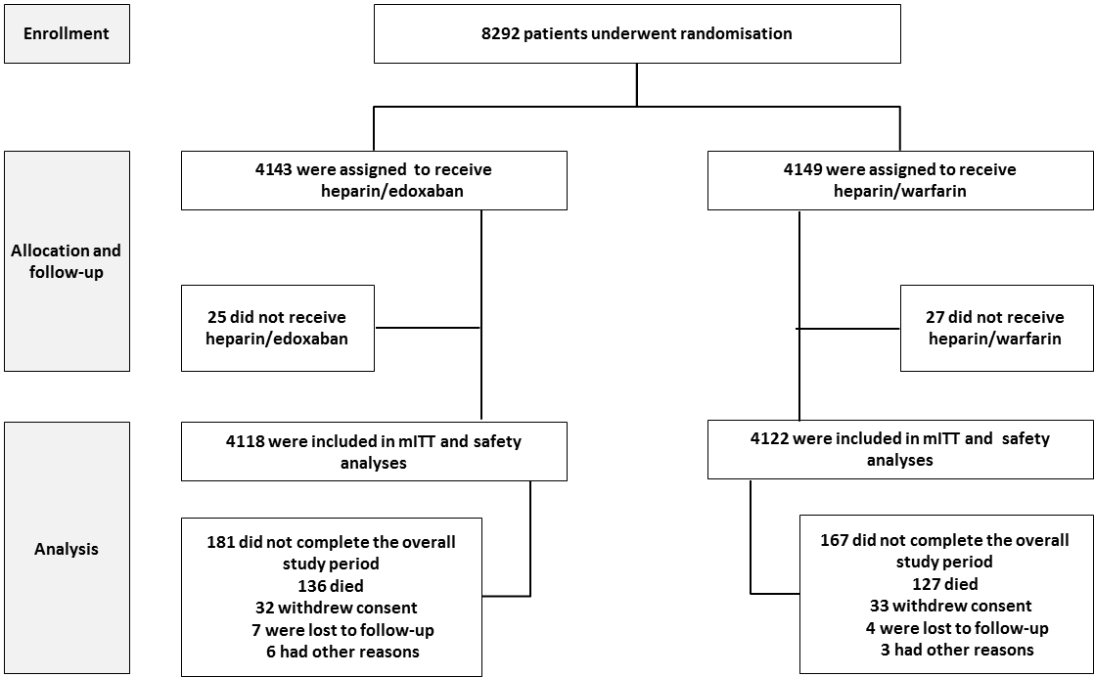
Participant flow

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.**

From January 2010 through October 2012, a total of 8292 patients were enrolled in Hokusai-VTE across 439 centres in 37 countries. A total of 4118 patients randomised to edoxaban and 4122 randomised to warfarin received at least one dose of study treatment and comprised the mITT population.

Figure B 5 presents the enrolment and study completion outcomes.

Figure B 5. Enrolment and study completion outcomes



No subjects experienced treatment misallocation; therefore the Safety population is identical to the mITT population.

In this study, subjects were allowed to interrupt and resume treatment with study drug on multiple occasions, if necessary, but all subjects were to be followed continuously until the end of the study.

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 10.3, appendix 3 for a suggested format.**

Section 9.3 Appendix 3 presents the complete quality assessment for Hokusai-VTE.

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 B 8 presents a summary of the responses applied to each of the critical appraisal criteria for Hokusai-VTE.

Table B 8. Quality assessment results for Hokusai-VTE

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

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.**

As stated in section 6.3.2, several sets (mITT, PP and Safety) and several study periods (overall study treatment[2] and on-treatment period[3]) were used to present the Hokusai-VTE clinical results. In this section, all efficacy results are presented for the mITT set, for both the overall study period and the on-treatment period.

1. **Efficacy analyses**

Primary efficacy endpoint: adjudicated recurrent VTE (mITT analysis set, overall study period)

The primary efficacy analysis (mITT analysis set, overall study period) for non-inferiority of edoxaban treatment compared to warfarin treatment for the time to the first occurrence of adjudicated symptomatic recurrent VTE is presented in Table B 9.

Table B 9. Primary efficacy endpoint: adjudicated symptomatic recurrent VTE (mITT analysis set, overall study period)

	Edoxaban N=4118	**Warfarin N=4122**
All Subjects with Recurrent VTE, n (%)	130/4118 (3.2)	146/4122 (3.5)
HR Edoxaban vs. Warfarin (95% CI)	**0.89 (0.703, 1.128)**	
p-value (for non-inferiority)	**<0.0001**	
p-value (for superiority)	0.3362	
Type of First Recurrent VTE, n (%)		
PE With/Without DVT	73 (1.8)	83 (2.0)
PE-Related Deaths	24 (0.6)	24 (0.6)
Fatal PE	4 (<0.1)	3 (<0.1)
Unexplained Death (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Non-Fatal PE	49 (1.2)	59 (1.4)
With DVT	2 (<0.1)	2 (<0.1)
Without DVT	47 (1.1)	57 (1.4)
DVT Only	57 (1.4)	63 (1.5)

Sources: (62) and reproduced from Daiichi Sankyo 2013 (63)
The HR, two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomisation stratification factors as covariates: presenting diagnosis (PE with or without DVT; DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomisation (yes/no).
Note: Events are included in the overall study period if they occurred on or after the randomisation date up to Day 365.

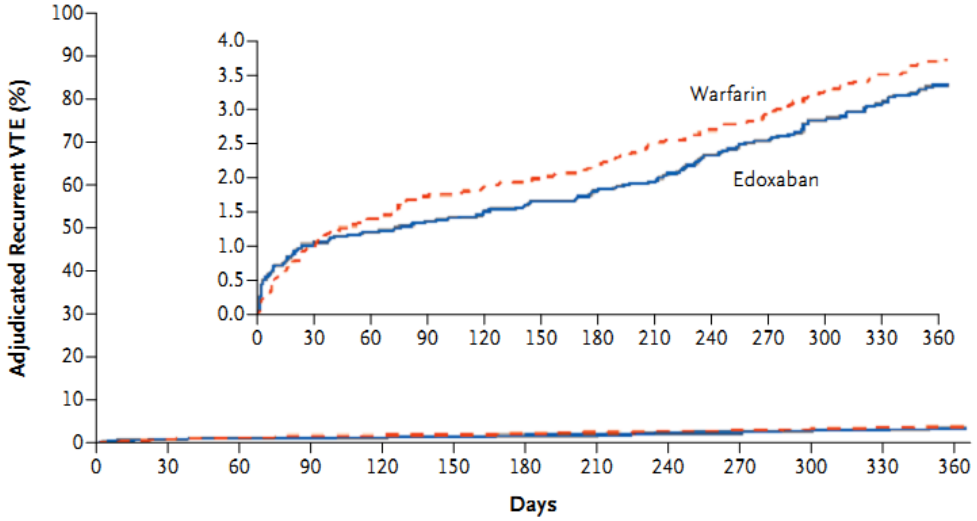
Symptomatic recurrent VTE occurred in a total of 130 subjects (3.2%) in the edoxaban group, compared to 146 (3.5%) subjects in the warfarin group, during the Overall Study Period. The Hazard Ratio for the edoxaban group vs. the warfarin group was 0.89 (95% CI: 0.703, 1.128). The upper bound of the 95% CI is 1.128, which was below the pre-specified non-inferiority margin of 1.5, and the difference

[2] The time from the reference date (randomisation date/initial dose of study drug date) to the last study follow-up visit.
[3] The time period the subject was taking study drug up to 3 days after their last dose for that time period. A subject may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study.

between edoxaban and warfarin in the time to first occurrence of adjudicated symptomatic recurrent VTE was statistically significant for non-inferiority (p<0.0001).

Kaplan-Meier cumulative event rate estimates for the primary endpoint in the mITT Analysis Set, Overall Study Period are shown in Figure B 6. Recurrent VTE events for edoxaban subjects exceeded warfarin subjects for the first 30 days, but this difference was not statistically significant. The numerical imbalance was driven by an early excess of recurrent VTE in the edoxaban subjects with index DVT (Index PE subjects with recurrent VTE in the first 10 days: 9 edoxaban vs. 7 warfarin and Index DVT subjects with recurrent VTE in the first 10 days: 21 edoxaban vs. 15 warfarin). The recurrent VTE rate for edoxaban subjects beyond 30 days falls below and remains consistently below warfarin for the remaining 12-month study period.

Figure B 6. Kaplan-Meier cumulative event rate estimates for primary efficacy endpoint (mITT analysis set, overall study period)



No. at Risk													
Edoxaban	4118	4050	4024	4002	3985	3974	3959	3885	3692	3524	3358	3190	2918
Warfarin	4112	4055	4023	4001	3992	3975	3962	3864	3683	3519	3367	3184	2936

Source: (62)

<u>Sensitivity primary efficacy endpoint</u>: adjudicated recurrent VTE (mITT analysis set, on-treatment period)

In addition, the primary efficacy outcome was evaluated for the on-treatment period (the time during which the patients were receiving the study drug or within 3 days after the study drug was stopped or interrupted). This analysis is particularly important given the design of the Hokusai-VTE study; more events occurred after the end of the on-treatment period (which could have been as short as 3 months), and were therefore counted for the analysis of the overall study period (which included events occurring up to 12 months after the randomisation).

A recurrence of VTE during the on-treatment study period occurred in 66 of 4118 patients (1.6%) in the edoxaban group and in 80 of 4122 patients (1.9%) in the warfarin group (hazard ratio with edoxaban, 0.82; 95% CI, 0.60 to 1.14; P<0.001 for non-inferiority).

This is presented in Table B 10.

Table B 10. Primary efficacy endpoint: adjudicated symptomatic recurrent VTE (mITT analysis set, on-treatment study period)

	Edoxaban N=4118	**Warfarin N=4122**
All Subjects with Recurrent VTE, n (%)	66/4118 (1.6)	80/4122 (1.9)
HR Edoxaban vs. Warfarin (95% CI)	**0.82 (0.60, 1.14)**	
p-value (for non-inferiority)	**<0.0001**	

Source: (62)

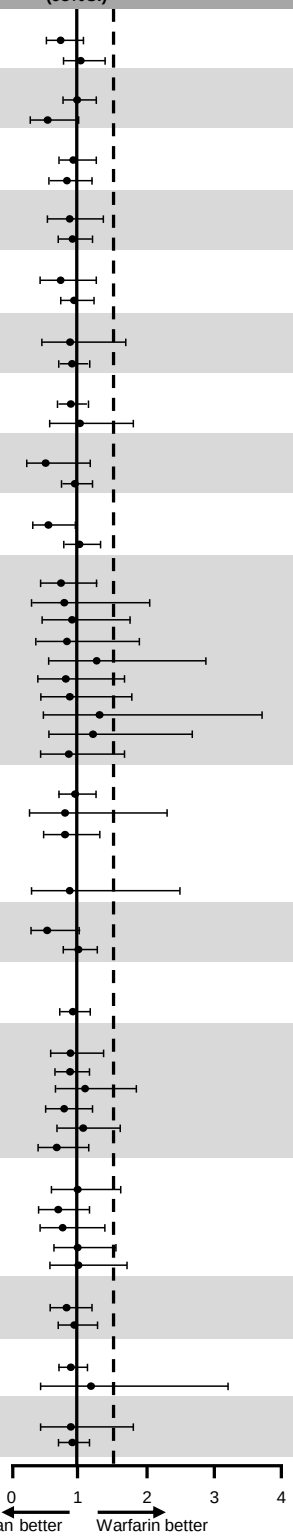
Primary efficacy endpoint in subgroups (mITT analysis set, overall study period)

Overall, the primary efficacy endpoint results were broadly consistent across the subgroups assessed. In the mITT analysis population overall study period, more than 80% of subgroup analyses favoured edoxaban (Figure B 7).

These analyses demonstrate consistency across major subgroups. Further details regarding notable subgroup results are presented below.

Figure B 7. Forest plot of primary efficacy endpoint by subgroup (mITT analysis set, overall study period)

Subgroup	Edoxaban 60 mg (30 mg dose adj) n/M	(%/yr)	Warfarin n/M	(%/yr)	P-value for interaction
Presenting diagnosis					
PE with/without DVT	47/1650	(2.8)	65/1669	(3.9)	0.1772
DVT only	83/2468	(3.4)	81/2453	(3.3)	
Age group					
<75 years	116/3558	(3.3)	119/3578	(3.3)	0.0586
≥75 years	14/560	(2.5)	27/544	(5.0)	
Gender					
Male	82/2360	(3.5)	87/2356	(3.7)	0.5810
Female	48/1758	(2.7)	59/1766	(3.3)	
Baseline risk factors					
Temporary factors	32/1132	(2.8)	38/1140	(3.3)	0.8274
All others	98/2986	(3.3)	108/2982	(3.6)	
Need for 30 mg edoxaban dose at randomisation					
Yes	22/733	(3.0)	30/719	(4.2)	0.4217
No	108/3385	(3.2)	116/3403	(3.4)	
Body weight at randomisation (IXRS)					
≤60 kg	15/524	(2.9)	18/519	(3.5)	0.8714
>60 kg	115/3594	(3.2)	128/3603	(3.6)	
Body weight at randomisation					
≤100 kg	108/3495	(3.1)	123/3455	(3.6)	0.6335
>100 kg	22/611	(3.6)	23/654	(3.5)	
Creatinine clearance at randomisation (IXRS)					
30-50 mL/min	8/268	(3.0)	16/273	(5.9)	0.1581
>50 mL/min	122/3850	(3.2)	130/3849	(3.4)	
Fragile					
Yes	18/715	(2.5)	34/706	(4.8)	0.0408
No	112/3403	(3.3)	112/3416	(3.3)	
Region					
Western Europe	22/680	(3.2)	30/679	(4.4)	0.9818
Central Europe	7/468	(1.5)	9/464	(1.9)	
Southern Europe	16/586	(2.7)	18/590	(3.1)	
Eastern Europe	10/483	(2.1)	12/485	(2.5)	
Nordic	12/174	(6.9)	10/180	(5.6)	
China/Japan	13/349	(3.7)	16/344	(4.7)	
Other Asian	14/501	(2.8)	16/503	(3.2)	
Australia/New Zealand	8/145	(5.5)	6/145	(4.1)	
South Africa/South America	13/316	(4.1)	11/312	(3.5)	
USA/Canada	15/416	(3.6)	18/420	(4.3)	
Race					
Caucasian	91/2867	(3.2)	98/2895	(3.4)	0.8264
Black or African American	6/156	(3.8)	7/144	(4.9)	
Asian	27/866	(3.1)	34/861	(3.9)	
American Indian or Alaska native	0/0	(0.0)	0/0	(0.0)	
Native Hawaiian or other Pacific Islander	0/0	(0.0)	0/0	(0.0)	
Other	6/220	(2.7)	7/211	(3.3)	
Medical history: cancer					
History of cancer	14/378	(3.7)	28/393	(7.1)	0.0734
No history of cancer	116/3740	(3.1)	118/3729	(3.2)	
Active cancer at randomisation					
Active cancer	4/109	(3.7)	7/99	(7.1)	-
No active cancer	126/4009	(3.1)	139/4023	(3.5)	
Centre-level INR percent time in therapeutic range for warfarin subjects					
<60%	38/1199	(3.2)	45/1271	(3.5)	0.9136
≥60%	89/2876	(3.1)	101/2845	(3.6)	
<25th percentile (55.82%)	28/713	(3.9)	27/748	(3.6)	
≥25th to <50th percentile (64.03%)	35/1329	(2.6)	44/1291	(3.4)	0.4678
≥50th to <75th percentile (70.41%)	41/1115	(3.7)	42/1180	(3.6)	
≥75th percentile	23/918	(2.5)	33/897	(3.7)	
Initial heparin treatment duration on or after randomisation					
0-5 days	34/870	(3.9)	24/583	(4.1)	0.4984
6 days	23/922	(2.5)	27/717	(3.8)	
7 days	18/726	(2.5)	25/749	(3.3)	
8-9 days	34/885	(3.8)	40/1011	(4.0)	
≥10 days	21/715	(2.9)	30/1062	(2.8)	
Initial heparin treatment duration					
<Median (7 days)	57/1792	(3.2)	51/1300	(3.9)	
≥Median (7 days)	73/2326	(3.1)	95/2822	(3.4)	
Initial type of heparin treatment received					
Enoxaparin	122/3958	(3.1)	138/3956	(3.5)	
UFH	8/148	(5.4)	7/151	(4.6)	
Concomitant aspirin use					
Yes	14/368	(3.8)	15/346	(4.3)	0.9779
No	116/3750	(3.1)	131/3776	(3.5)	



Source: (62)

Subgroup analyses by age, fragile status, and medical history of cancer

Table B 11 presents the results of the primary efficacy endpoint by age group, fragile status (age ≥75 years and/or body weight ≤50 kg and/or CrCl 30–50 mL/min) and medical history of cancer. These data indicate that the effect of edoxaban is maintained, even in these challenging pre-specified patient groups.

In total, 1104 patients (13.4%) were ≥75 years old; edoxaban was associated with a significant relative reduction in risk of recurrent VTE of 48%. Numerically fewer patients aged ≥65 years receiving edoxaban experienced the primary endpoint; relative risk reduction of 25%.

In total, 1421 patients (17.3%) met the fragile criteria. The primary endpoint occurred in significantly fewer patients in the edoxaban group vs warfarin, leading to a relative reduction in risk of 47%.

In total, 771 (9.4%) patients reported a history of cancer at randomisation, of which 208 patients (2.5%) reported the cancer as active. Edoxaban resulted in a lower rate of recurrent VTE compared with warfarin in patients with a history of cancer (leading to a relative reduction in risk of 47%).

Table B 11. Primary efficacy endpoint by age, fragile status, and medical history of cancer (mITT analysis set, overall study period)

Subgroup	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Age at randomisation			
<65 years	[redacted]	[redacted]	[redacted]
≥65 years			
<75 years			
≥75 years			
Fragile status*			
Cancer history			
Medical history	28/393 (7.1%)	14/378 (3.7%)	0.53 (0.278-1.002)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n/N (%). *Predefined at randomisation as age ≥75 years and/or body weight ≤50 kg, and/or CrCl 30–50 mL/min

Subgroup analyses by presenting diagnosis

Prespecified analyses of the primary efficacy outcome were performed in subgroups according to the presenting diagnosis (DVT or PE with/without DVT). Of the 3319 patients who presented with an index PE (with or without DVT), 1650 were randomised to edoxaban and 1669 to warfarin. These analyses indicate that edoxaban was non-inferior to warfarin in patients presenting with DVT or PE; furthermore, the risk of recurrence was significantly reduced in patients with more extensive PE (NT-proBNP level ≥500 pg/mL; relative risk reduction 48%; $p<0.05$).

Patients with DVT

Of the 4921 patients who presented with an index DVT only, 2468 were randomised to the edoxaban group and 2453 to the warfarin group. In these patients, the upper limits of the 95% confidence intervals of the hazard ratios for the primary outcome did not exceed the prespecified margin of 1.5. In patients presenting with an index DVT,

rates of the primary endpoint were similar between groups in each of the periods analysed. This is presented in Table B 12.

Patients with PE

In patients with an index PE, the primary endpoint occurred in numerically fewer patients receiving edoxaban than warfarin, leading to a (non-significant) relative reduction in risk of the primary endpoint of 27% (overall study period) or 40% (on-treatment period). This is presented in Table B 12.

Table B 12. Primary efficacy endpoint by presenting diagnosis (mITT analysis set, overall study period and on-treatment period)

Index diagnosis, n (%)	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Patients with index DVT*	2453/4122 (59.5)	2468/4188 (59.9)	
Overall study period	81/2453 (3.3)	83/2468 (3.4)	1.02 (0.750–1.384)
On-treatment period	50/2453 (2.0)	48/2468 (1.9)	0.96 (0.64–1.42)
Patients with index PE*	1669/4122 (40.5)	1650/4118 (40.1)	
Overall study period	65/1669 (3.9)	47/1650 (2.8)	0.73 (0.502–1.062)
On-treatment period	30/1669 (1.8)	18/1650 (1.1)	0.60 (0.34–1.08)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n/N (%). *Confirmed by CEC adjudication or by the investigator if CEC could not adjudicate.

Patients with severe PE

Additional a priori-specified analyses were performed based on three separate pre-specified criteria for PE severity (anatomic extent; NT-proBNP levels; and right ventricular dysfunction), presented in Table B 13.

[redacted].

Table B 13. Primary efficacy endpoint for patients with severe PE (mITT analysis set, overall study period)

PE severity criterion	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Anatomic Extent = extensive[a]	[redacted]	[redacted]	[redacted]
NT-proBNP ≥500 pg/mL[b]	[redacted]	[redacted]	[redacted]
Right ventricular dysfunction[c]	[redacted]	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n/N (%)
[a]Extensive extent: multiple lobes with ≥25% of entire vasculature.
[b]NT-proBNP level ≥500 pg/mL used to define right ventricular dysfunction.
[c]Defined as the ratio of right ventricular diameter to left ventricular diameter ≥0.9.

Subgroup analysis by centre level INR-TTR

Measurement of TTR indicates that the warfarin group was well managed during the study (Table B 14). The overall TTR (INR 2.0–3.0) across all patients in the study

was 63.5%. When the INR-TTR was expanded to a range of 1.8–3.2 to reflect geographic variations in warfarin clinical practice, the observed TTR was 77.1%.

Analysis of data by centre level TTR indicates that the result of the primary efficacy analysis was not driven by suboptimal management of warfarin therapy at a minority of centres. There was a similar level or risk reduction in the edoxaban group compared to the warfarin group for centres with TTR ≥60% and with TTR <60%. Moreover, there were no significant differences between edoxaban and warfarin when the data were analysed by TTR quartiles; in fact, the greatest reduction in risk (34%) was observed at centres with the best INR control.

Table B 14. Primary efficacy endpoint by centre level INR-TTR (mITT analysis set, overall study period)

TTR Subgroups	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Centres with TTR <60%	45/1271 (3.5%)	38/1199 (3.2%)	0.89 (0.574–1.364)
Centres with TTR ≥60%	101/2845 (3.6%)	89/2876 (3.1%)	0.87 (0.653–1.153)
Centres with TTR <25th percentile (55.82%)	27/748 (3.6%)	28/713 (3.9%)	1.09 (0.641–1.848)
Centres with TTR ≥25th to <50th percentile (55.82%–64.03%)	44/1291 (3.4%)	35/1329 (2.6%)	0.77 (0.496–1.205)
Centres with TTR ≥50th to <75th percentile (64.03%–70.41%)	42/1180 (3.6%)	41/1115 (3.7%)	1.05 (0.681–1.610)
Centres with TTR ≥75th percentile	33/897 (3.7%)	23/918 (2.5%)	0.66 (0.384–1.129)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n/N (%).

<u>Secondary efficacy endpoint</u>: recurrent VTE and all-cause mortality (mITT analysis set - overall study period)

The secondary efficacy analysis for superiority of edoxaban treatment compared to warfarin treatment for the time to the first occurrence of recurrent VTE and all-cause mortality, as well as the components and subcomponents of this endpoint, are presented in Table B 15 for the mITT Analysis Set, Overall Study Period.

The composite endpoint of recurrent VTE and all-cause mortality occurred in 228 of subjects (5.5%) in the edoxaban group and in 228 subjects (5.5%) in the warfarin group (HR: 1.00; 95% CI: 0.832, 1.200, p=0.9933).

All-cause mortality was reported for slightly more patients in the edoxaban group (3.0%) than with warfarin (2.6%), with the difference driven by a slightly higher incidence of other deaths (specifically, infectious disease mortality) in the edoxaban group. Fatal PE (<0.1%) and unexplained death (0.5%) were reported at the same incidence.

Table B 15. Recurrent VTE and all-cause mortality (mITT analysis set, overall study period)

	Edoxaban (n=4118)	Warfarin (n=4122)
Recurrent VTE and all-cause mortality	228 (5.5)	228 (5.5)
HR Edoxaban vs. Warfarin (95% CI)	**1.00 (0.832, 1.200)**	
p-value	**0.9933**	
Type of initial recurrent VTE or all-cause mortality		
All-cause mortality	122 (3.0)	106 (2.6)
VTE-related death	24 (<0.1)	24 (<0.1)
Fatal PE	4 (<0.1)	3 (<0.1)
Unexplained death	20 (0.5)	21 (0.5)
Other Death	98 (2.4)	82 (2.0)
Non-fatal PE	49 (1.2)	59 (1.4)
With DVT	2 (<0.1)	2 (<0.1)
Without DVT	47 (1.1)	57 (1.4)
DVT only	57 (1.4)	63 (1.5)

Source: reproduced from Daiichi Sankyo 2013 (63)
The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomisation stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo at randomisation (yes, no), p-value α =0.01 [two-sided].

Efficacy conclusions

In a broad range of patients with VTE, edoxaban was shown to be non-inferior to warfarin for the primary efficacy endpoint of symptomatic recurrent VTE.

For the primary efficacy endpoint, there was no significant difference in the time to first occurrence of adjudicated symptomatic recurrent VTE between edoxaban and warfarin in the majority of subgroups analysed.

There was also no significant difference between edoxaban and warfarin in patients presenting with DVT or PE, and in patients with more extensive PE (defined as extensive by baseline anatomic extent, or defined by presence of right ventricular dysfunction by CT at baseline).

Patients included in the Hokusai-VTE study were well managed on warfarin (TTR of 63.5%), and centre-level TTR did not affect the efficacy results.

2. Safety analysis

Treatment duration

Table B 16 depicts the actual treatment duration and treatment exposure to study drug for the Safety Analysis Set. In the edoxaban and warfarin treatment groups, the median treatment duration was comparable at 267 and 266 days, respectively. The median study drug exposure was also comparable at 265 and 261 days, respectively.

In the edoxaban and warfarin treatment groups, 11.8% and 12.8% of subjects received ≤3 months of treatment, respectively, 26.1% and 26.3% of subjects received > 3 months to 6 months of treatment respectively, 62.1% and 60.9% received more than 6 months of treatment, respectively (with 40.3% and 40.2% of subjects respectively receiving a full 12 months of treatment).

Table B 16. Treatment duration and study drug exposure (safety analysis set)

	Edoxaban N=4118	Warfarin N=4122
Duration of Actual Treatment (days)		
Mean (SD) Duration (days ± SD)	251.9 (112.04)	250.3 (113.01)
Median Duration (days)	267.0	266.0
≤3 Months (n/%)	485 (11.8)	528 (12.8)
>3 to ≤ 6 Months (n/%)	1076 (26.1)	1084 (26.3)
>6 Months (n/%)	2557 (62.1)	2510 (60.9)
≥ 12 Months (n/%)	1661 (40.3)	1659 (40.2)
Total Number of Days Exposed to Study Drug		
Mean (days ± SD)	250.3 (111.75)	248.4 (112.61)
Median (days)	265.0	261.0

Sources: (62) and reproduced from Daiichi Sankyo 2013 (63)

Permanent discontinuation of study drug (safety analysis set)

Permanent discontinuations of study drug are presented by treatment group in Table B 16. Subjects could permanently discontinue study drug at any time but were expected to still remain in follow-up to 12 months post-randomisation to complete the study.

The percentage of subjects who discontinued study drug for any reason was comparable between the edoxaban (16.9%) and warfarin (17.4%) treatment groups. Discontinuation for the composite of Suspected Endpoint/Adverse event (AE) was also comparable (8.8% and 8.9%, respectively). AEs were overall the most common single reason for study drug discontinuation (5.7% for edoxaban subjects and 5.4% for warfarin subjects).

The percentage of subjects in the edoxaban and warfarin treatment groups was also comparable for study drug permanent discontinuation for the 3, 6, and 12 month intended treatment subgroups.

Table B 17. Treatment duration and study drug exposure (safety analysis set)

	Edoxaban N=4118	Warfarin N=4122
Total Number of Subjects Completing Study Drug Treatment	3423 (83.1)	3404 (82.6)
Total Number of Subjects with Permanent Study Drug Discontinuations	695 (16.9)	718 (17.4)
Reason For Permanent Study Drug Discontinuation		
Suspected Endpoint/Adverse Event	364 (8.8)	367 (8.9)
Suspected Endpoint	138 (3.4)	158 (3.8)
Adverse Event	233 (5.7)	222 (5.4)
Elective Surgery	17 (0.4)	18 (0.4)
Concomitant Use of Prohibited Study Medication	4 (<0.1)	2 (<0.1)
Subject Withdrew Consent	21 (0.5)	22 (0.5)
Subject Lost to Follow-up	2 (<0.1)	3 (<0.1)
Pregnancy	8 (0.2)	4 (<0.1)
Protocol Violation	22 (0.5)	22 (0.5)
Other	255 (6.2)	279 (6.8)

Source: reproduced from Daiichi Sankyo 2013 (63)

<u>Primary safety endpoint:</u> adjudicated major or CRNM bleeding (safety analysis set, on-treatment study period)

The On-Treatment Study Period represented the primary period for all safety analyses, including bleeding.

Table B 18 shows that across all bleed categories, patients in the edoxaban group experienced numerically fewer bleeding events when compared with the warfarin group. Event rates for Major and CRNM bleeding were 8.5% in the edoxaban group and 10.3% in the warfarin group (HR: 0.81; 95% CI: 0.705, 0.936; p = 0.004 for superiority); edoxaban was associated with statistically significant reduction compared to warfarin for this endpoint (relative risk reduction of 19%).

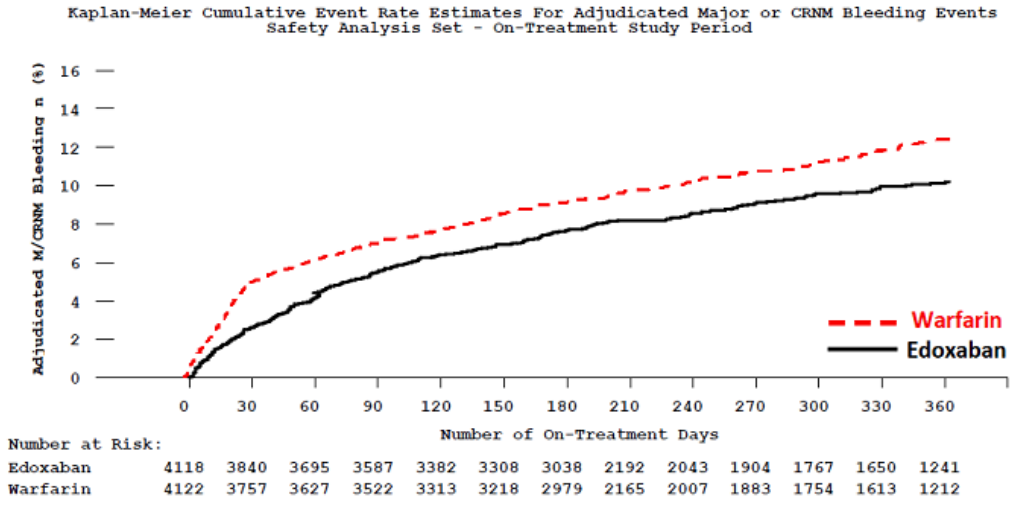
Table B 18. Primary safety endpoint: adjudicated bleeding events (safety analysis set – on-treatment study period)

	Edoxaban N=4118	**Warfarin N=4122**
Major and CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)
HR Edoxaban vs. Warfarin (95% CI)	**0.81 (0.705, 0.936)**	
p-value	**0.004**	
Major Bleeding, n (%)	56 (1.4)	66 (1.6)
HR Edoxaban vs. Warfarin (95% CI)	**0.84 (0.592, 1.205)**	
p-value	**0.3521**	
Fatal, n (%)	2 (<0.1)	10 (0.2)
CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
HR Edoxaban vs. Warfarin (95% CI)	**0.80 (0.68–0.93)**	
p-value	**0.004**	
All Bleeding, n (%)	895 (21.7)	1056 (25.6)

Sources: (62) and reproduced from Daiichi Sankyo 2013 (63)

Cumulative Kaplan-Meier event rate estimates for Major and CRNM Bleeding is displayed for the safety analysis set, on-treatment study period in Figure B 8. The edoxaban treated group had a lower event rate estimate of Major and CRNM bleeding than the warfarin treated group throughout the entire on-treatment study period.

Figure B 8. Kaplan-Meier cumulative event rate estimates for primary safety endpoint (safety analysis set, on-treatment study period)



Source: (62)

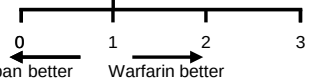
<u>Primary safety endpoint in subgroups</u> (safety analysis set, on-treatment study period)

Of the pre-specified subgroup comparisons, 49 favoured edoxaban, one was neutral (HR=1.00), two had no HR calculated (too few events), and three favoured warfarin, although the confidence interval for all three included 1.0.

Rates of bleeding events were numerically lower with edoxaban than with warfarin in the following group associated with a higher risk of bleeding: age ≥75 years; fragile status (age ≥75 years and/or body weight ≤50 kg and/or CrCl 30-50 mL/min); history of cancer or active cancer; PE with/without DVT; female gender; CrCl 30–50 mL/min; concomitant aspirin use (Figure B 9).

Figure B 9. Forest plot of principal safety by subgroup (safety analysis set, on-treatment study period)

Subgroup	Edoxaban 60 mg (30 mg dose adj) n/M (%/yr)		Warfarin n/M (%/yr)		Hazard ratio with warfarin (95%CI)	P-value for interaction
Presenting diagnosis						
PE with/without DVT	166/1650	(10.1)	187/1669	(11.2)		0.3463
DVT only	183/2468	(7.4)	236/2453	(9.6)		
Age group						
<75 years	279/3558	(7.8)	341/3578	(9.5)		0.9305
≥75 years	70/560	(12.5)	82/544	(15.1)		
Gender						
Male	144/2360	(6.1)	215/2356	(9.1)		0.0041
Female	205/1758	(11.7)	208/1766	(11.8)		
Baseline risk factors						
Temporary factors	110/1132	(9.7)	125/1140	(11.0)		0.5176
All others	239/2986	(8.0)	298/2982	(10.0)		
Need for 30 mg edoxaban dose at randomisation						
Yes	58/733	(7.9)	92/719	(12.8)		0.0695
No	291/3385	(8.6)	331/3403	(9.7)		
Body weight at randomisation (IXRS)						
≤60 kg	39/524	(7.4)	64/519	(12.3)		0.1111
>60 kg	310/3594	(8.6)	359/3603	(10.0)		
Body weight at randomisation						
≤100 kg	294/3495	(8.4)	368/3455	(10.7)		0.1470
>100 kg	54/611	(8.8)	54/654	(8.3)		
Creatinine clearance at randomisation (IXRS)						
30-50 mL/min	28/268	(10.4)	39/273	(14.3)		0.5926
>50 mL/min	321/3850	(8.3)	384/3849	(10.0)		
Fragile						
Yes	79/715	(11.0)	97/706	(13.7)		0.8759
No	270/3403	(7.9)	326/3416	(9.5)		
Region						
Western Europe	63/680	(9.3)	65/679	(9.6)		0.4667
Central Europe	29/468	(6.2)	34/464	(7.3)		
Southern Europe	56/586	(9.6)	55/590	(9.3)		
Eastern Europe	18/483	(3.7)	28/485	(5.8)		
Nordic	10/174	(5.7)	13/180	(7.2)		
China/Japan	31/349	(8.9)	47/344	(13.7)		
Other Asian	43/501	(8.6)	74/503	(14.7)		
Australia/New Zealand	19/145	(13.1)	17/145	(11.7)		
South Africa/South America	25/316	(7.9)	32/312	(10.3)		
USA/Canada	55/416	(13.2)	58/420	(13.8)		
Race						
Caucasian	236/2867	(8.2)	253/2895	(8.7)		0.0266
Black or African American	15/156	(9.6)	17/144	(11.8)		
Asian	75/866	(8.7)	125/861	(14.5)		
American Indian or Alaska native	0/0	(0.0)	0/0	(0.0)		
Native Hawaiian or other Pacific Islander	0/0	(0.0)	0/4	(0.0)		
Other	23/220	(10.5)	27/211	(12.8)		
Medical history: cancer						
History of cancer	47/378	(12.4)	74/393	(18.8)		0.1533
No history of cancer	302/3740	(8.1)	349/3729	(9.4)		
Active cancer at randomisation						
Active cancer	20/109	(18.3)	25/99	(25.3)		0.6544
No active cancer	329/4009	(8.2)	398/4023	(9.9)		
Centre-level INR percent time in therapeutic range for warfarin subjects						
<60%	83/1199	(6.9)	139/1271	(10.9)		0.0175
≥60%	265/2876	(9.2)	284/2845	(10.0)		
<25th percentile (55.82%)	47/713	(6.6)	92/748	(12.3)		0.0231
≥25th to <50th percentile (64.03%)	117/1329	(8.8)	140/1291	(10.8)		
≥50th to <75th percentile (70.41%)	95/1115	(8.5)	109/1180	(9.2)		
≥75th percentile	89/918	(9.7)	82/897	(9.1)		
Initial heparin treatment duration on or after randomisation						
0-5 days	82/870	(9.4)	63/583	(10.8)		0.6078
6 days	65/922	(7.0)	77/717	(10.7)		
7 days	56/726	(7.7)	84/749	(11.2)		
8-9 days	77/885	(8.7)	91/1011	(9.0)		
≥10 days	69/715	(9.7)	108/1062	(10.2)		
Initial heparin treatment duration						
<Median (7 days)	147/1792	(8.2)	140/1300	(10.8)		
≥Median (7 days)	202/2326	(8.7)	283/2822	(10.0)		
Initial type of heparin treatment received						
Enoxaparin	333/3958	(8.4)	403/3956	(10.2)		
UFH	16/148	(10.8)	18/151	(11.9)		
Concomitant aspirin use						
Yes	55/368	(14.9)	55/346	(15.9)		0.4628
No	294/3750	(7.8)	368/3776	(9.7)		



Source: (62)

Bleeding events by anatomic location

In the edoxaban treatment group, the incidence of bleeding events was lower or equal to that of the warfarin group at all sites except for gastrointestinal tract and vaginal bleeding events. Fatal major bleeding occurred in 2 (<0.1%) edoxaban patients versus 10 (0.2%) warfarin patients. Locations of major bleeding events are shown in Table B 19.

Table B 19. Primary safety endpoint by anatomic location (safety analysis set – on-treatment study period)

Major bleeding events in critical sites	**Warfarin (n=4122)**	**Edoxaban (n=4118)**
ICH	18 (0.4)	5 (0.1)
Fatal ICH	6 (0.1)	0
Retroperitoneal	4 (<0.1)	0
Fatal retroperitoneal	1 (<0.1)	0
Pericardial	1 (<0.1)	1 (<0.1)
Intraocular	4 (<0.1)	1 (<0.1)
Intra-articular	4 (<0.1)	4 (<0.1)
Intraspinal	1 (<0.1)	0
Other	0	2 (<0.1)
Major bleeding events in non-critical sites		
Cutaneous soft tissue	8 (0.2)	4 (<0.1)
Gastrointestinal tract	18 (0.4)	27 (0.7)
Fatal gastrointestinal tract	2 (<0.1)	1 (<0.1)
Macroscopic haematuria/urethral	1 (<0.1)	0
Puncture site	1 (<0.1)	1 (<0.1)
Vaginal	3 (0.2)	9 (0.5)
Intramuscular, no compartment syndrome	3 (<0.1)	2 (<0.1)
Fatal intramuscular	0	1 (<0.1)
Oral/pharyngeal	1 (<0.1)	0
Other (fatal)	1 (<0.1)	0

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).

Subgroup analyses by fragile status, age, and history of cancer

Table B 20 presents results for primary safety endpoint by age group, fragile status (age ≥75 years and/or body weight ≤50 kg and/or CrCl 30–50 mL/min) and history of cancer.

In total, 1421 (17.3%) met the fragile criteria. Fewer fragile patients in the edoxaban group experienced bleeding events versus warfarin, leading to a (non-significant) relative reduction in risk for edoxaban of 21%.

In total, 1104 (13.4%) were ≥75 years old. Treatment with edoxaban resulted in a relative reduction in risk of bleeding of 18%.

Treatment with edoxaban was associated with a lower rate of major and CRNM bleeding compared with warfarin. A significant relative reduction in risk of 36% was shown for patients with a history of cancer.

Table B 20. Primary safety endpoint by age group, fragile status and history of cancer (safety analysis set – on-treatment study period)

Subgroup analysis	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Fragile patients	97/706 (13.7%)	79/715 (11.0%)	0.79 (0.589-1.068)
Aged ≥75 years	82/544 (15.1%)	70/560 (12.5%)	0.82 (0.596-1.128)
Cancer diagnosis Medical history	74/393 (18.8%)	47/378 (12.4%)	0.64 (0.445-0.922)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).

Subgroup analyses by presenting diagnosis

Prespecified analyses of the principal safety outcome indicated that there was a relative reduction in risk of bleeding with edoxaban of [redacted] for patients presenting with an index PE (with/without DVT) and index DVT, respectively.

Table B 21. Primary safety endpoint by presenting diagnosis (safety analysis set – on-treatment study period)

Index diagnosis	Warfarin n/N (%)	Edoxaban n/N (%)	HR, edoxaban vs warfarin (95% CI)
Patients with index PE	[redacted]	[redacted]	[redacted]
Patients with index DVT	[redacted]	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).

Subgroup analyses by centre level INR-TTR

The overall TTR (INR 2.0–3.0) across all patients in the study was 63.5%, with 18.9% <2.0 and 17.6% >3.0. Subgroup analyses by centre-level TTR are presented below in Table B 22.

Table B 22. Primary safety endpoint by centre level INR-TTR (safety analysis set – on-treatment study period)

Subgroup analysis	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Centres with TTR <60%	139/1271 (10.9)	83/1199 (6.9)	0.61 (0.468–0.805)
Centres with TTR ≥60%	284/2845 (10.0)	265/2876 (9.2)	0.91 (0.770–1.077)
Centres with TTR <25th percentile (55.82%)	92/748 (12.3)	47/713 (6.6)	0.52 (0.366–0.738)
Centres with TTR ≥25th to <50th percentile (55.82%–64.03%)	140/1291 (10.8)	117/1329 (8.8)	0.80 (0.627–1.024)
Centres with TTR ≥50th to <75th percentile (64.03%–70.41%)	109/1180 (9.2)	95/1115 (8.5)	0.90 (0.686–1.189)
Centres with TTR ≥75th percentile	82/897 (9.1)	89/918 (9.7)	1.06 (0.786–1.439)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).

<u>Secondary safety endpoints</u>: all bleeding (safety analysis set, on-treatment study period)

Table B 23 shows investigator-confirmed bleeding events for the Safety Analysis Set On-Treatment Study Period. There were 828 (20.1%) investigator-confirmed bleeds in the edoxaban group compared with 980 (23.8%) in the warfarin group. The same trend of fewer bleeds in the edoxaban group was seen with bleeds that met serious criteria (2.7% in the edoxaban subjects compared with 3.2% in the warfarin subjects), life-threatening bleeds (0.1% in the edoxaban subjects compared with 0.3% in the warfarin subjects) and bleeds that led to hospitalisation (2.5% in the edoxaban patients compared with 2.9% in the warfarin patients).

Investigator-confirmed bleeding leading to study drug interruption was 2.9% in the edoxaban group vs. 5.2% in the warfarin group. The incidence of bleeds that led to study drug permanent discontinuation was 1.4% in both groups.

Table B 23. Investigator-confirmed bleeding events (safety analysis set, on-treatment period)

	Edoxaban (n=4118)	Warfarin (n=4122)
Any Investigator-confirmed Bleed	828 (20.1)	980 (23.8)
Met Serious Criteria (SAE)	111 (2.7)	132 (3.2)
Fatal	6 (0.1)	6 (0.1)
Life-threatening	5 (0.1)	11 (0.3)
Required/Prolonged Hospitalization	101 (2.5)	119 (2.9)
Led to Study Drug Interruption	121 (2.9)	213 (5.2)
Led to Study Drug Permanent Discontinuation	58 (1.4)	57 (1.4)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).

The number of patients who experienced intracranial bleeding was lower in edoxaban versus warfarin groups (6 vs. 18 patients). The same was observed for retroperitoneal bleeding (0 vs. 4 patients).

<u>Secondary safety endpoints</u>: major adverse cardiac events (MACE) (safety analysis set, on-treatment study period)

The composite endpoint of MACE (non-fatal MI, non-fatal stroke, non-fatal SEE, and cardiovascular death) was 1.2% in the edoxaban group and 1.0% in the warfarin group (HR: 1.22; 95% CI: 0.804, 1.854; p = 0.35).

<u>Secondary safety endpoints</u>: death (safety analysis set, on-treatment study period)

Deaths that occurred in the Safety Analysis Set, On-Treatment Study Period and in the Overall Study Period are presented in Table B 24.

All-cause mortality was comparable between the two groups: 35 (0.8%) in the edoxaban group and 33 (0.8%) in the warfarin group. Cardiovascular deaths in the edoxaban group compared with the warfarin group were 6 vs. 3, respectively, with the imbalance arising from ischemic stroke (2 vs. 0) and “other cardiac death” (3 vs. 1). In the category “Other Known Cause” deaths were 16 (0.4%) for edoxaban and

20 (0.5%) for warfarin, respectively. In this subcategory of “Other Known Cause”, cancer deaths were 4 (< 0.1%) in the edoxaban group vs. 7 (0.2%) in the warfarin group. Infectious disease was the cause of death in 7 (0.2%) subjects in the edoxaban group vs. 4 (< 0.1%) in the warfarin group, and bleeding deaths were 2 (<0.1%) in the edoxaban group and 5 (0.1%) in the warfarin group. The subcategory of all “Other” deaths was comparable between the 2 groups: 3 fatal edoxaban cases (perforated bowel, acute respiratory distress, and suicide) and 4 fatal warfarin cases (respiratory failure, motor vehicle accident, suicide, and homicide).

Table B 24. Adjudicated Primary Cause of Death (safety analysis set, on-treatment study period)

	Edoxaban (n=4118)	Warfarin (n=4122)
All Causes	35 (0.8)	33 (0.8)
VTE-Related Death	13 (0.3)	10 (0.2)
PE	2 (<0.1)	0 (0.0)
Unexplained Death (and VTE cannot be ruled out)	11 (0.3)	10 (0.2)
Cardiovascular Death	6 (0.1)	3 (<0.1)
Myocardial infarction	1 (<0.1)	2 (<0.1)
Ischemic stroke	2 (<0.1)	0 (0.0)
Systemic embolic event	0 (0.0)	0 (0.0)
Other Cardiac Death [a]	3 (<0.1)	1 (<0.1)
Other Known Cause	16 (0.4)	20 (0.5)
Cancer	4 (<0.1)	7 (0.2)
Bleeding (including Haemorrhagic Stroke)	2 (<0.1)	5 (0.1)[b]
Infectious Disease	7 (0.2)	4 (<0.1)
Other [b]	3 (<0.1)	4 (<0.1)

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).
[a] Other cardiac deaths were postoperative tamponade, heart failure, ruptured aortic aneurysm (edoxaban) and arrhythmia (warfarin).
[b] Three fatal edoxaban cases (perforated bowel, acute respiratory distress, and suicide) and four fatal warfarin cases (respiratory failure, MVA, suicide, and homicide).

Safety conclusions

Edoxaban was superior to warfarin for the principal safety endpoint (composite of major and clinically relevant non-major bleeding), and additional bleeding endpoints.

Edoxaban demonstrated broadly consistent bleeding profile across pre-specified subgroups. In subgroups typically associated with a high risk of bleeding (age ≥ 75 years, fragile status, history of cancer, presenting diagnosis), edoxaban was associated with numerically lower rates of bleeding events than warfarin.

There was no difference between edoxaban and warfarin with regards to additional safety endpoints, including major adverse cardiovascular events and with regards to all-cause mortality.

<u>Other events of interest</u>: Health-Related QoL

A total of [redacted] patients in Hokusai-VTE completed EuroQoL-5-Dimensions (EQ-5D) questionnaires. The regional distribution of these patients is shown in Table B 25.

Table B 25. Distribution of patients in Hokusai-VTE with EQ-5D-3L assessments by region

	Edoxaban	Warfarin
Western Europe	[redacted]	[redacted]
Central Europe	[redacted]	[redacted]
South Europe	[redacted]	[redacted]
Eastern Europe	[redacted]	[redacted]
Nordic	[redacted]	[redacted]
China/Japan	[redacted]	[redacted]
Other Asian	[redacted]	[redacted]
Australia-New Zealand	[redacted]	[redacted]
S Africa and S America	[redacted]	[redacted]
USA and Canada	[redacted]	[redacted]
Total	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)
Data are n (%).

The [redacted] patients returned a total of [redacted] complete EQ-5D-3L assessments at the various time points of the study.

Utility scores were determined for all patients using the UK time trade-off (TTO) value set, at baseline and at 3-month intervals thereafter. Table B 26, Table B 27 and Table B 28 show the calculated scores for patients in the two study arms at various timepoints for all patients, those with DVT only, and those with PE with or without DVT, respectively.

Table B 26. EQ-5D-3L index values by treatment group and visit (all patients in Hokusai-VTE with completed questionnaires)

	Edoxaban	Warfarin	Total
Baseline N Mean (sd)	[redacted]	[redacted]	[redacted]
3 months N Mean (sd)	[redacted]	[redacted]	[redacted]
6 months N Mean (sd)	[redacted]	[redacted]	[redacted]
9 months N Mean (sd)	[redacted]	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)

Table B 27. EQ-5D-3L index values by treatment group and visit, DVT only (all patients in Hokusai-VTE with completed questionnaires)

	Edoxaban	Warfarin	Total
Baseline N Mean (sd)	[redacted]	[redacted]	[redacted]
3 months N Mean (sd)	[redacted]	[redacted]	[redacted]
6 months N Mean (sd)	[redacted]	[redacted]	[redacted]
9 months N Mean (sd)	[redacted]	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)

Table B 28. EQ-5D-3L index values by treatment group and visit, PE with or without DVT (all patients in Hokusai-VTE with completed questionnaires)

	Edoxaban	Warfarin	Total
Baseline N Mean (sd)	[redacted]	[redacted]	[redacted]
3 months N Mean (sd)	[redacted]	[redacted]	[redacted]
6 months N Mean (sd)	[redacted]	[redacted]	[redacted]
9 months N Mean (sd)	[redacted]	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)

At baseline, the mean utility score for the [redacted] patients was approximately [redacted]. As can be seen from the tables and Figure B 10, HRQoL scores were [redacted] over the course of the study. However, there were no sufficient data to carry out an analysis of the differential effects of edoxaban and warfarin on HRQoL, nor was it possible to assign utility decrements to clinical events (e.g. bleeding or recurrence) occurring through the course of the study, with such a limited sample. These data should therefore be interpreted cautiously.

Figure B 10. Box plot of EQ-5D-3L utility scores (all patients in Hokusai-VTE with completed questionnaires)

[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)

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).**

No meta-analysis of the data obtained through the edoxaban clinical study programme has been conducted, as only 1 RCT was conducted.

However a network meta-analysis was conducted. Methodology and results are presented in Section 6.7.

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.**

Not applicable.

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.**

Not applicable.

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.

The strategies used to identify studies for use in the network meta-analysis (NMA) are shown in section 6.1.1.

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.

Identification of studies

The research question was "how do anticoagulants, including NOACs, VKAs, LMWHs, UH, indirect factor Xa inhibitors, and aspirin compare regarding efficacy and safety for the treatment and secondary prevention of VTE?"

The study selection criteria included five distinct parts, related to the populations, interventions, comparators, outcomes, and study designs of interest (PICOS), to answer the research question (
Figure B 29). For inclusion, a study must have met the population inclusion criteria, included at least one of the interventions of interest, fulfilled criteria for the comparators of interest, included at least one of the outcomes of interest, and fulfilled the study design criteria. In addition, records were restricted to full-text publications. No language restrictions were imposed.

Table B 29. PICOS criteria

Population	• VTE patients, including DVT and PE patients • Patients must have been included in the study for a newly treated VTE episode (treated for <1 month) • Subgroup analysis: PE patients only
Interventions	• Primary interventions of interest were NOACs, including direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (dabigatran) with or without initial treatment with one of the following approved parenteral anticoagulants (23;51;64) o LMWHs (certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) o UH o Indirect factor Xa inhibitors (fondaparinux, idraparinux,

	idrabiotaparinux, SR123781A) • Secondary interventions of interest included the following standard therapies: VKA (acenocoumarol, fluindione, phenindione, phenprocoumon, and warfarin) plus initial treatment with one of the above approved parenteral anticoagulants; and aspirin with or without one of the above approved parenteral anticoagulants.

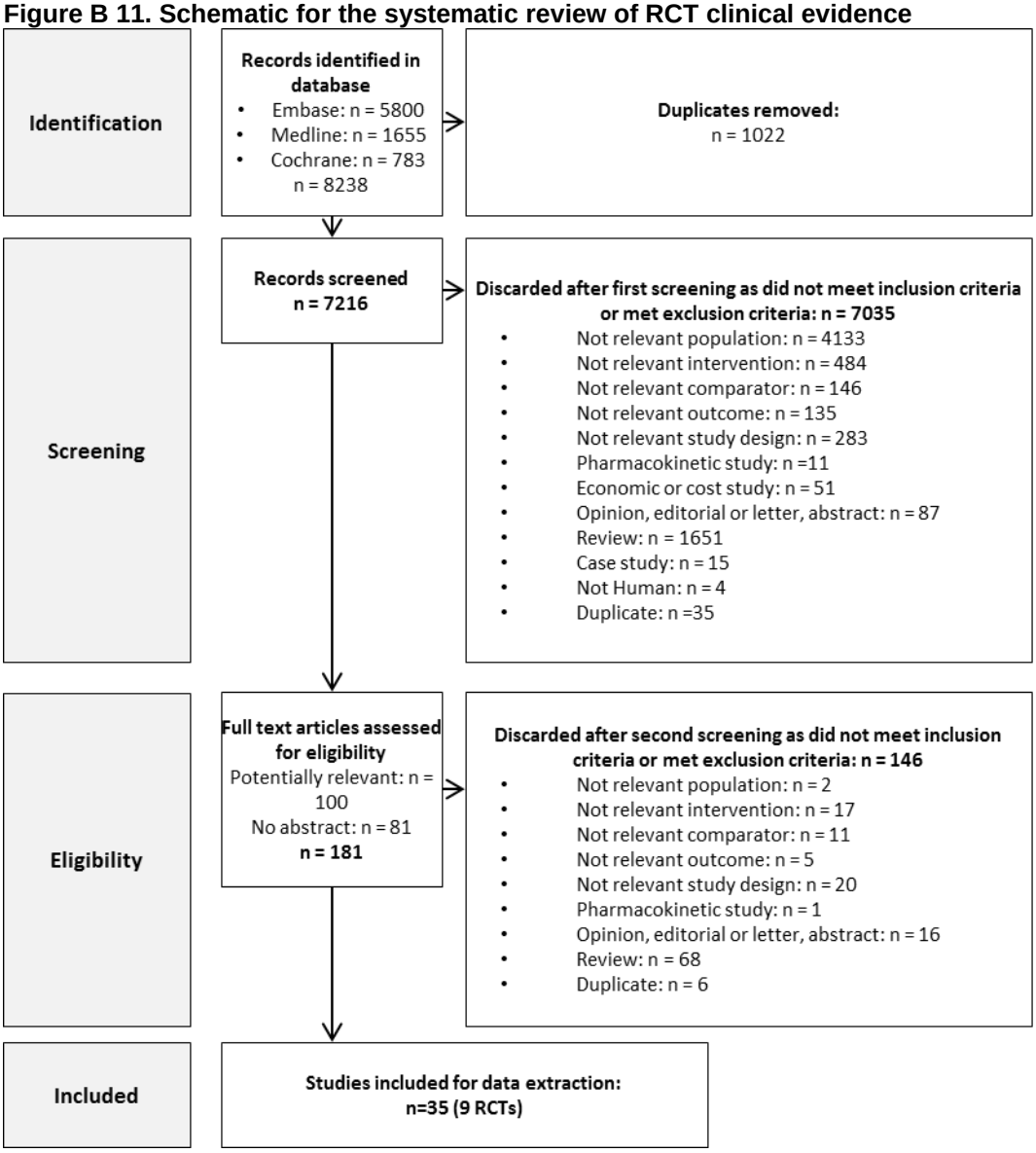
Comparators	• Eligible comparators included placebo or any active therapy providing:
	  ○ indirect or direct evidence for comparisons of primary interventions of interest Or
	  ○ direct evidence for comparisons of secondary interventions to one another or to primary interventions of interest
	• For the following drug classes, comparators were required to be from a different drug class (comparisons of different drug types, dosages, or administrations within drug classes were not allowed).
	  ○ UH
	  ○ LMWH
	  ○ Indirect factor Xa inhibitors
	  ○ Aspirin

Outcomes of interest	• Recurrent VTE (DVT, PE) • Major bleeding • CRNM bleeding • VTE-related mortality • All-cause mortality • Total adverse events • Post-thrombotic syndrome • Discontinuations • Anticoagulant-induced clotting • Cardiovascular outcomes (e.g. myocardial infarction) • Chronic thromboembolic pulmonary hypertension
Study Design	• RCTs • Phase II or Phase III RCTs (including open-label studies) • Follow-up duration of at least 3 months

Selection of studies

The process for studies selection in shown in Figure B 11.

Figure B 11. Schematic for the systematic review of RCT clinical evidence



The selection process led to the inclusion of 9 RCTs. These 9 RCTs used various fixed durations of anticoagulant treatment ranging from 84 days to 1 year. Hokusai-VTE allowed for a flexible duration of treatment, based on the physician's assessment of the patient risk profile. In order to reduce heterogeneity between studies, after careful review of the different designs, and discussion with clinicians, it was decided to carry out the indirect treatment comparison using fixed treatment duration of 6 months. This led to the exclusion from the indirect comparison of Botticelli (65), ODIXa-DVT (66) and EINSTEIN-DVT Dose-Ranging (67), which had shorter fixed treatment durations of 84 days, 12 weeks and 3 months, respectively.

AMPLIFY (68), RE-COVER I (69) and RE-COVER II (70) met the inclusion criteria since their design includes a fixed treatment duration of 6 months.

EINSTEIN-PE (71) and EINSTEIN-DVT (72) are designed with fixed treatment durations of 12 months, but 6-month data could be extracted from the Kaplan Meier curves.

A post-hoc analysis of Hokusai-VTE was conducted to provide 6-month endpoints for the on-treatment population.

A complete quality assessment for the 6 included trials (AMPLIFY, RE-COVER I, RE-COVER II, EINSTEIN-PE, EINSTEIN-DVT, Hokusai-VTE) provided in Section 9.5 Appendix 5.

Data extraction

The data extraction form included the following information:

- Study characteristics: authors, publication year, publication date, trial name, study location, number of study sites, size of study population, number of patients randomised per arm, follow-up time, end of RCT period, blinding, study phase, and types of outcome(s) reported, including time points

- Patient population/baseline characteristics: inclusion/exclusion criteria, diagnostic criteria, duration of symptoms, age, gender, weight, body mass index, type of VTE (DVT/PE/both), mean time since VTE diagnosis, duration of symptoms, first episode, recurrent episode, VTE severity, comorbidities and risk factors

- Interventions: dosage, mode of administration, frequency, duration (including bridging/initial treatments administered) and concomitant therapy

- Outcomes: Recurrent VTE, recurrent PE , recurrent DVT, composite of major and clinically-relevant non-major bleeding (‘composite bleeding’), major bleeding, CRNM bleeding, fatal bleeding, fatal intracranial bleeding, nonfatal intracranial bleeding, VTE-related death, PE-related death, death from any cause, TTR, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, chronic thromboembolic pulmonary hypertension, anticoagulant-induced clotting, cardiovascular outcomes (e.g. MI), other non-bleeding, total adverse events, withdrawals/discontinuations, AE resulting in permanent discontinuation of study drug, AE leading to or prolonging hospitalisation, net clinical benefit, and net clinical outcome

In addition, VTE recurrence, major bleeding, composite bleeding, and net clinical benefit (VTE recurrence and major bleeds) were collected for the following subgroups: patients stratified by type of VTE (DVT, PE with or without DVT), patients stratified by VTE treatment duration (3, 6, 12, ≥12 months), extensive PE, extensive DVT, unprovoked VTE (idiopathic), and patients with cancer, elderly patients, patients with renal insufficiency, and fragile patients.

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.

Table B 30 presents a summary of the six trials used to conduct the indirect comparison.

Table B 30. Summary of the trials used to conduct the indirect comparison

Study (primary ref)	Intervention	Blinding	Patient population	No randomised patients	Trial length
Edoxaban study					
Hokusai-VTE (12)	- LMWH + edoxaban - LMWH + VKA	Double blinding (initial therapy with LMWH was open-label)	VTE	8292	3-12 months
Comparator studies					
AMPLIFY (68)	- LMWH + VKA - Apixaban	Double blinding	VTE	5400	6 months
RE-COVER (70)	- LMWH + VKA - LMWH + dabigatran	Double blinding	VTE	2564	6 months
RE-COVER II (70)	- LMWH + VKA - LMWH + dabigatran	Double blinding	VTE	2568	6 months
EINSTEIN-DVT (72)	- LMWH + VKA - Rivaroxaban	Open-label, blind adjudication of outcomes	DVT	3449	3, 6, or 12 months
EINSTEIN-PE (71)	- LMWH + VKA - rivaroxaban	Open-label blind adjudication of outcomes	PE	4833	3, 6 or 12 months

In the absence of head-to-head studies, and with many important differences between the design and populations used in the NOAC pivotal trials, it is difficult to accurately compare the relative efficacy and safety of the four agents. This section is based on indirect comparative assessments of edoxaban versus other NOACs for the major efficacy and safety endpoints.

The design of Hokusai-VTE has several important differences which make comparison with the other NOAC studies difficult:

- In contrast to studies of other factor Xa inhibitors (rivaroxaban and apixaban) that used a single drug approach in the acute phase of VTE, Hokusai-VTE employed edoxaban after initial heparin therapy for at least 5 days.
- The ability to reduce edoxaban dose at randomisation or at any point during the trial is a unique feature of Hokusai-VTE among other NOAC trials.
- Hokusai-VTE is the only one of the NOAC pivotal studies to have flexible treatment duration (minimum 3 months, maximum 12 months). Therefore the study population was enriched with higher-risk patients as the duration of treatment increased. By contrast, all other studies have pre-specified fixed treatment durations.

- The rivaroxaban studies (EINSTEIN-DVT and EINSTEIN-PE) had open label designs.
- At the completion of each of the other pivotal NOAC trials, some patients entered into extension studies (NOAC vs placebo for 12 months). By contrast, Hokusai-VTE has an innovative design that rolls the treatment of VTE and prevention of recurrence into one study. This is more clinically relevant and therefore there is no need for an extension trial.

For the purpose of an indirect treatment comparison, it was more appropriate to carry out the indirect treatment comparison using estimates of event rates at 6 months for each of the studies that were included. However, taking into account these important differences listed above, any indirect treatment comparison using these studies must be interpreted with caution.

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

As stated in section 6.7.2 and 6.7.3, it was decided to carry out the network meta-analysis using a treatment duration of 6 months. A summary of data to be used is provided in the following tables, listed by population and endpoint.

1. All VTE patients

Efficacy endpoint: VTE recurrence

Table B 31. Data used in the NMA for recurrence (6 month)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen apixaban 5mg bd	71/2635 (2.69%)	59/2609 (2.26%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	27/1265 (2.13%)	30/1274 (2.35%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	28/1289 (2.17%)	30/1279 (2.35%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: Composite of Major and CRNM Bleeding

Table B 32. Data used in the NMA for Composite Bleeding (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen apixaban 5mg bd	261/2689 (9.71%)	115/2676 (4.30%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	111/1266 (8.77%)	71/1273 (5.58%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	102/1288 (7.92%)	64/1280 (5.00%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: Major Bleeding

Table B 33. Data used in the NMA for Major bleeding (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	49/2689 (1.82%)	15/2676 (0.56%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	24/1266 (1.90%)	20/1273 (1.57%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	22/1288 (1.71%)	15/1280 (1.17%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: Clinically Relevant Non-Major Bleeding

Table B 34. Data used in the NMA for Clinically Relevant Non-Major Bleeding (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	215/2689 (8.00%)	103/2676 (3.85%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	87/1266 (6.87%)	51/1273 (4.01%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	80/1288 (6.21%)	49/1280 (3.83%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: VTE related death

Table B 35. Data used in the NMA for VTE Related Death (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	16/2689 (0.60%)	12/2676 (0.45%)
RE-COVER (69)	VKA regimen vs dabigatran 150 mg bd	3/1265 (0.24%)	1/1274 (0.08%)
RE-COVER II (70)	VKA regimen vs dabigatran 150 mg bd	0/1289 (0.00%)	3/1279 (0.23%)
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Other endpoint: Net Clinical Benefit

Table B 36. Data used in the NMA for Net Clinical Benefit (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
EINSTEIN-DVT (72)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Net Clinical Benefit is defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, Major bleeding, and all-cause mortality

2. Subpopulation: PE population

Efficacy endpoint: VTE recurrence

Table B 37. Data used in the NMA for VTE Recurrence in PE population (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen apixaban 5mg bd	[redacted]	[redacted]
RE-COVER/Re-COVER II	VKA regimen vs dabigatran 150 mg bd	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: Composite of Major and CRNM Bleeding

Table B 38. Data used in the NMA for Composite Bleeding in PE population (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
RE-COVER/Re-COVER II	VKA regimen vs dabigatran 150 mg bd	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: Major Bleeding

Table B 39. Data used in the NMA of Major bleeding in PE population (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
AMPLIFY (68)	VKA regimen vs apixaban 5mg bd	[redacted]	[redacted]
RE-COVER/Re-COVER II	VKA regimen vs dabigatran 150 mg bd	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

Safety endpoint: Clinically Relevant Non-Major Bleeding

Table B 40. Data used in the NMA of Clinically Relevant Non-Major Bleeding in PE population (6 months)

Trial Name	Comparison	n/N – intervention1	n/N – intervention2
Hokusai-VTE (12)	VKA regimen vs edoxaban 60 mg od	[redacted]	[redacted]
RE-COVER/RE-COVER II	VKA regimen vs dabigatran 150 mg bd	[redacted]	[redacted]
EINSTEIN-PE (71)	VKA regimen vs rivaroxaban 20 mg od	[redacted]	[redacted]

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

A NMA was conducted to estimate the relative efficacy and safety of edoxaban compared with all treatments of interest. An advantage of this technique is that it allows for indirect comparisons to be made between pairs of treatments that have not been compared directly in clinical trials. Indeed, no RCTs comparing NOACs have been conducted.

The NMA included all treatments specified in the NICE scope; warfarin, edoxaban (60 mg once daily (OD), apixaban 5 mg twice daily (BD), dabigatran (150 mg) and rivaroxaban 20 mg OD.

Analyses were conducted in VTE population and secondary analyses were conducted in PE population. MTCs have been conducted on the following outcomes:

- Efficacy endpoints
  - VTE recurrence
- Safety endpoints
  - Composite bleeding (major and clinically relevant non major bleeding)
  - Major bleeding
  - Clinically Relevant Non Major bleeding
  - VTE-related death

- Other endpoint
    - Net clinical benefit (composite of VTE recurrence and major bleeding)

All these outcomes were extracted at 6 months from baseline, for patients on treatment. These were the primary and secondary endpoints in AMPLIFY, RE-COVER I and RE-COVER II. They were extracted from the Kaplan-Meier curves from EINSTEIN-PE and EINSTEIN-DVT which were fixed duration studies. A post-hoc analysis was conducted on Hokusai-VTE to generate these endpoints.

Methods

Bayesian NMA models were used to simultaneously synthesize the results of the included studies for each outcome of interest and to obtain relative treatment effects.(73-76) NMAs within the Bayesian framework involve data, a likelihood distribution, a model with parameters, and prior distributions.(74;75) The model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared to an overall reference treatment, i.e. the standard VKA regimen for these analyses. Based on these basic parameters, the relative efficacy between each of the competing interventions was obtained.

The NMA model used to analyse all efficacy and safety outcomes, aside from Kaplan-Meier survival curves, was the fixed effects model specified as follows:

$$\theta_{jk} = \begin{cases} \mu_{jb} & b = \mathrm{A,B,C}, \quad \text{if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \text{ alphabetically after } b \end{cases}$$

$$d_{AA} = 0$$

There are k treatments labelled as A, B, C, etc., and treatment A is taken to be the reference treatment for the analysis. μ_{jb} is the (transformed) outcome in study j on 'baseline' treatment b which will vary across studies. d_{bk} is the fixed effect of treatment k relative to 'baseline treatment' b. d_{bk} are identified by expressing them in terms of the reference treatment A: $d_{bk}=d_{Ak}-d_{Ab}$ with $d_{AA}=0$.

All analyses, apart from Kaplan-Meier survival curves, in this study concern outcomes which can be analysed as binary outcomes (i.e. VTE recurrence, bleeding outcomes, adverse events). Therefore, the following binomial likelihood function was used with a logit link function:

$r_{jk} \sim \text{binomial}(p_{jk}, n_{jk})$

For these outcomes, only fixed effects models were used, due to the limited number of studies available per comparison. The fixed effects model assumes that the differences in true relative treatment effects across studies in the network of evidence are only caused by the differences in treatment comparisons (i.e. that there is no variation in relative treatment effects for a particular pair wise comparison).(76;77)

With an NMA, randomization only holds within a trial and not across trials. As a result, there is the risk that patients who were studied in different comparisons are not similar, which leads to consistency violations. In order to minimize confounding bias, patients were analysed separately by subgroups where possible, given the limited amount of data available for meta-regression.

In order to avoid prior beliefs influencing the results of the model, non-informative prior distributions were used. Prior distributions of the relative treatment effects were normal distributions with mean 0 and a variance of 10^6. Models were run in OpenBUGS with an R interface. Model code was based on Dias 2013 and is found in section **Error! Reference source not found.**, Appendix 15.

Assessment of model convergence

The convergence of models was assessed by inspecting the Gelman and Rubin graphs using three overspread chains and checking the autocorrelation of the log-odds ratio (OR) Markov chain.

Assessment of inconsistency

The consistency assumption was based on qualitative assessment but not statistically tested.

Implementation of statistical analyses

Analyses were performed using OpenBUGS version 3.2.3 statistical software (MRC Biostatistics Unit, Cambridge, UK). These models take into account that data might come from multi-arm studies (studies with three or more arms). OpenBUGS codes used for the NMA analyses of the included outcomes are shown in section **Error! Reference source not found.**, Appendix 15.

Presentation and Interpretation of Results

The Bayesian NMA was used to obtain posterior distributions of estimates of the relative treatment effects for each primary intervention of interest, or log ORs compared to the VKA regimen, for each outcome of interest. These were transformed into ORs for ease of interpretation. The posterior distributions of the ORs were summarised with the mean and 95% credibility interval (CrI) reflecting the range of true underlying effects with 95% probability. Results are presented in a table showing ORs and 95% credible intervals for all pair-wise comparisons. Results are also presented in figures illustrating ORs and 95% CrIs for each intervention versus standard therapy and for edoxaban versus the other interventions. Results for ORs and CrIs can be interpreted using the following decision rules:

- "**More favourable**" if the OR suggests the treatment is expected to be better than the comparator (95% CrI does not include 1)
- "**Comparable**" if the 95% CrI includes 1
- "**Less favourable**" if the OR suggests the comparator is expected to be better than the treatment (95% CrI does not include 1)

6.7.6 Please present the results of the analysis.

1. Base case: patients with VTE

Efficacy endpoint: VTE recurrence

Six-month event rates for VTE recurrence were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

Edoxaban has a similar risk profile as other NOACS for VTE recurrence (OR of [redacted] vs. apixaban, OR of [redacted] vs. dabigatran, OR of [redacted] vs. rivaroxaban) and warfarin (OR of [redacted]).

Table B 41. Treatment Effects for VTE Recurrence

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

This presents the results of the MTC conducted on VTE recurrence events: the columns present the reference treatment for the OR while the rows present the comparator treatment. For example, warfarin (VKA regimen) has an OR of [redacted] compared to edoxaban with a credibility interval of [redacted] for the risk of VTE recurrence.

Figure B 12. OR for VTE recurrence of edoxaban vs. comparator

[redacted]

Safety endpoint: Composite of Major or Clinically Relevant Non Major Bleedings

Six-month event rates for composite bleedings were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

Edoxaban had a significant higher risk of composite (major or clinically relevant non major) bleeding than apixaban (OR of [redacted]) and dabigatran (OR of [redacted]). However, edoxaban has similar risk profile for composite bleeding as warfarin (OR [redacted]) and rivaroxaban (OR [redacted]).

Table B 42. Treatment Effects for Composite of Major or Clinically Relevant Non Major Bleedings

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI))	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

Figure B 13. OR for Composite of Major or Clinically Relevant Non Major Bleedings of edoxaban vs. comparator

[redacted]

Safety endpoint: Major Bleeding

Six-month event rates for major bleedings were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

Edoxaban has a significant higher risk of major bleedings compared to apixaban [redacted]. However, edoxaban shows a similar risk profile to warfarin [redacted], dabigatran [redacted] and rivaroxaban [redacted].

Table B 43. Treatment Effects for Major Bleeding

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

Figure B 14. OR for major bleeding of edoxaban vs. comparator

[redacted]

Safety endpoint: Clinically Relevant Non Major Bleeding

Six-month event rates for clinically relevant non major bleeding were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

Edoxaban had a significantly lower risk for clinically relevant non major bleeding compared to warfarin [redacted] and rivaroxaban [redacted].

Table B 44. Treatment Effects for clinically relevant non major bleeding

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

Figure B 15. OR for clinically relevant non major bleeding of edoxaban vs. comparator

[redacted]

Safety endpoint: VTE related death

Six-month event rates for VTE related death were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

Edoxaban shows a similar risk profile for VTE-related death to all the NOACs (OR of [redacted] vs. apixaban, OR of [redacted] vs. dabigatran, OR of [redacted] vs. rivaroxaban) and warfarin [redacted].

Table B 45. Treatment Effects for VTE Related Death

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

Figure B 16. OR for VTE-related death of edoxaban vs. comparator, general population

[redacted]

Other endpoint: net clinical benefit (composite of VTE recurrence events and major bleeding events)

Six-month event rates for net clinical benefit were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for rivaroxaban.

Edoxaban presents no statistically significant difference for net clinical benefit compared to warfarin [redacted] and rivaroxaban [redacted]

Table B 46. Treatment Effects for net clinical benefit

Comparator	VKA regimen	Edoxaban	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]
rivaroxaban OR (95% CrI)	[redacted]	[redacted]	

Figure B 17. OR for net clinical benefit of edoxaban vs. comparator

[redacted]

2. Subpopulation: patients with PE

Efficacy endpoint: VTE recurrence

VTE recurrence in the PE population is defined as in the overall VTE population, including fatal or non-fatal PE and/or DVT.

Six-month event rates for VTE recurrence in PE population were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

Edoxaban [redacted] for VTE recurrence in PE population. However, [redacted] compared to all the NOACs [redacted] vs. apixaban, OR of [redacted] vs. dabigatran, OR of [redacted] vs. rivaroxaban) and warfarin (OR of [redacted]).

Table B 47. Treatment Effects for VTE Recurrence (PE population)

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

Figure B 18. OR for VTE recurrence of edoxaban vs. comparator (PE population)

[redacted]

Safety endpoint: Composite of Major or Clinically Relevant Non Major Bleedings

Six-month event rates for composite bleedings were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

As for recurrence, the MTC on composite bleeding has been conducted on the PE population. The lack of available data in this population for apixaban does not allow us to compare the safety profile of edoxaban vs. apixaban. However, edoxaban [redacted] for the risk of composite bleedings in the PE population compared to warfarin (OR of [redacted]), dabigatran (OR of [redacted]) and rivaroxaban (OR of [redacted])

Table B 48. Treatment Effects for Composite Bleeding (PE population)

Comparator	VKA regimen	Edoxaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	

Figure B 19. OR for composite bleeding of edoxaban vs. comparator (PE population)

[redacted]

Safety endpoint: Major Bleeding

Six-month event rates for major bleedings were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for apixaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

As for efficacy outcomes (recurrence), the MTC of major bleeding was also run on the PE population in order to catch the specificity of this population. In this population, edoxaban [redacted] compared to apixaban ([redacted]) and rivaroxaban [redacted]. Edoxaban has [redacted].

Table B 49. Treatment Effects for Major Bleeding (PE population)

Comparator	VKA regimen	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]	[redacted]
Apixaban OR (95% CrI)	[redacted]	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]	

Figure B 20. OR for major bleeding of edoxaban vs. comparator (PE population)

[redacted]

Safety endpoint: Clinically Relevant Non Major Bleeding

Six-month event rates for clinically relevant non major bleedings were as follows: [redacted] for warfarin; [redacted] for edoxaban; [redacted] for dabigatran; [redacted] for rivaroxaban.

The analysis of the CRNMB risk has been also done on PE population. Edoxaban does not show any significant difference for the risk of CRNMB bleeding compared to warfarin (OR of [redacted]), dabigatran (OR of [redacted]) and rivaroxaban (OR of [redacted]). The profile of apixaban was not able to be compared to the other NOACs in this population due to the lack of available data.

Table B 50. Treatment Effects for clinically relevant non major bleeding (PE population)

Comparator	VKA regimen	Edoxaban	Dabigatran	Rivaroxaban
VKA regimen OR (95% CrI)		[redacted]	[redacted]	[redacted]
Edoxaban OR (95% CrI)	[redacted]		[redacted]	[redacted]
Dabigatran OR (95% CrI)	[redacted]	[redacted]		[redacted]
Rivaroxaban OR (95% CrI)	[redacted]	[redacted]	[redacted]	

Figure B 21. OR for clinically relevant non major bleeding of edoxaban vs. comparator (PE population)

[redacted]

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.

The heterogeneity between studies has not been investigated in the NMA due to the nature of the network. When examining Table B 30, there is a low number of studies having a similar design and similar comparators (maximum of two for dabigatran and rivaroxaban).

Random-effect models cannot be fitted due to the lack of information for estimating the between-study variance term. An alternative would have been to consider an informative prior for between-study variance but this kind of prior has not been found in the literature review.

Nevertheless a qualitative exploration of heterogeneity was performed. The studies were found to differ in a number of aspects such as:

- Blinding: most studies were double-blind except for the two EINSTEIN studies that were open-label
- Heparin lead-in: in the RE-COVER and Hokusai-VTE studies, not in AMPLIFY and EINSTEIN
- Duration of treatment: 6 months in RE-COVER and AMPLIFY studies, pre-specified 3, 6, or 12 months in EINSTEIN, flexible 3 to 12 months in Hokusai-VTE
- Proportion of extensive PE patients: from 24% in EINSTEIN-PE to 46% in Hokusai-VTE

These heterogeneous aspects raised the question of the appropriateness of conducting a mixed-treatment comparison. After discussion with clinicians, efforts were made to try to at least align the duration of treatment which was thought to be a driver of efficacy and safety.

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.**

No trial has been identified as a source of inconsistency.

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

Based on qualitative assessment, the NMA results for each NOAC versus warfarin are in general consistent with the direct evidence from the original pivotal trials, supporting the validity of the analysis.

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.

A systematic review for relevant non-RCTs has been described in sections 6.1 and 6.2.

Initial searches were performed in May 2014, and an updated search was conducted in December 2014, without any time span.

A complete list of the literature search strategy including search terms and filters employed are provided in Section 9.2, Appendix 2.

No RCTs were identified, therefore non-RCT evidence is not considered

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.**

A systematic review for relevant RCTs has been described in sections 6.1. Additionally safety data on edoxaban from the Hokusai-VTE study is summarised in this section.

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.**

At each visit, the Investigator or a medically qualified person determined whether any adverse event (AE) had occurred by evaluating the subject. AEs were directly observed, reported spontaneously by the subject, or identified by questioning the subject at each study visit. Treatment-emergent adverse events (TEAEs) were defined as events that started on or after the initial dose of study drug or started prior to but then worsened after the initial dose of study drug.

A treatment-emergent serious adverse event (TESAE) was a TEAE that meets one of the following:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event

Table B 51 provides an overview of TEAEs for the safety analysis set in the on-treatment and overall study period. The on-treatment study period includes all TEAES that were reported while a subject was on-treatment (the time period a subject was taking study drug or during the first three days after a study drug temporary interruption or permanent discontinuation).

The percentage of subjects in the edoxaban and warfarin treatment groups was comparable for TEAEs, and TEAEs considered severe that occurred during the On-Treatment Study Period and the Overall Study Period.

Fewer TEAEs and TESAEs in the edoxaban group were considered to be drug-related by the investigator. Subjects with TESAEs during the on-treatment study period were 503 (12.2%) in the edoxaban group vs. 544 (13.2%) in the warfarin group.

The on-treatment TESAEs that caused permanent discontinuation of study drug were 121 (2.9%) in the edoxaban group vs. 105 (2.5%) in the warfarin group. The on-treatment TESAEs that were associated with a fatal outcome were [redacted] in the edoxaban group vs. [redacted] in the warfarin group.

Table B 51. Overview of subjects with TEAEs and TESAEs (safety analysis set)

	Edoxaban (n=4118)	**Warfarin (n=4122)**
On-Treatment Period		
Subjects With TEAEs		
All	2821 (68.5)	2928 (71.0)
Drug-Related	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Subjects With TESAEs		
All	503 (12.2)	544 (13.2)
Drug-Related	[redacted]	[redacted]
With Fatal Outcome	[redacted]	[redacted]
Subjects With TEAEs That Caused Interruption of Study Drug		
All	[redacted]	[redacted]
Drug-Related	[redacted]	[redacted]
TESAEs	[redacted]	[redacted]
Subjects With TEAEs That Caused Permanent Discontinuation of Study Drug		
All	[redacted]	[redacted]
Drug-Related	41 (1.0)	51 (1.2)
TESAEs	121 (2.9)	105 (2.5)
Overall Study Period		
Subjects With TEAEs		
All	[redacted]	[redacted]
Drug-Related	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Subjects With TESAEs		
All	[redacted]	[redacted]
Drug-Related	[redacted]	[redacted]
With Fatal Outcome	[redacted]	[redacted]

Source: (62) and reproduced from Daiichi Sankyo 2013 (63)

XXX XXXXXX XX [redacted]

Table B 52 depicts the most frequently reported TEAEs (those that occurred in at least 2% of subjects by Preferred Term) for the Safety Analysis Set On-Treatment Period.

[redacted]

[redacted]

[redacted]

Table B 52. TEAEs reported by at least 2% of subjects by SOC and preferred term (safety analysis set, on-treatment period)

	Edoxaban (n=4118)	Warfarin (n=4122)

	Edoxaban (n=4118)	Warfarin (n=4122)
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
INR increased	[redacted]	[redacted]

Source: reproduced from Daiichi Sankyo 2013 (63)

[redacted]

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

Bleeding

Edoxaban was superior to warfarin for the principal safety endpoint (major or clinically relevant non-major bleeding), and additional bleeding endpoints.

Edoxaban demonstrated a consistent safety profile across pre-specified subgroups. In subgroups typically associated with a high risk of bleeding (age ≥ 75 years, fragile

status, history of cancer, presenting diagnosis), edoxaban was associated with numerically lower rates of bleeding events than warfarin.

Edoxaban was non-inferior to warfarin with regard to additional safety endpoints, including major adverse cardiovascular events and comparable with regard to all-cause mortality.

Other adverse events

The non-bleeding treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) were generally similar for both edoxaban and warfarin-treated subjects. Overall, non-bleeding TEAEs leading to study drug interruptions or discontinuations were also similar in both edoxaban and warfarin-treated subjects.

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.

The Hokusai-VTE study results demonstrate that once daily edoxaban was non-inferior to warfarin with significantly less clinically relevant bleeding in a broad spectrum of VTE subjects, including high-risk subgroups (elderly, fragile, and cancer subjects).

A total of 8292 subjects were randomised, with 4921 subjects with DVT only and 3319 subjects with PE with or without DVT in the mITT Overall Study period, comprising the largest single comparative VTE trial to date with a non-VKA oral anticoagulant.

Mean overall TTR for warfarin subjects was 63.5%. The number of subjects lost to follow-up was low (less than 0.2%), as was the rate of subjects withdrawing consent (less than 0.9%).

Notable features of this trial included: flexible treatment duration; follow-up to 12 months; dose reductions for subjects with low body weight, moderate renal impairment, and concomitant use of select P-gp inhibitors; enrolment and physiologic characterisation of subjects with more severe PE.

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

Strengths

Hokusai-VTE phase 3 programme for edoxaban was randomised, double-blind parallel-group trial, and included a total of 8292 patients with VTE at 439 centres in 37 countries), to ensure different cultures were represented.

The study enrolled a representative VTE population. Subjects with both provoked and unprovoked VTE were included. The Hokusai-VTE trial included a broader spectrum of VTE patients (ranging from limited proximal DVT to severe PE) compared to those

included in other recent oral anticoagulant trials, including a large subgroup (30%) of patients with PE and right ventricular dysfunction, and another subgroup (20%) at high risk for bleeding due to renal impairment and low body weight. A total of 4921 patients presented with DVT and 3319 with PE, ranging from limited proximal DVT to severe PE. Notably, the study had more patients with extensive VTE compared with other NOAC studies (42% of DVT patients had involvement of common femoral or iliac vein and 46% of PE patients had involvement of multiple lobes with 25% or more of the entire pulmonary vasculature).

Hokusai-VTE compared heparin/edoxaban to heparin/warfarin. VKAs (such as warfarin) are the gold standard for treatment of VTE and prevention of recurrent VTE, and are recognised by international guidelines. Warfarin was therefore an appropriate comparator to use for edoxaban in this indication. To ensure best practice with the comparator, the quality of warfarin therapy was proactively monitored throughout the study. Among patients receiving warfarin in the Hokusai-VTE study, the time in the therapeutic range was 63.5%, which is a higher percentage of time in the therapeutic range than the 40-50% seen in registries of clinical practice.(78;79) Hence, it is possible that event rates reported in the warfarin arm of the trial overestimate the potential performance in real world clinical practice.

However, the study was designed to reflect clinical practice using flexible treatment duration of 3 to 12 months. The minimum of 3 month duration is consistent with American College of Chest Physicians Guidelines.(23;64;80;81) After these 3 months, physicians were allowed to adjust the duration of treatment according to their clinical judgment or in keeping with evolving evidence. Moreover, efficacy of edoxaban was evaluated at 12 months of follow- up, regardless of the duration of treatment (a study design that is different from that of other NOAC studies). The number of subjects lost to follow-up was very low (less than 0.2%), as was the rate of subjects withdrawing consent (less than 0.9%).

In contrast to other factor Xa inhibitor studies, Hokusai-VTE used edoxaban after initial heparin therapy. This design resembles the usual practice worldwide given the widespread acceptance and confidence in acute heparin therapy (especially in patients with extensive PE).

An additional unique feature of this trial, was to halve the edoxaban dose from 60 mg to 30 mg OD for subjects with decreased renal function, low body weight, and/or use of concomitant P-gp inhibitors in order to maintain a comparable exposure to the 60 mg dose. It is important to note that the edoxaban subjects who qualified for and received a half dose of edoxaban (30 mg) had similar recurrent VTE rates as the standard edoxaban 60 mg subjects.

For the primary efficacy analysis, the study demonstrated the non-inferiority of edoxaban vs. the current standard of care. There was no significant difference in the time to first occurrence of adjudicated symptomatic recurrent VTE between edoxaban and warfarin in the majority of subgroups analysed. Additionally, edoxaban was superior to warfarin for the principal safety endpoint (composite of major and clinically relevant non-major bleeding), and additional bleeding endpoints. Finally, there was no difference between edoxaban and warfarin with regards to additional safety

endpoints, including major adverse cardiovascular events and with regards to all-cause mortality.

Limitations

Three recent studies focused on a single-drug approach for all treatment phases.(68;71;72) Thus, the use of the traditional sequence of a heparin lead-in followed by an oral agent may be considered a limitation of the Hokusai-VTE study. However, given the global acceptance of, and confidence in initial parenteral treatment, the parenteral heparin encouraged investigators to enrol a high proportion of patients with severe grades 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.

Hokusai-VTE is relevant to the scope of this appraisal. This study compares edoxaban with the current standard of care, warfarin. The population evaluated in Hokusai-VTE is representative of the population that would receive the product after marketing authorisation and similar to the population evaluated in other NOAC trials. Hokusai-VTE included 111 patients from the UK, accounting for 1.34% of the study population.

The outcomes measures are standard objective endpoints used in the assessment of the response to treatment in VTE patients.

The evidence base demonstrates that the edoxaban regimen is a safe and effective alternative to the current standard of care, warfarin, to treat and prevent DVT and PE in subjects with VTE and supports the use of edoxaban in different populations relevant to the decision problem.

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?

Patients recruited into Hokusai-VTE trial are representative of that likely to be seen in clinical practice.

The PREFER in VTE study is a prospective observational study aiming to gain detailed insight on the characteristics and management of patients with VTE in Europe.(58) 3132 patients were enrolled in 7 European countries in January 2013. The population from Hokusai-VTE and the UK subgroup population from PREFER in VTE have similar clinical characteristics:

- Median age (55.8 years old and 58.7 years old, respectively)
- Male proportion (57.2% and 63.0%, respectively)

Moreover, Hokusai-VTE was designed to reflect clinical practice using flexible treatment duration of 3 to 12 months. The minimum of 3 month duration is consistent with American College of Chest Physicians Guidelines.(23;64;80;81) After these 3 months, physicians were allowed to adjust the duration of treatment according to their clinical judgment or in keeping with evolving evidence.

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 section 10.10, appendix 10.**

A systematic literature review was conducted to identify cost-effectiveness studies relevant to the submission. The main objective of the study identification was to collect literature cost-effectiveness analyses involving NOACs or VKA in the treatment of VTE in an adult population.

The search was performed using Medline, Embase, the Cochrane Library and Econlit.

Initial searches were performed in May 2014, and updates were conducted in December 2014. The searches were conducted with no time limits.

Keywords used in the search strategy were defined according to the decision problem with a wide scope, to ensure that the maximum amount of relevant articles was detected in the search.

The population of interest was adults with VTE (including DVT and PE). Articles relating to cost-effectiveness of NOACs and VKAs were included. No restriction on comparators had been planned. Only cost-effectiveness and cost studies were selected in the search.

The complete search strategy is provided in section 9.10, appendix 10.

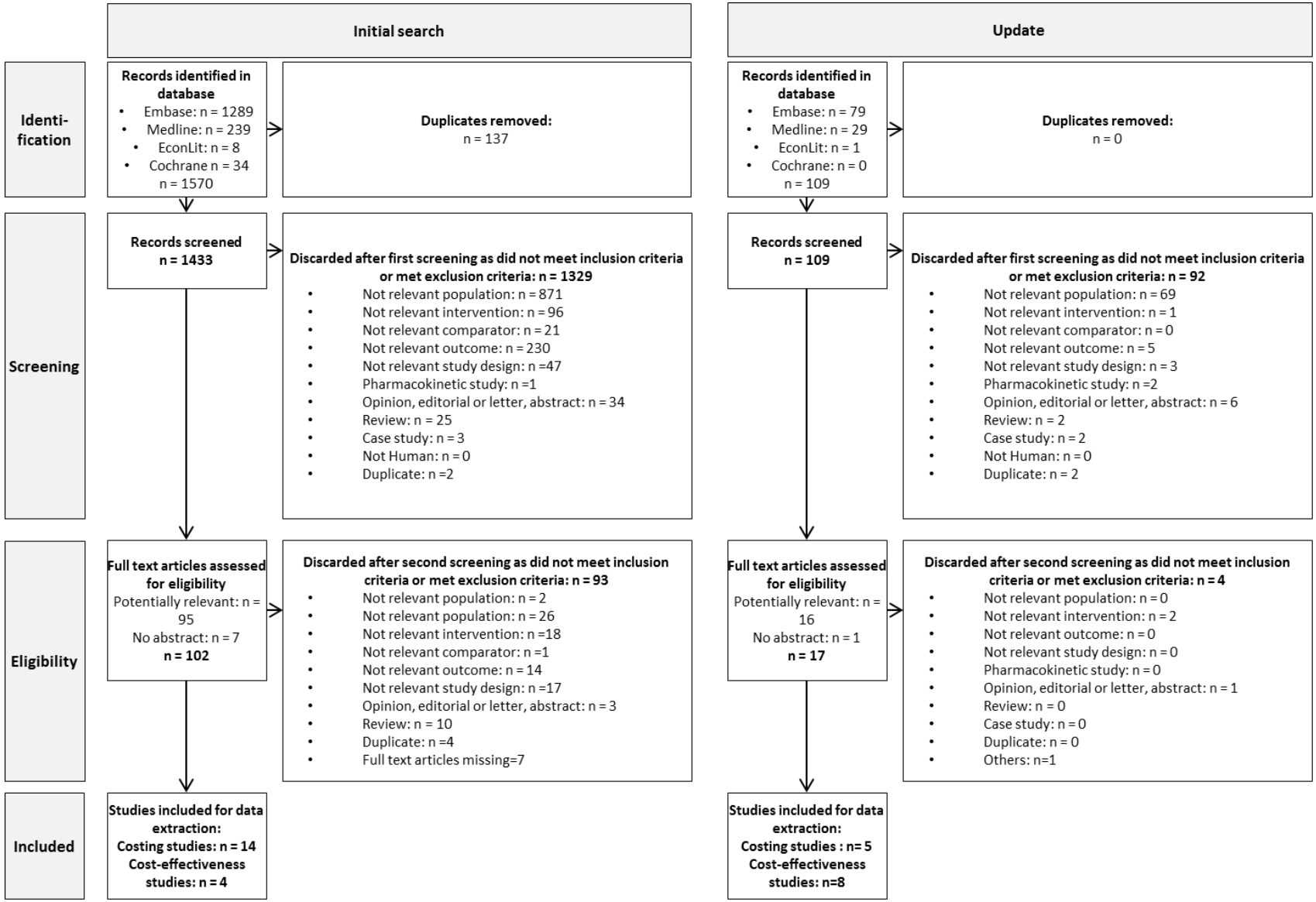
The search strategy to identify relevant articles was designed using the PICOS (population, intervention, comparator, outcome, study) methodology. The list of criteria is provided in Table B 53.

Table B 53. Inclusion/exclusion criteria (PICOS)

Elements	Inclusion	Exclusion
Population (P)	• Adults (≥18 years) with DVT and/or PE	• Children • Patients after surgery i.e. hip or knee replacement surgery
Interventions (I)	• NOACs: Direct thrombin inhibitors i.e. dabigatran • NOACs: Factor Xa inhibitors i.e. apixaban, rivaroxaban, edoxaban. • Coumarins/Vitamin K antagonists (VKA) i.e. Warfarin	• Studies not investigating edoxaban or relevant comparator
Comparators (C)	• All interventions listed above and Heparin i.e. LMWH, UFH	• No restriction on comparator
Outcomes (O)	• Cost studies: Total and sector specific (e.g. healthcare) costs and major resource quantities (e.g. length of hospital stay) • CEAs/CUAs: Economic model summary, effectiveness (i.e. QALYs), ICER and probability cost effective (at specified ICER threshold)	• No restriction outcomes
Study designs (S)	• CEA/CUA studies including decision analytic modelling studies (decision tree/Markov type (state transition)/discrete event simulation) and within trial analyses • Cost studies • Budget impact analyses	• Case report studies

The article selection process is summed up in Figure B 22.

Figure B 22. PRISMA diagram for inclusion and exclusion of studies (initial search and update)



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.**

A summary of the references included in this review is provided in Table B 54. These studies evaluated currently available pharmacological interventions in an active comparator setting, and were deemed relevant to this submission.

Twelve cost-effectiveness analyses were reviewed. The selected analyses were performed in US, Canada, UK, Colombia, Italy and Portugal. All analyses used Markov models.

Five studies evaluated the cost-effectiveness of rivaroxaban vs. another comparator (enoxaparin, placebo and warfarin), two studies evaluated the cost-effectiveness of dabigatran vs. warfarin and one study evaluated the cost-effectiveness of apixaban vs. warfarin. The remaining studies compared different treatment strategies.

The average patient age in the studies ranged between 56 and 64 years old, which corresponds to the average age of patients with VTE in clinical practice. The outcome of interest in each of the identified studies was the QALY.

None of the studies were directly relevant to the economic problem, since none included edoxaban. However, rivaroxaban is the intervention of interest in several cost-effectiveness analyses, and is one of the comparators in the edoxaban cost-effectiveness model submitted to NICE. Warfarin was often a comparator in the cost-effectiveness models included in the review, and is also one of the primary comparators used in the edoxaban cost-effectiveness model.

Several studies were performed in UK (82-87), therefore results that were obtained are potentially relevant to health evaluations in England and Wales. However, none of these studies have been published in a peer-reviewed journal. This lowers the credibility around these studies.

Table B 54. Summary list of other cost-effectiveness evaluations

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Lefebvre (88)	2014	US	• Rivaroxaban • Enoxaparin+VKA	• A 9 health states Markov model with 3-month cycle length, over a 5-year time horizon • To evaluate the costs, QALYs, and IERs associated with rivaroxaban compared to enoxaparin+VKA in adult patients treated for acute DVT or PE. • Transition probabilities were obtained from the EINSTEIN trials during treatment and published literature (observational studies).	56 (DVT) 58 (PE)	Discounted QALYs (5-years) • Rivaroxaban = 3.8486 • Enoxaparin + VKA = 3.8427	Discounted costs per patient ($): • Rivaroxaban= 13,806 • Enoxaparin + VKA = 16,253	ICER= $192,071/QALY (incremental cost of $1,118 when rivaroxaban index LOS was longer by 1 day)
Seaman (89)	2013	US	• Rivaroxaban • Warfarin	• Five states Markov model, monthly cycle, 10-year timeframe. States: Well, recurrent VTE, Major/Minor Bleed, Intracranial haemorrhage, Dead • To assess the CE of rivaroxaban compared with warfarin in the prevention of recurrent VTE • Cost estimates were derived from the Healthcare and Utilization Project and other sources. Probabilities were based on literature values (EINSTEIN-PE trial). Utilities for rivaroxaban and warfarin use were based on data from the medical literature	60	Discounted total QALYs (10-years) • Rivaroxaban= 9.29 • Warfarin= 9.14	Costs ($) • Rivaroxaban= $3,195 • Warfarin= $6,188	Rivaroxaban dominates warfarin
Wolowacz (82)	2013	UK	• Dabigatran (150 mg twice daily, oral) • No treatment (placebo)	• Markov model with a cycle length of 1 month. The time horizon was expected remaining lifetime (up to 60 years). • Adverse events that may occur in any health state during the active treatment period were modelled. • Health States: index VTE, PE (with coexisting health states), Proximal DVT, Distal DVT, Dead. Adverse events caused by the treatments are also modelled.	NR	Discounted QALYs (lifetime) • dabigatran = 13.088 • Placebo = 13.070	Costs (£) • dabigatran = £7,152 • Placebo = £7,520	Dabigatran dominates placebo

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				• Efficacy, safety parameters, and model probabilities were based on the RE-SONATE study. Other costs were taken from NHS Reference Costs or the published literature.				
Santos (90)	2014	Portugal	• Rivaroxaban • Enoxaparin/warfarin	• A Markov model was developed for 5 year time-horizon with 3% discount. • To project the long-term costs and outcomes for rivaroxaban compared to standard of care in Portugal for the treatment and secondary prevention of VTE. • The model was based on the results of the EINSTEIN-DVT and EINSTEIN-PE clinical trials, with long-term complications of treatment and utility values derived from published literature.	56-58	• Base-case: *DVT indication • Rivaroxaban 3.637 • LMWH/VKA 3.637 * PE indication • Rivaroxaban 3.585 • LMWH/VKA 3.581 • DVT – cost-minimisation analysis with LOS reduction • Rivaroxaban 3.637 • LMWH/VKA 3.637 • PE – cost-minimisation analysis without LOS reduction • Rivaroxaban 3.581 • LMWH/VKA 3.581 • PE – cost-effectiveness analysis with LOS reduction • Rivaroxaban	• Base-case: *DVT indication Total cost (€) • Rivaroxaban €4406 • LMWH/VKA €4728 Drug cost (€) • Rivaroxaban €597 • LMWH/VKA €87 Monitoring cost (€) • Rivaroxaban €133 • LMWH/VKA €953 Event costs (€) • Rivaroxaban €2814 • LMWH/VKA €2814 Bleed cost (€) • Rivaroxaban €63 • LMWH/VKA €74 PST/CTEPH (€) • Rivaroxaban €799 • LMWH/VKA €799	• Base case: Versus LMWH/VKA Rivaroxaban is dominant • PE – cost-effectiveness analysis with length of stay reduction ICER (€/QALY) Rivaroxaban is Dominant • VTE cross-indication analysis ICER (€/QALY) Rivaroxaban is Dominant

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						3.585 • LMWH/VKA 3.581 • <u>PE – cost-minimisation analysis with LOS reduction</u> • Rivaroxaban 3.581 • LMWH/VKA 3.581 • <u>VTE cross-indication analysis</u> • Rivaroxaban 3.620 • LMWH/VKA 3.619	* PE indication Total cost (€) • Rivaroxaban €8311 • LMWH/VKA €8604 Drug cost (€) • Rivaroxaban €670 • LMWH/VKA €89 * Monitoring cost (€) • Rivaroxaban €151 • LMWH/VKA €972 Event costs (€) • Rivaroxaban €5360 • LMWH/VKA €5358 Bleed cost (€) • Rivaroxaban €73 • LMWH/VKA €131 PST/CTEPH (€) • Rivaroxaban €2057 • LMWH/VKA €2053 • <u>DVT – cost-minimisation analysis with LOS reduction</u> • Rivaroxaban €4253	

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
							• LMWH/VKA €4728 • PE – cost-minimisation analysis without LOS reduction • Rivaroxaban €8344 • LMWH/VKA €8604 • PE – cost-effectiveness analysis with LOS reduction • Rivaroxaban €8102 • LMWH/VKA €8604 • PE – cost-minimisation analysis with LOS reduction • Rivaroxaban €8135 • LMWH/VKA €8604 • VTE cross-indication analysis • Rivaroxaban €5708 • LMWH/VKA €6020	
Coleman (80)	2014	US	• Rivaroxaban (20 mg once daily) • Placebo	• A Markov model with 16 health states. In addition, seven AC temporary disruption and eight re-initiation health states were also modelled. • Cycle length was one month, time	58	40 Year Time horizon (Base-case) • Rivaroxaban 16.167 • Placebo	40 Year time horizon (Base-case) • Rivaroxaban $22.645 • Placebo $22.083	40 Year time horizon (Base-case) • Rivaroxaban versus placebo $17.030

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				frame was 40 years. • To estimate the cost-effectiveness of extended duration rivaroxaban, 20 mg daily, compared to placebo using a Medicare perspective. • Transition probabilities between health states were derived using standard methods from the EINSTEIN-Extension trial data and other sources identified through the Tufts Cost-Effectiveness Analysis registry and a Medline database search.		16.134 35 Year Time horizon • Rivaroxaban 16.016 • Placebo 15.982 30 Year Time horizon • Rivaroxaban 15.574 • Placebo 15.541 25 Year time horizon • Rivaroxaban 14.665 • Placebo 14.634 20 Year Time horizon • Rivaroxaban 13.176 • Placebo 13.148 15 Year time horizon • Rivaroxaban 11.031 • Placebo 11.007 10 Year time horizon • Rivaroxaban 8.170 • Placebo 8.152	35 Year time horizon • Rivaroxaban $22.251 • Placebo $21.685 30 Year time horizon • Rivaroxaban $21.179 • Placebo $20.600 25 Year time horizon • Rivaroxaban $19.157 • Placebo $18.543 20 Year time horizon • Rivaroxaban $16.186 • Placebo $15.550 15 Year time horizon • Rivaroxaban $12.490 • Placebo $11.675 10 Year time horizon • Rivaroxaban $8.473 • Placebo $7.445 5 Year time horizon	35 Year time horizon • Rivaroxaban versus placebo $16.918 30 Year time horizon • Rivaroxaban versus placebo $17.697/QALY 25 Year time horizon • Rivaroxaban versus placebo $19.703/QALY 20 Year time horizon • Rivaroxaban versus placebo $24.119/QALY 15 Year time horizon • Rivaroxaban versus placebo $33.627/QALY 10 Year time horizon • Rivaroxaban versus placebo $56.562/QALY 5 Year time horizon • Rivaroxaban versus placebo $139.811/QALY

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						5 Year time horizon • Rivaroxaban 4.522 • Placebo 4.512	• Rivaroxaban $4.734 • Placebo $3.374	
Jugrin (83)	2014	UK	• Dabigatran (150 mg twice daily) • Warfarin (dose-adjusted)	• A life-time Markov state-transition cohort model was developed around the two primary composite endpoints in the pivotal trials: recurrent VTE and VTE-related death (rVTE), and major or clinically relevant bleeding (MCRB). • To assess the cost-effectiveness of dabigatran (150 mg twice daily) compared with warfarin (dose-adjusted) in the treatment and secondary prevention of acute VTE comprising DVT and PE from NHS and public Social services perspectives. • Intervention-specific probabilities of events were sourced from the pivotal trials. Beyond the trials follow-up period, the probability of rVTE was sourced from the literature.	Not reported	Not reported	Not reported	• Index DVT: £614 /QALY • Index PE: £1,285 /QALY • Pooled DVT/PE : £862 /QALY • Treatment followed by secondary prevention analysis: £8,319 /QALY.
Jugrin (84)	2014	UK	• Dabigatran • Warfarin • Rivaroxaban	• A life-time Markov model was developed that includes the following health states: recurrent VTE, major bleed, clinically-relevant non-major bleed, chronic thromboembolic pulmonary hypertension, and death. • To assess the cost-effectiveness of dabigatran etexilate for six months of treatment for acute PE compared with warfarin and rivaroxaban from NHS and public Social services • Transition rates among health states were based upon AMPLIFY and AMPLIFY-EXT clinical trial data, network meta-analyses, discontinuation	Not reported	Not reported	Not reported	Dabigatran versus • Warfarin: £1,285/QALY • Rivaroxaban : Dabigatran dominant

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				due to clinical events, and UK life tables. • Costs were from UK NHS Healthcare Resource Group tables				
Jugrin (85)	2014	UK	• Dabigatran • Rivaroxaban	• A life-time Markov model was developed, populated with data from pooled RE-COVER and RE-COVER II dabigatran trials and the 6 months treatment duration subgroup of the rivaroxaban EINSTEIN-DVT and EINSTEIN-PE trials • To assess the cost-effectiveness of dabigatran comapered to rivaroxaban over a 6 months treatment course with acute VTE in the UK health care setting • Utility values for modelled health states were EQ-5D data from RE-COVER studies, and published data.	Not reported	Not reported	Not reported	Dabigatran dominate ICER= £30,000/QALY gained
Rosselli (91)	2014	Colombia	• Dabigatran • Rivaroxaban • Apixaban • LMWH	• Markov decision model for a 5-year time horizon; with analysis for 6 months, 1 year and lifetime. • To evaluate cost-effectiveness of dabigatran and NOAC compared to currently reimbursed warfarin and LMWH for thromboembolic events • Efficacy, utilities and safety inputs were from clinical trials (CT) (RE-COVER I and II; EINSTEIN- DVT; EINSTEIN-PE; AMPLIFY; RE-SONATE; RE-MEDY and a meta-analysis of 18 CT for LMWH • Cost of medication was obtained from SISMED, Vademecum Med, and government reference prices; • Costs of events were estimated from hospital billing records, POS tariffs, SOAT Manual and local experts • Costs are reported in euros (1 = COP	Not reported	Not reported	Not reported	Dabigatran versus • Warfarin : €32,121/QALY • Rivaroxaban: €36,388/ QALY • Apixaban: €72,228/QALY • LMWH: €604,515/QALY

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				2,655)				
Lanitis (86)	2014	UK	• Apixaban • Rivaroxaban • Dabigatran • LMWH/VKA	• A life-time Markov model was developed with different health states: recurrent VTE, major bleed, clinically-relevant non-major bleed, chronic thromboembolic pulmonary hypertension, and death. • To evaluate the cost-effectiveness of apixaban compared to other NOACs and LMWH/warfarin from the perspective of the UK National Health Service • Transition rates among health states were based upon AMPLIFY and AMPLIFY-EXT clinical trial data, network meta-analyses, discontinuation due to clinical events, and UK life tables. • Costs were from UK NHS Healthcare Resource Group tables and utilities were from published literature.	Not reported	Not reported	Not reported	Apixaban versus • Dabigatran £2,781/QALY • Rivaroxaban £619/QALY • LMWH/VKA £10,820/QALY
Lanitis (87)	2014	UK	• Apixaban • LMWH/warfarin	• A life-time Markov model was developed to evaluate the lifetime clinical and economic impact of six-month treatment of patients following a VTE event with apixaban versus other NOACs and LMWH/warfarin. • A network meta-analysis was conducted to compare apixaban to other NOACs and LMWH/warfarin for the following end-points: recurrent VTE and related deaths, major bleeds, clinically relevant non-major bleeds, myocardial infarction, and ischemic stroke.	Not reported	Not reported	Not reported	Apixaban versus LMWH/warfarin: ICER= £7,000/QALY
Levac (92)	2014	Canada	• Rivaroxaban • LMWH/VKA	• A Markov model was developed. Patients entered the model with an index PE and required 3, 6 or 12 months of treatment.	56-58 years	QALY gained per patients: Rivaroxaban versus LMWH/ VKA	Cost savings per patients: Rivaroxaban versus LMWH/ VKA	Rivaroxaban is a cost-effective treatment for PE, dominating LMWH/VKA for

Study	Year	Country (ies)	Interventions	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				• To assess the incremental cost/QALY gained, from a Canadian provincial government perspective, for rivaroxaban compared to LMWH/ VKA for treatment of PE, over a 5 year horizon • Patients were exposed to treatment-specific risks of recurrent VTE and bleeding events, and associated mortality and long-term complications. • Clinical inputs were from EINSTEIN-PE and published literature.		• 3 months: 0.002 • 6 months: 0.004 • 12 months 0.005	• 3 months: $629 • 6 months: $561 • 12 months $341	patients requiring up to 12 months treatment.

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); LOS, Length of stay

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)(93) or Philips et al. (2004)(94). For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.**

Quality assessment of each cost-effectiveness studies is described in section 9.11, appendix 11.

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 included is adults with an acute VTE event (DVT or PE), to match the licensed indication, the pivotal Hokusai-VTE study, and the decision problem. Results are presented in the base case for patients receiving anticoagulation treatment for a duration of 12 months. Subgroup analyses include:

- Type of VTE event: patients with an index PE (± DVT)
- Duration of treatment: short-term (3 and 6 months) and long-term (lifelong)

Patients with active cancer for whom VKAs would be unsuitable have been excluded from the economic analysis, as these patients were not included in studies of edoxaban.

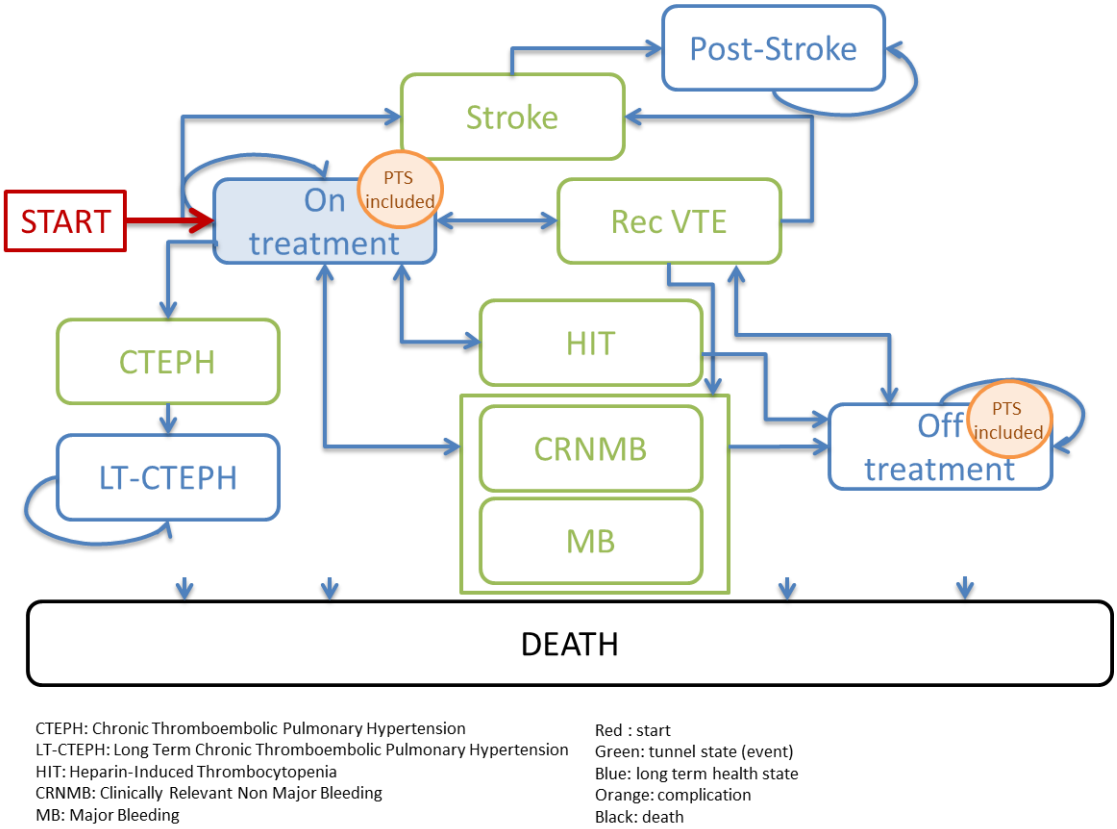
Model structure

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

A diagrammatical representation of the model is provided in

Figure B 23.

Figure B 23. Diagrammatical representation of the Markov model chosen



The model is a Markov model comprising 11 states, representing both the treatment and clinical events associated with the management and complications of VTE.

Patients enter the model in the “on treatment” state (represented by the red arrow). They can discontinue following an adverse event or at the end of specific treatment durations (12 months in the base case, 3 and 6 months and lifelong treatment in subgroup analyses). On or off treatment, patients are at risk of experiencing a recurrent VTE event.

While on anticoagulation treatment patients may experience the foillowing adverse events:

- Major bleeding
- CRNMB
- Heparin-induced thrombocytopenia (transition possible only when patients receive heparin as part of their anticoagulation treatment)

Patients on treatment may also develop CTEPH, which can be resolved or lead to long-term CTEPH.

Patients on treatment are also at risk of stroke. Patients suffering a stroke transit next to a “post-stroke” state.

Additionally, patients in the “on treatment” and the “off treatment” states are considered at risk of PTS. PTS is not modelled as an explicit health state, rather as a complication.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

A Markov structure was chosen because it allowed modelling a cohort of VTE patients on anticoagulation treatment and all relevant events that can occur, such as recurrent VTE or adverse events. The cycle length was set to 2 weeks, to accurately capture the effects of a heparin lead-in, and the costs and utilities associated with various adverse events represented in the model. For example, when a patient experiences an adverse event, he/she is assumed to stop treatment, to experience a decrease in their quality of life (represented by a decrement in their utility), and to incur additional costs (e.g. hospitalisation costs).

Importantly, the model used different transition matrices to account for the different probabilities of events occurring at different time points. The different periods captured in these matrices were the following:

- Day 1 to Day 14
- Day 15 to Day 98 (3 months)
- Day 99 (4 months) to Day 183 (6 months)
- Day 184 (6 months) to Day 364 (12 months)
- Day 365 (12 months) onwards

In cases where the evidence suggested that transition probabilities at various time points were the same (e.g., the estimates of the incidence of recurrent VTE from Day 99 to Day 183, and Day 184 to Day 364 are equal), separate rates are not listed in the tables shown in this section. However, full transition matrices for all of the model health states are incorporated in the model.

Since the NICE Reference Case incorporates the lifetime time horizon, long term complications (LT-CTEPH, stroke, PTS) were also included. The clinical pathway of care involves initial anticoagulation treatment of the VTE. Patients receiving a heparin lead-in (i.e. those receiving warfarin, edoxaban or dabigatran) can suffer heparin-induced thrombocytopenia (HIT). During treatment, a patient is subject to the risk of bleeding, CTEPH and stroke. In order to capture in the best way the costs and disutilities associated with bleeds, they were split in two states: clinically relevant non major bleeding and major bleeding. Major bleeds are more severe and are associated with an increased risk of mortality. Also, during treatment and subsequent to it, patients are at risk of VTE recurrence. Excess mortality associated with index VTE event, VTE recurrence, MB, CTEPH (long-term or not) and stroke are considered. The other-cause mortality is implemented separately from the transition matrices as it is age-dependent.

By assigning costs and utilities associated with these health states, the structure ensures that important consequences of VTE are captured.

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

A description of health states in the model is provided in Table B 55.

PTS was not considered as a health state in the model. PTS was applied to a proportion of patient in the “on treatment” and “off treatment” states, and impacted utility and costs.

Also, the other cause mortality was not included in the transition matrices but was considered separately using a background mortality table.

Table B 55. Health states in the model

#	State name	Description
1	On treatment	Patients who are diagnosed with an acute DVT (with or without PE) or PE and receive either the intervention or a comparator. The loss of utility due to the index VTE event is applied in the first cycle. For the following cycles, the utility associated with the “on treatment” state is the age-specific utility norm adjusted with a potential decrement associated with the treatment intake. The costs* are also different between the first cycle and the following ones. The first cycle includes the costs of management of the index VTE event and the potential costs of heparin, while following cycles include treatment costs only. In this state, a proportion of patients are considered as suffering of PTS. It impacts the utility and costs in every cycle.
2	Recurrent VTE	Patients who experience a recurrent VTE event (either DVT or PE) are transferred to this state and treated for the VTE event. After concluding their treatment they transition back to the “on-treatment” state. VTE recurrence includes both DVT and PE episodes VTE recurrence is associated with a decrement which is cumulated to the utility of index VTE event if it occurs in the second cycle. This decrement is subtracted from the age-specific utility norm if it occurs later. The costs* attributed in this health state are the costs associated with diagnosis and treatment of DVT or PE. This is a tunnel state.
3	HIT	Patients who experienced HIT during acute treatment are transferred to this state and receive appropriate treatment for HIT while in this state. That cannot occur if there is no heparin lead required for treatment. Patients can restart their anticoagulant treatment after treatment of HIT and transit back to the “on treatment” state or discontinue and transit to “off treatment”. HIT is associated with an increased risk of death. It is associated with a utility decrement and hospitalisation cost*. This is a tunnel state.
4	CRNMB	Patients who experience a CRNMB during long term treatment will temporarily discontinue treatment and will be able to continue anticoagulant therapy after resolution of the bleeding or definitively discontinue. It is not associated with an increased risk of death by definition. It is associated with a utility decrement and hospitalisation cost*. This is a tunnel state.

#	State name	Description
5	MB	Patients who experience a MB during treatment will temporarily discontinue treatment and will be able to continue anticoagulant therapy after resolution of the bleeding or definitively discontinue and transit to "off treatment" (based on Hokusai-VTE data: see section 7.3.6. It increases the risk of death. It is associated with a utility decrement and hospitalisation cost*. This is a tunnel state.
6	Off treatment	Patients enter the off treatment state when they discontinue anticoagulation treatment because of an adverse event, complications, or because they reach the end of the treatment duration. It is associated with no cost and no utility decrement. To be off treatment increases the risk of VTE recurrence.
7	Stroke	Patients who experience a primary stroke during treatment with intervention or comparator will discontinue treatment for VTE and undergo treatment/rehabilitation for stroke and so go to "post-stroke" state. They also have an increased risk of mortality. It is associated with utility decrement and hospitalisation cost*. This is a tunnel state.
8	Post stroke	Patients who experienced a stroke and receive long-term care (i.e. rehabilitation) related to complications of stroke. It is not associated with an increased risk of death. It is associated with a disutility and healthcare resource cost*.
9	CTEPH	Patients suffering from CTEPH are transferred to this state and receive appropriate treatment for CTEPH. It is associated with costs* of surgery and treatment of CTEPH and a utility decrement. This is a tunnel state.
10	LT-CTEPH	Patients not cured from CTEPH transfer to the long-term CTEPH phase. Patients continue treatment for CTEPH but will not resume anticoagulation VTE therapy. It is associated with costs* of treatment of CTEPH and a utility decrement.
11	Disease-related death	Terminal state which considers disease-related death only. Utility and costs associated are null.
12	Other-cause mortality	Terminal state which considers other-cause mortality only. Utility and costs associated are null.

* Appropriate HRG codes were used as described in section 7.5.1

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.

The objectives of anticoagulant treatment is to treat the more acute event and to prevent recurrence, while minimising the risk of bleeding compolications, such that the overall benefit-risk ratio associated with treatment is favourable.(23)

The probability of VTE recurrence varies with time with the highest risk occurring within the first year after the index event. The model accounts for this, using 5 transition matrices reflecting the time since the index event.

Bleeding varies in severity, and this is also captured in the model using two different states for bleeding: CRNMB and MB.

In addition to these two main aspects of VTE treatment, the model captures the specificities of VTE treatment in accounting for flexible duration of heparin lead-in. The model also accounts for rare complications of the condition and treatment: heparin-induced thrombocytopenia, CTEPH, and stroke.

Consequently, the model captures relevant health states and events corresponding to the context developed in the section 2.1, and allows capturing both the benefits and the potential risks of anticoagulation treatment.

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 B 56. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (maximum 50 years)	NICE Reference case	NICE Methods Guide
Cycle length	2 weeks (14 days)	14 days is short enough to allow flexibility in treatment duration and occurrence of adverse events and complications	
Half-cycle correction	Yes	NICE Reference case	
Were health effects measured in QALYs; if not, what was used?	Yes, QALYs	NICE Reference case	NICE Methods Guide
Discount of 3.5% for utilities and costs	Yes,3.5%	NICE Reference case	NICE Methods Guide
Perspective (NHS/PSS)	Yes, NHS	NICE Reference case	NICE Methods Guide

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?

The comparators included in the model are as per their marketing authorisations/CE marketing.

The analysis compares the following treatment strategies delivered over 3, 6, 12 months and lifelong:

- Edoxaban at a dose of 60mg once daily, as per EMA filing and Hokusai-VTE design

- Dual therapy with LMWH and VKA (current standard of care in the UK). LMWH therapy is continued at UK licensed dose until the INR is at least 2.0 or until therapeutic anticoagulation has been established. VKA overlaps with LMWH and is continued for the full duration of anticoagulation treatment.

- Rivaroxaban (Xarelto®) according to its licence for VTE treatment: 15 mg twice daily for 21 days followed by 20 mg once daily for the remaining duration of anticoagulation treatment

- Dabigatran (Pradaxa®) according to its licence for VTE treatment: 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for 5 days.

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.**

There is no treatment continuation rule based on the response. Patients can discontinue because of complications or adverse event or when their anticoagulant treatment ends.

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

Clinical data were mostly derived from Hokusai-VTE, the NMA presented in section 6.7 and published literature.

Specifically, Hokusai-VTE was used to estimate:

- Time-dependent probabilities of recurrence with warfarin
- Occurrence of bleeding adverse events VTE-related mortality with warfarin
- Occurrence of HIT and stroke with both warfarin and oral anticoagulants
- Probabilities of discontinuation after adverse events
- Mortality due to adverse events.

The NMA provided the following estimates:

- Odds-ratios of experiencing VTE recurrence with edoxaban, dabigatran, rivaroxaban, compared to warfarin
- Odds-ratios of experiencing CRNMB and MB with edoxaban, dabigatran, rivaroxaban, compared to warfarin

Published literature was used to inform model inputs for which there were no data in Hokusai-VTE:

- Risk of CTEPH and long-term CTEPH
- Probability of death due to VTE recurrence
- Transition probabilities while off treatment
- Death due to HIT
- Risk of PTS

Most probabilities required an adjustment to be adapted to the cycle length using the following formula:

Equation 1. Formula to convert a probability based on a particular timeframe into probability relative to the cycle length

$$p_{cycle}=1-(1-p)^{(1/\text{number of cycles})}$$

Where:

- p_{cycle} the probability relative to the cycle length
- p the probability available in the clinical trial or literature
- And the number of cycles on which this probability is based (for example, for annual probability, number of cycles = 26)

Probability of recurrent VTE with warfarin

Time-dependent probabilities of recurrent VTE were estimated through a post-hoc analysis of Hokusai-VTE and are presented in Table B 57.

Table B 57. Recurrent VTE in the warfarin arm as a function of the time period based on Hokusai-VTE on-treatment period

Time period	N	n	p	95% CI
From index event to 14 days	4,122	23	0.56%	0.331% - 0.785%
From 15 days to 98 days	3,972	43	1.083%	0.761% - 1.404%
From 99 days to 364 days	3,578	16	0.447%	0.229% - 0.666%

Source: Hokusai-VTE post-hoc analysis table 1.4.9.4.2

These were converted to transition probabilities using Equation 1. The probability to have a VTE recurrence after 364 days was assumed to be equal to the probability between the 99th day and the 364th day.

The probability of a VTE recurrence in the edoxaban arm is calculated by applying the appropriate hazard ratio to the probability of VTE recurrence in the warfarin arm. Equation 2 below was used, to obtain the transition probabilities from “on treatment” to “VTE recurrence”:

Equation 2. Probability of recurrence with edoxaban

$$Risk_{edoxaban} = 1-(1-((1-(1-Risk_{warfarin})^{1/14})*RR))^{14}$$

where:

- $Risk_{warfarin}$ is the risk (of recurrent VTE in this case) in the warfarin arm for a particular time period;
- RR is the riskratio, specifically 0.86 for recurrent VTE
- $Risk_{Edoxaban}$ is the risk of recurrent VTE in the edoxaban arm for that patient group and time period.

The risk-ratios for VTE recurrence for edoxaban, rivaroxaban and dabigatran are estimated through the odds-ratios coming from the NMA (section 6.7) and are presented in Table B 58.

Table B 58. Time-dependent odds-ratios for VTE recurrence vs. warfarin as a function of the time period

Treatment	Time period	Odds-ratio	Confidence interval
Edoxaban	From index event to 14 days	0.82	(0.59-1.17)
Edoxaban	From 15 days to 98 days	0.82	(0.59-1.17)
Edoxaban	From 99 days	0.82	(0.59-1.17)
Rivaroxaban	From index event to 14 days	0.81	(0.6-1.1)
Rivaroxaban	From 15 days to 98 days	0.81	(0.6-1.1)
Rivaroxaban	From 99 days	0.81	(0.6-1.1)
Dabigatran	From index event to 14 days	1.07	(0.75-1.58)
Dabigatran	From 15 days to 98 days	1.07	(0.75-1.58)
Dabigatran	From 99 days	1.07	(0.75-1.58)

The formula used to obtain the risk-ratio using the odds-ratio is presented in Equation 3.

Equation 3. Risk ratio estimated through probability of reference and odds-ratio

$$RR=OR/(1-P_{ref})+(P_{ref}*OR)$$

Where:

- RR is the risk ratio
- OR is the corresponding odds-ratio
- P_{ref} is that probability of reference for the odds-ratio and the risk-ratio

The probabilities of having a VTE recurrence when off treatment were derived from Coleman et al. 2014 (80) and are presented in Table B 59. The probability from 15 days to 98 days was assumed to be equal to the probability of VTE recurrence form 99 days to 364 days.

Table B 59. Probabilities of recurrent VTE when off treatment in function of the time period

Time period	Estimate (%)	Number of cycles	Probability per cycle
From 15 days to 98 days	5.6%	26	0.0022
From 99 days to 364 days	5.6%	26	0.0022
From 365 days	3.5%	26	0.0014

Probability of CRNMB and MB

The probabilities of CRNMB and MB while treated with warfarin were estimated from Hokusai-VTE and are not time dependent. They are presented in Table B 60.

Table B 60. Incidence of CRNMB an MB with warfarin over one year based on Hokusai-VTE Safety analysis set

Type of bleed	N	n	p	Confidence interval
CRNMB	4,122	368	8.93%	8.06%-9.80%
MB	4,122	66	1.60%	1.22%-1.99%

Source: Hokusai-VTE clinical study report table 12.6

The probabilities of CRNMB or MB in the edoxaban, dabigatran and rivaroxaban arms were calculated by applying the appropriate OR to the probability of a CRNMB or MB in the warfarin arm. These OR were estimated in the NMA (see section 6.7).

Table B 61. Odds-ratio of risk of CRNMB and MB for NOACs compared to warfarin

Treatment	Event	Odds-ratios	Confidence interval
Edoxaban	CRNMB	0.78	0.66 - 0.93
Edoxaban	MB	0.94	0.62 - 1.37
Rivaroxaban	CRNMB	1.06	0.89 - 1.26
Rivaroxaban	MB	0.56	0.37 - 0.83
Dabigatran	CRNMB	0.58	0.45 - 0.75
Dabigatran	MB	0.77	0.48 - 1.16

HIT

The risk of HIT has been considered in the model only for the first 14 days given that the initial treatment with warfarin, edoxaban and dabigatran requires administration of heparin.

The probabilities of HIT with warfarin and edoxaban were taken from Hokusai-VTE. The risk of HIT associated with dabigatran was assumed to be the same as with edoxaban.

Table B 62. Incidence of HIT with warfarin, edoxaban and dabigatran based on Hokusai-VTE Safety analysis set

Treatment	N	n	p	Confidence interval
Warfarin	4,122	1	0.02%	0.00%-0.07%
Edoxaban	4,118	1	0.02%	0.00%-0.07%
Dabigatran	NA	NA	0.02%	0.00%-0.07%

Source: Hokusai-VTE post-hoc analysis table 1.4.2

Stroke

The probabilities of stroke with warfarin and edoxaban were taken from Hokusai-VTE and adjusted to the cycle length using Equation 1. The risks of stroke associated with other NOACs (dabigatran, rivaroxaban) were assumed to be the same as with edoxaban.

Table B 63. Incidence of stroke for warfarin, edoxaban and other NOACs

Treatment	N	n	p	Confidence interval
Warfarin	4,122	26	0.63%	0.39%-0.87%
Edoxaban	4,118	26	0.63%	0.39%-0.87%
Rivaroxaban, dabigatran	NA	NA	0.63%	0.39%-0.87%

Source: Hokusai-VTE clinical study report table 12.15

CTEPH

According to clinical experts, since acute pulmonary hypertension needs to be present for three months at least before a diagnosis of CTEPH can be made. As a consequence, based on clinical expert advice, CTEPH was only modelled from Day 99 to lifetime.

Pengo and colleagues (31) found that in 223 patients with PE the probability of developing CTEPH within 2 years was 3.8%. The probability of PE (3.8%) was multiplied with PE population from Hokusai-VTE. The final transformation equation is p[2 weeks]=1-(1-p[2 years])^(1/52).

Table B 64. Incidence of CTEPH in function of the time periods

Time period	Estimate (%)	Number of cycles
From index event to 14 days	Assumed to be 0	-
From 15 days to 98 days	Assumed to be 0	-
From 99 days to 364 days	3.8%*1671/4122 = 1.55%	52

The probability to have a CTEPH after 364 days was assumed to be equal to the probability between the 99th day and the 364th day.

Probabilities of discontinuation after HIT, CRNMB and MB

The probability to discontinue treatment after HIT was assumed to be 40% with all the treatments as there was no data available. The probabilities of discontinuation after CRNMB and MB with warfarin and edoxaban were derived from Hokusai-VTE. The probability to discontinue after CRNMB and MB with rivaroxaban and dabigatran were assumed to be equal to this probability with edoxaban.

Table B 65. Probabilities of discontinuation after CRNMB

Treatment	N	n	p	Confidence interval
Warfarin	368	19	5.2%	4.5%-5.8%
Edoxaban	298	25	8.4%	7.5%-9.2%
Dabigatran, rivaroxaban	NA	NA	8.4%	7.5%-9.2%

Source: Hokusai-VTE post-hoc analysis table 1.4.3.7

Table B 66. Probabilities of discontinuation after MB

Treatment	N	n	p	Confidence interval
Warfarin	67	26	38.8%	37.3%-40.3%
Edoxaban	57	17	29.8%	28.4%-31.2%
Dabigatran, rivaroxaban	NA	NA	29.8%	28.4%-31.2%

Source: Hokusai-VTE post-hoc analysis table 1.4.6.7

Probability of disease-related deaths

The probability of VTE-related death was directly taken from Hokusai-VTE independtly of the treatment. It was applied for one year after index date in all health states. For “On treatment”, “Off treatment”, “long-term CTEPH”, “Post stroke”, VTE-related death is the only type of death considered as disease-related. In other health states (VTE recurrence, HIT, CRNMB, MB, CTEPH, stroke), additional risk of death associated with the event is considered.

VTE-, CRNMB-, MB- and stroke-related deaths were not considered as treatment specific: these probabilities were estimated from the overall population in Hokusai-VTE.

Table B 67. Probabilities of disease-related death derived from Hokusai-VTE

Event	N	n	p	Confidence interval
VTE-related death	8,240	48	0.58%	0.35%-0.81%
CRNMB related death	666	0	0%	NA
MB related death	124	12	9.7%	8.8%-10.6%
Stroke related death	52	2	3.85%	0.0%-0.09%

Source: Hokusai-VTE clinical study report tables 11.10 and 12.15; and Hokusai-VTE post-hoc analysis tables 1.4.3.6.2 and 1.4.6.7

Probability of death from HIT was derived from Prandoni et al, 2005(95), that showed that the incidence of thromboembolic events in patients who developed HIT was remarkably higher than that observed in patients who did not, leading to an OR of 16.6 (95% CI, 5.0-55.0).

The probability of death after recurrence was taken from Carrier et al.(96) and estimated at 11.3%.

Probability of other-cause related deaths

Other-cause mortality was taken from UK life tables (97) and is age-and-gender-dependent. This mortality is then adjusted on the proportion of female at the index event in Hokusai-VTE and afterwards adjusted on the evolutive proportion of female vs. male considering that males are more at risk of death than female at the same age.

Table B 68. Other-cause mortality by age and gender

Age	Male	Female
55	0.005	0.003
56	0.006	0.004
57	0.006	0.004
58	0.007	0.004
59	0.007	0.005
60	0.008	0.005
61	0.009	0.006
62	0.010	0.006
63	0.010	0.007
64	0.011	0.007
65	0.012	0.008
66	0.014	0.009
67	0.015	0.010
68	0.016	0.011
69	0.019	0.012
70	0.021	0.010
71	0.023	0.010
72	0.025	0.020
73	0.027	0.020
74	0.030	0.020
75	0.033	0.020
76	0.037	0.030
77	0.041	0.030
78	0.046	0.030
79	0.051	0.040
80	0.057	0.040
81	0.065	0.050
82	0.072	0.050
83	0.081	0.060
84	0.090	0.070
85	0.101	0.080
86	0.112	0.090
87	0.125	0.090
88	0.137	0.110
89	0.157	0.120
90	0.169	0.140
91	0.183	0.150
92	0.197	0.170
93	0.212	0.180
94	0.236	0.200
95	0.259	0.220
96	0.282	0.240

Age	Male	Female
97	0.303	0.260
98	0.323	0.280
99	0.345	0.300
100	0.361	0.320

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.

In order to reflect the change in risk patients face over time the model incorporates five transition matrices, which cover the time periods: Day 1 to Day 14, Day 15 to Day 98 (3 months), Day 99 (4 months) to Day 183 (6 months), Day 184 (6 months) to Day 364 (12 months), Day 365 (12 months) onwards. It must be noted that when the treatment duration ends, all patients exit the “on treatment” state. Therefore, it may appear that some transition probabilities (e.g. the probabilities of transition to death) might not align with the treatment duration, but this is because the patient cannot be in the “on treatment” state, after the end of the treatment period. It should also be noted that patients are at risk of death from all other causes at all times, based on the national mortality tables shown previously.

The matrices presented below are the ones for warfarin. All other tables are provided in section **Error! Reference source not found.** appendix 18.

Table B 69. Transition matrix 1. First cycle (Day 1 to Day 14) with warfarin

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0.9895	0.0056	0	0.0002	0.0036	0.0006	0	0	0.0002	0	0.0002
VTE Recurrence	0.8823	0	0	0.0002	0.0036	0.0006	0	0	0.0002	0	0.113
Off treatment	0	0	0.9998	0	0	0	0	0	0	0	0.0002
HIT	0.5961	0	0.4	0	0	0	0	0	0	0	0.0039
CRNMB	0.9481	0	0.0516	0	0	0	0	0	0	0	0.0002
MB	0.5149	0	0.3881	0	0	0	0	0	0	0	0.097
CTEPH	0	0	0	0	0	0	0.9998	0	0	0	0.0002
LT CTEPH	0	0	0	0	0	0	0	0.9998	0	0	0.0002
Stroke	0	0	0	0	0	0	0	0	0	0.9613	0.0387
After stroke	0	0	0	0	0	0	0	0	0	0.9998	0.0002
Death	0	0	0	0	0	0	0	0	0	0	1

Table B 70. Transition matrix 2. Six cycles (Day 15 to Day 98 (3 months)) with warfarin

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0.9935	0.0018	0	0	0.0036	0.0006	0	0	0.0002	0	0.0002
VTE Recurrence	0.8825	0	0	0	0.0036	0.0006	0	0	0.0002	0	0.113
Off treatment	0	0.0022	0.9976	0	0	0	0	0	0	0	0.0002
HIT	0.5961	0	0.4	0	0	0	0	0	0	0	0.0039
CRNMB	0.9481	0	0.0516	0	0	0	0	0	0	0	0.0002
MB	0.5149	0	0.3881	0	0	0	0	0	0	0	0.097
CTEPH	0	0	0	0	0	0	0.9998	0	0	0	0.0002
LT CTEPH	0	0	0	0	0	0	0	0.9998	0	0	0.0002
Stroke	0	0	0	0	0	0	0	0	0	0.9613	0.0387
After stroke	0	0	0	0	0	0	0	0	0	0.9998	0.0002
Death	0	0	0	0	0	0	0	0	0	0	1

Table B 71. Transition matrix 3. Six cycles (Day 99 (4 months) to Day 183 (6 months)) with warfarin

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0.9947	0.0002	0	0	0.0036	0.0006	0.0004	0	0.0002	0	0.0002
VTE Recurrence	0.8822	0	0	0	0.0036	0.0006	0.0004	0	0.0002	0	0.113
Off treatment	0	0.0022	0.9976	0	0	0	0	0	0	0	0.0002
HIT	0	0	0	0.9961	0	0	0	0	0	0	0.0039
CRNMB	0.9481	0	0.0516	0	0	0	0	0	0	0	0.0002
MB	0.5149	0	0.3881	0	0	0	0	0	0	0	0.097
CTEPH	0	0	0.6698	0	0	0	0	0.33	0	0	0.0002
LT CTEPH	0	0	0	0	0	0	0	0.9998	0	0	0.0002
Stroke	0	0	0	0	0	0	0	0	0	0.9613	0.0387
After stroke	0	0	0	0	0	0	0	0	0	0.9998	0.0002
Death	0	0	0	0	0	0	0	0	0	0	1

Table B 72. Transition matrix 4. Thirteen cycles (Day 184 (6 months) to Day 364 (12 months)) with warfarin

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0.9947	0.0002	0	0	0.0036	0.0006	0.0004	0	0.0002	0	0.0002
VTE Recurrence	0.8822	0	0	0	0.0036	0.0006	0.0004	0	0.0002	0	0.113
Off treatment	0	0.0022	0.9976	0	0	0	0	0	0	0	0.0002
HIT	0	0	0	0.9961	0	0	0	0	0	0	0.0039
CRNMB	0.9481	0	0.0516	0	0	0	0	0	0	0	0.0002
MB	0.5149	0	0.3881	0	0	0	0	0	0	0	0.097
CTEPH	0	0	0.6698	0	0	0	0	0.33	0	0	0.0002
LT CTEPH	0	0	0	0	0	0	0	0.9998	0	0	0.0002
Stroke	0	0	0	0	0	0	0	0	0	0.9613	0.0387
After stroke	0	0	0	0	0	0	0	0	0	0.9998	0.0002
Death	0	0	0	0	0	0	0	0	0	0	1

Table B 73. Transition matrix 5. Following cycles (Day 365 (12 months) onwards) with warfarin

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0	0.0002	0.995	0	0.0036	0.0006	0.0004	0	0.0002	0	0
VTE Recurrence	0	0	0.8822	0	0.0036	0.0006	0.0004	0	0.0002	0	0.113
Off treatment	0	0.0014	0.9986	0	0	0	0	0	0	0	0
HIT	0	0	0	0.9963	0	0	0	0	0	0	0.0037
CRNMB	0	0	1	0	0	0	0	0	0	0	0
MB	0	0	0.9032	0	0	0	0	0	0	0	0.0968
CTEPH	0	0	0.67	0	0	0	0	0.33	0	0	0
LT CTEPH	0	0	0	0	0	0	0	1	0	0	0
Stroke	0	0	0	0	0	0	0	0	0	0.9615	0.0385
After stroke	0	0	0	0	0	0	0	0	0	1	0
Death	0	0	0	0	0	0	0	0	0	0	1

Table B 74. Transition matrix 3b. Six cycles (Day 99 (4 months) to Day 183 (6 months)) off treatment

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0	0.0002	0.9947	0	0.0036	0.0006	0.0004	0	0.0002	0	0.0002
VTE Recurrence	0	0	0.8822	0	0.0036	0.0006	0.0004	0	0.0002	0	0.1130
Off treatment	0	0.0022	0.9976	0	0	0	0	0	0	0	0.0002
HIT	0	0	0	0.9961	0	0	0	0	0	0	0.0039
CRNMB	0	0	0.9998	0	0	0	0	0	0	0	0.0002
MB	0	0	0.9030	0	0	0	0	0	0	0	0.0970
CTEPH	0	0	0.6698	0	0	0	0	0.3300	0	0	0.0002
LT CTEPH	0	0	0	0	0	0	0	0.9998	0	0	0.0002
Stroke	0	0	0	0	0	0	0	0	0	0.9613	0.0387
After stroke	0	0	0	0	0	0	0	0	0	0.9998	0.0002
VTE-related death	0	0	0	0	0	0	0	0	0	0	1.0000

Table B 75. Transition matrix 4b. Thirteen cycles (Day 184 (6 months) to Day 364 (12 months)) off treatment

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0	0.0002	0.9947	0	0.0036	0.0006	0.0004	0	0.0002	0	0.0002
VTE Recurrence	0	0	0.8822	0	0.0036	0.0006	0.0004	0	0.0002	0	0.1130
Off treatment	0	0.0022	0.9976	0	0	0	0	0	0	0	0.0002
HIT	0	0	0	0.9961	0	0	0	0	0	0	0.0039
CRNMB	0	0	0.9998	0	0	0	0	0	0	0	0.0002

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
MB	0	0	0.9030	0	0	0	0	0	0	0	0.0970
CTEPH	0	0	0.6698	0	0	0	0	0.3300	0	0	0.0002
LT CTEPH	0	0	0	0	0	0	0	0.9998	0	0	0.0002
Stroke	0	0	0	0	0	0	0	0	0	0.9613	0.0387
After stroke	0	0	0	0	0	0	0	0	0	0.9998	0.0002
Death	0	0	0	0	0	0	0	0	0	0	1.0000

Table B 76. Transition matrix 5b. Following cycles (Day 365 (12 months) onwards) off treatment

	On treatment	VTE Recurrence	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke	Death
On treatment	0	0.0002	0.9950	0	0.0036	0.0006	0.0004	0	0.0002	0	0.0000
VTE Recurrence	0	0	0.8822	0	0.0036	0.0006	0.0004	0	0.0002	0	0.1130
Off treatment	0	0.0014	0.9986	0	0	0	0	0	0	0	0.0000
HIT	0	0	0	0.9963	0	0	0	0	0	0	0.0037
CRNMB	0	0	1.0000	0	0	0	0	0	0	0	0.0000
MB	0	0	0.9032	0	0	0	0	0	0	0	0.0968
CTEPH	0	0	0.6700	0	0	0	0	0.3300	0	0	0.0000
LT CTEPH	0	0	0	0	0	0	0	1.0000	0	0	0.0000
Stroke	0	0	0	0	0	0	0	0	0	0.9615	0.0385
After stroke	0	0	0	0	0	0	0	0	0	1.0000	0.0000
Death	0	0	0	0	0	0	0	0	0	0	1.0000

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.**

There is clear evidence that the risk of VTE-recurrence after the index VTE event decreases over time according to Hokusai-VTE. This was captured in this evaluation and transition probabilities vary over time to capture the natural history of the disease.

Overall mortality of the patients entering the model is strongly associated with the age. This has been included to the evaluation and calculated in parallel of the transition matrices using the appropriate UK mortality table.

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?**

There was no linking of one set of outcomes to another.

7.3.5 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:**

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical 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).**

Expert opinion was utilised at an advisory board with the aims of validating a preliminary version of the model regarding the structure, decision problem, assumptions, parameters and outcomes.

[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 expert advice received was used to inform the further development of a robust economic analysis, specifically to address the following questions:

- Structure – does the model reflect the real-life practice and is the structure consistent with medical science?
- Decision problem – what are the relevant populations, comparators, settings, subgroups, etc?
- Assumptions – what is the rationale behind the assumptions and how do the models account for the impact of the assumptions on the results?
- Outcomes – are all the relevant clinical outcomes captured in the model?
- Parameters – are all relevant parameters accounted for in the models?
- Complexity – is the complexity of the model well justified, would a reduction in complexity affect fit for purpose?

Expert opinion was elicited using a qualitative technique. All opinions were collected and represented but not quantified. Clinical experts were selected by Daiichi Sankyo, and were recruited based on expertise and international reputation. Health economics (HE) experts were recommended by an external agency (Hayward Medical), given their extensive expertise within health economics and health technology appraisal experience. Three HE experts and two clinical experts were approached and recruited. There were no conflicts of interest recorded. Experts were provided with details of the pivotal trial, drafts of the model and model protocol, the NMA, key points for discussion, and a summary of past NOAC appraisals. Following discussion of the key issues by the experts, the health economists formulated an answer which was then agreed or discussed until consensus was agreed by the experts. Following a two week interlude the minutes of the meeting were circulated for clarification and approval. No discrepancies were identified and a further consensus meeting was not required.

The recommendations from the experts included:

- The model phases – initial phase, long-term phase and extended phase – were considered to reflect treatment guidelines.
- Two-week cycles were considered appropriate.
- The inclusion of HIT in the model was discussed. The consensus was to include HIT in the initial phase (0–14 days) of the model, even if it is uncommon, as it demonstrates consideration of all possibilities. In the long-term treatment (day 15 to day 98) phase, the advisors noted that HIT would only occur in patients receiving heparin.
- The clinicians advised that acute pulmonary hypertension needs to be present for three months before a diagnosis of CTEPH is made. CTEPH should, therefore, be considered only in the extended phase (three months to lifetime).

The risk of post-thrombotic syndrome should be applied to the number of living patients per model cycle. The resulting number of patients will accumulate costs, clinical effects and quality of life effects associated with post-thrombotic syndrome. The clinical advisors noted that the utility decrement associated with this syndrome was a real issue but was equal to both groups; as the decrement is related to having the event and not the treatment, it should be applied to both groups equally.

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 B 77 presents all variables included in the cost-effectiveness analysis.

Table B 77. Summary of variables applied in the economic model

Event/Outcome	Point estimate	Source
Probability of VTE Recurrence 1-14 days with warfarin	0.0056	DS internal statistical analysis - post hoc for model. Table 1.4.9.4.2,N=4122, Recurrent events=23 pcycle=1-(1-p)^(1/number of cycles)
Probability of VTE Recurrence 15 days-3 months with warfarin	0.0018	DS internal statistical analysis - post hoc for model. Table 1.4.9.4.2,N=3972, Recurrent events=43 pcycle=1-(1-p)^(1/number of cycles)
Probability of VTE Recurrence after 4 months with warfarin	0.0002	DS internal statistical analysis - post hoc for model. Table 1.4.9.4.2,N=3578, Recurrent events=16 pcycle=1-(1-p)^(1/number of cycles)
Recurrent VTE Edoxaban vs. Warfarin hazard ratio	[redacted]	NMA
Recurrent VTE Rivaroxaban vs. Warfarin hazard ratio	[redacted]	NMA
Probability of VTE Recurrence 15 days-12 months when off treatment	0.0022	Coleman et al 2014 (80), Annual rate of rVTE after anticoagulation is stopped, year 1: 5.6%
Probability of VTE Recurrence after 12 months when off treatment	0.0014	Coleman et al 2014 (80), Annual rate of rVTE after anticoagulation is stopped, year 2+: 3.5%
Probability of HIT	0.0002	DS internal statistical analysis - post hoc for model Hokusai-VTE. Table 1.4.2. N=4122, Subjects with HIT=1 pcycle=1-(1-p)^(1/number of cycles)
Probability of CRNMB	0.0036	Hokusai-VTE CSR Table 12.6 , N=4122, Subjects with CRNMB=368 pcycle=1-(1-p)^(1/number of cycles)
CRNMB Edoxaban vs. Warfarin odds ratio	[redacted]	Calculated from NMA - Sensitivity analysis including all trials Studies included: Hokusai-VTE, AMPLIFY, RE-COVER, RE-COVER II, EINSTEIN-PE, EINSTEIN-DVT, Botticelli, ODIXa-DVT, EINSTEIN-DVT dose-ranging
CRNMB Rivaroxaban vs. Warfarin odds ratio	[redacted]	Calculated from NMA - Sensitivity analysis including all trials Studies included: Hokusai-VTE, AMPLIFY, RE-COVER, RE-COVER II, EINSTEIN-PE, EINSTEIN-

Event/Outcome	Point estimate	Source
		DVT, Botticelli, ODIXa-DVT, EINSTEIN-DVT dose-ranging
Probability of MB	[redacted]	Hokusai-VTE CSR Table 12.6 ,N=4122, Subjects with MB=66 pcycle=1-(1-p)^(1/number of cycles)
MB Edoxaban vs. Warfarin odds ratio	[redacted]	NMA - Sensitivity analysis including all trials Studies included: Hokusai-VTE, AMPLIFY, RE-COVER, RE-COVER II, EINSTEIN-PE, EINSTEIN-DVT, Botticelli, ODIXa-DVT, EINSTEIN-DVT dose-ranging
MB Rivaroxaban vs. Warfarin odds ratio	[redacted]	NMA - Sensitivity analysis including all trials Studies included: Hokusai-VTE, AMPLIFY, RE-COVER, RE-COVER II, EINSTEIN-PE, EINSTEIN-DVT, Botticelli, ODIXa-DVT, EINSTEIN-DVT dose-ranging
Probability of stroke	0.0002	Hokusai-VTE CSR Table 12.15 CSR,N =4122,Subjects with Stroke=26 pcycle=1-(1-p)^(1/number of cycles)
Probability of CTEPH 3 months-12 months	0.0003	Pengo et al. 2004 (31) DS internal statistical analysis - post hoc for model Hokusai-VTE. Tbl 1.2.25.
Probability of LT CTEPH 3 months-12 months	0.33	Expert opinion
Probability of going off treatment after HIT	0.40	Expert opinion
Probability of going off treatment after CRNMB	0.05	DS internal statistical analysis - post hoc for model. Table 1.4.3.7,Number of permanent discontinuations=19,Hokusai-VTE CSR Table 12.6 , N =4122,Subjects with CRNMB=368 pcycle=1-(1-p)^(1/number of cycles)
Probability of going off treatment after MB	0.39	DS internal statistical analysis - post hoc for model. Table 1.4.6.7 Number of permanent discontinuations=26, DS internal statistical analysis - post hoc for model. Table 1.4.6.7,MB events= 67
Probability of death due to VTE	0.0002	Hokusai-VTE CSR Table 11.10 CSR, Both warfarin and edoxaban arm were used, Fatal PE=3+4, Unexplained death (and VTE cannot be ruled out)=21+20, N=4122+4118. Other mortality is captured through adverse events and recurrence.
Probability of death due to recurrence	0.113	Carrier et al 2010 (96)
Probability of death after HIT	0.0037	Prandoni et al 2005 (95)
Probability of death after MB	0.10	DS internal statistical analysis - post hoc for model. Table 1.4.6.6.2 ,Total number of fatal events=10+2, DS internal statistical analysis - post hoc for model. Table 1.4.6.7,MB events= 67+57
Proportion of patient with PTS during the first year	0.0011	Prandoni et al. 1997 (98)
Proportion of patient with PTS during the following years	0.0005	Prandoni et al. 1997 (98)

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.

The time horizon for the economic model is a patient's lifetime (50 years), as per the Decision Problem, so extrapolation has been necessary. The risk of VTE recurrence is known to decrease with time. The data from Hokusai-VTE are calculated over one year. In the base case scenario of 12 months of treatment, Hokusai-VTE was used up to one year, then published literature to extrapolate clinical pathways of patients off treatment. In the scenario analysis of life-long treatment, the risk of VTE recuurence at the end of the treatment period in Hokusai-VTE was extrapolated beyond 12 months.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption 1: patients experiencing a bleeding event will discontinue anticoagulation therapy for a part of the duration of a model cycle.

Justification: This in line with clinical practice; the priority is to reverse bleeding and continued anticoagulation would be inappropriate.

Assumption 2: Patients who have experienced a recurrent VTE will be identically treated as patients experiencing a first event of VTE. The costs of treating an index event and a recurrent event are therefore assumed to be equal.

Justification: This is in line with clinical practice has been validated in discussion with clinical experts.

Assumption 3: PTS is included in the model but not as an explicit health state. All patients are at risk of PTS. The risk of PTS is applied to all patients, irrespective of whch health state they are in. Two probabilities are applied in the model: one probability for the first 12 months, and a different probability for subsequent months. The resulting number of patients with PTS will accumulate costs and utilities associated with PTS.

Justification: All patients who have experienced a VTE event are at risk of PTS. Clinical experts confirmed that this is a relatively rare complication. In this model, we make the conservative assumption that the risk of PTS is independent of treatment and furthermore that the risk is not affected by other clinical events.

Assumption 4: Patients in the health state "stroke" may only transfer to the health states "post-stroke" and "death". Patients in the health state "post-stroke" can only transfer to the health state "death".

Justification: Patients who have experienced a stroke are associated with a particular set of costs and utilities; it is appropriate to model these separately and not to consider a return to the starting health state in this model.

Assumption 5: Patients who experience a bleed, HIT, or CTEPH are not susceptible for recurrence of VTE in the cycle in which these adverse events occur.

Justification: Patients are not considered to be at risk of recurrence during the cycle in which these adverse events occur. Those who experience bleeding or HIT discontinue treatment, while those who experience CTEPH also discontinue while receiving appropriate treatment for CTEPH. In addition, the cycle length is only 14 days, and the probability of recurrence over this period is low.

Assumption 6: The 'Recurrent VTE' state models the combined events of non-fatal DVT and non-fatal PE events. The total cost of the VTE recurrence is estimated using the weighted average cost of DVT and PE (based on the incidence of DVT and PE).

Justification: As the costs and the utility applied are proportional to the proportion of DVT and PE, it is an appropriate assumption. Since the nature of the recurrent event (DVT or PE) does not impact the transition probabilities, there is no need to dissociate them into different health states.

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.

Several worldwide studies highlighting the impaired quality of life of patients with VTE are available (99-101), using adjustment on gender and age. VTE has a significant negative on quality of life, and subsequent events may further decrease this already impaired quality of life.

This may be due the large number of symptoms that patients experience: swelling, pain, tenderness, shortness of breath, difficulty in breathing, fatigue and fear of recurrence.(102;103) Furthermore, PE patients may be more readily emotionally disturbed and may experience more social isolation than prior to the PE.(103)

A study reported that patients with lower limb DVT showed a SF-36 physical component score at baseline and 1 month lower than for patients with other chronic disorders such as lung disease or arthritis.(100)

In addition to symptoms, long-term complications of VTE may also have a significant impact on patients' quality of life. CTEPH is a complication of PE that may provique fatigue, limited exercise tolerance, shortness of breath and chest pain.(104-106)

Symptoms of severe PTS, a complication of DVT, are heaviness, pain, cramps, pruritus and paraesthesia.(106)

Finally, treatment may have adverse events. Anticoagulation with VKAs, today's gold standard to treat patients with VTE may can also negatively impact patients' perceptions of their HRQL. Lifestyle modifications and frequent INR monitoring are necessary, which may found to be burdensome.(107;108)

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

When using both generic and disease-specific instruments, patients with VTE report a HRQL that tends to significantly improve in the course of several months after the initial event.(99)

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.(109) 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.(100)

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.**

As stated in section 6.5.1, a total of [redacted] patients in Hokusai-VTE completed EQ-5D questionnaires. The [redacted] patients returned a total of [redacted] complete EQ-5D-3L assessments at the various time points of the study. Utility scores were determined for all patients using the UK time trade-off (TTO) value set, at baseline and at 3-month intervals thereafter.

This was considered as a small sample and therefore not appropriate for use in the cost-effectiveness analysis.

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 carried out.

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 systematic literature review has been performed to identify HRQoL data relevant to the submission. The main objective of the study identification was to collect evidence on utility associated with VTEs, including events such as DVT, major bleeding, and CTEPH, in patient populations with VTE.

The search was performed using Medline, Embase, the Cochrane Library and Econlit.

An initial search was run on May 13th, 2014. Searches were updated on December 4th, 2014.

Keywords used in the search strategy were defined according to the decision problem with a wide scope, to ensure that the maximum amount of relevant articles was detected in the search.

The search strategy to identify relevant articles was designed using the PICOS (population, intervention, comparator, outcome, study) methodology.

The complete search strategy is provided in section 9.12, Appendix 10.

The article selection process is summed up in Figure B 24. The search strategy through database searching identified 1,342 records. Additional 51 records were identified subsequently while looking at references of included studies:

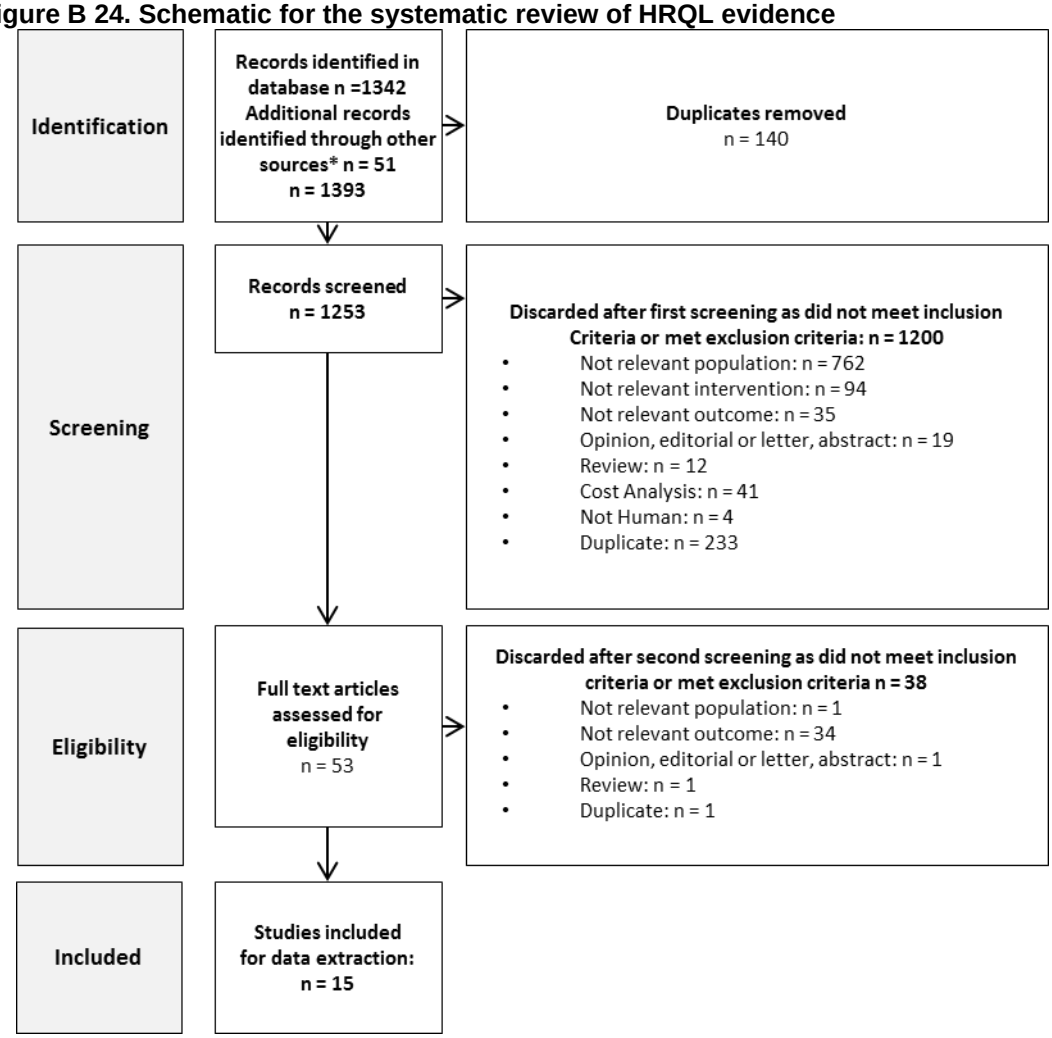
- primary study references of a literature review on multi-attribute utility (MAU) values associated with venous thromboembolism (VTE) events, identified in this systematic literature review and published only as a conference poster (110)

- references of utility data sources identified in the review of published cost-effectiveness evaluations

After removing duplicates (N=140), screening of these records based on the information provided in their titles and abstracts excluded 1200 records. Full texts were obtained for the remaining 53 records and were screened based on the information provided in their full texts. Finally, the literature review identified 15

references that assessed utility values in VTE population or in associated complications (i.e. post-thrombotic syndrome, PE).

Figure B 24. Schematic for the systematic review of HRQL evidence



7.4.6 **Please 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.**

Fifteen references were identified in this systematic review. They are summarised in Table B 78.

Only two studies evaluated utility values in line with the NICE recommendation (111;112).

With the exception of patients who received thrombolysis, the health states presented in the studies were appropriate to the relevant treatment pathway.

Table B 78. Included studies

Study (Ref ID)	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD	Appropriateness to this submission and for cost effectiveness analysis
Bosma 2011 (113)	The Netherlands	•PSVT patients •Mean age 40 years	•Case-control study •Recruitment: consecutive cases from 1994 to 2008 (record review)	45	•EQ-5D and EQ-VAS •Probably UK eights(EuroQol Group., 1990)	Group 1 (oral anticoagulants only)	0.86 (SD 0.15)	•Use of EQ-5D and probably UK weight tariffs
						Group 2 (thrombolysis and anticoagulants)	0.62 (SD 0.46)	
						Group 3 (thrombolysis combined with first rib resection)	0.78 (SD 0.27)	
						Successful thrombolysis	0.771	
						Unsuccessful thrombolysis	0.54	
Cohen 2014 (111)	Seven European countries	•VTE or PE	•Prospective, observational, multicentre study	•Baseline: 2790 •1 month follow up:1453 •3 month follow up: 1417 •6 month follow up	•EQ-5D-5L	**EQ-5D-5L index value by VTE type**		•Yes
						DVT, baseline	0.71 (SD 0.26)	
						DVT, 1 month	0.79 (SD 0.22)	
						DVT, 3 months	0.84 (SD 0.19)	
						DVT, 6 months	0.85 (SD 0.19)	
						PE±DVT, baseline	0.67 (SD 0.32)	
						PE±DVT, 1 month	0.75 (SD 0.24)	
						PE±DVT, 3 months	0.79 (SD 0.22)	
						PE±DVT, 6 months	0.81 (SD 0.23)	
						TOTAL, baseline	0.69 (SD 0.28)	
						TOTAL, 1 month	0.77 (SD 0.23)	
						TOTAL, 3 months	0.82 (SD 0.20)	
						TOTAL, 6 months	0.83 (SD 0.20)	
						EQ-5D-5L index value by treatment class		
						Heparin, baseline	0.66 (SD 0.31)	
						Heparin, 1 month	0.70 (SD 0.28)	
						Heparin, 3 months	0.78 (SD 0.25)	
						Heparin, 6 months	0.75 (SD 0.27)	
						Heparin/VKA, baseline	0.70 (SD 0.29)	
						Heparin/VKA, 1 month	0.77 (SD 0.23)	
						Heparin/VKA, 3 months	0.82 (SD 0.20)	
						Heparin/VKA, 6 months	0.84 (SD 0.19)	
Comerota 2000 (114)	US	•Patients with DVT treated 6 to 44 months earlier (mean 16 months)	• Observational study • Recruitment: national DVT registry and invitation from treating physicians	•178 invited to participate •111 completed and returned the initial questionnaire	•Health Utilities Index (HUI) MARK 2/3 version •Short Form-12 (SF-12)	**Mean scale scores post treatment, HUI**		•No UK specific data •Utility elicited using HUI (valuation method not reported)
						Urokinase, at 16 months	0.81 (SE 0.02)	
						Heparin, at 16 months	0.73 (SE 0.03)	
						Urokinase, at 22 months	0.73 (SE 0.03)	
						Heparin, at 22 months	0.74 (SE 0.07)	

Study (Ref ID)	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD	Appropriateness to this submission and for cost effectiveness analysis
		• Urokinase mean age ± SE : 53± 17 years • Heparin mean age: 61 ± 6 years		• Of these, 98 were included and 13 excluded				
Enden 2013 (109)	Norway	• High proximal DVT • 18-75 years	• Open-label RCT • Recruitment: from 19 hospitals	• 189 (of 209 recruited patients)	• EQ-5D and VEINES-QOL/Sym • Norwegian weights	**EQ-5D according to treatment allocation**		• EQ-5D but Norway tariffs
						Additional catheter-directed thrombolysis, at baseline	0.46 (SD 0.39)	
						Standard treatment only, at baseline	0.63 (SD 0.99)	
						Additional catheter-directed thrombolysis, at 6 months	0.82 (CI: 0.780-0.856)	
						Standard treatment only, at 6 months	0.81 (CI:0.777-0.852)	
						Additional catheter-directed thrombolysis, at 24 months	0.80 (CI:0.746-0.849)	
						Standard treatment only, at 24 months	0.84 (CI:0.807-0.875)	
						EQ-5D according to PTS development		
						PTS, at 6 months	0.80 (CI:0.770-0.837)	
						No PTS, at 6 months	0.82 (CI:0.788-0.869)	
						PTS, at 24 months	0.77 (CI:0.730-0.819)	
						No PTS, at 24 months	0.86 (CI:0.823-0.903)	
Hogg 2013 (115)	Canada	• History of lower limb DVT	• A prospective cohort study • Recruitment: from a Hospital, diagnosed as having either lower extremity DVT or PE	• 216 consented to participate • 215 participated in the study	• Standard Gamble	DVT	median 0.81 IQR (0.55-0.94)	• No UK specific input data • Utility elicited by SG
						PE	median 0.75 IQR (0.45-0.91)	
						Minor intracranial bleeding event	median 0.75 IQR (0.55-0.92)	
						Gastrointestinal tract bleeding event	median 0.65 IQR (0.15-0.86)	
						Major intracranial bleeding event	median 0.15 IQR (0.00-0.65)	
Hogg 2014 (116)	Canada	• Diagnosed with DVT or PE	• A prospective cohort study • Recruitment: from a	• 44 consented to participate	• Standard Gamble	PE (calibrated to death by stroke rating)	median 0.93 IQR (0.82-1)	• No UK specific input data • Utility elicited
						DVT	median 0.99 IQR	

Study (Ref ID)	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD	Appropriateness to this submission and for cost effectiveness analysis
			Hospital, diagnosed as having either DVT or PE				(0.85-1)	by SG
						Stroke rated against death	Median 0.15 IQR (0-0.55)	
Isma 2007 (117)	Sweden	•DVT patients •Mean age: 54.27 ±14	•Observational study • Recruitment: output patients at Malmö University Hospital	•72	•VAS	**Exercise group**		•No UK specific data •Utility elicited using VAS
						baseline	median 42 range (1-88)	
						1 month	median 13.5 range (0-83)	
						6 months	median 4 range (0-74)	
						Control group		
						baseline	median 45.5 range (9-93)	
						1 month	median 12 range (0-71)	
						6 months	median 7.5 range (0-95)	
Lenert 1997 (118)	US	•30 healthy women, 20-40 years •30 physicians	•Survey research •Recruitment: physicians in the institution and the communities surrounding the institution	•60	•Standard gamble: evaluated how much a patient will take risk of death to avoid life with post-thrombotic syndrome	Mild post-thrombotic syndrome	median 1.00 (CI:0.91–1.00)	•No UK specific data •Utility elicited using SG
						Severe post-thrombotic syndrome	median 0.95 (CI:0.79–1.00)	
						Central nervous system bleeding	median 0.60 (CI:0.02–1.00)	
Locadia 2004 (119)	The Netherlands	•Patients with 1st or 2nd episode of VTE •History of major bleeding •Post thrombotic syndrome, diagnosed at least 1 year after an episode	•Observational study •Recruitment: Invitation by researchers	•124	•Direct rating •Conventional TTO	**Time trade-off**		•No UK specific data •Utility elicited using TTO
						No VKA treatment	median 0.96 IQR (082-1)	
						Own current health	median 0.95 IQR (0.81-1)	
						VKA treatment	median 0.92 IQR (0.77-0.98)	
						Post-thrombotic syndrome	median 0.82 IQR (0.66-0.97)	
						DVT	median 0.84 IQR (0.64-0.98)	
						Muscular bleeding	median 0.76 IQR (0.59-0.95)	
						Gastrointestinal bleeding	median 0.65 IQR (0.49-0.86)	

Study (Ref ID)	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD	Appropriateness to this submission and for cost effectiveness analysis
		of DVT				PE	median 0.63 IQR (0.36-0.86)	
						Non-fatal haemorrhagic strok	median 0.33 IQR (0.14-0.53)	
Locadia 2004 (118)	The Netherlands	• Patients with 1st or 2nd episode of VTE • History of major bleeding • Post thrombotic syndrome, diagnosed at least 1 year after an episode of DVT	• Observational study • Recruitment: Invitation by researchers	• 84	• Direct rating • Conventional TTO • Chained TTO	**Results of direct rating**		• No UK specific data • Utility elicited using TTO
						PE	35.4	
						Gastrointestinal bleeding	40	
						Muscular bleeding	50	
						DVT	60	
						Treatment with oral anticoagulants	80	
						Conventional TTO		
						PE	13	
						Gastrointestinal bleeding	18	
						Muscular bleeding	25	
						DVT	67	
						Treatment with oral anticoagulants	97	
						Chained TTO		
						PE	50	
						Gastrointestinal bleeding	49	
						Muscular bleeding	62	
						DVT	84	
						Treatment with oral anticoagulants	100	
Mathias 2013 (120)	US	• DVT patients • Mean age ±SE: 54.27 ±17.5	• Observational study • Recruitment: Invitation by researchers	• 111	• Health Utilities Index • Short Form-12, and • DVT-specific scales	**Mean Scale Scores at Pre-DVT Assessment**		• No UK specific data • Utility elicited by HUI (valuation method not reported)
						No Symptoms	0.84 (SE 0.04)	
						Moderate Symptoms	0.78 (SE 0.03)	
						Severe Symptoms	0.73 (SE 0.05)	
						Baseline		
						No Symptoms	0.84 (SE 0.03)	
						Moderate Symptoms	0.79 (SE 0.02)	
						Severe Symptoms	0.69 (SE 0.04)	
						Follow-up Assessment		
						No Symptoms	0.66 (SE 0.07)	
						Moderate Symptoms	0.76 (SE 0.04)	
						Severe Symptoms	0.66 (SE 0.09)	
O'Meara 1994 (121)	USA	• Age ≥ of 50 years	• Survey research • Recruitment: random	• 36	• Standard Gamble	**No history of DVT**		•
						Good health	1	

Study (Ref ID)	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD	Appropriateness to this submission and for cost effectiveness analysis
			selection of 36 patients			DVT with mild postphlebitic syndrome	0.995	
						DVT with severe postphlebitic syndrome	0.977	
						Central nervous system bleeding	0.29	
						DVT with postphlebitic syndrome		
						Good health	1	
						DVT with mild postphlebitic syndrome	0.997	
						DVT with severe postphlebitic syndrome	1	
						Central nervous system bleeding	Not applicable	
						All patients		
						Good health	1	
						DVT with mild postphlebitic syndrome	0.995 (CI:0.99-1)	
						DVT with severe postphlebitic syndrome	0.982 (CI:0.962-1)	
						Central nervous system bleeding	0.29 (CI:0.127-0.453)	
Sullivan 2006 (16)	USA	• Medical Expenditure Penal Survey from 2000 to 2002 • Age > 18 years	• Retrospective study	• 38,678 individual include in the study. • 100 patients with ICD-9 453	• EQ-5D	ICD-9 453 Other Venous Thrombosis	0.727 IQR (0.597, 0.827)	• EQ-5D use but USA tariffs
Sullivan 2011 (RE-COVER Trial) (112)	NR	• Acute VTE patients	• RCT	• 2509 `randomised • 2299 completed	• EQ-5D • UK weights • Reported as magnitude changes in EQ-5D index scores	Increment associated with 6 month post VTE	0.21	• Use of EQ-5D and UK weight tariffs
						Increment associated with 3 month post VTE	0.192	
						Decrement associated with recurrent DVT	-0.17	
						Decrement associated with underweight	-0.09	
						Decrement associated with female	-0.08	
						Decrement associated with morbidly obese	-0.07	
						Decrement associated with recurrent PE	-0.06	

Study (Ref ID)	Country	Patient population	Study design, recruitment	Sample size and response	Elicitation Method, Valuation and mapping	Health States/Patient groups	Results (mean) with SD	Appropriateness to this submission and for cost effectiveness analysis
						Decrement associated with heart failure	-0.05	
						Decrement associated with age >65	-0.04	
						Decrement associated with clinically relevant bleeding	-0.03	
Tavoly 2013 (122)	Norway	•208 PE patients, 23-86 years •114 age- and sex-matched (+ 5 years) controls	•Case-control study •Recruitment: PE patients and control group from relatives or friends having no previous history of VTE (two age- and sex-matched (+ 5 years)	•322	•EQ-5D •EQ-VAS	PE Patients	median 0.81 (SD 0.22)	•Use of EQ-5D but method of valuation not reported
						Controls	median 0.92 (SD 0.16)	

IQR, Interquartile Range; SF-12, Short Form-12-CDT, Catheter Directed Thrombolysis; DVT, Deep Vein Thrombosis-HRQOL , Health Related Quality Of Life; HUI, Health Utilities Index; NICE, National Institute for Health and Care Excellence; PE, Pulmonary Embolism-PSVT, Primary Subclavian Vein Thrombosis; PTS, Post-Thrombotic Syndrome; QoL, Quality of Life; SD, Standard Deviation; SE, Standard Error; TTO, Time Trade Off; VTE, Venous Thromboembolism; VTK, Vitamin K Antagonist

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.

Not applicable.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

The adverse events that were considered in this model were the clinical outcomes modelled as events, namely CRNMB, MB, HIT. These were assumed to reduce a patient's HRQL for a limited time period and not permanently.

This is based on published literature and consistent with assumptions in previous dabigatran STA for VTE. In the economic model, each of these adverse events was associated with a temporary disutiliy.

These events were associated with a utility decrement using two methods:

- For HIT, a disutility was subtracted from the health state utility of the patient experiencing the event, and applied for the duration of the event. A patient experiencing the HIT event had a reduction of 0.0712 applied to his utility in the appropriate cycle.
- For CRNMB and MB, a relative decrement was applied from the health state utility of the patient experiencing the event. A patient experiencing the CRNMB event had a reduction of 19% applied to his utility in the appropriate cycle, and a patient experiencing the MB event had a reduction of 38% applied to his utility in the appropriate cycle.

All disutilities applied in this model and their respective durations can be found in Table B 79 in section 7.4.9.

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 model, all patients are assigned a baseline utility value adjusted on age according to the UK population norm. Health state-related disutilities are applied to patients in each health state. For the recurrent VTE and HIT states, disutilities are applied additively whereas for the other states, they are multiplicative.

A summary of quality-of-life values for cost-effectiveness analysis is presented in Table B 79.

Table B 79. Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
Treatment	-0.0120*	-0.24 ; 0.000	Marchetti et al,	Well documented limitations of

State	Utility value	Confidence interval	Reference in submission	Justification
with warfarin			2001 (107)	warfarin (frequent INR monitoring, numerous food and drug interactions, etc.)
Treatment with NOAC	0.0000*	Not applicable	-	Set to 0 since Utility decrement from with warfarin estimated vs. NOAC.
Recurrent VTE	-0.1047*	-0.233;0.024	Sullivan et al, 2011 (112)	Unweightened QALY decrement of recurrent DVT and recurrent PE
HIT	-0.0712*	-0.14 ; -0.000	Gould et al, 1999 (123)	The QALY decrement is 0.00274 (1 day of null utility over 1 year). Loss of QALY over one cycle only = 0.00274*26= 0.0712
VTE index event	[redacted]	[redacted]	Hokusai-VTE substudy	Used for face validity for all first cycles Data from Hokusai-VTE substudy, EQ-5D utility at baseline
CRNMB	-19%**	-30.91% ; -6.56%	Locadia et al, 2004 (118)	Relative decrement estimated at 55 years of age from Locadia et al, 2004 (utility 0.648)
MB	-38%**	-65.26% ; -10.83%	Locadia et al, 2004 (118)	Relative decrement estimated at 55 years of age from Locadia et al, 2005 (utility 0.494)
CTEPH	-30%**	-59.99% ; 0.45%	Meads et al, 2008 (124)	Relative decrement estimated at 55 years of age from Meads et al, 2008 (utility 0.56)
LT CTEPH	-30%**	-59.99% ; 0.45%	Meads et al, 2008 (124)	Relative decrement estimated at 55 years of age from Meads et al, 2008 (utility 0.56)
Stroke	-59%**	-156.68 ; 39.45%	Locadia et al, 2004 (118)	Relative decrement estimated at 55 years of age from Locadia et al, 2004 (utility 0.33)
Post-stroke	-11%**	-21.11% ; 3.32%	Lunde, 2013 (125)	Relative decrement estimated at 55 years of age from Lunde, 2013 (utility 0.713)
Post thrombotic syndrome	-16%**	-24.45% ; -6.76%	Locadia et al, 2004 (118)	Relative decrement estimated at 55 years of age from Locadia et al. 2004 (utility 0.673)
Deaths	0.0000	Not applicable	-	By definition

* absolute utility decrement ** relative utility decrement

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**

[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.

- **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).**

No clinical experts were consulted to assess the utilities included in the analysis.

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?

Except for the utility associated with the VTE index event, all disutilities associated with each health state or event in the model are applied to the national utility norm associated with the age of the patients. Details are presented in section 7.4.9.

The utility estimates associated with each health state or event are assumed to be constant for a patient of a given age (with an adjustment for age being included in the model) in the base case analysis, with the between-subject variance accounted for in the PSA, based on the standard deviation provided by the same source as the base case.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects identified in the literature or clinical trials was excluded from the analysis.

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?

At entry in the model, utilities of the index VTE event were applied for the duration of one cycle, and were derived from the Hokusai-VTE EQ-5D data. This had no impact on the results since it is applied uniformly across treatment arms, but was included for face validity.

In following cycles, a UK age-specific utility norm is applied as baseline, from which decrements relative to each health state (VTE recurrence, major bleeding, CRNMB, stroke, post-stroke rehabilitation, CTEPH and long-term CTEPH), expressed as proportions of the norm, are subtracted.

In addition, in the warfarin arm, in the on treatment states, a further decrement is applied to account for the loss in quality-of-life of using warfarin instead of an oral anticoagulant.(107)

7.4.14 **Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.**

Health related quality of life is not assumed to be constant over time as adjustments were made for cohort aging. All the disutilities are applied to the utility norm of the UK population in function of the age.(126) As a result, the global utility is decreasing with age.

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.**

The values described in sections 7.4.37.4.8 have not been amended.

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.**

Table B 80 to Table B 82 present the unit costs that were applied to each clinical event, and how the costs were estimated. NHS Reference costs (2012/2013) were used for hospitalizations and the exhaustive list of HRGs considered can be found in Table B 80. BNF costs were used for drugs. The cost of stroke and post-stroke came from published literature.

7.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.**

In the base case analysis, 2012/13 NHS reference costs were used where possible. Where procedures do not have HRG codes or the codes are not sufficiently disaggregated, such as for long term care and type and severity of stroke, unit costs have been identified from published literature.

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-**

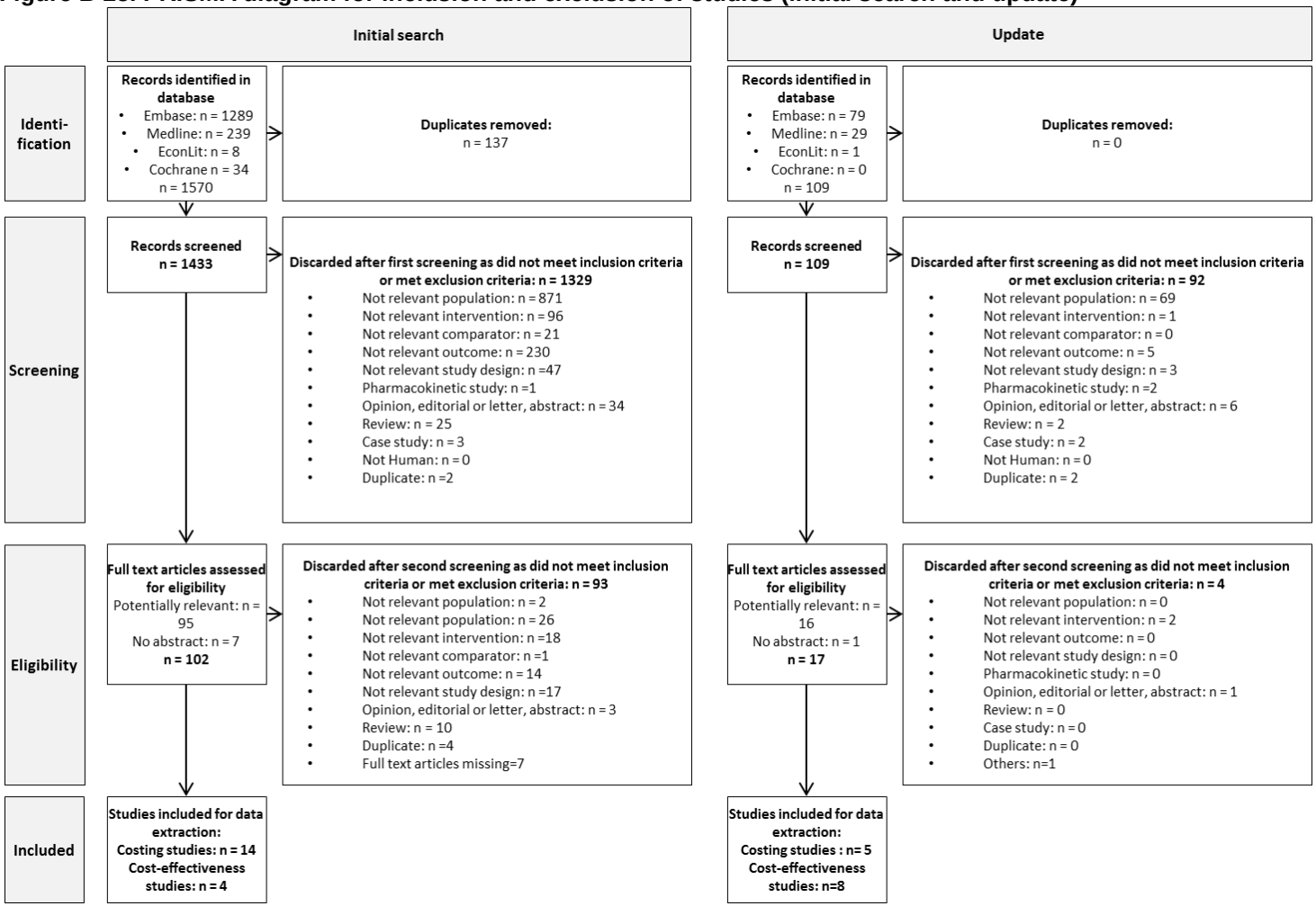
specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology cost**

The strategies used to identify relevant resource data for the UK is similar to the strategies used to identify cost-effectiveness studies, described in section 7.1.

The article selection process is summed up in Figure B 25. Out of the 19 costing studies identified, none was performed in the UK.

Figure B 25. PRISMA diagram for inclusion and exclusion of studies (initial search and update)



7.5.4 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:**

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical 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).

No clinical experts were consulted to assess the resource use included in the analysis.

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.**

For all the treatments, the costs associated with the first cycle of treatment (corresponding to the treatment of the index VTE event) were calculated independently of the costs of the following cycles. First, the intermediate calculation for the costs of LMWH/heparin is presented.

Cost associated with the use of LMWH/heparin

For warfarin, edoxaban and dabigatran, treatment is initiated either following a heparin lead-in, or overlapping with heparin lead-in. The daily drug cost is estimated as the average cost of four different heparin products available on the market.The daily cost of administration of heparin was calculated using a weighted average of self-administration costs and the cost of administration by professionals.

Administration cost is estimated as daily cost and is applied for the number of days with LMWH/heparin, whereas the cost of instructions is considered only once,

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

irrespective of the duration of LMWH/heparin therapy. Unit costs for LMWH/heparin are presented in Table B 80.

Table B 80. Unit costs associated with the technology in the economic model - LMWH/heparin

Instructions of self-administration of LMWH	£38.00	NHS reference cost 2012-2013:N02AF "District Nurse, Adult, Face to face" 24,729,481 stays $38
Administration of LMWH by professionals	£38.00	NHS reference cost 2012-2013:N02AF "District Nurse, Adult, Face to face" 24,729,481 stays $38
Proportion of patients self-administering vs. done by professional	92%	Assumption supported by STA for rivaroxaban (page 148) based on NICE Clinical Guideline 92 (CG92). Venous thromboembolism: reducing the risk. http://guidance.nice.org.uk/CG92 and National Collaborating Centre for Acute Care. Venous Thromboembolism. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. http://www.nice.org.uk/nicemedia/pdf/CG92FullGuideline.pdf
Cost of dalteparin per day	£8.50	BNF Price: £8.47, dose:15,000-unit (0.6-mL) syringe
Proportion of patients receiving dalteparin	25%	Assumption supported by STA for rivaroxaban (page 323)
Cost of tinzaparin per day	£11.90	BNF Price:£11.90,dose:20 000 units/mL:0.7-mL (14 000-unit) syringe
Proportion of patients receiving tinzaparin	25%	Assumption supported by STA for rivaroxaban (page 323)
Cost of enoxaparin per day	£8.00	BNF Price: £8.03,dose:100-mg (1-mL, 10 000-units) syringe
Proportion of patients receiving enoxaparin	25%	Assumption supported by STA for rivaroxaban (page 323)
Cost of unfractioned heparin per day	£7.60	BNF Price: £7.58,dse:5000 units/mL:5-mL amp
Proportion of patients receiving unfractionated heparin	25%	Assumption
Total LMWH/heparin cost	**£9.00**	

The total cost associated with the use of LMWH/heparin depends on the number of days this drug is taken and therefore is calculated for each treatment of interest.

This cost applies only for the first cycle.

Cost of treatment with warfarin

Warfarin was considered to be initiated in co-administration with LMWH/heparin during 8.5 days. The daily cost of warfarin was estimated to be £0.06. As a result, the cost of treatment associated with warfarin was £138.00 for the first cycle and £0.88 for the following ones.

Cost of treatment with edoxaban

Edoxaban was considered to be started after 5 days of LMWH/heparin treatment. The daily cost of edoxaban was assumed to be £[redacted]. The cost of treatment associated with edoxaban during the first cycle was £[redacted] and £[redacted] for the following ones.

Table B 81 presents the unit costs associated with edoxaban and warfarin.

Table B 81. Unit costs associated with the technology in the economic model – edoxaban and warfarin

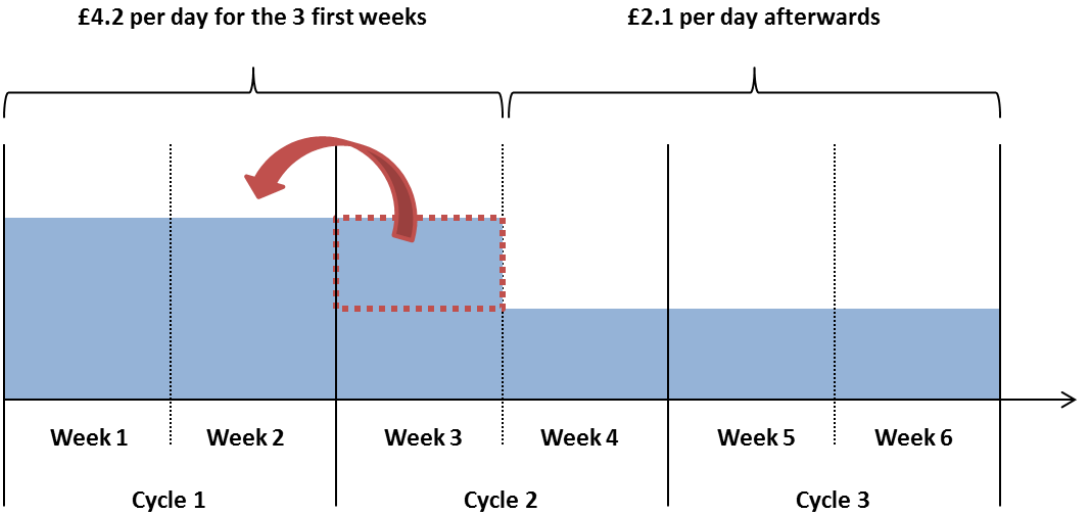
Items	Edoxaban	Ref. in submission	Warfarin	Ref. in submission
INR monitoring	£0.00	No monitoring with NOAC	£24.00	NHS reference cost 2012-2013: -"324 Non- consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,149,507 stays £18.00 -"324 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,588,225 stays £29
Number of INR monitoring visits per cycle	0	No monitoring with NOAC	1.1	Rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year)*
Total Monitoring cost	**£0.00**		**£26.41**	
Daily cost of drug	£[redacted]	[redacted]	£0.06	Daiichi Sankyo
Number of days of LMWH/heparin	5.0 (lead-in)	Assumption of SmPC similar to dabigatran	8.5 (overlapping)	Hokusai-VTE CSR Table 12.2: Warfarin 8.5 days (n= 4,122)
Total cost of drug(first cycle)	**£[redacted]**		**£138.14**	
Total cost of drug (following cycles)	**£[redacted]**		**£0.88**	

* VKA treatment requires frequent INR testing to ensure treatment is both safe and effective. This is most intensive at initiation of treatment. On the basis of BCSH guidelines (127;128), SIGN guidelines (125), an observational research study of UK anticoagulation services (129) and information in the BNF (130), it is estimated that the frequency of monitoring visits on VKA treatment is 9 monitoring visits in the first 3 months of treatment and 5 visits per quarter thereafter.

Cost of treatment with rivaroxaban

Rivaroxaban has a 21-day twice-daily initiation dose; the subsequent maintenance dose is once-daily. The daily cost of rivaroxaban is therefore £4.20 during the first three weeks and £2.10 afterwards. To make it easier to model the 21-day initiation dose in a 14-day cycle, the following calculation is applied for the first cycle of the model: (£4.20*14) + (£2.10*7). The first term corresponds to the first two weeks of treatment, and the second term corresponds to cost of the second daily dose during the third week of treatment. The cost of rivaroxaban is therefore artificially increased to £88.20 during the first cycle, and is £30.76 during subsequent cycles. This is illustrated in Figure B26.

Figure B 26. Rivaroxaban cost per cycle



The cost of twice-daily treatment in week three is moved into the first cycle, so that from the second cycle onward the cost of the once-daily maintenance dose can be used.

Cost of treatment with dabigatran

As edoxaban, dabigatran required a 5-day LMWH/heparin lead-in. The daily cost of dabigatran was considered to be £2.20 resulting in a first-cycle cost of £114.90 and a following-cycle cost of £30.80.

Table B 82 presents the unit costs associated with rivaroxaban and dabigatran.

Table B 82. Unit costs associated with the technology in the economic model – rivaroxaban and dabigatran

Items	Rivaroxaban	Dabigatran
INR monitoring	£0.00	£0.00
Number of INR monitoring per cycle	£0.00	£0.00
Total Monitoring cost	£0.00	£0.00
Daily cost of drug	BNF net price 1st cycle: £4.20 Following cycles: £2.10	BNF net price £2.20
Number of days of LMWH/heparin	0 day	Dabigatran submission 5 as lead-in
Total cost of drug (first cycle)	**£88.20**	**£114.90**
Total cost of drug (following cycles)	**£29.40**	**£30.80**

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.**

All the costs by health state are presented in Table B 83. Appropriate HRGs codes (2012/2013) were used when relevant.

On treatment state

The costs of the "on treatment" state for the first cycle include the costs associated with the diagnosis and the treatment of the index VTE event: outpatient and inpatient costs. For the following cycles, the cost of the "on treatment" state corresponds directly to the cost of treatment. Costs of PTS are also applied in this state. During the first year, 3 appointments for vascular surgery are considered: The first one costs £162 and the following ones cost £111 each. They are applied on the cycles 2, 10 and 18 respectively. During the following years, PTS lead to two additional GP visits per year (£36 per visit so £2.80 per cycle).

Warfarin treatment requires monitoring that was estimated to be £26.40 per cycle considering. 9 visits in first three months, then 5 visits per quarter (24 per year) and a unit cost for visit of £24.

VTE recurrence state

The costs of VTE recurrence include the costs of diagnosis and treatment of DVT (£731) and diagnosis and treatment of PE (£1,500).

Off treatment state

No costs are applied in the off-treatment state.

HIT state

Costs associated with HIT are included in this state: £693.

CRNMB state

Costs associated with CRNMB are estimated to be £138.

MB state

Costs associated with MB are £1,092.

CTEPH state

This state includes the costs for the treatment of CTEPH including surgery and drug therapy. 56.8% of patients with CTEPH undergo pulmonary endodartectomy with a unit cost of £7,006. 51.5% of patients are receiving a drug therapy (sildenafil or bosentan). The total costs per event were estimated to be £4,164.

LT-CTEPH state

Costs of therapy for LT-CTEPH are included in this state. Using the proportion of patients treated, among them the distribution between sildenafil and bosentan and the unit costs of the drugs, the total costs per cycle were estimated to be £184.

Stroke state

Costs associated with a stroke event are estimated to be £3,118.

Post-stroke state

Annual cost for stroke survivors was estimated to be £6,880 so a cost per cycle estimated at £265.

Death states

No costs are included in these states (disease-related death and other-cause mortality).

Table B 83. List of health states and associated costs in the economic model

Health states	Items	Value	Reference in submission
On treatment	Doppler Ultrasound	£51.00	NHS reference cost 2012-2013"RA23Z Ultrasound Scan less than 20 minutes": 3,253,774 £51
	CT angiography	£90.00	NHS reference cost 2012-2013"RA08Z Computerised Tomography Scan, one area, no contrast": 651,669 £90
	Electrocardiogram (ECG)	£31.00	NHS reference cost 2012-2013"DA01 CECG [12 Lead]": 241,662 £31
	D-dimer	£12.00	Assumption from Rivaroxaban submission
	Proportion of patients receiving imaging and diagnosis	50%	Assumption from Rivaroxaban submission
	Total Outpatient cost	**£92.00**	**Sum of outpatient costs, weighted by proportion of patients receiving imaging**
	INR monitoring	£24.00	NHS reference cost 2012-2013: -"324 Non- consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,149,507 stays £18 -"324 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 1,588,225 stays £29
	Number of INR monitoring per cycle	1.1	Rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year)
	Total Monitoring cost on warfarin	**£26.41**	**Product of unit cost and number of units per cycle**
	Diagnosis and treatment of DVT	£732.00	NHS reference cost 2012-2013: "QZ20A Deep Vein Thrombosis with CC Score 12+": 3,108 stays £726 "QZ20B Deep Vein Thrombosis with CC Score 9-11" :3,093 stays £884 "QZ20C Deep Vein Thrombosis with CC Score 6-8": 4,773 stays £1,102 "QZ20D Deep Vein Thrombosis with CC Score 3-5": 9,441 stays £869 "QZ20E Deep Vein Thrombosis with CC Score 0-2": 16,764 stays £522
	Diagnosis and treatment of PE	£1,500	NHS reference cost 2012-2013: -DZ09A "Pulmonary Embolus with Major CC":15,799 stays £1,876 -DZ09B "Pulmonary Embolus with CC":15,404 stays £1,354 -DZ09C "Pulmonary Embolus without CC":6,330 stays £920
	Total Inpatient costs	**£1,044.00**	Assuming 59.3% of DVT only
	Instructions of self-administration of LMWH	£38.00	NHS reference cost 2012-2013:N02AF "District Nurse, Adult, Face to face" 24,729,481 stays $38
	Administration of LMWH by professionals	£38.00	NHS reference cost 2012-2013:N02AF "District Nurse, Adult, Face to face" 24,729,481 stays $38
	Proportion of patients self-administering vs. done by professional	0.9200	Assumption supported by STA for rivaroxaban (page 148) based on National Institute for Health and Clinical Excellence. Clinical Guideline 92 (CG92). Venous thromboembolism: reducing the risk. http://guidance.nice.org.uk/CG92 and

Health states	Items	Value	Reference in submission
			National Collaborating Centre for Acute Care. Venous Thromboembolism. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. http://www.nice.org.uk/nicemedia/pdf/CG92FullGuideline.pdf
	Cost of dalteparin per day	£8.50	BNF Price: £8.47, dose:15,000-unit (0.6-mL) syringe
	Proportion of patients receiving dalteparin	0.2500	Assumption
	Cost of tinzaparin per day	£11.90	BNF Price:£11.90,dose:20 000 units/mL:0.7-mL (14 000-unit) syringe
	Proportion of patients receiving tinzaparin	0.2500	Assumption
	Cost of enoxaparin per day	£8.00	BNF Price: £8.03,dose:100-mg (1-mL, 10 000-units) syringe
	Proportion of patients receiving enoxaparin	0.2500	Assumption
	Cost of unfractioned heparin per day	£7.60	BNF Price: £7.58,dse:5000 units/mL:5-mL amp
	Proportion of patients receiving unfractionated heparin	0.2500	Assumption
	Total daily heparin cost	**£9.00**	**Weighted average**
	Additional cost due to PTS		
	Cost of vascular surgery outpatient appointment (first)	£162.00	Goodacre et al. 2006 (131) In the first year three vascular surgery outpatient appointments. NHS reference cost
	Cost of vascular surgery outpatient appointment (following)	£111.00	Goodacre et al. 2006 (131) In the first year three vascular surgery outpatient appointments. NHS reference cost
	Cost of one GP visit	£36.00	Goodacre et al. 2006 (131) Thereafter two GP visits per year. NHS reference cost
	Warfarin		
	Daily cost of warfarin	£0.06	BNF price:Dose: 5–10 mg ,28-tab pack = 88p; 5mg
	Number of days of heparin co-adminitration	8.5	Hokusai-VTE CSR Table 12.2: edoxaban 7.5 days (n=4,118), warfarin 8.5 days (n= 4,122)
	Total cost of warfarin (first cycle)	**£138.14**	**Daily cost multiplied by 14 days in a cycle added to heparin co-ad**
	Total cost of warfarin (following cycles)	**£0.88**	**Daily cost multiplied by 14 days in a cycle**
	Edoxaban		
	Daily cost of edoxaban	£[redacted]	Daiichi Sankyo
	Number of days of heparin lead-in	5.0	Assumption of SmPC similar to dabigatran
	Total cost of edoxaban (first cycle)	**£[redacted]**	**Daily cost multiplied by 14 days in a cycle added to heparin lead-in**
	Total cost of edoxaban (following cycles)	**£[redacted]**	**Daily cost multiplied by 14 days in a cycle**
	Dabigatran		
	Daily cost of dabigatran	£2.20	BNF net price 150 mg 60-cap pack =£65.90 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days
	Number of days of heparin lead-in	5.0	Dabigatran SmPC: recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days
	Dabigatran + heparin (first cycle)	**£114.91**	The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. So we must have cost of heparin for 5 days, and cost of dabigatran for 9 days

Health states	Items	Value	Reference in submission
			(twice daily). Cost per day: £2.197 (150 mg, 60-cap pack = £65.90)
	Dabigatran (following cycles)	**£30.76**	BNF net price 110 mg 10-cap pack = £10.98,dose:75 mg,once daily,cost per day=10.98/10=£1.098
	Rivaroxaban		
	Rivaroxaban (first cycle)	**£88.20**	15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE
	Rivaroxaban (following cycles)	**£29.40**	14-tab pack = £29.40 dose:15 mg once daily,cost per day=29.40/14=£2.1
VTE recurrence	Cost of hospitalisation for DVT	£731.00	NHS reference cost 2012-2013: "QZ20A Deep Vein Thrombosis with CC Score 12+": 3,108 stays £726 "QZ20B Deep Vein Thrombosis with CC Score 9-11" :3,093 stays £884 "QZ20C Deep Vein Thrombosis with CC Score 6-8": 4,773 stays £1,102 "QZ20D Deep Vein Thrombosis with CC Score 3-5": 9,441 stays £869 "QZ20E Deep Vein Thrombosis with CC Score 0-2": 16,764 stays £522
	Cost of hospitalisation for PE	£1,500.00	NHS reference cost 2012-2013: -DZ09A "Pulmonary Embolus with Major CC":15,799 stays £1,876 -DZ09B "Pulmonary Embolus with CC":15,404 stays £1,354 -DZ09C "Pulmonary Embolus without CC":6,330 stays £920
	Total	£1,044.00	Assuming 59.3% of DVT only
Off treatment	**Total**	**£0.00**	Assumption
HIT	Cost of hospitalisation	£693.00	NHS Reference costs year 2012-13, weighted average of: - SA12G "Thrombocytopenia with CC score 8+" : 619 stays, £2,452 - SA12H "Thrombocytopenia with CC score 5-7" : 1,146 stays, £1,279 - SA12J "Thrombocytopenia with CC score 2-4" : 3,346 stays, £816 - SA12K "Thrombocytopenia with CC score 0-1" : 9,764 stays, £470 All pertaining to ICD10 code D69.5 "Secondary thrombocytopenia"
	Total	**£693.00**	**Weighted average**
CRNMB	Cost of hospitalisation	£138.00	NHS Reference Costs year 2012-2013: VB07Z "Emergency Medicine, Category 2 Investigation with Category 2 Treatment" Activity:1,966,223
	Total	**£138.00**	**Weighted average**
MB	Cost of hospitalisation	£1,092.00	NHS Reference costs year 2012-13, weighted average of: - FZ38G Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+: 774 stays, £4993 - FZ38H Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4: 1217 stays, £3097 - FZ38J Gastrointestinal Bleed, with Single Intervention, with CC Score 8+: 661 stays, £3591 - FZ38K Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7: 1721 stays, £2693 - FZ38L Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4: 7265 stays, £1872 - FZ38M Gastrointestinal Bleed, without Interventions, with CC Score 9+: 1619 stays, £2121 - FZ38N Gastrointestinal Bleed, without Interventions, with CC Score 5-8: 10300 stays, £1373 - FZ38P Gastrointestinal Bleed, without Interventions, with CC Score 0-4: 66817 stays, £791 All HRGs related to bleeds

Health states	Items	Value	Reference in submission
	Total	**£1,092.00**	**Weighted average**
CTEPH	Pulmonary endodartectomy	£7,006.00	NHS Reference costs year 2012-13, weighted average of: - DZ02E "Complex Thoracic Procedures with CC score 5-7" in "Cardiothoracic surgery": 463 stays, £8,061 - DZ02E "Complex Thoracic Procedures with CC score 5-7" in "Thoracic surgery": 1,015 stays, £8,246 - DZ02F "Complex Thoracic Procedures with CC score 2-4" in "Cardiothoracic surgery": 1,361 stays, £7,211 - DZ02F "Complex Thoracic Procedures with CC score 2-4" in "Thoracic surgery": 2,519 stays, £6,894 - DZ02G "Complex Thoracic Procedures with CC score 2-4" in "Cardiothoracic surgery": 825 stays, £6,465 - DZ02G "Complex Thoracic Procedures with CC score 2-4" in "Thoracic surgery": 1,469 stays, £6,125 All pertaining to OPCS code L041 "Pulmonary thromboendodartectomy"
	Per cycle cost of sildenafil	£208.00	BNF - Revatio (sildenafil) 20 mg, 90-tab pack = £446.33 Indication 20 mg three times daily
	Per cycle cost of bosentan	£755.00	BNF - Tracleer (bosentan) 62.5 mg, 56-tab pack = £1,510.21 Indication 62.5 mg twice daily
	Proportion of patients undergoing surgery	56.8%	Pepke-Zaba et al. 2011 (132)
	Proportion of patients receiving drug therapy	51.5%	Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 38)
	Proportion of patients receiving sildenafil	69.4%	Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 36)
	Proportion of patients receiving bosentan	28.3%	Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 36)
	Total	**£4,164.00**	**Average total costs weighted by proportion of patients undergoing surgery, and distribution of market shares between sildenafil and bosentan**
LT CTEPH	Per cycle cost of sildenafil	£208.30	BNF - Revatio (sildenafil) 20 mg, 90-tab pack = £446.33 Indication 20 mg three times daily
	Per cycle cost of bosentan	£755.10	BNF - Tracleer (bosentan) 62.5 mg, 56-tab pack = £1,510.21 Indication 62.5 mg twice daily
	Proportion of patients receiving drug therapy	51.5%	Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 38)
	Proportion of patients receiving sildenafil	69.4%	Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 36)
	Proportion of patients receiving bosentan	28.3%	Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013 (page 36)
	Total	**£184.00**	**Average total costs weighted by distribution of market shares between sildenafil and bosentan**
Stroke	Cost of hospitalisation	£3,118.00	NHS Reference costs year 2012-13, weighted average of: -AA35A "Stroke with CC Score 16+" :1,970 stays,£9,105 -AA35B "Stroke with CC Score 13-15":6,187 stays,£6,844 -AA35C "Stroke with CC Score 10-12":13,534 stays,£5,104 -AA35D "Stroke with CC Stroke 7-9":26,807 stays,£3,442 -AA35E "Stroke with CC Score 4-6":46,942 stays, £2,590 -AA35F "Stroke with CC Score 0-3":44,927,£2,100
	Total	**£3,118.00**	**Weighted average**
Post stroke	Annual cost for stroke survivors	£6,880.00	Lunego-Fernandez et al. 2012 (133)
	Total	**£265.00**	**Cost per cycle**
Death	**Total**	**£0.00**	**Assumption**

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.**

Adverse events included are HIT, CRNMB and MB and are considered as independent health states. The costs associates with these states are already described in the previous section and correspond to the related cost of hospitalisation.

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.**

No additional costs were included in the model.

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.**

Structural assumptions about treatment duration and timeframe were investigated. The treatment duration can vary: 3 months, 6 months, 12 months and lifelong. The

different timeframes that can be chosen are: 3 months, 6 months, 1 year, 2 years, 5 years, 10 years, 20 years and lifetime. These structural modifications impact the transition matrices

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.

One way deterministic sensitivity analyses were run on the following inputs:

- Transition probabilities for warfarin using 95%-confidence interval bounds as low and high values
- Probabilities of complications while on warfarin or NOAC using 95%-confidence interval bounds as low and high values
- Probability of death using 95%-confidence interval bounds as low and high values
- Hazard ratio for VTE recurrence compared to warfarin using 95%-confidence interval bounds as low and high values
- Utility values and utility decrement using 95%-confidence interval bounds as low and high values
- Costs with a variation of +/-20% (assumption)

The variables included in the sensitivity analysis are presented in section **Error! Reference source not found.** Appendix 16.

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).

A PSA was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. Key parameters were varied by sampling from probability distributions.

The model was run for 2,000 simulations to generate total costs and QALYs for each treatment arm by varying event rates, costs, risks and utilities and population characteristics simultaneously. Time horizon and model settings were kept constant.

A number of probability distributions were employed including the beta, lognormal, normal, normal positive and non-parametric distributions. The PSA parameters are provided in Section **Error! Reference source not found.** Appendix 17.

Probabilities, such as VTE-related death rate and event rates, were sampled from a beta distribution. This distribution is a conjugate of the binomial and is bounded by 0 and 1. The parameterisation consists of denoting the shape parameter (i.e. alpha) as the number of events and the scale parameter (i.e. beta) as the number of non-events. Patient numbers obtained from the trials or from published estimates were used to represent this source of variation. For baseline event rates for warfarin, alpha and beta was estimated by calculating the mean alpha (number of events per cycle), and the mean beta (number of non-events per cycle) over the trial period.

Odds-ratios were assumed to be distributed according to a lognormal distribution except for the ones estimated from the NMA. Indeed, the non-parametric distribution of ORs generated from the NMA was used for the risk of recurrence, of MB and CRNMB. For other ORs, the standard error around the ORs found in the literature or Hokusai-VTE RCT was estimated from the reported 95% confidence intervals, by taking the natural logarithms of the upper and lower limit, and dividing the width of the adjusted interval by 1.96*2.

Costs were sampled from a normal distribution assumed the base case as the mean and 10% of the mean as standard deviation.

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.**

Clinical trial results are compared against model outcomes in Table B 84. The follow-up duration of the Hokusai-VTE trial is 12 months, so the model outcomes have been evaluated at this time point, calculating the total number of clinical outcomes represented by health states in the first 26 cycles of the model.

It is important to note that the incidence of these outcomes (Recurrent VTE, HIT, CRNMB, MB, Stroke, CTEPH and death) as captured in the Hokusai-VTE study represent the number of first events. However due to the structure of this cost-effectiveness model, it was not possible to estimate the number of first events; instead, the estimates in the model refer to the total number of events experienced.

The model appears to provide a good approximation of the clinical trial for the majority of clinical outcomes.

Table B 84. Summary of model results compared with clinical data

Outcome	Hokusai-VTE events*		Model events	
	Edoxaban N=4118	Warfarin N=4122	Edoxaban N=4118	Warfarin N=4122
Recurrent VTE	66	80	74	86
HIT	-	-	1	1
CRNMB	298	368	296	376
MB	56	66	61	65
Stroke	26	26	26	26
CTEPH	-	-	27	27
Death	35	33	39	40

* Hokusai-VTE: mITT on-treatment population; Model predictions: for one year time horizon when discontinuations due to adverse events set to 0 for comparability with Hokusai-VTE on treatment population

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 displaying the proportion of patients in each health state for each comparator are presented in Section **Error! Reference source not found.** Appendix 19.

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.

Markov traces displaying the QALYs accrued in each health state for each comparator are presented in section **Error! Reference source not found.**, appendix 20.

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 B 85 and Table B 86 present the total costs and QALYs accrued for each health state and event in the model, for each comparator.

Table B 85. Model outputs: total costs per patient (discounted)

Health state	Edoxaban	Warfarin	Dabigatran	Rivaroxaban
On treatment	£ 1,977.29	£ 1,973.09	£ 2,012.71	£ 1,936.38
VTE recurrence	£ 581.32	£ 584.39	£ 586.78	£ 581.18
Off treatment	£ 0.58	£ 0.58	£ 0.58	£ 0.58
HIT	£ 0.17	£ 0.17	£ 0.17	£ -
CRNMB	£ 10.50	£ 13.32	£ 7.79	£ 14.15
MB	£ 17.18	£ 18.22	£ 14.09	£ 10.30
CTEPH	£ 29.26	£ 29.22	£ 29.31	£ 29.24
LT CTEPH	£ 182.86	£ 182.61	£ 183.19	£ 182.78
Stroke	£ 20.44	£ 20.40	£ 20.47	£ 20.43
Post stroke	£ 719.60	£ 718.02	£ 720.70	£ 719.28
Death	-	-	-	-
TOTAL (undiscounted)	**£ 4,423.68**	**£ 4,423.27**	**£ 4,460.96**	**£ 4,378.77**
TOTAL (discounted)	**£ 3,539.20**	**£ 3,540.02**	**£ 3,575.79**	**£ 3,494.34**

Table B 86. Model outputs: QALYs and life year gained per patient (discounted)

Health state	Edoxaban	Warfarin	Dabigatran	Rivaroxaban
Total Life years gained (undiscounted)	25.44	25.43	25.42	25.45
Total Life years gained (discounted)	16.32	16.31	16.31	16.33
QALYs On treatment	0.7848	0.7718	0.7859	0.7845
QALYs VTE recurrence	0.0143	0.0144	0.0145	0.0143
QALYs Off treatment	11.7483	11.7432	11.7433	11.7563
QALYs HIT	0.0000	0.0000	0.0000	0.0000
QALYs CRNMB	0.0019	0.0024	0.0014	0.0026
QALYs MB	0.0003	0.0003	0.0002	0.0002
QALYs CTEPH	0.0002	0.0002	0.0002	0.0002
QALYs LT CTEPH	0.0208	0.0207	0.0208	0.0208
QALYs Stroke	0.0001	0.0001	0.0001	0.0001
QALYs Post stroke	0.0712	0.0710	0.0713	0.0711
QALYs Death	0.0000	0.0000	0.0000	0.0000
TOTAL QALYs (undiscounted)	**19.5240**	**19.5032**	**19.5175**	**19.5368**
TOTAL QALYs (discounted)	**12.6418**	**12.6242**	**12.6376**	**12.6500**

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.**

Table B 87. Summary of QALY gain by health state

Health state	Total QALYs				Increment: Edoxaban vs. comparator			Absolute increment: Edoxaban vs. comparator			% Absolute increment		
	Edoxaban	Warfarin	Dabigatran	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban
On treatment	0.7848	0.7718	0.7859	0.7845	0.0130	-0.0011	0.0004	0.0130	0.0011	0.0004	74%	26%	4%
VTE recurrence	0.0143	0.0144	0.0145	0.0143	-0.0001	-0.0001	0.0000	0.0001	0.0001	0.0000	0%	3%	0%
Off treatment	11.7483	11.7432	11.7433	11.7563	0.0051	0.0050	-0.0080	0.0051	0.0050	0.0080	29%	120%	98%
HIT	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0%	0%	0%
CRNMB	0.0019	0.0024	0.0014	0.0026	-0.0005	0.0005	-0.0007	0.0005	0.0005	0.0007	3%	12%	8%
MB	0.0003	0.0003	0.0002	0.0002	-0.0000	0.0001	0.0001	0.0000	0.0001	0.0001	0%	1%	1%
CTEPH	0.0002	0.0002	0.0002	0.0002	0.0000	-0.0000	0.0000	0.0000	0.0000	0.0000	0%	0%	0%
LT CTEPH	11.7483	11.7432	11.7433	11.7563	0.0051	0.0050	-0.0080	0.0051	0.0050	0.0080	29%	120%	98%
Stroke	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0%	0%	0%
Post stroke	0.0019	0.0024	0.0014	0.0026	-0.0005	0.0005	-0.0007	0.0005	0.0005	0.0007	3%	12%	8%
Death	0.0003	0.0003	0.0002	0.0002	-0.0000	0.0001	0.0001	0.0000	0.0001	0.0001	0%	1%	1%
TOTAL (undiscounted)	19.5240	19.5032	19.5175	19.5368	0.0208	0.0065	-0.0128	0.0208	0.0065	0.0128	NA	NA	NA
TOTAL (discounted)	12.6418	12.6242	12.6376	12.6500	0.0177	0.0042	-0.0082	0.0177	0.0042	0.0082	100%	100%	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B 88. Summary of costs by health state

Health state	Total Costs				Increment: Edoxaban vs. comparator			Absolute increment: Edoxaban vs. comparator			% Absolute increment		
	Edoxaban	Warfarin	Dabigatran	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban
On treatment	£1,977.29	£ 1,973.09	£ 2,012.71	£ 1,936.38	£4.20	-£35.42	£ 40.91	£ 4.20	£ 35.42	£ 40.91	512%	97%	5%
VTE recurrence	£ 581.32	£584.39	£586.78	£581.18	-£ 3.07	-£ 5.45	£0.14	£ 3.07	£5.45	£0.14	374%	15%	0%
Off treatment	£ 0.58	£0.58	£0.58	£0.58	£0.00	£0.00	-£ 0.00	£ 0.00	£0.00	£0.00	0%	0%	0%
HIT	£ 0.17	£0.17	£0.17	-	£0.00	-	£0.17	£ 0.00	-	£0.17	0%	0%	0%
CRNMB	£10.50	£ 13.32	£7.79	£14.15	-£ 2.82	£2.71	-£ 3.65	£ 2.82	£2.71	£3.65	343%	7%	8%
MB	£17.18	£ 18.22	£ 14.09	£ 10.30	-£ 1.04	£3.09	£6.88	£ 1.04	£3.09	£6.88	127%	8%	1%
CTEPH	£29.26	£ 29.22	£ 29.31	£ 29.24	£0.04	-£ 0.05	£0.01	£ 0.04	£0.05	£0.01	5%	0%	0%
LT CTEPH	£ 182.86	£182.61	£183.19	£182.78	£0.25	-£ 0.33	£0.08	£ 0.25	£0.33	£0.08	30%	1%	0%
Stroke	£20.44	£ 20.40	£ 20.47	£ 20.43	£0.04	-£ 0.03	£0.01	£ 0.04	£0.03	£0.01	5%	0%	0%
Post stroke	£ 719.60	£718.02	£720.70	£719.28	£1.57	-£ 1.10	£0.32	£ 1.57	£1.10	£0.32	192%	3%	0%
Death	-	-	-	-	-	-	-	-	-	-	-	-	-
TOTAL (undiscounted)	£4,423.68	£ 4,423.27	£ 4,460.96	£ 4,378.77	£0.41	-£37.28	£ 44.90	£ 0.41	£ 37.28	£ 4.90	-	-	-
TOTAL (discounted)	£3,539.20	£ 3,540.02	£ 3,575.79	£ 3,494.34	-£ 0.82	-£36.59	£ 44.86	£ 0.82	£ 36.59	£ 44.86	100%	100%	100%

Base-case analysis

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.**

The deterministic base case results for each comparator option are presented below.

In Table B 89, ICERs are presented for each NOAC versus warfarin. Incremental results for edoxaban versus each NOAC are presented in Table B 90.

Table B 89. Cost-effectiveness base-case results

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban	£ 3,494	16.328	12.65	-	-	-	Dominated	-
Edoxaban	£ 3,539	16.317	12.64	£ 44.86	-0.011	-0.82%	-	Dominated
Warfarin	£ 3,540	16.310	12.62	£ 0.82	-0.007	-1.77%	£2654.97	Dominated
Dabigatran	£ 3,576	16.312	12.64	£ 35.77	0.002	1.35%	Dominant	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 90. Incremental base-case results for edoxaban versus NOACs

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Rivaroxaban	£ 44.86	0.016	0.01	Dominated
Warfarin	-£ 0.82	0.007	0.02	Dominant
Dabigatran	-£ 36.59	0.006	0.00	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Edoxaban vs warfarin

As edoxaban is dominant compared to warfarin in the base case, it is not possible to generate the associated Tornado chart. The large majority of the one-way sensitivity analyses led to the same conclusion as the base case: edoxaban is dominant against warfarin.

For the high value of the probability of CTEPH between 3 months and 12 months with NOACs, the ICER raised to £20,922 per QALY gained. The high value of probability of stroke with NOAC had a similar impact, resulting in an ICER of £19,907 per QALY gained.

The low value of the probability of stroke with warfarin led the ICER to being £19,833 per QALY gained. The other variables that led to an impact on the conclusion (i.e. edoxaban is not dominant) are (listed in order of decreasing ICER):

- Probability of CTEPH 3 months-12 months – warfarin: Lower case ICER: £7,813
- Probability of CTEPH 14 days-3 months – NOAC: Higher case ICER: £4,459
- Probability of death while on LT-CTEPH – warfarin: Higher case ICER: £4,252
- Other variables were related to an ICER lower than £1,000:
    - Probability of CTEPH 0-14 days – NOAC
    - Probability of death due to recurrence
    - Probability of LT CTEPH 3 months-12 months – warfarin
    - Probability of LT CTEPH 3 months-12 months - NOAC
    - Odds ratio for VTE recurrence
    - Odds ratio for MB

Edoxaban vs dabigatran

Edoxaban is also dominant compared to dabigatran in the base case; therefore the tornado chart is not available.

As with the comparison versus warfarin, the majority of the variables tested had no impact on the conclusion (i.e., dominant). The high value for odds-ratio for VTE recurrence between 14 days and 3 months for edoxaban vs. warfarin led the ICER to be £43,743 per QALY gained. Oppositely, the low value for the same odds-ratio for dabigatran vs. warfarin led to an ICER of £27,035 per QALY gained. The same trend

was observed concerning the odds ratio for MB with an ICER of £7,455 per QALY gained with the high value of the OR for edoxaban and £20,266 per QALY gained for the low value of the OR for dabigatran.

Edoxaban vs rivaroxaban

Finally, edoxaban is dominated by rivaroxaban in the base case, and the tornado chart is not available. All tested parameters did not show any impact on the conclusion (i.e., edoxaban dominated).

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

For each comparator, this section presents the following:

- The cost-effectiveness plane
- Percentages of simulations falling into each quadrant
- The cost-effectiveness acceptability curve

Edoxaban vs. warfarin

Figure B 27 presents the cost-effectiveness plane for edoxaban vs. warfarin.

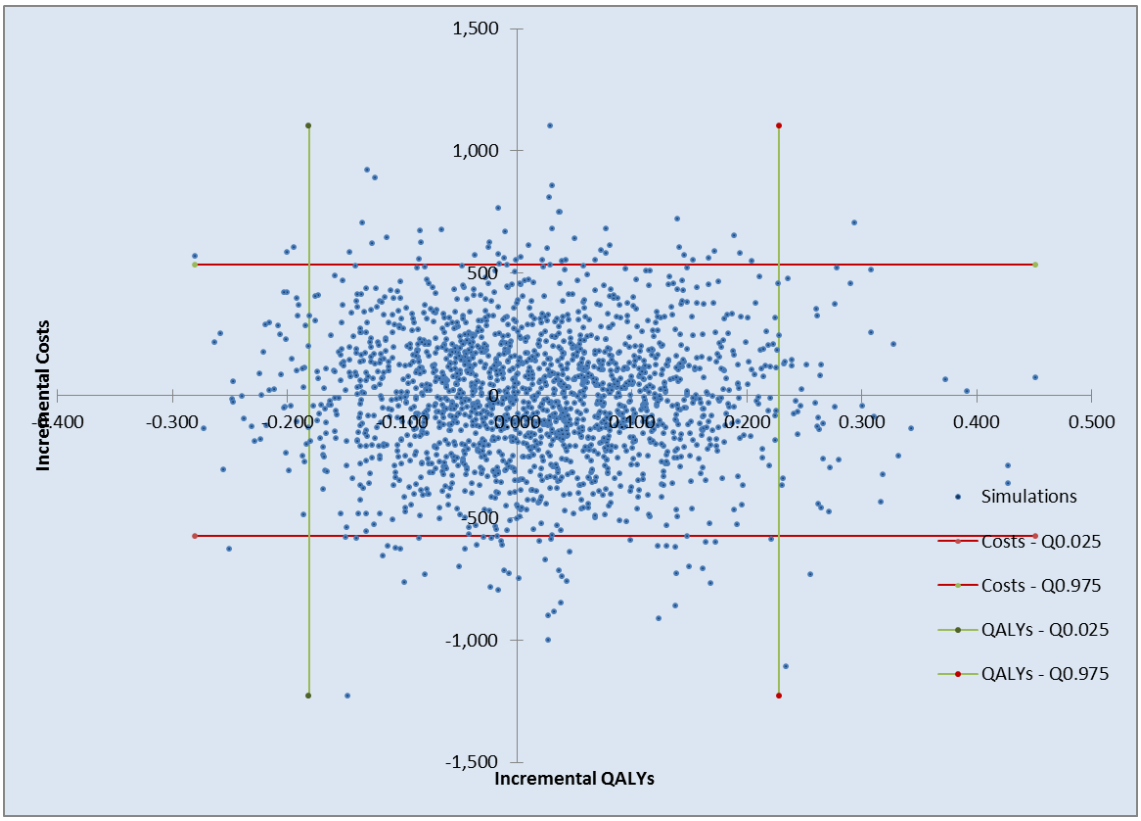


Figure B 27. Incremental cost-effectiveness plane edoxaban vs. warfarin

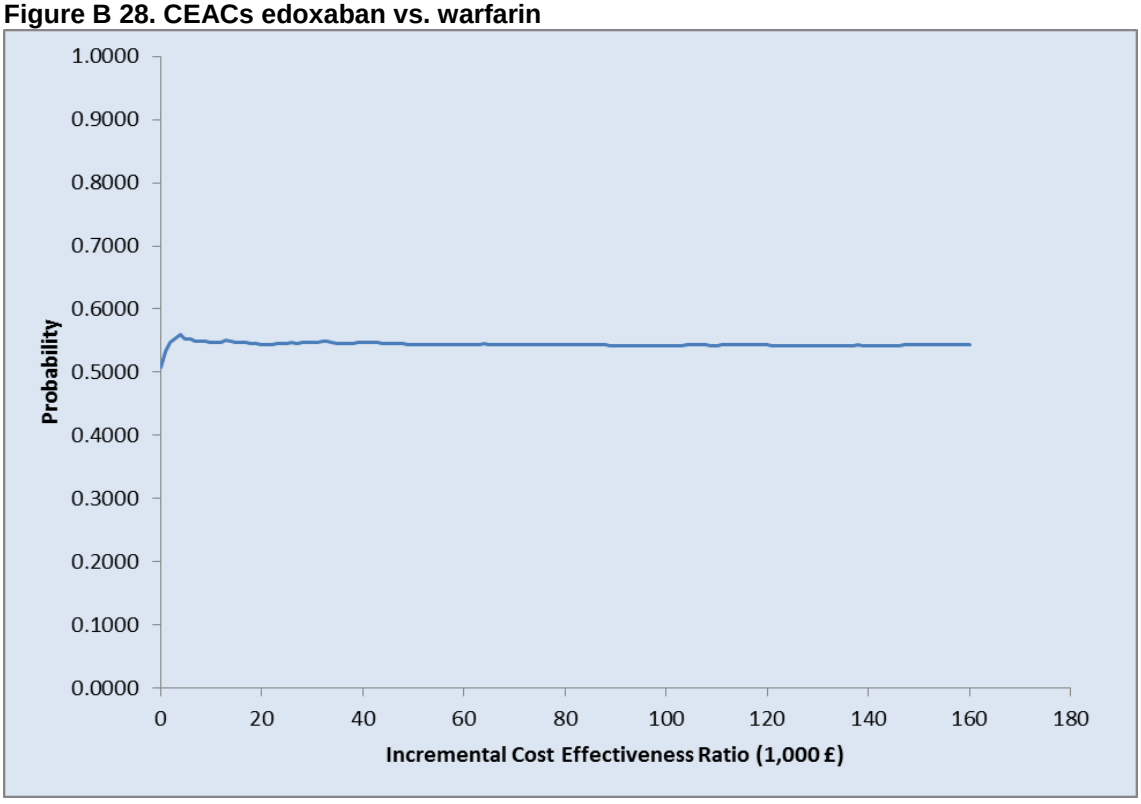
The base case analysis is almost uniformously distributed across the cost-effectiveness plane, with 28% of simulations concluding that edoxaban is dominant and 22% that it is dominated (Table B 91). This distribution illustrates the uncertainty surrounding the NMA results due to the small number of studies in the network and the likely high heterogeneity in study designs, as highlighted in section 6.7.7.

Table B 91. Percentages of simulations falling into each quadrant Edoxaban vs. Warfarin

Quadrant	Proportion
North-East	28%
South-East (Dominant)	28%
South-West (Dominated)	22%
North-West	22%

Figure B 28 presents the CEAC for edoxaban vs. warfarin.

Figure B 28. CEACs edoxaban vs. warfarin

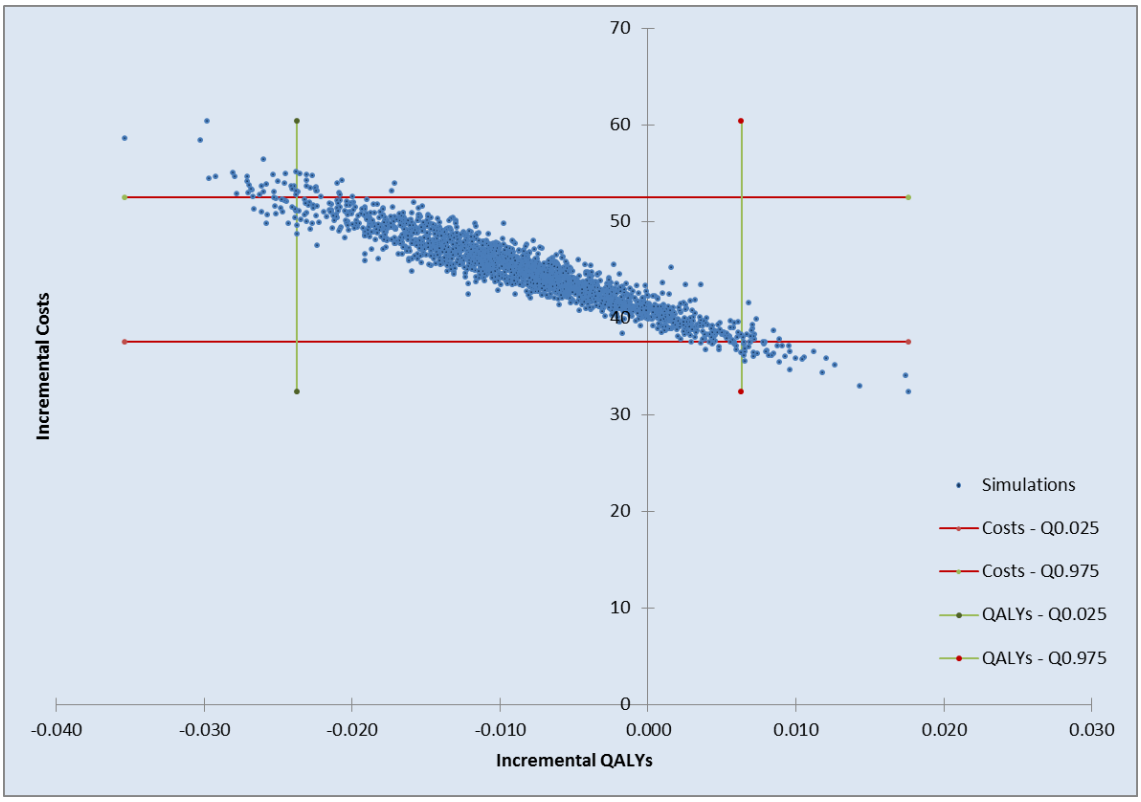


The almost uniform distribution of the scatter plot translates in a CEAC that is almost flat: when the threshold increases, the lower number of cost-effective simulations in the north-east quadrant is compensated by a higher number of cost-effective simulations in the south-west quadrant.

<u>Edoxaban vs. Rivaroxaban</u>

Figure B 29 presents the cost-effectiveness plane for edoxaban vs. rivaroxaban.

Figure B 29. Incremental cost effectiveness edoxaban vs. rivaroxaban



The relatively linear shape of the scatter plot is due to the high number of inputs assumed to be equivalent for all NOACs. Most variability in this analysis comes from the posterior distributions derived from the NMA.

All simulations show edoxaban to cost more than rivaroxaban (Table B 92), and this is mostly driven by the heparin lead-in with edoxaban which represents an incremental cost of £40.54 in the first cycle.

Table B 92. Percentages of simulations falling into each quadrant edoxaban vs. rivaroxaban

Quadrant	Proportion
North-East	14%
South-East (Dominant)	0%
South-West (Dominated)	0%
North-West	86%

Figure B 30 presents the CEAC for edoxaban vs. rivaroxaban.

Figure B 30. CEACs edoxaban vs. rivaroxaban

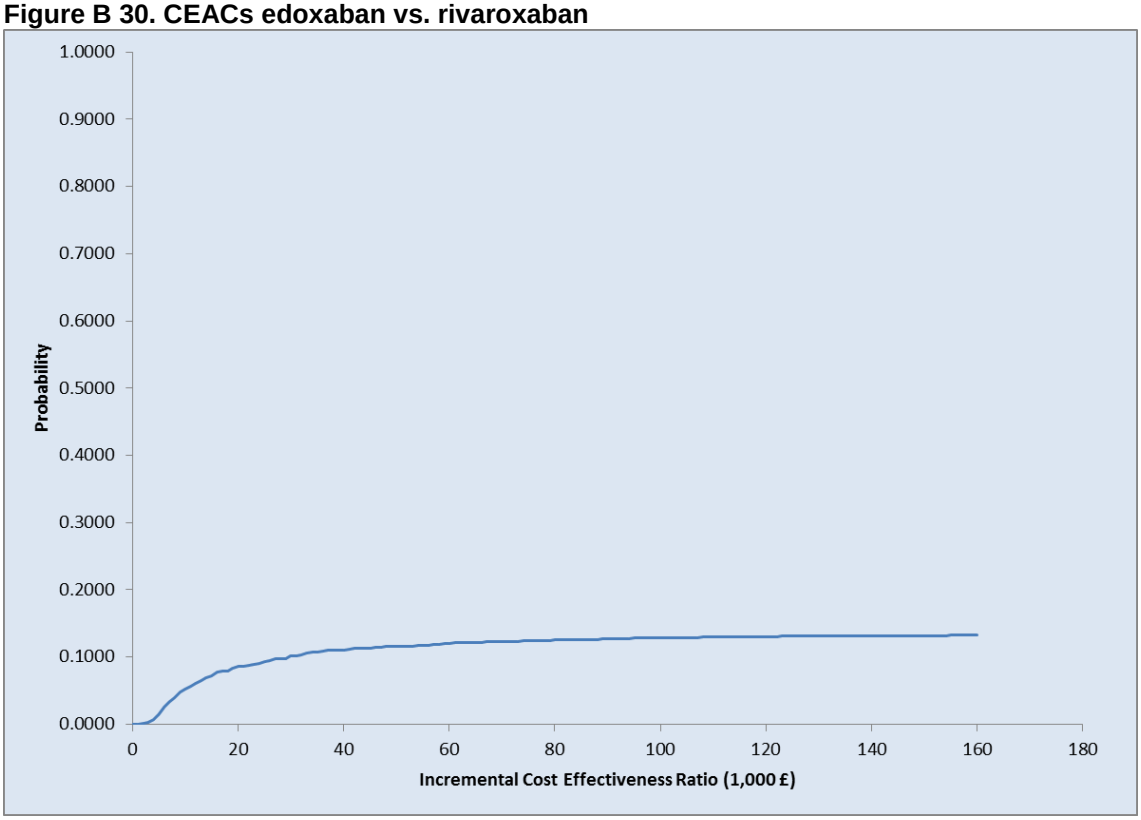
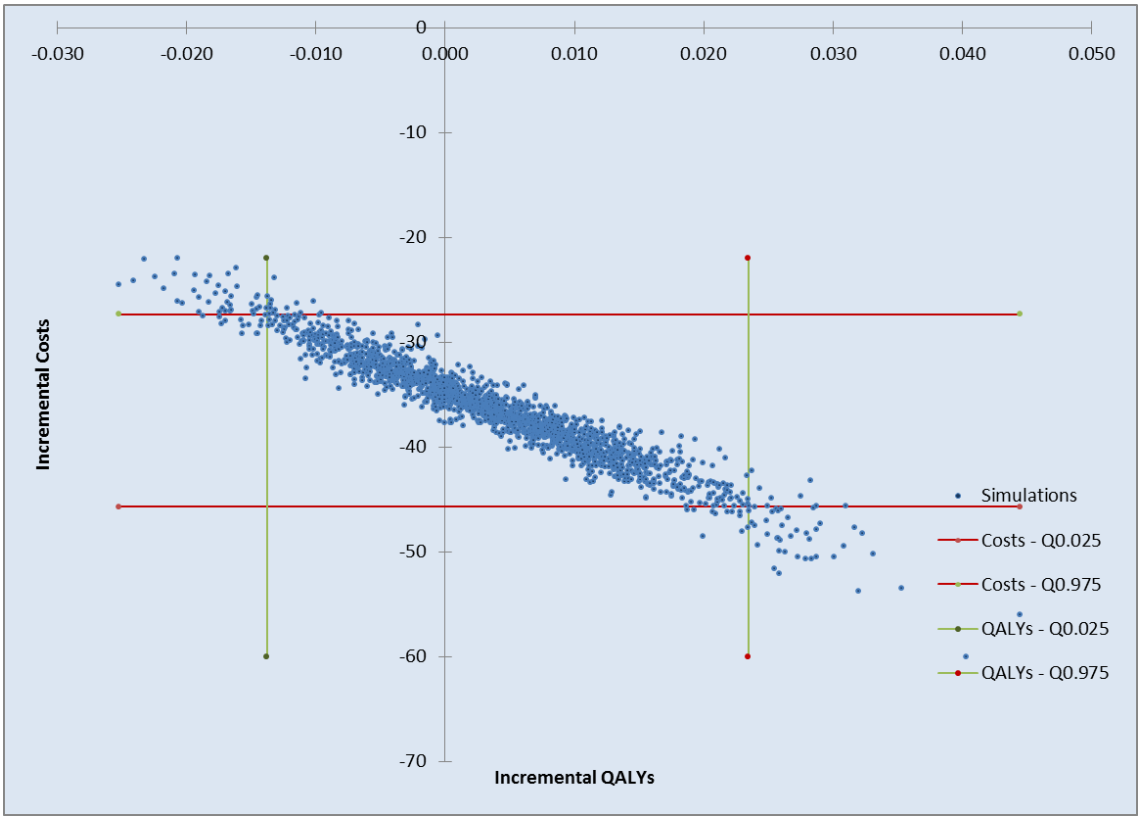


Figure B 31. Incremental cost effectiveness edoxaban vs. dabigatran



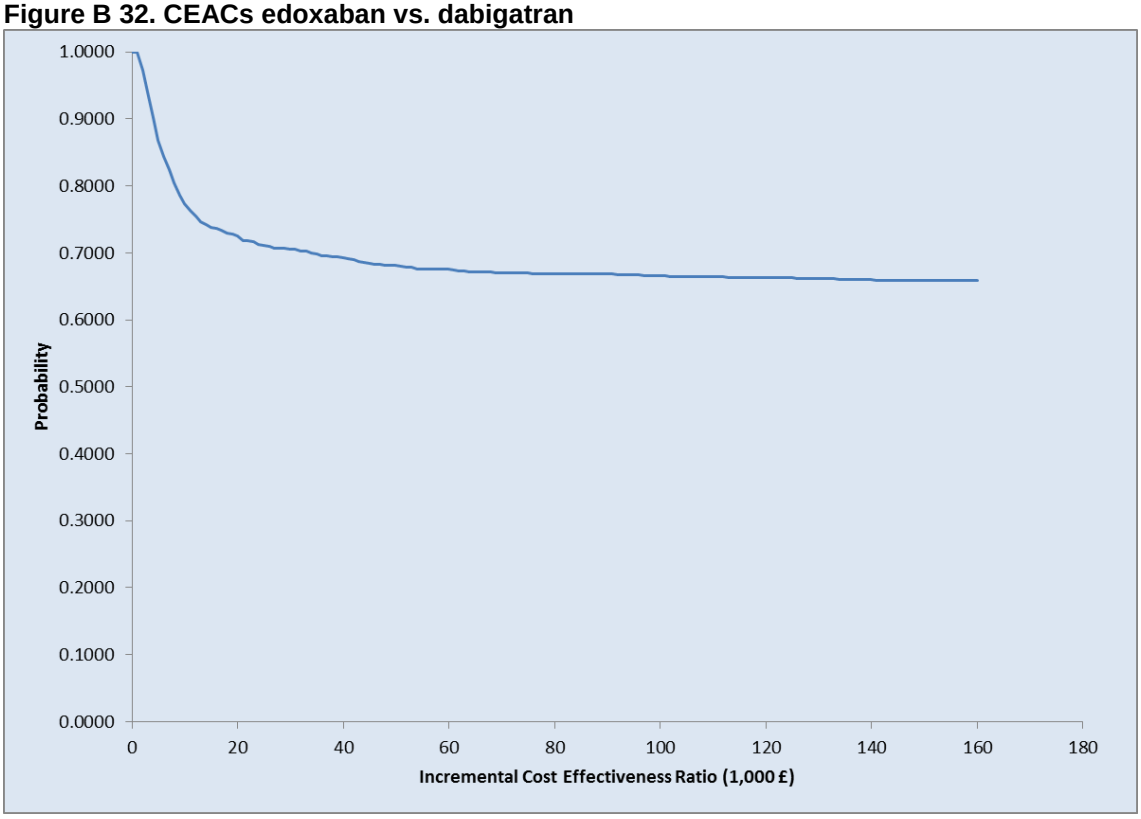
All simulations predict edoxaban to be cheaper than dabigatran and to be dominant in 65% of them (Table B 93).

Table B 93. Percentages of simulations falling into each quadrant edoxaban vs. dabigatran

Quadrant	Proportion
North-East	0%
South-East (Dominant)	65%
South-West (Dominated)	35%
North-West	0%

Figure B 32 presents the CEAC for edoxaban vs. dabigatran.

Figure B 32. CEACs edoxaban vs. dabigatran



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Scenario analyses were undertaken around the OR for VTE recurrence vs. warfarin for edoxaban. The base case analysis assumes values estimated from the NMA, while the scenario analysis considers an OR estimated from Hokusai-VTE RCT, as shown in Table B 94.

Table B 94. Cost-effectiveness analysis, scenario analysis

OR for edoxaban vs. warfarin	Estimations from NMA	Estimations from Hokusai-VTE RCT
OR for VTE recurrence	[redacted]	0.800
OR for CRNMB	[redacted]	0.796
OR for MB	[redacted]	0.840

When the values from Hokusai-VTE RCT were used there was no difference to the overall results, i.e. treatment options were in the same order as the base case. Table B 95 show the results of the scenario analysis associated to OR vs. warfarin for edoxaban.

Table B 95. Cost-effectiveness analysis, scenario analysis

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus warfarin (QALYs)
Edoxaban	£ 3,537.50	16.322	12.645	-£ 2.50	0.012	0.0211	Dominant
Warfarin	£ 3,540.00	16.310	12.624	-	-	-	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analysis shows that there for all the comparators, the top variables with the largest effect on the results include the following:

- Probability of stroke with NOAC
- Probability of CTEPH (3 months, 12 months)
- Probability of death due to CTEPH
- Probability of death due to recurrence

All other parameters in the model had limited effect on the results.

7.7.11 What are the key drivers of the cost-effectiveness results?

As identified by the deterministic sensitivity analysis, most of parameters did not show any significant impact. The only parameters driving the results of the model include the parameters listed in section 7.7.10.

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.

Validation was assessed using two primary criteria, internal (verification) and external consistency (validation). Internal validity addresses whether the model has been implemented correctly, and examines the extent to which the mathematical calculations are performed correctly and are consistent with the model's specifications. Face validation helps ensure a model is constructed and used in accord with most current medical science and best available evidence. This process enhances credibility with experts and increases acceptance of results.

Internal validity was assessed firstly using the techniques of extreme value analysis, where minimum and maximum values for appropriate parameter values were substituted, parallel inputs for all interventions for efficacy, costs and utilities, and logical consistency tests. Secondly, equations (i.e. those for converting rates to probabilities) were validated against their source, and coding accuracy was checked by verification of separate parts of a model one by one.

External consistency was assessed by assessing the face validity of the model, and comparing the results of the analysis against published results (cross validation). For the model structure, it was assessed whether the model includes all aspects of the patient pathway considered important, and whether they are related in ways consistent with medical science. It was also assessed whether the best available data sources were used, and whether the setting, population, interventions, outcomes, assumptions, and time horizons correspond to those of decision problem.

A comparison of the results of the model with the results of published models is discussed in further detail in Section 7.10.1.

Furthermore, the model was delivered to an independent academic modeller not involved in the design and development. This independent modeller reviewed all assumptions and calculations of the model, and provided comments to enhance the transparency and robustness of the model.

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.

Subgroup analyses were undertaken focusing on groups of:

- Patients with an index PE, with or without DVT
- Patients undergoing fixed durations of treatment of: 3 months, 6 months, Life-long

Subgroups were selected in line with the NICE scope. Evidence did not allow for sub-group analyses in the DVT population (with respect to the NMA), therefore no results for a DVT-only subgroup are presented.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Details of the patients in the subgroups are presented in section 6.3.7.

Patients with an index PE with or without DVT were identified at diagnosis of VTE. They are at risk of recurrent VTE, which can be any fatal or non fatal PE and or DVT, independently of the index event they experienced.

Subgroup analyses on the duration of treatment include VTE patients with the same characteristics as the base case analysis.

7.9.3 Please describe how the statistical analysis was undertaken.

ORs for each event for each comparator compared with warfarin were generated from the NMA. Limited data was available to inform the NMA for the subgroups (data availability is presented in Section 7.3.1). Baseline time-dependent event rates for warfarin were extracted from the Hokusai-VTE trial for each subgroup (PE with/without DVT, DVT only). Transition probabilities were calculated using the methodology presented in section 7.3.1, where these rates were converted to probabilities, and ORs were converted to relative risks henceforth applied multiplicatively to generate probabilities for each comparator arm. Where there were no available data for an event, it was assumed that the odds-ratio was equivalent to the odds-ratio estimated in the base case analysis (i.e. for all patients).

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).

Patients with an index PE, with or without DVT

The results for each comparator option are presented below.

In Table B 96, ICERs are presented for each NOAC versus warfarin. Incremental results for edoxaban versus each NOAC are presented in Table B 97.

Table B 96. Cost-effectiveness results (patients with an index PE, with or without DVT: treatment duration = 12 months)

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban	£ 3,702	16.304	12.63	-	-	-	Dominant	-
Edoxaban	£ 3,745	16.305	12.63	£ 42.51	0.001	0.001	Dominant	Weakly dominated
Dabigatran	£ 3,776	16.308	12.64	£ 31.23	0.003	0.002	Dominant	£ 21,446
Warfarin	£ 4,158	16.297	12.61	£ 382.19	-0.011	-0.026	NA	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 97. Incremental base-case cost-effectiveness results for edoxaban versus NOACs (patients with an index PE, with or without DVT)

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Rivaroxaban	£ 42.51	0.007	0.02	£ 37,427
Warfarin	-£ 413.41	-0.004	0.00	Dominant
Dabigatran	-£ 31.23	0.007	0.02	£ 13,563

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Patients undergoing fixed durations of treatment of: 3 months, 6 months, Life-long

For each length of treatment duration, rivaroxaban was found to be the dominant strategy. Edoxaban is always the second option. Table B 98 to Table B 103 show the results of the scenario analyses associated with treatment duration.

When the PE (±DVT) subgroup was considered, different durations of treatment affected the ICER for the edoxaban vs rivaroxaban comparison, as follows:

- 3 months treatment: edoxaban vs rivaroxaban, ICER: £7,862/QALY
- 6 months treatment: edoxaban vs rivaroxaban, ICER: £10,771/QALY
- Lifelong treatment: edoxaban vs rivaroxaban, ICER: £2,668/QALY

The results of the lifelong treatment duration scenario anlysis in the PE (±DVT) subgroup are shown in Table B 104 and B 105.

Table B 98. Cost-effectiveness analysis (treatment duration = 3 months)

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban	£ 2,273	16.270	12.62	-	-	-	Dominated	-
Edoxaban	£ 2,316	16.267	12.62	£ 42.26	-0.004	-0.29%	-	Dominated
Dabigatran	£ 2,328	16.260	12.61	£ 11.90	-0.007	-0.50%	Dominant	Dominated
Warfarin	£ 2,354	16.261	12.61	£ 26.75	0.001	-0.23%	Dominant	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 99. Incremental results (treatment duration = 3 months)

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Rivaroxaban	£ 42.26	0.009	0.01	Dominated
Warfarin	-£ 38.65	0.004	0.00	Dominant
Dabigatran	-£ 11.90	0.010	0.01	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 100. Cost-effectiveness analysis (treatment duration = 6 months)

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban	£ 2,665	16.289	12.63	-	-	-	Dominated	-
Edoxaban	£ 2,708	16.283	12.63	£ 43.12	-0.006	-0.46%	-	Dominated
Dabigatran	£ 2,728	16.277	12.62	£ 19.54	-0.006	-0.48%	Dominant	Dominated
Warfarin	£ 2,735	16.278	12.62	£ 7.08	0.000	-0.59%	Dominant	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 101. Incremental results (treatment duration = 6 months)

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Rivaroxaban	£ 43.12	0.012	0.02	Dominated
Warfarin	-£ 26.62	0.006	0.00	Dominant
Dabigatran	-£ 19.54	0.012	0.01	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 102. Cost-effectiveness analysis (treatment duration = lifelong)

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban	£ 3,494	16.328	12.65	-	-	-	Dominated	-
Edoxaban	£ 3,539	16.317	12.64	£ 44.86	-0.011	-0.82%	-	Dominated
Warfarin	£ 3,540	16.310	12.62	£ 0.82	-0.007	-1.77%	£ 2655	Dominated
Dabigatran	£ 3,576	16.312	12.64	£ 35.77	0.002	1.35%	Dominant	Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 103. Incremental results (treatment duration = lifelong)

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Rivaroxaban	£ 44.86	0.016	0.01	Dominated
Warfarin	-£ 0.82	0.011	0.01	Dominant
Dabigatran	-£ 36.59	0.018	0.03	Dominant

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year

Table B 104. Cost-effectiveness analysis, patients with an index PE, with or without DVT (treatment duration = lifelong)

Technologies	Total costs (£)	Total LYG (discounted)	Total QALYs	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Edoxaban	£20,278.50	16.634	12.713	-	-	-		-
Rivaroxaban	£20,413.00	16.703	12.763	£134.4	0.069	0.05		2,668
Dabigatran	£21,154.50	16.719	12.775	£741.5	0.016	0.012		61,841
Warfarin	£23,268.40	16.605	12.484	£2,114.0	-0.114	-0.291		Dominated

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table B 105. Incremental results, patients with an index PE, with or without DVT (treatment duration = lifelong)

Technologies	Incremental costs (£)	Incremental LYG (discounted)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Warfarin	-£2,990	-0.029	0.2293	Dominant
Dabigatran	-£876	0.085	-0.0624	£14,041
Rivaroxaban	-£134	0.069	-0.0504	£2,668

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life year

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.

The subgroup of patients with DVT only, specified in the scope, was not analysed. . Evidence did not allow for sub-group analyses in the DVT population (with respect to the NMA), therefore no results for a DVT-only subgroup are presented.

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?

The systematic review detailed in Section 7.1 did not identify any economic evaluations which estimated the cost-effectiveness of edoxaban in VTE. However, several evaluations identified were based in a UK setting, which compared warfarin, rivaroxaban and dabigatran in patients with VTE. Dabigatran and rivaroxaban STAs were also available.

- Wolowacz et al. estimated the cost-effectiveness of dabigatran for the secondary prevention of DVT and PE from the perspective of the UK (NHS) using a Markov model over a lifetime horizon. (82) QALYs were estimated to be 13.088 for dabigatran and 13.070 for placebo. Costs (£) were found to be £7,152 for dabigatran and -£7,520 for placebo. Dabigatran was evaluated as dominating placebo.

- Three posters were published by Jugrin in 2014 (83-85), to assess the cost-effectiveness over a lifetime horizon of dabigatran compared with warfarin or rivaroxaban, in the treatment and secondary prevention of acute VTE comprising DVT and PE, in the UK health care setting, based on safety and efficacy data collected during pivotal phase III trials. These analyses concluded that dabigatran was cost-effective or dominant vs. warfarin. No results were reported concerning total QALYs or total costs (only abstracts were published).

- The Dabigatran STA estimated that costs were around £7.5k and the rivaroxaban STA around £11K.

- The QALYs gained in of the model in the current submission are around 12.6 QALYs, which are broadly in line with those presented in the dabigatran STA and rivaroxaban STA (both around 13 QALYs).

The costs in the current submission are in the order of £4K which is lower than the costs found in the dabigatran and rivaroxaban STAs. Differences in costs may result from cost inputs, as shown in Table B 106.

Table B 106. Comparison of input costs between present submission and dabigatran/rivaroxaban STAs

Health states	Present submission	Dabigatran STA	Rivaroxaban STA
VTE	Index VTE: about £1100 Recurrent VTE: about £1050	Index DVT: about £500 Index PE: about £1400 Recurrent DVT: about £800 Recurrent PE: about £2000	DVT: about £900 PE: about £1900
CRNMB	About £140	About £400	About £130
CTEPH	About £4200 for event About £5000 per following year	About £5000 for event About £16000 per following year	About £8000 for event About £13000 per following year
MB	About £1100	About £10200 for intra-cranial haemorrhage event About £3000 for long term management About £2400 for MB extra-cranial	About £950 for extra-cranial MB About £7000 for intra-cranial MB
Stroke	About £3,100 per event About £7,000 per following year	Not included	Not included
Myocardial Infarction and Unstable Angina	Not included	About £4,600 for acute event About £400 per following year	Not included

In terms of structure, the results in the submission could be given more credence than preceding evaluations due to the research methods and assumptions employed in the evaluation. The model was designed based on previous economic analyses that were submitted to NICE, since the critique from the ERGs provided a firm basis on which to inform the best techniques and assumptions to use in the model.

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?

Edoxaban is licensed for treatment of VTE including DVT and PE, and prevention of recurrent VTE in adults. The Hokusai-VTE study was designed with the aim of broadening applicability to real-world practice, so it is reasonable to expect that the economic evaluation is relevant to all groups of patients who could potentially use the technology as identified in the decision problem 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. The economic model builds on recommendations from previous technology appraisals and good practice in published economic models.

The model was developed in consultation with UK clinical and health economic experts, ensuring that the model clinical pathway is in line with UK clinical practice and the most appropriate inputs are utilised.

The main weakness of the analysis is the heterogeneity in the design of the clinical studies of edoxaban and its comparators, which led to a small number of eligible studies and no significance in the results of the NMA.

Conversely, data on baseline risk and patient characteristics were based on the Hokusai-VTE study, which presented a very realistic design aiming at representing clinical practice: inclusion of older and more severe patients, no pre-specified duration of treatment.

There are often concerns that the effectiveness of different treatments in clinical practice will be less than that the efficacy observed in clinical trials, and that event costs underestimated and quality of life overestimated in economic models as a result. The strengths of the analysis and the extensive sensitivity analyses suggest that the results of this model are robust.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive sensitivity analyses (deterministic and probabilistic) were undertaken to determine the robustness of the results. Further evidence generation programmes may improve the overall robustness of the analysis, such as a head-to-head trial of the licensed NOACs and warfarin.

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 Martinez et al., which reported 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.(38)

The incidence rates from this study conducted by Martinez et al. are shown in Table C 1.

Table C 1. Age-specific incidence rates of VTE

	Events	Person-Years	IR	95% CI
Age-group	N		Per 100 000 PY	
<18	90	5 284 814	1.7	1.4-2.1
18-29	1266	2 883 101	32.6	30.8-34.4
30-39	2064	3 838 841	53.8	51.5-56.1
40-49	2543	4 093 014	62.1	59.7-64.6
50-59	3569	3 585 120	99.6	96.3102.9
60-69	5084	2 874 437	176.9	172.0-181.8
70-79	6606	2 015 974	327.7	319.8-335.7
80-89	5980	1 100 959	543.2	529.5-557.1
≥90	1579	221 078	714.2	679.4-750.3
Total	28 871	26 897 337	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 2015-2019 from the Office of National Statistics shown in Table C 2.(39)

Table C 2. Age-specific population projections for 2015-2019

	2015	2016	2017	2018	2019
20-29	7 783 303	7 799 922	7 819 608	7 798 090	7 762 906
30-39	7 520 317	7 618 551	7 721 534	7 839 640	7 906 997
40-49	7 877 886	7 737 234	7 585 408	7 458 622	7 383 010
50-59	7 472 175	7 626 387	7 759 074	7 855 517	7 938 291
60-69	6 278 595	6 312 910	6 212 229	6 197 260	6 236 291
70-79	4 336 548	4 448 610	4 707 896	4 894 128	5 036 590
≥80	2 824 914	2 899 066	2 980 130	3 069 515	3 159 386
Total	44 093 738	44 442 680	44 785 879	45 112 772	45 423 471

The summarised results of the total eligible population for the treatment indication are shown in Table C 3.

Table C 3. Estimated population eligible for treatment indication

	2015	2016	2017	2018	2019
Cohort 1	60 453	60 453	60 453	60 453	60 453
Cohort 2		61 410	61 410	61 410	61 410
Cohort 3			62 624	62 624	62 624
Cohort 4				63 764	63 764
Cohort 5					64 844

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact model assumes that NOACs will replace a proportion of the existing treatments and that edoxaban will have a share within the NOAC market share.

8.3 What assumption(s) were made about market share (when relevant)?

An increasing market uptake from NOACs is assumed, up to 60% of the market from start of the model until year 5 after introduction of edoxaban, as presented in Table C 4.

Table C 4. Current and future competitor market share

	2015	2016	2017	2018	2019
World without edoxaban					
Warfarin	77.93%	69.62%	62.30%	56.41%	51.51%
NOACs*	22.07%	30.38%	37.70%	43.59%	48.49%
Rivaroxaban	21.41%	27.01%	29.75%	31.47%	34.34%
Dabigatran	0.22%	0.70%	1.42%	2.24%	2.64%
Edoxaban	0%	0%	0%	0%	0%
World with edoxaban					
Warfarin	77.93%	69.45%	61.99%	44.23%	40.14%
NOACs*	22.07%	30.55%	38.01%	55.77%	59.86%
Rivaroxaban	21.36%	25.85%	26.90%	26.93%	29.09%
Dabigatran	0.22%	0.66%	1.28%	1.91%	2.21%
Edoxaban	0.05%	1.27%	3.60%	6.22%	7.42%

* calculated as the sum of percentages of market share for rivaroxaban, dabigatran, apixaban and edoxaban

It is noteworthy mentioning that these market shares are supposed to be applied to newly treated patients in the year, and not to patients treated the years before (these patients are assumed not to switch).

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).

The cost-effectiveness model described in section 7.2 was used to derive annual costs of VTE with each treatment at a five-year time horizon. These annual costs include index event costs (outpatient and inpatient), intervention costs, including monitoring for patients receiving warfarin, costs of PTS, costs for recurrence, the costs of stroke (including post-stroke management costs), the costs of CTEPH (including post-CTEPH management costs), and adverse events such as bleeds or HIT if the use of heparin is required in the initiation of the treatment. Table C 5 lists these annual costs by treatment option.

Table C 5. Annual costs used in budget impact calculations

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Warfarin	£ 2079	£ 105	£ 89	£ 88	£ 87
Rivaroxaban	£ 2033	£ 106	£ 89	£ 88	£ 88
Dabigatran	£ 2111	£ 107	£ 89	£ 88	£ 88
Edoxaban	£ 2076	£ 106	£ 89	£ 88	£ 88

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 assumed to be identical to those assumed in the cost-effectiveness evaluation in section 7. Unit costs are presented in section 7.5.5.

8.6 Were there any estimates of resource savings? If so, what were they?

Edoxaban is not expected to lead to any additional resource savings than those realised by preventing VTE.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact of edoxaban for the NHS in England and Wales is approximately £1403 in Year 1 rising to approximately £226 415 in Year 5. Total budget impact for the 5 years is £558 973.

This is detailed in Table C 6.

Table C 6. Detailed budget impact (£)

	2015	2016	2017	2018	2019
World without edoxaban					
Warfarin	£ 97 958 944	£ 93 643 037	£ 89 396 037	£ 86 262 588	£ 83 183 717
Rivaroxaban	£ 26 849 858	£ 38 588 241	£ 49 298 381	£ 58 474 740	£ 67 589 943
Dabigatran	£ 285 503	£ 1 008 372	£ 2 355 319	£ 4 097 493	£ 5 116 081
Edoxaban	-	-	-	-	-
Total cost	**£ 125 094 305**	**£ 133 239 651**	**£ 141 049 737**	**£ 148 834 820**	**£ 156 552 466**
World with edoxaban					
Warfarin	£ 97 958 944	£ 93 643 037	£ 89 396 037	£ 86 262 588	£ 83 837 994
Rivaroxaban	£ 26 783 540	£ 36 880 233	£ 43 983 185	£ 48 680 826	£ 55 330 278
Dabigatran	£ 284 790	£ 962 012	£ 2 084 392	£ 3 378 359	£ 4 121 597
Edoxaban	£ 68 433	£ 1 789 949	£ 5 692 857	£ 10 701 890	£ 13 489 012
Total cost	**£ 125 095 707**	**£ 133 275 231**	**£ 141 156 470**	**£ 149 023 662**	**£ 156 778 882**
Budget impact					
Warfarin	-	-	-	-	-
Rivaroxaban	-£ 66 318	-£ 1 708 008	-£ 5 315 195	-£ 9 793 914	-£ 12 259 665
Dabigatran	-£ 713	-£ 46 361	-£ 270 927	-£ 719 134	-£ 1 002 932
Edoxaban	£ 68 433	£ 1 789 949	£ 5 692 857	£ 10 701 890	£ 13 489 012
Total budget impact	**£ 1 403**	**£ 35 580**	**£ 106 734**	**£ 188 842**	**£ 226 415**
Grand total (5 years)					**£ 558,973**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No other opportunities are expected.

9 References

(1) Stambler BS. A new era of stroke prevention in atrial fibrillation: comparing a new generation of oral anticoagulants with warfarin

(2) Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler Thromb Vasc Biol 2007 Jun;27(6):1238-47.

(3) Weitz JI, Bates SM. New anticoagulants. J Thromb Haemost 2005 Aug;3(8):1843-53.

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Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

Draft included as a separate document.

9.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library**

The literature search was conducted in:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- EMBASE (Ovid), 1974 to 2014 Week 17.
- The Cochrane Library, 1898 to present.

9.2.2 The date on which the search was conducted.

An initial search was conducted in May 2014. An update conducted in December 2014.

9.2.3 The date span of the search.

There was no restriction on the date of publication.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline search terms (RCT)

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	24,608	26,154
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	46,810	53,019
#3			(dvt or vte or dvts or vtes).mp.	9,743	11,744
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	39,136	42,968
#5	**Hits of P**		**1 or 2 or 3 or 4**	**90,508**	**99,942**
#6	I and C	Interventions and Comparators	(edoxaban or lixiana or DU-176b).mp.	162	295
#7			(warfarin$ or coumadin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	20,958	24,595
#8			(dabigatran or bibr 1048 or pradax*).mp.	1,428	2,189
#9			(apixaban or bms 562247 or bms562247).mp.	624	1,048
#10			(rivaroxaban or bay 597939 or xarelto).mp.	1,048	1,725
#11	**Hits of I and C**		**6 or 7 or 8 or 9 or 10**	**22,004**	**26,189**
#12	S	RCTs	Randomized Controlled Trials as Topic/	92,091	100,107
#13			randomized controlled trial/	370,572	401,552
#14			Random Allocation/	80,101	84,222

ID	PICOS	Category	Search terms	Initial	Update
#15			Double Blind Method/	125,080	132,775
#16			Single Blind Method/	18,889	20,696
#17			clinical trial/	486,131	501,893
#18			clinical trial, phase i.pt	14,010	15,391
#19			clinical trial, phase ii.pt	22,529	24,644
#20			clinical trial, phase iii.pt	8,802	10,102
#21			clinical trial, phase iv.pt	923	1,040
#22			controlled clinical trial.pt	88,127	90,822
#23			randomized controlled trial.pt	370,572	401,552
#24			multicenter study.pt	170,156	189,360
#25			clinical trial.pt	486,131	501,893
#26			exp Clinical Trials as topic/	278,667	295,658
#27			or/12-26	1,018,358	1,093,752
#28			(clinical adj trial$).tw	196,348	237,248
#29			((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	122,491	137,602
#30			PLACEBOS/	32,475	34,060
#31			placebo$.tw	149,756	170,060
#32			randomly allocated.tw	15,477	18,367
#33			(allocated adj2 random$).tw	17,920	21,048
#34			or/28-33	390,907	454,771
#35			27 or 34	1,137,319	1,255,433
#36			case report.tw	181,492	216,868
#37			letter/	808,856	888,074
#38			historical article/	300,087	313,126
#39			or/36-38	1,279,229	1,405,835
#40			35 not 39	1,107,916	1,224,149
#41	**Hits of P and I and C and O and S**		**5 and 11 and 40**	**1,563**	**1,816**
#42	**Limits**	**Humans**	**limit 41 to humans**	**1,553**	**1,730**
#43	**Limits**	**Date**	**limit 42 to ed=20140425-20141204**	**-**	**90**

Cochrane search terms (RCT)

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	MeSH descriptor: [Venous Thromboembolism] this term only	400	420
#2			MeSH descriptor: [Venous Thrombosis] explode all trees	2,283	2,298
#3			MeSH descriptor: [Pulmonary Embolism] explode all trees	909	921
#4			((venous or vein) near/2 (thrombosis or thromboses or thrombus or thromboembolism)):ti,ab,kw	4,908	5,154
#5			(dvt or vte or dvts or vtes):ti,ab,kw	1,233	1,310
#6			((pulmonary or lung) near/2 (embolism* or emboli)):ti,ab,kw	1,969	2,120
#7	**Hits of P**		**(#1 or #2 or #3 or #4 or #5 or #6)**	**6,257**	**6,588**
#8	I and C	Interventions and Comparators	(edoxaban or lixiana or DU-176b):ti,ab,kw	44	58
#9			(warfarin$ or coumadin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA):ti,ab,kw	2,330	2,535
#10			(dabigatran or bibr 1048 or pradax*):ti,ab,kw	220	256
#11			(apixaban or bms 562247 or bms562247):ti,ab,kw	122	161
#12			(rivaroxaban or bay 597939 or xarelto):ti,ab,kw	215	274
#13	**Hits of I and C**		**(#8 or #9 or #10 or #11 or #12)**	**2,641**	**2,898**
#14	**Hits and P and I and C**		**(#7 and #13)**	**609**	**662**
#15	**Limits**		**#14 (Publication Year from 2014 to 2014)**	**-**	**41**

Embase search term (RCT)

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	180,233	188,020
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	99,009	103,716

ID	PICOS	Category	Search terms	Initial	Update
#3			(dvt or vte or dvts or vtes).mp.	17,728	19,214
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	67,648	70,835
#5	**Hits of P**		**or/1-4**	**195,817**	**204,252**
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	788	993
#7			(warfarin$ or coumadin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	67,466	70,982
#8			(dabigatran or bibr 1048 or pradax*).mp.	5,313	6,269
#9			(apixaban or bms 562247 or bms562247).mp.	2,766	3,322
#10			(rivaroxaban or bay 597939 or xarelto).mp.	4,405	5,271
#11	**Hits of I**		**or/6-10**	**70,422**	**74,441**
#12	S	RCTs	Clinical trial/	834,401	838,297
#13			Randomized controlled trial/	342,362	355,617
#14			Randomization/	61,710	63,900
#15			Single blind procedure/	18,122	19,033
#16			Double blind procedure/	115,178	118,503
#17			Crossover procedure/	38,578	40,609
#18			Placebo/	250,182	259,915
#19			Randomi?ed controlled trial$.tw.	96,828	105,688
#20			Rct.tw.	13,600	15,313
#21			Random allocation.tw.	1,333	1,385
#22			Randomly allocated.tw.	20,175	21,348
#23			Allocated randomly.tw.	1,926	1,982
#24			(allocated adj2 random).tw.	790	798
#25			Single blind$.tw.	14,306	15,153
#26			Double blind$.tw.	145,371	151,211
#27			((treble or triple) adj (blind$)).tw.	383	429
#28			Placebo$.tw.	200,232	209,692
#29			Prospective study/	247,186	266,696
#30			Or/12-29	1,364,871	1,415,665
#31			Case study/	25,462	28,994
#32			Case report.tw.	264,722	277,134
#33			Abstract report/ or letter/	904,567	923,345
#34			Or/31-33	1,189,225	1,223,558
#35	**Hits of S**		**30 not 34**	**1,327,056**	**1,377,012**
#36	**Hits of P and I and S**		**5 and 11 and 35**	**5,900**	**6,063**
#37	**Limits**	**Humans**	**limit 36 to humans**	**5,754**	**5,916**
#38	**Limits**	**Date**	**limit 37 to dd=20140502-20141204**	**-**	**166**

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Bibliographies of systematic reviews articles were examined to obtain additional references. Bibliographies of accepted references were also reviewed to identify other potentially relevant references.

9.2.6 The inclusion and exclusion criteria.

Elements	Inclusion	Exclusion
Population (P)	• Adults with DVT or PE	• Children • Patients after surgery i.e. hip or knee replacement surgery
Interventions (I)	• NOACS: Direct thrombin inhibitors i.e. dabigatran • NOACS: Factor Xa inhibitors i.e. apixaban, rivaroxaban, edoxaban • Coumarins/VKA i.e. warfarin	• Studies not investigating edoxaban or relevant comparator
Comparators (C)	• All interventions listed above and Heparin i.e. LMWH • UFH	• Studies not investigating edoxaban or relevant comparator
Outcomes (O)	• Mortality • Recurrent VTE • Complications following DVT or PE, including post thrombotic syndrome, heart	• Cost • Quality of life

Elements	Inclusion	Exclusion
	failure and chronic thrombotic pulmonary hypertension • Adverse effects of treatment including bleeding events, incranial and gastrointestinal bleeding	
Study designs (S)	• RCTs (Randomised Controlled Trials) • Meta-analysis of RCTs • Systematic Literature Reviews of RCTs	• Economic or cost studies • Review (systematic or not) of economic models or economic studies • Studies on quality of life outcomes • Editorial, Letter to Editor, Opinion, clinical review • Not controlled trials

9.2.7 The data abstraction strategy.

For both the initial search and the update, the study selection process followed 2 phases:

- **Level 1 screening**: Titles and abstracts of the identified studies from the electronic databases and Internet searches were independently reviewed by two independent reviewers using criteria outlined in section 9.2.6. All decisions on the inclusion/exclusion criteria were compared and any difference was resolved in a discussion with a third reviewer. For abstracts that were deemed relevant to the first level of review, the full-text articles were retrieved for further review.

- **Level 2 screening**: Full texts of the identified studies at level 1 were independently reviewed for eligibility by two independent reviewers using criteria outlined in section 9.2.6. All decisions on the inclusion/exclusion criteria were compared and any difference was resolved in a discussion with a third reviewer. For each excluded study, a specific reason for exclusion was recorded.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Relevant information was abstracted into the STA template/ into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

9.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study question reference	Support for judgement	Judgement
Hokusai-VTE		
1	Quote: 'Randomization was performed with the use of an interactive Web-based system, with stratification according to the qualifying diagnosis (deepvein thrombosis or pulmonary embolism), presence or absence of temporary risk factors, and the dose of edoxaban'	Low risk
2	Quote: 'randomized, double-blind, non inferiority study'	Low risk
3	Quote: 'edoxaban (or placebo) was started after discontinuation of initial heparin/ Warfarin (or placebo) was started concurrently with the study regimen of heparin, with adjustment of the dose to maintain the international normalized ratio (INR) between 2.0 and 3.0. All measurements were performed by means of a point-of-care device that provided an actual INR value for patients receiving warfarin and a sham INR value for patients receiving edoxaban'	Low risk
4	Quote: 'Patients were instructed to report symptoms suggestive of recurrent venous thromboembolism or bleeding.' Quote: 'Patients were instructed to report symptoms suggestive of recurrent venous thromboembolism or bleeding.'	Unclear risk
5	Quote: 'Death was adjudicated as related to venous thromboembolism, other cardiovascular disease, bleeding, or other causes. Pulmonary embolism was considered to be the cause of death if there was objective documentation that a pulmonary embolism caused the death or if the death could not be attributed to a documented cause and pulmonary embolism could not be ruled out.'	Unclear risk
6	Quote: 'Patients underwent assessment, in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug.'	Low risk
7	Quote: 'Patients underwent assessment, in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug.'	Low risk
8	All the analyses mentioned in method are reported	Low risk

9.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The clinical search described in sections 6.1 and 9.2 was also designed to identify eligible studies for the NMA, relevant to the decision problem.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

Study question reference	Domain	Questions
1	Random sequence generation (selection bias)	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
2	Allocation concealment (selection bias)	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
3	Blinding of participants and personnel (performance bias)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
4	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
5	Blinding of outcome assessment (detection bias) (Mortality)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
6	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
7	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
8	Selective reporting (reporting bias)	State how the possibility of selective outcome reporting was examined by the review authors, and what was found

Study question reference	Support for judgement	Judgement
EINSTEIN-DVT		
1	Quote: “patients were randomly assigned to a study group with the use of a computerized voice–response system, with stratification by country.”	Low risk
2	Open label study	High risk
3	Open label study	High risk
4	Open label study	High risk
5	Open label study	High risk
6	Quote: “In the rivaroxaban group, 15 patients (0.9%) were lost to follow-up as compared with 18 patients (1.0%) in the standard- therapy group.” “Follow-up for the primary efficacy outcome was complete for 601 patients (99.8%) in the rivaroxaban group and for 593 patients (99.8%) in the placebo group.”	Low Risk
7	Quote: “In the rivaroxaban group, 15 patients (0.9%) were lost to follow-up as compared with 18 patients (1.0%) in the standard- therapy group.” “Follow-up for the primary efficacy outcome was complete for 601 patients (99.8%) in the rivaroxaban group and for 593 patients (99.8%) in the placebo group.”	Low Risk
8	The authors report on all primary outcomes that they set out to measure	Low Risk
EINSTEIN-PE		

1	Quote: “Randomization was performed with the use of a computerized voice-response system and was stratified according to country and the intended treatment duration (3, 6, or 12 months).”	Low risk
2	Open label study	High risk
3	Open label study	High risk
4	Open label study	High risk
5	Open label study	High risk
6	Quote: “A total of 8 patients (0.3%) in the rivaroxaban group and 10 atients (0.4%) in the standard-therapy group were lost to follow-up.” “The number of patients who were lost to follow up was negligible.”	Low Risk
7	Quote: “A total of 8 patients (0.3%) in the rivaroxaban group and 10 atients (0.4%) in the standard-therapy group were lost to follow-up.” “The number of patients who were lost to follow up was negligible.”	Low Risk
8	The authors report on all primary outcomes that they set out to measure	Low Risk
RE-COVER II		
1	Quote: “Patients were randomized using an interactive voice response system and a computer generated randomization scheme in blocks of 4. The randomization was stratified according to presence or absence of symptomatic pulmonary embolism or active cancer.”	Low Risk
2	Quote: “Patients were assigned in a 1:1 ratio to receive active fixed dose dabigatran 150 mg twice daily and warfarin-like placebo, or active warfarin and dabigatran-like placebo.”	Low Risk
3	Quote: “On the day of randomization warfarin or warfarin-like placebo was added to the parenteral treatment and adjusted to achieve an INR of 2.0 to 3.0 using a point-of-care instrument that provided an encrypted INR. An interactive voice response system provided a true or sham INR. This was the “single-dummy phase”, which lasted for at least 5 days and until the true or sham INR had been 2.0 or higher for 2 consecutive measurements. Then, parenteral anticoagulation was stopped and the first dose of dabigatran was given within 2 hours before the time that the next dose of subcutaneous parenteral therapy would have been due, or at the time of discontinuation of intravenous unfractionated heparin. The study drugs were then given for 6 months from randomization (“double-dummy phase”).”	Low risk
4	Quote: “We had not planned for independent central adjudication of acute coronary syndromes, but this decision was revised by the steering committee and performed at the end of the trial, after database lock but while the committee was still blinded to the treatment allocation.”	High risk
5	Quote: “We had not planned for independent central adjudication of acute coronary syndromes, but this decision was revised by the steering committee and performed at the end of the trial, after database lock but while the committee was still blinded to the treatment allocation.”	
6	Quote: “Allowing for a possible 20% loss to follow-up during 6 months, the required sample size was 2550 patients, with 1275 patients per group and a total of at least 46 events.” “The study drug was stopped before planned treatment completion in 188 patients (14.7%) in the dabigatran group (102 because of an adverse event, 39 because of nonadherence, 6 because of loss to follow-up, 33 because of withdrawal of consent, and 8 for other reasons) and in 182 patients (14.1%) in the warfarin group (101 because of an adverse event, 37 because of nonadherence, 3 because of loss to follow-up, 38 because of withdrawal of consent, and 3 for other reasons).” “The planned observation time for analysis of efficacy was not completed in 125 patients (9.8%) in the dabigatran group (47 because of an adverse event, 31 because of nonadherence, 11 because of loss to follow-up, 32 because of withdrawal of consent, and 4 for other reasons) and in 116 patients (9.0%) in the warfarin group (44 because of an adverse event, 26 because of nonadherence, 6 because of loss to follow-up, 39 because of withdrawal of consent, and 1 for other reasons).”	Low risk
7	Quote: “Allowing for a possible 20% loss to follow-up during 6 months, the required sample size was 2550 patients, with 1275 patients per group and a total of at least 46 events.” “The study drug was stopped before planned treatment completion in 188 patients (14.7%) in the dabigatran group (102 because of an adverse event, 39 because of nonadherence, 6 because of loss to follow-up, 33 because of withdrawal of consent, and 8 for other reasons) and in 182	Low risk

	patients (14.1%) in the warfarin group (101 because of an adverse event, 37 because of nonadherence, 3 because of loss to follow-up, 38 because of withdrawal of consent, and 3 for other reasons).” “The planned observation time for analysis of efficacy was not completed in 125 patients (9.8%) in the dabigatran group (47 because of an adverse event, 31 because of nonadherence, 11 because of loss to follow-up, 32 because of withdrawal of consent, and 4 for other reasons) and in 116 patients (9.0%) in the warfarin group (44 because of an adverse event, 26 because of nonadherence, 6 because of loss to follow-up, 39 because of withdrawal of consent, and 1 for other reasons).”	
8	The authors report on all primary outcomes that they set out to measure	Low risk
Hokusai-VTE		
1	Quote: ‘Randomization was performed with the use of an interactive Web-based system, with stratification according to the qualifying diagnosis (DVT or PE), presence or absence of temporary risk factors, and the dose of edoxaban’	Low risk
2	Quote: ‘randomized, double-blind, non inferiority study’	Low risk
3	Quote: ‘edoxaban (or placebo) was started after discontinuation of initial heparin/ Warfarin (or placebo) was started concurrently with the study regimen of heparin, with adjustment of the dose to maintain the international normalized ratio (INR) between 2.0 and 3.0. All measurements were performed by means of a point-of-care device that provided an actual INR value for patients receiving warfarin and a sham INR value for patients receiving edoxaban’	Low risk
4	Quote: ‘Patients were instructed to report symptoms suggestive of recurrent venous thromboembolism or bleeding.’	Unclear risk
5	Quote: ‘Death was adjudicated as related to venous thromboembolism, other cardiovascular disease, bleeding, or other causes. Pulmonary embolism was considered to be the cause of death if there was objective documentation that a pulmonary embolism caused the death or if the death could not be attributed to a documented cause and pulmonary embolism could not be ruled out.’	Unclear risk
6	Quote: ‘Patients underwent assessment, in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug.’	Low risk
7	Quote: ‘Patients underwent assessment, in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug.’	Low risk
8	All the analyses mentioned in method are reported	Low risk
Amplify		
1	Quote: ‘Randomization was performed with the use of an interactive voice-response system and was stratified according to the qualifying diagnosis of either symptomatic proximal deep-vein thrombosis or symptomatic pulmonary embolism.’	Low risk
2	Quote: ‘double-blind trial’	Low risk
3	Quote: ‘Patients were assigned to receive apixaban tablets plus placebo enoxaparin injections and placebo warfarin tablets or conventional therapy with enoxaparin injections and warfarin tablets plus placebo apixaban tablets’ Quote: ‘blinded INR monitoring with a point-of-care device that generated an encrypted code for INR results. Investigators reported the code to the interactive voice-response system and received either an actual INR value (for patients assigned to warfarin) or a sham INR value (for patients receiving apixaban).’	Low risk
4	Quote: ‘Patients were instructed to report to the study center if they had symptoms suggestive of recurrent venous thromboembolism or bleeding.’	Unclear risk
5	Quote: ‘Death was adjudicated as related to venous thromboembolism, related to cardiovascular disease, caused by bleeding, or due to other causes’	Unclear risk
6	Quote: ‘Patients underwent assessment, either in the clinic or by telephone, at weeks 2, 4, 8, 12, 16, 20, and 24 (6 months) after randomization and 30 days after the end of the intended treatment period.’	Low risk
7	Quote: ‘Patients underwent assessment, either in the clinic or by	Low risk

	telephone, at weeks 2, 4, 8, 12, 16, 20, and 24 (6 months) after randomization and 30 days after the end of the intended treatment period.'	
8	All the analyses reported in the methods have their results reported	Low risk
RE-COVER		
1	Quote: 'We used a computer generated randomization scheme with variable block sizes, stratified according to presentation (pulmonary embolism or deep-vein thrombosis without symptomatic pulmonary embolism) and the presence or absence of active cancer'	Low risk
2	Quote: 'double-blind, double dummy, randomized trial'	Low risk
3	Quote: 'Administration of dabigatran or a placebo that looked identical to dabigatran was initiated, and the parenteral anticoagulant was stopped, once the parenteral anticoagulant had been given for at least 5 days and the true or sham INR was recorded as 2.0 or higher on 2 consecutive days.' Quote: 'Warfarin or a placebo that looked identical to warfarin was generally started on the day of random assignment and was adjusted to achieve an INR of 2.0 to 3.0 on a point-of-care coagulometer that was programmed, in conjunction with the randomization schedule, to yield either a true INR or a sham INR ("single dummy phase").'	Low risk
4	Quote: 'Patients […] were told to contact their study site immediately if symptoms developed that were suggestive of venous thromboembolism or bleeding.'	Unclear risk
5	Quote: 'All suspected outcome events and deaths were classified by central adjudication committees, whose members were unaware of the treatment assignments.'	Low risk
6	Quote: 'Patients were assessed at 7 days and then monthly until 6 months'	Unclear
7	Quote: 'Patients were assessed at 7 days and then monthly until 6 months' Quote: 'The study drug was stopped before 6 months in 204 patients (16.0%) in the dabigatran group (126 because of an adverse event, 21 because of nonadherence, 9 because of loss to follow-up, 39 because of withdrawal of consent, and 9 for other reasons) and in 183 patients (14.5%) in the warfarin group (102 because of an adverse event, 35 because of nonadherence, 6 because of loss to follow-up, 36 because of withdrawal of consent, and 4 for other reasons).'	High risk
8	all mentioned analyses in method are reported	Low risk

9.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The literature search was conducted in:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- EMBASE (Ovid), 1974 to 2014 Week 17
- The Cochrane Library, 1898 to present

9.6.2 The date on which the search was conducted.

All searches were conducted on the 1st of December 2014.

9.6.3 The date span of the search.

There was no restriction on the date of publication.

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	71,704	75,388
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	46,810	53,019
#3			(dvt or vte or dvts or vtes).mp.	9,743	11,744
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	39,136	42,968
#5	**Hits of P**		**or/1-4**	**91,857**	**101,378**
#6	I	Edoxaban	edoxaban.mp.	149	282
#7			lixiana.mp.	5	6
#8			DU-176b.mp.	20	23
#9	**Hits of I**		**or/6-8**	**162**	**295**
#10	S	Non-RCTs	Epidemiologic studies /	5,912	6,286
#11			Exp case control studies/	652,243	713,948
#12			Exp cohort studies/	1,335,882	1,444,254
#13			Case control.tw.	71,262	85,783
#14			(cohort adj (study or studies)).tw.	77,913	100,702
#15			Cohort analy$.tw.	3,383	4,260
#16			(Follow up adj (study or studies)).tw.	35,510	39,541
#17			(observational adj (study or studies)).tw.	39,059	51,450

ID	PICOS	Category	Search terms	Initial	Update
#18			Longitudinal.tw.	127,525	156,873
#19			Retrospective.tw.	249,615	301,988
#20			Cross sectional.tw.	149,443	190,638
#21			Cross-sectional studies/	172,912	193,902
#22	**Hits of S**		**Or/10-21**	**1,805,412**	**2,043,714**
#23	**Hits of P and I and S**		**5 and 9 and 22**	**2**	**1**
#24	**Limits**	**Humans**	**limit 23 to humans**	**1**	**1**
#25	**Limits**	**Date**	**limit 24 to ed=20140425-20141204**	**-**	**0**

Cochrane

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	MeSH descriptor: [Venous Thromboembolism] this term only	400	420
#2			MeSH descriptor: [Venous Thrombosis] explode all trees	2,283	2,298
#3			MeSH descriptor: [Pulmonary Embolism] explode all trees	909	921
#4			((venous or vein) near/2 (thrombosis or thromboses or thrombus or thromboembolism)):tiabkw	4,908	5,154
#5			(dvt or vte or dvts or vtes):tiabkw	1,233	1,310
#6			((pulmonary or lung) near/2 (embolism* or emboli)):tiabkw	1,969	2,120
#7	**Hits of P**		**(#1 or #2 or #3 or #4 or #5 or #6)**	6,257	6588
#8	I	Intervention	edoxaban:tiabkw	36	50
#9			lixiana:tiabkw	0	1
#10			DU-176b:tiabkw	10	11
#11	**Hits of I**		**(#8 or #9 or #10)**	44	58
#12	**Hits and P and I and C**		**(#7 and #11)**	17	21
#13	**Limits**		**#12 (Publication Year from 2014 to 2014)**	-	2

Embase

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	139,731	146,149
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	99,009	103,716
#3			(dvt or vte or dvts or vtes).mp.	17,728	19,214
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	67,648	70,835
#5	**Hits of P**		**or/1-4**	**157,458**	**164,598**
#6	**I**	**Interventions**	**(Edoxaban or DU 176b or lixiana).mp**	**788**	**993**
#7	S	Non-RCTs	Clinical study/	100,263	106,319
#8			Case control study/	76,923	82,777
#9			Family study/	10,348	10,559
#10			Longitudinal study/	65,654	70,738
#11			Retrospective study/	340,438	366,910
#12			Prospective study/	247,186	266,696
#13			Randomized controlled trials/	50,183	60,811
#14			12 not 13	245,794	264,997
#15			Cohort analysis/	164,579	182,266
#16			(Cohort adj (study or studies)).mp.	113,512	125,662
#17			(Case control adj (study or studies)).tw.	73,709	78,589
#18			(follow up adj (study or studies)).tw.	45,325	46,990
#19			(observational adj (study or studies)).tw.	62,253	69,440
#20			(epidemiologic$ adj (study or studies)).tw.	73,271	76,439
#21			(cross sectional adj (study or studies)).tw.	83,480	92,033
#22	**Hits of S**		**or/7-11,14-21**	**1,182,879**	**1,271,879**
#23	**Hits of P and I and S**		**5 and 11 and 35**	**8**	**12**
#24	**Limits**		**limit 23 to dd=20140502-20141204**	**-**	**3**

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Bibliographies of systematic reviews articles were examined to obtain additional references. Bibliographies of accepted references were also reviewed to identify other potentially relevant references.

9.6.6 The inclusion and exclusion criteria.

Elements	Inclusion	Exclusion
Population (P)	• Adults with DVT or PE	• Children • Patients after surgery i.e. after hip or knee replacement surgery
Interventions (I)	• Edoxaban	• Studies not investigating edoxaban or relevant comparator
Comparators (C)	• No restriction on comparators	• No restriction on comparators
Outcomes (O)	• Mortality • Recurrent VTE • Complications following DVT or PE, including post thrombotic syndrome, heart failure and chronic thrombotic pulmonary hypertension • Adverse effects of treatment including bleeding events, incranial and gastrointestinal bleeding	• Cost • Quality of life

9.6.7 The data abstraction strategy.

For both the initial search and the update, the study selection process followed 2 phases:

- **Level 1 screening**: Titles and abstracts of the identified studies from the electronic databases and Internet searches were independently reviewed by two independent reviewers using criteria outlined in section 9.2.6. All decisions on the inclusion/exclusion criteria were compared and any difference was resolved in a discussion with a third reviewer. For abstracts that were deemed relevant to the first level of review, the full-text articles were retrieved for further review.

- **Level 2 screening**: Full texts of the identified studies at level 1 were independently reviewed for eligibility by two independent reviewers using criteria outlined in section9.6.6. All decisions on the inclusion/exclusion criteria were compared and any difference was resolved in a discussion with a third reviewer. For each excluded study, a specific reason for exclusion was recorded.

No relevant studies were identified.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

Not applicable.

9.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The clinical search described in section 6.1 and section 9.2 was also designed to identify eligible studies for AEs associated with edoxaban.

9.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

Not applicable.

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **EconLIT**
- **NHS EED.**

The literature search was conducted in:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- EMBASE (Ovid), 1974 to 2014 Week 17
- NHS EED
- Econlit

9.10.2 The date on which the search was conducted.

The search was conducted in December 2014.

9.10.3 The date span of the search.

There was no restriction on the date of publication.

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline

ID	PICOS	Category	Search terms	Hits Medline
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	26,108
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	52,866
#3			(dvt or vte or dvts or vtes).mp.	11,671
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	42,880
#5	**Hits of P**		**or/1-4**	**99,707**
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	293
#7			(warfarin$ or coumadin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	24,081
#8			(dabigatran or bibr 1048 or pradax*).mp.	2,173
#9			(apixaban or bms 562247 or bms562247).mp.	1,041
#10			(rivaroxaban or bay 597939 or xarelto).mp.	1,707
#11	**Hits of I**		**or/6-10**	**25,662**
#12	S	Economic	Economics/	27,421
#13			"costs and cost analysis"/	43,095
#14			Cost allocation/	1,976
#15			Cost-benefit analysis/	63,206
#16			Cost control/	20,813

ID	PICOS	Category	Search terms	Hits Medline
#17			Cost savings/	9,189
#18			Cost of illness/	19,026
#19			Cost sharing/	2,065
#20			"deductibles and coinsurance"/	1,482
#21			Medical savings accounts/	487
#22			Health care costs/	29,059
#23			Direct service costs/	1,058
#24			Drug costs/	12,751
#25			Employer health costs/	1,080
#26			Hospital costs/	8,169
#27			Health expenditures/	14,390
#28			Capital expenditures/	1,968
#29			Value of life/	6,025
#30			exp economics, hospital/	20,195
#31			exp economics, medical/	13,982
#32			Economics, nursing/	4,025
#33			Economics, pharmaceutical/	2,601
#34			exp "fees and charges"/	27,925
#35			exp budgets/	12,343
#36			(low adj cost).mp.	27,629
#37			(high adj cost).mp.	8,727
#38			(health?care adj cost$).mp.	5,105
#39			(fiscal or funding or financial or finance).tw.	90,229
#40			(cost adj estimate$).mp.	1,551
#41			(cost adj variable).mp.	35
#42			(unit adj cost$).mp.	1,698
#43			(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	189,309
#44	**Hits of S**		**or/12-43**	**503,846**
#45	**Hits of P and I and S**		**5 and 11 and 44**	**281**
#46	**Limits**	**Humans**	**limit 45 to humans**	**264**

Cochrane

ID	PICOS	Category	Search terms	Hits Cochrane
#1	P	Indication	MeSH descriptor: [Venous Thromboembolism] this term only	400
#2			MeSH descriptor: [Venous Thrombosis] explode all trees	2,283
#3			MeSH descriptor: [Pulmonary Embolism] explode all trees	909
#4			((venous or vein) near/2 (thrombosis or thromboses or thrombus or thromboembolism)):ti,ab,kw	4,908
#5			(dvt or vte or dvts or vtes):ti,ab,kw	1,233
#6			((pulmonary or lung) near/2 (embolism* or emboli)):ti,ab,kw	1,969
#7	**Hits of P**		**(#1 or #2 or #3 or #4 or #5 or #6)**	**6,588**
#8	I and C	Interventions and Comparators	(edoxaban or lixiana or DU-176b):ti,ab,kw	58
#9			(warfarin$ or coumandin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA):ti,ab,kw	2,502
#10			(dabigatran or bibr 1048 or pradax*):ti,ab,kw	256
#11			(apixaban or bms 562247 or bms562247):ti,ab,kw	161
#12			(rivaroxaban or bay 597939 or xarelto):ti,ab,kw	274
#13	**Hits of I and C**		**(#8 or #9 or #10 or #11 or #12)**	**2,865**
#14	**Hits and P and I and C**		**(#7 and #13)**	**654**
#15	**Limit**	**Cochrane Database (CDSR)**	**#14 in Economic Evaluations**	**34**

Embase

ID	PICOS	Category	Search terms	Hits Embase
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	188,020
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	103,716
#3			(dvt or vte or dvts or vtes).mp.	19,214
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	70,835

ID	PICOS	Category	Search terms	Hits Embase
#5	**Hits of P**		**or/1-4**	**204,252**
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	993
#7			(warfarin$ or coumandin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	70,982
#8			(dabigatran or bibr 1048 or pradax*).mp.	6,269
#9			(apixaban or bms 562247 or bms562247).mp.	3,322
#10			(rivaroxaban or bay 597939 or xarelto).mp.	5,271
#11	**Hits of I**		**or/6-10**	**74,441**
#12	S	Economic	Socioeconomics/	110,974
#13			Cost benefit analysis/	65,668
#14			Cost effectiveness analysis/	101,453
#15			Cost of illness/	14,534
#16			Cost control/	50,100
#17			Economic aspect/	103,913
#18			Financial management/	101,610
#19			Health care cost/	132,781
#20			Health care financing/	11,532
#21			Health economics/	33,957
#22			Hospital cost/	14,270
#23			(fiscal or financial or finance or funding).tw.	109,623
#24			Cost minimization analysis/	2,562
#25			(cost adj estimate$).mp.	2,094
#26			(cost adj variable$).mp.	170
#27			(unit adj cost$).mp.	2,622
#28	**Hits of S**		**or/12-27**	**680,327**
#29	**Hits of P and I and S**		**5 and 11 and 28**	**1,365**

EconLit

ID	PICOS	Category	Search terms	Hits EconLit
#1	P	Indication	TX ((venous or vein) AND (thrombosis or thromboses or thrombus or thromboembolism))	2
#2			TX (dvt or vte or dvts or vtes)	2
#3			TX ((pulmonary or lung) AND (embolism* or emboli))	6
#4	**Hits of P**		**or/1-3**	**9**

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Bibliographies of systematic reviews articles were examined to obtain additional references. Bibliographies of accepted references were also reviewed to identify other potentially relevant references.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

	Lefebvre 2014 (88)		Seaman 2013 (89)		Wolowacz 2013 (82)	
1. Was a well-defined question posed in answerable form? 1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	Both costs and effects, QALYs and outcomes, are considered. The analysis compares rivaroxaban to enoxaparin + VKA. Direct medical costs from the US payer's perspective were considered.	Yes	The study examined both costs and effectiveness (QALYs) of extended duration prophylaxis of recurrent VTE with rivaroxaban compared with no therapy (placebo). The analysis was conducted from a Medicare/ United States payer perspective.	Yes	The study question was well defined in an answerable form: to estimate the cost effectiveness of dabigatran versus no treatment (placebo) for the secondary prevention of DVT and PE from the perspective of the UK National Health Service (NHS).
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? 2.1. Were there any important alternatives omitted? 2.2. Was (should) a do-nothing alternative be considered?	Yes	Alternative enoxaparin + VKA is frequently used to treat VTE and minimise the risk of recurrence.	Yes	The two alternatives were rivaroxaban, compared to no therapy.	Yes	A quick description of the treatment has been given.
3. Was the effectiveness of the programme or services established? 3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Was effectiveness established through an overview of clinical studies? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Yes	Effectiveness of rivaroxaban and enoxaparin + VKA was estimated from results of EINSTEIN trial. EINSTEIN was a randomised controlled trial, and open-label. No meta-analysis was performed.	Yes	Effectiveness of rivaroxaban and enoxaparin + VKA was estimated from results of EINSTEIN-Extension trial. EINSTEIN was a randomised controlled trial, and open-label. No meta-analysis was performed.	Yes	Efficacy and safety parameters were based on the results of RE-SONATE trial. No network meta-analysis was performed.
4. Were all the important and relevant costs and consequences for each alternative identified? 4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?	Yes	Range of direct costs was wide enough for the research question at hand in the US payer's perspective (medications, visit costs, inpatient costs, outpatient costs: management of VTE, bleed costs, PTS management). Productivity costs are not included.	Yes	Relevant costs within the Medicare/US payer perspective was wide enough: it covered drug acquisition costs and direct costs resulting from inpatient treatment of major complications (VTE or bleeding), procedures and office visits, as well as costs associated with each permanent health state (post-ICH and/or post-PTS care)	No	Only key model inputs were displayed on the poster. Information is incomplete.
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)? 5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no	Yes		Yes	Previously identified costs and consequences were included in the model, and were measured in the appropriate physical unit.	No	Incomplete information on the poster.

	Lefebvre 2014 (88)		Seaman 2013 (89)		Wolowacz 2013 (82)	
weight in the subsequent analysis? 5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?						
6. Were the cost and consequences valued credibly? 6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	Yes	Costs and consequences were valued credibly, sources were clearly identified.	Yes	Sources of costs and inputs of the models were correctly identified.	No	Sources of inputs are incompletely entered.
7. Were costs and consequences adjusted for differential timing? 7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was there any justification given for the discount rate used?	Yes	Future costs and effectiveness were discounted at 3% per year.	Yes	Costs and QALYs were discounted at 3% annual rates. Source: Gold 1996.	Yes	Discount rate for costs and consequences was 3.5%.
8. Was an incremental analysis of costs and consequences of alternatives performed? 8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	Yes	Incremental cost-effectiveness between rivaroxaban and enoxaparin + VKA was computed, in terms of costs/QALY gained.	Yes	Incremental cost per QALY between rivaroxaban and no treatment was computed.	Yes	ICER in terms of costs per QALYs did not need to be computed, since dabigatran was dominating placebo in the base case analysis.
9. Was allowance made for uncertainty in the estimates of costs and consequences? 9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed? 9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)? 9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	Yes	Uncertainty in the estimates of costs and consequences was evaluated using one-way sensitivity analyses, and probabilistic sensitivity analyses. Results were not sensitive in the changes of value.	Yes	Uncertainty was characterised by performing a deterministic sensitivity analysis. Ranges were determined a priori by adding/subtracting 25% or 50% to the base case value. The results were sensitive to several major parameters (annual rate of bleed, annual rate of rVTE, discount rate, HR of rVTE on rivaroxaban). Results by time horizon were also computed.	No	Deterministic sensitivity analysis was performed. However, information on the range around parameters was not displayed on the poster. Results were robust to deterministic sensitivity analyses. A probabilistic sensitivity analysis was also performed. A cost-effectiveness plane as well as a cost-effectiveness acceptability curve has been constructed.
10. Did the presentation and discussion of study results	Yes	Several limitations of the model were	Yes	An extensive discussion that dealt	No	Conclusions were based on the cost-

	Lefebvre 2014 (88)		Seaman 2013 (89)		Wolowacz 2013 (82)	
include all issues of concern to users? 10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups? 10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)? 10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?		addressed and discussed.		with lots of issues of the model		effectiveness ratio. No discussion of results.

	Santos (90)		Coleman (80)		Jugrin (83)	
1. Was a well-defined question posed in answerable form? 1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	The question was well defined, in answerable form, examining both costs and effects rivaroxaban versus enoxaparin/warfarin in Portugal.	Yes	The question was well defined, in answerable form, examining both costs and effects of rivaroxaban versus placebo using a Medicare perspective.	Yes	The study examined both costs and effectiveness (QALYs) ofdabigatran compared with warfarin in the treatment and secondary prevention of acute venous thromboembolism (VTE) comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) from NHS and public Social services perspectives.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? 2.1. Were there any important alternatives omitted? 2.2. Was (should) a do-nothing alternative be considered?	Yes	Treatment alternatives were clearly defined.	Yes	Treatment alternatives were clearly defined.	Yes	The two alternatives were dabigatran, compared to with warfarin.
3. Was the effectiveness of the programme or services established? 3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Was effectiveness established through an overview of clinical studies? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Yes	Effectiveness inputs were based on the results of the EINSTEIN-DVT and EINSTEIN-PE clinical trials. No meta-analyses have been conducted.	Yes	Effectiveness inputs were from the EINSTEIN-Extension trial data and other sources identified through the Tufts Cost-Effectiveness Analysis registry and a Medline database search.	Yes	Effectiveness was sourced from the pivotal trials.
4. Were all the important and relevant costs and consequences for each alternative identified? 4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?	No	Only key model inputs were detailed on the abstract.	Yes	Relevant costs within the Medicare/US payer perspective was wide enough: it covered drug acquisition costs and direct costs resulting from inpatient treatment of major complications (VTE or bleeding), procedures and office visits, as well as costs associated with each permanent health state (post-ICH and/or post-PTS care)	No	Only key model inputs were displayed on the poster.

	Santos (90)		Coleman (80)		Jugrin (83)	
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)? 5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? 5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	Yes	Costs and consequence were measured in appropriate physical units for each scenario.	Yes	Previously identified costs and consequences were included in the model, and were measured in the appropriate physical unit.	Yes	Incomplete information on the poster
6. Were the cost and consequences valued credibly? 6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	No	The costs sources were not clear.	Yes	Sources of costs and inputs of the models were correctly identified.	Yes	Sources inputs of the models were correctly identified. However, sources of costs were not detailed.
7. Were costs and consequences adjusted for differential timing? 7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was there any justification given for the discount rate used?	Yes	Future costs and effectiveness were discounted at 5% per year.	Yes	Costs and QALYs were discounted at 3% annual rates. Source: Gold 1996.	No	Not reported
8. Was an incremental analysis of costs and consequences of alternatives performed? 8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	Yes	Incremental cost per QALY between rivaroxaban and enoxaparin/warfarin was computed for different scenarios.	Yes	Incremental cost per QALY between rivaroxaban and no treatment was computed for different scenarios.	Yes	The incremental costs between dabigatran and warfarin were computed
9. Was allowance made for uncertainty in the estimates of costs and consequences? 9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed? 9.2. If a sensitivity analysis was employed, was	No	Uncertainty was characterised by performing a sensitivity analysis. However the justification of ranges around parameters is not provided.	Yes	Uncertainty was characterised by performing a deterministic sensitivity analysis. Ranges were determined a priori by adding/subtracting 25% or 50% to the base case value. The	Yes	Uncertainty was characterised by performing a probabilistic sensitivity analysis.

	Santos (90)		Coleman (80)		Jugrin (83)	
justification provided for the range of values (or for key study parameters)? 9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?				results were sensitive to several major parameters (annual rate of bleed, annual rate of rVTE, discount rate, HR of rVTE on rivaroxaban). Results by time horizon were also computed.		
10. Did the presentation and discussion of study results include all issues of concern to users? 10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups? 10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)? 10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	Yes	An extensive discussion that dealt with lots of issues of the model.	Yes	An extensive discussion that dealt with lots of issues of the model.	No	Conclusions were based on the cost-effectiveness ratio. No discussion of results.

	Jugrin (84)		Jugrin (85)		Rosselli (91)	
1. Was a well-defined question posed in answerable form? 1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	The study examined both costs and effectiveness (QALYs) of dabigatran etexilate for six months of treatment for acute pulmonary embolism (PE) compared with warfarin and rivaroxaban from NHS and public Social services.	Yes	• The study examined both costs and effectiveness (QALYs) of dabigatran etexilate for six months of treatment for acute venous thromboembolism (VTE) compared with rivaroxaban from NHS and public Social services	Yes	The study question was well defined in an answerable form: to estimate the cost effectiveness of of dabigatran comapered to new oral anticoagulants (NOA) in the UK health care setting
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? 2.1. Were there any important alternatives omitted? 2.2. Was (should) a do-nothing alternative be considered?	Yes	The three alternatives were dabigatran, compared to with warfarin and rivaroxaban	Yes	The two alternatives were dabigatran, compared to with rivaroxaban	Yes	A quick description of the different alternatives, dabigatran and new oral anticoagulants (NOA).
3. Was the effectiveness of the programme or services established? 3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Was effectiveness established through an overview of clinical studies? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Yes	Effectiveness were based upon AMPLIFY and AMPLIFY-EXT clinical trial data, network meta-analyses, discontinuation due to clinical events, and UK life tables.	Yes	Effectiveness of dabigatran and rivaroxaban were sourced from pooled RE-COVER and RE-COVER II dabigatran trials and the 6 months treatment duration subgroup of the rivaroxaban EINSTEIN-DVT and EINSTEIN-PE trials	Yes	Efficacy, utilities and safety inputs were from clinical trials (CT) (RE-COVER I and II; EINSTEIN- DVT; EINSTEIN-PE; AMPLIFY; RE-SONATE; RE-MEDY and a meta-analysis of 18 CT for LMWH.
4. Were all the important and relevant costs and consequences for each alternative identified? 4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?	Yes	Costs were from UK NHS Healthcare Resource Group tables. However, Information is incomplete.	Yes	Only key model inputs were displayed on the poster.	Yes	Costs of events were estimated from hospital billing records, POS tariffs, SOAT Manual and local experts.
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)? 5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no	Yes	Previously identified costs and consequences were included in the model, and were measured in the appropriate physical unit.	Yes	Previously identified costs and consequences were included in the model, and were measured in the appropriate physical unit.	No	Previously identified costs and consequences were included in the model, and were measured in the appropriate physical unit.

	Jugrin (84)		Jugrin (85)		Rosselli (91)	
weight in the subsequent analysis? 5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?						
6. Were the cost and consequences valued credibly? 6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	Yes	Sources of costs and inputs of the models were correctly identified.	Yes	Sources of costs and inputs of the models were correctly identified.	Yes	Sources of costs and inputs of the models were correctly identified.
7. Were costs and consequences adjusted for differential timing? 7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was there any justification given for the discount rate used?	No	Not reported	No	Not reported	Yes	Discount rate for costs and consequences was 3%.
8. Was an incremental analysis of costs and consequences of alternatives performed? 8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	Yes	The incremental costs between dabigatran, warfarin and rivaroxaban.	Yes	The incremental costs between dabigatran and rivaroxaban.	Yes	The incremental costs between dabigatran and new oral anticoagulants (NOAC)
9. Was allowance made for uncertainty in the estimates of costs and consequences? 9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed? 9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)? 9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	Yes	Uncertainty was characterised by performing a probabilistic sensitivity analysis.	Yes	Uncertainty was characterised by performing a probabilistic sensitivity analysis.	Yes	Sensitivity analysis was conducted but information is detailed.
10. Did the presentation and discussion of study results	No	Conclusions were based on the cost-	No	Conclusions were based on the cost-	No	Conclusions were based on the cost-

	Jugrin (84)		Jugrin (85)		Rosselli (91)	
include all issues of concern to users? 10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups? 10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)? 10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?		effectiveness ratio. No discussion of results.		effectiveness ratio. No discussion of results.		effectiveness ratio. No discussion of results.

	Lanitis (86)		Lanitis (87)		Levac (92)	
1. Was a well-defined question posed in answerable form? 1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	No	• The study question is posed in an answerable form. Both costs and effectiveness (QALYs) of apixaban compared to other NOACs and LMWH/warfarin from the perspective of the UK National Health Service have been examined.	Yes	The study question is well defined in answerable form. It examines both costs and effects of treatment of patients following a VTE event with apixaban versus other NOACs and LMWH/warfarin. The chosen viewpoint for the analysis was the National Health Service perspective.	Yes	The question was well defined, in answerable form, examining both costs and effects of rivaroxaban compared to LMWH/ VKA from a Canadian provincial government perspective.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)? 2.1. Were there any important alternatives omitted? 2.2. Was (should) a do-nothing alternative be considered?	Yes	Treatment alternatives were clearly defined.	Yes	Treatment alternatives were clearly defined.	Yes	Treatment alternatives were clearly defined.
3. Was the effectiveness of the programme or services established? 3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Was effectiveness established through an overview of clinical studies? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Yes	Effectiveness data were based upon AMPLIFY and AMPLIFY-EXT clinical trial data, network meta-analyses, discontinuation due to clinical events, and UK life tables.	Yes	A network meta-analysis was conducted to compare apixaban to other NOACs and LMWH/warfarin.	Yes	Effectiveness inputs were from EINSTEIN-PE and published literature. No meta-analyses have been conducted.
4. Were all the important and relevant costs and consequences for each alternative identified? 4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?	Yes	Costs were from UK NHS Healthcare Resource Group tables. However, Information is incomplete.	No	Only key model inputs were detailed on the abstract.	Yes	Economic inputs were from publically available Canadian sources. However, Information is incomplete.
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life	Yes	Identified costs and outcomes were measured in appropriate physical units.	Yes	Costs and consequence were measured in appropriate physical	Yes	Costs and consequences were measured accurately for each period.

	Lanitis (86)		Lanitis (87)		Levac (92)	
years)? 5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? 5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?				units.		
6. Were the cost and consequences valued credibly? 6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	Yes	Costs were from UK NHS Healthcare Resource Group tables. However, Information is incomplete.	No	The costs sources were not clear.	Yes	Economic inputs were from publically available Canadian sources. However, the sources were not detailed.
7. Were costs and consequences adjusted for differential timing? 7.1. Were costs and consequences that occur in the future 'discounted' to their present values? 7.2. Was there any justification given for the discount rate used?	No	Not reported	Yes	Future costs and effectiveness were discounted at 3.5% per year.	No	Not reported
8. Was an incremental analysis of costs and consequences of alternatives performed? 8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	Yes	ICER has been computed.	Yes	Incremental analysis of costs was computed.	Yes	Incremental cost effectiveness ratio between costs and QALYs was computed. But only dominance has been reported.
9. Was allowance made for uncertainty in the estimates of costs and consequences? 9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed? 9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)? 9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis,	No	Uncertainty was characterised by performing a sensitivity analysis. However the justification of ranges around parameters is not provided.	No	Uncertainty was characterised by performing a sensitivity analysis. However the justification of ranges around parameters is not provided.	No	Uncertainty was characterised by performing a sensitivity analysis. However the justification of ranges around parameters is not provided.

	Lanitis (86)		Lanitis (87)		Levac (92)	
or within the confidence interval around the ratio of costs to consequences)?						
10. Did the presentation and discussion of study results include all issues of concern to users? 10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? 10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? 10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups? 10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)? 10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No	Conclusions were based on the cost-effectiveness ratio. No discussion of results.	No	Conclusions were based on the cost-effectiveness ratio. No discussion of results.	No	Conclusions were based on the cost-effectiveness ratio. No discussion of results.

9.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **NHS Economic Evaluation Database (NHS EED)**
- **EconLIT.**

The literature search was conducted in:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- EMBASE (Ovid), 1974 to 2014 Week 17
- NHS EED
- Econlit

9.12.2 The date on which the search was conducted.

Initial searches were conducted in May 5th, 2014. Updates were conducted in December 4th, 2014.

9.12.3 The date span of the search.

There was no restriction on the date of publication.

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	24,702	26,154
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	46,974	49,757
#3			(dvt or vte or dvts or vtes).mp.	9,784	10,620
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).ti,ab,ot.	24,558	25,814
#5	**Hits of P**		**or/1-4**	**79,462**	**83,622**
#6	S	QoL	Quality-Adjusted Life Years/	6,934	7,642
#7			(sf36 or sf 36 or short form 36 or shortform 36).ti,ab.	14,722	16,297
#8			(sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix).ti,ab.	1	1
#9			(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.	967	1,014
#10			(sf20 or sf 20 or short form 20 or shortform 20 or	323	344

ID	PICOS	Category	Search terms	Initial	Update
			sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.		
#11			(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab.	396	457
#12			(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.	2,474	2,849
#13			(sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab.	239	262
#14			(euroqol or euro qol or eq5d or eq 5d).ti,ab.	3,598	4,136
#15			(Time trade-off or time tradeoff or TTO or Standard gamble).ti,ab.	1,458	1,577
#16			(hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab.	9,226	10,437
#17			(health$ year$ equivalent$ or hye or hyes).ti,ab.	62	63
#18			(health utilit$ ind$ or hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab.	1,063	1,156
#19			(health state$ utilit$ or HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab.	467	514
#20			(quality of well being or quality of wellbeing or qwb).ti,ab.	345	382
#21			(QALY$ or quality adjusted life year$).ti,ab.	6,474	7,216
#22			(Disability adjusted life year$ or DALY$ or health adjusted life year$ or HALY$ or years of healthy life or YHL or years of potential life lost or YPLL or years of health life lost or YHLL).ti,ab.	2,129	2,373
#23			(quality adjusted life day$ or qald$ or quality adjusted life expectancy or qale$ or Quality time or qtime$).ti,ab.	685	746
#24			(Perception of Anticoagulant Treatment or VEnous INsufficiency Epidemiological).ti,ab.	12	13
#25			(PACT-Q or VEINES).ti,ab.	37	40
#26	**Hits of S**		**or/6-25**	**39,321**	**43,783**
#27	**Hits of P and S**		**5 and 26**	**196**	**223**
#28	**Limits**	**Humans**	**Limit 27 to humans**	**190**	**217**
#29	**Limits**	**Date**	**Limit 28 to yr="2014"**	**-**	**7**

Cochrane

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	MeSH descriptor: [Venous Thromboembolism] this term only	400	420
#2			MeSH descriptor: [Venous Thrombosis] explode all trees	2,283	2,298
#3			MeSH descriptor: [Pulmonary Embolism] explode all trees	909	921
#4			((venous or vein) near/2 (thrombosis or thromboses or thrombus or thromboembolism)):ti,ab,kw	4,908	5,154
#5			(dvt or vte or dvts or vtes):ti,ab,kw	1,232	1,310
#6			((pulmonary or lung) near/2 (embolism* or emboli)):ti,ab,kw	1,969	2,120
#7	**Hits of P**		**(#1 or #2 or #3 or #4 or #5 or #6)**	**6257**	**6,257**
#8	**Limit**	**Cochrane Database (CDSR)**	**#7 in Economic Evaluations**	**226**	**251**
#9	**Limit**	**Date**	**#8 Online Publication Date from May 2014 to Dec 2014**	**-**	**3**

Embase

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	180,736	188,020

ID	PICOS	Category	Search terms	Initial	Update
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	99,306	103,716
#3			(dvt or vte or dvts or vtes).mp.	17,803	19,214
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).ti,ab,ot.	35,455	37,254
#5	**Hits of P**		**or/1-4**	**196,007**	**203,884**
#6	S	QoL	Quality-Adjusted Life Years/	11,857	12,893
#7			(sf36 or sf 36 or short form 36 or shortform 36).mp	25,583	27,630
#8			(sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix).mp	3	4
#9			(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).mp	1,513	1,571
#10			(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).mp	354	363
#11			(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).mp	701	800
#12			(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).mp	4,559	5,104
#13			(sf8 or sf 8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).mp	453	488
#14			(euroqol or euro qol or eq5d or eq 5d).mp	6,852	7,875
#15			(Time trade-off or time tradeoff or TTO or Standard gamble).mp	1,982	2,128
#16			(hql or hrql or hqol or h qol or hrqol or hr qol).mp	14,750	16,242
#17			(health$ year$ equivalent$ or hye or hyes).mp	111	115
#18			(health utilit$ ind$ or hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).mp	2,439	2,564
#19			(health state$ utilit$ or HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).mp	783	880
#20			(quality of well being or quality of wellbeing or qwb).mp	441	452
#21			(QALY$ or quality adjusted life year$).mp	15,785	17,234
#22			(Disability adjusted life year$ or DALY$ or health adjusted life year$ or HALY$ or years of healthy life or YHL or years of potential life lost or YPLL or years of health life lost or YHLL).mp	2,992	3,245
#23			(quality adjusted life day$ or qald$ or quality adjusted life expectancy or qale$ or Quality time or qtime$).mp	966	1,022
#24			(questionnaire$ adj6 (Fibrillation or Defibrillator or Anticoagulant Treatment)).mp	382	494
#25			(AF-QOL18 or PACT-Q or ICD-QOL).mp	9	11
#26	**Hits of S**		**or/6-25**	**67,010**	**73,161**
#27	**Hits of P and S**		**5 and 26**	**813**	**898**
#28	**Limit**		**limit 27 to dd=20140502-20141204**	**-**	**94**

QoL EconLit

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	TX ((venous or vein) AND (thrombosis or thromboses or thrombus or thromboembolism))	2	2
#2			TX (dvt or vte or dvts or vtes)	2	2
#3			TX ((pulmonary or lung) AND (embolism* or emboli))	5	6
#4	**Hits of P**		**or/1-3**	**8**	**9**
#5	**Limit**		**limit 4 to yr="2014 -Current" (1)**	**-**	**1**

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Bibliographies of systematic reviews articles were examined to obtain additional references. Bibliographies of accepted references were also reviewed to identify other potentially relevant references.

9.12.6 The inclusion and exclusion criteria.

Elements	Inclusion	Exclusion
Population (P)	• Adults with DVT or PE	• Children • Patients after surgery i.e. hip or knee replacement surgery
Interventions (I)	• NOACS: direct thrombin inhibitors i.e. dabigatran • NOACS: factor Xa inhibitors i.e. apixaban, rivaroxaban, edoxaban • Coumarins/VKA i.e. warfarin	• Studies not investigating edoxaban or relevant comparator
Comparators (C)	• All interventions listed above and Heparin i.e. LMWH or UFH	• No restriction on comparator
Outcomes (O)	• Functional status (SF-36) • Utilities (direct e.g. by TTO) or indirect (e.g. EQ-5D)	• Studies not reporting HRQoL outcomes
Study designs (S)	• No restriction	• No restriction

9.12.7 The data abstraction strategy.

For both the initial search and the update, the study selection process followed 2 phases:

- **Level 1 screening**: Titles and abstracts of the identified studies from the electronic databases and Internet searches were independently reviewed by two independent reviewers using criteria outlined in section 9.12.6. All decisions on the inclusion/exclusion criteria were compared and any difference was resolved in a discussion with a third reviewer. For abstracts that were deemed relevant to the first level of review, the full-text articles were retrieved for further review.

- **Level 2 screening**: Full texts of the identified studies at level 1 were independently reviewed for eligibility by two independent reviewers using criteria outlined in section 9.12.6. All decisions on the inclusion/exclusion criteria were compared and any difference was resolved in a discussion with a third reviewer. For each excluded study, a specific reason for exclusion was recorded.

9.13

Related procedures for evidence submission

9.14 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

9.15 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may

change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its

guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.