NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Apixaban (Eliquis®) for the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery

Submitted by Bristol-Myers Squibb Pharmaceuticals Ltd. and Pfizer Ltd.

Single Technology Appraisal (STA)

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Abbreviations

ACCP	American College of Chest Physicians
ACS	Acute Coronary Syndrome
AE	Adverse event
AES	Adverse event
ALT	Alanine aminotransferase
ARD	Absolute Risk Difference
ARR	Absolute Risk Reduction
AST	Aspartate aminotransferase
Asym	Asymptomatic
AT	Serum alanine aminotransferase and aspartate aminotransferase
BD	Twice daily
BMI	Body mass index
BNF	British National Formulary
CC	Complications and Co-morbidities
CCA	Cost-consequences analysis
CCT	Controlled clinical trial
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CrCl	Creatinine Clearance
CPM	Continuous passive motion
CRT	Catheter related thrombosis
CQUIN	Commissioning for Quality and Innovation
CRNM	Clinically relevant non major
CSR	Clinical Study Report
CTEPH	Chronic thromboembolic pulmonary hypertension
CUA	Cost-utility analysis
CVC	Central venous catheters
DH	Department of Health

DVT	Deep vein thrombosis
EMEA	European Medicines Agency
ERG	Evidence Review Group
F	Female
FID	Foot impulse device or foot pump
FP	Forest Plot
GCS	Graduated elastic compression stockings / anti-embolism stockings
GDG	Guideline Development Group
GGT	Gamma Glutamyl Transpeptidase
GP	General Practitioner
GPRD	General Practice Research Database
GRADE	Guidelines Recommendations Assessment Development Evaluation
GRP	Guideline Review Panel
hazards	Hazard ratios or hazard rates
HD	High dose
HES	Hospital Episode Statistics
HIT	Heparin induced thrombocytopaenia
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HSU	Health state utility
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
ICU	Intensive Care Unit
INB	Incremental net benefit
INR	International normalized ratio
IPCD	Intermittent pneumatic compression device
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
LD	Low dose

LFT	Liver Function Test
LMWH	Low molecular weight heparin
LOS	Length of stay
LY	Life-year
LYG	Life years gained
M	Male
MB	Major Bleeding
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MTC	Mixed Treatment Comparison
M/M	Mild to moderate
N/A	Not applicable
NCC-AC	National Collaborating Centre for Acute Care
NCGC	National Clinical Guideline Centre for Acute and Chronic Conditions
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
NNT	Numbers Needed to Treat
NJR	National Joint Registry
NMCR	Non major clinically relevant bleed
NOAC	New Oral Anticoagulant
OAC	Oral anticoagulants
OD	Once daily
OR	Odds ratio
PASA	Purchasing and Supply Agency (NHS)
PBR	Payment by results
PCT	Primary care trust
PE	Pulmonary embolism
PHT	Pulmonary hypertension
PICO	Patients, interventions, comparisons, outcomes
po	Orally/by mouth

Apixaban. BMS and Pfizer

PP	Per protocol
PPIP	Patient and Public Involvement Programme
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PTS	Post thrombotic syndrome
QIPP	Quality Innovation Productivity and Prevention
QoL	Quality of life
QALY(s)	Quality-adjusted life year(s)
RBC	Red blood cell
RCT	Randomised controlled Trial
RR	Relative risk
SAEs	Serious adverse events
sc	subcutaneous
SD	Standard deviation
SE	Standard error
SPC	Summary of Product Characteristics
SR	Systematic review
Sym	Symptomatic
THR	Total hip replacement
TKR	Total knee replacement
UFH	Unfractionated heparin
UK	United Kingdom
UKOSS	United Kingdom Obstetric Surveillance System
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VTE	Venous thromboembolism
WTP	Willingness to pay
YRS, yr or Y	Years

Executive summary

Venous Thromboembolism (VTE) is a significant burden and an NHS priority

- Venous thromboembolism (VTE) is a condition in which a blood clot (thrombus) forms in a vein. This thrombus may dislodge from its site of origin and travel in the blood to obstruct a blood vessel (embolism), which can be life-threatening or fatal.
- VTE represents a considerable, preventable, morbidity and mortality burden, resulting in approximately 25,000 deaths annually in the UK.
- Patients undergoing major orthopaedic surgery, which includes elective hip and knee replacement, are at particularly high risk for VTE (>40% without prophylaxis).
- Preventing VTE is recognised to be a priority for the NHS. It is included within the Quality, Innovation, Productivity and Prevention (QIPP) program and the Government is explicitly highlighting VTE as a patient safety priority in its National VTE Prevention Programme. VTE risk screening is linked to specific financial incentives through the Commissioning for Quality and Innovation (CQUIN) payment framework, and it has been addressed by one of the first Quality Standards written by NICE. VTE risk assessment has also been mandated in the recently published NHS Outcomes Framework.
- NICE Clinical Guideline (CG 92) "Venous thromboembolism: reducing the risk" recommends for patients undergoing hip or knee replacement surgery that one of the following pharmacological interventions is used for VTE prevention: dabigatran etexilate; fondaparinux sodium; low molecular weight heparin (LMWH); unfractionated heparin (UFH) (for renal failure patients); or rivaroxaban.
- LMWHs are considered the standard of care for VTE prophylaxis in the UK, as they are used in the majority of patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery (71% and 69% respectively). However, LMWHs are given by injection, which requires staff time to train or administer once patients are discharged from hospital. LMWHs also require dose adjustment for renally impaired patients and require initiation prior to surgery. The anticoagulants, dabigatran and rivaroxaban represent an oral alternative to LMWHs. However, dabigatran requires dose adjustment for patients with renal impairment and the elderly and both are indicated soon after surgery. Fondaparinux is used in less than one percent of patients undergoing TKR or THR and it is given by injection, and requires similar administration resources as the LMWHs.

Apixaban - a new oral anticoagulant

- Apixaban (Eliquis®) is a new, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It inhibits free and clot-bound factor Xa, and prothrombinase activity. This prevents thrombus development by preventing thrombin generation and the platelet aggregation induced by thrombin.
- Apixaban is indicated for prevention of VTE in adult patients who have undergone elective total knee replacement (TKR) or total hip replacement (THR) surgery. It is indicated for use for 10-14 days following TKR and 32-38 days following THR as a single course of treatment. The acquisition cost of apixaban will be £3.43 per day based on the dose of one 2.5mg tablet taken twice a day.
- Apixaban addresses the following unmet needs:

- Apixaban is proven to be superior at preventing VTE events, without increasing bleeding in patients undergoing elective total knee and hip replacement surgery compared with enoxaparin.
- Apixaban is an oral treatment which allows convenient administration both in and out of hospital, potentially leading to better treatment compliance and lower administration costs than with injectable anticoagulation therapy such as LMWHs and fondaparinux.
- Apixaban is indicated for initiation 12–24 hours after surgery, which is crucial to allow patients to stop bleeding post-surgery before they start to receive anticoagulant therapy. It also allows timely post-operative patient observation and wound assessment.
- Apixaban does not need dose adjustment in patients with mild or moderate renal impairment or the elderly. This is in contrast to other oral anticoagulants, some of which require dose adjustment for renal impairment and age. This would allow simplified dosing protocols to be applied to the majority of orthopaedic patients, potentially reducing the risk of medication errors.

Apixaban: Clinical Efficacy and Safety

Apixaban significantly reduces the VTE burden in elective THR and TKR patients without increased bleeding, compared with enoxaparin

- Apixaban has been studied in three Phase 3 double blind randomised controlled trials involving over 11,600 patients. ADVANCE 2 (TKR patients) and ADVANCE 3 (THR patients) involved over 8,500 patients and are most relevant to the UK as they study the comparator, enoxaparin at doses licensed in Europe. ADVANCE 1 was a North American study employing a dosing regimen of enoxaparin not licensed in Europe.
- ADVANCE 2 and 3 showed apixaban 2.5mg bd is statistically superior to enoxaparin 40mg od in the primary composite endpoint of adjudicated, symptomatic or asymptomatic DVT, non-fatal PE and death from any cause during the treatment period (RR 0.62, 95% CI 0.51-0.74, p<0.0001; RR 0.36, 95% CI 0.22-0.54, p<0.0001 respectively).
- In both trials major VTE (adjudicated symptomatic or asymptomatic proximal DVT, non-fatal PE and VTE related death) is significantly lower for apixaban compared with enoxaparin (RR 0.50 95% CI 0.26-0.97, p=0.019; RR 0.40 95% CI 0.15-0.8, p<0.0001 for ADVANCE 2 and 3 respectively) whereas incidence of PE occurred very infrequently and were not statistically significantly different.
- The safety data from ADVANCE 2 showed that the bleeding rates (both major and clinically relevant non major [CRNM] bleeding events) were numerically lower for apixaban compared with enoxaparin, although this was not statistically significant (Absolute Risk Difference (ARD) of -1.24 (95% CI -2.66, 0.18; p=0.088). In ADVANCE 3 the bleeding rate was similar in both the apixaban and the enoxaparin groups, with no significant differences (ARD -0.2 (95% CI -1.4, 1.0; p=0.72).
- The apixaban clinical trial data show that the overall adverse event rate and discontinuation rate with apixaban was no different to that with enoxaparin. Across all these studies, apixaban was generally well tolerated with no unexpected safety signals.

Apixaban reduces the VTE burden in THR and TKR patients compared with dabigatran and is of comparable efficacy to rivaroxaban, with similar bleeding profiles

- In the absence of head to head RCT evidence for apixaban versus the newer oral anticoagulants, rivaroxaban and dabigatran, and fondaparinux an indirect comparison was undertaken.

[redacted]

- Trials comparing fondaparinux with enoxaparin 40mg od were only available in THR patients, and for any DVT and major bleeding only. The adjusted indirect comparison found that fondaparinux had higher but non-significant rates of any DVT (OR 1.293, 95%CI 0.688-2.428, p=0.43) and [redacted] compared to apixaban in the THR population.

Apixaban: Cost Effectiveness

Apixaban has the lowest acquisition cost and is a cost effective VTE prophylaxis agent with a minimal budget impact in England and Wales

- Compared with enoxaparin and dabigatran, apixaban is estimated to be less costly and more effective (dominant) in both TKR and THR patients (savings of £67.08 and £154.26 per patient respectively; additional QALYs of 0.012 and 0.048 respectively over dabigatran).
- Compared with rivaroxaban, apixaban has a lower acquisition cost (£3.43 vs. £4.42 per day) and delivers comparable QALYs in both TKR and THR patients (9.53 vs 9.53; 9.08 vs 9.09 respectively). Differences between apixaban and rivaroxaban in total costs per patient were small in TKR and THR populations (£29 savings in THR and £28 cost in TKR) over the 35 year time horizon.
- Sensitivity analyses show that changes to the key parameters underpinning the model such as comparator costs and efficacy rates, result in slight changes to the incremental costs and QALYs for apixaban versus each comparator but overall the differences remain small and results are robust to these changes.

Apixaban: Budget Impact

- The budget impact analysis estimated the number of patients aged 18 years and over who will undergo TKR and THR in NHS facilities in England and Wales between 2012 and 2016 using National Joint Registry data for 2009. Of these patients (51,804 and 45,150 in TKR and THR respectively in 2012), the number likely to use apixaban as a prophylaxis was estimated to be 1036 TKR and 903 THR patients in 2012.
- Based on acquisition and administration costs alone, apixaban is estimated to deliver cost savings to the NHS in England and Wales in both TKR and THR populations. Total savings are predicted to increase from an estimated £66,857 and £112,568 for TKR and THR respectively to £108,104 in TKR and £182,017 in THR in 2016. These savings derive from lower acquisition costs (compared with the therapies most used in England and Wales i.e. enoxaparin, dabigatran and rivaroxaban) and reduced need for nursing time for injection training and administration. Savings in nursing time can be redistributed to other uses in the NHS, thus boosting productivity.

- Results were robust to variations in the key assumptions about duration of therapy and the cost of LMWHs (enoxaparin and dalteparin costs were used instead of weighted mean LMWH costs).

Conclusion

Apixaban should be recommended as an option for VTE prophylaxis as:

- Apixaban provides improved VTE protection in adult patients who undergo elective THR or TKR surgery compared to enoxaparin 40mg od and dabigatran. Overall, apixaban is of similar efficacy and safety to rivaroxaban in both THR and TKR patients.
- There are no increased bleeding rates with apixaban 2.5mg bd compared to enoxaparin 40mg od.
- Apixaban has convenient oral administration, with a 12-24 hours post-operative timing of treatment initiation window.
- Apixaban does not require dose adjustment even in extremes of age, or in patients with mild to moderate renal impairment.
- Apixaban has the lowest acquisition cost of all the comparators (a weighted mean cost was used for comparison for LMWHs) and is a cost effective VTE prophylactic agent with a minimal budget impact 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: Eliquis; Approved name: apixaban; Therapeutic class: not assigned yet.

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

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

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).

Yes, apixaban, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 17th March 2011 and the European Medicines Agency granted Marketing Authorisation on 20th May 2011.

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

The conclusions from the "Scientific discussion" section of the draft EPAR on clinical efficacy were as follows:

- The benefit of apixaban in VTEp in patients undergoing THR and TKR is considered acceptable. No explanation can be given for the higher incidence of PE reported in the TKR studies, even after thorough analysis of possible patient characteristics, timing of initiation of apixaban and the Posology that could have contributed to this observation. Based on the current knowledge and compared to other studies, this higher PE incidence was considered by the CHMP to be probably a chance finding, and the facts are presented in the SmPC.

The conclusions on clinical safety were as follows:

- Safety profile of apixaban in VTE-p in THR and TKR appears to be comparable to that of enoxaparin, with a bleeding profile that appears favourable compared to the higher dose of enoxaparin.

- The most frequent observed adverse reactions are anaemia, haemorrhage, nausea and contusion.
- Based on the current clinical and pre-clinical data, the hepatotoxic potential of apixaban is not supported. Because “Transient elevation of liver tests” were reported, this is included as an Identified Risk in the RMP and “hepatotoxicity” willbe closely monitored in the post marketing period.
- The SmPC clearly identifies the limitations of the clinical studies and the recruitedpopulations:
    - *ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3). It is not recommended in patients with severe hepatic impairment (see sections 4.4. and 5.2).*
    - *It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).*
    - *Patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore Eliquis should be used with caution in this population (see sections 4.4 and 5.2). ALT should be measured as part of the standard pre-operative evaluation (see section 4.4).*

In conclusion, the CHMP considered that the benefit/risk of apixaban is positive for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

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

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

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.

There is no additional evidence concerning the indication being appraised for this submission anticipated to be available in the next 12 months. The following studies have all completed and are included in this submission:

- **ADVANCE-1** CV185034: A phase 3, randomised, double-blind, active-controlled (enoxaparin 30mg bd), parallel-group, multi-center study to evaluate the safety and efficacy of oral apixaban in subjects undergoing elective total knee replacement surgery.
- **ADVANCE-2** CV185047: A phase 3, randomised, double-blind, active-controlled (enoxaparin 40 mg od), parallel-group, multi-center study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total knee replacement surgery.
- **ADVANCE-3** CV185035:- A phase 3, randomised, double-blind, active-controlled, parallel-group, multi-center study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total hip replacement surgery.

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

To be confirmed

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

Yes, the Marketing Authorisation granted via the centralised procedure by the European Medicines Agency is applicable in the European member states.

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?

Apixaban will be appraised by the Scottish Medicines Consortium. Timelines are to be confirmed.

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 1: Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet
Acquisition cost (excluding VAT)	£3.43 per day (10, 20, 60 pack prices are £17.15; £34.30; £102.90 respectively)
Method of administration	Oral
Doses	2.5 mg
Dosing frequency	Twice daily
Average length of a course of treatment	Hip replacement: 32-38 days Knee replacement: 10-14 days
Average cost of a course of treatment	£41.16 (TKR); £116.62 (THR) based on trial durations of 12 and 34 days in TKR and THR respectively.
Anticipated average interval between courses of treatments	Single course
Anticipated number of repeat courses of treatments	Single course
Dose adjustments	No dose adjustments are required in patients with mild or moderate renal impairment

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?

Not applicable.

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

No additional tests or monitoring over and above usual clinical practice are anticipated with apixaban.

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?

Not applicable.

2 Context

Venous thromboembolism (VTE) represents a considerable, preventable, morbidity and mortality burden. NICE Guidelines published in 2007 and 2010 recommending appropriate VTE prophylaxis have not been widely followed in clinical practice in the UK. Despite a number of VTE prophylactic agents being available, there are significant drawbacks to these therapies and an unmet need still exists for convenient prophylaxis, which could improve compliance with treatment guidelines.

Apixaban is a new oral anticoagulant which has been shown to be clinically more effective than enoxaparin, with a comparable safety profile. An indirect comparison showed that apixaban had similar efficacy compared with rivaroxaban and improved efficacy compared with dabigatran, both had comparable safety profiles. Apixaban also has the convenience of the widest time-frame for treatment initiation of any VTE prophylactic pharmacological agent available in the UK, following elective total knee replacement surgery (TKR) or elective total hip replacement surgery (THR). There is no need for dose adjustment in mild or moderate renal impairment or for patient weight with apixaban and it is not associated with heparin induced thrombocytopaenia (HIT).

Because of these specific characteristics, apixaban offers considerable benefits over current pharmacological prophylactic agents for VTE. It is not only effective and well tolerated – apixaban's dosing and timing of treatment initiation could lead to better compliance with VTE prophylactic treatment and the recommended guidelines. Considered together, these features may lead to better patient outcomes and improve NHS resource utilisation.

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

Venous thromboembolism (VTE) is a condition in which a blood clot (thrombus) forms in a vein. It most commonly occurs in the deep veins of the legs where it causes a deep vein thrombosis (DVT). The thrombus may dislodge from its site of origin and travel in the blood to obstruct a blood vessel, a phenomenon called an embolism (1). If an essential blood vessel is blocked this can be life threatening or fatal. For example, a pulmonary embolism (PE) is caused when a thrombus detaches and travels to block a pulmonary artery or one of its branches.

Overall, VTE represents a considerable preventable morbidity and mortality burden to patients. It is estimated to be responsible for 25,000 deaths annually in the UK (2).

The risk of developing a VTE depends on the health of the patient, the surgical procedure for which the patient is admitted, and on any predisposing risk factors (such as age, obesity and concomitant conditions) (1). Patients undergoing major orthopaedic surgery, which includes hip and knee replacement, represent a group that is at particularly high risk for VTE (>40% without prophylaxis) (3). Thromboprophylaxis, both mechanical and pharmacological, have been the routine standard of care for these patients for many years. Indeed, the Department of Health has mandated, within the Operating Framework for the NHS in 2010/11, that a VTE and bleeding risk assessment should be conducted for all patients admitted to hospital to reduce avoidable deaths, as well as make considerable cost savings for the NHS (4). The Commissioning for Quality and Innovation (CQUIN) payment framework for 2010/11 makes a proportion of

healthcare provider income conditional on locally agreed goals and defines that hospitals will only receive payment if more than 90% of adults are VTE risk assessed on admission to hospital.

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

In 2012 it is estimated that 51,804 patients are eligible for TKR and 45,150for THR (see Table 2 for 2012 to 2016 estimates) (5). Apixaban is indicated for use as thromboprophylaxis following elective total knee replacement (TKR) and elective total hip replacement (THR). It is contra-indicated in hepatic disease associated with coagulopathy and clinically relevant bleeding risk and in patients with clinically significant active bleeding, who are unlikely to be eligible for THR or TKR surgery. Apixaban would therefore be appropriate for use in the majority of adult patients undergoing THR and TKR. It is estimated that in 2012 in England and Wales 752 TKR and 683 THR patients would be potentially likely to use apixaban (See Section 7 for the economic modeling estimating potential use of apixaban)..

Table 2: Estimated number of elective NHS TKRs and THRs in England and Wales for 2011 to 2016

	2012	2013	2014	2015	2016
Total population of England and Wales (18 years and over)	44,303,857	44,650,490	44,991,680	45,333,590	45,526,654
Annual number of TKR	51,804	52,209	52,608	53,008	53,234
Annual number of THR	45,150	45,503	45,851	46,200	46,396

Derived from National Joint Registry 2010 (5); Office for National Statistics 2010 (6, 7)

Derivation of eligible patient numbers

The total number of NHS[a] patients in England and Wales having a TKR or THR in 2009 was taken from the National Joint Registry for England and Wales published in 2010 (5). Combining the number of TKRs and THRs with the latest population estimates for 2009 (total population of England and Wales 18 years and over), from the Office for National Statistics (ONS) mid year population estimates (6), provided an annual TKR incidence rate of 0.12% and a THR rate of 0.10% (see Table 3). Assuming that the incidence rate remains constant, and applying it to the ONS population projections for 2012-2016 (7), gives the TKR and THR estimates provided in Table 2 above..

Table 3: Incidence of NHS elective TKR and THR in England and Wales

	2009
Annual number of TKR	50,475
Annual number of THR	43,992
Total population 18 years and over	43,167,400
Incidence rate TKR	0.12%
Incidence rate THR	0.10%

[a] excludes patients undergoing TKR or THR in independent hospitals and independent sector treatment centres

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

The National Institute for Health and Clinical Excellence-Clinical Guideline Number 92. Venous thromboembolism: reducing the risk. January 2010 (1). This guideline characterises patients as either 'Medical' or 'Surgical', and then considers various subgroups of these (e.g. stroke, cancer, major trauma, knee or hip replacement). The knee or hip replacement subgroup is relevant for the use of apixaban.

The following NICE Technology appraisals are recent Single Technology Assessments of oral anticoagulants licensed for thromboprophylaxis in elective total hip replacement (THR) and elective total knee replacement (TKR) groups of patients:

National Institute for Health and Clinical Excellence – Rivaroxaban for the prevention of venous thromboembolism. Technology appraisal TA170. April 2009 (8).

National Institute for Health and Clinical Excellence – Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. Technology appraisal TA157. September 2008 (9).

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

The NICE Clinical Guideline Number 92, VTE (1) makes the following recommendations in orthopaedic surgery, for both elective hip and knee replacements:

- Patients should be protected preoperatively by non-drug, mechanical VTE prophylaxis and postoperatively with pharmacological VTE prophylaxis.
- Provided there are no contraindications, pharmacological VTE prophylaxis should be started after surgery. Choose any one of the following 5 alternatives:
  - − dabigatran etexilate, starting 1–4 hours after surgery
  - − fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - − LMWH, starting 6–12 hours after surgery
  - − Unfractionated heparin (UFH) (for renal failure patients, starting 6–12 hours after surgery)
  - − rivaroxaban, starting 6–10 hours after surgery
- Pharmacological VTE prophylaxis should be continued for:
  - 28–35 days post hip replacement or
  - 10–14 days post knee replacement surgery

Apixaban will be a valuable additional therapeutic option to the existing pharmacological VTE prophylactic drugs available in the treatment pathway for both hip and knee replacement surgery patients.

Apixaban is indicated for use in patients with mild or moderate renal impairment without the need for dose adjustment. Use of apixaban in patients with a CrCl <15ml/min is not recommended and its use is cautioned in severe renal impairment (CrCl 15-29ml/min). Other pharmacological VTE prophylactic agents have restrictive indications:

- enoxaparin requires dose adjustment in severe renal impairment (CrCl<30ml/min) (10)
- fondaparinux and dabigatran are both contra-indicated in severe renal impairment (CrCl <20 and <30ml/min respectively) (11, 12).
- fondaparinux requires dose adjustment in moderate renal impairment (20-50ml/min) and dabigatran use is cautioned (CrCl 30-50ml/min) (11, 12).

Apixaban is indicated for use for 32-38 days post elective hip replacement or 10-14 days post elective knee replacement surgery, consistent with the current NICE VTE Guidelines. Apixaban is orally dosed, which will allow convenient administration both within and out of hospital, reducing the need for daily community nurse visits to administer subcutaneous injections or the need to teach patients or their carers to inject. As apixaban is an oral formulation, as opposed to an injection, it may lead to better compliance with anticoagulation therapy, which may help further reduce the risk of VTE.

Apixaban is indicated to be initiated 12–24 hours after surgery, which will allow for treatment initiation upto a whole day after surgery. This delayed and wider time frame for starting treatment has the advantage of being able to fit in with routine ward activities (for example ward drug rounds) and allows for timely post-operative patient observation and wound assessment. In addition, this also allows a longer time period for epidural catheter removal, which is ideally done before anticoagulant prophylaxis is started.

Other agents have a more restrictive, narrower time frame for treatment initiation. Apixaban will not only allow more time for postoperative haemostasis to be achieved, it will also reduce nursing time to administer, compared with not only injectable medications, but also other oral anticoagulants that have a less straightforward administration schedule.

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

The NICE Clinical Guideline for VTE (1) referred to above states that for VTE prophylaxis, low molecular weight heparin (LMWH) should be initiated following surgery. The licensed indication for enoxaparin, the most widely used LMWH in the UK (13), is to start treatment 12 hours prior to surgery – which is how enoxaparin was used in the apixaban trials. The UK NICE clinical guideline recommends starting LMWH 6-12hr after surgery. However, LMWH is often started post-operatively, with anecdotal evidence suggesting considerable variation in clinical practice.

In the previous NICE Guidelines (14), and the current ones (1), NICE (and others) recommend VTE prophylaxis for up to 35 days following total hip replacement (THR) and up to 14 days post total knee replacement (TKR), and these regimens were investigated in the apixaban trials. However, this regimen is rarely followed in the UK.

An international survey of 50 English speaking orthopaedic units (published in 2010) in the UK, Canada and Australia, investigated current VTE prophylaxis practice following THR surgery. Forty-three units (86%) responded to the survey, 25 being UK district general hospitals and 6 UK teaching hospitals. The remaining 12 units were in Canada or Australia. LMWH was used by 29 out of 31 (94%) of the UK units, but only 2 units (UK

district general hospitals) prescribed as long as 4 weeks of LMWH. Overall, only 4 out of 39 units (10.2%) that routinely prescribed LMWH did so for at least 4 weeks (15).

Finally, the National Joint Registry for England and Wales showed that in 2009 aspirin was used for thromboprophylaxis in 20% of both hip and knee replacements (5). Aspirin is generally not recommended in any UK or international guideline.

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

Low molecular weight heparin (LMWH), dabigatran, rivaroxaban and fondaparinux were considered comparators in the NICE scope. LMWH is considered the main comparator as it was used in 71% and 69% of patients undergoing THR or TKR respectively in England and Wales in 2009 (5). Enoxaparin is the most widely used LMWH in the UK (13), and is the most widely studied. Enoxaparin was used as the comparator in the apixaban registrational trials.

Enoxaparin is licensed for use in VTE prophylaxis following major orthopaedic surgery at 40mg od starting 12 hours pre-operatively in the UK. In the US it is licensed at this dose regimen for THR and licensed at 30mg bd starting 12 hours post operatively, following TKR. Both of the dosing regimens for TKR have been studied directly against apixaban as well as the dosing regimen of 40mg od for THR.

Fondaparinux is not widely used in the UK, being only used in 1% of both THR and TKR patients in 2009 (5).

Two new oral anticoagulants have recently been launched in the UK. Dabigatran was licensed for this indication in the UK in March 2008 and has only been used in small numbers of elective THR and TKR patients to date (5). Rivaroxaban was licensed in September 2008 for thromboprophylaxis in elective THR and TKR, but likewise is not yet widely used in the UK (13).

As fondaparinux, dabigatran and rivaroxaban have been recommended by NICE following health technology assessments, they have been taken into consideration as comparators in this submission, despite their low usage in the UK.

Aspirin use is variable in the UK. The National Joint Registry 2010 reports usage at 20% for both THR and TKR, however, it is not clear if it was used as monotherapy or in combination with other prophylactic measures. The NICE Guidelines VTE 2010 reviewed all the available data and recommended against aspirin use in these indications (1). This is in line with other international guidelines in this area (16-19). Therefore aspirin was not used as a comparator in this submission.

The NICE Guidelines VTE 2010 reviewed all the available data on warfarin usage for VTE prophylaxis and recommended against its use for this indication. Warfarin is not commonly used for VTE prevention following orthopaedic surgery in England and Wales (2% reported for both hip and knee replacements respectively in 2009) (5). Therefore, warfarin was not used as a comparator in this submission.

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

No significant use of therapies to manage adverse reactions is anticipated for the management of any common side effects of apixaban.

Bleeding may occur during any anticoagulant therapy, especially if risk factors are present, such as organic lesions that are liable to bleed. The NICE VTE Guidelines (1) only recommend the use of anticoagulants if the risk of VTE outweighs the defined risk factors for bleeding.

In the uncommon event of haemorrhagic complications, anticoagulant treatment should be discontinued and appropriate treatment (e.g. surgical haemostasis or transfusion of fresh frozen plasma) should be considered. If a life-threatening bleed cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience of the use of recombinant factor VIIa in individuals receiving apixaban.

As apixaban is not derived from heparin, heparin induced thrombocytopaenia (HIT), which is associated with the use of heparins (UFH and LMWHs), is not considered to be a potential side effect of apixaban.

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

Use of apixaban is not expected to require new additional resource costs.

Treatment with apixaban will be initiated and dispensed in secondary care during hospital admission. Treatment should continue for up to 38 days following elective THR, and for up to 14 days following elective TKR.

As apixaban is an oral treatment, there is no need for patients to be trained to inject themselves nor for daily community nurse visits to administer injections for those unable to do so, which may be required when using LMWH.

No additional tests or monitoring are anticipated for patients on apixaban.

Resource savings could also be made from decreased monitoring requirements compared to current standard treatments. For example, regular platelet counts are required for patients using LMWH and UFH to monitor for HIT. Patients using LMWH also require additional monitoring of potassium levels. Such additional tests are not required for patients using apixaban.

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

No additional infrastructure is required to be put in place for apixaban as it is an oral treatment initiated after surgery, and continued after hospital discharge without requiring regular monitoring. This could save NHS costs, as longer hospital inpatient stays for daily sub-cutaneous injections, or daily community nurse visits after discharge for drug administration and patient monitoring will not be needed.

3 Equity and equality

3.1 Identification of equity and equalities issues

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

None expected

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

None expected

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

Not applicable

4 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People undergoing elective knee or hip replacement surgery	People undergoing elective knee or hip replacement surgery	Not different from scope
Intervention	Apixaban	Apixaban	Not different from scope
Comparator(s)	Pharmacological methods of prophylaxis using one of the following drugs: • low molecular weight heparin • fondaparinux • rivaroxaban • dabigatran etexilate	Pharmacological methods of prophylaxis using one of the following drugs: • low molecular weight heparin • fondaparinux • rivaroxaban • dabigatran etexilate	Not different from scope
Outcomes	The outcome measures to be considered include: • mortality • incidence of VTE • post DVT complications including post-thrombotic syndrome • length of hospital stay • joint outcomes (medium and long term), including joint infection • adverse effects of treatment including bleeding events • health-related quality of life	Mortality, incidence of VTE and adverse events are addressed in the clinical evidence. In addition, post-DVT complications and health related quality of life are addressed in the economic evaluation.	Post DVT complications, length of hospital stay, joint outcomes and health related quality of life were not available from the clinical trials for apixaban
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	Cost effectiveness of treatments are expressed in terms of incremental cost per quality-adjusted life year. Time horizon for estimating clinical and cost effectiveness is long enough to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and Personal Social	Personal Social Services perspective not deemed relevant and all costs and benefits likely to fall on NHS only.

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	Social Services perspective.	Services perspective.	
Subgroups to be considered	No sub groups were considered in the final scope	No sub groups were considered in the final scope	Not different from scope
Special considerations, including issues related to equity or equality	None raised in the final scope	None identified	Not different from scope

Section B – Clinical and cost effectiveness

5 Clinical evidence

Overview

Apixaban demonstrates improved efficacy over the current standard of care, enoxaparin, without compromising the expected safety of this type of VTE prophylaxis.

Apixaban's efficacy and safety also compares favourably with the newer oral anticoagulants licensed for elective THR or TKR.

Summary of data from the RCTs (from CSRs)

ADVANCE 2

- A phase 3, double-blind RCT to compare the efficacy and safety of oral apixaban 2.5mg twice daily with enoxaparin 40 mg od for the prevention of VTE after elective total knee replacement surgery.
- ADVANCE 2 had a high proportion of European participants (over 70%) and the dosing of enoxaparin was according to the UK licensed dose.
- Apixaban was superior to enoxaparin for the prevention of the primary efficacy outcome of all VTE and all-cause death during the treatment period (RR 0.62; 95% CI 0.51–0.74; p <0.0001 when tested for non-inferiority and superiority).
    - Absolute risk reduction was 9.3% (95% CI 5.8–12.7) in favour of apixaban (p <0.0001 for non-inferiority).
- Apixaban was superior to enoxaparin for prevention of the key secondary efficacy endpoint of the composite of adjudicated proximal DVT, non-fatal PE, and VTE-related death during the treatment period (RR 0.50; 95% CI 0.26–0.97, 2 sided p- value=0.0373, for superiority)
    - Absolute risk reduction was 1.04% (95% CI 0.05–2.03) in favour of apixaban.
- Observed bleeding event rates were numerically lower for apixaban-treated subjects than for enoxaparin-treated subjects during the treatment period, but these were not statistically significant.
    - Major or clinically relevant non-major bleeding occurred in 4% of patients receiving apixaban and 5% treated with enoxaparin (p=0.09).
    - Major bleeding events were infrequent, and event rates were numerically lower in the apixaban group (0.6%) than in the enoxaparin group (0.9%) (p=0.3).

ADVANCE 3

- A phase 3, double-blind RCT to compare the efficacy and safety of oral apixaban 2.5mg twice daily with enoxaparin 40 mg od, for the prevention of VTE after elective total hip replacement surgery.
- ADVANCE 3 had a large proportion of European participants (55%) and the dosing of enoxaparin was according to the UK licensed dose.

- Apixaban was superior to enoxaparin for the prevention of the primary efficacy outcome of all VTE and all-cause death during the intented treatment period (RR 0.36; 95% CI 0.22–0.54; p <0.0001 when tested for non-inferiority and superiority).
    - Absolute risk reduction was 2.5% (95% CI 1.5–3.5) in favour of apixaban.
- Apixaban was superior to enoxaparin for prevention of the key secondary efficacy endpoint of the composite of adjudicated proximal DVT, non-fatal PE, and VTE-related death during the intented treatment period (RR 0.40; 95% CI 0.15–0.80, p<0.0001 for non-inferiority, 2-sided p-value=0.01, for superiority).
    - Absolute risk reduction was 0.7% (95% CI 0.02–1.3) in favour of apixaban.
- Observed bleeding event rates were similar for apixaban and enoxaparin treated subjects during the treatment period.
    - Major or clinically relevant non-major bleeding occurred in 4.8% of patients receiving apixaban and 5% treated with enoxaparin (p=0.72).
    - Major bleeding events occurred in 0.8% of apixaban treated patients and 0.7% of enoxaparin treated patients (p=0.54).

ADVANCE 1

- A phase 3, double-blind RCT to compare the efficacy and safety of oral apixaban, 2.5mg bd, with 30 mg enoxaparin bd, for the prevention of VTE after elective total knee replacement surgery.
- The majority of randomised patients were North American and the dosing of enoxaparin was according to the U.S. licensed dose.
- The rate of the primary efficacy outcome of all VTE and all-cause death was 9.0% with apixaban, compared with 8.8% with enoxaparin during the intented treatment period (RR 1.02; 95% CI 0.78–1.32) (p=0.06).
    - Apixaban did not meet pre-specified statistical criteria for non-inferiority.
    - The observed rates of the primary outcome were similar for apixaban and enoxaparin but the overall event rate was lower than expected, which resulted in the study being underpowered.
- The key secondary efficacy endpoint (composite of the adjudicated proximal DVT, non-fatal PE, and all-cause death) occurred in 2.05% of patients in the apixaban group versus 1.64% in the enoxaparin group during the intented treatment period (RR 1.25; 95% CI 0.70–2.23) (p=0.78)
- Apixaban was associated with lower rates of bleeding than enoxaparin during the treatment period.
    - The composite incidence of major bleeding and clinically relevant non-major bleeding was 2.9% with apixaban and 4.3% with enoxaparin (p=0.03).
    - Major bleeding events occurred in 0.7% of apixaban treated patients and 1.4% of enoxaparin treated patients (p=0.053).

5.1 Identification of studies

Two systematic literature searches were conducted to retrieve relevant clinical data from the published literature;

1) To identify all RCT evidence for apixaban and relevant comparators
2) To identify non-RCT evidence for apixaban

This was supplemented by hand searching the bibliographies of relevant review articles and with unpublished data from the manufacturer's clinical trial database.

Using Boolean operators, the RCT search combined terms (including MeSH headings as appropriate) for 1) VTE, 2) Interventions, 3) Clinical trial design, and 4) hip/knee indication; and the non-RCT search combined terms (including MeSH headings as appropriate) for 1) VTE, 2) Interventions, 3) Clinical trial design.

The search strategy for RCT evidence is provided in Section 9.2 (Appendix 2), and for non-RCT evidence in Section 9.6 (Appendix 6).

5.2 Study selection

5.2.1 Eligibility criteria

Studies identified (i1) were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded (e1), and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage (i2) were then assessed based on the full text; further papers were excluded (e2), yielding the final data set for inclusion (i3).

Inclusion and exclusion selection criteria for the RCT search are shown in Table 4, and for the non-RCT search in Table 5.

Table 4: Eligibility criteria used in search strategy for RCT evidence

	Description	Justification
Inclusion criteria		
Population	Adult patients (≥ 18 years) undergoing elective knee or hip replacement surgery	As specified by final scope
Interventions	• Apixaban • Low molecular weight heparins (to include enoxaparin) • Fondaparinux • Rivaroxaban • Dabigatran	As specified by final scope
Outcomes	• Mortality (VTE-related, all cause) • Incidence of VTE • Post DVT complications including post thrombotic syndrome (PTS) • Length of hospital stay • Joint outcomes, including joint infection • Adverse events including bleeding	As specified by final scope

	Description	Justification
	events o Intracranial bleeding o Major bleeding o Clinically relevant, non-major bleeding • Health-related quality of life	
Study design	Prospective, randomised controlled trials, phase II-IV	Non-RCT studies were identified through a separate search
Language restrictions	Only abstracts in English were included	
Exclusion criteria		
Population	Patients: • undergoing emergency hip or knee surgery • undergoing surgery for hip fracture repair • undergoing other types of surgery • treated under non-surgical indications; e.g. to prevent VTE in acute medical illness • treated only once a VTE event has occurred (i.e. active treatment of VTE event)	In line with final scope
Interventions	Mechanical • graduated elastic compression stockings • intermittent pneumatic compression devices • vena cava filters Nursing care/physiotherapy	In line with final scope

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism

Table 5: Eligibility criteria used in search strategy for non-RCT evidence

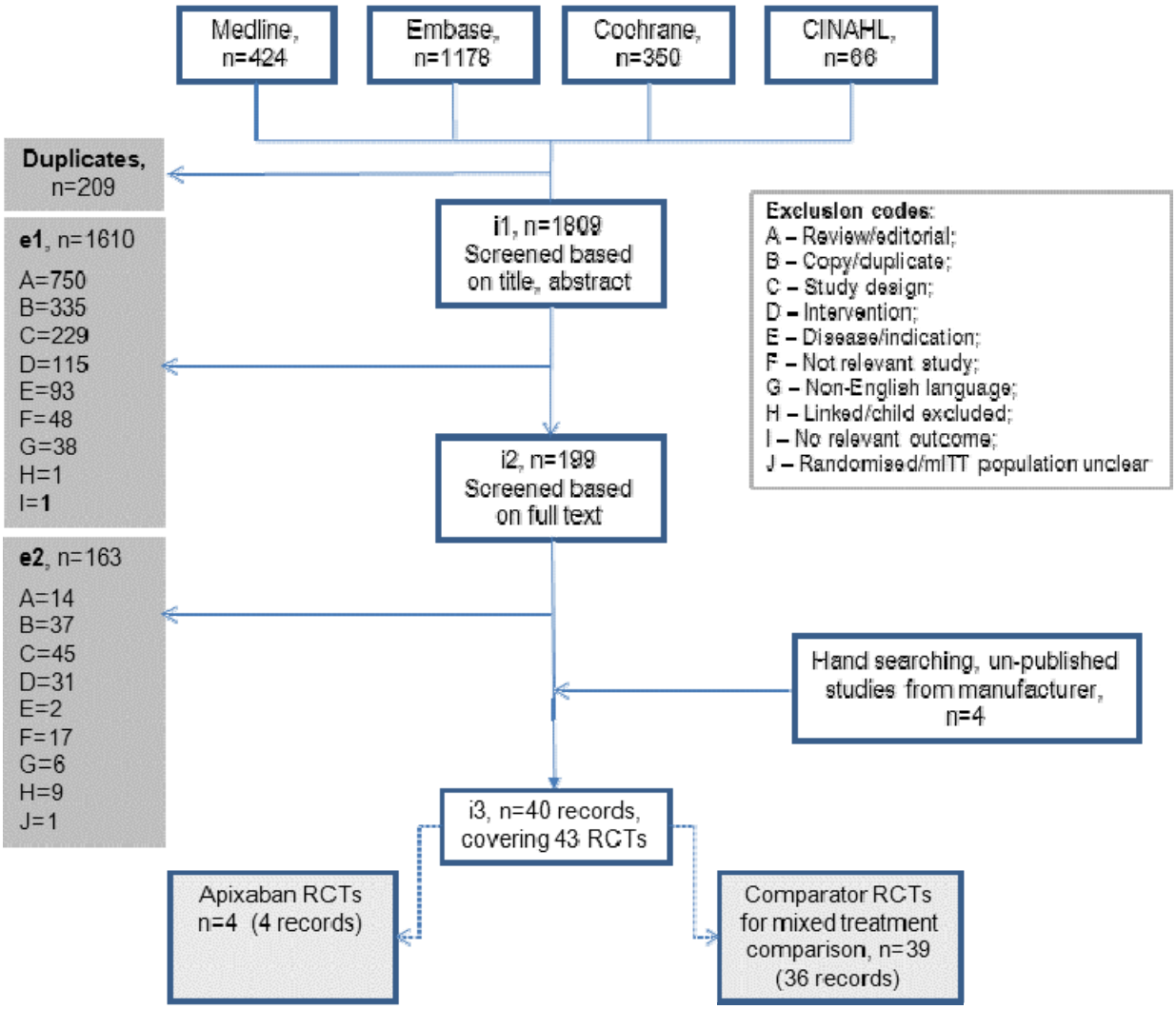
	Description	Justification
Inclusion criteria		
Population	Adult patients (≥ 18 years) undergoing elective knee or hip replacement surgery	As specified by final scope
Interventions	• Apixaban	As specified by final scope
Outcomes	• Mortality (VTE-related, all cause) • Incidence of VTE • Post DVT complications including post thrombotic syndrome (PTS) • Length of hospital stay • Joint outcomes, including joint infection	As specified by final scope

Apixaban. BMS and Pfizer

	Description	Justification
	• Adverse events including bleeding events o Intracranial bleeding o Major bleeding o Clinically relevant, non-major bleeding • Health-related quality of life	
Study design	Observational studies	RCTs were identified through a separate search
Language restrictions	Only abstracts in English were included	
Exclusion criteria		
Population	Patients: • undergoing emergency hip or knee surgery • undergoing surgery for hip fracture repair • undergoing other types of surgery • treated under non-surgical indications; e.g. to prevent VTE in acute medical illness • treated only once a VTE event has occurred (i.e. active treatment of VTE event)	In line with final scope
Interventions	Mechanical • graduated elastic compression stockings • intermittent pneumatic compression devices • vena cava filters Nursing care/physiotherapy	In line with final scope

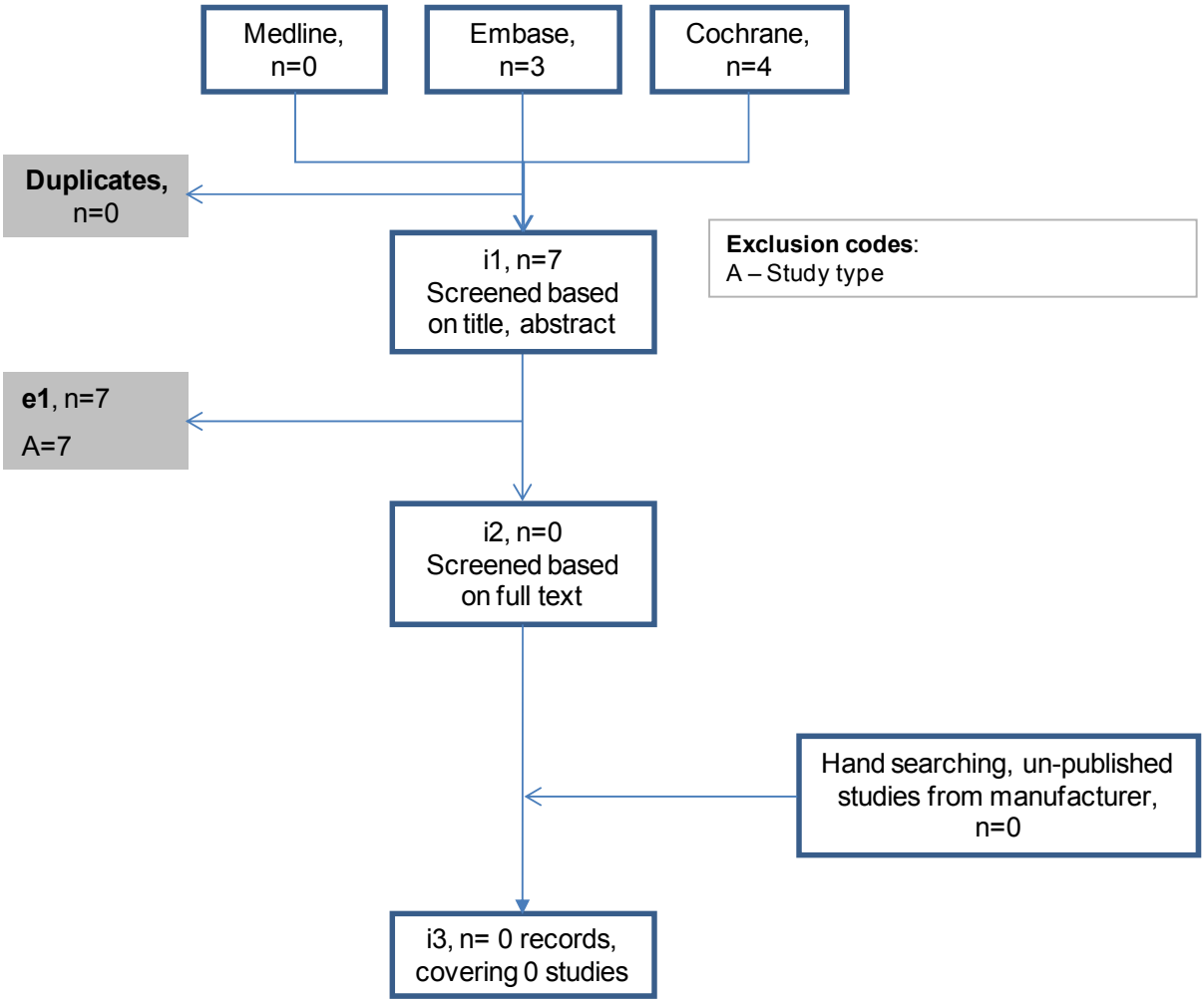
5.2.2 Flow diagram of included and excluded studies

Figure 1: Schematic for the systematic review of RCT evidence for apixaban and relevant comparators



Following assessment and exclusion of studies based on title, abstract and full text, 40 records were included in the final data set, reporting on 43 RCTs. Of the 43 included RCTs, 4 trials examined the intervention of interest (apixaban). The remaining 39 RCTs reported on comparator interventions that are of relevance to the decision problem. These studies are reported further in Section 5.7 and Appendix 5.

Figure 2: Schematic for the systematic review of non-RCT evidence for apixaban



Following assessment and exclusion of studies based on title, abstract and full text, no records for non-RCTs were identified.

5.2.3 Data sources of identified studies

The systematic review identified three published RCTs examining apixaban and a further unpublished study was provided by the manufacturer prior to publication, this has now been published (20). In describing these studies data were drawn from the following additional sources available to the manufacturer:

- Clinical study report for Study CV185034: A phase 3, randomised, double-blind, active-controlled (enoxaparin 30mg bd), parallel-group, multi-center study to evaluate the safety and efficacy of oral apixaban in subjects undergoing elective total knee replacement surgery (ADVANCE 1)
- Clinical study report for Study CV185047: A phase 3, randomised, double-blind, active-controlled (enoxaparin 40 mg od), parallel-group, multi-center study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total knee replacement surgery (ADVANCE 2)

- Clinical study report CV185035 - A phase 3, randomized, double-blind, active-controlled (enoxaparin 40mg od), parallel-group, multi-center study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total hip replacement surgery (ADVANCE 3)

5.2.4 Complete list of relevant RCTs

The systematic review of clinical evidence identified 4 RCTs of apixaban in the population of interest to this submission (Table 6).

Table 6: List of relevant RCTs

Trial no. (acronym)	Phase	Intervention	Comparator	Population	Primary study ref.
ADVANCE 2 (CV185047)	III	Oral apixaban 2.5 mg bd	Subcutaneous enoxaparin 40 mg od	Subjects scheduled to undergo elective unilateral or same day bilateral total knee replacement surgery	Lassen et al, 2010 (21) Clinical study report (22)
ADVANCE 3 (CV185035)	III	Oral apixaban 2.5 mg bd	Subcutaneous enoxaparin 40 mg od	Subjects scheduled to undergo elective unilateral total hip replacement	Lassen et al, 2010 (20) Clinical study report (23)
ADVANCE 1 (CV185034)	III	Oral apixaban 2.5 mg bd	Subcutaneous enoxaparin 30 mg bd	Subjects scheduled to undergo elective total knee replacement surgery	Lassen et al, 2009 (24) Clinical study report (25)
APROPOS	II	Oral apixaban 5mg, 10mg, 20mg, od and bd (6 arms)	Enoxaparin 30mg bd Warfarin	Subjects (18-90 years), scheduled to undergo elective total knee replacement surgery	Lassen et al, 2007 (26)

Abbreviations: bd, twice daily; od, once daily

5.2.5 Studies comparing the intervention directly with the appropriate comparator(s) stated in the decision problem

All relevant RCTs directly compare apixaban with enoxaparin, which is included amongst the appropriate comparators stated in the decision problem. ADVANCE 2 and ADVANCE 3 compare apixaban with the UK licensed dose of enoxaparin (40 mg od), and are consequently most relevant to this submission for UK clinical practice. In APROPOS and ADVANCE 1 the dosing of enoxaparin is according to U.S. licensed dose (30 mg bd).

5.2.6 Studies excluded from further discussion

No identified studies were excluded from further discussion. The two pivotal studies relevant to this submission are ADVANCE 2 and 3, as they compare the UK licensed doses of

apixaban and enoxaparin. ADVANCE 1 is less relevant as it uses dosing of enoxaparin according to U.S. licensed dose, however it is presented in full in this submission for completeness. APROPOS is a phase II dose finding study and as such is not presented in full in this submission. However, a brief overview is provided in Appendix 14.

5.2.7 List of relevant non-RCTs

No non-RCTs relevant to this submission were identified.

5.3 Summary of methodology of relevant RCTs

5.3.1 Methods

The methodology of the relevant RCTs is summarised in Table 7.

Table 7: Comparative summary of methodology of the RCTs

	ADVANCE 1	ADVANCE 2	ADVANCE 3
Location	Multicentre in 14 countries, including 6 European (none UK)	Multicentre in 27 countries, including 15 European (2 UK centres)	Multicentre in 21 countries, including 13 European (3 UK centres)
Design	Phase 3, randomised, active controlled, parallel group study	Phase 3, randomised, active controlled, parallel group study	Phase 3, randomised, active controlled parallel group study
Duration of study	• Screening period 30 days prior to surgery to 24 hours after surgery • Treatment period of 12 (±2) days starting on the day of surgery or the next day • Follow-up period for 60 (±3) days after the last dose of study drug	• Screening period up to 14 days prior to randomisation • Randomisation period 1-4 days prior to surgery • Treatment period, starting with first dose of sc study drug 12 (±3) hours prior to surgery and extending 10-14 days after surgery • Follow-up period for 60 (±5) days after last dose of study drug	• Screening period up to 14 days prior to randomisation • Treatment period, starting with first dose of sc study drug 12 (±3) hours prior to surgery. Study medications were continued for 32-38 days • Follow-up period for 60 (±5) days
Method of randomisation	Subjects were randomised 1:1 via IVRS to: • Apixaban 2.5 mg bd po and matching enoxaparin-placebo injection or • Enoxaparin 30 mg bd sc and matching apixaban-placebo tablets bd. Randomisation was stratified according to study site and type of surgery (unilateral or bilateral TKR), with a block size of four.	Subjects were randomised 1:1 via IVRS to: • Apixaban 2.5 mg bd po and matching enoxaparin-placebo injection od or • Enoxaparin 40 mg od sc and matching apixaban-placebo tablets bd. Randomisation was stratified by study site and type of surgery (unilateral or bilateral TKR) with a block size of four.	Subjects were randomised 1:1 using an interactive telephone system to: • Apixaban 2.5 mg bd po and matching enoxaparin-placebo injection od or • Enoxaparin 40 mg od sc and matching apixaban-placebo tablets bd. The randomisation schedule was generated by the BMS randomisation centre and was stratified by study site with a block size of four.

	ADVANCE 1	ADVANCE 2	ADVANCE 3
Method of blinding (care provider, patient and outcome assessor)	Study drugs were prepared in a double-dummy design using placebo matching the active treatments. Subjects, investigators, administrative/ adjudicating committees, and the sponsors were blind to treatment assignments.	Study drugs were prepared in a double-dummy design using placebo matching the active treatments. Subjects, investigators, administrative/ adjudicating committees, and the sponsors were blind to treatment assignments.	Study drugs were prepared in a double-dummy design using placebo matching the active treatments. Subjects, investigators, administrative/ adjudicating committees, and the sponsors were blind to treatment assignments.
Intervention(s) (n =) and comparator(s) (n =)	• Apixaban 2.5 mg bd po + placebo injection (n = 1599) • Enoxaparin 30 mg bd sc + placebo tablets (n = 1596) First oral dose of apixaban or matching placebo 12-24 hours after skin wound closure; twice daily schedule for 12 days. First sc dose of enoxaparin or matching placebo 12-24 hours after skin wound closure; 12 hourly dose schedule for 12 days	• Apixaban 2.5 mg bd po + enoxaparin-placebo injection (n = 1528) • Enoxaparin 40 mg od sc + apixaban-placebo tablets (n = 1529) First oral dose of apixaban or matching placebo 12-24 hours after skin wound closure; bd dosing through 11 days after surgery day. Initial dose of enoxaparin or placebo injected 12±3 hours prior to surgery. Next dose injected after skin wound closure; od dosing through 11 days after surgery day.	• Apixaban 2.5 mg bd po + enoxaparin-placebo injection (n = 2708) • Enoxaparin 40 mg od sc + apixaban-placebo tablets (n = 2699) First oral dose of apixaban or placebo was given 12-24 hours after wound closure; bd dosing for 32-38 days. First sc dose of enoxaparin or placebo was started 12±3 hours before surgery and resumed after surgery according to investigator's standard of care; od dosing for 32-38 days
Assessments	• While hospitalised, subjects were evaluated daily for suspected symptomatic VTE, bleeding events, and surgical wound assessment • During the interval between hospital discharge and day 12 (ADVANCE 1) or day 11 ± 2 days (ADVANCE 2) subjects were instructed to report to the investigators all AEs including signs and/or symptoms suggestive of VTE and any bleeding events. Appropriate diagnostic evaluation was conducted as necessary • A mandatory bilateral ascending contrast venogram was obtained; after 12±2 days of study drug (ADVANCE 1) or 11±2 days after surgery day (ADVANCE 2). • During the follow-up period subjects were instructed to report to the investigators all AEs including signs and/or symptoms suggestive of VTE and any bleeding events. Appropriate diagnostic evaluation was conducted as necessary • Follow-up visits occurred at day 42 (30±3 days (ADVANCE 1) or 30±5 days (ADVANCE 2) after last dose of study drug) and day 72 (60±3 days (ADVANCE 1) or 60±5 days (ADVANCE 2) after last		• A mandatory bilateral ascending contrast venogram was obtained; after 32-38 days of study drug • Follow-up evaluations occurred at 60 (±5)days and 95±5 days after surgery

	ADVANCE 1	ADVANCE 2	ADVANCE 3
	dose of study drug)		
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic DVT, non-fatal PE, and all-cause death following 12±2 days of double-blind treatment.	The primary efficacy endpoint was the composite of all adjudicated VTE (PE, symptomatic DVT, asymptomatic DVT) and all-cause death during the intended treatment period.	The primary efficacy outcome was the composite of adjudicated asymptomatic or symptomatic DVT, non-fatal PE and all-cause death during the intended treatment period (32-38 days or within 2 days of the last dose of study drug)
Secondary outcomes (including scoring methods and timings of assessments)	The key secondary efficacy endpoint was the composite of adjudicated proximal DVT, non-fatal PE and all-cause death during the intended treatment period	The key secondary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period.	The key secondary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period.

Abbreviations: AEs, adverse events; bd, twice daily; DVT, deep vein thrombosis; IVRS, interactive voice response system; PE, pulmonary embolism; po, by mouth; od, once daily; sc, subcutaneous; TKR, total knee replacement;

5.3.2 Participants

The inclusion and exclusion criteria for the relevant RCTs are summarised in Table 8.

Table 8: Eligibility criteria of the RCTs

Inclusion criteria	Key exclusion criteria
ADVANCE 1 and ADVANCE 2: • Male and female subjects, ≥ 18 years scheduled to undergo either elective unilateral or same-day bilateral TKR or a revision of at least one component of a TKR • Subjects had to be willing and able to undergo bilateral ascending contrast venography **ADVANCE 3:** • Male and female subjects, ≥ 18 years scheduled to undergo elective unilateral total hip replacement or revision of at least one component of a previously inserted hip prosthesis	**ADVANCE 1, ADVANCE 2 and ADVANCE 3:** *Medical History and Concurrent Diseases* • Hereditary (first degree) or acquired bleeding or coagulation disorder • Known or suspected history of heparin-induced thrombocytopaenia • Known coagulopathy • Active bleeding or at high risk for bleeding • Brain, spinal, ophthalmologic, or major surgery or trauma within the past 90 days • Active hepatobiliary disease • Alcohol or substance abuse within the past year *Physical and Laboratory Test Findings* • Two consecutive blood pressure readings within 15 to 30 minutes with supine systolic blood pressure > 180 mmHg or supine diastolic blood pressure > 105 mmHg • Clinically significant laboratory abnormalities at the enrolment visit: o Haemoglobin (Hb) <10 g/dL o Platelet count <100,000/mm^3 o Creatinine clearance <30 mL/min o Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 x upper limit of normal (ULN) or a total bilirubin ≥ 1.5 x ULN *Allergies and Adverse Drug Reactions* • Hypersensitivity to UFH, LMWH, porcine products, or iodinated contrast medium *Prohibited Therapies and/or Medications* • Need for ongoing treatment with a parenteral or oral anticoagulant • Current use of dextrans or fibrinolytics • Treatment with medications affecting coagulation or platelet function as follows: o UFH, LMWH, warfarin (or any other VKA), glycoprotein IIb/IIIa inhibitors within 4 days before surgery o Clopidogrel, ticlopidine, dipyridamole, sulfinpyrazone within 7 days before surgery o Non-selective non-steroidal anti-inflammatory drugs with a half life >17 hours within 7 days before surgery o Fondaparinux within 7 days before surgery o Aspirin >165 mg/day within 4 days before surgery o Anti-fibrinolytics, with exception of the use of tranexamic acid where it represents the standard of care for the investigator *Other exclusion criteria* • Planned indwelling intrathecal or epidural catheter that cannot be removed at least 5 hours prior to first dose of post-operative study drug • Administration of any investigational drug currently or within 30 days prior to enrolment into this study

Abbreviations: LMWH, low molecular weight heparin; TKR, total knee replacement; UFH, unfractionated heparin; VKA, vitamin K antagonist

5.3.3 Baseline characteristics

Patient characteristics at baseline for ADVANCE 1, ADVANCE 2 and ADVANCE 3 are summarised in Table 9. Baseline demographic characteristics were balanced between treatment groups for all three trials.

Table 9: Characteristics of participants in the RCTs across randomised groups

ADVANCE 1 (CV185034)	**Apixaban 2.5mg bd N = 1599**	**Enoxaparin 30mg bd N = 1596**
Age (years), mean (SD)	65.9 (9.26)	65.7 (9.22)
Gender n (%) Female	997 (62.4)	986 (61.8)
Weight (kg) Mean (range)	86.7 (41.0–163.7)	86.7 (40.5–163.3)
BMI Mean (range)	31.2 (18.1–54.7)	31.1 (17.7–57.6)
Race White Black/African American Asian Other	1515 (94.7) 63 (3.9) 9 (0.6) 12 (0.8)	1515 (94.9) 58 (3.6) 16 (1.0) 7 (0.4)
Previous orthopaedic surgery n (%) Knee replacement Hip replacement Hip or knee fracture surgery	374 (23.4) 91 (5.7) 65 (4.1)	347 (21.7) 73 (4.6) 62 (3.9)
History of venous thromboembolism, n (%) DVT PE	57 (3.6) 10 (0.6)	47 (2.9) 6 (0.4)
Type of surgery, n (%) Unilateral, right Unilateral, left Bilateral	802 (50.2) 763 (47.7) 34 (2.1)	782 (49.0) 779 (48.8) 35 (2.2)
Type of anaesthesia, n (%) General Spinal Regional Other	674 (42.2) 947 (59.2) 440 (27.5) 310 (19.4)	704 (44.1) 920 (57.6) 462 (28.9) 303 (19.0)
Duration of surgery, hr Mean Range	1.53 0.45–13.90	1.55 0.08–4.72
Use of a tourniquet, n (%)	168 (10.5)	168 (10.5)
Use of cement, n (%)	1513 (94.6)	1521 (95.3)
Indication for surgery, n (%) Osteoarthritis Degenerative joint disease Rheumatoid arthritis Other	1291 (80.7) 357 (22.3) 33 (2.1) 82 (5.1)	1283 (80.4) 367 (23.0) 37 (2.3) 84 (5.3)
Duration of hospitalisation, days Mean (range)	6.3 (2.0–37)	6.4 (2.0–67)
Geographic region, n (%) North America Europe Latin America	1018 (63.7) 308 (19.3) 223 (13.9)	1022 (64.0) 300 (18.8) 220 (13.8)

Asia and Pacific Islands	50 (3.1)	54 (3.4)
Renal status, n (%) Estimated creatinine clearance >60 ml/min	1388 (86.8)	1377 (86.3)
ADVANCE 2 (CV185047)	**Apixaban 2.5mg bd N = 1528**	**Enoxaparin 40mg od N = 1529**
Age (years), mean (SD)	65.6 (9.85)	65.9 (9.82)
Gender n (%) Female	1089 (71.3)	1127 (73.7)
Weight (kg) Mean Range	78 68.0–89.0	78 68.0–88.0
BMI Mean (range)	29.1 (25.8–32.4)	29.3 (26.1–32.7)
Race White Black/African American Asian Native Hawaiian/other Pacific Islander Other	1216 (79.6) 14 (0.9) 252 (16.5) 1 (<0.1) 45 (2.9)	1211 (79.2) 17 (1.1) 254 (16.6) 1 (<0.1) 46 (3.0)
Previous orthopaedic surgery n (%) Knee replacement Hip replacement Hip or knee fracture surgery	257 (16.8) 90 (5.9) 55 (3.6)	286 (18.7) 80 (5.2) 49 (3.2)
History of venous thromboembolism, n (%) DVT PE	36 (2.4) 10 (0.7)	32 (2.1) 10 (0.7)
Type of surgery, n (%) Unilateral, right Unilateral, left Bilateral	759 (49.7) 687 (45.0) 31 (2.0)	747 (48.9) 714 (46.7) 30 (2.0)
Type of anaesthesia, n (%) General Spinal Regional Other	540 (35.3) 950 (62.2) 295 (19.3) 77 (5.0)	548 (35.9) 974 (63.7) 305 (20.0) 72 (4.7)
Duration of surgery, hr Mean Range	1.58 1.25–2.00	1.58 1.25–2.00
Use of a tourniquet, n (%)	708 (46.3)	688 (45.0)
Use of cement, n (%)	1387 (90.8)	1406 (92.0)
Indication for surgery, n (%) Osteoarthritis Degenerative joint disease Rheumatoid arthritis Other	970 (63.5) 346 (22.6) 57 (3.7) 196 (12.8)	960 (62.8) 333 (21.8) 77 (5.0) 210 (13.7)
Duration of hospitalisation, days Mean Range	12.0 7–14	12.0 8–14
Geographic region, n (%) South Africa Europe Latin America Asia and Pacific Islands	56 (3.7) 1112 (72.8) 114 (7.5) 246 (16.1)	56 (3.7) 1110 (72.6) 116 (7.6) 247 (16.2)

Apixaban. BMS and Pfizer

Renal status, n (%) Estimated creatinine clearance >60 ml/min	1258 (82.3)	1291 (84.5)
ADVANCE 3 (CV185035)	**Apixaban 2.5mg bd N = 2708**	**Enoxaparin 40mg od N = 2699**
Age (years), mean (SD)	60.9 (11.79)	60.6 (11.82)
Gender n (%) Female	1430 (52.8)	1451 (53.8)
Weight (kg) Mean Range	79.9 37.0–179.9	79.5 28.0–152.4
Race White Black/African American American Indian/Alaska Native Asian Native Hawaiian/other Pacific Islander Other	2451 (90.5) 69 (2.5) 2 (<0.1) 182 (6.7) 1 (<0.1) 3 (0.1)	2446 (90.6) 63 (2.3) 1 (<0.1) 188 (7.0) 0 1 (<0.1)
Previous orthopaedic surgery n (%) Knee replacement Hip replacement Hip or knee fracture surgery	124 (4.6) 624 (23.0) 194 (7.2)	116 (4.3) 623 (23.1) 195 (7.2)
History of venous thromboembolism, n (%) DVT PE	41 (1.5) 17 (0.6)	47 (1.7) 11 (0.4)
Type of surgery, n (%)† Unilateral, right Unilateral, left	1430 (53.5) 1220 (45.6)	1386 (52.1) 1257 (47.3)
Type of anaesthesia, n (%)† General Spinal Regional Other	1052 (39.4) 1636 (61.2) 186 (7.0) 204 (7.6)	1073 (40.4) 1593 (59.9) 208 (7.8) 221 (8.3)
Duration of surgery, hr† Mean Range	1.48 0.0–6.75	1.50 0.0–8.75
Use of a tourniquet, n (%)†	0 (0)	1 (<0.1)
Use of cement, n (%)†	734 (27.5)	763 (28.7)
Indication for surgery, n (%)† Osteoarthritis Degenerative joint disease Rheumatoid arthritis Other	1529 (57.2) 633 (23.7) 55 (2.1) 739 (27.6)	1536 (57.8) 630 (23.7) 45 (1.7) 726 (27.3)
Duration of hospitalisation, days† Mean Range	9.3 1.0–82.0	9.2 1.0–62.0
Geographic region, n (%) Europe North America Asia and Pacific Islands Latin America	1495 (55.2) 809 (29.9) 278 (10.3) 126 (4.7)	1495 (55.4) 797 (29.5) 279 (10.3) 128 (4.7)
Renal status, n (%) Estimated creatinine clearance >60 ml/min	2381 (87.9)	2376 (88.0)

Abbreviations: bd, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; od, once daily; SD, standard deviation
[†]These surgery-specific characteristics were measured after first dose of study drug; therefore, they are not baseline characteristics. Summaries on these characteristics are for treated subjects and primary subjects.

5.3.4 Outcomes

The outcomes investigated in the identified RCTs and their relevance to the decision problem are presented in Table 10.

Table 10: Primary and secondary outcomes of the RCTs

Primary outcome(s) and measures	Secondary outcome(s) and measures	Outcome measures	Reliability/validity/ current use in clinical practice
ADVANCE 1 & 2 • The primary efficacy endpoint was the composite of all adjudicated VTE (PE, symptomatic DVT, asymptomatic DVT), and all-cause death during the intended treatment period • The primary safety endpoint was bleeding and included (if occurring in the treatment period): o Confirmed adjudicated major bleeding events o Composite of confirmed adjudicated major bleeding events and confirmed adjudicated clinically relevant non-major bleeding events o All bleeding endpoints **ADVANCE 3** • The primary efficacy endpoint was the composite of adjudicated, symptomatic or asymptomatic DVT, non-fatal PE and death from any cause during the intended treatment period	**ADVANCE 1 & 2** • The key secondary efficacy outcome in ADVANCE 1 was the composite of adjudicated proximal DVT, non-fatal PE and all-cause death during the intended treatment period • The key secondary efficacy endpoint in ADVANCE 2 was the composite of adjudicated asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period • Other secondary efficacy endpoints in ADVANCE 1 and 2 (intended treatment period and confirmed by adjudication): o All VTE/VTE-related death (defined as the combination of fatal or non-fatal PE, and symptomatic or asymptomatic DVT) o Proximal DVT/non-fatal PE/VTE-related death (ADVANCE 1 only) o Proximal DVT/non-fatal PE/all-cause death (ADVANCE 2 only) o Total VTE/all-cause death (total VTE is defined as the combination of fatal or nonfatal PE, symptomatic DVT, and asymptomatic proximal DVT) o Total VTE/VTE-related death o All-cause death o VTE-related death o Symptomatic VTE/all-cause death o Symptomatic VTE/VTE-related death (defined as the combination of fatal or nonfatal PE, and symptomatic DVT)	**ADVANCE 1, 2 & 3** Efficacy • The presence or absence of DVT was assessed with bilateral venograpy • Clinically suspected DVT was confirmed or excluded with ultrasonograpy or venography • Suspected PE was confirmed with ventilation-perfusion lung scanning, spiral computed tomography, or pulmonary angiography • In case of death, autopsy was done wherever possible Safety • The definition of major bleeding was adapted from the criteria for bleeding in non-surgical patients of the International Society of Thrombosis and Haemostasis (27) • Major bleeding was defined as acute clinically overt bleeding accompanied by one or more of the following: a decrease in blood haemoglobin concentration of 20g/L or more during 24h; transfusion of ≥ 2 units of packed red blood cells; critical site bleeding (including intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint needing	**ADVANCE 1, 2 & 3** Venography is the gold standard used in clinical research for the diagnosis of DVT (3, 28). The secondary endpoint of major VTE (which includes proximal DVT and all PE) is clinically relevant as it is associated with a high complication rate.

Primary outcome(s) and measures	Secondary outcome(s) and measures	Outcome measures	Reliability/validity/ current use in clinical practice
• The primary safety endpoint was bleeding during treatment or within 2 days of the last dose of study medication. Severity was defined a priori as major, clinically relevant non-major or minor, and as the composite of major and clinically relevant non-major bleeding.	o PE (fatal or non-fatal) • Other secondary endpoints in ADVANCE 1 and 2 (combined intended treatment and intended follow-up periods, confirmed by adjudication): o All-cause death o VTE-related death o The composite of symptomatic VTE and all-cause death o symptomatic VTE/VTE-related death o PE (fatal or non-fatal) o non-fatal PE o symptomatic DVT o symptomatic proximal DVT o symptomatic distal DVT • A clinical net-benefit endpoint was the composite of adjudicated VTE, major bleeding, and all-cause death during the intended treatment period • Secondary safety endpoints included review of all reported AEs, vital signs, laboratory test results, and events of special interest **ADVANCE 3** • The key secondary efficacy outcome was major VTE; a composite of adjudicated symptomatic or asymptomatic proximal DVT, non-fatal PE and VTE-related death during the intended treatment period	reoperation or intervention; intramuscular bleeding with compartment syndrome; or fatal bleeding • Clinically relevant non-major bleeding included acute clinically overt episodes such as wound haematoma, bruising or ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that did not meet criteria for major bleeding • Minor bleeding was defined as clinically overt but not adjudicated as major or clinically relevant non-major bleeding	

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

5.3.5 Statistical analysis and definition of study groups

Table 11: Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ADVANCE 1	Apixaban (2.5 mg bd) is non-inferior and potentially superior to enoxaparin (30 mg bd) for the composite endpoint of VTE events (asymptomatic and symptomatic DVT and non-fatal PE) and all-cause death in subjects undergoing elective TKR surgery.	Point estimates and 95% CIs for the risk ratio and risk difference between apixaban and enoxaparin were calculated for primary and key secondary outcomes using knee replacement surgery type as stratification factor. Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if both of the following conditions were met: • Upper bound of the two-sided 95% CI for relative risk <1.25, and • Upper-bound of the two-sided 95% CI for risk difference <5.6% Test for superiority was planned if apixaban met the prespecified criteria for non-inferiority	With a total of 3058 planned randomised subjects allocated in a 1:1 ratio to apixaban or enoxaparin treatment, there was more than 99% power to establish non-inferiority and 90% power to demonstrate superiority at a one-sided 0.025 level, if the true event rates were 11.2% and 16% in the apixaban and enoxaparin groups, respectively.	Analysis populations for ADVANCE 1 and 2 were: • **Randomised subjects data set**: all randomised subjects • **Primary efficacy data set**: all randomised subjects who during the intended treatment period had; an adjudicated and evaluable bilateral venogram; or had an adjudicated VTE; or died due to any cause. • **Secondary efficacy data sets**: the data sets used to perform the analyses of the secondary efficacy endpoints were o all randomised subjects if asymptomatic events were not part of the endpoint o all randomised subjects with either an adjudicated event that was part of the endpoint or an adjudicated evaluable bilateral venogram to detect presence or absence of the asymptomatic event of interest (proximal DVT, distal DVT, or both depending on the endpoint). • **Treated subjects dataset**: all subjects who received at least 1
ADVANCE 2	Apixaban (2.5 mg bd) is non-inferior and potentially superior to enoxaparin (40 mg od) for composite endpoint of VTE events (asymptomatic and symptomatic DVT and non-fatal PE) and all-cause death in subjects undergoing elective TKR	Non-inferiority of apixaban versus enoxaparin for the primary efficacy endpoint was tested first at a 1-sided $\alpha = 0.025$ level. If non-inferiority was demonstrated, superiority for the primary efficacy outcome was tested. If superiority was demonstrated, non-inferiority was then tested on the key secondary efficacy endpoint and if demonstrated, superiority for the key secondary efficacy endpoint was	With a total of 3058 randomised subjects allocated in a 1:1 ratio to apixaban or enoxaparin groups, there was > 99% power to demonstrate non-inferiority and 90% power to demonstrate superiority at a 1-sided 0.025 level, if the true event rates were 11% and 16% in the apixaban and enoxaparin groups, respectively.	

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	surgery.	tested. Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if both conditions below were met: • Upper bound of the two-sided 95% CI for relative risk <1.25, and • Upper-bound of the two-sided 95% CI for risk difference <5.6% Non-inferiority for apixaban on the key secondary efficacy endpoint would be demonstrated if the upper bound of the 2-sided 95% CI for RR <1.5. Superiority for an efficacy outcome would be demonstrated if the upper bound of the 2-sided 95% CI for relative risk was <1.		dose of study drug during the treatment period. • **Per Protocol analysis data set**: primary efficacy data set excluding subjects with significant protocol deviations expected to affect the primary efficacy endpoint (per-protocol efficacy analysis set).
ADVANCE 3	Apixaban (2.5 mg bd) is non-inferior and potentially superior to enoxaparin (40 mg od) for the primary and secondary outcomes in subjects undergoing elective total hip replacement	Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if the upper limit of the 95% CI for RR <1.25. If non-inferiority was established for the primary outcome, the secondary efficacy outcome would be tested for non-inferiority. Non-inferiority for apixaban on the key secondary efficacy endpoint would be demonstrated if the upper bound of the CI for RR <1.5. If apixaban met the pre-specified criteria for non-inferiority on both the primary and secondary efficacy outcomes,	4022 subjects allocated in a 1:1 ratio to apixaban or enoxaparin were planned to achieve 92% power to establish non-inferiority for the primary efficacy outcome, assuming true event rates of 3.85% with apixaban and 5.5% with enoxaparin, and 80% power to establish non-inferiority for the secondary efficacy outcome. The protocol pre-specified a review after 80% of patients had been randomised, to permit an increased sample size if needed. At this review, the aggregate primary event rate was 3.3%, so sample size was increased to 5406 to	• **Primary efficacy data set**: all randomised subjects who during the intended treatment period had; an adjudicated and evaluable bilateral venogram; or had an adjudicated VTE; or died due to any cause. • **Secondary efficacy data set**: as for primary efficacy data set, however venograms with evaluable proximal venous segments were accepted regardless of whether distal segments were adequately visualised.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		superiority would be tested using Pearson's Chi-square test. This sequential testing procedure maintained the 1-sided alpha level of 0.025.	maintain 90% power to establish non-inferiority for the primary efficacy outcome, assuming true event rates of 2.72% in the apixaban group and 3.88% in the enoxaparin group. The new sample size also provided 66% power to establish non-inferiority on the secondary efficacy outcome	• **Safety population**: all randomised patients who received at least one dose of study medication

Abbreviations: bd, twice daily; CI confidence interval; DVT, deep vein thrombosis; od once daily; PE, pulmonary embolism; TKR, total knee replacement

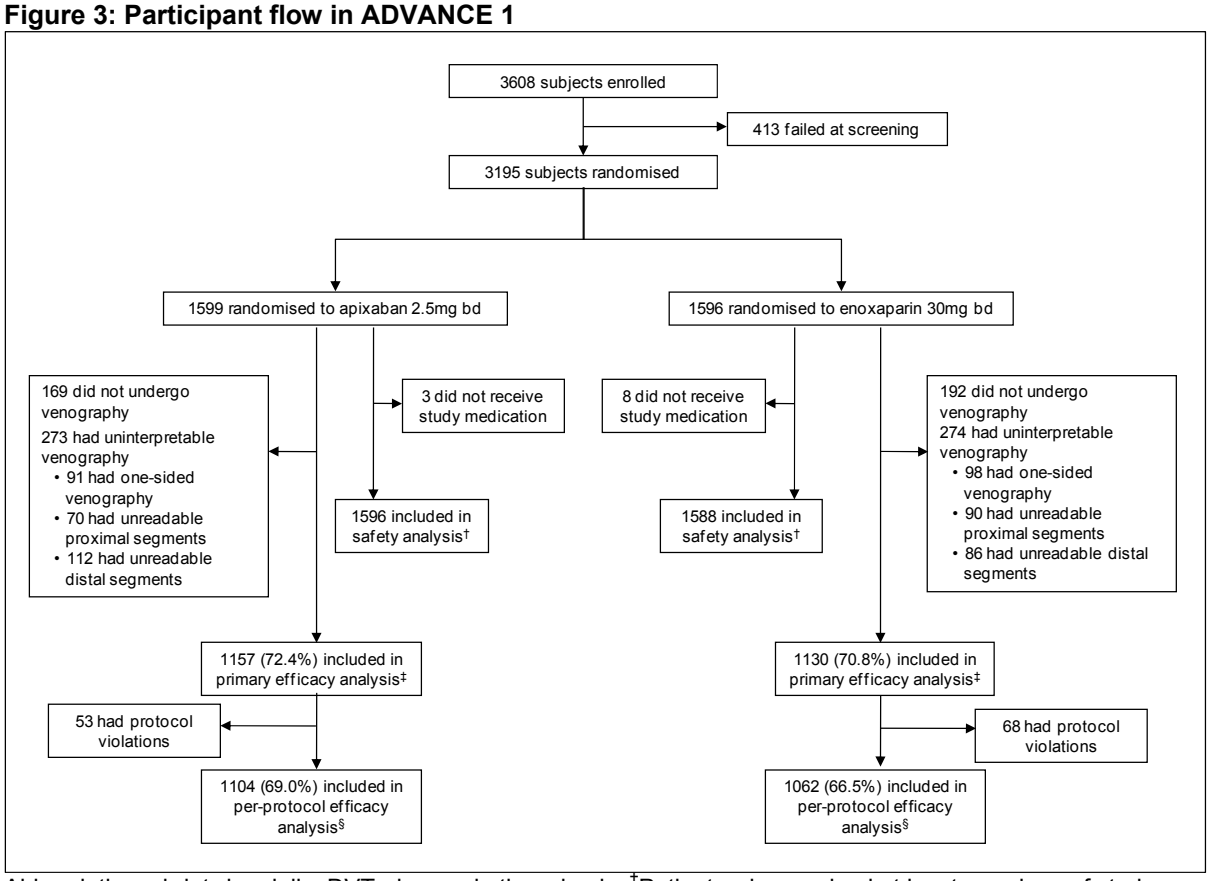
5.3.6 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

[redacted] ***'academic / commercial in confidence information removed'***

Participant flow

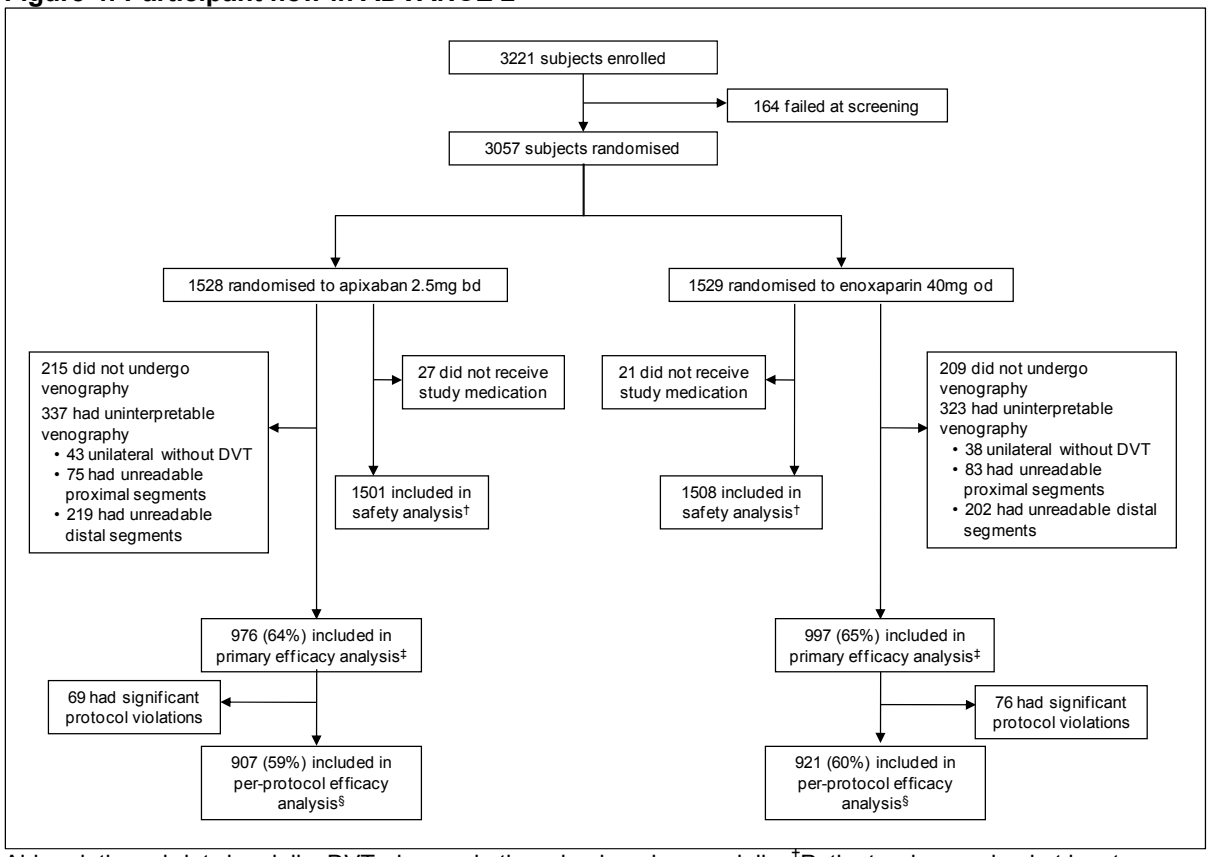
CONSORT flow charts showing the numbers of patients who were eligible to enter ADVANCE 1, ADVANCE 2 and ADVANCE 3, and who were randomised and allocated to each treatment are presented in Figure 3, Figure 4 and Figure 5, respectively. For all three trials, similar proportions of venograms were evaluable in both treatment groups.

Figure 3: Participant flow in ADVANCE 1



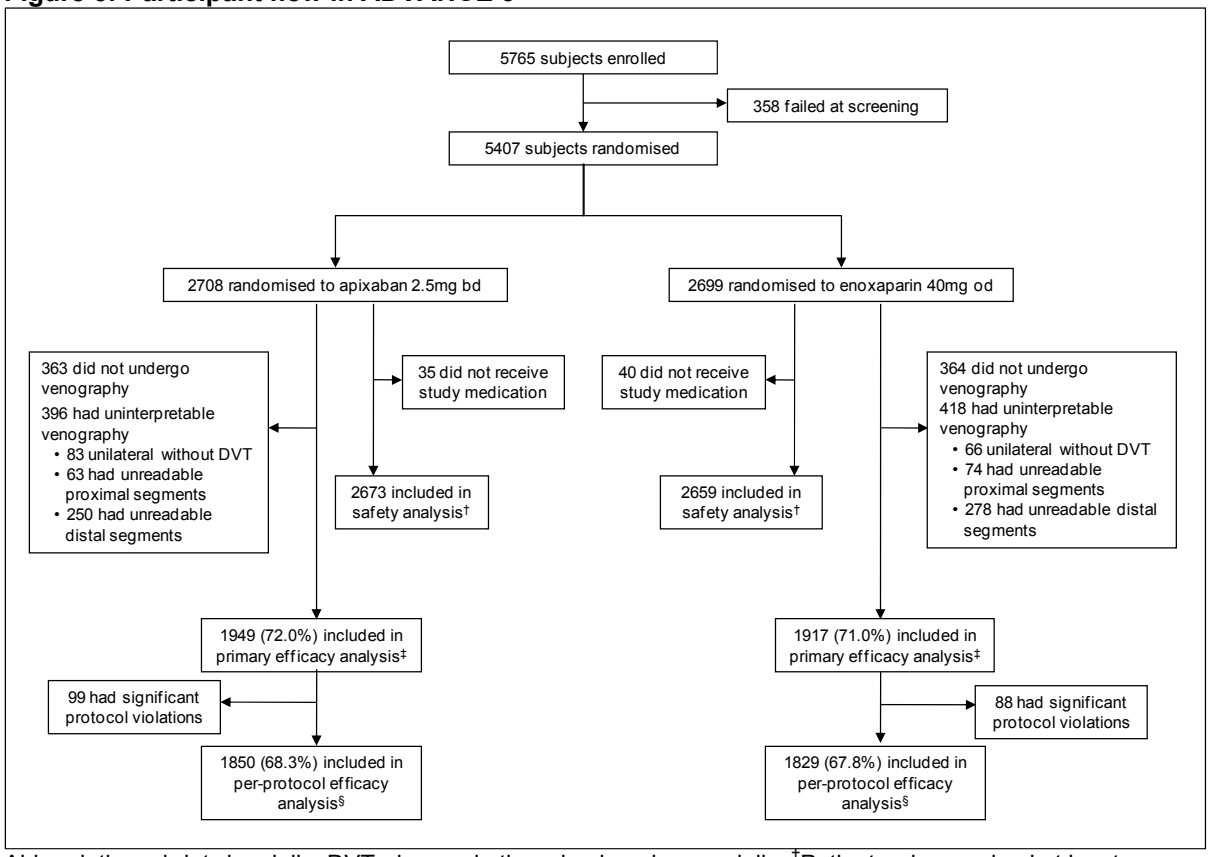
Abbreviations: bd, twice daily; DVT, deep vein thrombosis. †Patients who received at least one dose of study drug; ‡Randomised patients with interpretable venography or adjudicated VTE/death; §Excludes patients with significant protocol violations. Numbers taken from publication.

Figure 4: Participant flow in ADVANCE 2



Abbreviations: bd, twice daily; DVT, deep vein thrombosis; od, once daily. †Patients who received at least one dose of study drug; ‡Randomised patients with interpretable venography or adjudicated VTE/death; §Excludes patients with significant protocol violations. Numbers taken from publication.

Figure 5: Participant flow in ADVANCE 3



Abbreviations: bd, twice daily; DVT, deep vein thrombosis; od, once daily. †Patients who received at least one dose of study drug; ‡Randomised patients with interpretable venography or adjudicated VTE/death; §Excludes patients with significant protocol violations. Numbers taken from publication.

5.4 Critical appraisal of relevant RCTs

Critical appraisals of the relevant RCTs are presented in Table 12. A complete quality assessment for each RCT is provided in Appendix 3.

Table 12: Quality assessment results for RCTs

Trial no. (acronym)	ADVANCE 1	ADVANCE 2	ADVANCE 3
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary efficacy analysis dataset included all randomised subjects who had; an adjudicated and evaluable bilateral venogram; or had an adjudicated VTE; or died due to any cause. The key secondary efficacy analysis data sets included all randomised subjects if asymptomatic events were not part of the endpoint or all randomised subjects with either an adjudicated event that was part of the endpoint or an adjudicated evaluable bilateral venogram (Table 11). This was deemed clinically appropriate since asymptomatic DVT can only be detected with an evaluable venogram. The ITT analysis assumes that no readable venogram represents no event, therefore potentially underestimating the number of VTE events occurring within the ITT population. The remaining efficacy and safety outcome analyses were conducted on the ITT population		

5.5 Results of the relevant RCTs

5.5.1 ADVANCE 2

Efficacy

- Apixaban was statistically superior to enoxaparin in the primary composite endpoint of all VTE and all cause death.
- In addition, apixaban was superior to enoxaparin in reducing the secondary endpoint of major VTE.
- This means that for every 93 patients treated with apixaban instead of enoxaparin, one major blood clot, pulmonary embolus or VTE-related death is avoided.

Summary

- ADVANCE 2 had a high proportion of European participants and the dosing of enoxaparin was according to the UK licensed dose.
- Apixaban was superior to enoxaparin for the prevention of the primary efficacy outcome all VTE and all-cause death during the intended treatment period (RR 0.62; 95% CI 0.51–0.74; p <0.0001 when tested for non-inferiority and superiority).
    - Absolute risk reduction was 9.3% (95% CI 5.8–12.7) in favour of apixaban (p<0.0001 for non-inferiority).
- Apixaban was superior to enoxaparin for prevention of the key secondary efficacy endpoint of the composite of adjudicated proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period (RR 0.50; 95% CI 0.26–0.97, 2-sided p-value=0.0373, for superiority).
    - Absolute risk reduction was 1.04% (95% CI 0.05–2.03) in favour of apixaban
- Rates of symptomatic VTE and VTE-related death did not differ between study groups; apixaban 0.46% versus enoxaparin 0.46% (RR 1.00, 95% CI 0.35–2.85).
- For PE, observed event rates were higher for apixaban than for enoxaparin although the event rates in both groups were very small.
- For DVT, observed event rates were lower for apixaban than for enoxaparin.

Datasets analysed

The data sets used in the analyses are summarised in Table 13. The proportion of subjects (with respect to the number of subjects randomised) in each of the data sets was similar in the two treatment groups.

Table 13: Summary of datasets analysed – randomised subjects

	Apixaban 2.5mg bd	Enoxaparin 40mg od
Randomised subjects, n	1528	1529
Treated subjects, n (%)	1501 (98.2)	1508 (98.6)
Per-protocol subjects, n (%)	907 (59.4)	921 (60.2)
Primary subjects, n (%)	976 (63.9)	997 (65.2)

The primary and secondary efficacy analyses were performed on the primary subjects dataset.

Mean duration of treatment

The mean duration of treatment was 12.1±3.2 days for apixaban and 12.1±2.8 days for enoxaparin.

Analysis periods

Analysis periods for efficacy endpoints were:

- Intended treatment period – the period that started on the day of randomisation; for treated subjects, the period ended at the latter of a) 2 days after last dose of study drug or b) 14 days after the first dose of study drug; for randomised subjects that were not treated, the period ended 14 days after randomisation
- Intended Follow-up Period – the 60-day period starting after the intended treatment period ended. VTE prophylaxis could be continued during this period at the investigators discretion.

Primary Efficacy Results

The non-inferiority criteria for the primary efficacy endpoint were met (Table 14); the upper bound of the 95% CI for risk difference was below 5.6% (the non-inferiority margin for the risk difference), and the upper bound of the 95% CI for RR was below 1.25 (the non-inferiority margin for the risk ratio). The corresponding 1-sided p-values for both non-inferiority tests were < 0.0001. As non-inferiority for the primary efficacy endpoint was demonstrated, superiority of apixaban versus enoxaparin was assessed. The upper bound of the 2-sided 95% CI for the RR was < 1; therefore, superiority for the primary efficacy endpoint was demonstrated. The corresponding 1-sided p-value was <0.0001.

Table 14: Summary of adjudicated VTE events and all-cause death with onset during the intended treatment period – primary subjects

	Apixaban 2.5mg bd N = 976	Enoxaparin 40mg od N = 997
All VTE/All-cause death, N	147	243
Event rate (%)	15.1	24.4
95% CI for event rate	(12.95, 17.46)	(21.81, 27.14)
Relative risk (apixaban/enoxaparin)	0.62	
95% CI for relative risk	(0.51, 0.74)	
One-sided p-value for non-inferiority test on RR	<0.0001	
Two-sided p-value for non-inferiority test on RR	<0.0001	
Risk difference (%) (apixaban–enoxaparin)	–9.27	
95% CI for risk difference	(–12.74, –5.79)	
One-sided p-value for non-inferiority test on difference	<0.0001	
Two-sided p-value for non-inferiority test on difference	<0.0001	
One-sided p-value for superiority test on RR	<0.0001	
Two-sided p-value for superiority test on RR	<0.0001	

Abbreviations: bd, twice daily; CI, confidence interval; od, once daily; RR, relative risk; VTE, venous thromboembolism

Key Secondary Efficacy Results

Apixaban was also superior to enoxaparin for prevention of the key secondary efficacy endpoint (composite of adjudicated proximal DVT, non-fatal PE, and VTE-related death), (Table 15). Results for both non-inferiority and superiority tests were statistically significant at the 1-sided α = 0.025 level.

Table 15: Summary of adjudicated proximal DVT, non-fatal PE and VTE-related death with onset during the intended treatment period

	Apixaban 2.5mg bd N = 1195†	Enoxaparin 40mg od N = 1199†
Proximal DVT/non-fatal PE/VTE-related death, N	13	26
Event rate (%)	1.1	2.2
95% CI for event rate	(0.62, 1.88)	(1.47, 3.18)
Relative risk (apixaban/enoxaparin)	0.50	
95% CI for relative risk	(0.26, 0.97)	
One-sided p-value for non-inferiority test on RR	0.0003	
Two-sided p-value for non-inferiority test on RR	0.0006	
Risk difference (%) (apixaban–enoxaparin)	–1.04	
95% CI for risk difference	(–2.03, –0.05)	
One-sided p-value for superiority test on RR	0.0186	
Two-sided p-value for superiority test on RR	0.0373	

Abbreviations: bd, twice daily; CI, confidence interval; DVT, deep vein thrombosis; od, once daily; RR, relative risk; VTE, venous thromboembolism. †Patients randomly allocated to treatment, with a bilateral venogram that could be assessed for proximal DVT or who had a proximal DVT or non-fatal or fatal PE

Other Secondary Efficacy Analyses

Intended treatment period

Table 16 shows the contribution of each individual efficacy endpoint to the primary and key secondary efficacy endpoints. Rates of symptomatic VTE and VTE-related death did not differ between study groups; apixaban 7/1528 (0.46%) versus enoxaparin 7/1529 (0.46%) (RR 1.00, 95% CI 0.35–2.85; absolute risk reduction 0.00%, 95% CI –0.48 to 0.48).

Table 16: Summary of individual components of primary and key secondary efficacy endpoints with onset during the intended treatment period

	Apixaban 2.5mg bd	Enoxaparin 40mg od
All-cause death, n/N†	2/1528	0/1529
Event rate (%)	0.13	0.00
VTE-related death, n/N†	1/1528	0/1529
Event rate (%)	0.07	0.00
PE (fatal or non-fatal), n/N†	4/1528	0/1529
Event rate (%)	0.26	0.00
Non-fatal PE, n/N†	3/1528	0/1529
Event rate (%)	0.20	0.00
All DVT, n/N‡	142/971	243/997
Event rate (%)	14.62	24.37
Proximal DVT, n/N§	9/1192	26/1199
Event rate (%)	0.76	2.17
Distal DVT, n/N¶	142/978	239/1000
Event rate (%)	14.52	23.90
Symptomatic DVT, n/N†	3/1528	7/1529
Event rate (%)	0.20	0.46
Asymptomatic DVT, n/N‡	139/968	236/990
Event rate (%)	14.36	23.84
Symptomatic proximal DVT, n/N†	1/1528	1/1529
Event rate (%)	0.07	0.07
Asymptomatic proximal DVT, n/N§	8/1191	25/1198
Event rate (%)	0.67	2.09
Symptomatic distal DVT, n/N†	3/1528	7/1529
Event rate (%)	0.20	0.46
Asymptomatic distal DVT, n/N¶	139/975	232/993
Event rate (%)	14.26	23.36

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism. †Data set = randomised subjects; ‡Data set = randomised subjects with an adjudicated and evaluable bilateral venogram or an adjudicated event associated with the endpoint, during the intended treatment period; §Data set = randomised subjects with either an adjudicated and evaluable bilateral proximal venograms or an adjudicated event associated with the event, during the intended treatment period; ¶Data set = randomised subjects with either an adjudicated and evaluable bilateral distal venograms or an adjudicated event associated with the endpoint, during the intended treatment period

Intended follow-up period

The follow-up period was completed by 1458 (95%) apixaban patients and 1469 (96%) enoxaparin patients. Symptomatic VTE developed during follow-up in 5/1458 (<1%) apixaban patients and 2/1469 (<1%) of enoxparin patients. There was one fatal PE in the apixaban group.

Table 17: Summary of secondary efficacy endpoints in the follow-up period

	Apixaban 2.5mg bd	Enoxaparin 40mg od
Symptomatic DVT, n/N	2/1458	1/1469
Event rate, %	0.14%	0.07%
All PE, n/N	3/1458	1/1469
Event rate, %	0.21%	0.07%
Death, n/N	1/1458	1/1469
Event rate, %	0.07%	0.07%

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism

Subgroup analyses

Event rates for the primary efficacy endpoint (all VTE and all-cause death) during the intended treatment period were summarised, using the primary efficacy data set, by age group, gender, race, geographic region, BMI, and type of surgery.

The effect of apixaban relative to enoxaparin on the primary efficacy endpoint within each subgroup was consistent with that observed in the overall population. The observed relative risk reduction (RRR) in the subgroups ranged between 28% and 57%. RRR outside the above range were observed for small subgroups (with a size <4% of the primary population), but due to the small size, no conclusions could be drawn from the analyses on these subgroups:

In the bilateral TKR subgroup, 4 (17%) subjects in the apixaban group and 9 (43%) subjects in the enoxaparin group had a primary efficacy event

In the Black/African American race subgroup, 1 (17%) subject in the apixaban group and 1 (14%) subject in the enoxaparin group had a primary efficacy event

In the African region subgroup, 1 (2.9%) subject in the apixaban group and 5 (16%) subjects in the enoxaparin group had a primary efficacy event.

5.5.2 ADVANCE 3

Efficacy

- Apixaban was statistically superior to enoxaparin in the primary composite endpoint of all VTE and all cause death.
- In addition, apixaban was superior to enoxaparin in reducing the secondary endpoint of major VTE.
- This means that for every 145 patients treated with apixaban instead of enoxaparin, one major blood clot, pulmonary embolus or vascular death is avoided.

Summary

- ADVANCE 3 had a high proportion of European participants and the dosing of enoxaparin was according to the UK licensed dose.
- Apixaban was superior to enoxaparin for the prevention of the primary efficacy outcome all VTE and all-cause death during the intented treatment period (RR 0.36; 95% CI 0.22–0.54; p <0.0001 when tested for non-inferiority and superiority).
    - Absolute risk reduction was 2.5% (95% CI 1.5–3.5) in favour of apixaban.
- Apixaban was superior to enoxaparin for prevention of the key secondary efficacy endpoint of composite of adjudicated proximal DVT, non-fatal PE, and VTE-related death during the intented treatment period (RR 0.40; 95% CI 0.15–0.80, p<0.0001 for non-inferiority, 2-sided p-value=0.01, for superiority).
    - Absolute risk reduction was 0.7% (95% CI 0.02–1.3) in favour of apixaban.
- Rates of symptomatic VTE and VTE-related death were numerically lower in the apixaban group versus the enoxaparin group.
- For PE, observed event rates were similar between the apixaban and enoxaparin groups.
- For DVT, observed event rates were lower for apixaban than for enoxaparin.

Datasets analysed

The data sets used in the analyses are summarised in Table 18. The proportion of subjects (with respect to the number of subjects randomised) in each of the data sets was similar in the two treatment groups.

Table 18: Summary of datasets analysed – randomised subjects

	Apixaban 2.5mg bd	Enoxaparin 40mg od
Randomised subjects, n	2708	2699
Per-protocol subjects, n (%)	1850 (68.3)	1829 (67.8)
Primary subjects, n (%)	1949 (72.0)	1917 (71.0)
Key secondary subjects, n (%)	2199 (81.2)	2195 (81.3)
Treated subjects, n (%)	2673	2659

The primary and secondary efficacy analyses were performed on the primary subjects dataset.

Mean duration of treatment

The mean duration of treatment was 34.0±7.7 days for apixaban and 33.9±7.8 days for enoxaparin.

Primary Efficacy Results

The primary efficacy outcome occurred in 27/1949 (1.4%) subjects in the apixaban group and 74/1917 (3.9%) subjects in the enoxaparin group (relative risk: 0.36, 95% CI: 0.22–0.54, one-sided p<0.0001 for both non-inferiority and superiority), (Table 19). The absolute risk reduction was 2.5% (95% CI: 1.5%-3.5%) in favour of apixaban.

Table 19: Summary of adjudicated VTE events and all-cause death with onset during the intended treatment period – primary subjects

	Apixaban 2.5mg bd N = 1949	Enoxaparin 40mg od N = 1917
All VTE/All-cause death, N	27	74
Event rate (%)	1.39	3.86
95% CI for event rate	(0.95, 2.02)	(3.08, 4.83)
Relative risk (apixaban/enoxaparin)	0.36	
95% CI for relative risk	(0.22, 0.54)	
One-sided p-value for non-inferiority test on RR	<0.0001	
Risk difference (%) (apixaban–enoxaparin)	–2.47	
95% CI for risk difference	–3.54 to –1.50	
One-sided p-value for superiority test	<0.0001	
Two-sided p-value for superiority test	<0.0001	

Abbreviations: bd, twice daily; CI, confidence interval; od, once daily; RR, relative risk; VTE, venous thromboembolism

Key Secondary Efficacy Results

The key secondary efficacy outcome of major VTE occurred in 10/2199 (0.45%) subjects in the apixaban group and 25/2195 (1.14%) subjects in the enoxaparin group (relative risk: 0.40, 95% CI: 0.15–0.80, one-sided p<0.0001 for non-inferiority, p=0.0054 for superiority), (Table 20). The absolute risk reduction was 0.7% (95% CI: 0.2%-1.3%) in favour of apixaban.

Table 20: Summary of adjudicated proximal DVT, non-fatal PE and VTE-related death with onset during the intended treatment period

	Apixaban 2.5mg bd N = 2199	Enoxaparin 40mg od N = 2195
Proximal DVT/non-fatal PE/VTE-related death, N Event rate (%) 95% CI for event rate	10 0.45 (0.24, 0.85)	25 1.14 (0.77, 1.69)
Relative risk (apixaban/enoxaparin) 95% CI for relative risk One-sided p-value for non-inferiority test on RR	0.40 (0.15, 0.80) <0.0001	
Risk difference (%) (apixaban–enoxaparin) 95% CI for risk difference	–0.68 –1.27 to –0.17	
One-sided p-value for superiority test on RR Two-sided p-value for superiority test on RR	0.0054 0.0107	

Abbreviations: bd, twice daily; CI, confidence interval; DVT, deep vein thrombosis; od, once daily; RR, relative risk; VTE, venous thromboembolism

Other Secondary Efficacy Analyses

Intended treatment period

Incidences of the composite of symptomatic VTE and VTE-related death, and of symptomatic DVT, proximal DVT, PE and death are summarised in Table 21. The secondary outcomes, shown in the table, occurred less frequently in the apixaban group compared with the enoxaparin group in all DVT and proximal DVT.

Table 21: Summary of other secondary efficacy endpoints

	Apixaban 2.5mg bd	Enoxaparin 40mg od
Symptomatic VTE and VTE-related death n/N (%) 95% CI	4/2708 (0.15) 0.04–0.40	10/2699 (0.37) 0.19–0.69
All DVT n/N (%) 95% CI	22/1944 (1.13) 0.74–1.71	68/1911 (3.56) 2.81–4.50
Symptomatic DVT, n/N (%) 95% CI	1/2708 (0.04) 0.00–0.24	5/2699 (0.19) 0.07–0.45
Proximal DVT, n/N (%) 95% CI	7/2196 (0.32) 0.14–0.68	20/2190 (0.91) 0.59–1.42
All PE, n/N (%) 95% CI	3/2708 (0.11) 0.02–0.35	5/2699 (0.19) 0.07–0.45
Fatal PE, n/N (%)	1/2708 (0.04)	0/2699 (0)

	Apixaban 2.5mg bd	Enoxaparin 40mg od
95% CI		
Death, n/N (%) 95% CI	3/2708 (0.11) 0.02–0.35	1/2699 (0.04) 0.00–0.24

Abbreviations: bd, twice daily; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; od, once daily; VTE, venous thromboembolism

Intended follow-up period

Follow-up for 60 days after the last dose of study medication was completed by 2598 (96%) apixaban patients and 2577 (95%) enoxaparin patients. No subject had a PE in the apixaban group compared with 4 (0.2%) subjects treated with enoxparin (Table 22).

Table 22: Summary of secondary efficacy endpoints in the follow-up period

	Apixaban 2.5mg bd	Enoxaparin 40mg od
Symptomatic DVT, n/N Event rate, %	0/2598 0	3/2577 0.12
All PE, n/N Event rate, %	0/2598 0	4/2577 0.16
Fatal PE, n/N Event rate, %	0/2598 0	0/2577 0
Death, n/N Event rate, %	2/2598 0.08	1/2577 0.04

Abbreviations: bd, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; od, once daily; VTE, venous thromboembolis

Subgroup analyses

[redacted] 'academic / commercial in confidence information removed'

5.5.3 ADVANCE 1

Efficacy

- ADVANCE 1 employed a North American dosing regimen of enoxaparin not used in Europe. Key differences were:
    - A higher daily dose and frequency of enoxaparin was used in line with US labelling
    - Tourniquet use was lower than in Europe
    - Duration of hospitalisation was shorter than in Europe
- The overall event rate was much lower than anticipated.
- Against the North American regimen of enoxaparin, numerically events in the primary composite of all VTE and all cause death were similar, but the statistical test of non-inferiority was not met.
- These data are not considered clinically relevant to European clinical practice, although the data do contribute to our knowledge about the overall efficacy and safety profile of apixaban.

Summary

- The majority of randomised patients were North American and the dosing of enoxaparin was according to U.S. licensed indication.
- The rate of the primary efficacy outcome of the composite of all VTE and all cause death was 9.0% with apixaban, compared with 8.8% with enoxaparin (RR 1.02; 95% CI 0.78–1.32) (p=0.06).
    - Apixaban did not meet pre-specified statistical criteria for non-inferiority.
    - The observed rates were similar for apixaban and enoxaparin but the enoxaparin rate was lower than expected and was lower than seen in previous orthopaedic VTE prevention trials.
- The key secondary efficacy endpoint (the composite of adjudicated proximal DVT, non-fatal PE, and all-cause death) occurred in 2.05% patients in the apixaban group versus 1.64% in the enoxaparin group during the treatment period (RR 1.25; 95% CI 0.70–2.23).
- The observed rate of DVT was similar for apixaban and enoxaparin.
- Patients treated with apixaban had an observed higher rate of PE than those treated with enoxaparin (1.0% versus 0.4%).

Datasets analysed

The data sets used in the analyses are summarised in Table 23. The proportion of subjects (with respect to the number of subjects randomised) in each of the data sets was similar in the two treatment groups.

Table 23: Summary of dataset analysed – randomised subjects

	Apixaban 2.5mg bd	Enoxaparin 30mg bd
Randomised subjects, n	1599	1596
Treated subjects, n (%)	1595 (99.7)	1589 (99.6)
Per-protocol subjects, n (%)	1104 (69.0)	1062 (66.5)
Primary subjects, n (%)	1157 (72.4)	1130 (70.8)

Abbreviations: bd, twice daily

The primary and secondary efficacy analyses were performed on the primary subjects dataset.

Mean duration of treatment

The mean duration of treatment with study medication was 11.7±2.5 days in the apixaban group and 11.6±2.5 days in the enoxaparin group.

Analysis periods

Analysis periods for efficacy endpoints were:

- Intended treatment period – the period that started on the day of randomisation; for treated subjects, the period ended at the latter of a) 2 days after last dose of study drug or b) 14 days after the first dose of study drug; for randomised subjects that were not treated, the period ended 14 days after randomisation.
- Intended Follow-up Period – the 60-day period starting after the intended treatment period ended.

Primary Efficacy Results

The primary efficacy outcome occurred in 104/1157 (8.99%) patients in the apixaban group, as compared with 100/1130 (8.85%) patients in the enoxaparin group (Table 24). The observed relative risk (RR) of apixaban versus enoxaparin for the primary efficacy endpoint was 1.02 and the adjusted risk difference was 0.11%. Although the upper bound of the 95% CI for risk difference (2.44%) was below 5.6% (the non-inferiority margin for the risk difference), the upper bound of the 95% CI for RR (1.32) was above 1.25 (the non-inferiority margin) and, therefore, the non-inferiority criteria for the primary efficacy endpoint was not met.

Table 24: Summary of adjudicated VTE events and all-cause death with onset during the intended treatment period – primary subjects

	Apixaban 2.5mg bd N = 1157	Enoxaparin 30mg bd N = 1130
All VTE/All-cause death, N	104	100
Event rate (%)	8.99	8.85
95% CI for event rate	7.47, 10.79	7.33, 10.66
Relative risk (apixaban/enoxaparin)	1.02	
95% CI for relative risk	0.78, 1.32	
One-sided p-value for non-inferiority test on RR	0.0635	
Risk difference (%) (apixaban–enoxaparin)	0.11	
95% CI for risk difference	–2.22, 2.44	
One-sided p-value for non-inferiority test on difference	<0.0001	

Abbreviations: bd, twice daily; CI, confidence interval; VTE, venous thromboembolism

Secondary Efficacy Results

Intended treatment period

The key secondary efficacy endpoint (the composite of adjudicated proximal DVT, non-fatal PE, and all-cause death) occurred in 26/1269 (2.05%) patients in the apixaban group and 20/1216 (1.64%) patients in the enoxaparin group (Table 25). The observed RR for the key secondary endpoint was 1.25 with 95% CI of (0.70-2.23).

Table 25: Key secondary efficacy endpoint - adjudicated proximal DVT, non-fatal PE and all-cause death with onset during the intended treatment period

	Apixaban 2.5mg bd N = 1269	Enoxaparin 30mg bd N = 1216
Proximal DVT/Non-fatal PE/All-cause death, N	26	20
Event rate (%)	2.05	1.64
95% CI for event rate	1.39, 3.01	1.06, 2.55
Relative risk (apixaban/enoxaparin)	1.25	
95% CI for relative risk	0.70, 2.23	
Risk difference (%) (apixaban–enoxaparin)	0.36	
95% CI for risk difference	–0.68, 1.40	
One-sided p-value for non-inferiority test on difference	0.7779	

Abbreviations: bd, twice daily; CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism

The results of the analyses for other adjudicated secondary efficacy endpoints show the contribution of each individual efficacy endpoint to the primary and key secondary efficacy endpoints during the intended treatment period (Table 26).

Table 26: Summary of other secondary efficacy endpoints with onset during the intended treatment period

	Apixaban 2.5mg bd	Enoxaparin 30mg bd
Symptomatic VTE and VTE-related death, n/N Event rate,% (95% CI) Relative risk (95% CI) Risk difference (%) (95% CI)	19/1599 1.19 (0.75, 2.95) 1.46 (0.72, 2.95) 0.38 (–0.30, 1.06)	13/1596 0.81 (0.46, 1.41)
All DVT, n/N Event rate, % (95% CI)	89/1142 7.8 (6.37, 9.51)	92/1122 8.2 (6.73, 9.97)
Symptomatic DVT, n/N Event rate, % (95% CI)	3/1599 0.2 (0.04, 0.59)	7/1596 0.4 (0.20, 0.93)
Proximal DVT, n/N Event rate, % (95% CI)	9/1254 0.7 (0.36, 1.39)	11/1207 0.9 (0.49, 1.65)
All PE, n/N Event rate, % (95% CI)	16/1599 1.0 (0.61, 1.64)	7/1596 0.4 (0.20, 0.93)
Fatal PE, n/N Event rate, % (95% CI)	2/1599 0.1 (0, 0.49)	0 0 (0, 0.30)
All-cause death, n/N Event rate, % (95% CI)	3/1599 0.2 (0.04, 0.59)	3/1595 0.2 (0.04, 0.59)

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

Intended follow-up period

Follow-up for 60 days after the last dose of study medication was completed in 1562/1599 (97.7%) patients assigned to apixaban and in 1554/1596 (97.4%) assigned to enoxaparin. During the follow-up period, symptomatic VTE occurred in 4/1562 (0.3%) patients in the apixaban group and in 7/1554 (0.5%) in the enoxaparin group (Table 27).

Table 27: Summary of secondary efficacy endpoints in the follow-up period

	Apixaban 2.5mg bd	Enoxaparin 30mg bd
Symptomatic DVT, n/N Event rate, % (95% CI)	3/1562 0.2 (0.04, 0.60)	2/1554 0.1 (0.01, 0.51)
All PE, n/N Event rate, % (95% CI)	1/1562 0.1 (0, 0.41)	5/1554 0.3 (0.12, 0.78)
Fatal PE, n/N Event rate, % (95% CI)	0 0 (0, 0.30)	2/1554 0.1 (0.01, 0.51)
Death, n/N Event rate, % (95% CI)	0 0 (0, 0.30)	3/154 0.2 (0.04, 0.60)

Abbreviations: bd, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism.

Subgroup analyses

Event rates for the primary efficacy endpoint (all VTE and all-cause death) during the intended treatment period were summarised, using the primary efficacy data set, by age group, gender, race, geographic region, BMI, and type of surgery.

The incidence of primary efficacy events was similar in the apixaban and enoxaparin groups for subjects <65 years of age, for male and female subjects, for white subjects, for subjects in North America and Europe, and for subjects in all BMI categories. Although an imbalance in the incidence of primary efficacy events between apixaban and enoxaparin groups was observed for subjects in other age categories, for subjects of other race, for subjects from other geographic regions, and for subjects with same-day bilateral surgery, these rates were based on a very small number of observed events in each treatment group.

Since type of surgery was a stratification factor, Fieller's theorem was used to produce 95% two-sided confidence intervals for RR in the primary efficacy analysis by type of surgery. This formula assumes special conditions on the observed denominator rate to produce valid confidence intervals. This condition was not met for the bilateral TKR subgroup and, therefore, the confidence interval was reported to be not estimable.

5.6 Meta-analysis

5.6.1 Meta-analysis methods and results

Identification of key apixaban and comparator studies

As reported in section 5.1 above, a systematic literature search was conducted to identify all RCT evidence for apixaban and relevant comparators, supplemented by hand searching the bibliographies of relevant review articles and unpublished data from the manufacturer's clinical trial database. The search strategy for the RCT evidence is provided in Section 9.2 (Appendix 2). The study population, treatments of interest and study design eligibility criteria are documented in Table 4, section 5.2 and Figure 1 in section 5.2.2 displays the literature search results.

Of the 43 RCTs identified by the literature search, 15 were direct head-to-head comparisons of treatments identified in the NICE STA scope for apixaban (see Table 28 below). A quality assessment of these 15 RCTS is presented in Appendix 3 (the 4 apixaban 2.5mg bd trials) and Appendix 5 (the 11 comparator treatment trials). Table 28 presents information on orthopaedic surgery population, treatments, and doses used in these RCTs.

Table 28: RCTs of head-to-head comparisons of treatments listed as interventions of interest in the NICE STA scope for apixaban

RCTs included in main THR and TKR analyses					
Total Hip Replacement (THR)			**Total Knee Replacement (TKR)**		
Study	**Treatment**	**Comparison**	**Study**	**Treatment**	**Comparison**
ADVANCE-3 (20)	Apixaban 2.5 mg bd	Enoxaparin 40 mg od	ADVANCE-2 (21)	Apixaban 2.5 mg bd	Enoxaparin 40 mg od
RECORD 1 (29)	Rivaroxaban 10 mg od	Enoxaparin 40 mg od	RECORD 3 (30)	Rivaroxaban 10 mg od	Enoxaparin 40 mg od
RECORD 2 (31)	Rivaroxaban 10 mg od	Enoxaparin 40 mg od	RE-MODEL (32)	Dabigatran 220 mg od	Enoxaparin 40 mg od
RE-NOVATE (33)	Dabigatran 220 mg od	Enoxaparin 40 mg od	APROPOS (26)	Apixaban 2.5 mg bd	Enoxaparin 30 mg bd
Huo 2010 (RE-NOVATE II) (34)	Dabigatran 220 mg od	Enoxaparin 40 mg od	ADVANCE 1 (24)	Apixaban 2.5 mg bd	Enoxaparin 30 mg bd
Lassen 2002 (35)	Fondaparinux 2.5 mg od	Enoxaparin 40 mg od	RECORD 4 (36)	Rivaroxaban 10 mg od	Enoxaparin 30 mg bd
Turpie 2002 (37)	Fondaparinux 2.5 mg od	Enoxaparin 30 mg bd	RE-MOBILIZE (38)	Dabigatran 220 mg od	Enoxaparin 30 mg bd
			Bauer 2001(39)	Fondaparinux 2.5 mg od	Enoxaparin 30 mg bd

Abbreviations: bd, twice daily; od, once daily

Intervention, comparators, and feasibility of pair-wise meta-analysis

The RCTs that compare apixaban 2.5mg bd and other comparator treatments of interest with the UK/EU licensed dose of enoxaparin (40mg od) were deemed the most relevant to this NICE STA submission, and form the main analysis presented in sections 5.6 and 5.7. In accordance with the NICE STA scope for apixaban, no pooling of trials across the different surgery populations was conducted. In terms of comparator trials, only dabigatran 220mg od (standard UK dose) was included in the submission analyses, since it is inappropriate to compare the 150mg od dabigatran dose indicated for elderly patients with the apixaban 2.5mg bd, rivaroxaban 10mg od, and fondaparinux 2.5mg od doses indicated for general population use. Enoxaparin was the only LMWH considered for inclusion, as it is the most widely used LMWH VTE prophylaxis option in the UK (13) for the THR and TKR populations.

Table 29 below presents the 15 RCTs, the outcomes for which treatment effect sizes could be calculated for each, and the trial combinations where pair-wise meta-analysis was possible. Eight RCTs (ADVANCE-2 (21); ADVANCE-3 (20); Lassen 2002 (35); RECORD 1 (29); RECORD 3 (30); RE-NOVATE (33); Huo 2010 (RE-NOVATE II) (34); RE-MODEL (32)) compared treatments of interest with enoxaparin 40 mg od and are included in the main analysis. Pair-wise meta-analysis of specific treatments could only be undertaken for dabigatran 220 mg in the THR population (RE-NOVATE (33) and Huo 2010 (RE-NOVATE II (34)). The results from the dabigatran 220 mg pair-wise meta-analysis and individual trials of the other treatments are presented in Section 5.7 below. The associated forest plots are presented in Appendix 15.

Six studies (APROPOS (26), ADVANCE 1 (24), RECORD 4 (36), RE-MOBILIZE (38), Bauer 2001(39), and Turpie 2002 (37)) compared the treatments of interest against enoxaparin 30mg bd (US licensed dose), with pair-wise meta-analysis vs. enoxaparin 30 mg only feasible for apixaban (APROPOS (26), ADVANCE 1 (24)). The US dose enoxaparin RCTs are presented as a sensitivity analysis in appendix 15 in the interests of presenting all the relevant evidence.

Table 29 also displays where specific treatments in one orthopaedic surgery population were compared against both the UK (40 mg od) and US (30mg bd) doses of enoxaparin in separate RCTs, thereby allowing for a meta-analysis that combines these different trials (combined enoxaparin doses grouping). This analysis was performed for completeness, so that the combined EU and US enoxaparin dose grouping could be compared to the respective single EU and US enoxparin doses on the efficacy and safety outcomes of interest. The results are presented in Appendix 15.

Table 29 indicates that RECORD 2 (31), comparing rivaroxaban with enoxaparin 40 mg od in the THR population, was excluded from the main analysis, since the enoxaparin arm had a shorter treatment duration (10-14 days) compared to the rivaroxaban arm (31-35 days). This could result in an overestimation of the treatment effect associated with rivaroxaban, since enoxaparin was administered for half the amount of time recommended in the NICE VTE guideline (1). However in order to assess the variation in treatment effect contributed by this study, RECORD 1 (29) and RECORD 2 (31) were pooled, and the pair-wise meta-analysis results are presented in Appendix 15 as a sensitivity analysis.

Table 29: Studies and outcomes available for analysis

Studies	Any VTE*	Any DVT	Major VTE†	Asymptomatic DVT	Symptomatic DVT	PE	Any bleed‡	Major bleed	CRNM bleed	Minor bleed
THR vs. enoxaparin 40 mg od (main analysis)										
ADVANCE-3 (20)	y	y	y	y	y	y	y	y	y	y
RECORD 1 (29)	y	y	y	NR	NR	y	y	y	y	y
RE-NOVATE (33)	y	y	y	y	y	y	y	y	y	y
Huo 2010 (RE-NOVATE II) (34)	y	NR	y	NR	NR	NR	(A)	y	NR	NR
RE-NOVATE + RE-NOVATE II meta-analysis	y		y					y		
Lassen 2002 (35)	(B)	y	NR	y	y	y	(A)	y	NR	NR
TKR vs. enoxaparin 40 mg od (main analysis)										
ADVANCE-2 (21)	y	y	y	y	y	y	y	y	y	y
RECORD 3 (30)	y	y	y	NR	NR	y	y	y	y	y
RE-MODEL (32)	y	y	y	y	y	y	y	y	y	y
THR vs. enoxaparin 40 mg od (sensitivity analysis)										
RECORD 2 (31)	y	y	y	NR	NR	y	y	y	y	y
RECORD 1 + RECORD 2 meta-analysis	y	y	y			y	y	y	y	y
THR vs. enoxaparin 30 mg bd (sensitivity analysis)										
Turpie 2002 (37)	(B)	y	NR	y	y	y	(A)	y	NR	NR
TKR vs. enoxaparin 30 mg bd (sensitivity analysis)										
APROPOS (26)	y	y	y	y	y	y	y	y	y	y

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ADVANCE 1 (24)	y	y	y	y	y	y	y	y	y	y
APROPOS + ADVANCE 1 meta-analysis	y	y	y	y	y	y	y	y	y	y
RECORD 4 (36)	y	y	y	y	y	y	y	y	y	y
RE-MOBILIZE (38)	y	y	y	y	y	y	y	y	y	NR
Bauer 2001(39)	NR	y	NR	NR	NR	y	NR	y	NR	NR
THR vs. enoxaparin 40 mg od + 30 mg bd (sensitivity analysis)										
Lassen 2002 +(35) Turpie 2002 meta-analysis		y		y	y	y		y		
TKR vs. enoxaparin 40 mg od + 30 mg bd (sensitivity analysis)										
APROPOS + ADVANCE 1 + ADVANCE-2 meta-analysis	y	y	y	y	y	y	y	y	y	y
RECORD 3 + RECORD 4 meta-analysis	y	y	y			y	y	y	y	y
RE-MODEL + RE-MOBILIZE meta-analysis	y	y	y	y	y	y	y	y	y	

(A): Not used in any bleeding indirect comparison as reported major bleeding only
(B): Data not used as composite VTE = DVT + PE where deaths are reported in the study
NR = not reported
*composite of any DVT, non-fatal PE, any death
†composite of proximal DVT, PE and VTE-related death
‡composite of major, clinically relevant non-major, and minor bleeding outcomes

Limitations in trial coverage and outcome reporting

Table 29 shows that no RCTs comparing fondaparinux 2.5mg od with enoxaparin 40 mg od in the TKR population were identified by the systematic review. In addition, not all RCTs reported on all outcomes of interest. Huo 2010 (RE-NOVATE II) (34) only reported results for the VTE composite outcome, major VTE, and major bleeding. Data for this trial were only available from a published conference abstract identified at the time the systematic review for this submission was completed, and it is possible that other outcomes will be available in the full publication. Furthermore**,** asymptomatic DVT and symptomatic DVT outcomes were not reported in the rivaroxaban trials (RECORD 1 (29), RECORD 3 (30) included in the main analysis**.**

In the THR population, the fondaparinux 2.5 mg od versus enoxaparin 40 mg od RCT (Lassen 2002 (35) study reported a VTE composite that included DVT + PE only, with deaths reported separately. As there may have been overlap between the deaths and VTE events, this study was excluded from the analyses of the VTE composite outcome (composite of any DVT, non-fatal PE and death). This study also only reported major bleeding as a safety outcome, with other bleeding outcomes not reported.

Table 30 below indicates that all studies included in the main UK licence dose analysis fulfilled the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding. Major bleeding conforming to the main ISTH criteria for this outcome (27, 40) was defined as:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin level of 2g/dL (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

In terms of CRNM bleeding, Table 31 below indicates that the RE-NOVATE (33) and RE-MODEL (32) trials reported the most criteria, followed by ADVANCE-2 (21) and ADVANCE-3 (20). RECORD 1 (29) and RECORD 3 (30) reported CRNM bleeding as an outcome but did not specify any criteria used to define this.

Not all studies reported ‘any bleeding’ as a distinct endpoint (the total number of patients with bleeding). (see Table 32 below). ADVANCE-2 (21), ADVANCE-3 (20), RECORD 1 (29), and RECORD 3 (30) all reported a distinct any bleeding endpoint, whereas for RE-NOVATE (33) and RE-MODEL (32), major, minor and CRNM bleeds were added together to calculate an any bleeding outcome. Since Huo 2010 (RE-NOVATE II) (34) and (Lassen 2002 (35)) reported only major bleeding as an outcome, no any bleeding endpoint could be calculated for these two trials.

Table 30: Definition of major bleeding across included studies

Study	Indication	Main ISTH def*			Additional inclusions			Other definition/ inclusions	Location of bleeding						
		1) Fatal bleeding	2) In a critical organ	3) Decrease in haemoglobin >=2g/dL or transfusion >=2units	4) Requires re-intervention	clinically overt	requiring treatment cessation		intracranial	retroperitoneal	intraocular	Intra-spinal	pericardial	into operated joint	intramuscular
Studies with ISTH and additional major bleed definitions included in pair-wise meta-analyis and adjusted indirect comparison															
ADVANCE-3	THR	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓
RENOVATE II	THR	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓			
Lassen 2002	THR	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓		
Lassen 2010 (ADVANCE-2)	TKR	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓
RECORD 1	THR	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	
RECORD 3	TKR	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓		✓
RE-MODEL	TKR	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓			
RE-NOVATE	THR	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓			

Abbreviations: THR, total hip replacement; TKR, total knee replacement; ISTH, International Society on Thrombosis and Haemostasis

Table 31: Definition of CRNM bleeding across included studies

Unique study ID	Indication	Multiple source bleeding	haematoma >25 cm2	excessive wound haematoma	epistaxis >5 min	macroscopic hematuria (spontaneous, or lasting >24 h if associated with an intervention)	spontaneous rectal bleeding	gingival bleeding >5 min	haemoptysis	haematemesis	prolonged bleeding (>5 min) after venipuncture	Other definition
ADVANCE-3	THR			✓	✓	✓			✓			
ADVANCE-2	TKR			✓	✓	✓			✓			
RE-NOVATE	THR		✓	✓	✓	✓	✓	✓				
RE-MODEL	TKR		✓	✓	✓	✓	✓	✓				
RECORD 1	THR											NR
RECORD 3	TKR											NR

Abbreviations: THR, total hip replacement; TKR, total knee replacement; NR, not recorded

Table 32: Definition of any bleeding across included studies

Unique study ID	Indication group	Data as reported in trial	Data calculated from other bleed endpoints	Bleed endpoints used in calculation		
				Major	CRNM	Minor
ADVANCE-3	THR	✓				
Lassen 2010 (ADVANCE-2)	TKR	✓				
RECORD 1	THR	✓				
RECORD 3	TKR	✓				
RE-NOVATE	THR		✓	✓	✓	✓
RE-MODEL	TKR		✓	✓	✓	✓

Abbreviations: CRNM, clinically relevant not major; THR, total hip replacement; TKR, total knee replacement

There was variation in the definition of minor bleeding across the trials included in the main analysis. Studies were included in the analysis of minor bleeding if:

- Minor bleed events were reported where there was no overlap with CRNM events: A bleed that did not meet the criteria for major bleed *and* did not meet the criteria for a CRNM (ADVANCE-2 (21), ADVANCE-3 (20), RE-NOVATE (33) and RE-MODEL (32))
- Minor bleeds were defined as a bleed that did not meet the criteria for major bleed (RECORD 1 (29) and RECORD 3 (30)).

Use of intention-to-treat (ITT) and primary efficacy population numbers for treatment effect size calculations

Head-to-head comparisons from individual RCTs and pair-wise meta-analyses were calculated for all outcomes using the intention-to-treat (ITT) population analysis numbers where ITT population was defined as the number of participants randomised to treatment arms within a trial. Modified intention-to-treat (mITT = number actually receiving treatment at baseline) was used if the number randomised to treatment was not reported

However, since the asymptomatic DVT outcome can only be detected via an evaluable venogram, it was deemed clinically appropriate to use the population for which an evaluable venogram was available as the denominator in all the analyses involving this outcome. For most trials, the primary efficacy analysis population included patients with an evaluable venogram or with a confirmed, adjudicated symptomatic VTE event, so this was the denominator used (i.e. randomised patients with non-evaluable venograms or where venography was not conducted, were excluded).

Within the VTE clinical context, this approach is more appropriate than the ITT method as the latter would assume that the lack of an evaluable venogram represents a 'no event', therefore potentially underestimating the number of VTE events occurring within the ITT population. Since asymptomatic DVT is a component of 1) the any VTE composite outcome, 2) any DVT, and 3) major VTE, the individual trial and pair-wise meta-analysis effect size calculations for these outcomes used the primary efficacy population rather than the intention to treat (ITT) population. However, ITT analyses for these outcomes are presented for transparency in Appendix 15. The remaining efficacy and safety outcomes were analysed on an ITT basis.

A table of the primary efficacy analysis definitions used across the 15 RCTs is presented in Appendix 5. An adequate assessment of VTE was usually defined as an adjudicated readable venogram or adjudicated confirmed symptomatic event, although this was not explicitly stated in the rivaroxaban trials. The RE-NOVATE II study definition was based on the limited information available from a published conference abstract.The relevant numbers for the ITT and primary efficacy analysis populations are reported per outcome for the 15 RCTs in Table 33 and Table 34.

Some studies reported the percentage rate of events but did not report the actual number of patients with the event in each treatment arm. The number of events was therefore calculated from this using the number of patients who had this outcome measured at follow-up (rounded to nearest whole number).

Table 33: Data inputs for main analyses (head-to-head comparisons from individual trials, pair-wise meta-analyses, and adjusted indirect comparisons) by key outcome

							Number of events							
Study	**Surgery**	**Treatment arm**	**N (ITT)**	**N (PE VTE)**	**N (PE Major VTE)**	**N (PE DVT)**	**Major VTE**	**Any DVT**	**PE**	**VTE comp-osite**	**Major bleed**	**CRNM bleed**	**Minor bleed**	**Any bleed**
ADVANCE-3 (20)	THR	Apixaban 2.5 mg bd	2708	1949	2199	1944	10	22	3	27	22	109	184	313
		Enoxaparin 40 mg od	2699	1917	2195	1911	25	68	5	74	18	120	200	334
Huo 2010 (RE-NOVATE II) (34)	THR	Dabigatran etexilate 220 mg od	792	792	805	NR	18	NR	NR	61	14	NR	NR	NR
		Enoxaparin 40 mg od	785	785	794	NR	33	NR	NR	69	9	NR	NR	NR
Lassen 2002 (35)	THR	Enoxaparin 40 mg od	1154	NR	NR	918	NR	83	2	NR	32	NR	NR	NR
		Fondaparinux 2.5 mg od	1155	NR	NR	908	NR	36	2	NR	47	NR	NR	NR
ADVANCE-2 (21)	TKR	Apixaban 2.5 mg bd	1528	976	1195	971	13	142	4	147	9	44	51	104
		Enoxaparin 40 mg od	1529	997	1199	997	26	243	0	243	14	58	54	126
RECORD 1 (29)	THR	Enoxaparin 40 mg od	2275	1558	1678	1558	33	53	1	58	2	54	129	131
		Rivaroxaban 10 mg od	2266	1595	1686	1595	4	12	4	18	6	65	128	133
RECORD 3 (30)	TKR	Enoxaparin 40 mg od	1277	878	925	878	24	160	4	166	6	28	54	142
		Rivaroxaban 10 mg od	1254	824	908	824	9	79	0	79	7	33	53	160
RE-MODEL (32)	TKR	Dabigatran etexilate 220 mg od	694	503	506	503	13	182	0	183	10	40	60	110
		Enoxaparin 40 mg od	699	512	511	511	18	192	1	193	9	37	69	115
RE-NOVATE (33)	THR	Dabigatran etexilate 220 mg od	1157	880	909	874	28	46	5	53	23	48	70	141
		Enoxaparin 40 mg od	1162	897	917	894	36	57	3	60	18	40	74	132

Abbreviations: THR, total hip replacement; TKR, total knee replacement ; NR- data not reported; N (ITT) - denominator used in intent-to-treat analysis; N (PE DVT) - denominator used in primary efficacy population analysis of the Any DVT outcome; N (PE VTE) -denominator used in primary efficacy population analysis of the VTE composite outcome

Table 34: Data inputs for main analyses (head-to-head comparisons from individual trials, pair-wise meta-analyses, and adjusted indirect comparisons) available for the symptomatic DVT and asymptomatic DVT outcomes

Study	Indication	Treatment arm	N (ITT)	N (PE Asym)	Symptomatic DVT	Asymptomatic DVT	
ADVANCE-3 (20)	THR	Apixaban 2.5 mg bd	2708	1943	1	21	Reported
		Enoxaparin 40 mg od	2699	1907	5	63	
Lassen 2002 (35)	THR	Enoxaparin 40 mg od	1154	918	1	82	Calculated
		Fondaparinux 2.5 mg od	1155	908	3	33	
RE-NOVATE (33)	THR	Dabigatran etexilate 220 mg od	1157	874	6	40	Reported
		Enoxaparin 40 mg od	1162	894	1	56	
ADVANCE-2 (21)	TKR	Apixaban 2.5 mg bd	1528	968	3	139	Reported
		Enoxaparin 40 mg od	1529	990	7	236	
RE-MODEL (32)	TKR	Dabigatran etexilate 220 mg od	694	503	1	181	Reported
		Enoxaparin 40 mg od	699	511	8	184	

Abbreviations: THR, total hip replacement; TKR, total knee replacement; N (ITT) - denominator used in intent-to-treat analysis; N (PE Asym) -denominator used in primary efficacy population analysis of the asymptomatic DVT outcome
Reported asymptomatic DVT: Cases of DVT confirmed by venography or ultrasound with no prior clinical diagnosis of DVT.
Calculated asymptomatic DVT: Any DVT minus symptomatic DVT (defined as cases of DVT where the patient reported symptoms during the treatment period, which were subsequently confirmed by venography, ultrasound or other objective methods)

Statistical methods

Treatment estimates for effects on each outcome of interest were calculated for each drug and then pooled according to the UK licensed dose indicated for prophylaxis of VTE following orthopaedic (either THR or TKR) surgery. Pair-wise comparisons were conducted for TKR and THR populations respectively. Pair-wise comparisons allow for 1) apixaban 2.5mg bd to be compared with the standard UK practice (enoxaparin 40mg od) as well as 2) providing the basis for indirect comparisons of apixaban 2.5mg bd against the other treatments of interest listed in the NICE scope.

Wherever a pair-wise meta-analysis was required, this was conducted in Stata IC version 10.1 using the *metan* package SJ9_2: sbe24_3 (41, 42). Since all outcomes of interest were dichotomous, results were expressed as odds ratios (ORs) and pooled using the DerSimonian and Laird random effects method which takes account of between-study variance. ORs have superior statistical properties compared to other measures of risk in the conduct of indirect comparisons, since they allow for consistent estimation of risk differences across common comparator arms (43). The I^2 statistic was calculated to describe the proportion of variability (inconsistency) in effect estimates due to heterogeneity rather than chance (I^2 > 50% suggests substantial heterogeneity) (44).

Meta-analysis publication for apixaban for VTE prophylaxis

Although it was not part of the NICE scope to pool trial results across surgery populations, a a pooled analysis of the ADVANCE -2 (21) and ADVANCE-3 (20) RCTs was recently published as a conference abstract (45). The analysis is presented for information only and does not play any further role in the submission. It included 8,564 patients randomized in the ADVANCE-2 and 3 trials, and reported the following outcomes listed in Table 35 below.

Table 35: Main outcomes from the pooled analysis of ADVANCE-2 and 3 trials as reported by Raskob et al (2010) (45)

1. Major VTE in 23/ 3394 evaluable patients (0.68%) in the apixaban arm vs. 51/3394 (1.50%) in the enoxaparin arm (absolute risk difference [ARD, -0.76%, 95% CI, -1.23%, -0.30%).
2. Major bleeding in 31/4174 patients (0.74%) who received apixaban (18 occurred before the first dose) vs. 32/4167 patients (0.77%) given enoxaparin (ARD -0.02%, 95% CI, -0.40%, 0.35%).
3. Major bleeding at the surgical site in 26 apixaban vs. 27 enoxaparin patients (ARD -0.02%, 95% CI, -0.37%, 0.32%).
4. Major or clinically relevant non-major bleeding composite outcome in 182 apixaban (4.36%) vs. 206 enoxaparin patients (4.94%) (ARD -0.58%, 95% CI, -1.49%, 0.32%).
5. Major or clinically relevant non-major bleeding events at surgical site in 135 (3.23%) apixaban vs. 155 (3.72%) enoxaparin patients (ARD -0.49%, 95% CI, -1.27%, 0.30%).
6. Myocardial infarction or stroke during treatment or follow-up in 13 (0.31%) apixaban vs. 10 enoxaparin patients (0.24%) (ARD 0.07%, 95% CI, -0.15%, 0.30%).

5.6.2 Qualitative overview if meta-analysis inappropriate

N/A

5.6.3 Trials excluded from analysis

One study of rivaroxaban 10mg od (ODIXa-HIP Study (46)) in the THR population was excluded from the analyses in the submission , since the duration of treatment for both the

rivaroxaban and enoxparin 40mg od treatment arms was 5-9 days. This is shorter than the UK licensed dose duration recommended for either therapy in the THR population, and that recommended by NICE, and in particular is likely to result in an underestimate of the treatment effect of rivaroxaban 10mg od in this population.

5.7 Indirect and mixed treatment comparisons

In the absence of head to head RCT evidence for apixaban versus rivaroxaban, dabigatran, and fondaparinux, an adjusted indirect comparison with enoxaparin 40mg od was used to derive efficacy and safety effect sizes for these treatments. A mixed treatment comparison (MTC) was conducted for the outcomes where sufficient data was available to do this. Both approaches conducted separate analyses on the THR and TKR populations.

The adjusted indirect comparison found that compared with apixaban, dabigatran 220 mg od was:

- Significantly less efficacious in both THR and TKR in preventing all VTE plus all cause death; any DVT; asymptomatic DVT; symptomatic DVT (THR only). No statistically significant differences were found in symptomatic DVT (TKR); major VTE; or PE.
- Similar in the incidence of bleeding, as no statistically significant differences were found for any of the outcomes, although the majority of these differences (apart from minor bleeding in TKR patients) favoured apixaban.

The adjusted indirect comparison of apixaban with rivaroxaban showed :

- No statistically significant difference in preventing the composite outcome of all VTE plus all cause death, any DVT and major VTE in patients undergoing THR and TKR. There was no statistically significant difference in the prevention of PE events in the THR population, but in TKR patients the PE rate was significantly higher for apixaban, although the number of events was small.
- No statistically significant difference in the incidence of bleeding events (any, major, CRNM and minor) in patients undergoing THR and TKR.

The adjusted indirect comparison of apixaban with fondaparinux showed:

- No statistically significant difference in preventing any DVT, asymptomatic DVT, symptomatic DVT, and PE in patients undergoing THR.
- No statistically significant difference in the incidence of major bleeding in patients undergoing THR (no other bleeding outcomes reported).

No TKR fondaparinux vs. enoxaparin 40 od mg RCT was identified for inclusion in the adjusted indirect comparison

5.7.1 Identification of studies

The following indirect comparisons have been conducted:

- An adjusted indirect comparison of apixaban 2.5 mg bd versus other oral anticoagulant treatments of interest with enoxaparin 40 mg od as the common comparator for TKR or THR.
- A mixed treatment comparison (MTC) was also undertaken for both surgery populations and the methodology and results for this are presented in Appendix 16.

The search methods used to identify trials for use in the indirect comparison and MTC have been described in Section 5.1, and the relevant literature search strategies are presented in Appendices 2 and 4.The study population, treatments of interest and study design eligibility criteria are documented in Table 4, section 5.2. Figure 1 in section 5.2.2 displays the literature search results.

5.7.2 Study selection, and methodology, quality assessment and results of relevant RCTs

The 15 head-to-head RCTs included in the adjusted indirect comparison analyses were described in section 5.6 above. The apixaban, rivaroxaban, dabigatran, and fondaparinux trials all used enoxaparin to evaluate their efficacy and safety in VTE prophylaxis, meaning that enoxaparin was the common comparator in all the adjusted indirect comparison analyses.

As with the pair-wise comparisons reported in section 5.6 above, adjusted indirect comparisons were conducted vs. the UK dose of enoxaparin, the US dose of enoxaparin, and the pooled UK and US doses (see section 5.6 and Table 29 for RCTs pooled). The latter two analyses are presented in Appendix 15. The UK enoxaparin dose comparison is presented below.

Eight RCTs comparing treatments of interest with enoxaparin 40 mg od in the THR and TKR populations (see **Error! Not a valid bookmark self-reference.** and Figure 7) were included in this adjusted indirect comparison. As described in section 5.6 above, RECORD 2 (31) was only included in the adjusted indirect comparison as a sensitivity analysis (see Appendix 15).

Figure 6: Diagram of THR RCTs included in the main (UK license dose) adjusted indirect comparison analyses (common comparator is enoxaparin 40 mg od)

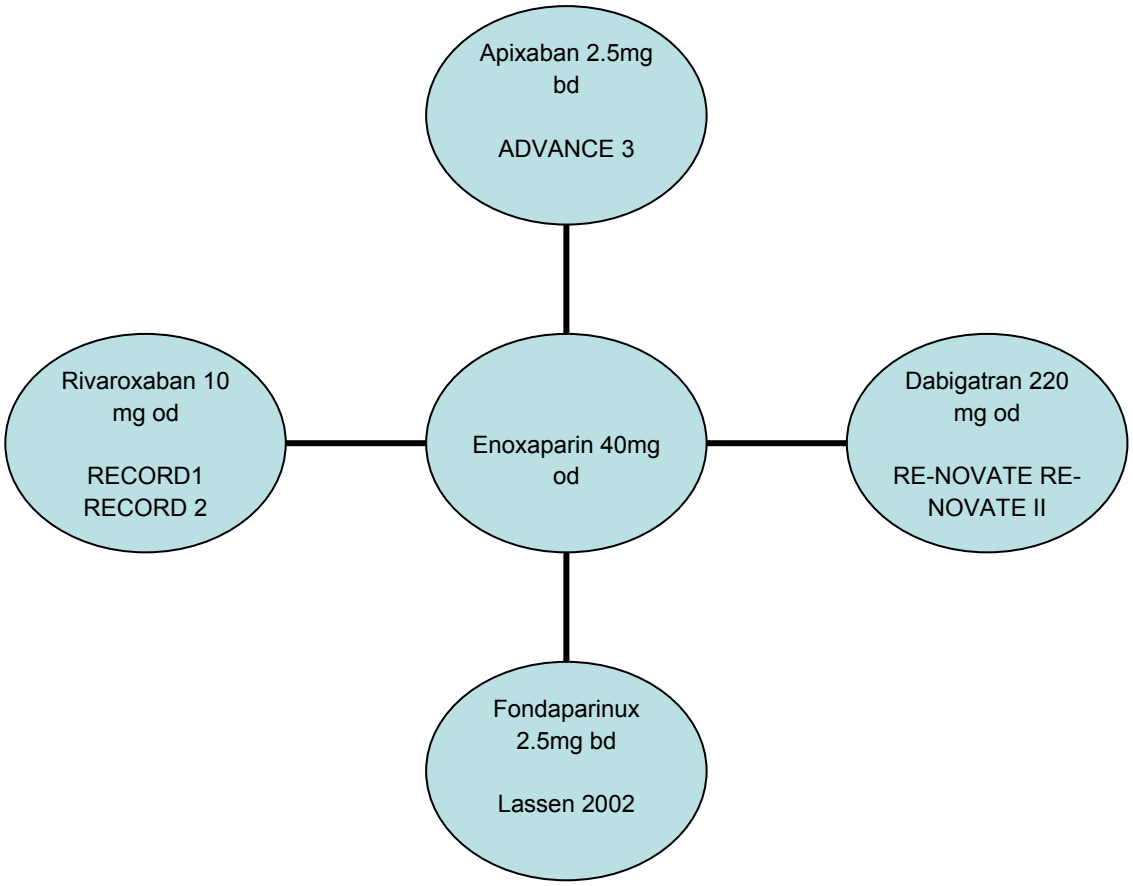
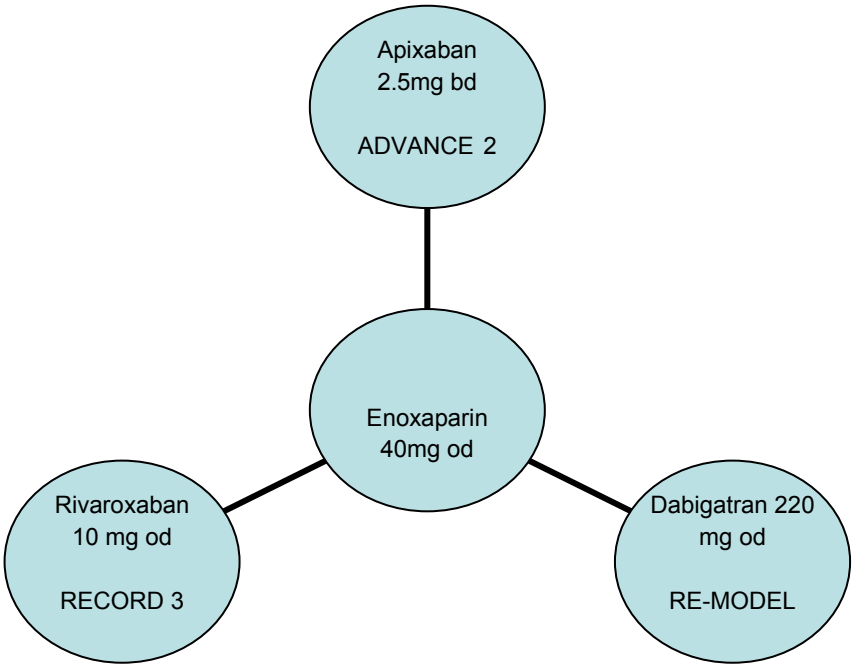


Figure 7: Diagram of TKR RCTs included in the main (UK license dose) adjusted indirect comparison analyses (common comparator is enoxaparin 40 mg od)



5.7.3 Summary of trials used to inform the comparison

Key outcomes of trials included in the main (UK dose) individual head-to-head comparisons, pair-wise meta-analyses and adjusted indirect comparisons are summarised in Table 29 in section 5.6. A summary of the numerical data available for each outcome from each of the 15 studies is provided in Table 33 and Table 34 in section 5.6. As discussed in section 5.6 above, the ITT population analysis was used for all outcomes apart from the four involving asymptomatic DVT for which the primary efficacy population numbers were used instead. However, ITT analyses were also run for these 4 outcomes and are presented in Appendix 15.

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

See Table 33 and Table 34 in section 5.6.

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

Both an adjusted (Bucher) indirect comparison and a mixed treatment comparison (MTC) were undertaken to determine the relative efficacy of apixaban vs. enoxaparin and other relevant treatments at UK licensed doses. The MTC methods and code are presented in Appendix 16.

The indirect comparisons between apixaban (A) and other treatments of interest (B) via a common comparator (C) were made using the Bucher method (47) and the pooled odds ratios produced from the direct meta-analysis and individual head-to-head RCT

comparisons. This method does not break the randomisation of treatments being compared indirectly.

The (indirect) OR between apixaban and the treatment of interest is given by

$$\log(OR_{AvB}) = \log(OR_{AvC}) - \log(OR_{BvC})$$

With standard error given by

$$SE[\log(OR_{AvB})] = \sqrt{SE[\log(OR_{AvC})]^2 + SE[\log(OR_{BvC})]^2}$$

5.7.6 Please present the results of the analysis

The adjusted indirect comparison is regarded as the most appropriate analysis for informing the clinical efficacy and safety of apixaban versus relevant treatment comparators in this submission, since the MTC results were inconsistent with some of the head-to-head RCT data. However, the MTC results are presented in Appendix 16 for comparison.

Table 36: VTE composite (primary efficacy population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
ADVANCE-3 (20) RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; N/A, non applicable

Table 37: Any DVT event (primary efficacy population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.31 (0.191-0.504)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.531 (0.423-0.668)
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	0.22 (0.11-0.4)	RECORD 3 (30)	Rivaroxaban 10 mg od	0.476 (0.357-0.635)
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	0.816 (0.547-1.217)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.942 (0.73-1.216)
Lassen 2002 (35)	Fondaparinux 2.5 mg od	0.415 (0.278-0.621)	N/A	Fondaparinux 2.5 mg od	N/A
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	0.709 (0.304-1.652)	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	0.895 (0.621-1.294)
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	2.63 (1.402-4.931)	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	1.772 (1.258-2.498)
ADVANCE-3 (20) Lassen 2002 (35)	Fondaparinux 2.5 mg od	1.339 (0.713-2.514)	N/A	Fondaparinux 2.5 mg od	N/A
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.318 (0.197-0.512)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.6 (0.498-0.724)
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	0.22 (0.12-0.41)	RECORD 3 (30)	Rivaroxaban 10 mg od	0.526 (0.409-0.677)
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	0.825 (0.566-1.204)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.963 (0.82-1.131)
Lassen 2002 (35)	Fondaparinux 2.5 mg od	0.439 (0.3-0.641)	N/A	Fondaparinux 2.5 mg od	N/A

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; N/A, non applicable

Table 38: Asymptomatic DVT (primary efficacy population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.32 (0.194-0.526)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.536 (0.425-0.675)
N/A	Rivaroxaban 10 mg od Excluding RECORD 2	N/A	N/A	Rivaroxaban 10 mg od	N/A
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	0.718 (0.473-1.089)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.999 (0.773-1.291)
Lassen 2002 (35)	Fondaparinux 2.5 mg od	0.385 (0.254-0.582)	N/A	Fondaparinux 2.5 mg od	N/A
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
N/A	Rivaroxaban 10 mg od Excluding RECORD 2	N/A	N/A	Rivaroxaban 10 mg od	N/A
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	2.244 (1.172-4.297)	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	1.865 (1.32-2.635)
ADVANCE-3 (20) Lassen 2002 (35)	Fondaparinux 2.5 mg od	1.202 (0.629-2.299)	N/A	Fondaparinux 2.5 mg od	N/A
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.327 (0.2-0.534)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.602 (0.498-0.728)
N/A	Rivaroxaban 10 mg od Excluding RECORD 2	N/A	N/A	Rivaroxaban 10 mg od	N/A
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	0.731 (0.492-1.084)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.999 (0.848-1.178)
Lassen 2002 (35)	Fondaparinux 2.5 mg od	0.407 (0.275-0.603)	N/A	Fondaparinux 2.5 mg od	N/A

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; N/A, non applicable

Table 39: Symptomatic DVT (ITT population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.199 (0.023-1.705)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.428 (0.11-1.657)
N/A	Rivaroxaban 10 mg od Excluding RECORD 2	N/A	N/A	Rivaroxaban 10 mg od	N/A
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	6.052 (0.727-50.349)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.125 (0.016-0.999)
Lassen 2002 (35)	Fondaparinux 2.5 mg od	3.003 (0.312-28.908)	N/A	Fondaparinux 2.5 mg od	N/A
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
N/A	Rivaroxaban 10 mg od Excluding RECORD 2	N/A	N/A	Rivaroxaban 10 mg od	N/A
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	30.407 (1.489-621.101)	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.291 (0.024-3.492)
ADVANCE-3 (20) Lassen 2002 (35)	Fondaparinux 2.5 mg od	15.085 (0.665-342.024)	N/A	Fondaparinux 2.5 mg od	N/A
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.199 (0.023-1.705)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.429 (0.111-1.655)
N/A	Rivaroxaban 10 mg od Excluding RECORD 2	N/A	N/A	Rivaroxaban 10 mg od	N/A
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	6.026 (0.727-49.974)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.126 (0.016-1.004)
Lassen 2002 (35)	Fondaparinux 2.5 mg od	2.997 (0.312-28.773)	N/A	Fondaparinux 2.5 mg od	N/A

Apixaban. BMS and Pfizer

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

Table 40: Major VTE (primary efficacy population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
ADVANCE-3 (20) RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]

Apixaban. BMS and Pfizer

RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; N/A, non applicable

Table 41: PE (ITT population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
Lassen 2002 (35)	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
ADVANCE-3 (20) Lassen 2002 (35)	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33)	Dabigatran etexilate	[redacted]	RE-MODEL (32)	Dabigatran etexilate	[redacted]

Apixaban. BMS and Pfizer

	220 mg od			220 mg od	
Lassen 2002 (35)	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

Table 42: Any bleeding (ITT population analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]

Apixaban. BMS and Pfizer

	Excluding RECORD 2				
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

Table 43: Major bleeding (ITT population analysis)

Total hip replacement (THR)			**Total knee replacement (TKR)**		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
Lassen 2002 (35)	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
ADVANCE-3 (20) RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
ADVANCE-3 (20)	Fondaparinux 2.5 mg	[redacted]	N/A	Fondaparinux 2.5 mg	[redacted]

Apixaban. BMS and Pfizer

Lassen 2002 (35)	od			od	
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33) Huo 2010 (RE-NOVATE II) (34)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
Lassen 2002 (35)	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

Table 44: CRNM bleeding (ITT population analysis)

Total hip replacement (THR)			**Total knee replacement (TKR)**		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]

Apixaban. BMS and Pfizer

Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	[redacted]	ADVANCE-2 (21)	Apixaban 2.5 mg bd	[redacted]
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	[redacted]	RECORD 3 (30)	Rivaroxaban 10 mg od	[redacted]
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	[redacted]	RE-MODEL (32)	Dabigatran etexilate 220 mg od	[redacted]
N/A	Fondaparinux 2.5 mg od	[redacted]	N/A	Fondaparinux 2.5 mg od	[redacted]

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

Table 45: Minor bleeding (ITT analysis)

Total hip replacement (THR)			Total knee replacement (TKR)		
Studies	**Treatments**	**Results**	**Studies**	**Treatments**	**Results**
Direct Odds Ratio (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.91 (0.74-1.12)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.94 (0.64-1.39)
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	1 (0.77-1.28)	RECORD 3 (30)	Rivaroxaban 10 mg od	1 (0.68-1.47)
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	0.95 (0.68-1.33)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.86 (0.6-1.24)
N/A	Fondaparinux 2.5 mg od	N/A	N/A	Fondaparinux 2.5 mg od	N/A
Indirect Odds Ratio (95% CI) vs. Apixaban 2.5 mg bd (Via Enoxaparin 40 mg od pooled)					
ADVANCE-3 (20) RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	1.099 (0.787-1.534)	ADVANCE-2 (21) RECORD 3 (30)	Rivaroxaban 10 mg od	1.064 (0.617-1.834)
ADVANCE-3 (20) RE-NOVATE (33)	Dabigatran etexilate 220 mg od	1.044 (0.705-1.547)	ADVANCE-2 (21) RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.915 (0.54-1.549)

Apixaban. BMS and Pfizer

N/A	Fondaparinux 2.5 mg od	N/A	N/A	Fondaparinux 2.5 mg od	N/A
Direct Relative Risk (95% CI) vs. Enoxaparin 40 mg od pooled					
ADVANCE-3 (20)	Apixaban 2.5 mg bd	0.92 (0.76-1.11)	ADVANCE-2 (21)	Apixaban 2.5 mg bd	0.95 (0.65-1.38)
RECORD 1 (29)	Rivaroxaban 10 mg od Excluding RECORD 2	1 (0.79-1.26)	RECORD 3 (30)	Rivaroxaban 10 mg od	1 (0.69-1.45)
RE-NOVATE (33)	Dabigatran etexilate 220 mg od	0.95 (0.69-1.3)	RE-MODEL (32)	Dabigatran etexilate 220 mg od	0.88 (0.63-1.22)
N/A	Fondaparinux 2.5 mg od	N/A	N/A	Fondaparinux 2.5 mg od	N/A

Abbreviations: bd, twice daily; od, once daily; CI, confidence interval; ITT, intention-to-treat; N/A, non applicable

Head-to-head and adjusted indirect comparison results: Efficacy

Apixaban comparison with enoxaparin

- [redacted] removed' academic / commercial in confidence information removed'
- In both RCT head-to-head comparisons with enoxaparin 40 mg od (ADVANCE-3 (20); ADVANCE-2 (21)), apixaban 2.5mg bd had a significantly lower incidence of:
  - any DVT (THR: OR 0.31, 95% CI 0.191-0.504, p<0.0001; TKR: OR 0.531, 95% CI 0.423-0.668, p<0.00001),
  - asymptomatic DVT (THR: OR 0.32, 95%CI 0.194-0.526, p<0.00001;TKR: OR 0.536, 95% CI 0.425-0.675, p<0.00001), and
- [redacted] removed' academic / commercial in confidence information removed'

  and no statistically significant difference in the incidence of :
  - symptomatic DVT (THR: OR 0.199, 95% CI 0.023-1.705, p=0.14; TKR: OR 0.428, 95% CI 0.11-1.657, p=0.22) and
    - [redacted] removed' academic / commercial in confidence information removed'

Adjusted indirect comparison of apixaban with dabigatran

- [redacted] removed' academic / commercial in confidence information removed'
- Dabigatran 220mg od was significantly less efficacious than apixaban 2.5mg bd for the prevention of:
  - any DVT (THR: OR 2.63 95% CI 1.402-4.931, p=0.003; TKR: OR 1.772, 95% CI 1.258-2.498, p=0.001)
  - asymptomatic DVT (THR: OR 2.244, 95% CI 1.172-4.297, p=0.015; TKR: OR 1.865, 95% CI 1.32-2.635, p=0.0004), and
  - symptomatic DVT in THR (OR 30.407, 95% CI 1.489, 621.101, p=0.027)

  and not statistically different to apixaban 2.5mg bd for the prevention of:
  - [redacted] removed' academic / commercial in confidence information removed'
  - [redacted] removed' academic / commercial in confidence information removed'
  - symptomatic DVT in TKR(OR 0.291, 95% CI 0.024-3.492, p=0.33)

Adjusted indirect comparison of apixaban with rivaroxaban

- [redacted] removed' academic / commercial in confidence information removed'
- There were no statistically significant differences between apixaban 2.5mg bd and rivaroxaban 10mg od in preventing:
  - any DVT (THR: OR 0.709, 95% CI 0.304-1.652, p=0.43; TKR OR 0.895, 95% CI 0.621-1.294, p=0.56)
  - [redacted] removed' academic / commercial in confidence information removed'
  - [redacted] removed' academic / commercial in confidence information removed'
- In the TKR population, rivaroxaban 10mg od compared with apixaban 2.5mg bd had a significantly lower incidence of :
- [redacted] removed' academic / commercial in confidence information removed'

Note that all PE results from the adjusted indirect comparisons are limited by the very small number of events in each treatment arm. For example, in the THR population there were 3/2708 (0.11%) PEs in the apixaban 2.5 mg bd treatment group and 4/2266 (0.18%) in the rivaroxaban 10 mg od group. In the TKR population, there were 4/1528 (0.26%) PEs in the apixaban 2.5 mg bd arm and 0/1254 in the rivaroxaban 10 mg od arm (Table 33). None of the trials included in the adjusted indirect comparisons were powered to evaluate the PE outcome.

Adjusted indirect comparison with fondaparinux

- In the THR population, there were no statistically significant differences between apixaban 2.5mg bd and fondaparinux 2.5mg od on the available VTE outcomes:
  - any DVT (OR 1.339, 95% CI 0.713-2.514, p=0.36)
  - asymptomatic DVT (OR 1.202, 95% CI 0.629-2.299, p=0.58)
  - symptomatic DVT (OR 15.085, 95% CI 0.665-342.024, p=0.088)
  - [redacted] removed' academic / commercial in confidence information removed'
- No fondaparinux 2.5mg od versus enoxaparin 40mg od RCT was available in the TKR population, hence an adjusted indirect comparison was not feasible.

Head-to-head and adjusted indirect comparison results: Safety

Head-to-head comparison with enoxaparin

- [redacted] removed' academic / commercial in confidence information removed'
- In the RCT head-to-head comparisons for the THR (ADVANCE-3 (20)) and TKR (ADVANCE-2 (21)) populations, there were no statistically significant differences between apixaban 2.5mg bd and enoxaparin 40mg od in the incidence of:

- [redacted] removed' academic / commercial in confidence information removed'
- [redacted] removed' academic / commercial in confidence information removed'

  - minor bleeding events (THR: OR 0.91, 95% CI 0.74-1.12, p=0.37; TKR: OR 0.94, 95% CI 0.64-1.39, p=0.75).

Adjusted indirect comparison with dabigatran

- [redacted] removed' academic / commercial in confidence information removed'
- In the THR and TKR populations, there were no statistically significant differences between apixaban 2.5mg bd and dabigatran 220mg od in the incidence of:
- [redacted] removed' academic / commercial in confidence information removed'
- [redacted] removed' academic / commercial in confidence information removed'
  - minor bleeding events (THR: OR 1.044, 95% CI 0.705-1.547, p=0.83; TKR: OR 0.915, 95% CI 0.54-1.549, p=0.74)

Adjusted indirect comparison with rivaroxaban

- [redacted] removed' academic / commercial in confidence information removed'
- In the THR and TKR populations, there were no statistically significant differences between apixaban 2.5mg bd and rivaroxaban 10mg od in the incidence of:
- [redacted] removed' academic / commercial in confidence information removed'
- [redacted] removed' academic / commercial in confidence information removed'
  - minor bleeding events (THR: OR 1.099, 95% CI 0.787-1.534, p=0.58; TKR: OR 1.064, 95% CI 0.617-1.834, p=0.82)

Adjusted indirect comparison with fondaparinux

- [redacted] removed' academic / commercial in confidence information removed' No other bleeding outcomes were available for this indirect comparison. No fondaparinux 2.5 mg od versus enoxaparin 40mg od RCT was available in the TKR population, hence an adjusted indirect comparison was not feasible.

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

Appendix 15 presents the results from the single trial head-to-head comparisons, the pair-wise meta-analyses and the adjusted indirect comparisons vs. enoxaparin 30 mg bd on its own and combined enoxaparin (40mg od + 30mg bd) respectively. For pair-wise meta-analyses of apixaban 2.5mg bd or comparator trials (see Table 29, section 5.6) , I^2 statistics were calculated (where sufficient trials were available) to describe the proportion of variability (inconsistency) in effect estimates due to heterogeneity rather than chance (I^2 > 50% suggests substantial heterogeneity) (44). Calculation of the I^2 statistic requires the pooling of data from at least two trials. Where only one RCT was available per surgery population for apixaban 2.5mg bd and other treatments versus enoxaparin 40mg od or enoxaparin 30mg bd respectively, an I^2 statistic could not be calculated for the individual treatments. For this reason many of the forest plots depicting treatment comparisons with enoxaparin 40 mg od or 30 mg bd respectively do not contain I^2 statistics, meaning that a statistical exploration of heterogeneity was not possible.

For the combined enoxaparin dose (40mg od + 30mg bd) group, pooling results from more than one RCT was possible for most treatments, particularly in the TKR population (see Table 29), and so more I^2 values were reported in the forest plots. However, in this scenario, any observed substantial between-study heterogeneity (i.e.where I^2 is equal to or more than 50%), may be 1) due to variation in the treatment effect caused by the different doses of enoxaparin, or 2) to study methods/population characteristics that varied between the UK and US enoxaparin dose trials, or 3) to a combination of these two factors.

One way of exploring the impact of the different enoxaparin doses on treatment outcomes is to compare the combined enoxaparin (40mg od + 30mg bd) analysis of apixaban 2.5 mg bd, and comparator treatments with the respective enoxaparin 40 mg od and 30 mg bd analyses. This allows for an investigation of across-dose variation in VTE prevention efficacy and safety compared to the enoxaparin 40mg od dose analyses presented in Section 5.7 above. The enoxaparin dose-group sensitivity analyses enable exploration of the variation in VTE prevention efficacy and safety between apixaban 2.5 mg bd and the other comparator treatments across the individual and combined UK and US licensed enoxaparin doses.

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

As discussed in section 5.6 above, RECORD 2 (31) was excluded from the main enoxaparin 40 mg od analyses reported in section 5.7 since it contained a shorter duration of enoxaparin 40 mg od treatment (10-14 days), while rivaroxaban 10mg od was administered for 31-39 days. However, in order to assess the variation in treatment effect contributed by this study, the relevant direct pair-wise and adjusted indirect comparisons which include a pooling of the RECORD 1 (29) and RECORD 2 (31) results are presented in Appendix 15 as a sensitivity analysis.

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

Adjusted (Bucher) indirect comparison and mixed treatment comparison (MTC) analyses were undertaken to determine the relative efficacy of apixaban vs. enoxaparin and other relevant treatments at UK licensed doses. The MTC results were found to have the following methodological characteristics:

- The 1) apixaban 2.5mg bd vs. enoxaparin 40mg od and 2) rivaroxaban 10mg od vs. enoxaparin 40 mg od results were inconsistent with the direct head-to-head RCT comparisons of these treatments on the primary composite endpoint (VTE plus all-cause death) and some of the secondary outcomes.
- Wider credibility intervals around treatment differences on specific outcomes compared to narrower confidence intervals observed in the adjusted indirect comparisons for the same outcomes.
- Inconsistent findings between the MTC and the adjusted indirect comparison for apixaban 2.5 mg bd vs. dabigatran 220 mg od on the VTE composite, any DVT, and asymptomatic DVT outcomes (both orthopaedic surgery populations) due to the wider credibility intervals in the MTC.

The reason for the inconsistent results and wider credibility intervals may be due to the large number of trials contributing to the enoxaparin 40mg od node within the MTC network in addition to the trial sub-set included in the adjusted indirect comparison. The former tended to 1) be older, 2) have fewer study quality criteria reported (Appendix 16), 3) have smaller sample sizes, and 4) compare enoxaparin 40mg od against treatments not within the NICE STA scope for apixaban (Appendix 16, table 34), compared to the adjusted indirect comparison sub-set. These factors could have contributed to a lack of precision and an increase in uncertainty (i.e. wider credibility intervals) in the relative treatment effects for enoxaparin 40 mg od observed in the MTC results, despite the apparent increase in power (i.e. more eligible studies) afforded by the MTC study inclusion criteria.

Review of the recently published full version of the NICE Clinical Guideline Number 92, Venous Thromboembolism: Reducing the risk (48) indicated that the guideline developers only conducted MTCs on 3 VTE outcomes (any DVT, symptomatic PE, and any bleeding). The any bleeding MTC included 5 distinct surgery populations (including THR and TKR) in order to build a viable network, since the data were too sparse within any one surgery population. There was also insufficient data to carry out an MTC for symptomatic PE in the TKR population.

The MTCs in NICE Clinical Guideline Number 92 (48) also included many pharmacological and non-pharmacological interventions outside the NICE STA scope for apixaban, which increased the power of the network analyses in the guideline. The experience from the NICE Clinical Guideline Number 92, with its wider scope suggests that the MTC results in this submission may be limited by:

- The relatively small size of respective TKR and THR evidence networks relevant to the NICE apixaban STA scope
- Fewer treatments relevant to the NICE apixaban STA scope in these networks

In addition, low or zero event rates for some outcomes of interest made MTC analysis unfeasible in our submission, e.g. PE, symptomatic DVT, and major VTE.

The adjusted indirect comparison necessarily restricted the number of studies for inclusion to those possessing a common comparator (enoxaparin 40 mg od in the main analysis), which may have allowed for more precision in the relative treatment effect estimates of interest to the submission in this instance. This sub-set of studies tended to report and fulfil more study quality criteria, have larger patient numbers (all in excess of 600 patients randomised per arm), and reported similar outcome definitions and measures (See Table 33 and Table 34, and Appendices 3 and 5), although there was inconsistency across the comparators of interest on some bleeding outcomes (see Table 31 and Table 32).

For these reasons the adjusted indirect comparison, for which results on all outcomes of interest were available, is regarded as the most appropriate analysis for informing the clinical efficacy and safety of apixaban versus relevant treatment comparators in this submission. However, the results from the MTC are presented in Appendix 16 for comparison. The results of the adjusted indirect comparison and MTC are in broad agreement, apart from the inconsistency in the apixaban 2.5 mg bd vs. dabigatran 220 mg od results on the VTE outcomes mentioned above.

5.8 Non-RCT evidence

A systematic literature search was conducted to identify relevant non-RCTs on apixaban from the published literature, however none were identified (the literature search is described in Sections 5.1 and 5.2 and Appendix 6). Therefore, non-RCT evidence was not considered.

5.9 Adverse events

Summary of RCTs

ADVANCE 2

- Observed bleeding event rates were numerically lower for apixaban-treated subjects than enoxaparin-treated TKR subjects
    - Major or clinically relevant non-major bleeding occurred in 4% of patients receiving apixaban and 5% treated with enoxaparin (p=0.09)
    - Major bleeding events were infrequent, and event rates were numerically lower in the apixaban group (0.6%) than in the enoxaparin group (0.9%) (p=0.30)
- The overall safety profile (AEs, SAEs, discontinuation due to AEs) was similar for apixaban and enoxaparin

ADVANCE 3

- Observed bleeding event rates were similar for apixaban-treated and enoxaparin-treated THR subjects
    - Major or clinically relevant non-major bleeding occurred in 4.8% of patients receiving apixaban and 5% treated with enoxaparin (p=0.72)
    - Major bleeding events occurred in 0.8% apixaban-treated patients and 0.7% enoxaparin-treated patients (p=0.54)
- The overall safety profile (AEs, SAEs, discontinuation due to AEs) was similar for apixaban and enoxaparin

ADVANCE 1

- Apixaban was associated with lower rates of clinically relevant bleeding than enoxaparin in TKR patients
    - The composite incidence of major bleeding and clinically relevant non-major bleeding was 2.9% with apixaban and 4.3% with enoxaparin (p=0.03)
    - Major bleeding events occurred in 0.7% apixaban-treated patients and 1.4% enoxaparin treated patients (p=0.053)
- The observed rates for AEs, SAEs, all-cause death and discontinuations due to AEs were similar for apixaban and enoxaparin

The identification of clinical evidence is described in Sections 5.1 and 5.2. All trials relevant to this submission are listed in Table 6 in Section 5.2.4 The methodology, critical appraisal and efficacy results of relevant trials are presented in Sections 5.3, 5.4 and 5.5 respectively, safety results are presented here.

Analysis periods for all studies

Analysis periods for safety endpoints were:

- Treatment period – includes measurements or events with onset from first dose of double-blind study drug (pre- or post-surgery) through:
    - 2 days after the last dose of double-blind study drug when summarising bleeding endpoints, bleeding-related serious or non-serious AEs, myocardial infarction (MI), stroke, or thrombocytopaenia endpoints, and laboratory measurements
    - 30 days after the last dose of double-blind study drug when summarising deaths as an outcome of a SAE and SAEs
    - 2 days (for non-serious AEs) or 30 days (for SAEs) after the last dose of double-blind study drug when summarising liver function test (LFT) related AEs or neurologic AEs and overall AEs
- Follow-up Period – the period that started after the treatment period and ended through 60 days after discontinuation of the double-blind study drug.

5.9.1 ADVANCE 2

Safety

- Bleeding rates (both major and clinically relevant non-major [CRNM]) were numerically lower with apixaban compared with enoxaparin, although not statistically significant.
- Apixaban was generally well tolerated, with no unexpected safety signals arising from the data.

Primary safety endpoints

There were no fatal bleeding events in either arm of this trial. Major bleeding events were infrequent, and event rates were numerically lower in the apixaban group than in the enoxaparin group Of nine major bleeding events with apixaban, five occurred before and four after the first dose was administered. Observed event rates for clinically relevant non-major bleeding, the composite of major or clinically relevant non-major bleeding endpoint, and any bleeding (adjudicated or reported by the investigator), were also numerically lower in the apixaban group than in the enoxaparin group (

Table 46

Table 46: Summary of bleeding events that occurred in the treatment period of Advance 2–treated subjects

Outcome	Apixaban 2.5mg bd N = 1501		Enoxaparin 40mg od N = 1508		Absolute risk difference (95% CI)	P Value
	n (%)	*95% CI*	*n (%)*	*95% CI*		
Adjudicated major bleeding events[†]	9 (0.6)	0.30–1.16	14 (0.9)	0.54–1.57	–0.33 (–0.95 to 0.29)	0.3014
Diagnostic criteria for major bleeding event						
Clinically overt bleeding	8 (0.5)		14 (0.9)			
Haemoglobin drop of ≥ 20g/L within 24hr	8 (0.5)		9 (0.6)			
Transfusion of ≥ 2 units of packed RBCs	5 (0.3)		9 (0.6)			
Bleeding at a critical site						
Intracranial, intraspinal, intraocular, pericardial, intramuscular, retroperitoneal location, or fatal	0		0			
Haemarthrosis	1 (0.1)		2 (0.1)			
Other	1 (0.1)		0			
Bleeding at surgical site						
Total	8 (0.5)		11 (0.7)			
Haematoma	1 (0.1)		0			
Haemarthrosis	0		4 (0.3)			
Haemarthrosis with intervention	1 (0.1)		0			
Bruising or ecchymosis	1 (0.1)		1 (0.1)			
Other surgical site bleeds	5 (0.3)		6 (0.4)			
Nonsurgical bleeding events						
Total	1 (0.1)		3 (0.2)			
Bruising or ecchymosis	0		1 (0.1)			
Gastrointestinal	1 (0.1)		2 (0.1)			
Adjudicated clinically relevant non-major bleeding events[‡]	44 (2.9)	2.19–3.93	58 (3.8)	2.98–4.95	–0.91 (–2.20 to 0.38)	0.1668
Bleeding at surgical site						
Total	32 (2.1)		44 (2.9)			
Haematoma	13 (0.9)		11 (0.7)			
Haemarthrosis	3 (0.2)		3 (0.2)			
Haemarthrosis with intervention	1 (0.1)		0			
Bruising or ecchymosis	6 (0.4)		10 (0.7)			
Other	9 (0.6)		20 (1.3)			
Nonsurgical bleeding events						
Total	12 (0.8)		16 (1.1)			
Haematoma	3 (0.2)		3 (0.2)			
Bruising or ecchymosis	3 (0.2)		3 (0.2)			
Epistaxis	1 (0.1)		2 (0.1)			
Gastrointestinal	2 (0.1)		2 (0.1)			
Haematuria	2 (0.1)		5 (0.3)			
Haemoptysis	1 (0.1)		1 (0.1)			
Adjudicated major or clinically relevant non-major bleeding events[§]	53 (3.5)	2.71–4.6	72 (4.8)	3.81–5.98	–1.24 (–2.66 to 0.18)	0.0881
Minor bleeding events	51 (3.4)		54 (3.6)			
All bleeding events	104 (6.9)	5.75–8.34	126 (8.4)	7.06–9.87	–1.39 (–3.29 to 0.51)	0.1412

Abbreviations: bd, twice daily; CI, confidence interval; od, once daily; RBC, red blood cells. [†]Five patients in the apixaban group and five in the enoxaparin group had major bleeding events that occurred before the first post-surgery dose of study drug. [‡]Seven patients in the apixaban group and 11 in the enoxaparin group had clinically relevant non-major bleeding events that occurred before the first post-surgery dose of study drug. [§]12 patients in the apixaban group and 16 in the enoxaparin group had major or clinically relevant non-major bleeding events that occurred before the first post-surgery dose of study drug.

[redacted] removed' academic / commercial in confidence information removed'

Other safety measures

Adverse events

The incidence of AEs during the treatment period was similar between the apixaban and enoxaparin groups (academic [redacted] removed' academic / commercial in confidence information removed'

Table 47).[redacted] removed' academic / commercial in confidence information removed'

Table 47: Adverse events reported by investigators during treatment (not including study endpoints)

Adverse events **Number (%) subjects**	**Apixaban 2.5mg bd** **(n = 1501)**	**Enoxaparin 40mg od** **(n = 1508)**
AE	786 (52%)	836 (55%)
AEs occurring in ≥ 5% of patients		
Nausea	102 (7%)	120 (8%)
Vomiting	77 (5%)	88 (6%)
Constipation	73 (5%)	77 (5%)
SAE	72 (5%)	88 (6%)
Drug related SAE	16 (1%)	17 (1%)
Drug related AE	207 (14%)	214 (14%)
Discontinuations due to AE	40 (3%)	44 (3%)
Bleeding AE	90 (6%)	112 (7%)
Deaths	2 (0.1%)	0

Abbreviations: AE, adverse event; bd, twice daily; od, once daily; SAE, serious adverse event

Bleeding-related AEs

The incidence of bleeding-related AEs with onset during the treatment period was similar in both groups (apixaban 6.0%, enoxaparin 7.4%).[redacted] removed' academic / commercial in confidence information removed'

[redacted] removed' academic / commercial in confidence information removed'

Deaths

Two deaths occurred in the treatment period, both in the apixaban group. One of the deaths was considered by the investigator to be unrelated to study drug. The adjudicated cause of death of the other subject was "query infection and hepatitis leading to aspiration pneumonia and multi-organ failure".

In the follow-up period two deaths were reported; suspected MI and/or PE in one subject in the apixaban group and a fatal bleeding event in one subject in the enoxaparin group. The deaths were considered by the investigators to be unrelated to the study drug.

Serious adverse events

SAEs were reported in 72 (4.8%) subjects in the apixaban group and 88 (5.8%) subjects in the enoxaparin group (academic [redacted] removed' academic / commercial in confidence information removed'

Table 47).[redacted] removed' academic / commercial in confidence information removed'

DVT was also an efficacy endpoint in this study, the results of the efficacy analyses are described above in Section 5.5. [redacted] removed' academic / commercial in confidence information removed'

In the follow-up period the incidence of SAEs was similar in the apixaban (0.9%) and enoxaparin (1.0%) groups.

Events of special interest

Myocardial infarction, stroke, thrombocytopaenia, some elevations of liver function tests and neurologic events were designated to be of possible clinical significance.

Arterial thromboembolic events (MI or stroke) during the combined treatment and follow-up periods were confirmed by adjudication for 3 (0.2%) subjects in the apixaban group and for 1 (< 0.1%) subject in the enoxaparin group (Table 48). Thrombocytopaenia during the combined treatment and follow-up periods was confirmed by adjudication for 1 (< 0.1%) subject in the apixaban group (during the follow-up period) and for 2 (0.1%) subjects in the enoxaparin group (during the treatment period).

Liver transaminase concentrations were raised more than three times the upper limit of normal (ULN) and bilirubin concentrations more than twice the ULN in small proportions of patients in each treatment group (Table 48).

Table 48: Summary of safety outcomes of special interest during the intended treatment and follow-up periods

Outcome	Apixaban 2.5mg bd (n = 1501)		Enoxaparin 40mg od (n = 1508)	
	Treatment period	Follow-up period	Treatment period	Follow-up period
AT >3 times ULN on same date	25 (2%)	2 (<1%)	17 (1%)	7 (<1%)
Total serum bilirubin >2 times ULN	15 (<1%)	3 (<1%)	8 (<1%)	1 (<1%)
AT >3 time ULN and bilirubin >2 times ULN on same date	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Thrombocytopaenia[†]	0	1 (<1%)	1 (<1%)	0
Myocardial infarction	1 (<1%)	0	1 (<1%)	0
Stroke	2 (<1%)	0	0	0
≥ 1 SAE	72 (5%)	13 (<1%)	88 (6%)	15 (<1%)

Abbreviations: AT, serum alanine aminotransferase and aspartate aminotransferase; bd, twice daily; od, once daily; SAE, serious adverse event; ULN, upper limit of normal. [†]Thrombocytopaenia was defined as a decline in the platelet count to <100,000/mm^3 for subjects with a post surgery value of >150,000/mm^3 or more than a 50% decline if the baseline (post surgery) value was ≤ 150,000/mm^3. Numbers in table are from the publication.

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5.9.2 ADVANCE 3

Safety

- Bleeding rates were similar in both the apixaban and enoxaparin groups.
- Apixaban was generally well tolerated, with no unexpected safety signals arising from the data.

Primary safety endpoints

Major bleeding during the treatment period occurred in 22/2673 (0.8%) apixaban patients and 18/2659 (0.7%) patients receiving enoxaparin (absolute risk difference: 0.15%, 95% CI: –0.33% to 0.64%), (Table 49). Thirteen of the 22 major bleeding events in the apixaban group of patients occurred before the first dose, so the incidence of major bleeding with onset after the first apixaban dose was 9/2673 patients (0.3%, 95% CI: 0.2% to 0.7%). No bleeding event in either group was related to spinal or epidural anaesthesia.

The composite of major and clinically relevant non-major bleeding occurred in 129 (4.8%) apixaban and 134 (5.0%) enoxaparin patients (absolute risk difference: –0.21%, 95% CI: –1.38% to 0.95%). Of 129 apixaban group events, 33 occurred before the first dose. Thus, the incidence of major or clinically relevant non-major bleeding with onset after the first apixaban dose was 96 of 2,673 patients (3.6%, 95% CI: 3.0% to 4.4%). Site and severity of bleeding are summarised in Table 49.

Table 49: Bleeding events during the treatment period

Outcome	Apixaban 2.5mg bd N = 2673		Enoxaparin 40mg od N = 2659		Absolute risk difference (95% CI)	P Value
	n (%)	*95% CI*	*n (%)*	*95% CI*		
Adjudicated major bleeding events[†]	22 (0.82)	0.54–1.25	18 (0.68)	0.42–1.08	0.15 (–0.33 to 0.64)	0.54
Diagnostic criteria for major bleeding event						
Haemoglobin drop of ≥ 20g/L within 24hr	13 (0.49)		10 (0.38)			
Transfusion of ≥ 2 units of packed RBCs	16 (0.60)		14 (0.53)			
Bleeding at a critical site‡	0		0			
Haemarthrosis that required reoperation or reintervention	1 (0.04)		1 (0.04)			
Fatal bleeding	0		0			
Bleeding at surgical site						
Total	18 (0.7)		16 (0.6)			
Haemarthrosis in operated joint	2 (0.1)		4 (0.2)			
Other surgical site bleeds	17 (0.6)		15 (0.6)			
Nonsurgical bleeding events						
Total	5 (0.2)		2 (0.1)			
Gastrointestinal	4 (0.1)		0			
Other	5 (0.2)		2 (0.1)			
Adjudicated clinically relevant non-major bleeding events[†]	109 (4.08)	3.39–4.90	120 (4.51)	3.79–5.38	–0.44 (–1.53 to 0.66)	0.43
Bleeding at surgical site	79 (3.0)		88 (3.3)			
Nonsurgical bleeding events	32 (1.2)		36 (1.4)			
Adjudicated major or clinically relevant non-major bleeding events[†]	129 (4.83)	4.08–5.71	134 (5.04)	4.27–5.94	–0.21 (–1.38 to 0.95)	0.72
Minor bleeding events[§]	184 (6.9)		200 (7.5)			
All bleeding events[†]	313 (11.71)	10.55–12.99	334 (12.56)	11.36–13.88	–0.85 (–2.61 to 0.90)	0.34

Abbreviations: bd, twice daily; CI, confidence interval; od, once daily; RBCs, red blood cells. [†]Subjects may be counted in more than one bleeding event type category; [‡]Intracranial, intraspinal, intraocular, pericardial, retroperitoneal location, and intramuscular with compartment syndrome; [§]Includes subjects for whom the most severe bleeding event was a minor bleed.

Other safety measures

Adverse events

The incidences of reported AEs and SAEs were similar between the treatment groups (Table 50). AEs considered to be drug related occurred with similar frequency in both treatment groups (18% in the apixaban group and 20% in the enoxaparin group).

Drug-related AEs observed in > 1% of subjects in either group included:

nausea (apixaban 3.5%, enoxaparin 3.6%), contusion (apixaban 1.3%, enoxaparin 2.1%), constipation (apixaban 1.3%, enoxaparin 2.0%), peripheral oedema (1.9% in each group), AST increased (apixaban 1.1%, enoxaparin 1.8%), pyrexia (apixaban 1.5%, enoxaparin 1.4%), postoperative anaemia (apixaban 1.3%, enoxaparin 1.5%), vomiting (apixaban 1.2%, enoxaparin 1.5%), dizziness (apixaban 1.5%, enoxaparin 1.1%), ALT increased (apixaban 1.0%, enoxaparin 1.5%), insomnia (1.0% in each group), and GGT increased (apixaban 0.6%, enoxaparin 1.4%).

Table 50: Adverse events reported by investigators during treatment (not including study endpoints)

Adverse events Number (%) subjects	Apixaban 2.5mg bd (n = 2673)	Enoxaparin 40mg od (n = 2659)
AE	1752 (65.5%)	1811 (68.1%)
[redacted] removed' academic / commercial in confidence information removed'		
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'

Adverse events Number (%) subjects	Apixaban 2.5mg bd (n = 2673)	Enoxaparin 40mg od (n = 2659)
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'

Adverse events Number (%) subjects	Apixaban 2.5mg bd (n = 2673)	Enoxaparin 40mg od (n = 2659)
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
SAE	184 (6.9%)	172 (6.5%)
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'	[redacted] removed' academic / commercial in confidence information removed'
Discontinuations due to AE	91 (3.4%)	111 (4.2%)
Bleeding AE	268 (10.0%)	268 (10.1%)
Deaths	3 (0.1%)	2 (<0.1%)

Abbreviations: AE, adverse event; bd, twice daily; od, once daily; SAE, serious adverse event. Numbers in table from CSR.

Bleeding-related AEs

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[redacted] removed' academic / commercial in confidence information removed'

Deaths

Five deaths occurred in the treatment period; 3 in the apixaban group and 2 in the enoxaparin group. [redacted] removed' academic / commercial in confidence information removed'

Serious adverse events

SAEs were reported in 184 (6.9%) subjects in the apixaban group and 172 (6.5%) subjects in the enoxaparin group. [redacted] removed' academic / commercial in confidence information removed'

DVT was also an efficacy endpoint in this study, the results of the efficacy analyses are described above in Section 5.5. [redacted] removed' academic / commercial in confidence information removed'

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Events of special interest

Myocardial infarction, stroke, thrombocytopaenia, some elevations of liver function tests and neurologic events were designated to be of possible clinical significance.

Arterial thromboembolic events (MI or stroke) during the combined treatment and follow-up periods were confirmed by adjudication for 10 (0.4%) subjects in the apixaban group and for 9 (0.3%) subjects in the enoxaparin group. During the treatment period, these included 5 MIs and 1 stroke in the apixaban group and 3 MIs and 4 strokes in the enoxaparin group (Table 51). Thrombocytopaenia during the combined treatment and follow up periods was confirmed by adjudication for 3 (0.1%) subjects in the apixaban group and for 5 (0.2%) subjects in the enoxaparin group.

Elevated liver transaminase and bilirubin levels were uncommon in both treatment groups.

Table 51: Summary of safety endpoints with onset during the treatment and follow-up periods

Outcome	Apixaban 2.5mg bd		Enoxaparin 40mg od	
	Treatment period (n=2673)	Follow-up period (n=2599)	Treatment period (n=2659)	Follow-up period (n=2576)
AT >3 x ULN on same date	34/2629 (1.3%)	3/2436 (<0.1%)	40/2616 (1.5%)	6/2396 (<0.1%)
Total serum bilirubin >2 x ULN	24/2630 (0.9%)	3/2449 (<0.1%)	12/2617 (0.5%)	1/2416 (<0.1%)
AT >3 time ULN and bilirubin >2 x ULN on same date	7/2629 (0.3%)	3/2410 (0.1%)	3/2613 (0.1%)	1/2386 (<0.1%)
Myocardial infarction	5 (0.19%)	4 (0.15%)	3 (0.11%)	1 (0.04%)
Stroke	1 (0.04%)	0 (0)	4 (0.15%)	1 (0.04%)
Thrombocytopaenia†	2 (0.7%)	1 (0.04%)	3 (0.11%)	2 (0.08%)

Abbreviations: AT, serum alanine aminotransferase and aspartate aminotransferase; bd, twice daily; od, once daily; SAE, serious adverse event; ULN, upper limit of normal. †Thrombocytopaenia was defined as a decline in the platelet count to <100,000/mm^3 for subjects with a post surgery value of >150,000/mm^3 or more than a 50% decline if the baseline (post surgery) value was ≤ 150,000/mm^3. Numbers in table from publication.

5.9.3 ADVANCE 1

Safety

- Bleeding rates (both major and clinically relevant non-major [CRNM]) were lower with apixaban than enoxaparin.
- Apixaban was generally well tolerated, with no unexpected safety signals arising from the data.

Analysis periods

Analysis periods for safety endpoints were:

- Treatment period – includes measurements or events with onset from first dose of double-blind study drug (pre- or post-surgery) through:
    - 2 days after the last dose of double-blind study drug when summarising bleeding endpoints, bleeding-related serious or non-serious AEs, MI, stroke, or thrombocytopaenia endpoints, and laboratory measurements
    - 30 days after the last dose of double-blind study drug when summarising deaths as an outcome of a SAE and SAEs
    - 2 days (for non-serious AEs) or 30 days (for SAEs) after the last dose of double-blind study drug when summarising LFT-related AEs or neurologic AEs and overall AEs
- Follow-up Period – the period that started after the treatment period and ended through 60 days after discontinuation of double-blind study drug.

Primary safety endpoints

Major bleeding events during the treatment period were infrequent and numerically lower for apixaban-treated subjects than for enoxaparin-treated subjects, although this was not statistically significant (0.69% and 1.39%, respectively; p=0.053), (Table 52). Event rates during the treatment period for clinically relevant non-major bleeding and any bleeding (adjudicated or as reported by the investigator) were similar or lower (though not significantly) for apixaban-treated subjects than for enoxaparin-treated subjects (p=0.17 and p=0.08, respectively). The event rate for the composite of the adjudicated major or clinically relevant non-major bleeding endpoint during the treatment period was lower for apixaban-treated subjects than for enoxaparin-treated subjects (2.88% and 4.28%, respectively; p=0.03), (Table 52).

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Table 52: Summary of bleeding events that occurred in the treatment period – treated subjects

Outcome	Apixaban 2.5mg bd N = 1596		Enoxaparin 30mg bd N = 1588		Difference in risk (95% CI)	P Value
	n (%)	*95% CI*	*n (%)*	*95% CI*		
Adjudicated major bleeding events	11 (0.7)	0.4–1.3	22 (1.4)	0.9–2.1	–0.81 (–1.49 to 0.14)	0.053
Diagnostic criteria for major bleeding event						
Clinically overt bleeding	10 (0.6)		22 (1.4)			
Decrease in haemoglobin of ≥ 2g/dL within 24hr	10 (0.6)		16 (1.0)			
Transfusion of ≥ 2 units of packed red cells	9 (0.6)		18 (1.1)			
Bleeding at a critical site						
Intracranial bleeding	0		1 (<0.1)			
Bleeding from any intraspinal, intraocular, pericardial, intramuscular, or retroperitoneal location	0		0			
Fatal bleeding	0		1 (<0.1)			
Haemarthrosis	1 (<0.1)		4 (0.3)			
Other	3 (0.2)		5 (0.3)			
Bleeding at surgical site						
Total	8 (0.5)		14 (0.9)			
Haematoma	2 (0.1)		2 (0.1)			
Haemarthrosis	0		3 (0.2)			
Haemarthrosis with intervention	0		2 (0.1)			
Bruising or ecchymosis	1 (<0.1)		1 (0.1)			
Other surgical site						
Nonsurgical bleeding events						
Total	3 (0.2)		10 (0.6)			
Bruising or ecchymosis	0		1 (<0.1)			
Intracranial haemorrhage	0		1 (<0.1)			
Gastrointestinal bleeding	1 (<0.1)		6 (0.4)			
Other	2 (0.1)		2 (0.1)			
Adjudicated clinically relevant non-major bleeding events	35 (2.2)	1.6–3.1	47 (3.0)	2.2–3.4	–0.77 (–1.87 to 0.33)	0.17
Bleeding at surgical site						
Total	22 (1.4)		35 (2.2)			
Haematoma	7 (0.4)		16 (1.0)			
Haemarthrosis	2 (0.1)		2 (0.1)			
Haemarthrosis with intervention	1 (<0.1)		0			
Bruising or ecchymosis	7 (0.4)		10 (0.6)			
Other	7 (0.4)		11 (0.7)			
Nonsurgical bleeding events						
Total	13 (0.8)		11 (0.7)			
Haematoma	1 (<0.1)		2 (0.1)			
Bruising or ecchymosis	6 (0.4)		2 (0.1)			
Epistaxis	1 (<0.1)		1 (<0.1)			
Gastrointestinal	0		4 (0.3)			
Other	5 (0.3)		3 (0.2)			
Adjudicated major or clinically relevant non-major bleeding events	46 (2.9)	2.2–3.8	68 (4.3)	3.4–5.4	–1.46 (–2.75 to 0.17)	0.03
All bleeding events	85 (5.3)	4.3–6.6	108 (6.8)	5.7–8.2	–1.52 (–3.18 to 0.13)	0.08
Minor bleeding events	39 (2.4)		40 (2.5)			

Abbreviations: bd, twice daily; CI, confidence interval. There may have been >1 bleeding event/patient; thus, the total number of bleeding events may be greater than the total number of patients with major or clinically relevant non-major bleeding

There were no fatal bleeding events in the follow-up period. Bleeding event rates for major, clinically relevant non-major, or any bleeding endpoints during the follow-up period were low and similar for apixaban and enoxaparin treatment.

Other safety measures

Adverse events

The incidence of AEs during the treatment period was similar between the apixaban and enoxaparin groups. AEs were reported in 72.0% of apixaban-treated subjects and 73.8% of enoxaparin-treated subjects (Table 53). The most common AEs (reported for > 5% of subjects in either treatment group) in the treatment period were constipation, nausea, peripheral oedema, pyrexia, and DVT, and rates of these most common AEs were similar between apixaban and enoxaparin groups.

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Table 53: Adverse events reported by investigators during the treatment period (not including study endpoints)

Adverse events Number (%) subjects	Apixaban 2.5mg bd (n = 1596)	Enoxaparin 30mg bd (n = 1588)
AE	1149 (72.0)	1172 (73.8)
AEs occurring in ≥ 5% of patients		
Constipation	227 (14.2%)	234 (14.7%)
Nausea	208 (13.0%)	242 (15.2%)
Pyrexia	138 (8.6%)	152 (9.6%)
Oedema (peripheral)	133 (8.3%)	154 (9.7%)
Dizziness	103 (6.5%)	88 (5.5%)
Vomiting	99 (6.2%)	102 (6.4%)
Pain in extremity	86 (5.4%)	79 (5.0%)
Insomnia	77 (4.8%)	86 (5.5%)
SAE	123 (7.7)	123 (7.7)
Drug related SAE	15 (0.9%)	26 (1.6%)
Drug related AE	327 (20.5%)	344 (21.7%)
Bleeding AE	110 (6.9)	144 (9.1)
Discontinuations due to AE	60 (3.8)	58 (3.7)
Deaths	3 (0.2)	5 (0.3)

Abbreviations: AE, adverse event; bd, twice daily; SAE, serious adverse event

Drug-related AEs

AEs considered to be drug related (Table 53) occurred with similar frequency in apixaban-treated subjects (20.5%) and enoxaparin-treated subjects (21.7%). [redacted] removed' academic / commercial in confidence information removed'

Bleeding-related AEs

The incidence of bleeding-related AEs with onset during the treatment period was numerically lower in the apixaban treated subjects than in the enoxaparin treated subjects (6.9% and 9.1%, respectively) [redacted] removed' academic / commercial in confidence information removed'

Deaths

Eight deaths occurred during the treatment period, 3 (0.2%) in apixaban-treated subjects and 5 (0.3%) in enoxaparin-treated subjects. [redacted] removed' academic / commercial in confidence information removed'

In the follow-up period, cardio-respiratory arrest caused the death of 1 subject in the enoxaparin group. This death was adjudicated as a PE. No other deaths were reported in the follow-up period.

Serious adverse events

The incidence of SAEs during the treatment period was similar between the apixaban and enoxaparin groups (Table 53). [redacted] removed' academic / commercial in confidence information removed'

PE was also an efficacy endpoint in this study, the results of the efficacy analyses of PE are described in Section 5.5.

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Events of special interest

Myocardial infarction, stroke, thrombocytopaenia, some elevations of liver function tests and neurologic events were designated to be of possible clinical significance.

Arterial thromboembolic events (MI or stroke) during the combined treatment and follow-up period were confirmed by adjudication for 2 (0.13%) apixaban-treated subjects (1 MI in each of treatment and follow-up periods) and for 6 (0.38%) enoxaparin-treated subjects (treatment period: 1 subject had both an MI and a stroke, 3 subjects had an MI, 1 subject had a stroke; follow-up period: 1 subject had an MI), (Table 54). Thrombocytopaenia was confirmed by adjudication for 2 subjects during the treatment period, both of whom received enoxaparin.

Elevated aminotransferase or bilirubin levels were infrequent in both groups. The criteria for hepatotoxicity were not met in any patient receiving apixaban (95% CI for proportion of patients, 0 to 0.3%).

Table 54: Summary of safety outcomes of special interest during the intended treatment and follow-up periods

Outcome	Apixaban 2.5mg bd (n = 1596)		Enoxaparin 30mg bd (n = 1588)	
	Treatment period	Follow-up period	Treatment period	Follow-up period
AT >3 times ULN on same date	16 (1.0)	2 (0.1)	25 (1.6)	3 (0.2)
Total serum bilirubin >2 times ULN	2 (0.1)	1 (<0.1)	8 (0.5)	0

Outcome	Apixaban 2.5mg bd (n = 1596)		Enoxaparin 30mg bd (n = 1588)	
AT >3 times ULN and bilirubin >2 times ULN on same date	0	0	2 (0.1)	0
Thrombocytopaenia†	0	0	2 (0.1)	0
Myocardial infarction	1 (<0.1)	1 (<0.1)	4 (0.3)	1 (<0.1)
Stroke	0	0	2 (0.1)	0
≥ 1 SAE	123 (7.7)	14 (0.9)	123 (7.7)	15 (0.9)

Abbreviations: AT, serum alanine aminotransferase and aspartate aminotransferase; bd, twice daily; SAE, serious adverse event; ULN, upper limit of normal. †Thrombocytopaenia was defined as a decline in the platelet count to <100,000/mm^3 for subjects with a post surgery value of >150,000/mm^3 or more than a 50% decline if the baseline (post surgery) value was ≤ 150,000/mm^3.

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In the follow-up period, AEs related to neurological function were infrequent and similar between the apixaban and enoxaparin groups.

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

The bleeding rate was similar in both the apixaban and enoxaparin groups. Apixaban is generally well tolerated, with no unexpected signals arising from the data.

5.10 Interpretation of clinical evidence

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

Apixaban offers more efficacious VTE prophylaxis compared to enoxaparin and dabigatran with a comparable bleeding safety profile.

Apixaban is comparable with rivaroxaban in terms of both efficacy and safety.

Apixaban is a convenient oral dosage form. It offers ease of use and potentially improved compliance to VTE prohphylaxis, over injectable anti-coagulants such as enoxaparin and fondaparinux.

Apixaban also offers the advantages of having a more flexible time-frame for initiation of treatment postoperatively compared to other new oral anticoagulants.

Efficacy of apixaban

Apixaban clinical trial data includes over 11,600 patients. Apixaban showed statistical superior efficacy to enoxaparin in the European studies ADVANCE 2 and ADVANCE 3 in reducing the primary composite endpoint of all adjudicated VTE and all cause death following THR and TKR surgery. Apixaban was also better than enoxaparin in preventing significant clots (i.e. clots above the knee) which are more likely to cause serious complications.

Indeed, from the ADVANCE 2 data, apixaban can be expected to prevent one major blood clot, pulmonary embolus or VTE related death for every 93 TKR patients treated, while the ADVANCE 3 data show that one of these events can be avoided in every 145 THR patients treated. Considering there are nearly 160,000 primary arthroplasties per year in the UK (5) apixaban could have the potential to significantly reduce morbidity and mortality.

No trial of thromboprophylaxis, to date, has been powered to show the significance of effect on the rate of PE. Whilst PE is a most significant complication of VTE, it occurred infrequently in these studies. While the overall thrombotic burden was reduced with apixaban in all the studies, in ADVANCE 2 numerically more PEs occurred in the apixaban group. However, this trend was reversed in ADVANCE 3 (which had numerically more PEs in the enoxaparin group). As overall numbers of PEs were low, no conclusions can be made, and Expert CHMP Opinion regards this as an anomaly.

In the absence of head to head RCT evidence for apixaban 2.5mg bd versus rivaroxaban 10mg od, dabigatran 220mg od, or fondaparinux 2.5mg od, an adjusted indirect comparison approach using the Bucher method was adopted as the main analysis in order to derive efficacy and safety effect sizes for these treatments. The adjusted indirect comparison approach was also consistent with that undertaken by the manufacturer in the NICE appraisal of rivaroxaban for VTE prophylaxis, which was endorsed by the NICE ERG academic reviewers.

An MTC analysis was run in parallel to the adjusted indirect comparison for those outcomes where sufficient data was available to do this. However, there were potential methodological limitations to the MTC networks and some inconsistency observed compared to the direct RCT (apixaban 2.5mg bd vs. enoxaparin 40 mg od; rivaroxaban 10 mg od vs. enoxaparin 40mg od) and adjusted indirect comparison (apixaban 2.5 mg bd vs. dabigatran 220 mg od) results on some efficacy outcomes as outlined in Section 5.7.9 above. For these reasons,

the adjusted indirect comparison was adopted as the principal clinical efficacy and safety analysis.

Adjusted indirect comparison results for efficacy

For the prevention of the composite of all VTE plus all-cause death endpoint in the THR and TKR populations, the adjusted indirect comparison found that dabigatran 220mg od was significantly less efficacious than apixaban and although rivaroxaban was slightly more efficacious than apixaban, these differences were not statistically significant.

In both the THR and TKR populations, dabigatran 220 mg od was significantly less efficacious than apixaban 2.5mg bd for the prevention of any DVT and asymptomatic DVT. In the THR population, dabigatran 220mg od was significantly less efficacious than apixaban for the prevention of symptomatic DVT, whereas in the TKR population, there was no statistically significant difference between the two treatments on this outcome. The two treatments also did not differ significantly for the prevention of major VTE.

The indirect comparison found that in both THR and TKR populations, apixaban 2.5mg bd was slightly less efficacious than rivaroxaban 10mg od in preventing any DVT and major VTE, although these differences were not statistically significant.

For pulmonary embolism, the adjusted indirect comparison found that apixaban 2.5mg bd was slightly more efficacious than dabigatran in the THR population, and slightly less efficacious in the TKR population, although these differences were not statistically significant. Compared with apixaban, rivaroxaban has a higher but statistically non-significant rate of PE in THR but a significantly lower rate in TKR. It should be noted that in all these analyses there were very small numbers of PE events reported, confidence intervals were wide and none of the RCTs were actually powered to specifically analyse any secondary outcome, meaning that these results should be treated with caution.

In the THR population, the adjusted indirect comparison found that fondaparinux 2.5mg od had a higher, but statistically non-significant incidence of any DVT, asymptomatic DVT, symptomatic DVT, and PE compared to apixaban 2.5mg bd. No fondaparinux 2.5mg od versus enoxaparin 40mg od RCT was available in the TKR population, so no adjusted indirect comparison results were reported.

Safety of apixaban

Bleeding

It is important to have a favourable efficacy/safety balance for an anticoagulant. As all anticoagulants work by preventing clotting there is a propensity for them to also cause bleeding. Bleeds can be debilitating, result in an extended hospital stay, require re-operation, or even be fatal. The apixaban ADVANCE clinical trial programme set out to assemble a comprehensive evaluation of bleeding rates according to the ISTH (International Society of Thrombosis and Haemostasis) Guidelines (27, 40). Data were collected on major, clinically relevant non-major (CRNM) and minor bleeds, and also whether they were surgically related or not, providing a truly inclusive picture of apixaban's safety profile.

The safety data from the ADVANCE 2 study showed that the bleeding rates (major and CRNM) were numerically lower in the apixaban group than the enoxaparin group, although this was not statistically significant. In the ADVANCE 3 study the bleeding rate (major and CRNM) was similar in both the apixaban and the enoxaparin groups, with no significant differences.

Adjusted indirect comparison-results for bleeding

In the THR and TKR populations, the adjusted indirect comparison found that rivaroxaban 10 mg od and dabigatran 220 mg od respectively had a higher incidence of bleeding (any bleeding, major, CRNM and minor bleeding) compared with apixaban 2.5mg bd, although these differences were not statistically significant. The exception was dabigatran 220 mg od in the TKR population, which had a non-significant, lower incidence of minor bleeding compared to apixaban.

In the THR population, the adjusted indirect comparison found that fondaparinux 2.5mg od had a higher but statistically non-significant incidence of major bleeding compared to apixaban 2.5mg bd, with no other bleeding outcomes available for this indirect comparison. Since no fondaparinux 2.5mg od versus enoxaparin 40mg od RCTs were available in the TKR population, an adjusted indirect comparison was not possible.

General adverse events

The apixaban clinical trial data show that the overall adverse event rate and discontinuation rate with apixaban was no different to that with enoxaparin.

Across all the studies, apixaban was generally well tolerated with no unexpected adverse effects arising from the data.

Summary

Overall, not only does apixaban demonstrate improved efficacy over the current standard of care, enoxaparin, it also has a similar safety profile for bleeds, together with no excess of other side effects.

Apixaban also offers the beneficial convenience of a flexible time frame for initiation of treatment and oral administration.

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

The ADVANCE clinical trial programme consisted of a series of 3 robust, prospective, randomised, double-blind, double-dummy trials that were carried out in numerous countries across the world, including UK sites. Randomisation was carried out by a centrally managed Interactive Voice Response System, and all outcome and bleeding events were adjudicated by an independent Adjudication Committee that was blinded to the treatment allocation. This demonstrates the scientific veracity of the apixaban clinical trial programme, which was the basis for apixaban's license and accepted by the CHMP.

The ADVANCE 2 and ADVANCE 3 trials compared apixaban with the European and UK licensed dosage regimen of enoxaparin, and are the most relevant to UK practice.

The ADVANCE 1 trial was a North American study using an enoxaparin dosing regimen not used in Europe (the major differences being use of a more frequent and higher dose of enoxaparin). Although numerically the primary composite endpoint (all adjudicated VTE and all cause death) occurred at a similar rate in both the enoxaparin and apixaban groups, the criteria for non-inferiority were not met. Whilst it usefully adds to the overall efficacy and safety profile of apixaban, ADVANCE 1 data are not considered to be relevant to UK clinical practice.

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

Relevance of apixaban trials

The majority of the evidence for apixaban relates to the standard of care in the UK, enoxaparin. As LMWHs were used for VTE prophylaxis in 71% and 69% of patients undergoing THR and TKR respectively in England and Wales in 2009 (5) and enoxaparin is the most widely used LMWH in the UK (13). Enoxaparin use as the comparator in the apixaban registrational trials was very relevant.

Of the apixaban trials, the ADVANCE 2 and 3 trials are most relevant to UK clinical practice, using enoxaparin as a comparator at doses and regimens licensed in Europe. Whereas the ADVANCE 1 trial is a North American study using a dose regimen of enoxaparin that is not licensed in the UK. Therefore, ADVANCE 1 data were not considered relevant to the UK.

Relevance of outcomes

Venography was used to assess VTE in the ADVANCE trial programme, as well as for all other trials in this area. Venography is very sensitive, reproducible and specific, and is the gold standard for the assessment of VTE in clinical research. However, it is not used in clinical practice, where compression ultrasound is the standard of care. But, it is important to recognise that venography identifies small, asymptomatic, distal clots (occurring below the knee). While these would not be routinely identified in clinical practice, they are still a risk for propagation to become symptomatic, DVT emboli, or lead to the occurrence of post-thrombotic syndrome (PTS). PTS is a chronic condition that develops in 30–50% of patients within 1 to 2 years of symptomatic DVT (49), and also occurs in patients with asymptomatic DVT (50). PTS is characterised by chronic, persistent pain and swelling, in the affected limb.

In practical terms, use of venography in the ADVANCE clinical trial programme, meant that they could be conducted using smaller patient numbers than would have been needed to demonstrate benefit in symptomatic disease.

In addition, the secondary outcome of major VTE - comprised of proximal thrombus (occurring above the knee and associated with high morbidity), symptomatic VTE and VTE related death. This end point is of particular relevance to clinical practice and patient outcomes.

Flexible initiation of apixaban

In designing the ADVANCE clinical trial programme, consideration was made for the practical application of apixaban. As such, a later and wider timing period for treatment initiation was investigated, to reflect “real life” surgical practice.

The results of the studies show that initiating apixaban prophylaxis the day after surgery results in effective thromboprophylaxis. Such a wide window for the timing of treatment initiation allows time for initial haemostasis and wound healing, as well as surgical assessment of the wound to happen first. In addition, this schedule allows treatment initiation to occur at the next scheduled drug round, effectively reducing nurse workload by avoiding additional drug rounds.

The wider timing window for treatment initiation is also an important advantage when spinal or epidural catheters are used for analgesia. As catheters are likely to be removed within the first few hours post-operatively it is ideal if patients have not already received an anticoagulant before this procedure, which may lead to unwanted bleeding at the site. Therefore the delayed timing for initiation of anticoagulant medication permitted by apixaban (12-24 hours post-operatively) is advantageous.

Convenience

Because apixaban is an oral tablet, the whole course of treatment can be dispensed on one occasion for the entire thromboprophylaxis period recommended by NICE.

Apixaban also provides the additional convenient benefit of not needing dose adjustment for mild or moderate renal impairment, or the patient's weight. This allows simple protocols to be applied for the majority of orthopaedic patients, which may reduce the risk of medication errors.

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

The evidence base from both the ADVANCE 2 and 3 trials have been the focus of this submission as they use apixaban and comparator, enoxaparin doses that are in line with the UK licensed SPCs.

Apixaban is indicated for use as thromboprophylaxis following elective total knee replacement (TKR) or total hip replacement (THR) surgery. It is not recommended in patients with renal impairment with a creatinine clearance <15 ml/min, and is cautioned in patients with severe renal impairment (CrCl 15–29ml/min), severe hepatic impairment or active significant bleeding who are unlikely to be eligible for TKR or THR surgery due to the anaesthetic risk. Apixaban would therefore be appropriate for use in the majority of patients undergoing THR and TKR. (Please see Section 7 for the economic modelling for numbers of patients estimated to potentially use apixaban).

As discussed in Section 2, UK clinical practice often differs from NICE Guideline recommendations. In the ADVANCE trials enoxaparin was initiated 12–15 hours pre-operatively, as per its SPC. However, in practice in the UK, this pre-operative dose is often omitted. The ADVANCE trials also studied apixaban compared to enoxaparin's recommended duration of 10–14 days use post TKR, and 30–35 days post THR. However in current UK practice this duration of treatment is seldom adhered to. As a result, the benefits of apixaban when compared to current UK practice may have been understated.

6 Cost-effectiveness

Summary

The literature on VTE prophylaxis in THR and TKR revealed that prophylaxis was cost effective compared to no prophylaxis. The oral anticoagulants dabigatran and rivaroxaban were found to dominate the injectable LMWH enoxaparin. Current evidence suggests rivaroxaban dominates dabigatran. However, the differences in costs and QALYs in these analyses were found to be small.

A de novo economic model was developed utilising a two-stage decision tree/Markov approach similar to that used in a previous NICE appraisal of dabigatran. Events in the peri-operative acute phase (where the patient is at greatest risk of VTE and adverse events) were modelled within the decision tree. The health status of patients as they exit the decision tree is then used to inform the longer term (chronic phase) events within the Markov model.

Apixaban is compared with LMWHs, and the new oral anticoagulants (dabigatran and rivaroxaban). A comparison could not be made with fondaparinux as a relative effect size on the primary efficacy composite endpoint was not available from the indirect comparison.

With the lowest acquisition cost, apixaban is a cost effective VTE prophylaxis agent compared with other anti-coagulants currently in use. Compared with enoxaparin and dabigatran, apixaban is estimated to be less costly and more effective (dominant) in both THR and TKR patients. Compared with rivaroxaban, apixaban has a lower acquisition cost (£3.43 vs. £4.42 per day) and delivers comparable QALYs in both THR and TKR patients. In all comparisons the differences in costs and QALYs over the 35 year time horizon examined in this submission were small.

Sensitivity analyses show that changes to the key parameters underpinning the model such as comparator prices and efficacy rates, result in slight changes to the incremental costs and QALYs for apixaban versus each comparator but overall the differences remain small and results are robust to these changes

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

A systematic review of economic evaluations for interventions for the prophylaxis of venous thromboembolism (VTE) in patients undergoing elective total knee and hip replacement was undertaken in July 2010 (updated in November 2010). Relevant literature was identified by searching electronic databases (NHS EED, OVID Medline, OVID Medline In-Process and Other Non-Indexed Citations, OVID EMBASE and Econlit), conference proceedings and hand searching the reference lists of identified economic evaluations and systematic and qualitative economic reviews. Full details of the databases, conference proceedings and search strategies employed are presented in Appendix 10.

Inclusion criteria

Although pharmacologic interventions were the primary focus of the project, mechanical interventions, which may be used in conjunction or as comparators to the pharmacologic interventions, were also included in order to ensure a comprehensive overview of the relevant literature. The inclusion criteria for the literature review were:

1. Patients
- Patients undergoing hip and/or knee replacement or, in a mixed population, where information was reported specifically for the hip and/or knee replacement patient population.

2. Interventions
- Graduated elastic compression stockings / anti-embolism stockings (GCS)
- Intermittent pneumatic compression (IPCD) devices
- Foot pumps or foot impulse devices (FID)
- Vena cava filters
- Aspirin or antiplatelet therapy
- Low-dose unfractionated heparin administered subcutaneously (UFH)
- Low molecular weight heparin (LMWH)
- The synthetic pentasaccharide, Fondaparinux
- Vitamin K Antagonists (For example, warfarin, coumarin)
- Early mobilisation
- Foot elevation
- Hydration
- New oral anticoagulants licensed during the guideline development period (rivaroxaban and dabigatran)

Exclusion criteria
Papers not meeting the inclusion criteria above or published in a language other than English were excluded.

Review and data extraction
The results of the searches were reviewed independently on the basis of title or abstract by two reviewers. In the event that a decision could not be made on the title and/or the abstract was missing, the full publication was retrieved for checking.

The papers retrieved in full were filtered by hand to identify any relevant studies. Two reviewers independently assessed all retrieved articles for their suitability for inclusion according to the inclusion/exclusion criteria outlined above. The reviewers discussed any differences of opinion before deciding on the final list of included / excluded articles. Any differences of opinion were referred to a third party.

6.1.2 Description of identified studies

In addition to economic evaluations the searches also identified several systematic reviews that were used to validate the searches and results of the current review. These studies are listed in Appendix 10.

Four hundred and twenty five studies were identified and reviewed for inclusion on the basis of title and abstract (See Appendix 10). Of these studies 361 were excluded (and are listed in Appendix 10); 82 were excluded as duplicates, 260 were excluded on the basis of title and abstract, and a further 19 were excluded on examination of the full paper. Sixty four studies identified from the database searches were included (8 UK cost effectiveness studies, 40 non-UK cost effectiveness studies, and 16 other cost/resource use studies) (cost/resource use search was incorporated into the search for cost effectiveness evaluations). These

results were supplemented by 32 studies identified from hand searches (29 conference abstracts and three HTA documents). In total 96 studies were included.

Only one additional study was identified from the update search conducted in November 2010: Diamantopoulos et al. (51). This study reported data for Canada and was therefore not directly relevant to the UK setting. It should also be noted that this study was identified as an abstract by the original searches conducted in July 2010 and so was already counted as an included study.

In total 14 UK studies (eight publications (52-59), three abstracts (60-62), and three UK HTA documents (48, 63, 64) were included in Appendix 10 (Section 9.10.11). The NICE guideline document (48) was associated with a further two documents (65, 66); these were also reviewed for relevant information but not included as separate studies to avoid duplication. Forty non-UK studies are summarised in Appendix 10, (Section 9.10.10). Twenty six relevant conference abstracts from non-UK countries are provided as a list of references in Appendix 10, (Section 9.10.11). The focus of the rest of this section is on the UK studies as these are most relevant to the UK setting (Studies undertaken for non-UK countries are described in Appendix 10). Nineteen cost/resource use studies were also identified; these studies are discussed in more detail in Section 6.5. A list of excluded studies is provided in Appendices 10 and 13.

A variety of prophylactic treatments were represented although enoxaparin was the most commonly evaluated intervention (53-55, 57-64). One study used network meta-analysis to synthesise data for multiple comparators (48). Most studies included a mixed THR and TKR population (48, 55, 56, 58-60, 63, 64). Several studies reported a THR population (52-54, 57, 62) and one study included only TKR patients (61). One study investigated both the TKR and THR populations separately (48). One study focussed specifically on an older patient population aged 75 years or above (59). The reported methods of DVT detection were relatively consistent. Studies reported use of screening venography (53-55), ultrasound, or scanning or a mixture of methods (57).

All economic evaluations employed decision analytic modelling methods. Two studies (14%) did not report the techniques employed (52, 60); one was an abstract with word limit constraints (60) and was a relatively old study (52). Decision tree modelling was used in 43% of economic evaluations (48, 53-57) and two stage models, a decision tree of the acute phase leading into a Markov model of the long term phase were used in 43% of evaluations (58, 59, 61-64, 67, 68). The more recent economic evaluations (costing year 2006-2010; all evaluating new oral anticoagulants) tended to favour the two stage modelling approach whilst older studies (costing year 1997 – 2010) tended to favour using decision tree models alone.

Economic evaluations of VTE prophylaxis can broadly be divided into three areas of research. Firstly studies examining the value of prophylaxis versus no prophylaxis (48, 52); secondly evaluation of competing injectable prophylaxis methods, heparin, LMWH and fondaparinux (54, 55) and treatment duration (53); and thirdly evaluations of new oral anticoagulant medications against LMWH and each other.

Both Davies and Saltzman (TKR only) (52) and the NICE VTE clinical guideline (48) concluded that prophylaxis was superior to no prophylaxis in TKR and THR. In terms of injectable prophylaxis Drummond et al. (54) found the LMWH enoxaparin to be cost effective on a per patient cost compared to unfractionated heparin (THR patients). Davies et al. (53) found that extended enoxaparin (21 days post discharge) was cost effective compared with

enoxaparin for the hospital admission period only, with a cost per incremental QALY of £5,732 in THR patients. Gordois et al. (55) found fondaparinux to be cost effective compared to enoxaparin in THR and TKR with less VTE events and a lower per person cost; this result was sensitive to the difference in the price of the drugs and the rate of late DVT assumed. Nicolaides and Bosanquet (57) found desirudin to be more cost effective than enoxaparin with a cost per life year saved of £2,566.

The new oral anticoagulant dabigatran was found to dominate enoxaparin in TKR and THR at a dose of 220mg od (58, 59, 64, 67). 150mg od of dabigatran dominated enoxaparin in THR and the reverse was found in TKR (64, 67). Fondaparinux was cost effective compared to dabigatran 220mg od and 150mg od in THR and TKR with ICERs below £12,000 per QALY (64, 67). Rivaroxaban was found to dominate both enoxaparin and dabigatran in TKR and THR (56, 60-63, 68). Summary details of all these studies are presented in Appendix 10 (Section 9.10.10).

6.1.3 Quality assessment

An adapted version of the Drummond quality checklist was used to appraise the included studies (See Appendix 11). Most studies satisfied the aspects of quality addressed. The exceptions were the oldest study (52) and conference abstracts (60-62), which often did not report enough information. The primary weaknesses were poor discussion of economic relevance of the research question and poor justification of the type of economic analysis (model) used.

Several studies were of limited relevance due to year of publication (pre-2000) (52, 54, 57). One study was older (52) but also a UK adaptation of a US model (69), a further potential limitation. One study was undertaken in Ireland using the Euro (56).

Clinical data were collected from published literature. In many cases, the details of clinical data collection (especially where meta-analyses were mentioned) were poorly described. Two HTA documents (63, 64) were developed by manufacturers and refer in places to confidential (unpublished) information. The third HTA document was a clinical guideline developed by NICE investigating VTE prophylaxis with a number of treatments across a number of indications (48). The more recent studies comparing rivaroxaban or dabigatran and enoxaparin use published data from the Phase III trials RECORD (29-31, 36), RE-NOVATE (33, 34), RE-MODEL (32).

Older studies typically covered a more limited timeframe from hospitalisation and up to 21 days later (52, 53). More recent studies also included longer term complications (55-57). Other recent studies presented a more comprehensive approach with a decision tree for the acute phase alongside a Markov model of the chronic aspects of the condition (58, 59, 61-64). discounting rates varied; Davies et al (53) discounted outcomes (1.5%) but not costs, Gordois et al (55) discounted costs but did not mention the discounting of benefits, the more recent studies follow current recommendations (70) and report a 3.5 discount rate in both costs and benefits accompanied by a 0-6% sensitivity analyses (58, 59, 61-64). Productivity costs were not included and generalisability issues were often completely omitted.

The clinical pathways reflected in the decision tree studies were similar. Most studies compared relevant alternative interventions (with explicit justification of choice of comparator); however, most studies did not compare their results with those of others who have investigated the same question.

6.2 De novo analysis

6.2.1 Patients

The patient groups included in the economic evaluation reflect the licensed indication for apixaban, that is, patients aged 18 years and over who have undergone elective total hip or knee replacement surgery. This is consistent with the Advance 2 (21) and 3 (20) trials, which are of TKR and THR patients respectively and of most relevance to UK clinical practice. TKR and THR are modelled separately to reflect the differences in VTE risk, treatment duration, patient characteristics and to reflect the appraisal scope.

To ensure the results of the economic modelling are representative of the UK population the age and gender estimates were taken from the 10th National Joint Registry report (5) (see Table 55).

Table 55: Comparison of age and gender of TKR and THR patients in apixaban trials versus National Joint Registry

	THR		TKR	
	Advance 3 (20)	NJR	Advance 2 (21)	NJR
Males	46.2–47.6%[§]	44%	26–30%[§]	43%
Age at initial surgery for males		65.89[#]		68.26[#]
Age at initial surgery for females		68.51[#]		68.14[#]
Age at initial surgery all	60.0–60.9*		65.1–66.0*	

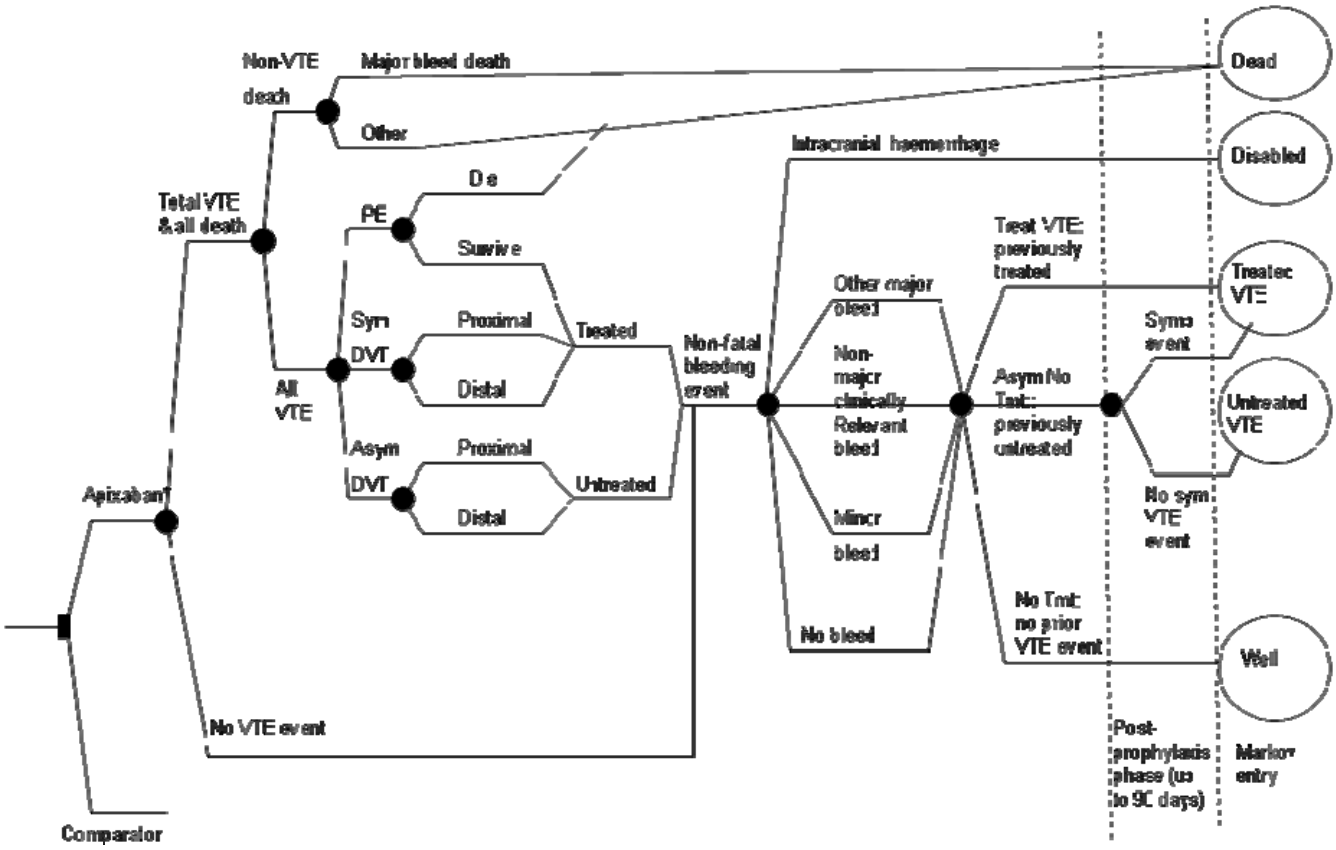
*Mean age in each arm of the trial; [#]Mean age; [§]% in each arm of the trial.

Model structure

6.2.2 Model schematic

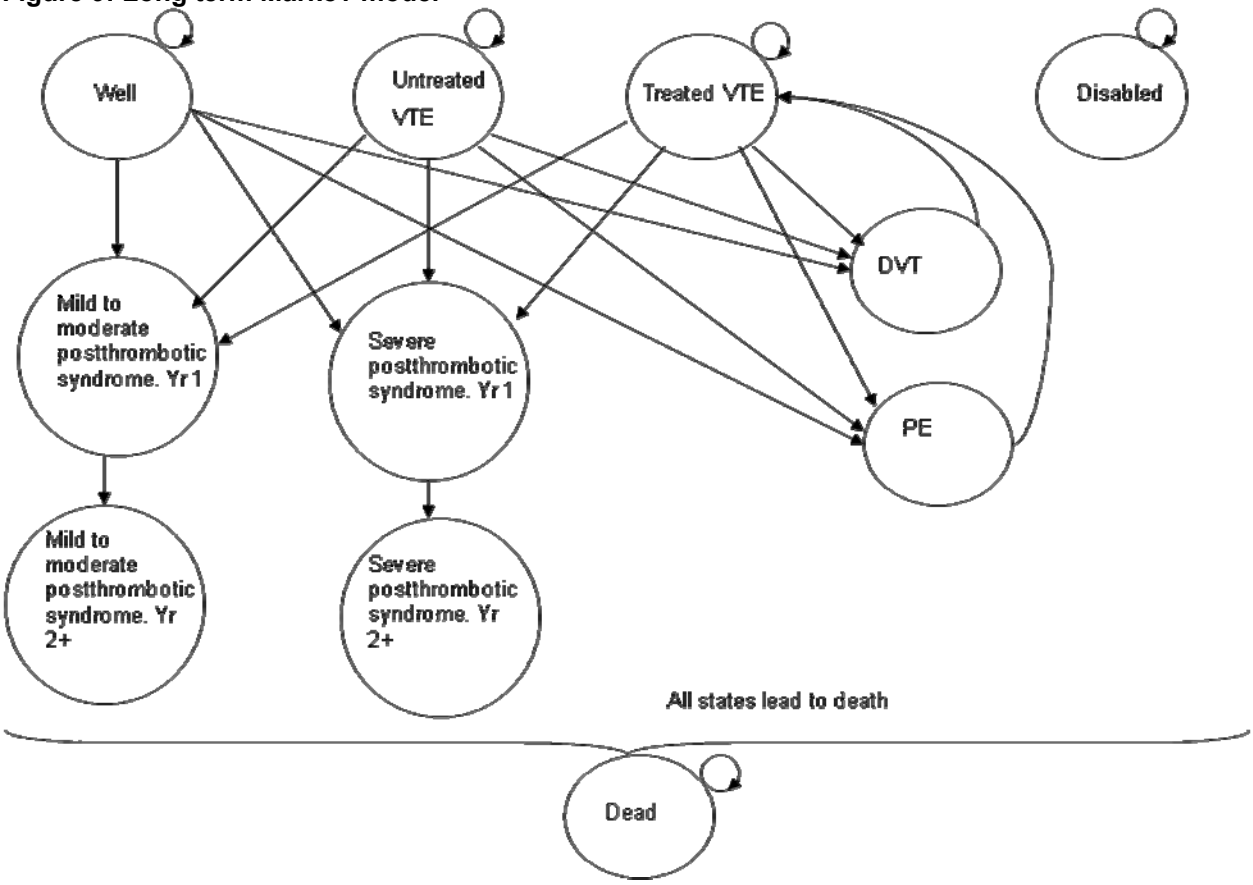
A two stage modelling approach has been adopted to model the VTE pathway. A decision tree has been used to model treatment in the acute phase (surgery to 90 days post surgery) and a Markov process model has been used to model the long-term events (90 days post surgery and beyond). The decision tree has been depicted in two figures for ease of examination, Figure 8 depicts the VTE events and bleeding events. Figure 9 depicts the long term Markov process model (90 days post surgery and beyond).

Figure 8: Prophylaxis and Post-Prophylaxis Phases – VTE and Bleeding Events



Note: Other deaths refer to non-VTE and non-treatment-related deaths.
Abbreviations: THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; Sym/Symp, symptomatic, Asym, asymptomatic; Tmt, treatment

Figure 9: Long term Markov model



Abbreviations: VTE; venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; Yr1, Year one; Yr2, Year two and beyond

6.2.3 Justification of model structure

The model is consistent with the clinical pathway of care identified in section 2.4 and meant to reflect the potential clinical events that a patient undergoing either THR or TKR may experience. The model treats TKR and THR separately as per the decision problem being addressed, and accounts for differential treatment periods for TKR and THR. Post surgery VTE and bleeding are captured in the decision tree and future events are modelled over the patients' lifetime in the Markov model. This modelling approach is consistent with the model for dabigatran which formed the basis of the submission to NICE in the appraisal of dabigatran (58, 71). The model structure is also based on those trial endpoints which are appropriately powered to show important clinical differences between apixaban and enoxaparin.

6.2.4 Definition of health states

The health states capture all the relevant conditions and events for TKR and THR patients at risk of developing VTE. The events covered include the VTE events of pulmonary embolism (PE), proximal symptomatic deep vein thrombosis (DVT), distal symptomatic DVT, proximal asymptomatic DVT, distal asymptomatic DVT; the bleeding events of intracranial haemorrhage, other major bleed, non-major clinically relevant bleed and minor bleed. The states in the Markov model component are: well, dead, disabled (intracranial haemorrhage),

untreated VTE (proximal and distal asymptomatic DVT), treated VTE (PE, proximal and distal symptomatic DVT), mild to moderate post thrombic syndrome (M/M PTS) and severe post-thrombic syndrome (severe PTS). The health states incorporated in the model allow the health related quality of life and costs (NHS and personal social services perspective) of VTE treatment in THR and TKR to be captured. Not all preceding models have accounted for asymptomatic DVT; it is included in the current model as it is a component of the primary outcome collected in the ADVANCE Trials (20, 21, 24). The American College of Chest Physicians (ACCP) consensus statement and EMEA (72) recommend the use of a composite endpoint comprising events with asymptomatic deep-vein thrombosis.

6.2.5 Context

As noted in section 2.1, VTE is a condition in which a blood clot (thrombus) forms in a vein. Thrombus' commonly form in the deep veins of the legs causing a DVT. The thrombus may dislodge and obstruct a blood vessel (embolism) (1). A PE occurs when a thrombus blocks a pulmonary artery or one of its branches. The immediate post surgery risks of VTE and bleeding events are captured in the decision tree. The long term events (treatment effects) are captured in the Markov model. The disease progression is graphically displayed in Figure 8 and Figure 9.

Prophylaxis and Post-Prophylaxis Phases
Once a patient is allocated to a treatment arm e.g. apixaban, they can experience no event or an event (total VTE or all cause death). No event leads to the non-fatal bleeding events element of the tree. From the events branch (label = Total VTE + All Death) a patient can die due to non-VTE causes and so cause of death is segregated into major bleed death and other causes of death. Alternatively, from the event branch a patient can experience a PE, symptomatic DVT or an asymptomatic DVT. A PE can lead to death or survival. Symptomatic and asymptomatic DVT patients are divided into those with a distal and a proximal DVT. Surviving PE patients and all symptomatic DVT patients receive treatment and progress to the non-fatal bleeding events state of the model. Asymptomatic DVT patients are not treated, as the patient is unaware of their condition, and they progress in the model to the non-fatal bleeding events state.

The non-fatal bleeding events element of the model accounts for the numerous types of adverse bleeding events possible following TKR and THR surgery. Patients experiencing an intracranial haemorrhage proceed immediately to the disabled health state and remain there for the duration of the model or until they die (depending on the model duration applied). Alternatively patients can experience no bleeding, minor bleeding, a non-major clinically relevant bleed or a major bleed (other than an intracranial haemorrhage).

In the period between the end of prophylaxis and 90 days post surgery asymptomatic patients can become symptomatic. At 90 days post surgery patients leave the decision tree model and enter the long term Markov model. Patients that have not experienced a VTE event enter the Markov in the well state whereas patients that are asymptomatic enter the Markov in the untreated VTE state. Patients that have had a PE or a DVT or have transitioned from asymptomatic to symptomatic (had a DVT) enter the Markov in the treated VTE state. Patients that have had an intracranial haemorrhage enter in the disabled state. Patients that died in the decision tree enter the Markov in the dead state.

In the long term Markov patients can remain well, die, have a PE, have a DVT, have mild to moderate post thrombic syndrome (segregated into year one and subsequent years) or a severe post thrombic syndrome (segregated into year one and subsequent years). The same transitions are possible for treated and untreated patients. Once a patient has a PE or DVT they transition to the treated VTE state.

6.2.6 Key features of the economic evaluation

Table 56: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	90 days + 35 years	The 90 day time horizon corresponds to the prophylaxis and post-prophylaxis periods as recommend by Sullivan et al. (2003) (73) (symptomatic VTE has been reported in patients undergoing THR or TKR at 90 days post-surgery). This is the period during which occurrence of events can reasonably be attributed to the anticoagulation given for surgical prophylaxis. The 35 year long-term period provides a life-time time horizon to capture changes in the rate of VTE recurrence and further longer term complications such PTS which is a chronic condition that develops in 30–50% of patients within 1 to 2 years of symptomatic DVT. The NICE reference case and the scope for this appraisal require a lifetime time horizon.	(20, 21, 70, 74, 75)
Cycle length	1 year	The 1 year cycle length was chosen to facilitate a maximum lifetime analysis. This cycle length is short enough to capture in sufficient detail the occurrence of events and long enough that the model is not technically overburdened. A one year cycle length has been used in preceding VTE models	(58)
Half-cycle correction	No	As was the case in the dabigatran STA model a half-cycle correction was not applied in the Markov model as the cycle length is short compared to the model time frame	(64)
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs and life years	As VTE and bleeding events result in morbidity and mortality the QALY is the most appropriate outcome measure to capture the health outcomes in this economic evaluation. Both the NICE reference case and the scope for this appraisal require benefits to patients to be valued in QALYs.	(70)
Discount of 3.5% for utilities and costs	Utilities and costs were discounted at 3.5%	Recommended in the NICE Guide to methods of technology appraisal	(70)
Perspective (NHS/PSS)	NHS	No significant PSS costs were identified in the clinical pathway.	(70)

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; QALYs, Quality-adjusted life years.

Technology

6.2.7 Intervention and comparator

Apixaban. BMS and Pfizer

The intervention and comparators are implemented as per their marketing authorisations/CE marking and doses. The indication considered in the economic evaluation is the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery.

As indicated in the SPC for apixaban (see Appendix 1):

- Administration is oral, a film-coated tablet.
- Dosing is 2.5mg tablet to be taken twice a day. The initial dose should be administered 12 to 24 hours post surgery.
- Average length of treatment is 32-38 days for hip replacement and 10-14 days for Knee replacement.
- Dose adjustments are not required. Apixaban can be used with caution in patients with a creatinine clearance 15-29 ml/min.

The scope of this appraisal requires apixaban to be compared with the low molecular weight heparin (LMWH) enoxaparin, dabigatran, rivaroxaban and fondaparinux. However, a comparison with fondaparinux could not be undertaken because of insufficient data on the primary endpoint to allow an indirect comparison. The licensed doses for each of these are as follows: enoxaparin 40mg od administered 12 hours before surgery (76), dabigatran 150mg and 220mg od, rivaroxaban 10mg od, fondaparinux 2.5mg od administered 6 hours post surgery (76, 77). For simplicity a comparison with enoxaparin only is made in the base case, as it is the most widely used LMWH. Therefore, the indirect comparison results for apixaban versus enoxaparin are used only. This approach assumes that LMWHs are broadly clinically equivalent, which was an assumption also made in the NICE appraisal of dabigatran for VTE prevention in orthopaedic patients (64) and is consistent with the analyses underpinning the VTE prevention NICE guidelines too (1). Sensitivity analyses are undertaken using a weighted cost of LMWHs but clinical data for tinzaparin and dalteparin are not explicitly incorporated into the model.

Enoxaparin 40mg od is the most appropriate dose as this is the licensed dose in Europe. Sensitivity analyses are undertaken to provide transparency, including evidence for enoxaparin 30mg bd even though this dose is not licensed for VTE prevention in Europe.

Table 57: Duration of treatment

Drug	Trial	Condition	Duration of treatment in days			
			Mean	SD	Median	Range
Apixaban	Advance-2 (21)	TKR	12.1	3.2	-	-
	Advance-3 (20)	THR	34	7.7	-	-
Enoxaparin/LMWH	Advance-2 (21)	TKR	12.1	2.8	-	-
	Advance-3 (20)	THR	33.9	7.8	-	-
Rivaroxaban	Record 3 (30)	TKR	11.9	NS	-	-
	Record 1 (29)	THR	33.4	NS	-	-
	Record 2 (31)	THR	33.5	6.9	-	-
Dabigatran	RE-MODEL (32)	TKR	-	-	8*	2–14 (92% 6 to 10)
	RE-NOVATE (33)	THR	-	-	32	1–47 (87% 28-35)

NS = not stated. * When Dabigatran was compared to the US dose of enoxaparin 30mg bd it was administered for a longer period of time (median duration = 14, range = 1 to 18)

No other concomitant therapies are required with apixaban. However, mechanical prophylaxis methods such as graduated elasticated compression stockings, intermittent pneumatic foot compression or foot impulse devices can be used with apixaban therapy and are used with its comparators (see trials listed in Table 57). It is therefore assumed that mechanical prophylaxis is used equally in all patients regardless of pharmacological intervention, and is not considered as a comparator in this economic evaluation. Duration of treatment is based upon mean trial length, and in the absence of these data it is based on the median trial length.

6.2.8 Treatment continuation rule

A clinical continuation rule has not been assumed as it is not applicable to this intervention or its comparators.

6.3 Clinical parameters and variables

6.3.1 How where clinical data implemented in the model?

1. Efficacy and safety model endpoints

The primary outcome collected in the ADVANCE (20, 21), RECORD (29, 30), RE-MODEL and RE-NOVATE (32, 33) trials was 'total VTE and all deaths' (See section 5.7.6). Total VTE and all deaths comprise of all adjudicated VTE and all cause death and adjudicated, symptomatic or asymptomatic DVT, non-fatal PE and death from any cause. The primary safety outcome for the ADVANCE (20, 21), RECORD (29, 30), RE-MODEL and RE-NOVATE (32, 33) trials was 'total bleeds' which comprised bleeding at the surgical site, non-surgical bleeding events, clinically relevant non-major bleeding and minor bleeding events (the RECORD trials also assessed these outcomes) (See section 5.7.6). The composites and their elements are displayed graphically in Figure 8. Total VTE and all deaths and all bleeds are therefore the primary efficacy and safety parameters that are implemented into the model.

Enoxaparin has been used as the reference treatment in the model. Both the reference treatment rates and the apixaban relative risk were taken from the ADVANCE-2 (21) head to head trial for TKR patients, and from the ADVANCE-3 (20) head to head trial for THR (see Table 58). In the absence of head to head RCT evidence for apixaban 2.5 mg bd versus rivaroxaban 10 mg od, dabigatran 220 mg od, and fondaparinux 2.5 mg od, an adjusted indirect comparison approach using the Bucher method (47) was adopted to derive efficacy and safety relative risks (see Table 58). As data for an indirect comparison was not available, apixaban could not be compared with fondaparinux in the model. A primary efficacy population was used rather than ITT for all VTE and all cause death as the asymptomatic DVT outcome can only be detected via an evaluable venogram, so a population for which an evaluable venogram was available was appropriate as the denominator in the analyses (see section 5.6.1 for further detail). A mixed treatment comparison (MTC) was also undertaken of relevant trial data, the results are assessed in a sensitivity analysis (ADVANCE 1 and MTC relative risks are presented in Appendix 22, methodology is discussed in Appendix 16).

Relative risks (RR) are used in the economic model rather than odds ratios (OR) because they can be applied directly to an absolute probability of an event to generate the absolute event rate for the comparator treatment (78).

Table 58: Composite VTE and bleed rates

	THR: All VTE & All cause death (95% CI)	TKR: All VTE & All cause death (95% CI)	THR: Any bleeding (95% CI)	TKR: Any bleeding (95% CI)
	Primary efficacy population analysis		ITT analysis	
Baseline risk (Enoxaparin 40mg OD)	4.58%	26.29%	9.39%	8.75%
Apixaban RR	0.359 (0.232–0.555)	0.618 (0.514–0.743)	0.93 (0.81–1.08)	0.83 (0.64–1.06)
Rivaroxaban RR	0.3 (0.18–0.51)	0.507 (0.395–0.651)	1.02 (0.81–1.29)	1.02 (0.72–1.44)
Dabigatran RR	0.887 (0.696–1.131)	0.965 (0.822–1.133)	1.07 (0.86–1.34)	0.96 (0.76–1.22)

2. Post event treatment independent probabilities

The remaining clinical probabilities in the decision tree element of the model were assumed to be treatment independent and assumed to not differ between apixaban, enoxaparin, dabigatran and rivaroxaban. This approach was taken as the trials for apixaban, rivaroxaban and dabigatran are only powered to detect differences in the composite primary efficacy and safety endpoints. Basing a cost effectiveness assessment on the components of these composite endpoints would introduce spurious chance findings and potentially bias the results. There is no reason to assume that the incidence of VTE events being detected pre discharge, VTE adverse event sequela or type of major bleed can be attributed to the type of prophylaxis employed (64). This approach was also adopted for pragmatic reasons as to derive relative risks for each probability in the decision tree from an adjusted indirect comparison would not be possible. Also, an alternative approach would be to use event incidence data from UK specific registry data, however, this type of data source was not available. To be consistent the approach taken in comparing with the NOACs was adopted in the comparison with enoxaparin in the base case analysis. However, a sensitivity analysis is undertaken where trial data from the ADVANCE 2 and ADVANCE 3 (20, 21) for total VTE and all-cause death, PE, Symptomatic DVT, asymptomatic DVT, all bleeding events, major, non major clinically relevant and minor bleeds were used rather than NOAC data to compare enoxaparin with apixaban.

Where possible the probabilities for the post event treatment independent probabilities were obtained from a synthesis of the published and available data for rivaroxaban (29-31, 36), dabigatran (32, 33), and apixaban (20, 21, 24). For endpoints that were not reported in the RECORD (29-31, 36), RE-MODEL (32) and RE-NOVATE (33) trials data was extracted from both arms of the ADVANCE-2 and 3 trials (20, 21) (See Table 59 and Table 60). The decision to combine both apixaban and enoxaparin outcomes (ADVANCE-2 and 3 trials) was taken as the number of events recorded was small and it was likely that using apixaban results alone would introduce chance findings and potentially bias the results for all the interventions evaluated.

The total numbers of events available in the literature were extracted for the event type distributions for VTE events and bleeding events. To obtain the blended rates, the sum of events was taken across trials and event types thus providing a numerator yielding a total count for each event type. The denominator was obtained by summing all event counts within an endpoint (VTE or any death, Bleeds) (cumulative incidence, see section 6.3.2). Appendix 17 provides the detail as to how each probability was derived.

Table 59: Conditional Post-Event Distributions for All VTE and all-cause death – drug treatment independent

	THR			TKR		
	Prob-ability	**Source**	**Calculation**	**Prob-ability**	**Source**	**Calculation**
All VTE Events	96.5%	All	100% – 3.5% (Non-VTE Death)	96.5%	All	100% – 3.5% (Non-VTE Death)
PE	3.6%	All	-	3.6%	All	-
Die (CFR)	12.5%	ADVANCE-3	-	25.0%	ADVANCE-2	-
Survive	87.5%	ADVANCE-3	100% – 12.5% (Die (CFR))	75.0%	ADVANCE-2	100%-25% (Die (CFR))
Sym DVT	2.6%	All	-	4.5%	All	-
Distal	16.7%	ADVANCE-3	-	80.0%	ADVANCE-2	-
Proximal	83.3%	ADVANCE-3	100% – 83.3% (Distal)	20.0%	ADVANCE-2	100%-80.0% (Distal)
Asym DVT	93.8%	All	100% – (3.6%+2.6%) (Pe+Sym DVT)	91.9%	All	100% – (3.6%+2.6%) (Pe+Sym DVT)
Distal	73.8%	ADVANCE-3	-	91.2%	ADVANCE-2	-
Proximal	26.2%	ADVANCE-3	100%–73.8% (Distal)	8.8%	ADVANCE-2	100%-91.2% (Distal)
% of Asym -> Sym (60 days)	0.0%	ADVANCE-3	-	0.5%	ADVANCE-2	-
Distal	0.0%	ADVANCE-3	-	58.0%	ADVANCE-2	-
Proximal	100.0%	ADVANCE-3	100%–0.0% (Distal)	42.0%	ADVANCE-2	100% – 58% (Distal)
Non-VTE Death	3.5%	All	-	3.5%	All	-
Due to Major Bleed	0.0%	ADVANCE-3	-	0.0%	ADVANCE-2	-
Other Cause	100.0%	ADVANCE-3	100% – 100% (Major Bleed)	100.0%	ADVANCE-2	100% – 100% (Major Bleed)

Note: All – all NOAC trial

Table 60: Conditional Post-Event Distributions for Bleeding Events – drug treatment independent

	THR		TKR	
	Probability	**Source**	**Probability**	**Source**
ICH	0.0%	All	0.0%	All
% Disabled	0.0%	All	0.0%	All
Major Bleed - Other	7.5%	All	7.5%	All
NMCR	34.1%	All	34.1%	All
Minor	58.3%	All	58.3%	All

Note: All – all NOAC trial

3. Long term recurrent risks of VTE and PTS – drug treatment independent

A literature review was carried out to identify parameter estimates for the long term risk of recurrent VTE and/or the development of PTS in TKR and THR patients who suffered a VTE event (75). Four searches were conducted using the Embase and PubMed search engines. Two of the searches were conducted in Embase and replicated in PubMed. The full methods and results of the search (75) are presented in Appendix 18. The data used to estimate these risks is described below by outcome. The method for estimating these risks is described in section 6.3.2.

DVT

One of the studies identified,(79) provided full cumulative rate curves showing the rate of DVT among VTE patients. Additionally, Prandoni reported a hazard ratio for surgery patients of 0.36 – indicating that surgery patients are less at risk of DVT than other types of VTE patients, as suspected. Using this hazard ratio combined with values of DVT digitized from the cumulative rate curves, rates of DVT among surgery VTE patients were found. This method is detailed in 'Rate Estimation Using Rate Curve and Hazard Ratio' (see section 6.3.2 below).

The estimate for the DVT risk among untreated patients was based on Table 3 of Imperiale and Speroff (1994) (80). This table reports an unadjusted pooled risk of 0.42 for all types of DVT in control arm patients with a confidence interval from 0.40 to 0.53. By assuming this is a life-time risk, rather than an annual risk (no time-specifics are given by Imperiale and Speroff), this rate was adjusted by assuming the rate would decrease in a manner similar to that seen in treated patients as reported by Prandoni et al. Since DVT risk is near 0 by year 7, the life-time risk was spread over 7 years.

Pulmonary embolism (PE)

PE rates were not provided in any of the articles identified in the review. As a result, a meta-analysis article by Imperiale and Speroff (1994) (80) was used as the reference for rates of pulmonary embolism in orthopaedic surgery patients. This meta-analysis is focused specifically on total hip replacement patients. Table 3 of Imperiale and Speroff (1994) (80) reports that of patients in study control arms, the unadjusted pooled risk of pulmonary embolism was 2.4%. Based on this result, 2.4% is the estimate used for the 7-year rate of PE among patients untreated for VTE. Heparin, low-molecular-weight heparin, compression stockings, and warfarin treatment groups all had unadjusted PE risks that were lower than the 2.4% found for the control arms. The risk estimates for these treatment groups were 2.1%, 0.4%, 0.5%, and 1.6%, respectively. The average of these four rates, 1.15%, is used as the estimate for the 7-year rate of PE among VTE treated patients. Since it is assumed that PE during the first year following surgery is more likely that during the 2nd year following surgery (which in turn is more likely than during the 3rd year after surgery), the overall rates

of 2.4% and 1.15% were then annualized assuming an annual risk decrease similar to that reported by Prandoni et al (1996) (79) for DVT.

Post Thrombotic Syndrome (PTS)
The literature search yielded five useful sources of data on PTS in hip and knee replacement surgery patients. These five sources were based on studies that varied widely in their timing of veinography screenings following surgery, the timing of follow-up, and the severity of PTS observed. This wide variation made a formal meta-analysis of PTS rates impossible.

Just as Prandoni et al (1996) (79) provided curves displaying the rate of DVT through time, curves of PTS were also provided. The rates for PTS in VTE treated patients was derived using the Prandoni et al PTS rate curves and the 0.36 surgery group hazard ratio provided for DVT using the same method detailed in the 'Rate estimation using rate curve and hazard ratio' above that was used to estimate the risk of DVT. This yielded a risk estimate of 0.0743 at year 1 (for all types: mild, moderate, and severe) with a recommended sensitivity analysis range from 0.034 to 0.1495. These results were then compared to the range of values reported in the five extracted studies to verify the 0.36 hazard ratio for DVT provided reasonable estimates for PTS. Since the rates reported in the five extracted studies ranged from 0.05 to 0.13 (each rate based on a different time frame, many over 1 year), the 0.034 to 0.1495 range was judged reasonable.

Severe PTS
The rate estimates for severe PTS at years 1 through 8 were made using the digitized values from the Prandoni et al. (1996) (79)rate curves for severe PTS that were then adjusted using the 0.36 surgery group hazard ratio. The estimate of risk in any one-year time window beginning in year t, was found by subtracting the cumulative risk of severe PTS by time t from the cumulative risk at time t+1. Using this approach, it became clear that the risk in years 5 through 8 was near zero.

Estimates of severe PTS among untreated patients were then found by assuming rates would be 2 to 2.5 times higher without treatment. This assumption is based on the following statements in Prandoni et al. (1996) (79), "Mild-to-moderate PTS occurred in 19 (20%) of the 96 patients with stockings and in 46 (47%) of the 98 patients without stockings" and "Eleven (11.5%) patients in the stocking group developed severe PTS, while this occurred in 23 (23.5%) patients without stockings." To implement this, the lower bound of the estimate range was multiplied by 2, the upper bound was multiplied by 2.5, and the point estimate was set to the midpoint of this new range.

Mild/Moderate PTS
The rate estimates for mild/moderate PTS at years 1 through 8 were made by first estimating the overall PTS risk. This was done because Prandoni et al. (1996) (79) reports a set of rate curves for "All PTS", but not for mild/moderate PTS specifically.

The overall PTS digitized rates were adjusted and analyzed using the same method applied when estimating risks for severe PTS. Once the risks of any type of PTS were found, the difference between these risks and the risks for severe PTS were found and used as the risk of mild/moderate PTS. Using this approach, it became clear that just as was seen in severe PTS, the risk in years 5 through 8 was near zero.

The treatment independent, time dependent rates of recurrent DVT, PE, mild/moderate PTS and severe PTS for well patients was zero in all years.

Table 61: Time Dependent Rates of Recurrent DVT by Treatment Status – drug treatment independent

	Treated VTE to DVT				Untreated VTE to DVT		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.054760	0.022320	0.108320		0.214495	0.182549	0.241877
year 2	0.022820	0.012280	0.041000		0.089386	0.076073	0.100797
year 3	0.014120	0.008460	0.026740		0.055308	0.047071	0.062369
year 4	0.009300	0.006020	0.019540		0.036428	0.031003	0.041078
year 5	0.009060	0.004240	0.014630		0.035488	0.030203	0.040018
year 6	0.005190	0.004200	0.015210		0.020329	0.017301	0.022924
year 7+	0.004740	0.001950	0.008890		0.018567	0.015801	0.020937

Table 62: Time Dependent Rates of Recurrent PE by Treatment Status – drug treatment independent

	Treated VTE to PE				Untreated VTE to PE		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.005248	0.009242	0.00194		0.010953	0.005933	0.000383
year 2	0.002187	0.003851196	0.000808		0.004564	0.002472	0.000160
year 3	0.001353	0.002383	0.0005		0.002824	0.001530	0.000099
year 4	0.000891	0.00157	0.000329		0.001860	0.001008	0.000065
year 5	0.000868	0.001529	0.000321		0.001812	0.000982	0.000063
year 6	0.000497	0.000876	0.000184		0.001038	0.000562	0.000036
year 7+	0.000454	0.0008	0.000168		0.000948	0.000514	0.000033

Table 63: Time Dependent Rates of Mild/Moderate PTS by Treatment Status – drug treatment independent

	Treated VTE to Mild/Moderate PTS				Untreated VTE to Mild/Moderate PTS		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.063240	0.031980	0.118970		0.180693	0.063960	0.297425
year 2	0.008290	0.003630	0.015420		0.022905	0.007260	0.038550
year 3	0.009920	0.003510	0.017550		0.025448	0.007020	0.043875
year 4	0.006370	0.005810	0.013250		0.022373	0.011620	0.033125
year 5+	0.002410	0.001000	0.003120		0.004900	0.002000	0.007800

Table 64: Time Dependent Rates of Severe PTS by Treatment Status – drug treatment independent

	Treated VTE to Severe PTS				Untreated VTE to Severe PTS		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.011210	0.002080	0.030740		0.040505	0.004160	0.076850
year 2	0.006290	0.006180	0.030100		0.043805	0.012360	0.075250
year 3	0.013460	0.004350	0.013710		0.021488	0.008700	0.034275
year 4	0.006590	0.001250	0.009140		0.012675	0.002500	0.022850
year 5+	0.006770	0.000100	0.000820		0.001125	0.000200	0.002050

6.3.2 Transition probabilities

Cumulative incidence

As the decision tree element of the model was designed to reflect the health states and time horizons of the relevant anticoagulant trials [ADVANCE, RECORD, RE-MODEL and RE-NOVATE] (20, 21, 29, 30, 32, 33) transition probabilities were calculated using the cumulative incidence method (81). For example if 2 of 500 patients experience a minor bleed within 90 days of surgery, the probability or cumulative incidence is 0.004 (2/500).

Rate estimation using rate curve and hazard ratio

Consider the hazard function h(t) where h(t)dt is the probability a person presents with VTE in the open time interval from t to t+dt, conditional on the person's not presenting with VTE prior to time t.

Let S(t), be the value of the survival function at time t as reported in the available survival curve.

Combining h(t) with S(t) allows us to determine f(t), the unconditional probability of a person first presenting with VTE in the t to t+dt time interval.

$$f(t) = h(t)dt \times S(t)$$

S(t) can be expressed as a mixture of $S_S(t)$, the survival function of surgery patients, and $S_N(t)$, the survival function of non-surgery patients, in the following way:

$$S(t) = (p_s \times S_s(t)) + (p_N \times S_N(t))$$

Where p_S=the proportion of study patients who are in the surgery subgroup and p_N=the proportion of patients not in the surgery subgroup. By this definition, $1-p_S=p_N$.

Additionally, $S_N(t)$ can be expressed as a function of $S_S(t)$ using the reported hazard ratio, r. Specifically,

$$S_N(t) = (S_S(t))^{1/r}.$$

From here it directly follows that:

$$S(1) = (p_S \times S_S(1)) + \left(p_N \times (S_S(1))^{1/r}\right).$$

From Prandoni et al. (1996) (79), p_S=68/355=0.1915 and p_N=287/355=0.8085. The rate of VTE at 1 year is 0.127 based on the curve presented in figure 1 (79). This rate indicates 0.873 is the rate of not yet presenting with recurrent VTE by year 1 so S(1)=0.873. This yields:

$$0.873 = \left(0.1915 \times S_S(1)\right) + \left(0.8085 \times \left(S_S(1)\right)^{1/0.86}\right)$$

which can be solved numerically using the Newton-Raphson method to minimize:

$$\left(\left(0.1915 \times S_S(1)\right) + \left(0.8085 \times \left(S_S(1)\right)^{1/0.86}\right) - 0.873\right)^2.$$

Newton-Raphson was applied using the R statistical software package. The results were presented in table form in Excel and these survival outcomes were transformed back into annual risk rates.

6.3.3 Variation of transition probabilities over time

Transition probabilities in the Markov model are assumed to vary over time for the transition from treated and untreated VTE to DVT, PE, mild to moderate and severe PTS. This has been accounted for in the model; see Table 58, Table 59, Table 60, Table 61, Table 62, Table 63 and Table 64 above in section 6.3.1.

6.3.4 Linking intermediate outcome measures to final outcomes

No intermediate or surrogate measures were used in the model. All progression (transition probabilities) was based on risks identified for the progression from one health state to another in the literature.

6.3.5 Clinical experts

Experts were not used to assess the applicability or estimate values used in the model.

Summary of selected values

6.3.6 Summary list of variables used

Table 65–

Table 69 below outline the parameter values used in the economic model.

Table 69 outlines the discounting values, demographic, treatment duration and all cause mortality parameters. The prophylaxis and post-prophylaxis efficacy and adverse event parameters**,** and the long term efficacy and adverse event parameters are presented in Table 66 and Table 67. Resource use and unit costs, and health state utilities (decrements and applicable durations) are presented in Table 68 and

Table 69. Tables 65 to 69 all contain the value used in the model, units in which the values are measured, standard error where applicable, distributions applied in the probabilistic sensitivity analysis, shape and scale parameters used in the probabilistic sensitivity analysis and the data sources.

Distributions selected

Cost data has been utilised in a gamma distribution. The gamma distribution was selected as it is considered to reflect the distribution of costs usually seen; all values are positive and are positively skewed (constrained by zero to positive infinity) (82). Utilities and utility decrements were utilised in beta and gamma distributions respectively as recommended by Briggs et al (2006) (82). Dichotomous bleeding and efficacy data which have a binomial distribution were used in a beta distribution which is conjugate to the binomial (82). As relative risks/risk ratios are made up of ratios it is natural to log transform the data to obtain confidence intervals. As a result the lognormal distribution can be used to fit this data (82). Duration of prophylaxis treatment was assumed to be normally distributed and was utilised in a normal distribution. The parameters, distributions and shape and scale parameters used in the probabilistic sensitivity analysis are presented in tables 65 to 69.

Table 65: Discounting, age, duration and all cause mortality parameters

Variable	Value	SE	Units	(distri-bution)	Shape and scale parameters		Reference	Ref to section in submission
					α	β		
Discount rate for costs	0.035	-	%	Fixed	-	-	(70)	6.2.6
Discount rate for health	0.035	-	%	Fixed	-	-		
Age at initial THR surgery for males	65.89	0.079111	Years	Fixed	-	-	(5)	
Age at initial THR surgery for females	68.51	0.066071	Years	Fixed	-	-		
Age at initial TKR surgery for males	68.26	0.054678	Years	Fixed	-	-		
Age at initial TKR surgery for females	68.14	0.050082	Years	Fixed	-	-		
Long-term time horizon	35	-	Years	Fixed	-	-	Life span of a max of 100 ys (83)	
Post Prophylactic Period Ends	90	-	Days	Fixed	-	-		
Treatment duration for THR								
Apixaban	34	0.179021	Days	Normal	-	-	(20)	2.6.7

Variable	Value	SE	Units	(distri-bution)	Shape and scale parameters		Reference	Ref to section in submission
					α	β		
Enoxaparin	34	0.182384	Days	Normal	-	-	(20)	
Rivaroxaban	33	0.179021	Days	Normal	-	-	(31)*	
Dabigatran	32	1.949918	Days	Normal	-	-	(33)#	
Treatment duration for TKR								
Apixaban	12	0.106254	Days	Normal	-	-	(21)	2.6.7
Enoxaparin	12	0.092263	Days	Normal	-	-	(21)	
Rivaroxaban	12	0.085052	Days	Normal	-	-	(30) SE (RECORD 4) (36)	
Dabigatran	8	1.053682	Days	Normal	-	-	(32) #	
Annual all cause mortality hazards								
Males								
40–44 (yrs)	0.001823	-	hazards	Fixed	-	-	Average of the 5 annual hazards in each age group (83)	
45–49 (yrs)	0.002685	-			-	-		
50–54 (yrs)	0.004215	-			-	-		
55–59 (yrs)	0.006719	-			-	-		
60–64 (yrs)	0.010458	-			-	-		
65–69 (yrs)	0.017071	-			-	-		
70–74 (yrs)	0.027292	-			-	-		
75–79 (yrs)	0.046499	-			-	-		
80–89 (yrs)	0.104027	-			-	-		
90–99 (yrs)	0.244843	-			-	-		
Females								
40–44 (yrs)	0.001125	-	hazards	Fixed	-	-	Average of the 5 annual hazards in each age group (83)	
45–49 (yrs)	0.001742	-			-	-		
50–54 (yrs)	0.002811	-			-	-		
55–59 (yrs)	0.004294	-			-	-		
60–64 (yrs)	0.006714	-			-	-		
65–69 (yrs)	0.010630	-			-	-		
70–74 (yrs)	0.017813	-			-	-		
75–79 (yrs)	0.031396	-			-	-		
80–89 (yrs)	0.078907	-			-	-		
90–99 (yrs)	0.221339	-			-	-		

* No SE recorded for rivaroxaban in THR so it was conservatively set equal to the lowest SE (Apixaban).
# Estimated 95% CI for the calculation of the SE based on extrapolating the based on 92% CI range in TKR and 87% CI in THR.

Table 66: Prophylaxis and post-prophylaxis phase efficacy and adverse event parameters

Variable	Value	95% CI	Units	(distri-bution)	Shape and scale parameters		Reference	Ref to section in sub-mission
					α	β		
THR: All VTE + All cause death (Base case)								
Enoxaparin 40mg od (baseline risk)	4.58%		%	Fixed				6.3.1
Apixaban	0.359	0.232–0.555	RR	Lognormal	–1.02443	0.222508		
Rivaroxaban	0.3	0.18–0.51	RR	Lognormal	–1.20397	0.265677		
Dabigatran	0.887	0.696–1.131	RR	Lognormal	–0.11991	0.123854		
THR: Bleeds								
Enoxaparin 40mg od (baseline risk)	9.39%		%	Fixed				6.3.1

Variable	Value	95% CI	Units	(distri-bution)	Shape and scale parameters		Reference	Ref to section in sub-mission
Apixaban	0.93	0.744–1.116	RR	Lognormal	–0.07257	0.103435		
Rivaroxaban	1.02	0.81–1.29	RR	Lognormal	0.019803	0.118715		
Dabigatran	1.07	0.86–1.34	RR	Lognormal	0.067659	0.113136		
TKR: Total VTE + All Death (Base case)								
Enoxaparin 40mg od (baseline risk)	26.29%		%	Fixed				6.3.1
Apixaban	0.618	0.514–0.743	RR	Lognormal	–0.48127	0.093998		
Rivaroxaban	0.507	0.395–0.651	RR	Lognormal	–0.67924	0.127455		
Dabigatran	0.965	0.822–1.133	RR	Lognormal	–0.03563	0.081858		
TKR: Bleeds								
Enoxaparin 40mg od (baseline risk)	8.75%		%	Fixed				6.3.1
Apixaban	0.83	0.64–1.06	RR	Lognormal	–0.18633	0.128713		
Rivaroxaban	1.02	0.72–1.44	RR	Lognormal	0.019803	0.118715		
Dabigatran	0.96	0.76–1.22	RR	Lognormal	–0.04082	0.120737		
THR - treatment independent								
All VTE Events	96.5%	-	%	Fixed	Inverse of Non-VTE Death		(20, 21, 24, 29-33, 36, 75)	6.3.1
PE	3.6%	-	%	Fixed	-	-		
Die (CFR)	12.5%	-	%	Fixed	-	-	(20)	
Survive	87.5%	-	%	Fixed	Inverse of Die (CFR)			
Sym DVT	2.6%	-	%	Fixed	-	-	(20, 21, 24, 29-33, 36, 75)	
Distal	16.7%	-	%	Fixed	Inverse of Proximal		(20)	
Proximal	83.3%	-	%	Fixed	-	-		
Asym DVT	93.8%	-	%	Fixed	Inverse of PE and Sym DVT		(20, 21, 24, 29-33, 36, 75)	
Distal	73.8%	-	%	Fixed	Inverse of Proximal		(20)	
Proximal	26.2%	-	%	Fixed	-	-		
% of Asym -> Sym (60 days)	0.0%	-	%	Fixed	-	-		
Distal	0.0%	-	%	Fixed	-	-		
Proximal	100.0%	-	%	Fixed	-	-		
Non-VTE Death	3.5%	-	%	Fixed	-	-	(20, 21, 24, 29-33, 36, 75)	
Due to Major Bleed	0.0%	-	%	Fixed	-	-	(20)	
Other Cause	100.0%	-	%	Fixed	-	-		
Bleeding								
ICH	0.0%	=	%	Fixed	-	-	(20, 21, 24, 29-33, 36, 75)	6.3.1
% Disabled	0.0%		%	Fixed	-	-		
Major Bleed - Other	7.5%		%	Fixed	-	-		
NMCR	34.1%		%	Fixed	-	-		
Minor	58.3%		%	Fixed	Inverse of Major Bleed – Other and NMCR			
TKR - treatment independent								
All VTE Events	96.5%		%	Fixed	Inverse of Non-VTE Death		(20, 21, 24, 29-33, 36, 75)	6.3.1
PE	3.6%		%	Fixed	-	-		
Die (CFR)	25.0%		%	Fixed	-	-	(21)	
Survive	75.0%		%	Fixed	Inverse of Die (CFR)			
Sym DVT	4.5%		%	Fixed	-	-	(20, 21, 24, 29-33, 36, 75)	
Distal	80.0%		%	Fixed	Inverse of Proximal		(21)	

Variable	Value	95% CI	Units	(distri-bution)	Shape and scale parameters		Reference	Ref to section in sub-mission
Proximal	20.0%		%	Fixed	-	-		
Asym DVT	91.9%		%	Fixed	Inverse of PE and Sym DVT		(20, 21, 24, 29-33, 36, 75)	
Distal	91.2%		%	Fixed	Inverse of Proximal		21)	
Proximal	8.8%		%	Fixed	-	-		
% of Asym -> Sym (60 days)	0.5%		%	Fixed	-	-		
Distal	58.0%		%	Fixed	-	-		
Proximal	42.0%		%	Fixed	-	-		
Non-VTE Death	3.5%		%	Fixed	-	-	(20, 21, 24, 29-33, 36, 75)	
Due to Major Bleed	0.0%		%	Fixed	-	-	(21)	
Other Cause	100.0%	-	%	Fixed	-	-		
Bleeding								
ICH	0.0%	-	%	Fixed	-	-	(20, 21, 24, 29-33, 36, 75)	6.3.1
% Disabled	0.0%		%	Fixed	-	-		
Major Bleed - Other	7.5%		%	Fixed	-	-		
NMCR	34.1%		%	Fixed	-	-		
Minor	58.3%		%	Fixed	Inverse of Major Bleed – Other and NMCR			

RR = Relative risk

Table 67: Long term efficacy and adverse event parameters

Variable	Value	SE	Units	(distri-bution)	Shape and scale parameters		Ref	Reference to section in submission
					α	β		
Well to PE*								
Y1	0	0	0.001	Beta	0	-1		
Y2	0	0	0.001		0	-1		
Y3	0	0	0.001		0	-1		
Y4	0	0	0.001		0	-1		
Y5	0	0	0.001		0	-1		
Y6	0	0	0.001		0	-1		
Y7+	0	0	0.001		0	-1		
Well to DVT								
Y1	0	0	0.001	Beta	0	-1		
Y2	0	0	0.001		0	-1		
Y3	0	0	0.001		0	-1		
Y4	0	0	0.001		0	-1		
Y5	0	0	0.001		0	-1		
Y6	0	0	0.001		0	-1		
Y7+	0	0	0.001		0	-1		
Well to mild/moderate PTS								
Y1	0	0	0.001	Beta	0	-1		
Y2	0	0	0.001		0	-1		
Y3	0	0	0.001		0	-1		
Y4	0	0	0.001		0	-1		
Y5+	0	0	0.001		0	-1		
Well to severe PTS								
Y1	0	0	0.001	Beta	0	-1		
Y2	0	0	0.001		0	-1		
Y3	0	0	0.001		0	-1		

Variable	Value	SE	Units	(distri-bution)	Shape and scale parameters		Ref	Reference to section in submission
					α	β		
Y4	0	0	0.001		0	-1		
Y5+	0	0	0.001		0	-1		
Untreated VTE to PE								
Y1	0.010953	0.002561	Annual transition risk estimates	Beta	18.077	1632.332	(75)	6.3.1
Y2	0.004564	0.001067			18.196	3968.736		
Y3	0.002824	0.00066			18.228	6436.490		
Y4	0.00186	0.000435			18.251	9794.335		
Y5	0.001812	0.000424			18.252	10054.782		
Y6	0.001038	0.000243			18.248	17561.792		
Y7+	0.000948	0.000222			18.269	19252.830		
Untreated VTE to DVT								
Y1	0.214495	0.015135	Annual transition risk estimates	Beta	157.560	577.002	(75)	6.3.1
Y2	0.089386	0.006307			182.808	1862.347		
Y3	0.055308	0.003903			189.689	3239.997		
Y4	0.036428	0.00257			193.533	5119.222		
Y5	0.035488	0.002504			193.724	5265.126		
Y6	0.020329	0.001434			196.745	9481.294		
Y7+	0.018567	0.00131			197.072	10417.038		
Untreated VTE to mild/moderate PTS								
Y1	0.180693	0.059557	Annual transition risk estimates	Beta	7.361	33.376	(75)	6.3.1
Y2	0.022905	0.007982			8.023	342.237		
Y3	0.025448	0.009402			7.114	272.453		
Y4	0.022373	0.005486			16.237	709.522		
Y5+	0.0049	0.00148			10.909	2215.392		
Untreated VTE to severe PTS								
Y1	0.040505	0.018543	Annual transition risk estimates	Beta	4.538	107.487	(75)	6.3.1
Y2	0.043805	0.016043			7.085	154.650		
Y3	0.021488	0.006524			10.593	482.380		
Y4	0.012675	0.005191			5.873	457.483		
Y5+	0.008563	0.004267			3.985	461.385		
Treated VTE to PE								
Y1	0.005248	0.001863	Annual transition risk estimates	Beta	7.890458	1495.627	(75)	6.3.1
Y2	0.002187	0.000776			7.916607	3611.931		
Y3	0.001353	0.00048			7.921454	5846.812		
Y4	0.000891	0.000317			7.913124	8873.258		
Y5	0.000868	0.000308			7.925981	9123.389		
Y6	0.000497	0.000177			7.921904	15931.52		
Y7+	0.000454	0.000161			7.925517	17449.16		
Treated VTE to DVT								
Y1	0.05476	0.021939	Annual transition risk estimates	Beta	5.834	100.708	(75)	6.3.1
Y2	0.02282	0.007327			9.457	404.969		
Y3	0.01412	0.004663			9.025	630.120		
Y4	0.0093	0.003449			7.194	766.346		
Y5	0.00906	0.002651			11.569	1265.389		
Y6	0.00519	0.002809			3.392	650.101		
Y7+	0.00474	0.00177			7.129	1496.980		
Treated VTE to mild/moderate PTS								
Y1	0.06324	0.022191	Annual transition risk estimates	Beta	7.544	111.752	(75)	6.3.1
Y2	0.00829	0.003008			7.526	900.306		
Y3	0.00992	0.003582			7.585	757.047		
Y4	0.00637	0.001898			11.186	1744.889		
Y5+	0.00241	0.000541			19.808	8199.149		
Treated VTE to severe PTS								
Y1	0.01121	0.007311	Annual transition risk estimates	Beta	2.313	204.049	(75)	6.3.1
Y2	0.00629	0.006102			1.050	165.815		
Y3	0.01346	0.002388			31.336	2296.722		
Y4	0.00659	0.002013			10.643	1604.323		

Variable	Value	SE	Units	(distri-bution)	Shape and scale parameters		Ref	Reference to section in submission
					α	β		
Y5+	0.00082	0.001702			0.231	281.763		

* Well to PE standard error assumed to be 0.001 as mean values were 0.

Table 68: Resource use and unit costs

Variable	Value	SE	Units	(distribution)	Shape and scale parameters		Reference	Ref to section in submission
					α	β		
Post-discharge for THR and TKR								
% re-hospitalized PE	1		%	Fixed			Assumption	
% re-hospitalized distal DVT	0.62	0.02*	%	Beta	583.303	357.508	(58)	
% re-hospitalized proximal DVT	0.62	0.02*			583.303	357.508		
Costs								
Drug acquisition (cost per day) for			£	- Fixed	-	-		
Apixaban	3.43	-			-	-	BMS-Pfizer	7.0
Dabigatran	4.20	-			-	-	(84)	
Enoxaparin	4.04	-			-	-		
Rivaroxaban	4.41	-			-	-		
Extra post-discharge cost					-	-		
Apixaban - THR	0.00	-	£	Fixed	-	-		
Apixaban - TKR	0.00	-	£	Fixed	-	-		
Dabigatran - THR	0.00	-	£	Fixed	-	-		
Dabigatran - TKR	0.00	-	£	Fixed	-	-		
Enoxaparin - THR	123.54	10[#]	£	Gamma	152.62	0.81	Calculation	6.5.1
Enoxaparin - TKR	46.32	10[#]			21.46	2.16		
Rivaroxaban - THR	0.00	-	£	Fixed	-	-		
Rivaroxaban - TKR	0.00	-	£	Fixed	-	-		
Prophylaxis and post-prophylaxis phase								
Decision Tree Cost								
THR and TKR								
Additional cost for event								
Symptomatic VTE								
PE	1929.42	-	£	Fixed	-	-	Calculation	6.5.1
Distal DVT	1306.54	-			-	-		
Proximal DVT	1314.20	-			-	-		
Asymptomatic VTE	0	-	£	Fixed	-	-	Assumption	6.5.1
Bleeds		-		Fixed	-	-		
IC	11043.99	-	£	Fixed	-	-	Calculation	6.5.1
Major	1250.16	-			-	-		
NMCS	1000.00	-			-	-		
Minor	274.00	-	£	Fixed			(85)	6.5.1
Long term events								
Treatment								
PE	4338.56	221.36[§]	£	Gamma	384.16	11.29363	Calculation	6.5.1
DVT	2788.87	142.29[§]			384.16	7.259657		
Mild/moderate PTS Y1	47.00	2.40[§]			384.16	0.122345		
Mild/moderate PTS Y2+	41.31	2.11[§]			384.16	0.107533		

Apixaban. BMS and Pfizer

Variable	Value	SE	Units	(distribution)	Shape and scale parameters		Reference	Ref to section in submission
					α	β		
Severe PTS Y1	4424.02	225.72§			384.16	11.51609		
Severe PTS Y2+	2028.27	103.48§			384.16	5.279753		
Caring for and treating disabled patients	7648.86	390.25§			384.16	19.91061		

Extra post-discharge costs are the drug administration costs associated with the discharged treatment period. The costs are those of training patients to self inject and provide a community nurse to inject patients that cannot self inject, weighted by the proportion of patients falling into each category (86) applied to the discharged treatment duration.

* 95% confidence interval assumed to be ±5%.

Standard error assumed to be £10.

§ 95% confidence interval assumed to be ±10%.

Table 69: Health state utilities, decrements and applicable durations

Variable	Value	SE	Distribution	Shape and scale parameters		Reference
				α	β	
Base utility						
THR & THR: General male	0.78	0.018543	Beta	388.472	109.56898	(87)
THR & THR: General female	0.78	0.015504	Beta	556.028	156.82832	(87)
Short-term utility decrement for THR and TKR						
Index Surgery/Hospitalization (inpatient)						
PE	–0.08	0.004082*	Gamma	384.16	0.00021	(88)
Distal DVT	–0.08	0.004082*		384.16	0.00021	
Proximal DVT	–0.08	0.004082*		384.16	0.00021	
Asymptomatic VTE	0.0		Fixed			
Intracranial haemorrhage: disabled state	–0.49	0.03*	Gamma	384.16	0.00128	(64)
Major	–0.03	0.001531*	Gamma	384.16	0.00008	(89) Median
NMCS	0		Fixed	-	-	Assumption
Minor	0			-	-	
Duration of short-term utility decrement for THR (in days)						
Index Surgery/Hospitalization (inpatient)						
PE	5.63	-	Fixed	-	-	Modelling assumption
Distal DVT	0.949	-		-	-	
Proximal DVT	0.949	-		-	-	
Asymptomatic VTE	0	-	Fixed	-	-	Assumption
Intracranial haemorrhage: disabled state	90	-	Fixed	-	-	Modelling assumption
Major	5.63	-	Fixed	-	-	Modelling assumption
NMCS	0.949	-	Fixed	-	-	Modelling assumption
Minor	0.949	-	Fixed	-	-	Modelling assumption
Duration of short-term utility decrement for TKR (in days)						
Index Surgery/Hospitalization (inpatient)						
PE	7.49	-	Fixed	-	-	Modelling

Variable	Value	SE	Distribution	Shape and scale parameters		Reference
				α	β	
						assumption
Distal DVT	1.73	-	Fixed	-	-	Modelling assumption
Proximal DVT	1.73	-	Fixed	-	-	Modelling assumption
Intracranial haemorrhage: disabled state	90	-	Fixed	-	-	Modelling assumption
Major	7.49	-	Fixed	-	-	Modelling assumption
NMCS	1.73	-	Fixed	-	-	Modelling assumption
Minor	1.73	-	Fixed	-	-	Modelling assumption
Utility decrement for THR and TKR						
Post-discharge						
Symptomatic VTE						
PE	0		Fixed			
Distal DVT	0.08	0.004082*	Gamma	384.16	0.00021	(88)
Proximal DVT	0.08	0.004082*	Gamma	384.16	0.00021	(88)
Intracranial haemorrhage: disabled state	0.49	0.03*	Gamma	384.16	0.00128	(64)
Duration of post-discharge decrement for TKR and THR (in days)						
PE	30.0	-	Fixed	-	-	Modelling assumption
Distal DVT	30.0	-	Fixed	-	-	Modelling assumption
Proximal DVT	30.0	-	Fixed	-	-	Modelling assumption
Intracranial haemorrhage: disabled state	90.0	-	Fixed	-	-	Modelling assumption
Long-term events utility decrement						
Annual aging impact	–0.00029	–0.000015*	Gamma	384.16	0.00000	(90)
Treated VTE	–0.01	–0.000510*	Gamma	384.16	0.00003	(91)
ICH: disabled state	–0.49	–0.025000*	Gamma	384.16	0.00128	(64)
PE	–0.08	–0.004082*	Gamma	384.16	0.00021	(88)
DVT	–0.08	–0.004082*	Gamma	384.16	0.00021	(88)
Mild/moderate PTS Y1	–0.02	–0.001020*	Gamma	384.16	0.00005	(92)
Mild/moderate PTS Y2+	–0.02	–0.001020*	Gamma	384.16	0.00005	(92)
Severe PTS Y1	–0.07	–0.003571*	Gamma	384.16	0.00018	(92)
Severe PTS Y2+	–0.07	–0.003571*	Gamma	384.16	0.00018	(92)
Duration of long-term events utility decrement (in months)						
Annual aging impact	12	-	Fixed	-	-	(90)
Treated VTE	1	-	Fixed	-	-	Modelling assumption
ICH: disabled state	12	-	Fixed	-	-	(93)
PE	1	-	Fixed	-	-	(93)
DVT	1	-	Fixed	-	-	(93)
Mild/moderate PTS Y1	12	-	Fixed	-	-	(92)

Variable	Value	SE	Distribution	Shape and scale parameters		Reference
				α	β	
Mild/moderate PTS Y2+	12	-	Fixed	-	-	(92)
Severe PTS Y1	12	-	Fixed	-	-	(92)
Severe PTS Y2+	12	-	Fixed	-	-	(92)

* 95% confidence interval assumed to be ±10%.

6.3.7 Extrapolation of trial outcomes

Costs and clinical outcomes are extrapolated beyond the end of the trial. Patients who experience an event are at risk of recurrence of a VTE event or complication over a longer timeframe. These risks are not assumed to be treatment dependent. The risk of future events depends on the health state and is independent of the initial treatment.

6.3.8 Summary of assumptions used

Table 70: Assumptions

Assumption	Justification
General	
1. The efficacy of each anticoagulant (apixaban, enoxaparin, rivaroxaban, dabigatran) is assumed to reflect combination prophylaxis with mechanical prophylaxis (e.g. graduated compression stocking) as background therapy as permitted in the clinical trials for these anticoagulants.	Mechanical prophylaxis recommended in the VTE Guideline (1)
2. The primary efficacy end point of the apixaban, rivaroxaban and dabigatran trials, total VTE and all-cause death, is applied as the primary efficacy measure in the model and was used to estimate the risk of VTE. The composite safety endpoint of all bleeding is also used in the model to capture drug specific variations in bleeding rates.	All new anticoagulant trials of apixaban dabigatran and rivaroxaban were designed and powered to capture these composite primary outcome measures (20, 21, 24, 29, 30, 32, 33). Every component of the efficacy and safety endpoints could not be populated by the indirect comparison nor UK registry data.
LMWHs are assumed to be clinically equivalent	This assumption was also made by NICE in CG92 VTE clinical guideline (1).
Mortality	
1. Hazard rates for mortality are assumed to change linearly with increasing age.	The mortality rates increase as individuals get older (83)
2. The probability of a minor or a non-major clinically relevant bleed being fatal is zero	A reasonable assumption given the events
Short-term VTE Risk	
1. VTE and bleeding events are independent.	No direct link between bleeding and VTE has been identified in the NOCA studies (20, 21, 24, 29, 30, 32, 33)
2. VTE and bleeding events are not mutually-exclusive.	Evidence indicates that a patients can experience both VTE and bleeding events (20, 21, 24, 29, 30, 32, 33)
3. Patients who died from PE are assumed to accumulate the same cost of treating the PE event as those who live.	Data on PE mortality prior, during and after treatment was not available and as a result a plausible assumption had to be applied.
4. Patients who experienced no event, treated VTE or untreated VTE events are all equally likely to experience an intracranial haemorrhage (IH).	In the absence of contradictory evidence this plausible assumption was applied.
5. Intracranial haemorrhage (IH) patients are assumed to survive the event but are disabled thereafter.	This was felt to be a reasonable simplifying assumption.
6. During the prophylactic phase, other and PE deaths are assumed to occur at the end of the treatment for each treatment arm.	In the absence of specific daily mortality data a simplifying assumption was required. As the assumption is applied to all VTE interventions it is considered to be a reasonable assumption.
7. During the post-prophylactic phase, PE deaths are assumed to occur at 63 days for THR and 52 days for TKR, which are the mid points of the post-prophylactic phase for each indication.	
8. Major bleeds deaths are assumed to occur at 35 days for THR and 14 days for TKR, regardless of whether the bleeding rates are based on the prophylactic duration or 90 days.	
Long-term risk	
1. Patients with mild/moderate or severe PTS do not transition to other states apart from death	This assumption has been applied in preceding VTE models (58, 64)

Assumption	Justification
Costs	
Costing assumptions e.g. 60/40 weighted cost for PE etc.	
1. The length of stay for the index hospitalisation will not be affected by type of anticoagulant, but may be affected by a major bleed or VTE event during the inpatient period.	There is currently no data to suggest any VTE intervention can reduce hospital length of stay over its comparators. Clinical evidence suggests that VTE interventions have differential bleeding rates (see section 6.3.1) and a bleeding event can result in longer hospital stays.
2. In the base case analysis, asymptomatic VTE events are not assumed to have any impact on resource use.	Treatment would not be given to a patient that does not have signs or symptoms of VTE.
3. A weighted average price of unit costs for enoxaparin is calculated based on the percentage usage of the following low-molecular weight heparins (LMWH: enoxaparin, dalteparin and tinzaparin) in England and Wales. The weights used were derived from the quantity data in the 2009 Prescription Cost Analysis data (94) (See Appendix 27). This approach assumes that these LMWHs are clinically equivalent, as assumed by NICE in CG92 VTE clinical guideline (1)	This approach has been applied in the past to costing LMWH (95, 96)
4. Patients incapable of self-administering LMWH who do not have a carer that can administer the prophylaxis require daily community nurse visits	A reasonable assumption which has been applied in previous VTE prophylaxis models (63, 64)
5. Patients able and willing to self-administer LMWH require training	The majority of patients will have no experience of self-administering a subcutaneous injection. These patients will require instruction from nursing staff prior to discharge to ensure safe administration.
Utility	
1. Utility for "Well" and "Untreated VTE" patients in the Markov model are assumed to be the same for a person of the same age.	Untreated VTE patients are asymptomatic and would not have any symptoms that reduce their quality of life in comparison to a well patient.
2. For VTE events, the assumed utility decrement was equal to the duration of hospitalisation for the event, plus a decrement of 0.08 for the duration of treatment after discharge.	This approach has been employed in other VTE economic models (58)
3. Asymptomatic VTE is assumed to have no impact on patient quality of life.	Asymptomatic VTE would result in no symptoms that reduce their quality of life in comparison to a well patient.
4. Minor and non-major clinically relevant bleeds are assumed to have no impact on patient quality of life.	A reasonable assumption given the events.

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 Affects of the condition on patients' quality of life

The occurrence of VTE or bleeding events affects patients' quality of life most. In particular, patients experiencing either a pulmonary embolism or major bleed will experience the greatest drop in quality of life according to the relevant literature.

6.4.2 Change in HRQL over time

Once a patient has experienced a VTE or bleeding event, their quality of life is assumed to be constant for the duration of that event. Depending on whether further clinical events occur, the patients' quality of life may either worsen or improve depending on the nature of the event and the associated utility. For example, a patient experiencing a PE in the long term model experiences a decrement in utility of 0.01 for one month and then returns to general public utility levels for a person of their age.

HRQL data derived from clinical trials

6.4.3 Description of trial based HRQL data

HRQL data were not collected in the apixaban clinical trials.

Mapping clinical trial HRQL data

6.4.4 Description of mapping exercise

It was not necessary to conduct mapping as utility information was available in the published literature for the health states in the model (see section 6.4.5).

HRQL studies

6.4.5 Literature search to identify HRQL studies

Systematic searches were undertaken to identify VTE-related utilities (search string reported in Appendix 12). In order to capture all relevant information studies from all countries were accepted. Studies were extracted into a table (See Appendix 12). Excluded studies are listed in Appendix 12. Results were also reviewed for relevant cost/resource use information; these studies are discussed in more detail in Section 6.5.

6.4.6 HRQL studies identified

One hundred and sixteen studies were identified and reviewed for inclusion on the basis of title and abstract; of the studies deemed potentially eligible and retrieved in full, two were included (97, 98) (Appendix 12A). The search also identified several UK and non-UK economic evaluations already identified by the cost searches (for example (53, 56, 58, 99-103)); these studies were excluded on the basis that economic studies included in Section 6.1 had already been checked for sources of quality of life information as a matter of course. Hand searching of conference proceedings (See Appendix 12), reference lists, and other systematic reviews provided 12 additional relevant studies (two studies were thought to be related (104, 105).

Only one additional study was identified from the update search conducted in November 2010: Diamantopoulos et al. (51). This study reported data for Canada and was therefore not directly relevant to the UK setting. It should also be noted that this study was identified as an abstract by the original searches conducted in July 2010 and so was already counted as an included study.

Not all of the included UK cost effectiveness analyses (Section 6.1) described detailed quality of life information for incorporated utilities. The quality of life and utilities applied and reported in these studies are described in Appendix 12. A detailed review of the information reported by the included UK cost effectiveness (Appendix 12) and non-UK quality of life studies (Appendix 10) revealed that most publications directly or indirectly referenced the same limited number of primary studies. Some studies (for example (99, 101)) seemed to report quality of life information; however, upon closer inspection and follow up of the reported references and subsequent cross-references no new information was found. Ultimately the references referred to the same handful of QoL studies presented in Appendix 12.

Studies of quality of life with VTE following TKR or THR

As reflected in the construction of the search strings (Appendix 10 and 12), studies that specifically addressed VTE-related utilities in the THR or TKR population were the focus for this review. Only two studies were found that satisfied these requirements. One study was available only as conference abstract reporting very limited information for distal DVT and is not discussed further (106). Brothers et al (97) report utilities for fatal PE, PE, DVT, and no DVT in patients undergoing hip or knee arthroplasty in the USA, these utilities were further discounted to account for anticoagulant use and complications arising from phlebography. Unfortunately these utilities were derived by consensus methods by the authors (who were vascular surgeons) and were not subject to any further validation questioning the generalised applicability of the estimates.

Given the lack of availability of the desired type of information, other studies e.g. VTE-related utilities from other populations and also specific utilities for a THR or TKR population (detected via hand searching) were also presented. It should be noted that the original searches were not designed to detect this type of information and thus does not represent an exhaustive review; however, this category includes the studies most frequently cross-referenced in the QoL/cost effectiveness for VTE in TKR and/or THR literature.

Lenert et al (92) was the most frequently directly and indirectly referenced publication for utilities in VTE. This study (set in the USA) used standard gamble techniques to elicit preferences from healthy women volunteers aged between 20-40 yrs. and 30 medical doctors for mild PTS, severe PTS, and stroke. O'Meara et al (107), another frequently cited study, also used standard gamble technique to derive estimates for good health, mild PTS, severe PTS, and central nervous system bleed from patients with and without a history of DVT and PTS. Three studies used SF-36 to evaluate the impact of PTS and VTE on QoL (108-110) but did not facilitate translation into utilities.

Three studies are presented that address quality of life following TKR and THR (98, 104, 111). However, it is likely that there are other studies available evaluating quality of life in this population that were not detected.

Further details of these studies are presented in Appendix 12.

6.4.7 Comparison of HRQL data

There was no mapping from clinical trials.

Adverse events

6.4.8 The impact of adverse events on HRQL

Adverse events that patient would consider significant, events that impact on areas of their HRQL such as mobility and pain, reduce the patients quality of life. In the economic model decrements (reductions in health state utilities (HSU); in this economic model death has a HSU of 0.0 and perfect health has a HSU score of 1.0) are subtracted from the patient's pre adverse event health status for the applicable period. For example, a THR patient experiencing a major bleed would have a reduction of 0.03 in their HSU for a period of 5.6 days. See section 6.4.9 for all the decrements applied in this economic evaluation.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Summary of HRQL values used

A systematic review (section 6.4.6) was conducted to identify quality of life values and decrements for VTE related events and health states utilised in the economic model (section 6.2.2). Health state utility values were identified for the health states of symptomatic distal DVT, symptomatic proximal DVT, PE, major bleed, well/treated VTE, mild to moderate post thrombic syndrome, severe post thrombic syndrome and intracranial haemorrhage/ disability following intracranial haemorrhage.

It is not always possible to obtain utility values for a UK population and there is some indication that valuations of health states may vary by country (112, 113). When UK values are not available, values that most closely resemble those of the UK are sought. European utilities are considered to be the best alternative, followed by North American values.

Well or treated VTE

The model uses a utility decrement of -0.01 for one month to represent the drop in quality of life of a patient experiencing a VTE event but receiving treatment for it (the treated VTE state in the model). This utility estimate came from Gage et al. (91) and was based on a sample of 70 patients with atrial fibrillation. A value of 0.095 (mean of 12 week utility minus 7 week utility for hip and knee patients receiving usual care) from Brunenberg et al. (111) is assessed in the one way sensitivity analysis (98 patients receiving usual care or a joint recovery programme). The quality of life literature review identified an additional four papers, Malachau et al. (98), Ostendorf et al. (104, 105) and Brothers et al. (97). These four papers were rejected as the studies collected utilities at one year following treatment rather than immediately post treatment, which was required for the model.

To represent the quality of life of a fully recovered well patient following surgery, the model uses a value of 0.78 per year for the health state of well derived from EQ-5D UK population norms by Kind et al. (1999) (87). These norms were based on data from a total sample of 3395 UK residents. The literature review identified four other papers with potential sources of utility data for well patients (Brothers et al. (97), McCullagh et al. (56), Fryback et al. (114) and Kind et al. (115). Brothers et al. (97), McCullagh et al. (56) and Fryback et al. (114)), however, these were not used in the model as the utilities were based on non UK populations and these were thought to be less relevant to a UK setting. The Kind et al. (115) paper was rejected in favour of the full report of UK norms (87), as the former did not report the relevant utility data required.

PE and DVT

The model uses utility decrements for PE and DVT (symptomatic proximal and distal) of -0.08 from Ingelgard et al. (88). This utility value is based on data obtained from 121 Swedish outpatients with DVT. The literature review also identified three other papers (Cykert et al. (116), Brother et al. (97) and Goodacre et al. (117)), however, these were rejected as they reported utilities based on US populations.

Post thrombic syndrome (PTS)

The model uses utility decrement of -0.02 for mild to moderate PTS and -0.07 for severe PTS from Lenert and Soetikno (92). These values were obtained from a sample of 30 healthy women (study also had a sample of 30 medical doctors). The literature review identified an additional study (O'Meara et al. (107)), however, this study was based on a small sample and as a result may suffer from a lack of generalisability. The O'Meara et al. study also produced counterintuitive results with a greater utility decrement for mild to moderate PTS than severe PTS and so was rejected in favour of the Lenert and Soetikno (92) paper.

Major bleed and disability following intracranial haemorrhage

A utility decrement of -0.03 is used for major bleed in the model and was taken from a study by Robinson et al. (89) of 54 patients with atrial fibrillation. The literature review also identified the McCullagh et al. (56) paper, however, there was insufficient detail reported on this study to enable it to be used in the model.

A utility decrement of -0.49 is used in the model to represent the drop in quality of life for patients who become disabled following an intracranial bleed. This decrement is based on an average of 109 published stroke utility decrements reported in Wolowacz (58, 59) and Ingleheim Bower (64) (related work). The literature review also identified a paper by Sarasin et al. (118), however, this paper was rejected as the utility reported was for temporary disability and was obtained from expert and not patients.

Other

Health states for which data was not identified in the systematic review was identified based on a subsequent unsystematic search. All utility values applied in the model are presented inTable 71Table 74.Table 71

Table 71: Base utility

State	Utility value or decrement	Confidence interval or Std Error	Reference in submission	Justification	Reference
General male population	0.78	0.018543	6.3.6		(87)
General female population	0.78	0.015504			(87)
Death	0	N/A		Theoretical value given to death utility	Assumption

Table 72: Events in prophylaxis & post-prophylaxis phases

State	Utility value or decrement	Confidence interval or Std Error	Reference in submission	Justification	Reference
Hospitalization Period					
PE	–0.08	0.004082*	6.3.6	Based on a study that involved 121 DVT patients and used EQ-5D.	(88)
Symptomatic Distal DVT	–0.08				
Symptomatic Proximal DVT	–0.08				
Asymptomatic DVT	0.0	N/A	Assumption		
ICH	–0.49	0.03*		Based on the mean of 109 published studies for stroke. Utility applied over a lifetime	(64)
Major Bleed – other	–0.03	0.001531*		Based on a study that involved 54 patients and use standard gamble methods.	(89) Median
NMCR Bleed	0	-		Assumed to resolve without impact to utility, thus no decrement	Assumption
Minor Bleed	0	-			

* 95% confidence interval assumed to be ±10%.

Table 73: Post-discharge

State	Utility value or decrement	Confidence interval or Std Error	Reference in submission	Justification	Reference
Post-Discharge Period					
PE	0	-	6.3.6		
Symptomatic Distal DVT	–0.08	0.004082*			(88)
Symptomatic Proximal DVT	–0.08				
ICH Disabled	–0.49	0.03*			(64)

* 95% confidence interval assumed to be ±10%.

Table 74: Events occurring in long-term phase

State	Utility value or decrement	Confidence interval or Std Error	Reference in submission	Justification	Reference
Long-term Markov phase			6.3.6		
Aging (annual impact)	–0.00029	–0.000015*			(90)
Treated VTE	–0.01	0.000510*			(91)
ICH Disabled State	–0.49	–0.025000*			(64)
PE	–0.08	–0.004082*			(88)
DVT	–0.08	–0.004082*			
Mild/Moderate PTS (yr 1)	–0.02	–0.001020*			(92)
Mild/Moderate PTS (yr 2+)	–0.02	–0.001020*			
Severe PTS (yr 1)	–0.07	0.003571*			
Severe PTS (yr 2+)	–0.07	0.003571*			

* 95% confidence interval assumed to be ±10%.

6.4.10 Input from clinical experts

Clinical experts did not assess the applicability of values available or estimated any values.

6.4.11 HRQL experienced in each health state

The decrements associated with each health state are presented in section 6.4.10. The disutility is subject to between subject variance which is accounted for in this economic evaluation by conducting probabilistic sensitivity analysis.

6.4.12 Health effects excluded from the analysis

No health effects in the form of health states were omitted from the de novo model and subsequent analysis.

6.4.13 Baseline HRQL

The baseline health state utility assumed for patients entering the model was 0.78 for individuals aged 65-74, taken from the UK EQ-5D norms (87). Yes adverse events were taken from this baseline value.

6.4.14 Changes in HRQL over time

No HRQL is not assumed to be constant over time, as is highlighted for well patients in Kind et al, (1998) (115). In addition to variation in HRQL states an age disutility adjustment is applied each year (90).

6.4.15 Have the values in Sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The only amendments made to utility values were age adjustment. Each year 0.00029 is subtracted from a patient's health state utility value before the QALYS for that year are calculated.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 How is the clinical management of the condition currently costed in the NHS?

For the purposes of this economic evaluation only costs that differ by intervention are considered as they will be utilised in an incremental cost effectiveness ratio. As a result the costs of TKR and THR, which are common to all patients regardless of prophylaxis method, have been excluded, for example the cost of elective inpatient stay for THR or TKR. Table 75 and Table 76 below contain the conditions, Healthcare Resource Group (HRG) 4.0 procedure codes and how they have been applied in the economic model. All costs are presented in 2008/09 pounds.

In the base case analysis 2008/09 NHS reference costs (85) were used. Payment by Results (PbR) tariff charges were used in the sensitivity analysis (the HRG codes are the same in both costing sources).

Where possible the HRG codes were selected based on those employed in the VTE guideline (1). This was not always possible as the guideline was produced prior to HRG code 4.0 being implemented; in such cases the equivalent code was sought.

Table 75: Reference costs and calculations

Item	Value		HRG Codes/Other Sources	Justification
Decision Tree Cost	**THR**	**TKR**		
Additional cost for event				
Symptomatic VTE				
PE	£1929.42	£1929.42	=Inpatient Ratio (68.9%) * index surgery for PE (£1831.52)+ non inpatient ratio (31.1%) * rehospitalisation for PE ratio (100%) * inpatient stay for PE (£2146.22) + non rehospitalisation ratio (0%) * Outpatient treatment (£300.96)	Inpatient Ratio (% of Symp VTE that occurs inpatient) 68.9% (119) (Appendix 21). Non inpatient ratio (% of Symp VTE that occurs at home) 31.1% (119). Rehospitalisation ratio for PE 100% (model assumption). Non rehospitalisation ratio PE 0% (model assumption).
Index surgery for PE	£1,831.52	£1,831.52	Weighted average of NHS codes (2008/09£) NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): DZ09A Pulmonary Embolus with Major CC; DZ09B Pulmonary Embolus with CC; DZ09C Pulmonary Embolus without CC	A weighted average of all Pulmonary Embolus costs was used to reflect the true cost of PE
Inpatient stay for PE	£2,146.22	£2,146.22	Weighted cost of NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): Z09A Pulmonary Embolus with Major CC, DZ09B Pulmonary Embolus with CC, and DZ09C Pulmonary Embolus without CC £1831.52 + Ambulance £263 Curtis (120) inflate to 08/09 using Curtis £274.84 (121) *5% using ambulance) £13.74 + Diagnosis cost £288 from Wolowacz et al. (58) inflate to 08/09 using Curtis (121) £300.96	A weighted average of all Pulmonary Embolus was used to reflect the true cost of PE
Outpatient treatment PE	£300.96	£300.96	Wolowacz used an outpatient cost of Outpatient + diagnosis (58) (outpatient = £0; diagnosis £288 calculated from NHS Reference costs 2005/6 & National Collaborating Centre for Acute Care. Venous thromboembolism: Reducing the risk of venous thromboembolism (93). Inflate to 08/09 using Curtis (121) £300.96	

Item	Value		HRG Codes/Other Sources	Justification
Distal DVT	£1306.54	£1306.54	= Inpatient Ratio (68.9%) * index surgery for distal DVT (£1,344) + non inpatient ratio (31.1%) * [rehospitalisation for distal DVT ratio (62%) * Inpatient stay Distal DVT (£1,580.29) + Non-rehospitalisation ratio for DVT (38%)* Outpatient treatment DVT (£641.63)	Inpatient Ratio (% of Symp VTE that occurs inpatient) 68.9% (Pei et al., 2010). Non inpatient ratio (% of Symp VTE that occurs at home) 31.1% (Pei et al., 2010). Rehospitalisation ratio for DVT 62% rounded mean of DVT readmission of standard and extended enoxaparin prophylaxis (53, 58). Non-rehospitalisation ratio for DVT 38% (53, 58).
Distal DVT	£1,344	£1,344	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis	
Inpatient stay Distal DVT	£1,580.29	£1,580.29	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis £1344 + ambulance £263 (120) inflate to 08/09 £274.84 (121) * 5% using ambulance) £13.74 + diagnosis £213 (121) [Inflate to 08/09 using Curtis (121)] £222.59	
Outpatient treatment Distal DVT	£641.63	£641.63	Wolowacz used an outpatient cost of Outpatient £401 + diagnosis £213 (derived from NHS reference costs and the NCC for Acute Care analysis for the VTE prevention clinical guideline) (58). Inflate to 08/09 using Curtis (121) £419.05 + £222.59	
Proximal DVT	£1314.20	£1314.20	= Inpatient Ratio (68.9%) * index surgery for proximal DVT (£1,344) + non inpatient ratio (31.1%) * [rehospitalisation ratio for proximal DVT (62%) * Inpatient stay Proximal DVT (£1580.29) + Non-rehospitalisation ratio for DVT (38%) * Outpatient treatment proximal DVT (£706.42)]	Inpatient Ratio (% of Symp VTE that occurs inpatient) 68.9% (Pei et al., 2010). Non inpatient ratio (% of Symp VTE that occurs at home) 31.1% (Pei et al., 2010). Rehospitalisation ratio for DVT 62% (53, 58). Non-rehospitalisation ratio for DVT 38% (53, 58).
Proximal DVT	£1,344	£1,344	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis	

Item	Value		HRG Codes/Other Sources	Justification
Inpatient stay Proximal DVT	£1,580.29	£1,580.29	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis £1344 + ambulance £263 Curtis (120) inflate to 08/09 £274.84 using Curtis (121) * 5% using ambulance) £13.74 + diagnosis £213 (121) [Inflate to 08/09 using Curtis (121) £222.59	
Outpatient treatment proximal DVT	£706.42	£706.42	Wolowacz used an outpatient cost of £463 and diagnosis of £213, (derived from NHS reference costs and the NCC for Acute Care analysis for the VTE prevention clinical guideline) (58). Inflate to 08/09 using Curtis (121) £483.84 + £222.59	
Asymptomatic VTE				
Distal DVT	£0.00	£0.00		Assumption - no overt symptoms so the patient is unaware of the condition and will not seek treatment
Proximal DVT	£0.00	£0.00		Assumption - no overt symptoms so the patient is unaware of the condition and will not seek treatment
Long Term Events	TKR and THR			
Treatment	Value	Unit		
PE	£4338.56	£ per event	PE £3046 taken from a conference abstract by Cohen et al. (122). Inflate to 08/09 (121).	
DVT	£2788.87	£ per event	Mild/moderate PTS Y1 £1958 from Cohen et al. (122). Inflate to 08/09 using Curtis (121).	
Mild/moderate PTS Y1	£47.00	£ per event	£33 Cohen et al. (122). Inflate to 08/09 using Curtis (121).	
Mild/moderate PTS Y2+	£41.31	£ per event	Mild/moderate PTS Y2+ £29 from Cohen et al. (122). Inflate to 08/09 using Curtis (121).	
Severe PTS Y1	£4424.02	£ per event	Severe PTS Y1 £3106 from Cohen et al. (122). Inflate to 08/09 using Curtis (121).	

Item	Value		HRG Codes/Other Sources	Justification
Severe PTS Y2+	£2028.27	£ per event	Severe PTS Y2+£1424 from Cohen et al. (122). Inflate to 08/09 using Curtis (121).	
Caring for and treating disabled patients	£7648.86	£ per year	Cost of a stroke including informal care over a 5 year period £29405/5 from Youman et al (123). Inflate to 08/09 using Curtis (121).	

CC = *complications* or *comorbidities*
Price inflation - updated to 2008/9 costs using the Hospital and Community Health Services Pay and Price Index (121) (See Appendix 19)

Table 76: Adverse event and associated costs in the economic model

Averse event and associated costs in the economic model	Value (2008/09 £)	HRG Codes/Other Sources	Justification
Decision Tree Cost			
Additional cost for event			
Bleeds			
IC	£11,043.91 (5 year cost)	Short term acute care + Long term follow-up care (5 years) £2,867 + (£1,635.38*5). Please see derivation below.	There are no events in the efficacy data and as a result the cost is not applied in this evaluation
Short term acute care	£2,867 (event cost)	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): AA23Z Haemorrhagic Cerebrovascular Disorders	
Long term follow-up care	£1,635.38 (annual cost)	£6287 (£15306 5 year cost of stroke - £9019 acute hospital cost) from the UK study by Youman (123). Refers to follow-up cost for all patients with intracranial bleed after discharge per year. Inflate to 08/09 using Curtis (121) £8176.91/5.	
Major	£1250.16 (event cost)	Weighted average of NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): FZ38D Gastrointestinal Bleed with length of stay 1 day or more with Major CC £1544 (weight 10906); FZ38E Gastrointestinal Bleed with length of stay 1 day or more without Major CC £1012 (weight	For costing purposes of costing a major bleed has been defined as one requiring a hospital stay. A weighted average of Gastrointestinal Bleed with a hospital stay was used to reflect the true cost of a major bleed

Averse event and associated costs in the economic model	Value (2008/09 £)	HRG Codes/Other Sources	Justification
		13465)	
NMCS	£1000.00 (event cost)	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): FZ38F Gastrointestinal Bleed with length of stay 0 days	For costing purposes of costing a NMCR bleed only a Gastrointestinal Bleed without a hospital stay was considered appropriate (one code only)
Minor	£274.00 (event cost)	NHS Trusts and PCTs combined Regular Day / Night Admissions data (2010): FZ38F Gastrointestinal Bleed with length of stay 0 days	

Price inflation - updated to 2008/9 costs using the Hospital and Community Health Services Pay and Price Index (121) (See Appendix 19)

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

In the base case NHS reference costs are used. This methodology has been used in the past in similar single technology appraisals (64). Payment by Results Tariffs (124) are used in a sensitivity analysis (See Appendix 21)

Resource identification, measurement and valuation studies

6.5.3 Literature search to identify resource data

Studies reporting relevant resource use information are presented in this section. Only UK specific information is presented. Eight fully published UK studies, three conference abstracts and three STA submissions from Section 6.1 plus an additional five UK abstracts reporting resource use data were extracted (Appendix 13). A further 16 cost studies were identified for other countries including Belgium, Canada, Denmark, Italy, Sweden, Switzerland, and the USA. These studies are presented in Appendix 13 but are not discussed further.

The references cited for resource use varied from NHS guidelines, hospital episode statistics, to other cost studies and the general published literature. The cost of drug acquisition, nursing/ GP time for administration, and hospital stays were reported, and almost all studies also included the cost of monitoring and/or blood tests. Only one paper (57) mentioned including needles and syringes. Only one study (54) included the use of a compression stocking.

The costs and resources associated with diagnosing VTE varied for different procedures (ultrasound or venography) and the nature of use (to confirm symptomatic DVTs or mandatory screening). Confirmation following documented DVT symptomatology was most frequently reported approach with all except one study (54) using ultrasound. Unfortunately several studies do not clearly describe the diagnostic method applied.

Several studies (52, 55, 57-59) only reported treatment costs in aggregate form; usually including hospitalisation, anticoagulant, drug administration, monitoring, compression stockings, anticoagulation clinic visits, and ICU services. The studies only available as abstracts typically reported limited information.

Further details of these studies are presented in Appendix 13.

6.5.4 Input from clinical experts

Clinical experts did not assess the applicability of values available or estimated any values.

6.5.5 Intervention and comparators' costs

Table 77 contains the drug acquisition costs, administration costs during inpatient stay and administration costs following discharge applied in the model for each intervention. Drug acquisition costs for a course of treatment are dependent upon the treatment durations assumed for each treatment. The treatment durations applied were - apixaban TKR = 12, THR = 34 (mean duration in ADVANCE 2 and 3 trials); enoxaparin/LMWH TKR = 12, THR = 34 (mean duration in ADVANCE2 and 3 trials); rivaroxaban TKR = 12, THR = 33 (mean duration in RECORD 1 and 3 trials) and dabigatran TKR = 8, THR = 32 (median duration in RE-MODEL and RE-NOVATE).

Only enoxaparin had testing costs that are not common to all the interventions considered. The costs comprise of 4 blood counts at a total cost of £40.44. Patients on LMWH need a blood count at baseline and every 4 days (4 counts, Bayer Schering Pharma, 2008). Unit cost were taken from the rivaroxaban STA submission (Bayer Schering Pharma, 2008) and were updated to 2008/9 costs using the Hospital and Community Health Services Pay and Price Index (121) (See Appendix 19).

Bayer Schering Pharma, (2008) (63) note that there is no need for patients receiving treatment with rivaroxaban to undergo a liver function test. However, it is now believed to be standard practice for patients undergoing elective hip or knee surgery to have this test on admission and as a result this cost has been omitted from Table 79.

Post discharge drug administration costs were applicable for enoxaparin as it is administered subcutaneously. Only 87% of patients are able to self inject or have a carer/relative that can inject them (86). Home visits to administer injections were assumed to be undertaken by a community nurse (£27) and training to self inject (for those that could) was assumed to comprise of 30 minutes of nurse time (24 hour ward nurse) (£50 per hour) (121). Post discharge treatment was assumed to be duration of treatment minus hospital inpatient stay. Inpatient stay was assumed to be 5 days, based on 2010 national reference cost data (THR: HB12C Major Hip Procedures for non Trauma Category 1 without CC; TKR: HB23C Intermediate Knee Procedures for non Trauma (85)

Table 77: Drug acquisition, monitoring and administration costs

Drug	Dose	Pack price	Pills/ injections per pack	Pills per day of treatment	Cost per day	Days of TKR treatment	Days of THR treatment	Cost per TKR course	Cost per THR course
Enoxaparin	40mg[#]	£40.36 (84)	10	1	£4.04	12 (21, 24)	34 (20)	£48.48	£137.36
Rivaroxaban	10mg[#]	£441.45 (84)	100	1	£4.41	12 (30, 36)	33 (29)	£52.97	£145.68
Dabigatran*	220mg[#]	£126.00 (84)	60	2	£4.20	8 (32)	32 (33)	£33.60	£1324.40
Apixaban	2.5[¥]	£102.90 (Pfizer/BMS)	60	2	£3.43	12 (21, 24)	34 (20)	£41.16	£116.62
	Inpatient				**Outpatient**				
	Number of blood counts	**Cost of blood count[@]**	**30 minutes training to self inject from a nurse**	**Cost of nurse* training for 30 minutes**	**Home visits from a community nurse to inject prophylaxis**	**Number of days where a home visit is required[¥]**		**Community nurse[#]**	**Total**
						TKR	**THR**		**THR** / **TKR**
Enoxaparin	4	£10.11	Yes 87% of patients	£25.00	Yes 13% of patients	7	29	£27.00	£163.98 / £86.76

[#]OD/ once a day; [¥]BID/ twice a day *First day of treatment only 110mg; a assumption; b TKR assumed to be the same as THR duration
*(24-hour ward [costs including qualifications]) (121)
[#](includes district nursing sister, district nurse) - home visit (including wages/salary, salary oncosts, qualifications, overheads, capital overheads and travel) (121)
[@]unit cost taken from the rivaroxaban STA submission to NICE (63) and updated to 2008/9 costs using the Hospital and Community Health Service Pay and Price Index (121) (See Appendix 19)
¥Treatment duration minus inpatient stay.

Apixaban. BMS and Pfizer

6.5.6 Health-state costs

The health state costs utilising the unit costs identified in Table 75 are presented below in Table 78. The PE cost comprises of the cost of treating PE that occurs during TKR or THR surgery and following discharge weighted by the proportion experiencing each event (Pei et al., 2010 (119); Appendix 21). All Patients experiencing PE following discharge were assumed to be rehospitalised (£1929.42 = £1831.52 * 68.89% + £2,146.22 * 31.11%; see Table 75). Distal DVT costs comprised of the cost of treating Distal DVT that occurs during TKR or THR surgery weighted by the proportion of patients experiencing this event (119) as an inpatient, plus the cost of treating the cost of distal DVT as an outpatient and readmission weighted by the proportion of patients experiencing each form of treatment (58, 119). (£1306.54 = £1344 * 68.89% + 31.11% (62% * £1580.29 + 38% * £641.63); see Table 21). Proximal DVT costs comprised of the cost of treating Distal DVT that occurs during TKR or THR surgery weighted by the proportion of patients experiencing this event (119) as an inpatient, plus the cost of treating the cost of proximal DVT as an outpatient and readmission weighted by the proportion of patients experiencing each form of treatment (58, 119) (£1314.20 = 68.89% * £1344 + 31.11% (62% * £1580.29 + 38% * £706.42); see Table 75.

The long term costs, costs applied in the long term Markov model, for PE, DVT, mild to moderate PTS (year 1/first instance and subsequent years) and severe PTS (year 1/first instance and subsequent years) were taken from Cohen et al. (2001) (122) and inflated to 2008/09 costs using the Hospital and Community Health Services Pay and Price Index (121) (See Appendix 19). The cost of caring for and treating disabled patients was taken from Youman et al. (2003) and inflated to 2008/09 using the Hospital and Community Health Services Pay and Price Index (121).

Table 78: List of health states/adverse event and associated costs in the economic model

Item	Value		Reference in submission
Decision Tree Cost	**THR**	**TKR**	
Additional cost for event			
Symptomatic VTE			
PE	£1929.42	£1929.42	Table 76
Distal DVT	£1306.54	£1306.54	
Proximal DVT	£1314.20	£1314.20	
Asymptomatic VTE			
Distal DVT	£0.00	£0.00	
Proximal DVT	£0.00	£0.00	
Long Term Events			
Treatment	Value	Unit	
PE	£4338.56	£ per event	
DVT	£2788.87	£ per event	
Mild/moderate PTS Y1	£47.00	£ per event	
Mild/moderate PTS Y2+	£41.31	£ per event	
Severe PTS Y1	£4424.02	£ per event	
Severe PTS Y2+	£2028.27	£ per event	
Caring for and treating disabled patients	£7648.86	£ per year	

6.5.7 Adverse-event costs

Adverse event costs are presented in Table 79. Intracranial bleed costs comprised of Short term acute care plus long term follow-up care costs (5 year costs £11,043.91 = £2,867 + £8,176.91; see Table 76). Major, non major clinically relevant and minor bleeds comprised of the weighted mean costs of the codes identified in Table 76, £1,250.16, £1,000.00 and £274 respectively.

Table 79: List of health states/adverse event and associated costs in the economic model

Item	Value		Reference in submission
Decision Tree Cost	**THR**	**TKR**	
Additional cost for event			
Bleeds			
IC	£11,043.91	£11,043.91	
Major	£1250.16	£1250.16	
NMCS	£1000.00	£1000.00	
Minor	£274.00	£274.00	

6.5.8 Miscellaneous costs

Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

6.6 Sensitivity analysis

6.6.1 Uncertainty around structural assumptions

The model developed for this submission is based on the model developed by Boehringer Ingelheim (64) and published by Wolowacz et al. (58). The model was considered to have an acceptable structure when it was evaluated by the ERG (Holmes et al, 2008) in the dabigatran STA. The published model (Wolowacz et al., 2009) model was peer reviewed and published in an international journal. We do not believe that there is structural uncertainty relating to the model.

The de novo model and the Wolowacz et al. (58)/Boehringer Ingelheim (64) models does not allow movement from mild to moderate PTS to severe PTS and does not have bleeding events in the long term Markov model. In addition the de novo model developed for this submission does not account for HIT.

Ideally, if appropriate data were available, the de novo model would allow movement between mild to moderate and severe PTS. However, as this limitation applies to all interventions assessed in the model, cost-effectiveness results are not biased in favour of any intervention. As the de novo model, like the Wolowacz et al. (58)/Boehringer Ingelheim (64) models does not look at reoperation (no assumption of a greater likelihood by intervention), prophylaxis related bleeding states were not needed in the long term Markov phase of the model.

HIT is not accounted for in the de novo model. The only intervention evaluated that could produce HIT is enoxaparin, the omission of this state is a conservative assumption that may favour enoxaparin but in no way provides an advantage for apixaban which cannot cause HIT.

6.6.2 Deterministic sensitivity analysis

Table 80: Variables subject to one-way sensitivity analysis and the sensitivity parameters applied

Variable		Base case	One-way		
Discount rate		3.5%	0% and 6%		
Health care unit costs			+/-10% & PBR tariff costs (124)		
			10%	–10%	PBR
	Post-discharge for THR and TK				
	% re-hospitalised distal DVT	62.00%	68.20%	55.80%	62.00%
	% re-hospitalised proximal DVT	62.00%	68.20%	55.80%	62.00%
Treatment					
	PE	£4338.56	£4,772.42	£3,904.70	£4,338.56
	DVT	£2788.87	£3,067.76	£2,509.98	£2,788.87
	Mild/moderate PTS Y1	£47.00	£51.70	£42.30	£47.00
	Mild/moderate PTS Y2+	£41.31	£45.44	£37.18	£41.31
	Severe PTS Y1	£4424.02	£4,866.42	£3,981.62	£4,424.02
	Severe PTS Y2+	£2028.27	£2,231.10	£1,825.44	£2,028.27
	Caring for and treating disabled patients	£7648.86	£8,413.75	£6,883.97	£7,648.86
Utility (duration of decrement)			1 month & +/-10%		
	Duration of short-term utility decrement for THR (days)		10%	-10%	
	Index Surgery/ Hospitalisation (inpatient)				
	PE	5.63	5.067	6.193	
	Distal DVT	0.949	0.8541	1.0439	
	Proximal DVT	0.949	0.8541	1.0439	
	Intracranial hemorrhage: disabled state	90	81	99	
	Major	5.63	5.067	6.193	
	NMCS	0.949	0.8541	1.0439	
	Minor	0.949	0.8541	1.0439	
	Duration of				

	short-term utility decrement for TKR (days)			
	Index Surgery/ Hospitalization (inpatient)			
	PE	7.49	6.741	8.239
	Distal DVT	1.73	1.557	1.903
	Proximal DVT	1.73	1.557	1.903
	Intracranial hemorrhage: disabled state	90	81	99
	Major	7.49	6.741	8.239
	NMCS	1.73	1.557	1.903
	Minor	1.73	1.557	1.903
Utility (parameter estimates)			Treated VTE = -0.095	
Weighted mean of LMWH costs		£4.04	£3.76	
Lowest LMWH (dalteparin) cost =£2.82		£4.04	£2.83	
Dabigatran cost		£4.20	-50%	
Length of stay of index hospitalisation		5 days	+/- 10%, + 30%	
Wastage		12 days of apixaban for TKR and 34 for THR	15 days of apixaban for TKR and 45 for THR	
Treatment duration		Apixaban TKR 12 THR 34, Enoxaparin TKR 12 THR 34, Rivaroxaban TKR 12 THR 33, Dabigatran TKR 8 THR 32	Reduce TKR to 10 days and THR to 28 days for all except dabigatran. Dabigatran treatment for TKR remained at 8 days	
		Apixaban TKR 12 THR 34, Enoxaparin TKR 12 THR 34, Rivaroxaban TKR 12 THR 33, Dabigatran TKR 8 THR 32	Increased TKR to 14 days and THR to 38 days for apixaban	
Time horizon		35 years	1, 5, 10, 20 years	
Age at surgery		THR males 65.89, females 68.51; TKR males 68.26, females 68.14	40,50,80	
Worse efficacy			Composite efficacy– lower 95% confidence interval and +10%	

		THR: All VTE & All cause death	TKR: All VTE & All cause death	THR: All VTE & All cause death – upper 95% CI	TKR: All VTE & All cause death – upper 95% CI
	Apixaban RR	0.359	0.618	0.555	0.743
	Rivaroxaban RR	0.3	0.507	0.51	0.651
	Dabigatran RR	0.887	0.965	1.131	1.133
Worse bleeding				Composite bleeding – upper 95% CI and +10%	
		THR: Any bleeding	**TKR: Any bleeding**	**THR: Any bleeding – upper 95% CI**	**THR: Any bleeding – upper 95% CI**
	Apixaban RR	0.93	0.83	1.08	1.06
	Rivaroxaban RR	1.02	1.02	1.29	1.44
	Dabigatran RR	1.07	0.96	1.34	1.22

Variable		**Base case**	**Scenario analysis**		
Efficacy & bleeding data		See table 58	Indirect comparison group 2		
				TKR: All VTE & All cause death	**TKR: Any bleeding**
				Baseline risk	Baseline risk
			Direct relative risk	Versus Enoxaparin 40mg od and 30mg bd pooled	Versus Enoxaparin 40mg od and 30mg bd pooled dose
				18.6%	7.17%
				Indirect comparison group 2	Indirect comparison group 2
			Apixaban 2.5 mg bd (UK indication)	0.754	0.81
			Rivaroxaban 10 mg od (UK indication)	0.583	1.09
			Dabigatran etexilate 220 mg od (UK indication)	0.965	0.96
			MTC group 1 THR		
				THR: All VTE & All cause death	**THR: Any bleeding**
				Baseline risk	Baseline risk
				Enoxaparin	Enoxaparin 40 mg + Ext
				5.4%	9.35%

				MTC (Grp 1)	MTC (Grp 1)
			Apixaban	0.357	0.927
			Enoxaparin 40 mg	0.638	0.821
			Rivaroxaban	0.302	1.009
			Dabigatran	0.893	1.074
			MTC group 1 TKR		
				TKR: All VTE & All cause death	**TKR: Any bleeding**
				Baseline risk	Baseline risk
				Enoxaparin	Enoxaparin
				19.4%	6.96%
				MTC (Grp 1)	MTC (Grp 1)
			Apixaban	0.895	0.809
			Enoxaparin 40 mg	1.41	1.037
			Rivaroxaban	0.731	1.094
			Dabigatran	1.354	1.003
			MTC group 2 THR		
				THR: All VTE & All cause death	**THR: Any bleeding**
				Baseline risk	Baseline risk
				Enoxaparin	Enoxaparin Pooled
				11%	7.61%
			THR: Total VTE + All Death	MTC (Grp 2)	MTC (Grp 2)
			Apixaban	0.372	0.931
			Rivaroxaban	0.259	1.085
			Dabigatran	0.9	1.094
			MTC group 2 TKR		
				TKR: All VTE & All cause death	**TKR: Any bleeding**
				Baseline risk	Baseline risk
				Enoxaparin	Enoxaparin
				25.3%	6.94%
			TKR: Total VTE + All Death	MTC (Grp 2)	MTC (Grp 2)
			Apixaban	0.764	0.797
			Rivaroxaban	0.615	1.084
			Dabigatran	0.966	0.964
VTE events	PE	TKR = 3.6%	PE +/- 10%		

		THR = 3.6%		
	Symp DVT	TKR = 2.6% THR = 4.5%	Symp DVT +/- 10%	
	Asymp DVT	TKR = 93.8% THR = 91.9%	Asymp DVT +/- 10%	
All VTE & any bleeding components from Advance 2 & 3	Total VTE and all-cause death	Apixaban THR 1.6%, Apixaban TKR 16.2%, Enoxaparin THR 4.6%, Enoxaparin TKR 26.3%	Apixaban THR 1.4%, Apixaban TKR 15.1%, Enoxaparin THR 3.9%, Enoxaparin TKR 24.4%	
	PE	THR 3.6%, TKR 3.6%	Apixaban THR 8.3%, Apixaban TKR 2.1%	Enoxaparin THR 6.8%, Enoxaparin TKR 0.0%
	Sym DVT	THR 2.6%, TKR 4.5%	Apixaban THR 4.2%, Apixaban TKR 2.1%	Enoxaparin THR 6.8%, Enoxaparin TKR 2.9%
	Asym DVT	THR 93.8%, TKR 91.9%	Apixaban THR 87.5%, Apixaban TKR 95.9%	Enoxaparin THR 86.3%, Enoxaparin TKR 97.1%
	Bleeding Events	Apixaban THR 8.7%, Apixaban TKR 7.3%, Enoxaparin THR 9.4%, Enoxaparin TKR 8.8%	Apixaban THR 11.7%, Apixaban TKR 6.9%, Enoxaparin THR 12.6%, Enoxaparin TKR 8.4%	
	Major Bleed - Other	THR 7.5%, TKR 7.5%	Apixaban THR 7.0%, Apixaban TKR 8.7%	Enoxaparin THR 5.3%, Enoxaparin TKR 11.1%
	NMCR	THR 34.1%, TKR 34.1%	Apixaban THR 34.6%, Apixaban TKR 42.3%	Enoxaparin THR 35.5%, Enoxaparin TKR 46.0%
	Minor	THR 58.3%, TKR 58.3%	Apixaban THR 58.4% Apixaban TKR 49.0%	Enoxaparin THR 59.2%, Enoxaparin TKR 42.9%

Unit costs

The price of enoxaparin was assessed in the one–way sensitivity analysis with the lowest LMWH price (dalteparin) £2.82 and the weighted mean price of the LMWHs (enoxaparin, tinzaparin and dalteparin) used (£3.76) .. During the course of this STA appraisal it is anticipated that dabigatran will be licensed for use in patients with atrial fibrillation and that the daily cost of dabigatran will fall. As a result the price of dabigatran was reduced by 50% to assess the impact of such a change on the cost-effectiveness of apixaban. Additionally hospital event unit costs were varied to assess the sensitivity to the results to the ones utilised in the analysis.

Discounting and resource use

The discount rate was varied as this good economic practice. Resource use in the form of long term costs (age of patients and model duration), length of hospital stay and duration of prophylactic treatment were varied. TKR treatment duration was reduced to 10 days and the THR duration to 28 days for all except dabigatran. Dabigatran treatment for TKR remained at 8 days and THR was reduced from 32 to 28 days. In addition TKR and THR treatment

durations were held constant for comparators and the apixaban durations were increased to their recommended maximum of 14 and 38 days respectively.

Utility, efficacy and adverse events
As the utility of treated VTE was in doubt (see section 6.4.9) this parameter was assessed using an alternative value (utilities were also assessed probabilistically). The utility durations for events were also varied. Finally, efficacy and adverse event composite endpoints were assessed by increasing and decreasing the values by plus and minus 10% and in a scenario analysis.

Scenario analysis
Efficacy and bleeding was assessed in a scenario analysis by altering the sources of the data (Indirect comparison group 2 (TKR only), and MTC group 1 (TKR & THR) and group 2 (TKR only), and using 'All VTE' and 'any bleeding components' from the Advance 2 and 3 trials) (See Appendix 22 for MTC data utilised in the sensitivity analysis). In the later analysis the 'All VTE' and 'any bleeding' composite probabilities and the components of all VTE (PE, symptomatic DVT and asymptomatic DVT) and any bleeding (Major bleed, NMCR and Minor bleed) were taken from the Advance 2 and 3 trials. The analysis was only done for apixaban against enoxaparin as enoxaparin is the standard of care.

All parameters not assessed in the one-way and scenario sensitivity analysis were subject to probabilistic sensitivity analysis (See section 6.6.3). The only exception was national mortality data (83).

6.6.3 Probabilistic sensitivity analysis

PSA was undertaken using the distributions listed in section 6.3.6. The parameters in Table 80 of section 6.6.2 were not assessed probabilistically as they are more informative when evaluated in a deterministic form e.g. discount rate and precise ages and durations

6.7 Results

Clinical outcomes from the model

6.7.1 Summary of clinical outcomes from the model

Table 81: Summary of model results compared with clinical data

Outcome	Clinical trial and model results							
	Apixaban		Enoxaparin		Apixaban		Enoxaparin	
	ADVANCE -2	Model	ADVANCE -2	Model	ADVANCE-3	Model	ADVANCE-3	Model
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
VTE composite	147 (100%)	114.7 (100%)	243 (100%)	185.6 (100%)	27 (100%)	18.6 (100%)	74 (100%)	51.9 (100%)
Death	2 (1.4%)	5.2 (4.5%)	0 (0.0%)	8.4 (4.5%)	3 (11.1%)	0.8 (4.3%)	1 (1.35%)	2.1 (4.0%
DVTs								

Non fatal PE	3 (2.07%)	3.2 (2.8%)	0 (0.00%)	5.1 (2.7%)	2 (8.33%)	0.597 (3.2%)	5 (6.85%)	1.7 (3.3%)
Symptomatic DVT	3 (2.07%)	5.18 (4.5%)	7 (2.88%)	8.38 (4.5%)	1 (4.17%)	0.48 (2.6%)	5 (6.85%)	1.34 (2.6%)
Asymptomatic DVT	139 (95.86%)	106.3 (92.7%)	236 (97.12%)	172.1 (92.7%)	21 (87.50%)	17.6 (94.2%)	63 (86.30%)	48.9 (94.1%)
Any bleeding								
Major bleed	9 (9%)	4.4 (7.6%)	14 (11%)	5.3 (7.6%)	22 (7%)	6.6 (7.6%)	18 (5%)	7.1 (7.6%)
CRNM	44 (42%)	19.8 (34.1%)	58 (46%)	23.9 (34.1%)	109 (35%)	29.8 (34.1%)	120 (36%)	32.1 (34.1%)
Minor bleed	51 (49%)	33.9 (58.3%)	54 (43%)	40.8 (58.3%)	184 (58%)	51 (58.4%)	200 (59%)	54.8 (58.3%)

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 82: THR Markov trace proportions for the final year/cycle of the model

		Cycle	Well	Untreated VTE	Treated VTE	Disabled	Death	PE	DVT	M/M PTS Y1	Severe PTS Y1	M/M PTS Y2+	Severe PTS Y2+
Apixaban	M	35	1.91%	0.00%	0.01%	0.00%	98.06%	0.00%	0.00%	0.00%	0.00%	0.01%	0.00%
Apixaban	F	35	1.92%	0.00%	0.01%	0.00%	98.04%	0.00%	0.00%	0.00%	0.00%	0.01%	0.00%
Enoxaparin	M	35	1.85%	0.01%	0.04%	0.00%	98.06%	0.00%	0.00%	0.00%	0.00%	0.02%	0.01%
Enoxaparin	F	35	1.87%	0.01%	0.04%	0.00%	98.05%	0.00%	0.00%	0.00%	0.00%	0.02%	0.01%
Rivaroxaban	M	35	1.91%	0.00%	0.01%	0.00%	98.06%	0.00%	0.00%	0.00%	0.00%	0.01%	0.00%
Rivaroxaban	F	35	1.93%	0.00%	0.01%	0.00%	98.04%	0.00%	0.00%	0.00%	0.00%	0.01%	0.00%
Dabigatran	M	35	1.86%	0.01%	0.03%	0.00%	98.06%	0.00%	0.00%	0.00%	0.00%	0.02%	0.01%
Dabigatran	F	35	1.88%	0.01%	0.03%	0.00%	98.05%	0.00%	0.00%	0.00%	0.00%	0.02%	0.01%

M = Male; F= Female

Table 83: TKR Markov trace proportions for the final year/cycle of the model

		Cycle	Well	Untreated VTE	Treated VTE	Disabled	Death	PE	DVT	M/M PTS Y1	Severe PTS Y1	M/M PTS Y2+	Severe PTS Y2+
Apixaban	M	35	0.82%	0.02%	0.07%	0.00%	99.03%	0.00%	0.00%	0.00%	0.00%	0.04%	0.02%
Apixaban	F	35	1.64%	0.03%	0.14%	0.00%	98.06%	0.00%	0.00%	0.00%	0.00%	0.08%	0.05%
Enoxaparin	M	35	0.72%	0.03%	0.11%	0.00%	99.03%	0.00%	0.00%	0.00%	0.00%	0.07%	0.04%
Enoxaparin	F	35	1.44%	0.06%	0.22%	0.00%	98.07%	0.00%	0.00%	0.00%	0.00%	0.13%	0.08%
Rivaroxaban	M	35	0.85%	0.01%	0.06%	0.00%	99.03%	0.00%	0.00%	0.00%	0.00%	0.03%	0.02%
Rivaroxaban	F	35	1.70%	0.03%	0.11%	0.00%	98.05%	0.00%	0.00%	0.00%	0.00%	0.07%	0.04%
Dabigatran	M	35	0.73%	0.03%	0.11%	0.00%	99.03%	0.00%	0.00%	0.00%	0.00%	0.06%	0.04%
Dabigatran	F	35	1.46%	0.05%	0.21%	0.00%	98.06%	0.00%	0.00%	0.00%	0.00%	0.13%	0.08%

M = Male; F= Female

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The Markov trace below in Table 84 illustrates how the model assumes that QALYs accrued over time.

Table 84: Markov trace of undiscounted QALY accrual for males receiving apixaban undergoing TKR

Cycle	Well	Untreated VTE	Treated VTE	Disabled	Death	PE	DVT	M/M PTS Y1	Severe PTS Y1	M/M PTS Y2+	Severe PTS Y2+
0	280.9068	48.07893	4.048611	0	0	0	0	0	0	0	0
1	276.0494	27.59305	3.448628	0	0	0.540089	9.412956	7.983016	1.777645	0	0
2	271.2759	22.82499	13.10834	0	0	0.132001	2.415556	0.636336	1.095706	7.844896	1.746841
3	263.8741	19.85183	14.74146	0	0	0.081377	1.399511	0.68475	0.601094	8.249739	2.764886
4	256.6742	17.87441	15.45069	0	0	0.049586	0.839195	0.51904	0.315663	8.690623	3.274017
5	249.6707	16.4917	15.69763	0	0	0.04537	0.755891	0.121355	0.150184	8.958286	3.491606
6	242.8583	15.47171	15.91493	0	0	0.024695	0.409529	0.115351	0.139638	8.831811	3.542291
7	236.2317	14.54293	15.77246	0	0	0.021696	0.356734	0.111004	0.131884	8.702947	3.581333
8	225.4147	13.40079	15.28148	0	0	0.02076	0.339132	0.106247	0.124569	8.410277	3.543057
9	215.0929	12.34835	14.79928	0	0	0.019466	0.316005	0.099657	0.115339	8.12647	3.499555
10	205.2437	11.37856	14.31973	0	0	0.01826	0.294554	0.093514	0.106813	7.849372	3.44924

6.7.4 Life years and QALYs accrued for each clinical outcome

Please see Table 85, Table 86, Table 87 and Table 88 below.

Table 85: Mean per person model outputs by clinical outcomes for Apixaban

	Apixaban - TKR			Apixaban - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	13.508	10.495		16.759	13.019	
Untreated VTE	0.791	0.615		0.086	0.067	
Treated VTE	0.878	0.681	£21.17	0.092	0.071	£1.65
PE	0.003	0.003	£14.75	0.000	0.000	£1.54
DVT	0.058	0.045	£161.79	0.006	0.005	£16.92
M/M PTS Y1	0.035	0.026	£1.64	0.004	0.003	£0.17
Severe PTS Y1	0.018	0.013	£1.41	0.002	0.001	£0.15
M/M PTS Y2+	0.493	0.373	£79.89	0.054	0.041	£8.38
Severe PTS Y2+	0.231	0.163	£35.41	0.026	0.018	£3.73

Table 86: Mean per person model outputs by clinical outcomes for enoxaparin

	Enoxaparin - TKR			Enoxaparin - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	11.888	9.236		16.259	12.630	
Untreated VTE	1.280	0.995		0.239	0.185	
Treated VTE	1.421	1.102	£34.26	0.257	0.199	£4.60
PE	0.006	0.004	£23.87	0.001	0.001	£4.28
DVT	0.094	0.072	£261.80	0.017	0.013	£47.13
M/M PTS Y1	0.056	0.043	£2.65	0.010	0.008	£0.47
Severe PTS Y1	0.029	0.021	£2.28	0.005	0.004	£0.41
M/M PTS Y2+	0.798	0.603	£129.26	0.150	0.114	£23.35
Severe PTS Y2+	0.373	0.264	£57.30	0.071	0.050	£10.38

Table 87: Mean per person model outputs by clinical outcomes for rivaroxaban

	Rivaroxaban - TKR			Rivaroxaban - THR		
	LY	QALY	Cost	LY	QALY	Cost
Well	13.978	10.860		16.805	13.054	
Untreated VTE	0.649	0.505		0.072	0.056	
Treated VTE	0.720	0.559	£17.37	0.077	0.060	£1.38
PE	0.003	0.002	£12.10	0.000	0.000	£1.28
DVT	0.048	0.037	£132.73	0.005	0.004	£14.14
M/M PTS Y1	0.029	0.022	£1.34	0.003	0.002	£0.14
Severe PTS Y1	0.015	0.010	£1.15	0.002	0.001	£0.12
M/M PTS Y2+	0.404	0.306	£65.54	0.045	0.034	£7.01
Severe PTS Y2+	0.189	0.134	£29.05	0.021	0.015	£3.11

Table 88: Mean per person model outputs by clinical outcomes for dabigatran

	Dabigatran - TKR			Dabigatran - THR		
	LY	**QALY**	**Cost**	**LY**	**QALY**	**Cost**
Well	12.036	9.351		16.347	12.699	
Untreated VTE	1.235	0.960		0.212	0.164	
Treated VTE	1.371	1.063	£33.06	0.228	0.177	£4.08
PE	0.005	0.004	£23.04	0.001	0.001	£3.80
DVT	0.091	0.070	£252.64	0.015	0.012	£41.80
M/M PTS Y1	0.054	0.041	£2.56	0.009	0.007	£0.42
Severe PTS Y1	0.028	0.020	£2.20	0.005	0.003	£0.36
M/M PTS Y2+	0.770	0.582	£124.74	0.133	0.101	£20.71
Severe PTS Y2+	0.360	0.254	£55.29	0.063	0.044	£9.20

6.7.5 Disaggregated incremental QALYs and costs

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 89 presents for THR the mean QALY gains and incremental differences per person per health state for all the interventions evaluated. The total mean incremental QALYs compared to apixaban was small for all comparators, ranging between 0.07 and 0.76 Rivaroxaban and apixaban produced most QALYS, closely followed by dabigatran and enoxaparin respectively. For all incremental comparisons the greatest difference was seen for the health state well (51.38%; % absolute increment). The next largest incremental differences (% absolute increment) were recorded for treated and untreated VTE, mild to moderate PTS in year two and beyond and severe PTS in year two and beyond.

Table 89: Summary of QALY accrued per person by health state[2] in THR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	13.02	12.63	0.39	0.39	51.38%
Untreated VTE	0.07	0.19	–0.12	0.12	15.71%
Treated VTE	0.07	0.20	–0.13	0.13	16.88%
PE	0.00	0.00	0.00	0.00	0.06%
DVT	0.00	0.01	–0.01	0.01	1.11%
M/M PTS Y1	0.00	0.01	0.00	0.00	0.65%
Severe PTS Y1	0.00	0.00	0.00	0.00	0.32%
M/M PTS Y2+	0.04	0.11	–0.07	0.07	9.65%
Severe PTS Y2+	0.02	0.05	–0.03	0.03	4.25%
Total	13.22	13.20	0.02	0.76	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	13.02	13.05	–0.04	0.04	51.38%
Untreated VTE	0.07	0.06	0.01	0.01	15.71%
Treated VTE	0.07	0.06	0.01	0.01	16.88%
PE	0.00	0.00	0.00	0.00	0.06%
DVT	0.00	0.00	0.00	0.00	1.11%
M/M PTS Y1	0.00	0.00	0.00	0.00	0.65%
Severe PTS Y1	0.00	0.00	0.00	0.00	0.32%
M/M PTS Y2+	0.04	0.03	0.01	0.01	9.65%
Severe PTS Y2+	0.02	0.02	0.00	0.00	4.25%
Total	13.22	13.23	0.00	0.07	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	13.02	12.70	0.32	0.32	51.38%
Untreated VTE	0.07	0.16	–0.10	0.10	15.71%
Treated VTE	0.07	0.18	–0.11	0.11	16.88%
PE	0.00	0.00	0.00	0.00	0.06%
DVT	0.00	0.01	–0.01	0.01	1.11%
M/M PTS Y1	0.00	0.01	0.00	0.00	0.65%
Severe PTS Y1	0.00	0.00	0.00	0.00	0.32%
M/M PTS Y2+	0.04	0.10	–0.06	0.06	9.65%
Severe PTS Y2+	0.02	0.04	–0.03	0.03	4.25%

[2] **Key to calculations**
The **increment** is calculated by subtracting the comparator results from the intervention results. For example, well patients on apixaban (15.03 QALYs) - well patients on enoxaparin (14.66 QALYs) = 0.37.
The **absolute increment** is the increment (difference between intervention and comparator) ignoring the sign (direction) of the difference. For example, an incremental difference of -2.5 has an absolute incremental value of 2.5.
The **total absoluter increment** is the sum (total) of the absolute increment for each health state. For example, if the absolute increment of untreated VTE, treated VTE and DVT are respectively 0.11, 0.11 and 0.01, the absolute difference is 0.23.
The **% absolute increment** is the absolute increment divided by the total absolute increment, multiplied by 100 e.g. if the absolute increment for well is 0.37 and the total absolute increment is 0.71, the % absolute increment is 52.11% (0.37/0.71 * 100).

Total	13.22	13.21	0.02	0.62	100.00%

Mean QALY values and incremental results for TKR by health state are presented in Table 90. As for THR, the total incremental differences for TKR were small, ranging between 0.71 and 2.44. Apixaban and rivaroxaban produced a similar number of QALYs. Enoxaparin and dabigatran provided less QALYs that apixaban (incremental differences of 2.22 to 2.44). As was the case for THR the greatest percentage of absolute increment was found for the health state well, followed by treated VTE, untreated VTE, mild to moderate PTS in year two and beyond, and severe PTS in year two and beyond.

Table 90: Summary of QALY gain by health state in TKR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	10.49	9.24	1.26	1.26	51.48%
Untreated VTE	0.62	1.00	–0.38	0.38	15.55%
Treated VTE	0.68	1.10	–0.42	0.42	17.22%
PE	0.00	0.00	0.00	0.00	0.07%
DVT	0.04	0.07	–0.03	0.03	1.13%
M/M PTS Y1	0.03	0.04	–0.02	0.02	0.67%
Severe PTS Y1	0.01	0.02	–0.01	0.01	0.32%
M/M PTS Y2+	0.37	0.60	–0.23	0.23	9.43%
Severe PTS Y2+	0.16	0.26	–0.10	0.10	4.12%
Total	12.41	12.34	0.07	2.44	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	10.49	10.86	–0.37	0.37	51.48%
Untreated VTE	0.62	0.50	0.11	0.11	15.55%
Treated VTE	0.68	0.56	0.12	0.12	17.22%
PE	0.00	0.00	0.00	0.00	0.07%
DVT	0.04	0.04	0.01	0.01	1.13%
M/M PTS Y1	0.03	0.02	0.00	0.00	0.67%
Severe PTS Y1	0.01	0.01	0.00	0.00	0.32%
M/M PTS Y2+	0.37	0.31	0.07	0.07	9.43%
Severe PTS Y2+	0.16	0.13	0.03	0.03	4.12%
Total	12.41	12.43	–0.02	0.71	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	10.49	9.35	1.14	1.14	51.48%
Untreated VTE	0.62	0.96	–0.35	0.35	15.55%
Treated VTE	0.68	1.06	–0.38	0.38	17.22%
PE	0.00	0.00	0.00	0.00	0.07%
DVT	0.04	0.07	–0.03	0.03	1.13%
M/M PTS Y1	0.03	0.04	–0.01	0.01	0.67%
Severe PTS Y1	0.01	0.02	–0.01	0.01	0.32%
M/M PTS Y2+	0.37	0.58	–0.21	0.21	9.43%
Severe PTS Y2+	0.16	0.25	–0.09	0.09	4.12%
Total	12.41	12.35	0.07	2.22	100.00%

Table 91 and

Table 92 present the incremental mean costs for THR and TKR. In THR the total incremental difference in costs for rivaroxaban and apixaban was small, with rivaroxaban being £5.35 cheaper. The incremental difference between apixaban and enoxaparin and dabigatran was greater with incremental differences of £47.85 and above in favour of apixaban. For all THR incremental comparisons, the greatest percentage of absolute increment was recorded for DVT, followed by mild to moderate PTS (year two and beyond) and severe PTS (year two and beyond).

In TKR the total incremental mean cost differences were larger than those for THR. The smallest total incremental difference with apixaban was found in relation to rivaroxaban at £56.77 (over a 35 year time horizon). Apixaban was £177.46 cheaper than dabigatran and £195.36 cheaper than enoxaparin. As was the case for THR the greatest percentage of absolute increment for all comparisons in

Table 92 was recorded respectively for DVT, mild to moderate PTS (year two and beyond) and severe PTS (year two and beyond).

Table 91: Summary of costs by health state in THR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£1.65	£4.60	–£2.95	£2.95	5.08%
PE	£1.54	£4.28	–£2.74	£2.74	4.72%
DVT	£16.92	£47.13	–£30.21	£30.21	52.00%
M/M PTS Y1	£0.17	£0.47	–£0.30	£0.30	0.52%
Severe PTS Y1	£0.15	£0.41	–£0.26	£0.26	0.45%
M/M PTS Y2+	£8.38	£23.35	–£14.97	£14.97	25.77%
Severe PTS Y2+	£3.73	£10.38	–£6.65	£6.65	11.45%
Total	£32.53	£90.62	–£58.09	£58.09	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£1.65	£1.38	£0.27	£0.27	5.08%
PE	£1.54	£1.28	£0.25	£0.25	4.72%
DVT	£16.92	£14.14	£2.78	£2.78	52.00%
M/M PTS Y1	£0.17	£0.14	£0.03	£0.03	0.52%
Severe PTS Y1	£0.15	£0.12	£0.02	£0.02	0.45%
M/M PTS Y2+	£8.38	£7.01	£1.38	£1.38	25.77%
Severe PTS Y2+	£3.73	£3.11	£0.61	£0.61	11.45%
Total	£32.53	£27.19	£5.35	£5.35	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£1.65	£4.08	–£2.43	£2.43	5.08%
PE	£1.54	£3.80	–£2.26	£2.26	4.72%
DVT	£16.92	£41.80	–£24.88	£24.88	52.00%
M/M PTS Y1	£0.17	£0.42	–£0.25	£0.25	0.52%
Severe PTS Y1	£0.15	£0.36	–£0.21	£0.21	0.45%
M/M PTS Y2+	£8.38	£20.71	–£12.33	£12.33	25.77%
Severe PTS Y2+	£3.73	£9.20	–£5.48	£5.48	11.45%
Total	£32.53	£80.38	–£47.85	£47.85	100.00%

Table 92: Summary of costs by health state in TKR

	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£21.17	£34.26	–£13.09	£13.09	6.70%
PE	£14.75	£23.87	–£9.12	£9.12	4.67%
DVT	£161.79	£261.80	–£100.01	£100.01	51.19%
M/M PTS Y1	£1.64	£2.65	–£1.01	£1.01	0.52%
Severe PTS Y1	£1.41	£2.28	–£0.87	£0.87	0.45%
M/M PTS Y2+	£79.89	£129.26	–£49.38	£49.38	25.28%
Severe PTS Y2+	£35.41	£57.30	–£21.89	£21.89	11.20%
Total	£316.06	£511.42	–£195.36	£195.36	100.00%
	Apixaban	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£21.17	£17.37	£3.80	£3.80	6.70%
PE	£14.75	£12.10	£2.65	£2.65	4.67%
DVT	£161.79	£132.73	£29.06	£29.06	51.19%
M/M PTS Y1	£1.64	£1.34	£0.29	£0.29	0.52%
Severe PTS Y1	£1.41	£1.15	£0.25	£0.25	0.45%
M/M PTS Y2+	£79.89	£65.54	£14.35	£14.35	25.28%
Severe PTS Y2+	£35.41	£29.05	£6.36	£6.36	11.20%
Total	£316.06	£259.29	£56.77	£56.77	100.00%
	Apixaban	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Well	£0.00	£0.00	£0.00	£0.00	0.00%
Untreated VTE	£0.00	£0.00	£0.00	£0.00	0.00%
Treated VTE	£21.17	£33.06	–£11.89	£11.89	6.70%
PE	£14.75	£23.04	–£8.28	£8.28	4.67%
DVT	£161.79	£252.64	–£90.85	£90.85	51.19%
M/M PTS Y1	£1.64	£2.56	–£0.92	£0.92	0.52%
Severe PTS Y1	£1.41	£2.20	–£0.79	£0.79	0.45%
M/M PTS Y2+	£79.89	£124.74	–£44.85	£44.85	25.28%
Severe PTS Y2+	£35.41	£55.29	–£19.88	£19.88	11.20%
Total	£316.06	£493.52	–£177.46	£177.46	100.00%

Table 93 and Table 94 present for THR and TKR the incremental cost for predicted resource use by cost category. In THR apixaban had the lowest total mean cost. Compared to rivaroxaban, apixaban had a mean total incremental cost saving of £29.47. Compared to dabigatran, apixaban gave a saving of £67.08. Compared to enoxaparin, apixaban gave a saving of £238.98. The majority of the incremental difference in costs with apixaban for rivaroxaban was explained by technology costs (drug acquisition costs), for dabigatran was explained by treatment costs (driven by efficacy and adverse events), and for enoxaparin was explained by administration costs (51.69%) (the cost of administering an injection following discharge) and treatment costs (22.71%). Predicted resource use costs are explained in detail in the budget impact model in section 7.0.

In TKR apixaban was more expensive than rivaroxaban with an absolute incremental cost of £51.52 (net increment = £27.88). Apixaban gave an absolute increment of £169.38 (£154.26

saving) compared to dabigatran and £273.63 (£273.63 saving) over enoxaparin. All of the incremental savings of rivaroxaban over apixaban was accounted for by savings in treatment cost (77.06% absolute increment). The majority of savings of apixaban over dabigatran was found in treatment costs (95.54%) (efficacy and adverse event costs). The incremental savings of apixaban compared with enoxaparin were predominantly a result of treatment cost (65.62%), administration cost (16.93%) and monitoring cost (14.78%).

Table 93: Summary of predicted resource use by category of cost for THR

Item	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Technology cost	£116.62	£137.36	–£20.74	£20.74	8.68%
Mean total treatment cost (event cost)	£80.19	£134.45	–£54.26	£54.26	22.71%
Administration cost	£0.00	£123.54	–£123.54	£123.54	51.69%
Monitoring cost	£0.00	£40.44	–£40.44	£40.44	16.92%
Total	£196.81	£ 435.79	–£238.98	£238.98	100.00%
Item	**Apixaban**	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£116.62	£145.70	–£29.08	£29.08	98.65%
Mean total treatment cost (event cost)	£80.19	£80.58	–£0.40	£0.40	1.35%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£196.81	£226.28	–£29.47	£29.47	100.00%
Item	**Apixaban**	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£116.62	£134.40	–£17.78	£17.78	26.51%
Mean total treatment cost (event cost)	£80.19	£129.49	–£49.30	£49.30	73.49%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£196.81	£263.89	–£67.08	£67.08	100.00%

Table 94: Summary of predicted resource use by category of cost for TKR

Item	Apixaban	Enoxaparin	Increment	Absolute increment	% absolute increment
Technology cost	£41.16	£48.48	–£7.32	£7.32	2.68%
Mean total treatment cost	£319.38	£498.93	–£179.55	£179.55	65.62%
Administration cost	£0.00	£46.32	–£46.32	£46.32	16.93%
Monitoring cost	£0.00	£40.44	–£40.44	£40.44	14.78%
Total	£360.54	£634.17	–£273.63	£273.63	100.00%
Item	**Apixaban**	**Rivaroxaban**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£41.16	£52.98	–£11.82	£11.82	22.94%
Mean total treatment cost	£319.38	£279.68	£39.70	£39.70	77.06%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%
Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£360.54	£332.66	£27.88	£51.52	100.00%
Item	**Apixaban**	**Dabigatran**	**Increment**	**Absolute increment**	**% absolute increment**
Technology cost	£41.16	£33.60	£7.56	£7.56	4.46%
Mean total treatment cost	£319.38	£481.20	–£161.82	£161.82	95.54%
Administration cost	£0.00	£0.00	£0.00	£0.00	0.00%

Monitoring cost	£0.00	£0.00	£0.00	£0.00	0.00%
Total	£360.54	£514.80	–£154.26	£169.38	100.00%

Base-case analysis

6.7.6 Summary of results

Table 95: Base-case results in THR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus enoxaparin (QALYs)
Apixaban	£196.81	12.269	9.535	–£238.98	0.014	0.015	Dominant
Enoxaparin	£435.79	12.254	9.520				
Rivaroxaban	£226.28	12.270	9.536	–£209.51	0.015	0.016	Dominant
Dabigatran	£263.89	12.257	9.523	–£171.90	0.002	0.003	Dominant
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus apixaban (QALYs)**
Apixaban	£196.81	12.269	9.535				
Rivaroxaban	£226.28	12.270	9.536	£29.47	0.001	0.001	£21,661.08
Dabigatran	£263.89	12.257	9.523	£67.08	–0.012	–0.012	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 96: Base-case results in TKR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus enoxaparin (QALYs)
Apixaban	£360.54	11.699	9.075	–£273.63	0.051	0.052	Dominant
Enoxaparin	£634.17	11.647	9.023				
Rivaroxaban	£332.66	11.714	9.090	–£301.51	0.066	0.068	Dominant
Dabigatran	£514.80	11.652	9.028	–£119.36	0.005	0.005	Dominant
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus rivaroxaban (QALYs)**
Apixaban	£360.54	11.699	9.075	£27.88	–0.015	–0.015	Dominated
Rivaroxaban	£332.66	11.714	9.090				
Dabigatran	£514.80	11.652	9.028	£182.15	–0.062	–0.063	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

In THR apixaban was less expensive and more effective (QALYs) (dominant) than dabigatran and enoxaparin. Apixaban was less expensive with negligible efficacy difference (QALYs) to rivaroxaban. Rivaroxaban can be described as cost-effective compared to apixaban with an ICER of £21,661.

In TKR like THR, apixaban was less expensive and more effective (QALYs) (dominant) than both enoxaparin and dabigatran. Apixaban was minimally more expensive and had a negligible efficacy difference (QALYs) to rivaroxaban; technically rivaroxaban could be

categorized as dominant. However, the differences in QALYs in both THR and TKR are very small, incremental results only differing at the second or third decimal place, and this raises questions about how stable the ICERs are (125).

Sensitivity analyses

6.7.7 Deterministic sensitivity analysis

The results of the one-way sensitivity analysis are presented in Table 97 and Table 98. Sensitivity analysis was conducted on the variables of discount rate (0% and 6%), unit costs, and duration of prophylaxis, efficacy and bleeding rates.

Table 97: One-way sensitivity analysis TKR

		Apixaban vs. Enoxaparin			Apixaban vs. Dabigatran			Apixaban vs. Rivaroxaban		
Results	**Base Case Parameter(s)**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Base Case		–£273.63	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
Discount rate 0%	3.5%	–£298.30	0.0735	Apixaban dominant	–£176.67	0.0667	Apixaban dominant	£35.05	–0.0214	Rivaroxaban dominant
Discount rate 6%	3.5%	–£260.83	0.0426	Apixaban dominant	–£142.64	0.0387	Apixaban dominant	£24.16	–0.0124	Rivaroxaban dominant
Health care unit costs –10%	See Table 80	–£289.52	0.0523	Apixaban dominant	–£168.70	0.0475	Apixaban dominant	£32.50	–0.0152	Rivaroxaban dominant
Health care unit costs +10%		–£257.73	0.0523	Apixaban dominant	–£139.83	0.0475	Apixaban dominant	£23.26	–0.0152	Rivaroxaban dominant
Health care unit costs PBR		–£273.63	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
Duration of short term utility decrement –10%	See Table 80	–£273.63	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
Duration of short term utility decrement +10%		–£273.63	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
Utility treated VTE = –0.095	–0.01	–£273.63	0.0550	Apixaban dominant	–£154.26	0.0499	Apixaban dominant	£27.88	–0.0160	Rivaroxaban dominant
Weighted mean of LMWH costs = £3.76	£4.04	–£270.27	0.0523	Apixaban dominant						
Lowest LMWH (dalteparin) cost =£2.82	£4.04	–£258.99	0.0523	Apixaban dominant						
Dabigatran cost = £2.20	£4.20				–£138.26	0.0475	Apixaban dominant			
Apixaban wastage cost (15 days of pills)	12 days TKR	–£263.31	0.0523	Apixaban dominant	–£143.94	0.0475	Apixaban dominant	£38.20	–0.0152	Rivaroxaban dominant
Treatment Duration reduced to 10 days for apixaban, enoxaparin and rivaroxaban	Apixaban 12 days, enoxaparin 12 days, dabigatran, 8 days, rivaroxaban 12 days	–£265.39	0.0523	Apixaban dominant	–£161.12	0.0475	Apixaban dominant	£29.85	–0.0152	Rivaroxaban dominant
Treatment Duration extended to maximum recommended of 14 days for apixaban		–£273.79	0.0523	Apixaban dominant	–£147.40	0.0475	Apixaban dominant	£34.74	–0.0152	Rivaroxaban dominant

		Apixaban vs. Enoxaparin			Apixaban vs. Dabigatran			Apixaban vs. Rivaroxaban		
Results	**Base Case Parameter(s)**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Time Horizon 1 year	35 years	–£183.47	0.0048	Apixaban dominant	–£72.37	0.0044	Apixaban dominant	£1.69	–0.0014	Rivaroxaban dominant
Time Horizon 5 year		–£243.96	0.0193	Apixaban dominant	–£127.31	0.0175	Apixaban dominant	£19.26	–0.0056	Rivaroxaban dominant
Time Horizon 10 year		–£258.30	0.0335	Apixaban dominant	–£140.34	0.0305	Apixaban dominant	£23.43	–0.0097	Rivaroxaban dominant
Time Horizon 20 year		–£271.10	0.0487	Apixaban dominant	–£151.97	0.0442	Apixaban dominant	£27.15	–0.0142	Rivaroxaban dominant
Age at surgery 40 years	THR males 65.89, females 68.51; TKR males 68.26, females 68.14	–£297.46	0.0872	Apixaban dominant	–£175.91	0.0792	Apixaban dominant	£34.81	–0.0253	Rivaroxaban dominant
Age at surgery 50 years		–£293.20	0.0802	Apixaban dominant	–£172.05	0.0728	Apixaban dominant	£33.57	–0.0233	Rivaroxaban dominant
Age at surgery 80 years		–£246.35	0.0290	Apixaban dominant	–£129.49	0.0264	Apixaban dominant	£19.96	–0.0084	Rivaroxaban dominant
LOS index hospitalisation +10%	5 days	–£271.87	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
LOS index hospitalisation –10%		–£275.38	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
LOS index hospitalisation +20%		–£270.12	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
LOS index hospitalisation –20%		–£277.14	0.0523	Apixaban dominant	–£154.26	0.0475	Apixaban dominant	£27.88	–0.0152	Rivaroxaban dominant
Apixaban worse composite 'Total VTE and all-cause death' +10%	See Table 80	–£246.01	0.0439	Apixaban dominant	–£126.65	0.0390	Apixaban dominant	£55.50	–0.0237	Rivaroxaban dominant
Comparator worse composite 'Total VTE and all-cause death' +10%		–£318.31	0.0660	Apixaban dominant	–£197.38	0.0607	Apixaban dominant	£5.23	–0.0083	Rivaroxaban dominant
Apixaban worse composite 'Total VTE and all-cause death' - upper 95% CI		–£217.77	0.0352	Apixaban dominant	–£98.41	0.0304	Apixaban dominant	£83.74	–0.0323	Rivaroxaban dominant
Comparator worse composite 'Total VTE and all-cause death' - upper 95% CI		–£273.63	0.0523	Apixaban dominant	–£229.33	0.0705	Apixaban dominant	-£36.46	0.0045	Apixaban dominant
Apixaban worse 'bleeding		–£269.30	0.0523	Apixaban	–£149.94	0.0475	Apixaban	£32.21	–0.0152	Rivaroxaban

		Apixaban vs. Enoxaparin			Apixaban vs. Dabigatran			Apixaban vs. Rivaroxaban		
Results	**Base Case Parameter(s)**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
events' +10%				dominant			dominant			dominant
Comparator worse 'bleeding events' +10%		–£278.84	0.0523	Apixaban dominant	–£159.26	0.0475	Apixaban dominant	£22.57	–0.0152	Rivaroxaban dominant
Apixaban worse 'bleeding events' - upper 95% CI		–£261.65	0.0523	Apixaban dominant	–£142.28	0.0475	Apixaban dominant	£39.86	–0.0152	Rivaroxaban dominant
Comparator worse 'bleeding events' - upper 95% CI		–£273.63	0.0523	Apixaban dominant	–£167.81	0.0475	Apixaban dominant	£6.00	–0.0152	Rivaroxaban dominant

Table 98: One-way sensitivity analysis THR

		Apixaban vs. Enoxaparin			Apixaban vs. dabigatran			Apixaban vs. rivaroxaban		
Results	Base Case Parameter(s)	Incre-mental costs	Incre-mental QALYs	ICER	Incre-mental costs	Incre-mental QALYs	ICER	Incre-mental costs	Incre-mental QALYs	ICER
Base Case		–£238.98	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,661
Discount rate 0%	3.5%	–£246.72	0.0211	Apixaban dominant	–£73.45	0.0174	Apixaban dominant	–£28.76	–0.0019	£14,831
Discount rate 6%	3.5%	–£235.02	0.0120	Apixaban dominant	–£63.82	0.0098	Apixaban dominant	–£29.84	–0.0011	£27,130
Health care unit costs –10%	See Table 80	–£243.75	0.0148	Apixaban dominant	–£71.00	0.0122	Apixaban dominant	–£29.03	–0.0014	£21,339
Health care unit costs +10%		–£234.22	0.0148	Apixaban dominant	–£63.16	0.0122	Apixaban dominant	–£29.91	–0.0014	£21,983
Health care unit costs PBR		–£238.98	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,661
Duration of short term utility decrement –10%	See Table 80	–£238.98	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,661
Duration of short term utility decrement +10%		–£238.98	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,662
Utility treated VTE = –0.095	–0.01	–£238.98	0.0156	Apixaban dominant	–£67.08	0.0128	Apixaban dominant	–£29.47	–0.0014	£20,568
Weighted mean of LMWH costs = £3.76	£4.04	–£229.46	0.0148	Apixaban dominant						
Lowest LMWH (dalteparin) cost =£2.82	£4.04	–£197.50	0.0148	Apixaban dominant						
Dabigatran cost = £2.20	£4.20				–£3.08	0.0122	Apixaban dominant			
Apixaban wastage cost (35 days of pills)	34 days	–£235.58	0.0148	Apixaban dominant	–£63.68	0.0122	Apixaban dominant	–£26.07	–0.0014	£19,162
Treatment Duration reduced (28 days)	Apixaban 34 days, Enoxaparin 34, dabigatran 32 days, rivaroxaban 33 days	–£214.26	0.0148	Apixaban dominant	–£87.66	0.0122	Apixaban dominant	–£27.98	–0.0014	£20,562
Treatment Duration extended to maximum recommended of 38 days for apixaban		-£239.30	0.0148	Apixaban dominant	-£53.36	0.0122	Apixaban dominant	-£15.75	-0.0014	£11,577.10
Time Horizon 1 year	35 years	–£211.69	0.0013	Apixaban dominant	–£44.60	0.0011	Apixaban dominant	–£31.98	–0.0001	£269,744
Time Horizon 5 year		–£229.69	0.0052	Apixaban dominant	–£59.42	0.0043	Apixaban dominant	–£30.33	–0.0005	£63,311

Apixaban. BMS and Pfizer

		Apixaban vs. Enoxaparin			Apixaban vs. dabigatran			Apixaban vs. rivaroxaban		
Results	Base Case Parameter(s)	Incre-mental costs	Incre-mental QALYs	ICER	Incre-mental costs	Incre-mental QALYs	ICER	Incre-mental costs	Incre-mental QALYs	ICER
Time Horizon 10 year		–£234.03	0.0092	Apixaban dominant	–£63.00	0.0075	Apixaban dominant	–£29.93	–0.0008	£35,527
Time Horizon 20 year		–£238.10	0.0136	Apixaban dominant	–£66.35	0.0112	Apixaban dominant	–£29.55	–0.0013	£23,605
Age at surgery 40 years	THR males 65.89, females 68.51; TKR males 68.26, females 68.14	–£245.54	0.0236	Apixaban dominant	–£72.48	0.0195	Apixaban dominant	–£28.87	–0.0022	£13,265
Age at surgery 50 years		–£244.28	0.0217	Apixaban dominant	–£71.44	0.0179	Apixaban dominant	–£28.98	–0.0020	£14,485
Age at surgery 80 years		–£230.35	0.0078	Apixaban dominant	–£59.97	0.0065	Apixaban dominant	–£30.27	–0.0007	£41,990
LOS index hospitalisation +10%	5 days	–£237.23	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,662
LOS index hospitalisation –10%		–£240.74	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,660
LOS index hospitalisation +20%		–£235.47	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,663
LOS index hospitalisation –20%		–£242.49	0.0148	Apixaban dominant	–£67.08	0.0122	Apixaban dominant	–£29.47	–0.0014	£21,659
Apixaban worse composite 'Total VTE and all-cause death' +10%	See Table 80	–£236.16	0.0140	Apixaban dominant	–£64.26	0.0114	Apixaban dominant	–£26.65	–0.0022	£12,177
Comparator worse composite 'Total VTE and all-cause death' +10%		–£246.84	0.0171	Apixaban dominant	–£74.05	0.0142	Apixaban dominant	–£31.83	–0.0007	£47,603
Apixaban worse composite 'Total VTE and all-cause death' - upper 95% CI		–£223.59	0.0103	Apixaban dominant	–£51.68	0.0077	Apixaban dominant	–£14.08	–0.0059	£2,393
Comparator worse composite 'Total VTE and all-cause death' - upper 95% CI		–£238.98	0.0148	Apixaban dominant	–£86.25	0.0178	Apixaban dominant	–£45.97	0.0035	Apixaban dominant
Apixaban worse 'bleeding events' +10%		–£233.78	0.0148	Apixaban dominant	–£61.88	0.0122	Apixaban dominant	–£24.27	–0.0014	£17,836
Comparator worse 'bleeding events' +10%		–£244.57	0.0148	Apixaban dominant	–£73.06	0.0122	Apixaban dominant	–£35.17	–0.0014	£25,858
Apixaban worse 'bleeding events' - upper 95% CI		–£230.60	0.0148	Apixaban dominant	–£58.70	0.0122	Apixaban dominant	–£21.09	–0.0014	£15,493

		Apixaban vs. Enoxaparin			Apixaban vs. dabigatran			Apixaban vs. rivaroxaban		
Results	**Base Case Parameter(s)**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**
Comparator worse 'bleeding events' - upper 95% CI		–£238.98	0.0148	Apixaban dominant	–£82.17	0.0122	Apixaban dominant	–£44.56	–0.0014	£32,775

6.7.8 Probabilistic sensitivity analysis

Table 99: PSA probabilities

	TKR		THR	
	£20,000	**£30,000**	**£20,000**	**£30,000**
Apixaban vs. Enoxaparin	100.00%	100.00%	100.00%	100.00%
Apixaban vs. Dabigatran	100.00%	100.00%	100.00%	100.00%
Apixaban vs. Rivaroxaban	1.80%	1.65%	54.70%	36.05%

See Appendix 23 for scatter plots and cost-effectiveness acceptability curves

6.7.9 Scenario analysis

The results of the scenario analyses are presented in Table 100 and

Table 101. In the scenario analyses the efficacy and bleeding parameters are simultaneously varied (see Table 80 for the parameters that are varied.)

Table 100: Scenario analysisTKR

		Apixaban vs. Enoxaparin			Apixaban vs. Dabigatran			Apixaban vs. Rivaroxaban		
Results	**Base Case Parameter(s)**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Indirect comparison group 2	See Table 80				–£65.55	0.0205	Apixaban dominant	£30.29	–0.0166	Rivaroxaban dominant
MTC Group 1		–£273.34	0.0520	Apixaban dominant	–£151.82	0.0464	Apixaban dominant	£30.45	–0.0166	Rivaroxaban dominant
MTC Group 2					–£86.20	0.0266	Apixaban dominant	£40.39	–0.0196	Rivaroxaban dominant
PE rate –10%	See Table 80	–£272.99	0.0523	Apixaban dominant	–£153.69	0.0475	Apixaban dominant	£27.70	–0.0152	Rivaroxaban dominant
PE rate +10%		–£274.26	0.0523	Apixaban dominant	–£154.84	0.0475	Apixaban dominant	£28.07	–0.0152	Rivaroxaban dominant
DVT rate –10%		–£267.90	0.0524	Apixaban dominant	–£149.07	0.0476	Apixaban dominant	£26.22	–0.0152	Rivaroxaban dominant
DVT rate +10%		–£279.12	0.0522	Apixaban dominant	–£159.25	0.0474	Apixaban dominant	£29.48	–0.0152	Rivaroxaban dominant
PTS rate –10%		–£270.77	0.0514	Apixaban dominant	–£151.66	0.0467	Apixaban dominant	£27.05	–0.0149	Rivaroxaban dominant
PTS rate +10%		–£276.27	0.0532	Apixaban dominant	–£156.67	0.0484	Apixaban dominant	£28.65	–0.0155	Rivaroxaban dominant
All VTE & any bleeding components from Advance 2 & 3	See Table 80	–£262.21	0.035	Apixaban dominant						

Table 101: Scenario analysisTHR

		Apixaban vs. Enoxaparin			Apixaban vs. Dabigatran			Apixaban vs. Rivaroxaban		
Results	**Base Case Parameter(s)**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**	**Incre-mental costs**	**Incre-mental QALYs**	**ICER**
MTC Group 1	See Table 80	–£204.84	0.0076	Apixaban dominant	–£75.60	0.0146	Apixaban dominant	–£28.55	–0.0015	£19,088
MTC Group 2					–£124.77	0.0293	Apixaban dominant	–£14.73	–0.0063	£2,354
PE rate -10%	See Table 80	–£238.79	0.0148	Apixaban dominant	–£66.92	0.0122	Apixaban dominant	–£29.49	–0.0014	£21,670
PE rate +10%		–£239.17	0.0148	Apixaban dominant	–£67.24	0.01218	Apixaban dominant	–£29.45	–0.0014	£21,652
DVT rate -10%		–£237.28	0.0148	Apixaban dominant	–£65.68	0.0122	Apixaban dominant	–£29.63	–0.0014	£21,717
DVT rate +10%		–£240.61	0.0147	Apixaban dominant	–£68.42	0.0122	Apixaban dominant	–£29.32	–0.00136	£21,607
PTS rate -10%		–£238.14	0.0145	Apixaban dominant	–£66.39	0.0119	Apixaban dominant	–£29.55	–0.0013	£22,160
PTS rate +10%		–£239.76	0.0151	Apixaban dominant	–£67.72	0.0124	Apixaban dominant	–£29.40	–0.0014	£21,205
All VTE & any bleeding components from Advance 2 & 3	See Table 80	–£232.17	0.013	Apixaban dominant						

6.7.10 Summary of main findings from sensitivity analysis

The findings of the one-way sensitivity analyses (Table 97 and Table 98) revealed that the findings of the base case analysis were robust. In TKR apixaban dominated enoxaparin in all sensitivity analysis. Apixaban dominated dabigatran under all assumptions.

Rivaroxaban dominated apixaban in all sensitivity analyses apart from when rivaroxaban's 'Total VTE and all-cause death' rate was set to its upper 95% CI (apixaban dominant).

In the scenario analyses apixaban dominated enoxaparin and dabigatran in all scenarios. Rivaroxaban dominated apixaban in all scenarios. The differences in costs and QALYs over 35 years between apixaban and rivaroxaban were small in both the one way and scenario sensitivity analysis, rivaroxaban produced savings of £1.69 to £83.74 over apixaban and 0.00141 to 0.03232 more QALYs.

In THR apixaban dominated enoxaparin under all one-way sensitivity analysis assumptions. The results for apixaban versus dabigatran mirrored those for apixaban versus enoxaparin, apixaban dominated dabigatran in all analyses. When rivaroxaban's 'Total VTE and all-cause death' rate was set to its upper 95% confidence interval apixaban was dominant. Under all other assumptions apixaban was less expensive and gave slightly less QALYs than Rivaroxaban.

In the THR scenario analyses apixaban dominated enoxaparin and dabigatran in all scenarios. apixaban was less expensive and gave slightly less QALYs than Rivaroxaban. The difference in QALYs between apixaban and rivaroxaban in the one-way and scenario analysis was small, between 0.00626 and 0.00012 QALYS.

The probabilistic sensitivity analyses were consistent with the one-way sensitivity analysis; with apixaban being more likely to be cost-effective than enoxaparin and dabigatran. Rivaroxaban was more likely to be cost-effective than apixaban. The probabilistic sensitivity analysis results for the willingness to pay (WTP) thresholds of £20,000 and £30,000 are presented in Table 99 and are presented graphically in scatter plots and cost-effectiveness acceptability curves (CEACs) (WTP £0 to £50,000) in Appendix 23.

In TKR apixaban had a probability of 100% at a WTP of £20,000 and £30,000 of being cost-effective compared to enoxaparin. Apixaban had a probability of 100% at a WTP of £20,000 and £30,000 of being cost-effective compared to dabigatran. At WTP thresholds of £20,000 and £30,000 apixaban had a probability of 1.80 to 1.65% of being cost-effective compared to rivaroxaban.

The probability of apixaban being cost-effective compared to enoxaparin in THR was 100% at a WTP of £20,000 and £30,000. Apixaban had a probability of 100% at a WTP of £20,000 and £30,000 of being more cost-effective than dabigatran. At a WTP of £20,000 apixaban had a probability of 54.7% of being cost-effective compared to rivaroxaban and 36.05% at £30,000.

6.7.11 Key drivers of the cost-effectiveness results

The main drivers of the cost effectiveness results are efficacy, bleeding and time horizon/age. However the differences between interventions in total cost and QALYs are small and given the uncertainty when projecting long term outcomes all treatments could be regarded as being similar in terms of cost-effectiveness.

6.8 Validation

Quality assurance was assessed by modellers that were not involved in producing the model. Two primary criteria were used in quality assessment, internal (verification) and external consistency (validation). Verification was assessed using the techniques of extreme value analysis (substituting minimum and maximum values for appropriate parameter values), using parallel inputs for all interventions for efficacy, costs and utilities. These techniques help reveal inappropriate algorithms in a model and identify any irregularities between the programming of treatment arms. External consistency was assessed by assessing the results of the model against published results.

The results of the de novo model developed for this single technology assessment is consistent with the economic literature identified in section 6.1. Rivaroxaban and dabigatran have been found to be marginally more cost effective than enoxaparin, and rivaroxaban was marginally more cost-effective than dabigatran

6.9 Subgroup analysis

6.9.1 Rationale for subgroup analysis

The primary analysis was segregated into TKR and THR as recommended in the STA scope. No further subgroups were identified

6.9.2 Subgroup patient characteristics

No subgroup analysis.

6.9.3 Please describe how the statistical analysis was undertaken.

No subgroup analysis.

6.9.4 Results of subgroup analyses

No subgroup analysis.

6.9.5 Relevant subgroups not considered

No all possible analysis was considered.

6.10 Interpretation of economic evidence

6.10.1 Comparison with published economic literature

The de novo economic model developed for this evaluation found that both dabigatran and rivaroxaban dominated enoxaparin in TKR and THR and rivaroxaban dominated dabigatran in TKR and THR. These findings were consistent with those reported in the published literature. The literature review revealed that dabigatran dominated enoxaparin in TKR and THR at a dose of 220mg od (58, 59, 64, 67) and rivaroxaban dominated both enoxaparin and dabigatran in TKR and THR (56, 60-63, 68). As enoxaparin is a new compound there

were no published economic evaluations of enoxaparin and as a result the consistency of the apixaban results cannot be assessed.

6.10.2 Relevance of the economic evaluation to all patient groups

The patient groups included in the economic evaluation reflect the licensed indication, patients aged 18 years and over who have undergone elective total hip or knee replacement surgery. Apixaban can be used across a broad range of patients (including renally impaired and elderly) undergoing THR and TKR surgery without a need for dose adjustment.

6.10.3 Strengths and weaknesses of the evaluation

The main strength of the analysis is that it draws on robust clinical trial data that has been synthesised using an indirect treatment comparison and national unit costs which are generalisable across UK NHS settings.

The primary weakness of the model is that it is projecting lifetime costs and outcomes where there is a greater deal of uncertainty surrounding the parameter values.

6.10.4 Further analyses

The model has been developed with the clinical evidence in mind and has been tested and validated. The results are robust and complete

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

Section Summary

- The number of patients aged 18 years and above that will undergo TKR and THR in NHS facilities in England and Wales in 2012 is estimated to be 96,954 and this is expected to rise to 99,630 in 2016.
- Of these patients, the number likely to be treated with apixaban in 2012 in TKR and THR is estimated to be 1,036 and 903 respectively.
- Apixaban is estimated to have a minimal budget impact, producing cost savings for the NHS in each year in the analysis. In 2012 savings of £66,857 and £112,568 are estimated for TKR and THR respectively. These savings are expected to increase over time such that in 2016 the TKR savings increase to £108,104 and THR savings to £182,017.
- These savings were achieved as apixaban has a lower daily acquisition cost than dabigatran, rivaroxaban and LMWHs (weighted average cost). Savings also accrue from reduced administrative costs (nursing time to train & administer injections) associated with apixaban as an oral therapy compared with injectable LMWHs.
- Results were robust to changes in assumptions on duration of treatment and cost of LMWH.

In contrast to the cost-effectiveness analysis where the low molecular weight heparin enoxaparin was assessed as a comparator treatment (as it was the LMWH used in the NOAC trials), in the following analysis LMWHs are treated as a class and costed as a class (weighted mean cost of dalteparin sodium, enoxaparin and tinzaparin sodium) in the base case. The reason for this is that sources of current treatment use treat and record usage of LMWH as a class.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

In 2012 it is estimated that 51,804 patients will be eligible for TKR and 45,150 for THR. By 2016 it is estimated that 53,234 patients will be eligible for TKR and 46,396 for THR; the estimates for 2012 to 2016 are presented in Table 102.

Table 102: Estimated number of elective NHS TKRs and THRs in England and Wales for 2012 to 2016

	2012	2013	2014	2015	2016
Total population of England and Wales 18 years and over	44,303,857	44,650,490	44,991,680	45,333,590	45,526,654
Annual number of TKR	51,804	52,209	52,608	53,008	53,234
Annual number of THR	45,150	45,503	45,851	46,200	46,396

Derivation of eligible patient numbers

The total number of NHS[3] patients having a TKR and THR in 2009 was taken from the National Joint Registry for England and Wales (NJR) (5). Combining the number of TKRs and THRs with the latest population estimates for 2009 (total population of England and Wales 18 years and over), the ONS midyear population estimates of England and Wales (6), provides an annual TKR incidence rate of 0.12% and a THR rate of 0.10% (See Table 103). Assuming that the incidence rate remains constant and applying it to the ONS population projections for 2012-2016 (7) gives the TKR and THR estimates (all eligible for prophylaxis) provided in Table 102.

Table 103: Incidence of NHS elective TKR and THR in England and Wales

	2009
Annual number of TKR	50,475
Annual number of THR	43,992
Total population 18 years and over	43,167,400
Incidence rate TKR	0.12%
Incidence rate THR	0.10%

7.2 What assumption(s) were made about current treatment options and uptake of technologies? and

7.3 What assumption(s) were made about market share (when relevant)?

The pattern of current treatment options in the budget impact model were modelled on 2009 data from the National Joint Registry for England and Wales and IMS sales data (Data on File BMS-Pfizer, Appendix 25) and extrapolated up to 2016. The proportions of patients on any kind of pharmacological prophylaxis for primary elective hip replacement (90.63%) and primary elective knee replacement (88.97%) in 2009 were obtained from data provided by the National Joint Registry (Personal communication, January 5th 2011) for 2009 (See Table 104). It was assumed that these rates (THR = 90.63% and TKR = 88.97%) would remain constant in future years.

In 2009 the majority of pharmacological prophylaxis was monotherapy (80.09% in THR and 79.77% in TKR) with a significant proportion of patients undergoing TKR (9.2%) and THR (10.54%) receiving more than one drug for prophylaxis (no drug was 9.37% THR and 11.03%TKR). Combination therapy was categorised according to which of the therapies NOACs were likely to replace. In this analysis, NOACs were assumed to replace aspirin and LMWH. Thus, if a patient had received LMWH plus a pentasaccharide, then this was counted as a LMWH patient.

As the NJR data did not itemise dabigatran and rivaroxaban use specifically even though both drugs were available in the UK, the category “Other chemical’ (whether as monotherapy or combination) was assumed to represent NOACs in 2009 (see Table 104). Within this category, the split of patients on each drug (28.4% dabigatran and 71.8% rivaroxaban) was calculated based on IMS sales estimates for 2009 (Data on File BMS-Pfizer).

[3] Excludes patients undergoing TKR or THR in independent hospitals and independent sector treatment centres

Extrapolation of the 2009 prophylaxis usage to the 2012-2016 period was done using the following assumptions:

- The market share of all NOACs is estimated to increase by 12% per annum (average growth estimate from BMS-Pfizer market share estimates).
- Apixaban will account for 2% of market share in 2012.
- In a world without apixaban dabigatran and rivaroxaban take patients from LMWH and aspirin in accordance with their respective market share for 2009 (TKR - LMWH 83.39%, aspirin 16.61%%, THR – LMWH 85.26%, aspirin 14.74%).
- Apixaban was assumed to take patients from dabigatran, rivaroxaban, LMWH and aspirin in accordance with their respective market share for 2009 (TKR - dabigatran 1.98%, rivaroxaban 4.99%, LMWH 77.58%, aspirin 15.45%, THR - dabigatran 2.06%, rivaroxaban 5.19%, LMWH 79.08%, aspirin 13.67%).
- It was assumed that all other prophylaxis use would remain constant over time.

The pre apixaban (world without apixaban) and with apixaban (world with apixaban) treatment option percentage estimates for TKR and THR from 2012 to 2016 are presented in Table 105–

Table 108 below. Actual numbers of patients are presented in Appendix 26 but overall the number of patients expected to be treated with Apixaban in 2012 is 1939. This is anticipated to increase to 3135 in 2016.

Table 104: National joint registry (aggregated data) and IMS Sales data

NJR 2009	**TKR**	**THR**
Summary	%	%
No Chemical Selected	11.03%	9.37%
Other Chemical	6.14%	6.48%
Warfarin +	0.39%	0.63%
Pentasaccharide +	0.58%	0.67%
LMWH+	68.27%	70.64%
Aspirin+	13.59%	12.21%
No information	0.00%	0.00%
Sum	100%	100.00%
IMS 2009	**% NOAC sales 2009**	
Rivaroxaban	71.60%	
Dabigatran	28.40%	

See Appendix 25 for IMS data calculations

Table 105: Estimated percentage of patients receiving prophylaxis by drug for TKR (world without apixaban) 2012 to 2016

Pre-apixaban	2012	2013	2014	2015	2016
No drug	11.03%	11.03%	11.03%	11.03%	11.03%
Dabigatran	2.45%	2.74%	3.07%	3.44%	3.85%
Rivaroxaban	6.17%	6.92%	7.75%	8.68%	9.72%
Warfarin	0.39%	0.39%	0.39%	0.39%	0.39%
Pentasaccharide	0.58%	0.58%	0.58%	0.58%	0.58%
LMWH	66.20%	65.34%	64.37%	63.29%	62.07%
Aspirin	13.18%	13.01%	12.82%	12.60%	12.36%
Sum	100.00%	100.00%	100.00%	100.00%	100.00%

Table 106: Estimated percentage of patients receiving prophylaxis by drug for THR (world without apixaban) 2012 to 2016

Pre-apixaban	2012	2013	2014	2015	2016
No drug	9.37%	9.37%	9.37%	9.37%	9.37%
Dabigatran	2.58%	2.89%	3.24%	3.63%	4.07%
Rivaroxaban	6.51%	7.30%	8.17%	9.15%	10.25%
Warfarin	0.63%	0.63%	0.63%	0.63%	0.63%
Pentasaccharide	0.67%	0.67%	0.67%	0.67%	0.67%
LMWH	68.41%	67.48%	66.44%	65.27%	63.96%
Aspirin	11.82%	11.66%	11.48%	11.28%	11.05%
Sum	100.00%	100.00%	100.00%	100.00%	100.00%

Table 107: Estimated percentage of patients receiving prophylaxis by drug for TKR (world with apixaban) 2012 to 2016

Post-apixaban	2012	2013	2014	2015	2016
No drug	11.03%	11.03%	11.03%	11.03%	11.03%
Dabigatran	2.41%	2.70%	3.02%	3.39%	3.79%
Rivaroxaban	6.07%	6.80%	7.62%	8.53%	9.56%
Apixaban	2.00%	2.24%	2.51%	2.81%	3.15%
Warfarin	0.39%	0.39%	0.39%	0.39%	0.39%
Pentasaccharide	0.58%	0.58%	0.58%	0.58%	0.58%
LMWH	64.65%	63.60%	62.42%	61.11%	59.63%
Aspirin	12.87%	12.66%	12.43%	12.17%	11.87%
Sum	100.00%	100.00%	100.00%	100.00%	100.00%

Table 108: Estimated percentage of patients receiving prophylaxis by drug for THR (world with apixaban available) 2012 to 2016

Post-apixaban	2012	2013	2014	2015	2016
No drug	9.37%	9.37%	9.37%	9.37%	9.37%
Dabigatran	2.54%	2.85%	3.19%	3.57%	4.00%
Rivaroxaban	6.41%	7.18%	8.04%	9.01%	10.09%
Apixaban	2.00%	2.24%	2.51%	2.81%	3.15%
Warfarin	0.63%	0.63%	0.63%	0.63%	0.63%
Pentasaccharide	0.67%	0.67%	0.67%	0.67%	0.67%
LMWH	66.83%	65.71%	64.45%	63.05%	61.47%
Aspirin	11.55%	11.36%	11.14%	10.90%	10.62%
Sum	100.00%	100.00%	100.00%	100.00%	100.00%

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

This analysis focuses on costs that differ by the pharmaceutical prophylaxis identified in

Table 108 (1, 5). Apart from drug acquisition costs apixaban is not associated with any additional technology costs. Although it is recommended that patients receiving apixaban receive a liver function test, this cost has been omitted as all patients entering hospital for THR and TKR will receive a liver function test as part of their care. This analysis will focus on the technology costs associated with comparator treatments such as administration and monitoring.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Treatment duration was taken from trials of the treatments. In the base case analysis patients undergoing TKR and THR are assumed to receive prophylaxis respectively for 8-12 days and 32-34 days (20, 21, 29, 30, 32, 33).

Aspirin, warfarin, fondaparinux, dabigatran and rivaroxaban costs were taken from Mims (84). LMWH costs were based on a weighted average of the costs of each LMWH. The unit costs of enoxaparin and tinzaparin were taken from MIMs (84) and the cost of dalteparin was taken from BNF 59 (77) (Mims did not have a cost for dalteparin 5,000 IU). The weighting of use applied to the costs was taken from the 'Prescription Cost Analysis, England 2009' (126) (See Appendix 27 for the weighted mean cost calculations).

In terms of technology costs associated with the comparator treatments, it has been assumed that patients receiving fondaparinux and LMWH are administered by injection there are costs associated with administering these prophylactics to outpatients. 13% of patients were assumed to be unable to self inject and 87% were assumed to be able to self inject following training (86). Home visits to administer injections were assumed to be done by a community nurse and training to self inject (for those that could) was assumed to comprise of 30 minutes of nurse time (24 hour ward nurse).

To estimate the costs associated with patients receiving prophylaxis injections in the community by district nurses following hospital discharge, it was necessary to estimate length of hospital stay. The average length of stay in hospital for TKR and THR were assumed to be 5 days (rounded to whole days) respectively, based on HRG codes HB12C major hip procedures for non trauma category 1 without cc and HB23C intermediate knee procedures for non trauma without cc (127).

Table 109: Drug acquisition and monitoring costs

Drug	Dose	Pack price	Pills/ injections per pack	Pills per day of treatment	Cost per day	Days of TKR treatment	Days of THR treatment	Cost per TKR course	Cost per THR course	Administration costs (See table 108)		Total cost per TKR course	Total cost per THR course
										TKR	THR		
Aspirin	75mg	£1.03	56	2	£0.04	12[a]	34[a]	£0.44	£1.25			£0.44	£1.25
LMWH	2500IU	Weighted mean		1	£3.76	12 (21, 24)	34 (20)	£45.12	£127.84	£85.42	£159.78	£131.88	£291.82
Fondaparinux	2.5mg	£62.79	10	1	£6.28	6 (128)	6 (128)	£37.67	£37.67	£24.70	£24.70	£62.93	£62.93
Warfarin	5mg	£0.47	28	1	£0.02	21 (129)	21 (129)	£0.35	£0.35			£0.35	£0.35
Rivaroxaban	10mg	£441.45	100	1	£4.41	12 (30, 36)	33 (29)	£52.97	£145.68			£52.97	£145.68
Dabigatran*	110mg	£126.00	60	2	£4.20	8 (32)	32 (33)	£33.60	£134.40			£33.60	£134.40
Apixaban	2.5mg	£102.90	60	2	£3.43	12 (21, 24)	34 (20)	£41.16	£116.62			£41.16	£116.62

[a]assumption
[β](24-hour ward [costs including qualifications]) (121)

Table 110: Drug monitoring costs

	Inpatient				Outpatient					
Drug	Number of blood counts	Cost of blood count[@]	30 minutes training to self inject from a nurse	Cost of nurse training for 30 minutes[β]	Home visits from a community nurse to inject prophylaxis	Number of days where a home visit is required[Ψ]		Community nurse[§]	Cost per TKR course	Cost per THR course
						TKR	THR			
LMWH	4	£10.11	Yes 87% of patients	£25.00	Yes 13% of patients	7	29	£27.00	£86.76	£163.98
Fondaparinux	0		Yes 87% of patients	£25.00	Yes 13% of patients	1	1	£27.00	£25.26	£25.26

[β] 24-hour ward [costs including qualifications]) (121)
[§](includes district nursing sister, district nurse) - home visit (including wages/salary, salary oncosts, qualifications, overheads, capital overheads and travel) (121)
[@]unit cost taken from the rivaroxaban STA submission to NICE (63) and updated to 2008/9 costs using the Hospital and Community Health Service Pay and Price Index (121) (See Appendix 19)
[Ψ]Treatment duration minus inpatient stay.

7.6 Were there any estimates of resource savings? If so, what were they?

The resource savings associated with apixaban include:

- No need for blood counts to be conducted (£40.44 per patient – see Table 110) compared with LMWHs.
- No need for the injecting costs associated with LMWHs and fondaparinux such as training the estimated 87% (86) of patients to self inject (£25.00 per patient) and home visits from a community nurse to inject the estimated 13% (86) who cannot inject themselves (£27 per visit per day) are avoided (see Table 110).

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Drug acquisition and administration costs

Table 111: Net cost per patient of changing to apixaban

Net cost of moving to apixaban from:		
	TKR	THR
Dabigatran	£7.56	–£17.78
Rivaroxaban	–£11.81	–£29.06
LMWH	–£90.72	–£175.20
Aspirin	£40.72	£115.37

Table 111 shows the net cost of a patient moving to apixaban from an alternative prophylaxis in TKR and THR. Table 111 only considers prophylaxis that apixaban is believed to be likely to replace. Moving to apixaban from aspirin, which is not advocated for VTE prevention (1) would incur and increased cost in both TKR and THR. If dabigatran, which has a higher daily cost than apixaban, is conservatively prescribed for 8 days in TKR, rather than the 10-14 suggested for all pharmacological prophylaxis in the VTE guideline (1), dabigatran provides a cost saving. However, these additional costs are outweighed by savings compared to the remaining interventions in both TKR and THR so that overall, apixaban is cost saving.

Table 112 shows the estimated budget impact of apixaban for the NHS in England and Wales of VTE prophylaxis for TKR and THR. The analysis indicates that the budget impact in both TKR and THR is minimal, producing cost savings of £66,857 and £112,568 are estimated for TKR and THR respectively in 2012. In 2016 the TKR savings are £108,104 and THR savings are £182,017. The estimated savings are a result of reduced administration costs associated with LMWH (injection and blood count costs) and fondaparinux (injection costs), and acquisition costs compared to LMWH, rivaroxaban and dabigatran.

Table 112: Budget impact of utilising apixaban for TKR and THR

TKR	2012	2013	2014	2015	2016
Dabigatran	£155.18	£175.16	£197.68	£223.08	£250.92
Rivaroxaban	–£611.30	–£690.01	–£778.72	–£878.80	–£988.44
LMWH	–£72,917.44	–£82,306.50	–£92,887.69	–£104,824.81	–£117,903.78

Aspirin	£6,516.72	£7,355.83	£8,301.49	£9,368.32	£10,537.20
Total net budget impact TKR	–£66,856.85	–£75,465.53	–£85,167.25	–£96,112.20	–£108,104.10
THR					
Dabigatran	–£330.57	–£373.13	–£421.10	–£475.22	–£534.51
Rivaroxaban	–£1,361.91	–£1,537.27	–£1,734.90	–£1,957.86	–£2,202.14
LMWH	–£125,114.54	–£141,224.65	–£159,380.25	–£179,862.42	–£202,303.81
Aspirin	£14,238.80	£16,072.22	£18,138.44	£20,469.44	£23,023.40
Total net budget impact THR	–£112,568.22	–£127,062.83	–£143,397.81	–£161,826.05	–£182,017.06
All patients					
Total net budget impact of apixaban	–£179,425.07	–£202,528.35	–£228,565.06	–£257,938.26	–£290,121.16

Scenario Analysis

Two scenario analyses were undertaken (see Appendix 28).

1) Varying treatment duration

   In both TKR and THR the introduction of apixaban continued to produce overall cost savings to the NHS when treatment durations were reduced to 10 days in TKR and 28 days in THR. In both scenarios, dabigatran and fondaparinux remained at their original durations of 8 and 6 days respectively in TKR, and 21 days for warfarin and 6 days for fondaparinux in THR.

   When the treatment duration of apixaban was increased to its maximum recommended duration of 14 days in TKR and 38 days in THR it continued to produce overall cost savings.

2) Varying LMWH cost

   The introduction of apixaban continued to produce cost savings in both TKR and THR between 2012 and 2016 when the cost of enoxaparin (£4.04 per day) and dalteparin (£2.82 per day) were used instead of a weighted LMWH cost of £3.76 per day.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The budget impact model does not include cost savings stemming from the prevention of VTE events and avoided bleeding. However, these offsets have been included in the cost-effectiveness analysis where Apixaban produced savings in discounted 35 year costs against dabigatran (£67.08), rivaroxaban (£29.47) and LMWH (£238.98) in THR and all except rivaroxaban in TKR (dabigatran = £154.26, rivaroxaban = –£27.88 and LMWH = £273.63). The events included in this analysis were pulmonary embolism, distal and proximal deep vein thrombosis, intracranial haemorrhage, major bleed, non major clinically relevant bleed and minor bleed.

LMWH should be initiated 12 hours before (76) surgery whilst apixaban is initiated 12-24 hours post operatively and so there is a potential reduction in length of hospital stay. This saving would be realised by the hospitals in most cases and the PCTs when patients stayed beyond the trim point for TKR and/or THR. As LMWH and fondaparinux are administered by injection there are potential savings of avoided needle stick injuries and sharps disposal by administering an oral prophylaxis. However, these savings could not be quantified and included in this budget impact analysis.

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9 Appendices – see separate document

10 Related procedures for evidence submission

10.1 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.

10.2 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, the NICE secretariat 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.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).