NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Apixaban (Eliquis®▼) for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

Submitted by

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Contents

Contents ... 2
List of tables ... 2
List of figures ... 5
Abbreviations ... 7
Executive summary ... 10
Section A – Decision problem ... 14
1 Description of technology under assessment ... 14
2 Context ... 19
3 Equality ... 30
4 Innovation ... 31
5 Statement of the decision problem ... 33
Section B – Clinical and cost effectiveness ... 36
6 Clinical evidence ... 36
7 Cost effectiveness ... 136
Section C – Implementation ... 228
8 Assessment of factors relevant to the NHS and other parties ... 228
9 References ... 233
10 Appendices ... 243

List of tables

Table 1: Incremental cost-effectiveness results ... 12
Table 2: Unit costs of technology for the indication being appraised ... 17
Table 3: Impact of apixaban on the clinical treatment pathway for VTE treatment and prevention. ... 24
Table 4: Eligibility criteria used in search strategy for clinical systematic review for RCTs ... 37
Table 5: Eligibility criteria used in search strategy for clinical systematic review for non-RCTs ... 38
Table 6: List of relevant RCTs ... 40
Table 7: Summary of AMPLIFY (14) and AMPLIFY-EXT (16) trial design ... 43
Table 8: Eligibility criteria in the RCTs ... 45
Table 9: Baseline demographic and disease characteristics of participants in the AMPLIFY RCT (14, 61) ... 48
Table 10: Baseline demographic and disease characteristics in the AMPLIFY-EXT RCT (16) ... 49
Table 11: Primary and secondary outcomes in AMPLIFY (14, 61) and AMPLIFY-EXT (16) ... 51
Table 12: Treatment compliance in AMPLIFY and AMPLIFY-EXT ... 54
Table 13. Summary of statistical analyses in AMPLIFY (14, 60) and AMPLIFY-EXT (16, 63) ... 56
Table 14: Pre-specified subgroups analysed in AMPLIFY (14) and AMPLIFY-EXT (16) ... 58
Table 15: Analysis population summary – AMPLIFY ... 61
Table 16: Analysis population summary – AMPLIFY-EXT ... 61
Table 17: Quality assessment results for AMPLIFY and AMPLIFY-EXT ... 62
Table 18: Summary of primary efficacy outcome (AMPLIFY) (14, 61) ... 64
Table 19: Summary of secondary efficacy outcomes (AMPLIFY, efficacy evaluable population) (14, 61) ... 65
Table 20: Summary of the primary efficacy outcome for DVT/PE subgroups indexed by type (AMPLIFY) (14, 61) ... 68
Table 21: Summary of secondary efficacy outcomes for DVT/PE subgroups indexed by type (AMPLIFY, efficacy evaluable) (61) ... 68
Table 22: Subgroup results in the pre-specified group of patients with active cancer at baseline (61) ... 69
Table 23: Post-hoc analysis of recurrent VTE or VTE-related death at early timepoints (AMPLIFY, efficacy evaluable population) (62) ... 69
Table 24: Summary of hospitalisation outcomes (AMPLIFY)(15) ... 70
Table 25: Summary of primary efficacy outcome at 12 months (AMPLIFY-EXT, ITT) (16, 64) ... 72
Table 26: Summary of secondary efficacy outcomes (AMPLIFY-EXT, ITT) (16, 64) ... 73

Table 27: Summary of the primary efficacy outcome for DVT/PE subgroups indexed by type (AMPLIFY-EXT) (16, 64) ... 76
Table 28: Summary of secondary efficacy outcomes for DVT/ PE subgroups indexed by type (AMPLIFY-EXT, ITT) (64) ... 76
Table 29: Summary of hospitalisation outcomes (AMPLIFY-EXT) ... 77
Table 30: RCTs included in NMA 1 (Treatment Period) ... 80
Table 31: RCTs included in NMA 2 (Prevention Period) ... 82
Table 32: Outcome data as reported by trials in the treatment period network (NMA 1) ... 84
Table 33: Outcome data as reported by trials in the prevention period network (NMA 2) ... 87
Table 34: Base case analysis for treatment period network (NMA 1) results – 6 month timepoint – fixed-effect model (statistically significant results are shown in bold) ... 90
Table 35: Analysis for Modified ITT population and RE-COVER/RE-COVER II pooled analysis. Sensitivity for treatment period network (NMA 1) results– 6 month timepoint – fixed-effect model (statistically significant results are shown in bold) ... 90
Table 36: DIC and residual deviance model fit statistics ... 92
Table 37: Base case analysis for the prevention period NMA (NMA 2) – fixed-effect model (statistically significant results are shown in bold) ... 94
Table 38: Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold) ... 96
Table 39: Patient characteristics for included studies in the treatment period network (NMA 1) ... 99
Table 40: Summary of heterogeneity across studies included in the extended treatment network ... 103
Table 41: Baseline patient characteristics for included studies in the prevention period network (NMA 2) ... 106
Table 42: Summary of primary safety outcome (AMPLIFY, treated patients) (14) ... 114
Table 43: Summary of major bleeding characteristics (AMPLIFY, treated subjects) (14) ... 116
Table 44: Summary of secondary safety outcomes (AMPLIFY, safety population) (14, 61) ... 117
Table 45: Summary of the primary safety outcome for DVT/PE subgroups indexed by event type (AMPLIFY, safety population) (14, 61) ... 119
Table 46: Safety results in the pre-specified subgroup of patients with active cancer at baseline (AMPLIFY, safety population) (61) ... 119
Table 47: Post-hoc analysis of major and CRNM bleeding at 3 month timepoint (AMPLIFY, safety population) (97) ... 120
Table 48: Summary of adverse events during the treatment period (AMPLIFY, safety population) (14, 61) ... 120
Table 49: Summary of primary safety outcome (AMPLIFY-EXT, safety population) (16, 64) ... 123
Table 50: Summary of secondary safety outcomes (AMPLIFY-EXT, safety population) (16, 64) ... 123
Table 51: Summary of adverse events during the treatment period (AMPLIFY-EXT, safety population) (16) . 127
Table 52: Inclusion and exclusion criteria for the economic evaluation reviews ... 138
Table 53: Patient characteristics employed in base case analysis ... 142
Table 54: Markov model health states ... 145
Table 55: Key features of analysis ... 148
Table 56: Comparison of health states relating to PE and DVT (base case) ... 153
Table 57: Absolute risk of recurrent VTE and VTE-related death ... 153
Table 58: Relative risks of recurrent VTE or VTE-related death based on the NMA ... 154
Table 59: Distribution of recurrent PE, recurrent DVT and VTE-related death ... 155
Table 60: Event rates of major bleeding ... 155
Table 61: Relative risks of major bleeding as based on the NMA* ... 155
Table 62: Absolute risk of CRNM bleeding ... 156
Table 63: Relative risks of CRNM bleeding based on the NMA ... 157
Table 64: Event rates of other treatment discontinuation ... 159
Table 65: Relative risks of overall treatment discontinuation from the NMA ... 159
Table 66: Assumptions in the economic analysis ... 161
Table 67: Summary of quality of life values for the cost-effectiveness analysis ... 170
Table 68: Drug acquisition costs ... 177
Table 69: Administration schedule ... 178
Table 70: Daily drug costs ... 179
Table 71: Unit costs and resource use associated with LMWH administration ... 180
Table 72: Unit costs associated with INR monitoring ... 180
Table 73: Resource use associated with INR monitoring ... 181
Table 74: Inpatient treatment costs of VTE ... 181
Table 75: Unit costs for items associated with outpatient treatment ... 182
Table 76: Acute event costs per episode ... 183

Table 77: Maintenance costs ... 184
Table 78: Summary of model results compared with clinical data ... 189
Table 79: Number of clinical events predicted among 1,000 patients with index VTE over a 6 month treatment duration ... 191
Table 80: Base case results – 6-month treatment duration ... 192
Table 81: Base case incremental analysis – 6-month treatment duration ... 193
Table 82: Number of clinical events predicted among 1,000 patients with index VTE over a lifelong treatment duration ... 193
Table 83: Base case results – Lifelong treatment duration ... 194
Table 84: Base case incremental analysis – Lifelong treatment duration ... 194
Table 85: Deterministic results, apixaban vs. LMWH/VKA for 6 months followed by no treatment – Lifelong treatment duration ... 195
Table 86: Deterministic results, apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran (index VTE, 3-month treatment duration) ... 211
Table 87: Scenario analysis apixaban vs. LMWH/VKA, rivaroxaban, and LMWH/dabigatran (index VTE, 6-month treatment duration) ... 212
Table 88: Deterministic results, apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran (index VTE, 18-month treatment duration) ... 214
Table 89: Scenario analysis apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran (index VTE, lifelong treatment duration) ... 215
Table 90: Scenario analysis apixaban vs. LMWH/VKA for 6 months followed by no treatment (index VTE, lifelong treatment duration) ... 218
Table 91: Scenario analysis apixaban vs. LMWH/VKA for 6 months followed by aspirin (index VTE, lifelong treatment duration) ... 219
Table 92: Scenario analysis apixaban vs. LMWH monotherapy (index VTE, 6-month treatment duration) ... 219
Table 93: Scenario analysis apixaban vs. LMWH monotherapy (index VTE, 6-month treatment duration) ... 220
Table 94: Base case results – 6-month treatment duration (index PE) ... 223
Table 95: Base case results – 6-month treatment duration (index DVT) ... 224
Table 96: Base case results – Lifelong treatment duration (index PE) ... 224
Table 97: Base case results – Lifelong treatment duration (index DVT) ... 225
Table 98: Eligible patient population ... 228
Table 99: Projected market share without apixaban (169) ... 229
Table 100: Projected market share with apixaban (169) ... 229
Table 101: Assumed treatment durations ... 229
Table 102: Costs of INR monitoring with and without apixaban ... 230
Table 103: Costs of training and administration for LMWH treatment with and without apixaban ... 230
Table 104: Unit costs assumed in budget impact calculations (induction) ... 230
Table 105: Unit costs assumed in budget impact calculations (concomitant LMWH) ... 231
Table 106: Unit costs assumed in budget impact calculations (up to 6 months) ... 231
Table 107: Unit costs assumed in budget impact calculations (after 6 months) ... 231
Table 108: Treatment costs with and without apixaban ... 231
Table 109: Budget impact ... 232

List of figures

Figure 1: Schematic for the systematic review of RCT evidence 39
Figure 2: Schematic for systematic review of clinical evidence (non-RCT) 39
Figure 3: AMPLIFY – Patient flow diagram (14) 59
Figure 4: AMPLIFY-EXT – Patient flow diagram (16) 60
Figure 5: Kaplan–Meier cumulative event rates for the first event of recurrent VTE or VTE-related death (AMPLIFY; ITT population)* (14) 64
Figure 6: Summary of the relative risk of the primary efficacy outcome according to pre-specified subgroups (AMPLIFY, efficacy evaluable population) (14, 61) 67
Figure 7: Kaplan–Meier cumulative event rates for the first event of recurrent symptomatic VTE or all-cause death over the intended treatment period (AMPLIFY-EXT, ITT)* (64) 72
Figure 8: Kaplan–Meier cumulative event rates for the first event of recurrent VTE or VTE-related death over the intended treatment period (AMPLIFY-EXT) (16) 74
Figure 9: Summary of the relative risk of the primary efficacy composite outcome of recurrent VTE or all-cause death according to pre-specified subgroups (AMPLIFY-EXT, ITT) (16) 75
Figure 10: Network diagram for the treatment period network 81
Figure 11: Network diagram for the prevention period network 83
Figure 12: Forest plots – Recurrent VTE and VTE-related death 104
Figure 13: Forest plot – Major or CRNM bleed 104
Figure 14: Forest plots – Major bleed 104
Figure 15: Forest plot – CRNM bleed 105
Figure 16: Forest plot – Overall treatment discontinuation 105
Figure 17: Consistency within a closed loop – Recurrent VTE or VTE-related death (Warfarin INR 2.0–3.0, dabigatran and placebo/observation of VKA) 110
Figure 18: Consistency within a closed loop – Recurrent VTE or VTE-related death (Warfarin INR 2.0–3.0, warfarin INR 1.5-1.9 and placebo) 111
Figure 19: Kaplan–Meier cumulative event rates for the first episode of major bleeding (AMPLIFY, treated patients) (14) 115
Figure 20: Summary of event rates for the secondary safety outcomes (AMPLIFY, safety population: Apixaban N=2676; Enoxaparin/warfarin N=2689) (61) 117
Figure 21: Relative risk of the primary safety outcome (adjudicated major bleeding) according to pre-specified subgroups (AMPLIFY, safety population) (60) 118
Figure 22: Kaplan–Meier cumulative event rates for the first episode of the composite of major or CRNM bleeding (AMPLIFY-EXT, safety population) (16) 124
Figure 23: Summary of event rates for the secondary safety outcomes (AMPLIFY-EXT, safety population) Apixaban 2.5 mg N=840; Placebo N=826) (64) 124
Figure 24: Summary of the relative safety for the composite outcome of major/CRNM bleeding across pre-specified subgroups (AMPLIFY-EXT, safety population) (16) 125
Figure 25: PRISMA flow diagram of number of journal articles identified and included at each stage of the cost-effectiveness review update 140
Figure 26: Model diagram 143
Figure 27: PRISMA flow diagram of number of journal articles identified and included at each stage of the Health Utilities Review Update 166
Figure 28: PRISMA flow diagram of number of journal articles identified and included at each stage of the Cost and Resource Use Review Update 176
Figure 29: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/VKA (index VTE, 6-Month treatment duration) 196
Figure 30: Tornado diagram illustrating results from univariate sensitivity analysis for incremental costs vs. rivaroxaban (index VTE, 6-month treatment duration) 197
Figure 31: Tornado diagram illustrating results from univariate sensitivity analysis for incremental QALYs vs. rivaroxaban (index VTE, 6-month treatment duration) 198
Figure 32: Tornado diagram illustrating results from univariate sensitivity analysis for incremental costs vs. LMWH/dabigatran (index VTE, 6-month treatment duration) 199
Figure 33: Tornado diagram illustrating results from univariate sensitivity analysis for incremental QALYs vs. LMWH/dabigatran (index VTE, 6-month treatment duration) 200
Figure 34: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/VKA (index VTE, lifelong treatment duration) 202

Figure 35: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. rivaroxaban (index VTE, lifelong treatment duration) 203
Figure 36: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/dabigatran (index VTE, lifelong treatment duration) 204
Figure 37: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/VKA followed by no treatment (index VTE, lifelong treatment duration) 205
Figure 38: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. LMWH/VKA, cost per QALY, index VTE, 6-month treatment duration 206
Figure 39: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. rivaroxaban, cost per QALY, 6-month treatment duration index VTE 207
Figure 40: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. LMWH/dabigatran, cost per QALY, index VTE, 6-month treatment duration 207
Figure 41: Multi-way cost-effectiveness acceptability curve, index VTE, 6-month treatment duration 208
Figure 42: Probabilistic analysis - results on the cost-effectiveness plane, apixaban vs. LMWH/VKA, cost per QALY, index VTE, lifelong treatment duration 209
Figure 43: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. rivaroxaban, cost per QALY, lifelong treatment duration index VTE 209
Figure 44: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. LMWH/dabigatran, cost per QALY, index VTE, lifelong treatment duration 210
Figure 45: Multi-way cost-effectiveness acceptability curve, index VTE, lifelong treatment duration 210

Abbreviations

AC	Anticoagulant
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ALT	Alanine aminotransferase
ASA	Acetylsalicylic Acid
ASH	American Society of Haematology
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BD	Twice daily
BMI	Body Mass Index
BMS	Bristol Myers Squibb
BNF	British National Formulary
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CDT	Complex Decongestive Therapy
CEAC	Cost-Effectiveness Acceptability Curve
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Cost-Effectiveness Ratio
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPMP	Committee for Proprietary Medicinal Products
CPRD	Clinical Practice Research Datalink
CrI	Credible Interval
CRNM	Clinically Relevant Non-Major
CRNMB	Clinically Relevant Non-Major Bleeding
CSR	Clinical Study Report
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CUS	Compression Ultrasonography
CV	Cardiovascular
DARE	Database of Abstracts of Reviews of Effects
DVT	Deep Vein Thrombosis
EC	Extracranial
EDT	Electronic Drug Tariff
EED	Economic Evaluation Database
EHS	European Haematology Society
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQL	Health-Related Quality of Life

HTA	Health Technology Assessment
IBD	Inflammatory Bowel Disease
IC	Intracranial
ICER	Incremental Cost-Effectiveness Ratio
INR	International Normalised Ratio
IQR	Interquartile range
IS	Ischaemic Stroke
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
KOL	Key Opinion Leader
LMWH	Low Molecular Weight Heparin
LY	Life Year
MA	Marketing Authorisation
MeSH	Medical Subject Headings
MI	Myocardial Infarction
mITT	Modified Intention-to-Treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NOAC	Novel Oral Anticoagulant
NR	Not Reported
NVAF	Non-Valvular Atrial Fibrillation
NYHA	New York Heart Association
OD	Once Daily
OR	Odds Ratio
OXVASC	Oxford Vascular Study
PCT	Primary Care Trust
PE	Pulmonary Embolism
PEA	Pulmonary Endarterectomy
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTS	Post-Thrombotic Syndrome
QALY	Quality-Adjusted Life Years
RCT	Randomised Controlled Trial
RecDVT	Recurrent Deep Vein Thrombosis
RecPE	Recurrent Pulmonary Embolism
RecVTE	Recurrent Venous Thromboembolism
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SG	Standard Gamble
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
TTO	Time Trade-Off
TTR	Time in Therapeutic Range

UFH	Unfractionated Heparin
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VAT	Value-Added Tax
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WTP	Willingness To Pay

Executive summary

Background

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) or pulmonary embolism (PE), a prevalent and potentially fatal condition.(1-3) It represents a considerable morbidity and mortality burden and is a costly public health problem; hospitalisations and inpatient management of VTE account for >50% of the total associated costs.(1) In England during 2012–2013, there were 23,578 hospital admissions for PE and 25,165 admissions for DVT.(4) VTE is estimated to be responsible for 25,000 hospital deaths annually in the UK,(1) and PE is one of the most common preventable causes of death in hospitalised patients.(5) It is estimated that 1.4% of patients with DVT, and 22.6% of patients with a PE, die within one month of the event occurring.(2) An episode of VTE also carries an increased risk of a recurrent VTE event – the cumulative risk of recurrent VTE over 10 years has been determined to be 25.2%. (6, 7) Incidence rates for VTE recurrence following a first DVT are highest in younger patients, particularly young males. Furthermore, complications for DVT and PE include post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH),(8) which carry significant morbidity in themselves.

The current NICE Clinical Guideline CG144 recommends that VTE events should be treated with a vitamin K antagonist (VKA) for at least 3 months and that long-term continuation of VKA may be appropriate in patients at risk of a VTE recurrence.(8) Warfarin is the oral VKA of choice in England and Wales.(8) Based on expert opinion on current clinical practice, patients with VTE in England and Wales may be treated for 3 to 6 months, at which point a decision is made on whether to continue long-term anticoagulation.(9) The effectiveness of warfarin anticoagulation may be compromised due to the difficulty of maintaining an optimal therapeutic level (balancing efficacy of treatment with risk of bleeding). Due to the limitations of warfarin, some patients will receive less effective treatments for prevention of recurrent VTE, such as aspirin or even no pharmacological treatment. (10) This has led to the need for new therapies, such as novel oral anticoagulants (NOACs), which have been developed for the treatment and long-term prevention of recurrent VTE. Since the publication of NICE CG144 in 2012, rivaroxaban, a NOAC, has been accepted for use by NICE, while dabigatran, another NOAC, is currently being appraised.(11-13) Warfarin and the other currently available treatments are all associated with a risk of bleeding, which is a serious and costly complication.(10) There remains a need for effective oral anticoagulation with a lower risk of bleeding than currently available treatments.

Eliquis® (apixaban), a direct factor Xa inhibitor, is newly indicated for the treatment of DVT and PE, and the prevention of recurrent DVT and PE in adults. It is available in the UK as 2.5 and 5 mg tablets. The recommended dose for the treatment of DVT or PE is 10 mg bd for the first 7 days, followed by 5 mg bd. Following the completion of 6 months of treatment for DVT or PE, 2.5 mg bd is recommended for the prevention of recurrent DVT and/or PE.

Clinical Evidence

Apixaban has been studied in two large double-blind, randomised controlled trials involving 7881 patients (see Section 6.5):

- AMPLIFY confirmed apixaban to be similarly effective to enoxaparin followed by warfarin in treating VTE as determined by preventing recurrent symptomatic VTE[1] or VTE-related death, but with a significantly lower risk of bleeding, specifically a reduction in the risk of major bleeding of 69% over a 6 month period.(14)

[1] Recurrent symptomatic VTE will for the remainder of the document be referred to as 'recurrent VTE'.

- Apixaban significantly reduced the risk of all-cause hospitalisation by 19% vs. enoxaparin/warfarin and significantly reduced the rate of all-cause hospitalisations by 32% within the first 30 days of acute VTE treatment vs. enoxaparin/warfarin.(15)
- AMPLIFY-EXT demonstrated that following 6 to 12 months of prior anticoagulation, long-term apixaban (2.5 mg bd) was superior to 'no treatment' (placebo) in reducing recurrent VTE or all-cause death by 67% and was associated with a similar risk of bleeding over a 12 month period.(16)
- Apixaban significantly reduced all-cause hospitalisations compared to placebo during the intended treatment period (p=0.030).(17)

In the absence of head-to-head RCT evidence, network meta-analyses were conducted to determine the relative efficacy and safety of apixaban compared to other NOACs for VTE in the treatment and prevention periods, and additionally to VKA and aspirin in the prevention period (NMA; Section 6.7):

For the treatment of VTE:

- There were no significant differences between apixaban and rivaroxaban or LMWH/dabigatran for the outcome of recurrent VTE or VTE-related death at 6 months (Section 6.7.5.1).
- Bleeding outcomes were significantly lower for apixaban compared with: rivaroxaban (major or clinically relevant non-major bleeds [CRNM]; and CRNM bleeds) and LMWH/dabigatran (major or CRNM bleeds; major bleeds).

For long-term therapy to prevent VTE recurrence:

- Apixaban had similar efficacy to warfarin, rivaroxaban and dabigatran for prevention of recurrent VTE or VTE-related death (Section 6.7.5.2)
- Bleeding outcomes were significantly lower for apixaban compared with: rivaroxaban (major or CRNM bleeds; major bleeds; and CRNM bleeds), dabigatran (major or CRNM bleeds) and warfarin (major or CRNM bleeds; major bleeds; and CRNM bleeds).

Cost-effectiveness and Budget Impact Analysis

The cost-effectiveness of apixaban was assessed using a Markov model similar to that used in previous rivaroxaban NICE appraisals (see Section 7.2).(18, 19)

For the treatment of VTE (6-month duration) apixaban was dominant vs. rivaroxaban and LMWH/dabigatran, and cost-effective vs. LMWH/VKA with an ICER of £2,406 per QALY gained in the incremental analysis (Table 1 and Section 7.7.6). Apixaban was associated with a reduced number of major and CRNM bleeds compared to all other treatments over this period which resulted in QALY gains for apixaban. Apixaban was associated with fewer costs compared to rivaroxaban due to a shorter initiation period (7 days vs. 21 days, respectively) and dabigatran which requires initial parenteral anticoagulant injections. In patients treated with LMWH/VKA, the high cost of LMWH and the cost of VKA monitoring are the main contributors to the cost of treatment vs. apixaban.

For the treatment and prevention of VTE recurrence (lifelong duration), rivaroxaban was dominated by LMWH/VKA, dabigatran was extendedly dominated by apixaban and apixaban was cost effective vs. LMWH/VKA with an ICER of £16,676 per QALY gained. Patients treated with apixaban have greater QALY gains compared to other treatments due to a reduced number of major bleeding events. However patients treated with apixaban incur additional costs in comparison to other treatments because they remain on treatment for longer periods due to fewer discontinuations associated with bleeding. (Section 7.7.6).

A conservative analysis explored apixaban for the treatment and prevention of recurrent VTE (lifelong duration) compared with LMWH/VKA for 6 months followed by no preventative therapy ('no treatment'), which resulted in an ICER of £17,917 per QALY gained (Section 7.7.6). This scenario

demonstrates that apixaban is cost-effective for patients who would benefit from long-term anticoagulation but who are currently not receiving long term preventative therapy. In a scenario analysis, a similar comparison between lifelong treatment with apixaban and 6-month treatment with LMWH/VKA followed by aspirin, apixaban had an ICER of £22,595 per QALY gained (Section 7.7.6).

In subgroup analyses (Section 7.9), apixaban was cost-effective vs. LMWH/VKA for the 6-month treatment duration for the index PE and index DVT subgroups. One-way sensitivity analyses, scenario analyses and probabilistic sensitivity analysis demonstrated that the findings were robust to changes in key parameters (Sections 7.7.7 to 7.7.9).

Table 1: Incremental cost-effectiveness results

Technology (and comparators)	Total cost	Total QALYs	Incremental cost for comparator vs. LMWH/VKA	Incremental QALYs for comparator vs. LMWH/VKA	ICERs for comparator vs. LMWH/VKA	Incremental analysis
6-month treatment duration						
LMWH/VKA	£4,954.94	8.389	-	-	-	-
Apixaban	£5,034.96	8.422	£80.02	0.033	£2,405.53	£2,405.53
Rivaroxaban	£5,069.16	8.412	£114.22	0.023	£5,016.99	Dominated
LMWH/ dabigatran	£5,100.37	8.396	£145.43	0.007	£19,782.46	Dominated
Lifelong treatment duration (including treatment and prevention periods)						
LMWH/VKA	£6,136.28	8.472	-	-	-	-
Rivaroxaban	£9,013.16	8.075	£2,876.88	-0.397	Dominated	Dominated
LMWH/ dabigatran	£9,083.28	8.591	£2,947.00	0.120	£24,621.57	Extendedly dominated
Apixaban	£9,497.37	8.673	£3,361.09	0.202	£16,675.53	£16,675.53

ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; QALY: Quality adjusted life year; VKA: Vitamin K antagonist

Budget impact analysis estimated that the number of patients beginning treatment for VTE in England and Wales will be 58,392 in 2015, rising to 60,045 in 2019 (Section 8.1.1). The cumulative total budget impact of apixaban is estimated to be £4,878,956 for the 5-year period to 2019. This is a conservative analysis which does not include potential savings from reduced hospitalisations and bleeding events avoided (Section 8.1.7).

Conclusions

Apixaban should be recommended as an option for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults because:

- It is similarly effective as LMWH/VKA for the treatment of DVT and PE and causes significantly fewer bleeds
- It has superior efficacy to ‘no treatment’ (placebo) with similar bleeding risk in patients undergoing long-term therapy to prevent VTE recurrence

- Indirect comparisons show that apixaban has similar efficacy and causes significantly fewer major or CRNM bleeds compared with LMWH/VKA, LMWH/dabigatran and rivaroxaban in the treatment and prevention of recurrent VTE
- It is not associated with the cost and inconvenience of initial parenteral LMWH therapy or INR monitoring, and it does not have the same degree of food and drug interactions as warfarin
- It dominates rivaroxaban and LWMH/dabigatran and is cost effective versus LWMH/VKA (£2,405.53 per QALY gained) for the treatment of DVT and PE (6-month duration)
- It is the most cost effective treatment compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran at a willingness to pay of £20,000 per QALY for the treatment and prevention of recurrent DVT and PE (lifelong duration)
- It is estimated to have an incremental budget impact for the population of England and Wales of £2,996,857 over 5 years

Apixaban addresses the unmet need for an effective oral anticoagulant with a lower risk of bleeding compared to the currently available treatments.

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: Direct Factor Xa inhibitors (oral anticoagulants)
ATC code: B01AF02

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

Apixaban is a potent, oral, direct and highly selective active site inhibitor of Factor Xa (20). It does not require antithrombin III for antithrombotic activity and inhibits Factor Xa activity both within and outside the prothrombinase complex. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting Factor Xa, apixaban prevents both 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).

Eliquis® (apixaban) received European marketing authorisation on 28th July 2014 for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and/or PE in adults.

Eliquis® (apixaban) has received previous European marketing authorisations for the following indications:

- In May 2011, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
- In November 2012, for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (New York Heart Association [NYHA] Class ≥ II).

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

During the assessment of apixaban for the new Marketing Authorisation (MA): 'for the treatment of deep vein thrombosis and pulmonary embolism and prevention of recurrent DVT and/or PE in adults', the following issues were discussed by the Committee for Medicinal Products for Human Use (CHMP) in the European Public Assessment Report (EPAR):(21)

Clinical Aspects

From a clinical perspective, the efficacy and safety of apixaban for the treatment and prevention of VTE indications were investigated in one Phase 2 study (CV185017, BOTTICELLI) and two pivotal Phase 3 studies (CV185056, AMPLIFY and CV185057, AMPLIFY-EXT). The EPAR concluded that 'the benefit/risk balance for the requested indication both in terms of treatment and prevention is positive.'

Risk Management Plan

As part of the marketing authorisation (MA) for apixaban, and in addition to regular periodic safety update reports, there is a requirement for a risk management plan (RMP) to be implemented. The following risk management measures for apixaban in the treatment and prevention of recurrent DVT and/or PE in adults were deemed acceptable and agreed by the Pharmacovigilance Risk Assessment Committee (PRAC).

A physician educational pack containing a Summary of Product Characteristics (SPC), Prescriber Guide and Patient Alert Cards, shall be provided by the marketing authorisation holder prior to launch, targeting all physicians who are expected to prescribe/use apixaban. The pack is aimed at increasing the awareness of the potential risk of bleeding during treatment and to provide guidance on how to manage that risk.

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

The new indication for Eliquis® (apixaban) in the UK is:

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see Section 4.4 [Eliquis® SPC] for haemodynamically unstable PE patients).

Apixaban is also licensed for the indications mentioned above in question 1.3.

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.

We do not anticipate any new studies relevant to the indication being appraised to become available within the next 12 months.

There is an open-label, randomised, active-control (UFH/warfarin [INR 1.5–2.5]) 24-week study ongoing in Japan (ClinicalTrials.gov identifier NCT01780987) to evaluate the safety and efficacy of apixaban (10 mg bd for 1 week followed by 5 mg bd for 23 weeks) for the treatment of symptomatic VTE in the Japanese population. Data collection has just been completed. The results are anticipated to be published in an abstract in April 2015 at the Japanese Circulation Society 2015 Scientific congress. However this study is not directly relevant to the current submission because the target warfarin INR therapeutic range was 1.5–2.5 and it was conducted in a cohort of Japanese patients and therefore lacks validity for the population of England and Wales.

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

Apixaban 2.5 mg and 5 mg tablets are already available in the UK. Apixaban was launched in the indication being appraised in this submission in September 2014.

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

All the marketing authorisations in Question 1.3 were granted by the European Medicine Agency's Centralised Procedure and are therefore applicable across the European member states.

Eliquis® (apixaban) has also been granted marketing authorisation in the United States of America for these indications.

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 is undergoing health technology assessment by the Scottish Medicines Consortium (SMC) for the indication considered in this submission. The evidence dossier was submitted in September 2014 and it is anticipated that advice will be issued in Q1 2015.

Apixaban has already been appraised, with positive recommendations, by both NICE and SMC for its other licensed indications:

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

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.

The unit costs of the technology for the indication being appraised are outlined in Table 2.

Table 2: Unit costs of technology for the indication being appraised

Pharmaceutical formulation	2.5 mg and 5 mg film-coated tablets
Acquisition cost (excluding VAT)	NHS list price £1.10 (2.5 mg or 5 mg) per tablet
Method of administration	Oral
Doses	Treatment of DVT/PE 10 mg bd for the first 7 days followed by 5 mg bd for at least 3 months Prevention of recurrent DVT/PE 2.5 mg bd (following completion of 6 months of treatment)
Average length of a course of treatment	For treatment of VTE , NICE recommends at least 3 months of treatment. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding.(8)
Average cost of a course of treatment	Treatment of DVT/PE The cost of apixaban 10 mg bd for the first 7 days, followed by 5 mg bd for up to 6 months is: £415.80 for 6 months Prevention of recurrent DVT/PE The cost of apixaban (2.5 mg bd) for prevention of recurrent DVT/PE is: £818.40 for first 12 months (including treatment period) £803.00 for subsequent 12 months
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	No dose adjustments are required for any patient subgroup.

Bd: Twice daily; DVT: Deep vein thrombosis; NHS: National Health Service; PE: Pulmonary embolism; VAT: Value added tax

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?

There are no further additional tests, investigations or administration requirements above and beyond routine clinical practice for the use of anticoagulants.(20) Prior to initiating apixaban, liver function testing should be performed.(20)

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

There is no need for monitoring over and above usual clinical practice.

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

No other therapies are required.

2 Context

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.

VTE is a condition in which a blood clot (thrombus) forms in a vein. DVT and PE are manifestations of VTE with serious and potentially fatal outcomes.(22) A DVT most commonly occurs in the deep veins of the legs, and can cause a spectrum of symptoms such as cramping pain, redness and/or swelling of the leg, or have no symptoms at all.(23) A PE is caused when a thrombus detaches and travels to block the main pulmonary artery or one of its branches, which delivers de-oxygenated blood to the lungs. PEs can cause breathlessness, chest pain, and sudden death.

Approximately two-thirds of patients with a VTE present with a DVT and one third present with a PE.(24) Up to 50% of patients with symptomatic DVT may have an asymptomatic PE and less than a third of patients with PE exhibit signs or symptoms of DVT.(25) When VTE is associated with an identifiable (and often reversible or transient) risk factor(s), such as surgery, trauma, or prolonged immobilisation, it is referred to as a provoked VTE.(23, 26). A VTE is considered unprovoked (idiopathic) if it occurs without a clearly identifiable provoking factor.

In the UK, the incidence of people presenting with clinical symptoms of VTE each year is 2 in 1,000 (7). The incidence of VTE varies with age – for people under 40 years the annual incidence of VTE is 1 in 10,000, rising to 1 in 100 for those over 80 years (27). VTE is estimated to be responsible for 25,000 hospital deaths annually in the UK (1). Mortality from VTE can be as high as 22% in the first year following an event (28), and PE is one of the most common preventable causes of death in hospitalised patients.(5) VTE is a major public health burden (29) and NICE Clinical Guideline 92 recommends, as a key NHS priority, that all patients are assessed on admission to hospital to identify those who are at an increased risk of VTE.(23)

An episode of DVT increases the risk of VTE recurrence.(30) The thrombus may dislodge from its site of origin and travel in the blood to obstruct another blood vessel, which is termed an ‘embolism’.(23) If an essential blood vessel is blocked, this can be life-threatening. DVT may also result in poor venous circulation causing venous ulceration and/or development of post-thrombotic syndrome (PTS) which is characterised by chronic pain, swelling and skin changes; the prevalence of severe PTS has been reported as 8.1% amongst patients with DVT.(31)

Following an episode of PE, the embolus may also increase blood flow resistance leading to chronic thromboembolic pulmonary hypertension (CTEPH) which can eventually lead to heart failure.(32) The rate of CTEPH amongst patients with PE is reported to be 1.25% over a period of 2.1 years, as obtained from a prospective study that followed up 831 patients with PE.(33)

Patients who experience a first episode of VTE have an increased risk of recurrence. The risk of recurrence decreases over time following the first event (being highest during the first 6 to 12 months), however it never falls to zero.(34, 35) The reported cumulative incidence of recurrent VTE in patients not receiving any treatment is reported to be 11.0% after 1 year, 19.6% after 3 years, 29.1% after 5 years, and 39.9% after 10 years.(3) Recurrent DVT is associated with a substantially higher likelihood of PTS (36), whilst PE predisposes patients to CTEPH (37), and recurrent PE is fatal in up to 9% of cases.(34)

VTE and its recurrences and complications (PTS, CTEPH) are a prevalent and costly public health problem associated with high morbidity and mortality (Section 7.5.7).(29)

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

2.2.1 *Indication under review: the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults*

It is estimated that there will be 58,392 incident patients in England and Wales who will begin treatment for VTE in 2015, rising to 60,045 in 2019 (see Section 8.1.1).

2.2.2 *Other indications not under consideration in this submission*

The number of patients covered by the other indications not under consideration in this submission were estimated in the relevant NICE technology appraisals, TA245 and TA275.(38, 39) The submission for TA245 estimated that in 2014–15 the number of eligible patients would be 98,459 while the submission for TA275 estimated that in 2014 the number of eligible patients would be 456,000.

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

PE is the primary cause of death in 10% of all hospitalised patients, with related annual mortality figures of 25,000 and 32,000 for DVT and PE respectively (1). The mortality figures for VTE exceed the pooled total deaths from acquired immunodeficiency syndrome (AIDS), breast cancer, prostate cancer and transport accidents combined (1). Mortality from VTE can be as high as 22% in the year following the first event (28). Of those who sustain an acute event, a proportion will die immediately. Overall, approximately 6% of patients die within 30 days after their first DVT event, while 12% die within 30 days of a PE (24).

VTE survivors, even when adequately treated, may go on to experience fatal or non-fatal recurrent episodes and/or may develop long-lasting and disabling sequelae (such as PTS and CTEPH). These complications, if they occur, usually develop within 2 years of the first VTE but may occur as much as 10 years later. Furthermore, patients who develop DVT or PE may also have one or more specific conditions that are commonly recognised as risk factors for VTE (e.g. malignancy, chronic heart failure). Some of these conditions themselves can affect an individual's life expectancy.

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

2.4.1 *NICE Guidelines*

The NICE Clinical Guidelines, CG144 on the management of VTE, and CG92 on the prevention of VTE in patients admitted to hospital, are relevant to the treatment and prevention of VTE recurrence, with CG144 being the most relevant to this submission. NICE CG92 discusses pharmacological prophylaxis for VTE, but only includes guidance on anticoagulants for the prevention of VTE in elective knee and hip surgery, and was published prior to NICE guidance on any NOACs for the treatment and prevention of recurrent DVT and PE. Therefore, CG92 is not discussed further.

NICE Clinical Guideline 144 (CG144, June 2012): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing (8).

This guideline gives best practice advice on the treatment and care of adults with VTE. It also gives recommendations for DVT and PE diagnostic investigations. The guideline was produced prior to the first NICE Technology Appraisal for the first factor Xa inhibitor, rivaroxaban, and therefore considers

only the older treatment options, i.e. low molecular weight heparin (LMWH), fondaparinux and vitamin K antagonists (VKAs).

- The guideline recommends that patients presenting with confirmed proximal DVT or PE be offered a choice of LMWH, unfractionated heparin (UFH) or fondaparinux for at least 5 days or until the international normalised ratio (INR) is ≥2 for at least 24 hours. A VKA should be started concomitantly and continued for 3 months.
- The guideline recommends reassessing the need for continued VKA treatment at 3 months, taking into account the risk of bleeding vs. the risk of recurrent VTE.
- Where patients have idiopathic VTE, the guideline recommends extending treatment beyond 3 months.
- Although this guideline supports extending anticoagulant therapy in patients with idiopathic VTE, the exact treatment duration is not specified.

Recommendations in NICE CG144 by patient subgroups and relevant considerations from the apixaban SPC (20)

- The recommendation for treatment in patients with PE and haemodynamic instability includes UFH and other thrombolytic therapies. In the SPC, apixaban is not recommended as an alternative to UFH in patients with pulmonary embolism who are haemodynamically unstable or who receive thrombolysis or pulmonary embolectomy.
- The recommendation for the treatment and prevention of recurrent DVT and PE in patients with active cancer is LMWH. This should be used for a duration of 6 months, at which point the risk/benefit ratio of continued anticoagulation is assessed. In the SPC, the efficacy and safety of apixaban in patients with active cancer is not established.
- The treatment recommendations for patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m2) includes UFH or LMWH. In the SPC, the limited clinical data indicate that apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance [CrCl] 15–29 mL/min) which may lead to an increased bleeding risk. Therefore, apixaban should be used with caution in patients with severe renal impairment (CrCl 15–29 mL/min) and is not recommended in CrCl < 15ml/min.
- The treatment recommendation for patients with an increased risk of bleeding is UFH. In the SPC, apixaban is to be used with caution in conditions with increased risk of haemorrhage. Apixaban should be discontinued if severe haemorrhage occurs and contra-indicated if there is active clinically significant bleeding.

NICE Technology Appraisals

The relevant NICE Single Technology Appraisals (STAs) of oral anticoagulants licensed for treatment and prevention of recurrence of DVT and/or PE include the following:

<u>Rivaroxaban</u>
NICE recommended rivaroxaban in the following two appraisals:

- NICE TA287. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. June 2013.(40)
- NICE TA261. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. July 2012.(41)

Dabigatran
Dabigatran is currently being appraised by NICE for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.(12)

2.4.2 *Other Guidelines*

The following additional guidelines are relevant to this submission as they are also used or referenced in the UK for VTE management:

- SIGN 122: Scottish Intercollegiate Guidelines Network 122, Prevention and management of venous thromboembolism (2010).(42)
- 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism (30)
- ACCP: American College of Chest Physicians Antithrombotic therapy for VTE disease (9th Edition, 2012).(26)

Of note, the ESC guidelines cover only PE, whereas the SIGN and ACCP guidelines cover both DVT and PE. As the published evidence base has rapidly developed over the time period covering the publication of these guidelines, there are some differences in the interventions that are recommended. The 2010 SIGN guidelines do not discuss NOAC use, the 2012 ACCP guidelines mention the paucity of data available for NOACs at the time of guideline preparation, whilst the 2014 ESC guidelines recommend NOACs as alternatives to treatment with LMWH/VKA. Aspirin is not recommended as a sole prophylactic agent in the SIGN guidelines and is not mentioned in the ACCP guidelines; however, the ESC guidelines recommend the use of aspirin for patients who refuse or are unable to take anticoagulants.

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

2.5.1 *Current Pathway of Care*

The current pathway of care is described in NICE CG144.(8) Between suspicion and diagnosis of VTE parenteral anticoagulants are administered. Patients with a confirmed diagnosis of proximal DVT or PE may undergo a combination of pharmacological therapy, thrombolytic therapy and/or mechanical interventions. Pharmacological treatment is currently initiated in secondary care and may involve a hospital admission; however, with the NICE approval of the oral treatment, rivaroxaban, it is being increasingly managed in a primary care setting.(43)

Currently, treatment with VKA (warfarin) is the recommended pharmacological therapy for treatment of VTE (CG144).(8) As a result of the delayed onset of action of VKA, which takes at least 5 days to achieve therapeutic levels, there is a sub-therapeutic gap bridged with a parenteral anticoagulant, such as LMWH (most commonly enoxaparin in England),(44) fondaparinux or UFH. Once therapeutic oral anticoagulation is achieved, parenteral therapy is discontinued and oral therapy with VKA continued for the remaining treatment period, the duration of which is dependent upon individual assessment of patient risk factors for VTE recurrence versus their risk of bleeding from the anticoagulant. Patients receiving a VKA initially require more frequent blood tests for INR monitoring and dose adjustments until their INR is within therapeutic range (INR of 2–3).

NICE Clinical Guideline (CG144) recommends 3 months of treatment in those with a provoked VTE and assessment of the risk/benefit of continuing treatment/prevention at 3 months. Clinical experts at a recent advisory board meeting indicated that in routine practice, patients may receive between 3–6 months of initial treatment because of the delay in stabilising patients on VKA, or there may be a delay in patients being seen by their GP or anticoagulation service.(9) Recent analysis using the

Clinical Practice Research Datalink (CPRD) database indicates that the time to discontinuation of anticoagulation after an acute VTE in UK routine practice is between 3 and 6 months (see Appendix 13g, Section 10.32). VKAs should be offered "beyond 3 months to patients with unprovoked PE or unprovoked proximal DVT, if their risk of VTE recurrence is high and there is no increased risk of bleeding or major bleeding".(8) The guideline does not specify the duration of treatment for preventing recurrent events. In clinical practice it is up to the clinician to evaluate the individual risk/benefit ratio of continuing anticoagulation or stopping treatment.

2.5.2 *Clinical Pathway for Apixaban*

Apixaban offers patients a simple oral treatment that is more convenient than LMWH/VKA. Apixaban eliminates the need for daily sub-cutaneous injections with LMWH and there is no requirement for patients to regularly attend hospitals or clinics for INR monitoring, or for the frequent dose adjustments required for VKAs.(45) Apixaban allows patients to be managed in primary care, offering potential savings on the inpatient stays associated with treatment with LMWH/VKA.

Apixaban compared with rivaroxaban minimises the duration of high dose anticoagulation (7 days versus 21 days respectively). Compared to dabigatran, apixaban eliminates the need for LMWH injections before initiation of oral treatment. Additionally, apixaban offers a lower prophylactic dose (compared to rivaroxaban and dabigatran) beyond 6 months with a bleeding profile that is comparable with placebo.

Over time, the use of apixaban could allow the NHS to make significant cost savings on the current infrastructure required for treating and monitoring patients on LMWH/VKA.

A comparison of the proposed treatment pathway using apixaban and the current clinical pathway of care is described in Table 3 below.

Table 3: Impact of apixaban on the clinical treatment pathway for VTE treatment and prevention.

Patient group	Existing pathway	Clinical pathway for apixaban
Treating DVT or PE	Treatment with LMWH is started as soon as diagnosis is confirmed, alongside initiation of oral VKA within 24 hours, with the LMWH continued for at least 5 days or until INR ≥2 for at least 24 hours, whichever is longer. INR monitoring to ensure warfarin is within therapeutic range. Rivaroxaban is an alternative treatment option (15 mg bd for 21 days, followed by 20 mg od thereafter). Dabigatran is an alternative (150 mg bd) but, like VKA, also requires initial LMWH treatment for at least 5 days.	Treatment with apixaban is started as soon as a diagnosis is made (10 mg bd for first 7 days, then 5 mg bd thereafter).
	Treatment should be for at least 3 months, according to risk/benefit.	Treatment should be for at least 3 months, according to risk/benefit.
Preventing recurrent DVT and/or PE	Treatment/prevention is continued, according to risk/benefit. Dosing schedule as above. Aspirin and no preventative therapy are also treatment options.	Prevention of VTE recurrence is with a prophylactic dose of apixaban (2.5 mg bd) following completion of at least 6 months of treatment. The duration of overall therapy can be individualised after careful assessment of the treatment benefit against the risk for bleeding.

DVT: deep vein thrombosis; PE: pulmonary embolism; LMWH: low molecular weight heparin; VKA: vitamin K antagonist; INR: International Normalised Ratio; mg: milligram; od: once daily; bd: twice daily

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

We describe the issues relating to the use of LMWHs, warfarin, rivaroxaban, dabigatran, aspirin and no preventative therapy and how these issues do not apply to a clinical pathway based around apixaban.

2.6.1 *Limitations of LMWH*

A summary of the limitations of LMWH is presented below:

- There is a need for daily sub-cutaneous injection of LMWH concomitant with warfarin until therapeutic INR levels are achieved (46) or prior to commencing treatment with dabigatran. This approach often requires patient hospitalisation with an inpatient stay and a requirement for daily injections for at least 5 days.
- If patients receive LMWH/VKA treatment as an outpatient, healthcare professionals' time is needed to educate patients to enable them to inject themselves and self-monitor INR levels.
- For patients requiring long term LMWH treatment there is a requirement for patient education to facilitate self-injection, daily injections for the duration of therapy, and frequent follow-up with healthcare professionals.
- For patients who are unable to self-inject, there is requirement for daily visits by a healthcare professional such as a nurse or trained carer to administer the injections and time to educate their carer.
- Risk of a potentially serious side effect, heparin-induced thrombocytopaenia (HIT). (46) The risk of medical patients developing HIT has been reported as up to 1%.(47) The mortality rate of HIT is approximately 20%, and approximately 10% of patients require amputations or suffer subsequent major morbidity.(48)

Treatment using apixaban eliminates the need for LMWH use and associated limitations.

2.6.2 *Limitations of VKA anticoagulants*

A summary of the limitations of VKA anticoagulants (specifically warfarin, the most commonly used VKA in UK) is presented below (49):

- A slow onset of action, requiring the addition of a parenteral drug to 'bridge' until it reaches therapeutic effect (see limitations of LMWH above).
- A narrow therapeutic window, outside of which the risk of thrombosis or bleed increases.
- The need for frequent INR monitoring and subsequent dose adjustments to ensure warfarin remains within therapeutic range. Unpredictable pharmacokinetics, heavily influenced by food, drug and alcohol interactions, genetic polymorphisms, and concurrent illnesses, affecting therapeutic dose of warfarin.
- The significant risk of bleeding associated with VKA therapy. Some patients who would otherwise benefit from long-term preventative therapy may stop treatment due to an unfavourable risk of bleeding.

Apixaban has a rapid onset of action, eliminating the need for parenteral therapy, does not require monitoring or dose reduction and has a predictable pharmacokinetic profile with minimal drug interactions.

2.6.3 *Limitations of rivaroxaban*

A summary of the limitations of rivaroxaban are presented below:

- A three week high dose period, that includes an additional health care professional visit to the treatment pathway (compared with the pathway for LMWH/warfarin).
- Following diagnosis, the dosing schedule of rivaroxaban is initially twice daily for 3 weeks and subsequently once daily, requiring re-education of patients to a new treatment regimen.
- It does not address the need for an oral anticoagulant therapy with a lower rate of bleeding compared with LMWH/warfarin – in clinical trials, rivaroxaban is associated with an equivalent risk of major or CRNM bleeding compared to LMWH/VKA for the treatment of DVT or PE (primary safety endpoint, pooled EINSTEIN PE and EINSTEIN DVT studies) whilst showing comparable efficacy. In patients for whom there was uncertainty in continuing therapy due to the bleeding risk associated with warfarin, rivaroxaban is associated with a significantly higher risk of major or CRNM bleeding compared to placebo for the long term prevention of DVT or PE (EINSTEIN-EXT study) whilst demonstrating superior efficacy to placebo.

Apixaban has a requirement for 7 days of initial higher dose therapy compared to 21 days with rivaroxaban, similar to duration to the period of parenteral treatment with LMWH in the warfarin pathway (at least 5 days). Dosing of apixaban is consistently twice daily.

2.6.4 *Limitations of dabigatran*

A summary of the limitations of dabigatran are presented below:

- Requires initial treatment with a parenteral anticoagulant (for example LMWH) for at least 5 days prior to dabigatran initiation (see limitations of LMWH, outlined above) .
- It does not address the need for an oral anticoagulant therapy with a lower rate of bleeding compared with LMWH/warfarin – in clinical trials, dabigatran is associated with an equivalent risk of major bleeding compared to LMWH/VKA for the treatment of DVT or PE (primary safety endpoint, RE-COVER studies) (50) whilst showing comparable efficacy. In patients for whom there was uncertainty in continuing therapy due to the bleeding risk associated with warfarin, dabigatran is associated with a significantly higher risk of major or CRNM bleeding

compared to placebo for the long term prevention of VTE (RE-SONATE study) whilst demonstrating superior efficacy to placebo.(51)

Apixaban does not require parenteral anticoagulation therapy at initiation, eliminating the disadvantages associated with LMWH use.

2.6.5 *Limitations of aspirin*

A summary of the limitations of aspirin are presented below:

- NICE (CG144) does not recommend aspirin as a treatment option for patients with DVT/PE
- The authors of a recent pooled analysis (52) of two randomised clinical trials assessing the efficacy of aspirin for treatment of DVT/PE concluded "*aspirin represents a reasonable treatment option only in patients who would otherwise not be receiving oral anticoagulation*."
- Indirect comparison has demonstrated inferior efficacy of aspirin compared to other anticoagulant therapies for the prevention of VTE recurrence (see Section 6).

There are no head to head data for apixaban versus aspirin; however indirect treatment comparison shows apixaban was associated with a significantly lower rate of recurrent VTE or VTE-related death and overall treatment discontinuation compared with aspirin, and there were no statistical differences for any of the other outcomes (Section 6.7.5.2).

2.6.6 *Current unmet need in long-term prevention ('no treatment')*

A summary of the limitations of no treatment is presented below:

- The reported cumulative incidence of recurrent VTE in those not receiving any treatment is reported to be 11.0% after 1 year, 19.6% after 3 years, 29.1% after 5 years, and 39.9% after 10 years.(53)
- Recurrent DVT is associated with a substantially higher likelihood of PTS (32), whilst PE predisposes patients to CTEPH (33) and recurrent PE is fatal in up to 9% of cases.(30)

The reasons for a patient not receiving pharmacological therapy may be associated with the limitations of alternative treatment already outlined. Furthermore, many patients do not receive continued treatment due to the risk of bleeding outweighing the benefit of prevention of recurrent VTE. In patients for whom there was uncertainty in continuing therapy due to the risk of bleeding associated with warfarin, apixaban demonstrated superior efficacy for the prevention of recurrent DVT/PE to placebo with a similar bleeding profile (AMPLIFY-EXT).

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

The final scope of the NICE appraisal of apixaban specifies the relevant comparator treatments:

- Initial treatment with a LMWH or fondaparinux and continued vitamin K antagonist
- Rivaroxaban

For people for whom a vitamin K antagonist is unsuitable:

- LMWH or fondaparinux alone
- Rivaroxaban

If evidence allows, the analysis should also consider people for whom the need for long term anticoagulation is uncertain and aspirin or no preventative treatment might be considered.

Population with DVT and/or PE for whom a VKA is suitable

LMWH/warfarin
When the apixaban clinical trial programme was designed, the standard of care for the treatment of VTE was LMWH/VKA; this is still reflective of current clinical practice and is recommended in CG144 as outlined in Section 2.4.1.(8) Some patients who require long-term preventative anticoagulation, due to their continued risk of a recurrent VTE still, receive a VKA, often warfarin.

Rivaroxaban
Since the publication of CG144, rivaroxaban has been recommended by NICE for the treatment and prevention of recurrent DVT and /or PE in adults (TA261 and TA287, respectively).(40, 41) It is increasingly used in routine clinical practice as an alternative to LMWH/VKA and is included in the final scope for this appraisal.

LMWH/dabigatran
Dabigatran, with initial bridging by LMWH, is now licensed for the treatment and prevention of recurrent DVT and /or PE, and is currently being appraised by NICE for this indication (anticipated publication of guidance due in late 2014).(12) LMWH/dabigatran was acknowledged at the scoping meeting for the apixaban appraisal by the NICE Chair and VTE clinical experts as being a relevant comparator, but it was not included in the final scope. Based on the discussion with stakeholders at the NICE apixaban scoping meeting, we have included LMWH/dabigatran as a comparator for this appraisal.

Aspirin
CG144 does not recommend aspirin for the treatment or prevention of recurrent VTE; however, it is used in clinical practice as an alternative to no preventative therapy. Two trials (ASPIRE and WARFASA), and an individual-patient-data pooled analysis of these trials, were published after NICE CG144 was developed,(8) which demonstrated that there is some benefit of aspirin over placebo for the prevention of recurrences or reduction in major vascular events with no significant increase in risk of bleeds.(52, 54, 55) It was confirmed by the VTE clinical experts at the scoping meeting for this appraisal that aspirin is used in clinical practice and acknowledged that this new pooled analysis evidence may be included in future VTE guidelines.(30)

No preventative therapy (placebo)
Many patients discontinue treatment after 3–6 months due to the significant risk of bleeding associated with the currently available therapies (see Appendix 13g). An individual's risk of bleeding is an important consideration in the decision to offer long-term anticoagulation. 'No treatment' (i.e. no preventative therapy) is represented by placebo in AMPLIFY-EXT, a pivotal apixaban clinical trial for the prevention of recurrent VTE, and is considered a valid relevant comparator for this appraisal.

Fondaparinux/VKA
We believe that fondaparinux is not a relevant comparator for this appraisal. In Section 4.2 of the NICE technology appraisals of rivaroxaban (TA287), the NICE Appraisal Committee stated that fondaparinux is rarely used and agreed that it was appropriate to consider only LMWH/VKA as a comparator for that appraisal.(40) Clinical experts at a recent BMS/Pfizer Advisory Board agreed that fondaparinux is not a relevant comparator for this appraisal.(9)

Population with DVT and/or PE for whom a VKA is unsuitable

People for whom a VKA may be unsuitable include, but are not limited to, cancer patients, intravenous (IV) drug users, pregnant women, patients allergic to warfarin or have exceptionally unstable warfarin control those with human immunodeficiency virus (HIV) or chronic alcoholism, as discussed at the apixaban NICE scoping meeting and as reported in local clinical protocols.(7, 56)

Apixaban has not been specifically studied in the population for whom a VKA is unsuitable. In its SPC, apixaban may be used in some sub-populations considered to be VKA-unsuitable e.g. patients allergic to warfarin as well as those with poor warfarin control. For other sub-populations who are unsuitable for VKA, for example, patients with HIV, IV drug users and patients with chronic alcoholism, the use of apixaban should be assessed with reference to the SPC, as to whether apixaban is suitable in these patients.

Furthermore, there will be some patients who are unsuitable for VKA in whom apixaban may not be used or the evidence for efficacy and safety has not been established. For example, there is no evidence for the efficacy and safety of apixaban in pregnant women and therefore, apixaban is not recommended during pregnancy.(20) In addition, the apixaban SPC states that the efficacy and safety in patients with active cancer have not been established.(20)

LMWH alone

No evidence from the systematic review was identified on the use of LMWH monotherapy in a population with DVT and/or PE for whom a VKA is unsuitable. However, an exploratory analysis was carried out to estimate the relative cost-effectiveness of apixaban against LMWH for a population with DVT and/or PE for whom a VKA is suitable (Section 7.6).

Fondaparinux alone

We believe that fondaparinux is not a relevant comparator for this appraisal, as in Section 4.2 of the NICE technology appraisals of rivaroxaban (TA287), the NICE Appraisal Committee stated that fondaparinux is rarely used.(40)

Rivaroxaban

No evidence from the systematic review was identified on the use of rivaroxaban in patients for whom a vitamin K antagonist (warfarin) is unsuitable. The evidence for the relative efficacy and safety of rivaroxaban is only available for a population with DVT and/or PE for whom a VKA is suitable.

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

There is a risk of bleeding during any anticoagulant therapy, especially if the patient already has risk factors for bleeding. There is currently no established antidote to any of the NOACs. However, evidence from a phase 3 study of andexanet alfa, a potential universal Factor Xa inhibitor antidote, showed that andexanet alfa immediately and significantly reversed the anticoagulation activity of apixaban meeting statistical significance for its primary and secondary endpoints.(57)

Apixaban has a short half-life of approximately 12 hours and treatment may be discontinued if necessary. Overdose of apixaban may result in a higher risk of bleeding. The apixaban SPC (20) makes the following recommendations in the event of haemorrhagic complications:

- Consult a coagulation expert in case of major bleeding.
- Treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered.
- If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in patients receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.
- In cases of an overdose or accidental ingestion, administration of activated charcoal may be useful.

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.

It is expected that, as the majority of VTE diagnoses occur in secondary care, apixaban will be initiated in secondary care with follow-up in primary care. However, it would be possible to manage patients in primary care if they were stable, and for a number of patients with DVTs, it may be appropriate to initiate apixaban therapy in primary care.(43) PE tends to require more secondary care involvement, due to the nature of the condition and diagnosis.

Apixaban is an oral tablet which does not require blood INR monitoring, with a one-off liver function test being the only intervention required at initiation, which is in line with tests carried out at initiation of anticoagulants in routine clinical practice. Therefore the introduction of apixaban to the clinical pathway could reduce the use (and associated costs) of the following NHS resources:

- Healthcare professionals' time and cost:
  - administering injections;
  - educating patients/carers to administer injections;
  - counselling patients on VKA (warfarin);
  - home visits for INR monitoring/administering injections;
  - managing bleeds/treatment discontinuations;
  - diagnosing and initiating treatment for recurrent events.
- Anticoagulation monitoring services (clinics in primary/secondary care) – involving frequent blood sampling, testing, interpreting results, informing patients of dose adjustments.
- Inpatient admissions and duration of stay.

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

No additional infrastructure is required with the introduction of apixaban.

3 Equality

3.1 Identification of equality issues

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

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

No equality issues are expected in this appraisal.

3.1.2 *How has the analysis addressed these issues?*

Not applicable

4 Innovation

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

4.1.1 *Innovation vs. LMWH/VKA*

- Apixaban is a single oral treatment without the need for parenteral therapy
- Apixaban does not require laboratory INR monitoring or subsequent dose adjustments
- Apixaban significantly reduces the risk of the composite of major or CRNM bleeding and major bleeding compared with LMWH/VKA.

VKA is the standard of care for treating VTE and long-term prevention of recurrent VTE or VTE-related death in patients in the UK. Apixaban does not require blood monitoring of INR levels or associated dose adjustments, nor does it have any known food or alcohol interactions or require bridging with initial parenteral LMWH. In the treatment of patients with VTE, apixaban significantly reduces the risk of the composite of major or CRNM and major bleeding compared to LMWH/VKA, whilst being non-inferior in outcomes of recurrent VTE or VTE-related death (Section 6.7).(14) Collectively these advantages have the potential to deliver significant health-related and resource use benefits both to patients and the NHS over the current standard of care (VKA).

4.1.2 *Innovation vs. other NOACs*

- Apixaban requires only one week of higher initial dose of therapy versus rivaroxaban which requires 3 weeks
- Apixaban does not require parenteral therapy compared to dabigatran
- Apixaban provides comparable effectiveness in terms of recurrent VTE or VTE-related death compared to dabigatran and rivaroxaban, but has significantly lower rates of major or CRNM bleeding, potentially affording the NHS considerable resource-use savings and health gains for patients with VTE.

As no direct head-to-head data are available comparing apixaban with other NOACs, network meta-analyses for the treatment of DVT or PE and prevention of recurrent VTE have shown that apixaban is associated with a lower risk of the composite of major or CRNM bleeding than both rivaroxaban and dabigatran (Section 6.7), whilst not being statistically different in terms of the risk of recurrent VTE or VTE-related death.

4.1.3 *Innovation vs. 'no treatment'*

- Some patients who may benefit from long-term anticoagulation to prevent VTE recurrence currently receive no treatment, due to a high risk of bleeding.
- Apixaban offers a step-change in treatment options by providing considerable benefit by reducing the risk of recurrent VTE and VTE-related death with a bleeding risk comparable to placebo.

Apixaban has been shown to have a similar bleeding risk to placebo, but significantly reduces the risk of recurrent VTE or VTE-related death.(16) Therefore for those patients for whom the risk of bleeding, with continuing anticoagulation with current treatments (VKA, rivaroxaban, dabigatran),

may outweigh the potential clinical benefit, apixaban represents a step-change in the treatment options available.

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

The following benefits and disadvantages of the treatments considered in this appraisal may not be fully captured within the QALY calculation:

- Ease of treatment administration of apixaban for patients, carers and health care professionals due to the simplicity of dosing, no requirement for regular injections, no need for INR monitoring or associated dose adjustments and minimal food and drug interactions.
- Apixaban reduces the fear and anxiety associated with the risk and consequences of being out of INR range among patients on VKAs.

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

The following data were used to make these judgments presented in Section 4, demonstrating the innovative nature of apixaban:

- The AMPLIFY trial (14) showed that in patients with VTE, apixaban significantly reduced the incidence of composite major and CRNM bleeding or major bleeding compared to LMWH/VKA, whilst being non-inferior in terms of recurrent VTE or VTE-related death (further details in Section 6.5).
- The AMPLIFY-EXT trial (16) showed that apixaban had a similar bleeding risk to placebo, but significantly reduced the risk of recurrent VTE or all cause death (further details in Section 6.5).
- A network meta-analysis of RCTs sourced from the systematic review in this submission demonstrated that apixaban has comparable efficacy against recurrent VTE or VTE-related death to dabigatran and rivaroxaban, but with significantly lower rates of major bleeding (further details in Section 6.7).

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with deep vein thrombosis and/or pulmonary embolism	No difference	Not applicable
Intervention	Apixaban	No difference	Not applicable
Comparator(s)	• Initial treatment with a low molecular weight heparin or fondaparinux and continued • Vitamin K antagonist • Rivaroxaban For people for whom a vitamin K antagonist is unsuitable: • Low weight molecular heparin or fondaparinux alone Rivaroxaban	As stated with the following exceptions: • Fondaparinux/VKA, and fondaparinux alone were not included as comparators in this submission. • LMWH monotherapy is a relevant comparator for the submission. However, no relevant evidence was identified in people for whom VKA is unsuitable (not including cancer patients). LMWH/dabigatran was however considered a relevant comparator and is therefore included in this submission.	• We believe that fondaparinux is not a relevant comparator for this appraisal, as in Section 4.2 of the NICE technology appraisals of rivaroxaban (TA287), the NICE appraisal committee stated that fondaparinux is rarely used and accepted that it was not a relevant comparator.(40) • There is no evidence identified in the systematic review on the use of LMWH monotherapy and rivaroxaban relative to apixaban for treatment and prevention of DVT and/or PE in unsuitable for warfarin population (not including cancer patients). The efficacy and safety of apixaban is not established in patients with active cancer. • LMWH/dabigatran is now licensed for the treatment and prevention of recurrent DVT and /or PE, and is currently being appraised by NICE for this indication.(12) LMWH/dabigatran was acknowledged at the scoping meeting for the apixaban appraisal by the NICE Chair and VTE clinical experts as being a relevant comparator; however it was not included in the final scope. Based on the discussion with stakeholders at the scoping meeting, we have included LMWH/dabigatran as a comparator for this submission.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Outcomes	The outcome measures to be considered include: • Mortality • Venous thromboembolism recurrence • Complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension • Adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • Health-related quality of life.	No difference with the exception of post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and health-related quality of life which were not addressed in the submission.	• There were insufficient data on post thrombotic syndrome and chronic thromboembolic pulmonary hypertension from the included trials to allow for any analysis to be carried out. However these have been included in the economic model from the published literature. • Health-related quality of life was not measured in the AMPLIFY and AMPLFY-EXT trials nor in any of the other NOAC trials identified in the systematic review.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	No difference	Not applicable

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Subgroups to be considered	If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis). The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). If evidence allows the analysis should also consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. If the evidence allows, the analysis should consider separately people with active cancer and include any effect on the person's cancer or cancer treatment.	No difference with the exception that a subgroup of patients with active cancer was not considered	There were no trials in this specific population and the safety and efficacy of apixaban is not established in patients with active cancer.(20)
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No difference	Not applicable

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

Two systematic reviews were carried out to identify clinical data from the literature in a population with DVT and/or PE in whom a VKA is suitable:

- RCT evidence on the efficacy and safety of novel oral anticoagulants (NOACs) and relevant comparators in the treatment and prevention of recurrent VTE (DVT and/or PE)

- Non-RCT evidence on the efficacy and safety of apixaban in the treatment and prevention of recurrent VTE (DVT and/or PE)

The search strategies for the RCT and non-RCT evidence are provided in the Appendices, Sections 10.2 and 10.21, respectively.

Following the final NICE scope, additional systematic reviews were conducted to identify evidence specifically relating to patients in whom a VKA is unsuitable (not including patients with active cancer as the SPC for apixaban states that the efficacy of apixaban in this population has not been established); however, no relevant evidence was identified. Full details of the eligibility criteria, search strategy and results are contained in an Appendix 9, Section 10.22.

The systematic review process adhered to the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting checklist to ensure transparency and a reproducible method of conducting and reporting data from systematic reviews.(58, 59) Flow charts of the study selection process (RCT and non-RCT evidence) are documented in Section 6.2.2.

The electronic databases were searched from inception to 14th July 2014. No limitations to publication status (published, unpublished or on-going) were applied; however, only publications in English were included. Furthermore, only studies on human subjects were eligible for inclusion.

The following electronic databases were searched:

- Medline (OVID)
- Medline In-Process Citations and Daily Update (OVID)
- Embase (OVID)
- The Cochrane Library, incorporating;
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Health Technology Assessment Database (HTA)
    - NHS Economic Evaluation Database (NHS EED)

To retrieve further studies not identified through the electronic database search, reference lists of included articles were scanned, and searches for grey literature as well as completed and on-going trials, were also carried out.

Furthermore, the following conference proceedings were searched (2011–2014):

- American Society of Hematology (ASH)
- International Society on Thrombosis and Haemostasis (ISTH)

- European Hematology Society (EHS)
- European Society of Cardiology (ESC)
- American College of Cardiology(ACC)
- American Heart Association (AHA)

6.2 Study selection

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

The screening process (titles ± abstracts and full paper stages) for both RCT and non-RCT evidence involved two reviewers working independently. Any disagreements were resolved through the involvement of a third reviewer or through team discussion until a consensus was reached. The identified studies were initially assessed based on titles ± abstracts. Thereafter, full papers of the eligible studies were obtained and assessed further for inclusion/exclusion. The reasons for exclusion are documented in the Appendix, Section 10.3.

The eligibility criteria for the systematic review of RCT evidence are outlined below (Table 4).

Table 4: Eligibility criteria used in search strategy for clinical systematic review for RCTs

Inclusion criteria	Description
Population	Adult patients (≥18) with symptomatic objectively confirmed VTE (DVT and/or PE)
Interventions	**Treatment:** • Apixaban • Dabigatran • Rivaroxaban • LMWH/VKA (any allowed) **Prevention:** • Apixaban • Dabigatran • Rivaroxaban • VKA (any allowed) • Aspirin • Placebo
Outcomes	The following efficacy and safety outcomes were considered for inclusion: • Recurrent VTE (DVT and/or PE) • VTE-related death • Major bleeding • CRNM bleeding • Intracranial bleeding • Other major bleeding • Other deaths • Overall treatment discontinuation • All-cause mortality
Study design	Prospective, randomised clinical trials, with open-label or double-blind designs Trials on both VTE treatment and/or prevention of recurrence were included

CRNM: Clinically relevant non-major; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism

The eligibility criteria for the systematic review of non-RCT evidence are outlined below (Table 5).

Table 5: Eligibility criteria used in search strategy for clinical systematic review for non-RCTs

Inclusion criteria	Description
Population	Adult patients (≥18) with symptomatic objectively confirmed VTE (DVT and/or PE)
Interventions	Apixaban
Comparators	Any allowed
Outcomes	The following efficacy and safety outcomes were considered for inclusion: • Recurrent VTE (PE/DVT) • VTE-related death • Major bleeding • CRNM bleeding • Intracranial bleeding • Other major bleeding • Other deaths • Overall treatment discontinuation • All-cause mortality
Study design	Study design was restricted to observational, non-randomised studies

CRNM: Clinically relevant non-major; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism

6.2.2 *A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (***www.consort-statement.org/?o=1065***). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.*

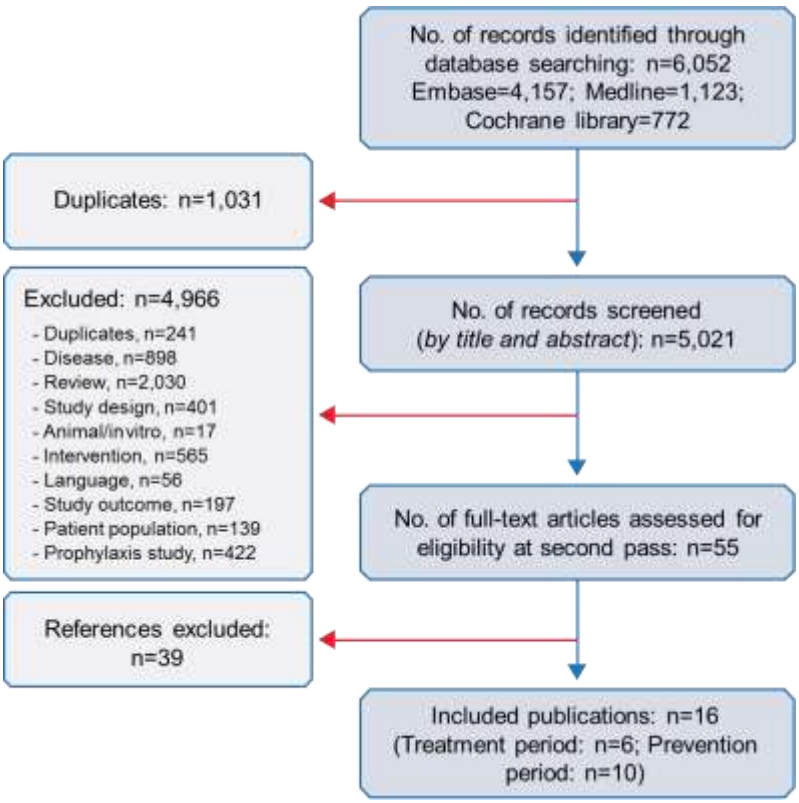
6.2.2.1 Study selection process for RCT evidence

The electronic database search (Section 10.2, accessed July 14th 2014) identified 6,052 articles, of which 5,021 were screened (after de-duplication). In total, 4,966 publications were excluded on the basis of title ± abstract. On reapplication of the review inclusion criteria to the remaining 55 full-text papers, a further 39 were excluded. Therefore, 16 publications met the inclusion criteria and were included in the systematic review, of which six reported on treatment and prevention of recurrent VTE. Of the included studies, two investigated apixaban, AMPLIFY and AMPLIFY-EXT, and the remaining RCTs reported on comparator interventions.

Furthermore, the conference searching (for both RCT and non-RCT evidence) yielded 4 additional articles; however, these data do not provide any new evidence from what is already presented in the primary publications of the relevant included articles. Therefore, data from these articles were not explicitly used to inform the NMA but rather acknowledged as supplementary/post hoc analyses in Section 6.2.4.

The schematic for the study selection process for the RCT evidence is shown in Figure 1.

Figure 1: Schematic for the systematic review of RCT evidence

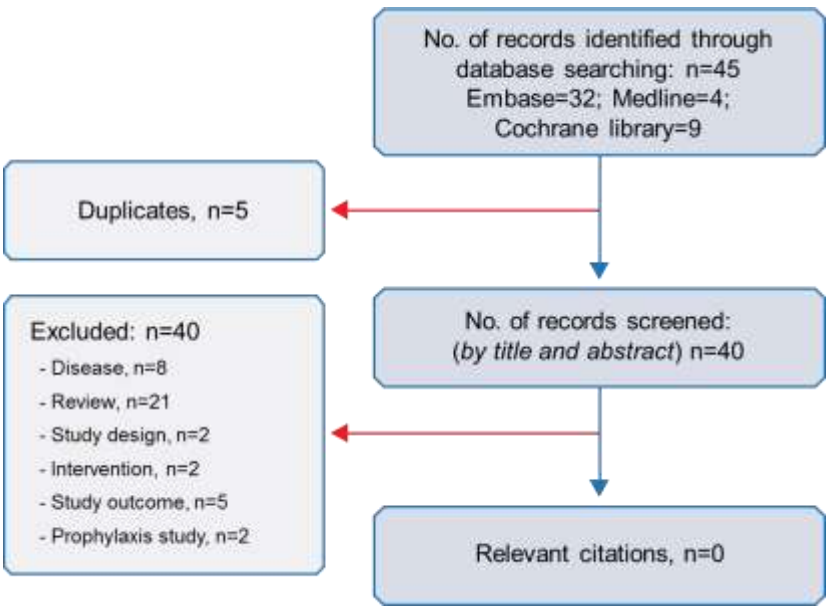


6.2.2.2 Study selection process for non-RCT evidence (apixaban)

The electronic database search (Section 10.21, accessed July 14th 2014) identified 45 articles, of which 40 were screened (after de-duplication). In total, 40 articles were excluded on the basis of title ± abstract. Therefore, no articles met the criteria for inclusion for non-RCT evidence on apixaban.

The schematic for the study selection process of non-RCT evidence (apixaban) is shown in Figure 2.

Figure 2: Schematic for systematic review of clinical evidence (non-RCT)



6.2.3 *When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.*

The data sources used for the identified RCTs are presented in Table 6, Section 6.2.4.

Complete list of relevant RCTs

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

The efficacy and safety of apixaban for the treatment and prevention of recurrent VTE has been compared to the relevant comparators of enoxaparin/warfarin (LMWH/VKA) and placebo in two phase III, randomised, double-blind, controlled trials (AMPLIFY and AMPLIFY-EXT, respectively):

- The AMPLIFY trial compared apixaban to enoxaparin/warfarin for the treatment of VTE over a 6 month period.
- The AMPLIFY-EXT trial compared apixaban 2.5 mg and 5 mg with placebo for the prevention of recurrent VTE over a 12-month period. Only the comparative effectiveness of the 2.5 mg apixaban dose with placebo will be discussed in this submission as this is the licensed dose for this indication.(20)

A summary of the two RCTs is provided in Table 6. No non-RCTs relevant to this submission were identified.

Table 6: List of relevant RCTs

Study acronym (Trial no.*)	Description	Intervention	Comparator	Population	Primary study references	Secondary study references
AMPLIFY (NCT00643201)	Phase III, double blind, randomised	Apixaban (10 mg bd for 7 days, then 5 mg bd for 6 months)	Enoxaparin (1 mg/kg bd SC) overlapping with and followed by warfarin (INR 2–3) for 6 months	Adult patients with symptomatic, proximal DVT or PE (with or without DVT).	Agnelli et al., 2013a (14)	Agnelli et al. 2013a supplementary material (60) CSR (61) Liu et al. 2014 (15) Raskob et al. 2014(62)
AMPLIFY-EXT (NCT00633893)	Phase III, double blind, randomised	Apixaban (2.5 mg bd or 5 mg bd for 12 months)	Placebo (12 months)[1]	Adult patients with symptomatic, proximal DVT or PE (with or without DVT), who had been treated for 6 to 12 months with standard anticoagulant therapy or had completed AMPLIFY study, without recurrence.	Agnelli et al., 2013b (16)	Agnelli et al. 2013b supplementary material (63) CSR (64) Liu et al. 2013 (17)

*ClinicalTrials.gov identifier
Bd: Twice daily; CSR: Clinical study report; DVT: Deep vein thrombosis; INR: International normalised ratio; PE: Pulmonary embolism; RCT: Randomised controlled trial; SC: Subcutaneous (injection); VTE: Venous thromboembolism
[1]Placebo was considered an appropriate comparator since patients in this study were those who had already received anticoagulation therapy for 6 to 12 months but for whom there was uncertainty about the benefits and risks of continued therapy.

A phase 2 dose-finding study (CV185017, BOTTICELLI) supported the dose regimen of AMPLIFY. However, the doses in the study are not in line with the current licence of apixaban for the treatment of DVT and/or PE and are therefore not discussed as part of this submission.

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

The AMPLIFY study (14) investigated apixaban vs. the active comparator enoxaparin/warfarin in patients with DVT and/or PE as specified in the decision problem. Enoxaparin is the most commonly used LMWH in England and Wales and warfarin is the most commonly used VKA; therefore this comparator can be considered representative of LMWH/VKA treatment, which is also considered the standard of care for the treatment of VTE.(9) Enoxaparin is considered representative of the LMWH class as used in the AMPLIFY trial.(65)

AMPLIFY-EXT trial included patients with DVT and/or PE, as specified in the decision problem. The AMPLIFY-EXT study compared long-term apixaban treatment following 6–12 months of prior anticoagulation to placebo. The decision problem stated that if evidence allowed, a comparison should be performed to no preventative therapy for patients for whom the need for long-term anticoagulation is uncertain. As part of the inclusion criteria for AMPLIFY-EXT patients in whom the need for continued anticoagulation was identified were included but the suitability of continuing therapy was uncertain due to the risk of bleeding with the currently available treatments. Therefore AMPLIFY-EXT also provides a direct comparison of apixaban to the relevant comparator of 'no preventative therapy' in the appropriate patient population as specified in the decision problem. Furthermore, given the proportion of patients with recurrent VTE (fatal or non-fatal) in the placebo group was 8.8%, it is evident that these entry criteria identified patients with an apprecieable risk of recurrence.(16)

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

No relevant studies were excluded from further discussion.

List of relevant non-RCTs

6.2.7 ***Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.***

No relevant non-RCTs were identified.

6.3 Summary of methodology of relevant RCTs

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

Methods

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

The methodology used in AMPLIFY and AMPLIFY-EXT are presented in Table 7.

Table 7: Summary of AMPLIFY (14) and AMPLIFY-EXT (16) trial design

	AMPLIFY (NCT00643201; (14))	**AMPLIFY-EXT** (NCT00633893; (16))
Study objective	The primary objective was to determine if apixaban was non-inferior to standard enoxaparin/warfarin therapy for the composite endpoint of adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death over 6 months of therapy.	The primary objective was to determine if at least one of the apixaban dose regimens was superior to placebo for the composite endpoint of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause death in patients who had an objectively documented index event of a proximal, symptomatic DVT or symptomatic PE, who had completed 6 to 12 months of anticoagulant therapy for the treatment of the index event, and had no objectively documented symptomatic recurrence of VTE after the index event.
Location	Multi-centre (N=358) in 28 countries, including 14 in Europe. There were no centres in the UK.	Multi-centre (N=328) in 28 countries, including 14 in Europe. There were 7 centres in the UK.
Design	Phase III, randomised, active controlled, parallel-group, double-blind, triple-dummy study	Phase III, randomised, parallel-group, double-blind, placebo-controlled study
Duration of study	6 months (plus 30-day follow-up)	12 months (plus 30-day follow-up)
Method of randomisation	Patients were randomised 1:1 to apixaban 5 mg bd or enoxaparin (1 mg/kg bd) /warfarin (INR 2.0–3.0) therapy via an interactive voice-response system (IVRS). Randomisation was stratified by type of disease treated (symptomatic, proximal DVT only or symptomatic PE with or without DVT) at baseline. If a subject had both symptomatic proximal DVT and symptomatic PE, the subject was stratified to the symptomatic PE group.	Patients were randomised 1:1:1 to apixaban 2.5 mg bd, apixaban 5 mg bd or placebo using the IVRS method. Randomisation was stratified according to the initial diagnosis (symptomatic, proximal DVT only or symptomatic PE with or without DVT) and participation or no participation in the AMPLIFY trial. If a subject had both symptomatic DVT and symptomatic PE, the subject was stratified to the symptomatic PE group.
Method of blinding (care provider, patient and outcome assessor)	Study medications were prepared using placebo that matched the active treatments. The study used blinded INR monitoring with a point-of-care device that generated an encrypted code. The IVRS produced either an actual INR value (for patients assigned to warfarin) or a sham INR value (for patients receiving apixaban), depending on the code provided by the investigators. All outcomes were adjudicated by a blinded, independent adjudication committee.	Study medications were prepared using placebo that matched the active treatments. Patients, investigators, members of any of the administrative and adjudicating committees, and the sponsors' staff involved in the conduct of the study did not have access to individual subject treatment assignments.
Intervention(s) (n =) and comparator(s) (n =)	Apixaban 10 mg bd x 7 days, then 5 mg bd (n=2691) Enoxaparin 1 mg/kg bd SC/warfarin (INR 2-3) (n=2704) Enoxaparin was administered for at least 5 days and was discontinued when a blinded INR for warfarin of 2.0 or more was achieved. The median duration of enoxaparin treatment was 6.5 days (interquartile range, 5.0 to 8.0).	Apixaban 2.5 mg (n=840) bd Apixaban 5 mg (n=813) bd Placebo (n=829)

Bd: Twice daily; CRNM: Clinically relevant non-major; CV: Cardiovascular; DVT: Deep vein thrombosis; INR: International normalised ratio; IVRS: Interactive voice-response system; SC, subcutaneous

Participants

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

A full list of the eligibility criteria (inclusion and exclusion) is provided in Table 8.

Table 8: Eligibility criteria in the RCTs

Study Acronym (Trial no.)	Inclusion criteria	Exclusion criteria

AMPLIFY
(NCT00643201) (14, 60)
	Target Population
	• Patients who had an unprovoked index event or a provoked index event with a risk for recurrence
	• Patients who had acute, symptomatic, proximal DVT with evidence of proximal thrombosis that involved at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound, or ascending contrast venography
	Or
	• Patients who had acute symptomatic PE with evidence of thrombosis demonstrated by imaging showing:
	  ○ An intraluminal filling defect in segmental or more proximal branches on spiral computed tomography scan, or
	  ○ An intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram, or
	  ○ A perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan
		Sex and Reproductive Status
		• Pregnancy or breastfeeding
		Target Disease Exceptions:
		• Less than 6 months of anticoagulation planned for the most recent DVT or PE (index event)
		• Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the concurrent episode of VTE
		• Active bleeding, or high risk for bleeding, contraindicating treatment with LMWH and a VKA
		• Patients with cancer who were treated for ≥6 months with LMWH therapy
		• Patients with contraindications according to the local prescribing information of enoxaparin or warfarin
		Medical History and Concurrent Diseases:
		• Patients with indications for long-term treatment with a VKA, such as:
		  ○ Mechanical valve
		  ○ Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism
		• Active and clinically significant liver disease (e.g. hepatorenal syndrome)
		• Life expectancy <6 months
		• Bacterial endocarditis
		• Uncontrolled hypertension: systolic blood pressure (BP) >180 mm Hg or diastolic BP >100 mm Hg
		Physical and Laboratory Test Findings:
		• Platelet count <100,000/mm^3
		• Haemoglobin <9 g/dL
		• Serum creatinine >2.5 mg/dL (221 µmol/L)
		• Calculated creatinine clearance <25 ml/min
		• Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >2 times upper limit of normal (ULN)

Study Acronym (Trial no.)	Inclusion criteria	Exclusion criteria
	Age and Sex • Men and women, aged 18 years or over • Women of childbearing potential must have been using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy was minimised	• Total bilirubin >1.5 times ULN (unless an alternative causative factor was identified [e.g. Gilbert's syndrome]) Allergies and Adverse Drug Reactions: • Heparin induced thrombocytopaenia • Allergic reaction to UFH, LMWH, fondaparinux or any VKA. Prohibited Treatments and/or Therapies: • DVT or PE treatment with more than 2 doses of fondaparinux or a LMWH that was labelled for once daily (od) dosing, or more than 3 doses of a LMWH that was labelled for twice daily (bd) dosing, or continuous infusion of UFH for more than 36 hours, before the first administration of study drug; and/or • DVT or PE treatment with more than 2 doses of oral VKA therapy before the first administration of study drug • Treatment with apixaban in a previous clinical trial • Patients who required acetylsalicylic acid (ASA) >165 mg/day at randomisation • Patients who required dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomisation. Patients who transitioned from dual antiplatelet therapy to monotherapy prior to randomisation were eligible for the trial

AMPLIFY-EXT (NCT00633893) (16, 63)	Target population:
	• Patients who had an objectively documented index event of symptomatic, proximal thrombosis, demonstrated by imaging with CUS, including grey-scale colour-coded Doppler, or ascending contrast venography
	• Symptomatic PE with evidence of thrombosis demonstrated by imaging as follows:
		Sex and Reproductive Status:
		• Pregnancy or breastfeeding
		Medical History and Concurrent Diseases:
		• Patients with a provoked index event without the existence of a persistent risk factor
		• More than 12 months of anticoagulation planned for the most recent DVT or PE (index event)
		• Patients with indications for long-term treatment with a VKA, such as:
		  ○ Mechanical valve
		  ○ Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism
		  ○ Multiple episodes of unprovoked DVT or PE

Study Acronym (Trial no.)	Inclusion criteria	Exclusion criteria
	○ An intraluminal filling defect in segmental or more proximal branches on a spiral CT scan; or ○ An intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or ○ A perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan • Had been treated for 6 to 12 months with standard anticoagulant therapy or had completed treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial • Had not had a symptomatic recurrence during prior anticoagulant therapy • There was clinical equipoise about the continuation or cessation of anticoagulant therapy Age and sex: • Men and women, aged 18 years or over • Women of childbearing potential must have been using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy was minimised	○ Documented anti-phospholipid antibodies, AT III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation. ○ Patients with cancer who were treated indefinitely with anticoagulation therapy • Active and clinically significant liver disease (e.g. hepatorenal syndrome) • Life expectancy <12 months • Bacterial endocarditis • Uncontrolled hypertension: systolic blood pressure (BP) >180 mm Hg or diastolic BP >100 mm Hg Physical and Laboratory Test Findings: • Platelet count <100,000/mm^3 • Haemoglobin <9 g/dL • Serum creatinine >2.5 mg/dL (221 µmol/L) • Calculated creatinine clearance <25 ml/min • Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >2 times upper limit of normal (ULN) • Total bilirubin >1.5 times ULN (unless an alternative causative factor was identified [e.g. Gilbert's syndrome]) Prohibited Treatments and/or Therapies: • Patients requiring acetylsalicylic acid (ASA) >165 mg/day at randomisation • Patients who required dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomisation. Patients who transitioned from dual antiplatelet therapy to monotherapy prior to randomisation were eligible for the trial • Patients who had used any oral direct factor Xa inhibitor, any oral direct thrombin inhibitor, or any investigational antithrombotic agent during the period between the onset of the index event to randomisation. Patients who participated in the AMPLIFY study could have participated in this study and were exempt from this exclusion

ALT: Alanine aminotransferase; ASA: Acetylsalicylic acid; AST: Aspartate aminotransferase; AT: antithrombin; bd: Twice daily; BP: Blood pressure; CUS: Compression ultrasonography; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; No.: Number; PE: Pulmonary Embolism; UFH: Unfractionated heparin; ULN: Upper limit of normal; VKA; Vitamin K Antagonist; VTE: Venous thromboembolism

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

Baseline demographic and disease characteristics of patients included in AMPLIFY are presented in Table 9. Overall, patient characteristics were similar between the apixaban and enoxaparin/warfarin groups, with no clinically relevant differences in either demographic or disease characteristics.

Table 9: Baseline demographic and disease characteristics of participants in the AMPLIFY RCT (14, 61)

AMPLIFY (NCT00643201; (14, 61))	**Apixaban (N=2691)**	**Enoxaparin/warfarin (N=2704)**
Age, years		
Mean (SD)	57.2 (16.0)	56.7 (16.0)
Gender, n (%)		
Male	1569 (58.3)	1598 (59.1)
Race, n (%)		
White	2218 (82.4)	2243 (83.0)
Black or African American	106 (3.9)	98 (3.6)
American Indian or Alaska Native	6 (0.2)	2 (<0.1)
Asian	227 (8.4)	226 (8.4)
Other race	89 (3.3)	85 (3.1)
Not reported	45 (1.7)	50 (1.8)
Weight, kg		
Mean (SD)	84.6 (19.8)	84.6 (19.8)
Weight distribution, n (%)		
≤60 kg	231 (8.6)	245 (9.1)
>60 to <100 kg	1932 (71.8)	1936 (71.6)
≥100 kg	522 (19.4)	518 (19.2)
Data missing	6 (0.2)	5 (0.2)
Creatinine clearance, n (%)		
≤30 ml/min	14 (0.5)	15 (0.6)
>30 to ≤50 ml/min	161 (6.0)	148 (5.5)
>50 to ≤80 ml/min	549 (20.4)	544 (20.1)
>80 ml/min	1721 (64.0)	1757 (65.0)
Data missing	246 (9.1)	240 (8.9)
Qualifying diagnosis, n (%)*		
DVT	1749 (65.0)	1783 (65.9)
PE	678 (25.2)	681 (25.2)
PE with DVT	252 (9.4)	225 (8.3)
Could not be evaluated	12 (0.4)	15 (0.6)
VTE clinical presentation, n (%)		
Unprovoked	2416 (89.8)	2429 (89.8)
Provoked with risk factor(s)	272 (10.1)	272 (10.1)
Not reported	3 (0.1)	3 (0.1)
Location of qualifying DVT, n (%)		
Popliteal vein	426/1749 (24.4)	441/1783 (24.7)
Femoral vein	570/1749 (32.6)	585/1783 (32.8)
Common femoral or iliac vein	753/1749 (43.1)	754/1783 (42.3)
Distal vein	0/1749	3/1783 (0.2)
Anatomic extent of qualifying PE, n (%)		
Limited	79/930 (8.5)	89/906 (9.8)
Intermediate	392/930 (42.2)	395/906 (43.6)
Extensive	357/930 (38.4)	326/906 (36.0)
Not assessable	102/930 (11.0)	96/906 (10.6)
Risk factors for recurrent VTE, n (%)		
Previous PE or proximal DVT	463 (17.2)	409 (15.1)
Known thrombophilia	74 (2.8)	59 (2.2)
Active cancer†	66 (2.5)	77 (2.9)

*See Table 8 for information on diagnostic methods
† Data are from the AMPLIFY clinical study report (61)
DVT: Deep vein thrombosis; PE: Pulmonary embolism; SD: Standard deviation; VTE: Venous thromboembolism

Table 10 summarises the baseline demographic and clinical characteristics of patients included in AMPLIFY-EXT. Overall, patient characteristics were similar between both of the apixaban groups and the placebo group.

Table 10: Baseline demographic and disease characteristics in the AMPLIFY-EXT RCT (16)

AMPLIFY-EXT (NCT00633893; (16))	**Apixaban 2.5 mg bd (N=840)**	**Apixaban 5 mg bd[ŧ] (N=813)**	**Placebo (N=829)**
Age, years			
Mean (SD)	56.6 (15.3)	56.4 (15.6)	57.1 (15.2)
Gender, n (%)			
Male	487 (58.0)	469 (57.7)	468 (56.5)
Weight, kg			
Mean (SD)	85.7 (19.8)	85.7 (19.1)	84.7 (18.6)
Weight distribution, n (%)			
≤60 kg	58 (6.9)	59 (7.3)	48 (5.8)
>60 kg	780 (92.9)	751 (92.4)	778 (93.8)
Data missing	2 (0.2)	3 (0.4)	3 (0.4)
Creatinine clearance, n (%)			
≤30 ml/min	1 (0.1)	3 (0.4)	2 (0.2)
>30 to ≤50 ml/min	47 (5.6)	41 (5.0)	44 (5.3)
>50 to ≤80 ml/min	174 (20.7)	168 (20.7)	194 (23.4)
>80 ml/min	595 (70.8)	580 (71.3)	564 (68.0)
Data missing	23 (2.7)	21 (2.6)	25 (3.0)
Qualifying diagnosis, n (%)*			
DVT	544 (64.8)	527 (64.8)	551 (66.5)
PE	296 (35.2)	286 (35.2)	278 (33.5)
VTE clinical presentation, n (%)			
Unprovoked	783 (93.2)	737 (90.7)	755 (91.1)
Associated with transient or reversible risk factor	56 (6.7)	76 (9.3)	72 (8.7)
Not reported	1 (0.1)	0	2 (0.2)
Risk factors for recurrent VTE, n (%)			
Active cancer	15 (1.8)	9 (1.1)	18 (2.2)
Persistent or permanent immobilisation	19 (2.3)	29 (3.6)	22 (2.7)
Previous DVT or PE	99 (11.8)	118 (14.5)	99 (11.9)
Known prothrombotic genotype	32 (3.8)	26 (3.2)	36 (4.3)
Use of antiplatelet agents	120 (14.3)	96 (11.8)	107 (13.0)

*See Table 8 for information on diagnostic methods
Bd: Twice daily; DVT: Deep vein thrombosis; PE: Pulmonary embolism; SD: Standard deviation; VTE: Venous thromboembolism
[ŧ]Unlicensed dose; only baseline characteristics and methodology are presented for this dose for completeness

Outcomes

6.3.5 *Provide details of the outcomes investigated and the measures used to assess those outcomes.*

Details of the primary and secondary outcomes investigated in AMPLIFY and AMPLIFY-EXT are presented in Table 11.

Table 11: Primary and secondary outcomes in AMPLIFY (14, 61) and AMPLIFY-EXT (16)

Trial (Trial no.)	Primary outcome(s)	Secondary outcome(s)	Outcome measures	Reliability/validity/ current use in clinical practice

AMPLIFY (NCT00643201; (14, 61))	**Efficacy**
	Incidence of the adjudicated composite of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or VTE-related death occurring at any time from randomisation until the end of the originally intended treatment period (6 months).
	
	Safety
	Incidence during treatment period of adjudicated major bleeding.
		Efficacy
		Incidence of the following adjudicated events:
		• symptomatic non-fatal PE
		• symptomatic non-fatal DVT
		• composite of recurrent symptomatic VTE or all-cause death
		• composite of recurrent symptomatic VTE or CV-related death
		• composite of recurrent symptomatic VTE, VTE-related death or major bleeding
		• composite of recurrent symptomatic VTE, myocardial infarction, stroke, CV-related death, major bleeding, CRNM bleeding
		• VTE-related death
		• CV-related death
		• All-cause death
		
		Time to first occurrence of:
		• Adjudicated composite of recurrent symptomatic VTE and all-cause death
		• Adjudicated composite of recurrent symptomatic VTE and VTE-related death
		
		Safety
		Incidence of the following adjudicated events:
		• composite of major or CRNM bleeding
		• minor bleeding
		• composite of major, CRNM bleeding, or minor bleeding (total adjudicated bleeding)
		• CRNM bleeding
			PE was judged to occur where symptoms of PE were present along with one of the following findings:
			• Intraluminal filling defect
			• Sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram
			• Perfusion defect of at least 75%
			
			DVT was judged to occur where symptoms of DVT were present along with one of the following findings:
			• Abnormal CUS
			• Intraluminal filling defect
			
			Bleeding was defined according to ISTH guidelines (66):
			• Major bleeding:
			  ○ Clinically overt bleeding accompanied by a decrease in haemoglobin of ≥ 2 g/dL and/or transfusion of ≥ 2 units of packed red blood cells
			  ○ Bleeding that occurred in a critical site
			  ○ Bleeding that was fatal
			
			• CRNM bleeding – clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to either:
			  ○ Hospital admission
			  ○ Physician guided medical or surgical treatment
			  ○ A change in antithrombotic therapy
				An independent central adjudication committee including independent physicians with experience in vascular medicine and thrombosis reviewed and adjudicated outcomes in a blinded manner.
				
				Outcomes are clinically important and objective outcomes that are considered in clinical practice.

Trial (Trial no.)	Primary outcome(s)	Secondary outcome(s)	Outcome measures	Reliability/validity/ current use in clinical practice

		Time to first occurrence during treatment period of:
		• Adjudicated major bleeding
		• Adjudicated composite of major or CRNM bleeding
		Additional analyses
		• Incidence of the adjudicated composite of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or VTE-related death occurring at any time from randomisation until the end of:
		  ○ 7 days
		  ○ 21 days
		  ○ 3 months
		• Rate of all-cause hospitalisations
		• Time from randomisation to first hospitalisation
			• All acute clinically overt bleeding events not meeting criteria for major bleeding or clinically relevant non-major bleeding were classified as minor bleeding
			
			Hospitalisations were captured by dedicated case report forms. Patients were censored at death, loss to follow-up (<2.5% in all treatment arms), or end of study, whichever came first.	

AMPLIFY-EXT (NCT00633893; (16))	**Efficacy** Incidence of an adjudicated composite of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or all-cause death occurring at any time from randomisation until the end of the originally intended treatment period (6 months). **Safety** Incidence during treatment period of adjudicated major bleeding.	**Efficacy** Incidence of the following adjudicated events: • Symptomatic non-fatal PE • Symptomatic non-fatal DVT • Composite of recurrent symptomatic recurrent VTE or VTE-related death • Composite of recurrent symptomatic VTE or CV-related death • VTE-related death • CV-related death • All-cause death Time to first occurrence of: • Adjudicated composite of symptomatic, recurrent VTE or all-cause death • Adjudicated composite of symptomatic, recurrent VTE or VTE-related death	As for AMPLIFY	As for AMPLIFY

Trial (Trial no.)	Primary outcome(s)	Secondary outcome(s)	Outcome measures	Reliability/validity/ current use in clinical practice
		Safety Incidence during treatment period of: • Adjudicated composite of major and CRNM bleeding • Adjudicated minor bleeding • Adjudicated major, CRNM, or minor bleeding (total adjudicated bleeding) Time to first occurrence during treatment period of: • Adjudicated major bleed • Adjudicated composite of major and CRNM bleeding **Additional analyses** • Rate of all-cause hospitalisations • Time from randomisation to first hospitalisation		

AE: Adverse event; CRNM: Clinically relevant non-major; CUS: Compression ultrasonography; CV: Cardiovascular; DVT: Deep vein thrombosis; ISTH: International Society on Thrombosis and Haemostasis; No.: Number; PE: Pulmonary embolism; VTE: Venous thromboembolism

As the administration methods and titration requirements differed between study drugs in AMPLIFY, it was considered particularly important to monitor the compliance of patients in this study. A summary of the methodology and results relating to treatment compliance for both AMPLIFY and AMPLIFY-EXT are summarised in Table 12. Treatment compliance with apixaban was comparable to the comparator arms in both studies.

Table 12: Treatment compliance in AMPLIFY and AMPLIFY-EXT

Trial	Method	Results
AMPLIFY (14, 61) NCT00643201	Apixaban compliance was based on pill counts, and enoxaparin/placebo compliance was based on unused syringe counts. As warfarin dosage was individually titrated, INR and TTR were indicators of compliance as they were direct measurements of anticoagulation.	[redacted] After exclusion of INR values during the first 15 days following randomisation and during study drug interruptions, patients in the enoxaparin/warfarin group had an INR in the therapeutic range (2.0 to 3.0) 61% of the time, above 3.0 for 16% of the time, and below 2.0 for 23% of the time.(14)
AMPLIFY-EXT (16, 64) NCT00633893	Compliance was based on pill counts for all treatment arms.	[redacted]

INR: International normalised ratio; TTR: Time in therapeutic range

Statistical analysis and definition of study groups

6.3.6 *State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses.*

The primary hypothesis of AMPLIFY tested whether apixaban was non-inferior to enoxaparin/warfarin for the primary efficacy endpoint of recurrent VTE or VTE-related death over 6 months of therapy. For AMPLIFY-EXT, the hypothesis tested whether apixaban was superior to placebo for the primary efficacy endpoint of recurrent VTE or all-cause death. Primary endpoints were selected for AMPLIFY and AMPLIFY-EXT in accordance with the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease.(67) Of these, recurrent VTE or VTE-related death is the most important analysis for non-inferiority trials and recurrent VTE or all-cause death is the most important analysis for superiority trials.

For AMPLIFY, a hierarchical statistical testing order was followed for the efficacy and safety analyses:

- Non-inferiority of apixaban relative to enoxaparin/warfarin was first tested for recurrent VTE or VTE-related death.
- If non-inferiority was demonstrated for both relative risk (RR) and risk difference (RD), then superiority of apixaban relative to enoxaparin/warfarin for major bleeding was tested.
- If superiority of apixaban relative to enoxaparin/warfarin for major bleeding was demonstrated, then superiority of apixaban relative to control treatment for recurrent VTE or VTE-related death was tested.

- If superiority of apixaban relative to enoxaparin/warfarin for recurrent VTE or VTE-related death was demonstrated, then superiority of apixaban relative to control treatment for major bleeding/CRNM bleeding was tested.

In AMPLIFY-EXT, hypotheses were tested using the Cochran-Mantel-Haenszel (CMH) test and superiority over placebo was to be claimed if the Hochberg adjusted p-value was ≤0.05 and the relative risk was <1. For the primary efficacy analysis, in accordance with agreements with regulatory authorities, patients who were lost to follow-up were classified as having had a primary outcome event. For the analyses of the secondary outcomes and for the safety analyses, patients who were lost to follow-up were classified as not having had an outcome event.

A full summary of the statistical methods used in AMPLIFY and AMPLIFY-EXT are presented in Table 13.

Table 13. Summary of statistical analyses in AMPLIFY (14, 60) and AMPLIFY-EXT (16, 63)

Study acronym (Trial No.)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
AMPLIFY NCT00643201 (14, 60)	The primary objective was to determine if apixaban was non-inferior to enoxaparin/warfarin (INR 2.0–3.0) for the composite endpoint of recurrent VTE or VTE-related death. Secondary objectives were to determine if apixaban was superior to enoxaparin/warfarin for: • Major bleeding • Recurrent VTE or VTE-related death • Major bleeding or CRNM bleeding	A hierarchical statistical testing order was followed for the efficacy and safety analyses. • Non-inferiority of apixaban relative to enoxaparin/warfarin was tested at a 1-sided α=0.025 for recurrent VTE or VTE-related death. • If non-inferiority was demonstrated for both RR and RD, then superiority of apixaban relative to enoxaparin/warfarin for major bleeding was tested at a 2-sided α=0.05. • If superiority of apixaban relative to enoxaparin/warfarin for major bleeding was demonstrated, then superiority of apixaban relative to control treatment for recurrent VTE or VTE-related death was tested at a 2-sided α=0.05. • If superiority of apixaban relative to enoxaparin/warfarin for recurrent VTE or VTE-related death was demonstrated, then superiority of apixaban relative to control treatment for major bleeding/CRNM bleeding was tested at a 2-sided α=0.05. Generally, continuous variables were summarised using mean and standard deviation and categorical variables were summarised using relative frequencies. Non-inferiority based on CIs was assessed for the primary endpoint only. The estimated RR and the 95% CI about the RR were provided using a stratified analysis.	Using the method of Farrington and Manning (68) with the assumption of a 3% incidence of the primary efficacy outcome over 6 months of therapy, a sample size of 4094 patients would have 90% power for a 1-sided α =0.025 non-inferiority test assuming true RR of 1 (non-inferiority margin of 1.8). The sample size was adjusted to 4816 (2408 per group) to account for approximately 15% of patients discontinuing treatment early and continuing to complete all scheduled treatment visits up to 6 months after randomisation. A provision by the steering committee increased the sample size up to 5400 after a protocol-defined blinded review of the overall incidence of the primary efficacy outcome performed after 80% of patients had been enrolled.	All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented. All safety analyses included data obtained from patients during study treatment, defined as the time from the administration of the first dose until 48 hours after the last dose was administered. No imputation for missing data was planned for the primary efficacy analysis as the primary efficacy data set included only randomised patients with a non-missing primary endpoint. No imputation was carried out for missing data in secondary analysis.

Study acronym (Trial No.)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		Statistical testing for non-inferiority was performed with the method of Farrington and Manning. Hypotheses tests of superiority for efficacy endpoints were based on the CMH test stratified by the qualifying diagnosis. Summaries of time-to-event data were displayed in graphical format using Kaplan-Meier estimates		
AMPLIFY-EXT NCT00633893 (16, 63)	The primary objective was to determine if apixaban was superior to placebo with respect to the primary efficacy outcome of the composite of recurrent VTE or all-cause death.	In general, continuous variables were summarised using mean and standard deviation and categorical variables were summarised using proportion of patients with an event. Descriptive statistics for binary endpoints included the proportion of patients with an event in each group with a 95% CI. The estimated relative risk and 95% CI about the relative risk were provided using a stratified analysis. Hypotheses were tested using the CMH test stratified by the qualifying diagnosis. The CMH statistic was used to test the hypothesis using the primary efficacy analysis set. Superiority over placebo was to be claimed for a dose if the Hochberg adjusted p-value was ≤0.05 and the relative risk was <1. Summaries of time-to-event data were displayed in graphical format using Kaplan-Meier estimates	Using the Hochberg multiple-testing method (69) and with the assumption of a 6.8% incidence of the primary efficacy outcome in the placebo group at 12 months and a decrease in the primary outcome of 41% with apixaban as compared with placebo, 810 patients were required in each group for the study to have 90% power to show the superiority of apixaban over placebo, at a two-sided α =0.05.	All efficacy analyses included data from the intention-to-treat population during the 12-month active study period. All safety analyses included data from patients during the time they were receiving treatment, which was defined as the time between administration of the first dose of a study drug and 48 hours after administration of the last dose. For the primary efficacy analysis patients who were lost to follow-up were classified as having had a primary outcome event. For the analyses of the secondary outcomes and for the safety analyses, patients who were lost to follow-up were classified as not having had an outcome event.

CI: Confidence interval; CMH: Cochran-Mantel-Haenszel; DVT: Deep vein thrombosis; INR: International normalised ratio; LMWH: Low molecular weight heparin; No.: Number; PE: Pulmonary embolism; RD: Risk difference (Risk difference is calculated as risk in the experimental group minus risk in the control group); RR: Relative risk; VTE: Venous thromboembolism

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

In both trials, the pre-planned subgroup analyses for the primary efficacy and safety endpoints for the subgroups of clinical interest are described in Table 14. Analyses were performed using the primary efficacy or safety data sets for each trial as described in Section 6.3.6. For AMPLIFY-EXT, the subgroup analyses specified for the primary safety endpoint (major bleeding) were analysed as a combination of major and CRNM bleeding due to the small number of adjudicated major bleeding events across the treatment arms. The combination of major and CRNM bleeding allowed for a comparison across sub-groups.

No hypothesis testing was conducted on the subgroups. P-values for the test of interaction were calculated for each subgroup, although, due to the small sample sizes, the study was not powered to detect significance within these subgroups.

Table 14: Pre-specified subgroups analysed in AMPLIFY (14) and AMPLIFY-EXT (16)

	AMPLIFY Subgroups	AMPLIFY-EXT Subgroups
Index event	PE (with or without DVT); DVT only	PE (with or without DVT); DVT only
Geographic region	North America; Latin America; Europe; Asia/Pacific	North America; Latin America; Europe; Asia/Pacific
Age Category I	<65 years; ≥65 to <75 years; ≥75 years	<65 years; ≥65 to <75 years; ≥75 years
Age Category II	<75 years; ≥75 years	-
Gender	Male; Female	Male; Female
Race	White; Black or African American; Asian; Other	White; Black or African American; Asian; Other
Ethnicity	Hispanic/Latino; Not Hispanic/Latino	Hispanic/Latino; Not Hispanic/Latino
Weight	≤60 kg; >60 kg to <100 kg; ≥100 kg	≤60 kg; >60 kg
BMI Category I	≤28 kg/m^2; >28 kg/m^2 to ≤33 kg/m^2; >33 kg/m^2	≤28 kg/m^2; >28 kg/m^2 to ≤33 kg/m^2; >33 kg/m^2
BMI Category II	≤25 kg/m^2; >25 to ≤30 kg/m^2; >30 to ≤35 kg/m^2; >35 kg/m^2	-
Level of renal function Category I	Normal; Mild; Moderate/Severe	Normal; Mild; Moderate/Severe
Level of renal function Category II	Normal; Mild; Moderate; Severe	-
Fragile/not fragile patients	Fragile (those meeting at least two of age ≥80, creatinine clearance ≥1.5 mg/dL, body weight ≤60 kg); Patients not meeting these criteria	-
Age, weight and serum creatinine criteria	Patients meeting at least one of age ≥75, creatinine clearance ≤50 ml/min, body weight ≤50 kg; Patients not meeting these criteria	-
Cancer	Active cancer at baseline; No active cancer at baseline	-
Centre TTR quartile	Q1; Q2; Q3; Q4	-

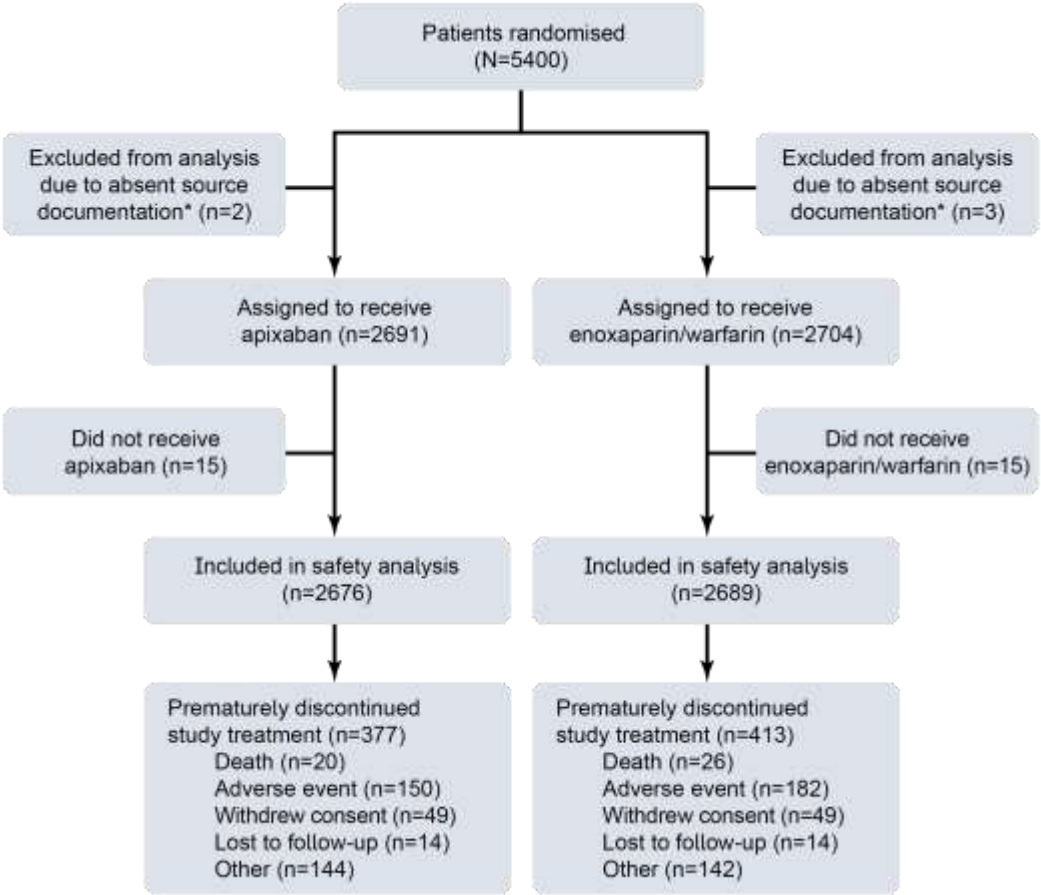
BMI: Body mass index; DVT: Deep vein thrombosis; PE: Pulmonary embolism; Q: Quartile; TTR: Time in therapeutic range

Participant flow

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

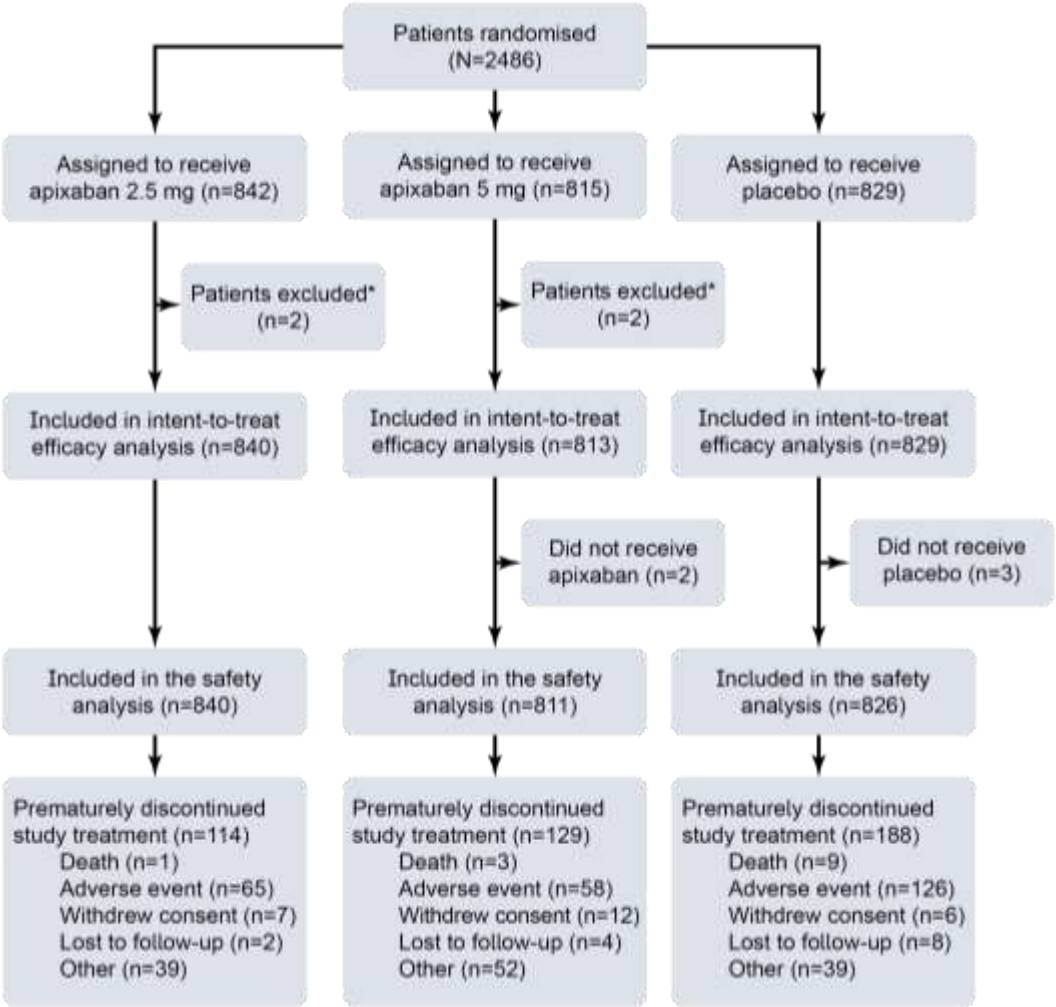
The flow of participants enrolled in the AMPLIFY and AMPLIFY-EXT trials are presented in Figure 3 and Figure 4, respectively.

Figure 3: AMPLIFY – Patient flow diagram (14)



*Due to missing source documentation, 2 patients in the apixaban group and 3 patients in the enoxaparin/warfarin group were excluded from all analyses.

Figure 4: AMPLIFY-EXT – Patient flow diagram (16)



*Due to missing source documentation, 2 patients in the 2.5 mg apixaban group and 2 patients in the 5 mg group were excluded from all analyses.

6.3.8.1 Discontinuation

Patients treated with apixaban had a low discontinuation rate in both AMPLIFY and AMPLIFY-EXT.

In AMPLIFY, the number of overall discontinuations between the apixaban and enoxaparin/warfarin groups were comparable (14.0% vs. 15.3%, respectively; Figure 3). (14, 60) The most frequent reason for discontinuation was adverse events (AE); the proportion of patients in the intention-to-treat (ITT) population who discontinued due to AEs was lower in the apixaban treatment group (5.6%) compared with the enoxaparin/warfarin treatment group (6.7%).(14) The smaller proportion of patients who discontinued due to AEs in the apixaban group was largely due to fewer bleeding related AEs in the apixaban treatment group (0.7%) compared to the enoxaparin/warfarin treatment group (1.7%).(61)

In AMPLIFY-EXT, apixaban had a lower rate of discontinuation during the intended treatment period than placebo (13.6% vs. 22.7%, respectively; Figure 4).(16, 64) The most frequent reason for discontinuation was AEs.(16) The proportion of patients in the ITT population who discontinued due to AEs was 7.7% in the apixaban 2.5 mg and 15.2% in the placebo group.(16, 64) The difference in discontinuation was primarily driven by higher numbers of recurrent VTE events in the placebo

groups compared to apixaban (0.6% and 6.9% due to DVT; and 0.5% and 2.2% patients due to PE in the apixaban 2.5 mg and placebo groups, respectively).(64)

6.3.8.2 Analysed Populations

In AMPLIFY, the efficacy evaluable population on which efficacy endpoints were analysed was defined as the ITT population (n=5395) for whom the outcome status at 6 months was documented (Figure 3).(14) The safety population (treated patients, n=5365) consisted of those patients who received at least one dose of the study medication.(14) A summary of the analysed populations are presented in Table 15**,** below.

Table 15: Analysis population summary – AMPLIFY

	Apixaban (N=2691)	**Enoxaparin/warfarin (N=2704)**	**Total (N=5395)**
ITT patients (n)*	2691	2704	5395
Treated patients (n)**	2676	2689	5365
Efficacy evaluable patients for primary endpoint (n)***	2609	2635	5244

ITT, intention-to-treat
*ITT population included all randomised patients and grouped patients by treatment allocation at randomisation
**Treated population included patients who received at least one dose of study drug
***Efficacy evaluable population included data for patients in the ITT population for whom the outcome status at 6 months was documented. Patients with missing endpoint information were excluded from the analysis.

In AMPLIFY-EXT, all efficacy endpoints were analysed on the ITT population (n=2482; Table 16).(16) The safety population (treated patients, n=2477) consisted of those patients who received at least one dose of study medication.(16) As 2.5 mg apixaban is the licensed dose for long-term prevention of recurrent VTE therapy, the 5 mg arm is presented in Figure 4 for completeness, and is only discussed further in the submission in relation to safety outcomes in the Appendix, Section 10.30.

Table 16: Analysis population summary – AMPLIFY-EXT

	Apixaban 2.5 mg (N=840)	**Apixaban 5 mg (N=813)**	**Placebo (N=829)**	**Total (N=2482)**
ITT patients (n)*	840	813	829	2482
Treated patients (n)**	840	811	826	2477

ITT, intention-to-treat
*ITT population included all randomised patients and grouped patients by treatment allocation at randomisation
**Treated population included patients who received at least one dose of study drug

6.4 Critical appraisal of relevant RCTs

6.4.1 *Please provide as an Appendix a complete quality assessment for each RCT.*

A complete quality assessment for each RCT is provided in Appendix 3, Section 10.4.

6.4.2 *If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria.*

Critical appraisals of AMPLIFY and AMPLIFY-EXT were performed using the format provided in the NICE submission template which adhered to the CRD guidance.(58) Results are presented in Table 17.The studies were of high quality based on the respective responses for each category thus indicating low risk of bias in study conduct and design. A complete quality assessment for each RCT is provided in Appendix 3, Section 10.4.

Table 17: Quality assessment results for AMPLIFY and AMPLIFY-EXT

Quality assessment	AMPLIFY (NCT00643201)	AMPLIFY-EXT (NCT00633893)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

6.5 Results of the relevant RCTs

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

AMPLIFY

Summary of AMPLIFY Efficacy Results

- Apixaban was non-inferior to enoxaparin/warfarin in reducing the risk of symptomatic, recurrent VTE or VTE-related death (RR 0.84, 95% CI 0.60, 1.18; p<0.001 for non-inferiority).
- The adjudicated composite secondary outcomes of recurrent VTE or all-cause death and of recurrent VTE or CV-related death was RR 0.82, 95% CI 0.61, 1.08 and RR 0.80, 95% CI 0.57, 1.11 in the apixaban group compared to the enoxaparin/warfarin comparator, although the difference between groups did not reach statistical significance for superiority (p=0.16 and p=0.18, respectively).
- Comparable overall discontinuation rates between apixaban and enoxaparin/warfarin were observed in AMPLIFY (14.0% vs. 15.3%, respectively).
- The efficacy of apixaban vs. enoxaparin/warfarin was maintained across all pre-specified subgroups, including when patients were grouped by index event of DVT or PE (with or without DVT).
- In a post-hoc analysis, the efficacy and safety results for apixaban and enoxaparin/warfarin at 3 months were consistent with those at 6 months.
- Apixaban significantly reduced all-cause hospitalisations compared to enoxaparin/warfarin over 6 months (RR 0.81, 95% CI 0.65, 1.00; p=0.048) and increased the median time to first hospitalisation (63.0 days vs. 34.5 days) compared to enoxaparin/warfarin over 6 months.

6.5.1.1 Study Drugs

The median duration of enoxaparin treatment was 6.5 days (interquartile range, 5.0 to 8.0).(14) After exclusion of INR values during the first 15 days following randomisation and during study drug interruptions, as per protocol, patients in the enoxaparin/warfarin group had an INR in the therapeutic range (2.0 to 3.0) 61% of the time.(14) Time in the therapeutic range was not calculated for apixaban treated patients as the sham INR measurements were only conducted to preserve blinding.

In AMPLIFY, the number of patients who prematurely discontinued treatment was comparable between apixaban and enoxaparin/warfarin (14.0% vs. 15.3%, respectively).

6.5.1.2 Primary Efficacy Results

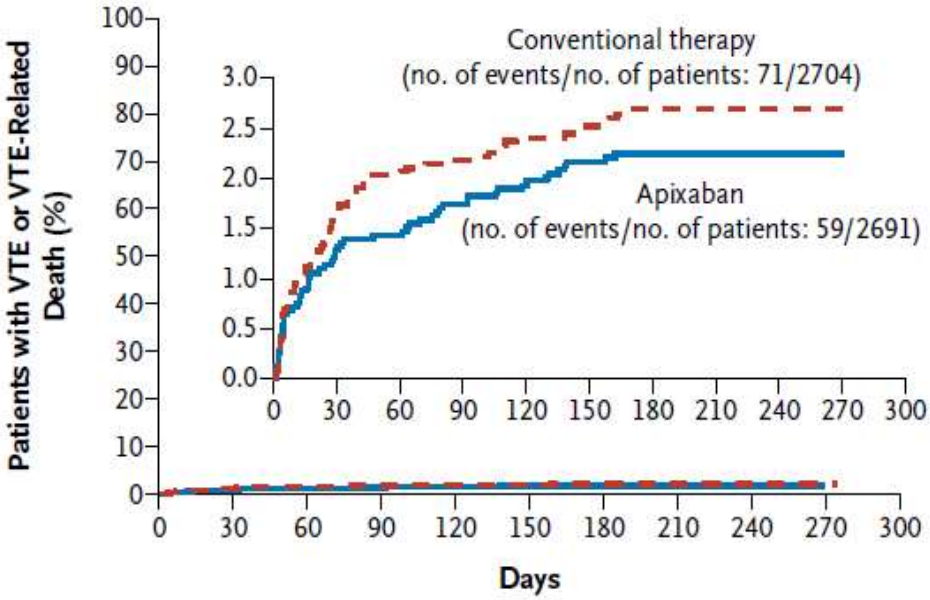
The primary efficacy endpoint of the AMPLIFY study was an adjudicated composite of symptomatic, recurrent VTE (non-fatal DVT or non-fatal PE) or VTE-related death over 6 months of therapy.(14) For the efficacy evaluable population, apixaban demonstrated non-inferiority compared to enoxaparin/warfarin with a relative risk of 0.84 (95% CI 0.60, 1.18; p<0.001 for non-inferiority) (Table 18). The Kaplan-Meier plot for the first event of recurrent VTE or VTE related death is presented in Figure 5. As the Kaplan-Meier plot has been plotted for the full ITT population, rather than the efficacy evaluable population, the results for the full ITT population are presented alongside the efficacy evaluable population in Table 18; similar results were obtained in the two populations.

Table 18: Summary of primary efficacy outcome (AMPLIFY) (14, 61)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)	p-value
Primary outcome, n (%) recurrent VTE or VTE-related death				
Efficacy evaluable population[a]	59/2609 (2.3)	71/2635 (2.7)	0.84 (0.60, 1.18)	<0.001[§] [redacted]*
ITT population[b]	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence interval; ITT: Intention-to-treat; VTE: Venous thromboembolism
[a]Efficacy evaluable population included data for patients in the ITT population for whom the outcome status at 6 months was documented. Patients with missing endpoint information were excluded from the analysis.
[b]ITT population included all randomised patients and grouped patients by treatment allocation at randomisation.
§The p-value tests for non-inferiority with respect to the relative risk of the primary efficacy outcome.
*The p-value tests for superiority with respect to the relative risk of the primary efficacy outcome, as a secondary analysis.

Figure 5: Kaplan–Meier cumulative event rates for the first event of recurrent VTE or VTE-related death (AMPLIFY; ITT population)* (14)



No. at Risk

Apixaban	2691	2606	2586	2563	2541	2523	62	4	1	0	0
Conventional therapy	2704	2609	2585	2555	2543	2533	43	3	1	1	0

Conventional therapy refers to enoxaparin/warfarin
ITT: intent to treat; VTE: venous thromboembolism

*Time to event analysis included data for patients in the ITT population. Patients lost to follow-up were not counted as having an event
Inset shows the same data on an enlarged y-axis.

6.5.1.3 Secondary Efficacy Results

Results for all secondary efficacy outcomes were consistent with and support the results for the primary outcome (Table 19). Even though apixaban demonstrated non-inferiority on the primary efficacy outcome, it was not superior to enoxaparin/warfarin for recurrent VTE or VTE-related death (RR [redacted] (Table 18).(14, 61)

The adjudicated composite secondary outcomes of recurrent VTE or all-cause death and of recurrent VTE or CV-related death were not significantly different in the apixaban group compared to the enoxaparin/warfarin group (RR 0.82; 95% CI 0.61, 1.08; p=0.16 and RR 0.80; 95% CI 0.57, 1.11; p=0.18, respectively) (Table 19).

Table 19: Summary of secondary efficacy outcomes (AMPLIFY, efficacy evaluable population) (14, 61)

	Apixaban N=2609	Enoxaparin/ warfarin N=2635	Relative risk (95% CI)	Risk difference	p-value[§]
Type of first recurrent VTE, n/N (%)					
Non-fatal PE	27/2609 (1.0)	23/2635 (0.9)	-	-	-
Non-fatal DVT	20/2609 (0.8)	33/2635 (1.3)	-	-	-
Composite outcomes, n/N (%)					
Recurrent VTE or all-cause death	84/2609 (3.2)	104/2635 (3.9)	0.82 (0.61, 1.08)	[redacted]	0.16
Recurrent VTE or CV-related death	61/2609 (2.3)	77/2635 (2.9)	0.80 (0.57, 1.11)	[redacted]	0.18
Recurrent VTE, VTE-related death or major bleeding	73/2609 (2.8)	118/2635 (4.5)	0.62 (0.47, 0.83)	[redacted]	0.001
Recurrent VTE, CV-related death, MI, stroke, major bleeding or CRNM bleeding[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death outcomes, n/N (%)					
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV-related death (including VTE-related death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause death	41[redacted]	52[redacted]	0.79 (0.53, 1.19)	[redacted]	[redacted]

CI: Confidence interval; CRNM: Clinically relevant non-major; CV: Cardiovascular; DVT: Deep vein thrombosis; PE: Pulmonary Embolism; VTE: Venous thromboembolism
The secondary efficacy outcomes included events that occurred at any time from randomisation until the end of the intended treatment period regardless of whether patients were receiving study medication (using the intention-to-treat principle). All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status (for each particular outcome) at 6 months was documented (efficacy evaluable population). Subjects with missing endpoint data were excluded from the analysis. As some patients had missing data for some outcomes but not others, the N numbers differ between the outcomes.
[a]Patients not in the efficacy evaluable population with a bleeding event that occurred during the treatment period were included in the analysis.
[§]The p-value tests for superiority with respect to the relative risk of the composite secondary efficacy outcomes. A p-value <0.05 indicates that there is a high probability of apixaban being superior to enoxaparin/warfarin for the respective outcome.

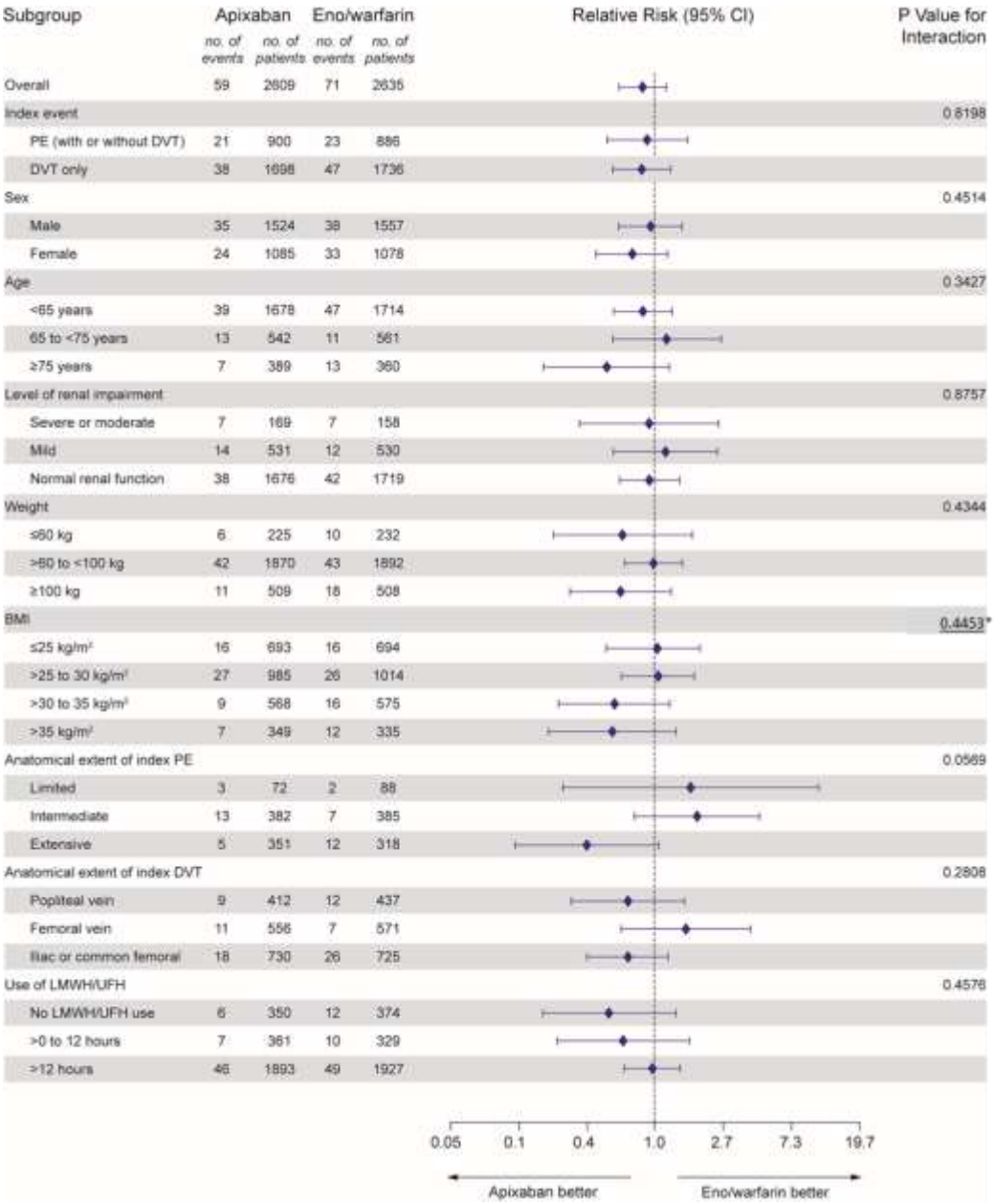
6.5.1.4 Subgroup Analyses

Analyses for the primary efficacy endpoint were performed for a large number of subgroups, both pre-specified and post-hoc. Treatment by subgroup interactions with a p-value <0.10 were investigated further, although no clinically important observations were noted (Figure 6).

[redacted]

Tabulated results for the primary efficacy outcome for all pre-specified subgroups are presented in the Appendices, Section 10.5.

Figure 6: Summary of the relative risk of the primary efficacy outcome according to pre-specified subgroups (AMPLIFY, efficacy evaluable population) (14, 61)



Subgroups for the anatomical extent of index PE and DVT, and the use of LMWH/UFH subgroup analysis were investigated although they were not pre-specified

[redacted]

BMI: Body mass index (category II); CI: Confidence interval; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; UFH: Unfractionated heparin; VTE: Venous thromboembolism

6.5.1.5 Primary Efficacy Endpoint by Index Event Type

The primary efficacy outcome of symptomatic, recurrent VTE or VTE-related death were consistent across DVT and PE subgroups. Among patients who had DVT at enrolment, the primary efficacy event occurred in 2.2% in the apixaban group and 2.7% in the enoxaparin/warfarin group ([redacted]) (Table 20).(14, 61) Similarly, among patients who had PE at enrolment, the primary efficacy outcome occurred in 2.3% patients in the apixaban group and in 2.6% patients receiving enoxaparin/warfarin ([redacted]) (Table 20).(14, 61)

Table 20: Summary of the primary efficacy outcome for DVT/PE subgroups indexed by type (AMPLIFY) (14, 61)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)
Primary efficacy outcome: recurrent VTE or VTE-related death, n/N (%)			
PE (with or without DVT) subgroup	21/900 (2.3)	23/886 (2.6)	[redacted]
DVT subgroup	38/1698 (2.2)	47/1736 (2.7)	[redacted]

CI: Confidence interval; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism
Efficacy evaluable population included data for patients in the ITT population for whom the outcome status at 6 months was documented.

6.5.1.6 Secondary Efficacy Endpoints by Index Event Type

Secondary efficacy endpoints were also stratified by index event and in all instances the outcomes were consistent across DVT and PE (with/without DVT) subgroups (Table 21).

Table 21: Summary of secondary efficacy outcomes for DVT/PE subgroups indexed by type (AMPLIFY, efficacy evaluable) (61)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)
DVT			
Type of first recurrent VTE, n/N (%)			
Non-fatal DVT	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]
Composite outcomes, n/N (%)			
Recurrent VTE or all-cause death	[redacted]	[redacted]	[redacted]
Recurrent VTE or CV-related death	[redacted]	[redacted]	[redacted]
Recurrent VTE, VTE-related death or major bleeding	[redacted]	[redacted]	[redacted]
PE			
Type of first recurrent VTE, n/N (%)			
Non-fatal DVT	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]
Composite outcomes, n/N (%)			
Recurrent VTE or all-cause death	[redacted]	[redacted]	[redacted]
Recurrent VTE or CV-related death	[redacted]	[redacted]	[redacted]
Recurrent VTE, VTE-related death or major bleeding	[redacted]	[redacted]	[redacted]

CI: Confidence interval; CV: Cardiovascular; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism

Subjects with missing endpoint data were excluded from the analysis. As some patients had missing data for some outcomes but not others, the N numbers differ between the outcomes.
N, total number of evaluated patients in the respective groups

6.5.1.7 Primary Efficacy Endpoint in Cancer Patients

One of the pre-specified subgroups in AMPLIFY was on patients with active cancer at baseline; the results are presented in Table 22. Although the number of cancer patients was small, the results in this pre-specified, high risk subgroup are consistent with the overall AMPLIFY findings.(61) Additional studies are warranted to compare the efficacy and safety of apixaban and extended LMWH, the recommended therapy for VTE treatment in many cancer patients.

Table 22: Subgroup results in the pre-specified group of patients with active cancer at baseline (61)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)	Treatment interaction p value
Primary efficacy outcome: recurrent VTE or VTE-related death, n/N (%)				
Active cancer at baseline	[redacted]	[redacted]	[redacted]	[redacted]
No active cancer at baseline	[redacted]	[redacted]	[redacted]	

6.5.1.8 Post-hoc Analysis of Recurrent VTE or VTE-related Death Prior to 6 Months

Post-hoc analyses were performed to compare the incidences of recurrent VTE or VTE-related death prior to 6 months to determine whether apixaban was non-inferior to enoxaparin/warfarin at these timepoints. As recurrent events tend to occur during the initial 3 weeks of treatment, the primary efficacy outcome was investigated at both 7 and 21 days.(62) Additionally, as the decision on whether to discontinue treatment could occur at 3 months [according to NICE CG144 (8)], the 3 month timepoint was also analysed.

Apixaban was non-inferior to enoxaparin/warfarin for recurrent VTE or VTE-related death at all early timepoints, including 3 months ([redacted]) (Table 23).

Table 23: Post-hoc analysis of recurrent VTE or VTE-related death at early timepoints (AMPLIFY, efficacy evaluable population) (62)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)	p-value for non-inferiority
Recurrent VTE or VTE-related death, n/N (%)				
7 days	18/2661 (0.68)	23/2676 (0.86)	0.79 (0.43, 1.46)	0.0033
21 days	29/2652 (1.09)	35/2667 (1.31)	0.83 (0.51, 1.36)	0.0008
3 months	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence interval; VTE: Venous thromboembolism
Efficacy evaluable population included data for patients in the intention-to-treat population for whom the outcome status at the investigated timepoint was documented.

6.5.1.9 Hospitalisation

The effects of apixaban vs. enoxaparin/warfarin on all-cause hospitalisations during the AMPLIFY trial were investigated.(15) The hospitalisation data are included in this section as they are relevant to both the comparative efficacy and comparative safety of the interventions. The results are based on analysis of the safety population (treated patients) as described in Section 6.3.8.2.

Outcomes of interest were rates of all-cause hospitalisations and time from randomisation to the first hospitalisation (Table 24). Compared with enoxaparin/warfarin, apixaban was associated with a significant reduction in all-cause hospitalisations over 6 months (hazard ratio [HR] 0.81; 95% CI 0.65, 1.00; p=0.048) and in the first 30 days after index VTE event (HR 0.68; 95% CI 0.49, 0.94; p=0.019).(15)

Reductions in hospitalisations associated with apixaban compared to enoxaparin/warfarin were mainly due to fewer recurrent VTE events requiring hospitalisation [redacted] and bleeding events that required hospitalisation [redacted]

Table 24: Summary of hospitalisation outcomes (AMPLIFY)(15)

	Apixaban N=2676	**Enoxaparin/ warfarin N=2689**	**Hazard ratio (95% CI)**	**p-value**
Hospitalisation outcomes				
Number of patients hospitalised during intended 6 month treatment period	153	190	0.81 (0.65, 1.00)	p=0.048
Rate of hospitalisation per year	11.1%	13.8%	-	-
Rate of hospitalisation in the first 30 days after VTE index event	2.3%	3.4%	0.68 (0.49, 0.94)	p=0.019
Median time to first hospitalisation (days)	63.0	34.5	-	-

CI: Confidence interval; VTE: Venous thromboembolism
Analysis is based on the safety population (those patients who received at least one dose of study medication)

AMPLIFY-EXT

Summary of AMPLIFY-EXT Efficacy Results

- Apixaban 2.5 mg was superior to placebo in preventing recurrent VTE or all-cause death (RR 0.33, 95% CI 0.22, 0.48; p<0.0001).
- The incidence of the composite secondary outcomes of recurrent VTE or VTE-related death and of recurrent VTE or CV-related death were significantly reduced in the apixaban 2.5 mg arm compared to placebo RR 0.19, 95% CI 0.11, 0.33 and [redacted], respectively; [redacted] for superiority for both outcomes).
- Apixaban had a lower rate of overall discontinuation compared with placebo (13.6% vs. 22.7%, respectively).
- The efficacy of apixaban over placebo was maintained across all pre-specified subgroups, including when patients are grouped by index event of DVT or PE (with or without DVT).
- Apixaban significantly reduced all-cause hospitalisations compared to placebo during the intended treatment period (p=0.030).

6.5.1.10 Study Drugs

A total of 19 patients in the placebo group (2.3%) and 13 patients in the 2.5 mg apixaban group (1.5%) were lost to follow-up and were counted as having had a primary efficacy event.(16) These patients are included in the summary of the primary efficacy outcome below (Table 25), although are not included in the time to event analysis (Figure 7).

Apixaban had a lower rate of overall discontinuation compared with placebo in AMPLIFY-EXT (13.6% vs. 22.7%, respectively).

6.5.1.11 Primary Efficacy Results

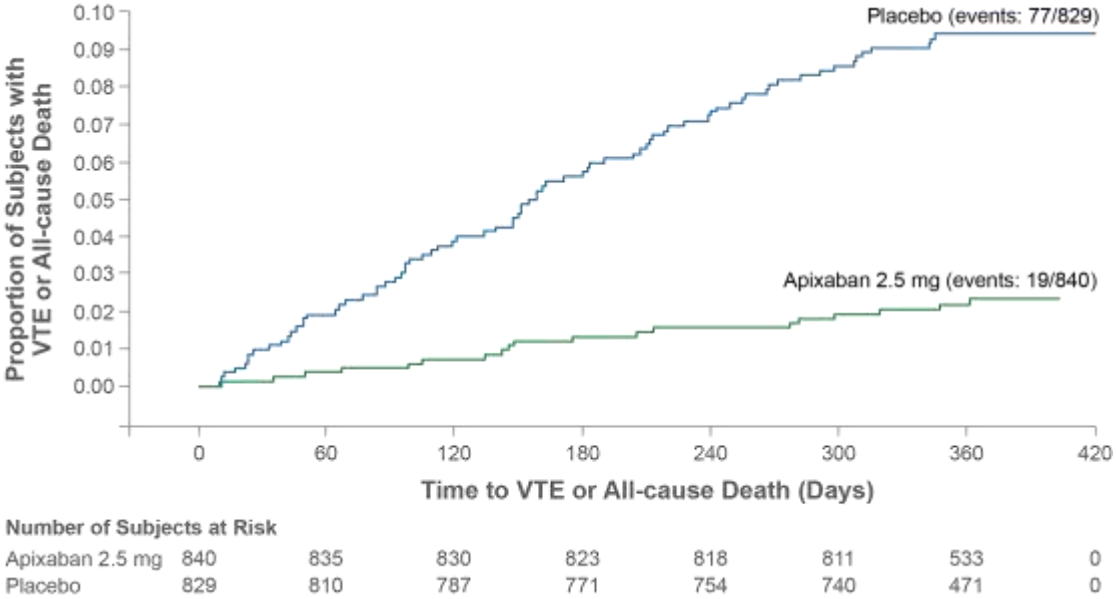
In AMPLIFY-EXT, apixaban was superior to placebo in preventing symptomatic, recurrent VTE or all-cause death over a 12-month treatment period (RR 0.33; 95% CI 0.22, 0.48; [redacted]) (Table 25).(16, 64) Time to event analysis of the primary efficacy outcome is presented in Figure 7.

Table 25: Summary of primary efficacy outcome at 12 months (AMPLIFY-EXT, ITT) (16, 64)

	Apixaban 2.5 mg N=840	Placebo N=829	Relative risk (95% CI)
Primary outcome, n (%)			
Recurrent VTE or all-cause death	32 (3.8)	96 (11.6)	0.33 (0.22-0.48) [redacted]

CI: Confidence interval; VTE: Venous thromboembolism
The primary endpoint included events that occurred at any time from randomisation until the end of the originally intended treatment period, regardless of whether patients were receiving study medication (using the intention-to-treat principle). The analysis included 19 patients in the placebo group and 13 patients in the apixaban group who were lost to follow-up and counted as having an event.
§The p-value tests for superiority with respect to the relative risk of the primary efficacy outcome.
Results for the primary outcome were imputed so that patients lost to follow-up were counted as having had a primary outcome event.

Figure 7: Kaplan–Meier cumulative event rates for the first event of recurrent symptomatic VTE or all-cause death over the intended treatment period (AMPLIFY-EXT, ITT)* (64)



*Patients who were lost to follow-up were not included in this analysis. This explains the lower number of events than presented in Table 25, where the primary outcome were imputed so that patients lost to follow-up were imputed.

6.5.1.12 Secondary Efficacy Results

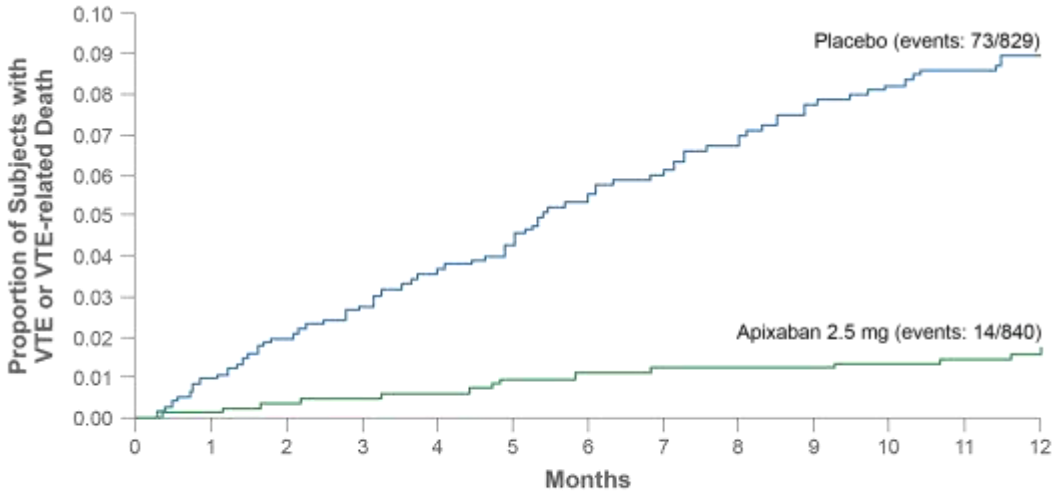
A statistically significant reduction in symptomatic, recurrent VTE or VTE-related death was observed for apixaban 2.5 mg compared to placebo (RR 0.19; 95% CI 0.11, 0.33; [redacted]) (Table 26).(16, 64) Event rates and time to event analyses of recurrent VTE or VTE-related death are presented in Figure 8.(64) The incidence of the composite outcome of recurrent VTE or CV-related death was also significantly reduced in the apixaban 2.5 mg arm compared to placebo ([redacted]) (Table 26).(64)

Table 26: Summary of secondary efficacy outcomes (AMPLIFY-EXT, ITT) (16, 64)

	Apixaban 2.5 mg N=840	Placebo N=829	Relative risk (95% CI)	Risk difference	p-value
Type of first recurrent VTE, n (%) (16)					
Non-fatal PE	[redacted]	[redacted]	-	-	-
Non-fatal DVT	[redacted]	[redacted]	-	-	-
Composite outcomes, n (%) (16, 64)					
Recurrent VTE or VTE-related death	14 (1.7)	73 (8.8)	0.19 (0.11-0.33)	[redacted]	[redacted]
VTE or CV-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non–VTE-related CV death, myocardial infarction, or stroke	4 (0.5)	11 (1.3)	0.36 (0.11-1.12)	-	-
VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	18 (2.1)	83 (10.0)	0.21 (0.13-0.35)	-	-
VTE, VTE-related death, myocardial infarction, stroke, cardiovascular disease–related death, or major bleeding as outcome	20 (2.4)	86 (10.4)	0.23 (0.14-0.37)	-	-
Death outcomes, n (%)(64)					
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence interval; CV: Cardiovascular; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism
For the analyses of the secondary outcomes patients who were lost to follow-up were classified as not having had an outcome event.

Figure 8: Kaplan–Meier cumulative event rates for the first event of recurrent VTE or VTE-related death over the intended treatment period (AMPLIFY-EXT) (16)



No. at Risk					
Apixaban 2.5 mg	840	836	825	818	533
Placebo	829	796	768	743	471

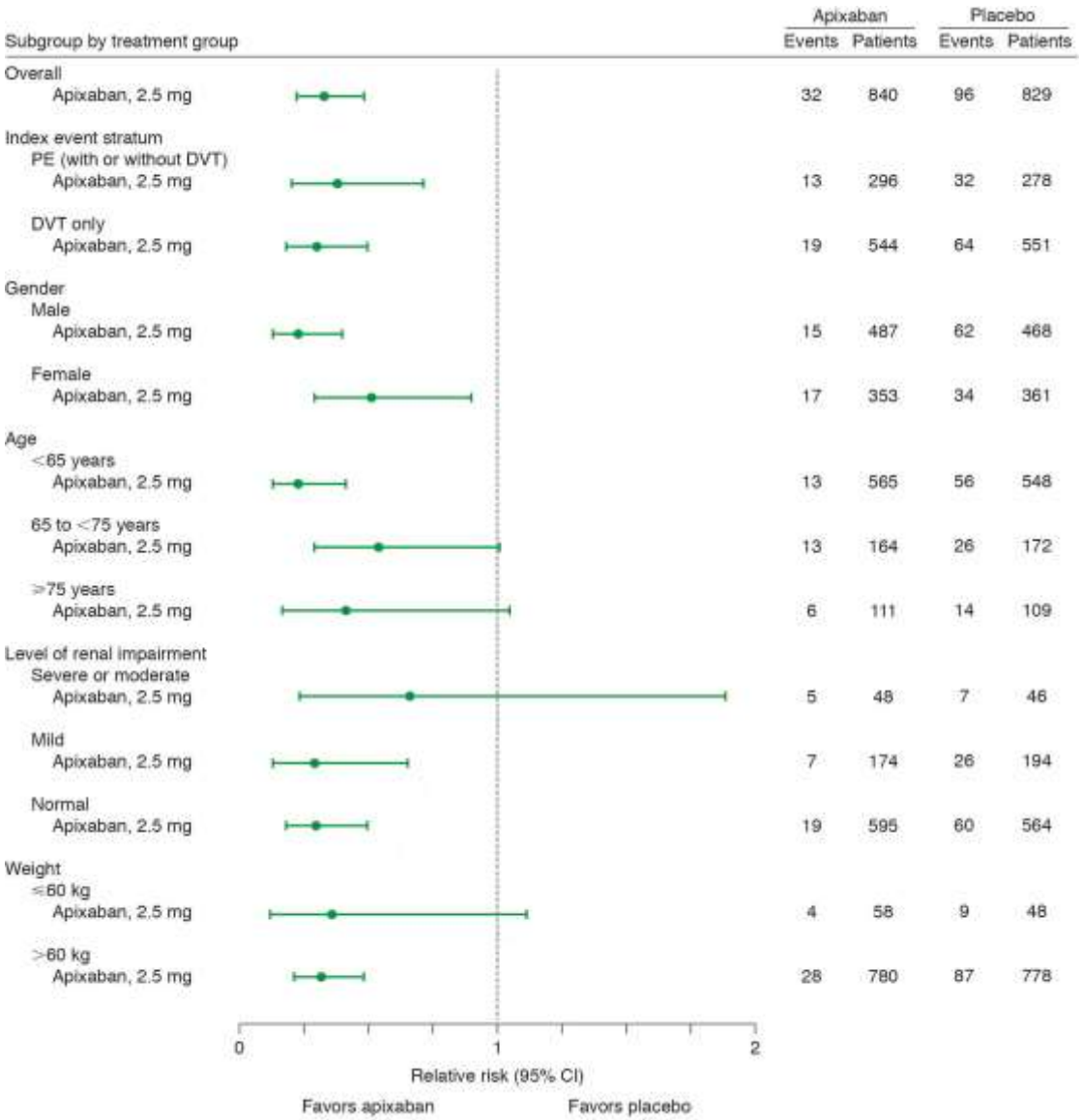
VTE: Venous thromboembolism

[redacted]

6.5.1.13 Subgroup Analyses

Pre-specified subgroup analyses were performed to investigate whether the efficacy profile of apixaban was markedly different within distinct subsets of patients, compared with that observed in the overall population. No clinically important observations were noted (Figure 9).(16, 64) Tabulated results for the primary efficacy composite outcome of recurrent VTE or all-cause death for all pre-specified subgroups are presented in the Appendices, Section 10.6.

Figure 9: Summary of the relative risk of the primary efficacy composite outcome of recurrent VTE or all-cause death according to pre-specified subgroups (AMPLIFY-EXT, ITT) (16)



CI: Confidence interval; DVT: Deep vein thrombosis; PE: Pulmonary embolism

6.5.1.14 Primary Efficacy Outcome by Index Event Type

Among patients who had DVT at enrolment, the primary efficacy outcome (recurrent VTE or all-cause death) occurred in 19 of 544 patients (3.5%) in the apixaban group and in 64 of 551 (11.6%) in the placebo group ([redacted]) (Table 27).(16, 64) Similarly, among patients who had PE (with or without DVT) at enrolment, the primary efficacy outcome occurred in 13 of 296 patients (4.4%) in the apixaban group and in 32 of 278 patients (11.5%) in the placebo group ([redacted]).(16, 64)

Table 27: Summary of the primary efficacy outcome for DVT/PE subgroups indexed by type (AMPLIFY-EXT) (16, 64)

	Apixaban	Placebo	Relative risk (95% CI)
Primary efficacy outcome: recurrent VTE or all-cause death, n/N (%)			
PE (with or without DVT) subgroup	13/296 (4.4)	32/278 (11.5)	[redacted]
DVT subgroup	19/544 (3.5)	64/551 (11.6)	[redacted]

CI: Confidence interval; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism

6.5.1.15 Secondary Efficacy Outcome by Index Event Type

Secondary efficacy outcomes were also stratified by index event and in all instances the outcomes were consistent across DVT and PE subgroups (Table 28).

Table 28: Summary of secondary efficacy outcomes for DVT/ PE subgroups indexed by type (AMPLIFY-EXT, ITT) (64)

	Apixaban 2.5 mg (N=840)	Placebo (N=829)
DVT	**N_1=544**	**N_1=551**
Type of first recurrent VTE, n (%)		
Non-fatal PE	[redacted]	[redacted]
Non-fatal DVT	[redacted]	[redacted]
Composite outcomes, n (%)		
Recurrent VTE or VTE-related death	[redacted]	[redacted]
VTE or CV-related death	[redacted]	[redacted]
PE	**N_1=296**	**N_1=278**
Type of first recurrent VTE, n (%)		
Non-fatal PE	[redacted]	[redacted]
Non-fatal DVT	[redacted]	[redacted]
Composite outcomes, n (%)		
Recurrent VTE or VTE-related death	[redacted]	[redacted]
VTE or CV-related death	[redacted]	[redacted]

CV: Cardiovascular; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism
N_1: Total number of evaluated patients in the respective groups

6.5.1.16 Hospitalisation

The rate of all-cause hospitalisations and time from randomisation to the first hospitalisation during the AMPLIFY-EXT trial were investigated.(17) Compared with placebo, apixaban was associated with a significant reduction in all-cause hospitalisations (HR 0.65; 95% CI 0.44, 0.96; p=0.030) (Table 29) and increased the mean time to hospitalisation.(17)

Table 29: Summary of hospitalisation outcomes (AMPLIFY-EXT)

	Apixaban N=840	**Placebo N=829**	**Hazard ratio (95% CI)**	**p-value**
Hospitalisation outcomes				
Number of patients hospitalised during intended 12 month treatment period	42	62	0.65 (0.44, 0.96)	p=0.030
Rate of hospitalisation per year	4.8%	7.5%	-	-
Mean time to first hospitalisation (days)	196.9	153.7	-	-

CI: Confidence interval; VTE: Venous thromboembolism
Analysis performed on the ITT population

Reductions in hospitalisations associated with apixaban compared to placebo was mainly due to fewer recurrent VTE events [redacted]

6.6 Meta-analysis

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

A meta-analysis was deemed neither feasible nor appropriate to conduct as there are only two apixaban trials under review, both using different comparators (LMWH/warfarin and placebo) and investigating a different period in the treatment pathway.

6.6.2 ***If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.***

Not applicable

6.7 *Indirect and mixed treatment comparisons*

Overview of indirect comparisons

In the absence of head-to-head RCT evidence, network meta-analyses were conducted to determine the relative efficacy and safety of apixaban compared to other anticoagulants for VTE in the treatment period and prevention of VTE recurrence (termed 'prevention') period.

- In the **treatment period (NMA 1)**:
  - There were no significant differences between therapies for the composite outcome of recurrent VTE or VTE-related death.
  - Apixaban demonstrated a significantly lower rate for the composite outcome of major or CRNM bleeding than dabigatran and rivaroxaban.
  - Apixaban also demonstrated a significantly lower rate of major bleeding vs. dabigatran, and of CRNM bleeding vs. rivaroxaban.
- In the **prevention period (NMA 2)**:
  - There were no significant differences in terms of the composite outcome of recurrent VTE or VTE-related death for apixaban 2.5 mg, dabigatran, rivaroxaban, or VKA.
  - Apixaban demonstrated a significantly lower rate of major or CRNM (composite) bleeding than dabigatran, rivaroxaban and VKA.
  - Apixaban also demonstrated a significantly lower rate of major bleeding and of CRNM bleeding compared to rivaroxaban and VKA.
  - Apixaban was associated with a significantly lower rate of recurrent VTE or VTE-related death and overall treatment discontinuation compared with aspirin and there were no statistical differences for any of the other outcomes.

6.7.1 *Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, Appendix 4.*

Please see Section 6.1 for the methods used to identify RCT and non-RCT evidence on the efficacy and safety of apixaban and relevant comparators for the treatment and prevention of recurrent VTE. Eligibility criteria and a flow diagram of included and excluded studies can be found in Section 6.2.

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

Two network meta-analyses (NMAs) were conducted to assess the relative efficacy and safety of apixaban vs. relevant comparators for both the treatment and prevention of recurrent VTE:

- **NMA 1**, which investigated the treatment period, assessed the relative efficacy and safety of anticoagulant therapy for the treatment of an initial VTE event.

- **NMA 2**, which investigated the prevention of recurrent VTE (termed 'prevention') period, evaluated the relative efficacy and safety of extended anticoagulant treatment in patients who had already received prior treatment for an initial VTE event.

No evidence was identified in a population with DVT and/or PE for whom a VKA is unsuitable from the systematic review (Appendix 9, Section 10.22), therefore it was not possible to conduct an NMA in this population.

6.7.2.1 NMA 1: Treatment Period – overview of trials

NMA 1 was conducted based on prospective RCTs, with open-label and double-blind study designs, comparing NOACs with the current standard of care for VTE, i.e. anticoagulation with LMWH in combination with VKA. It is assumed in this analysis that the effectiveness of all LMWH are comparable. Although fondaparinux is licensed in this indication, it does not represent an appropriate comparator for this appraisal, as in NICE technology appraisal, TA287, (Section 4.2), the NICE committee for rivaroxaban TA287 stated that fondaparinux is rarely used and agreed that it was appropriate to consider only LMWH/VKA as a comparator for that appraisal.(11) Clinical experts at a recent BMS/Pfizer Advisory Board endorsed that fondaparinux is not a relevant comparator for this appraisal.(9)

Five RCTs reported in six publications on three treatments were included in the NMA of the treatment period (Table 30). EINSTEIN-PE (70) and EINSTEIN-DVT (71) are represented by a pooled analysis in the table.(50) Most studies reported results at 6 months, with the exception of the rivaroxaban EINSTEIN trials, which reported results for patients at 3, 6 and 12 months of treatment.

Table 30: RCTs included in NMA 1 (Treatment Period)

Trial	Treatment (as described in trial)	Comparator (as described in trial)
AMPLIFY (14)	Apixaban 10 mg bd (initial 7 days)/apixaban 5 mg bd	Enoxaparin/warfarin
RE-COVER (72)	UFH or LMWH/dabigatran 150 mg bd	UFH or LMWH/warfarin
RE-COVER II (73)	UFH or LMWH/dabigatran 150 mg bd	UFH or LMWH/warfarin
EINSTEIN DVT and PE pooled data set (50)	Rivaroxaban 15 mg bd (initial 21 days)/rivaroxaban 20 mg od	Enoxaparin/VKA (INR 2.0–3.0)

bd: Twice daily; INR: International normalised ratio; LMWH: Low molecular weight heparin; od: once daily; UFH: Unfractionated heparin; VKA: Vitamin K antagonist Warfarin INR 2.0–3.0

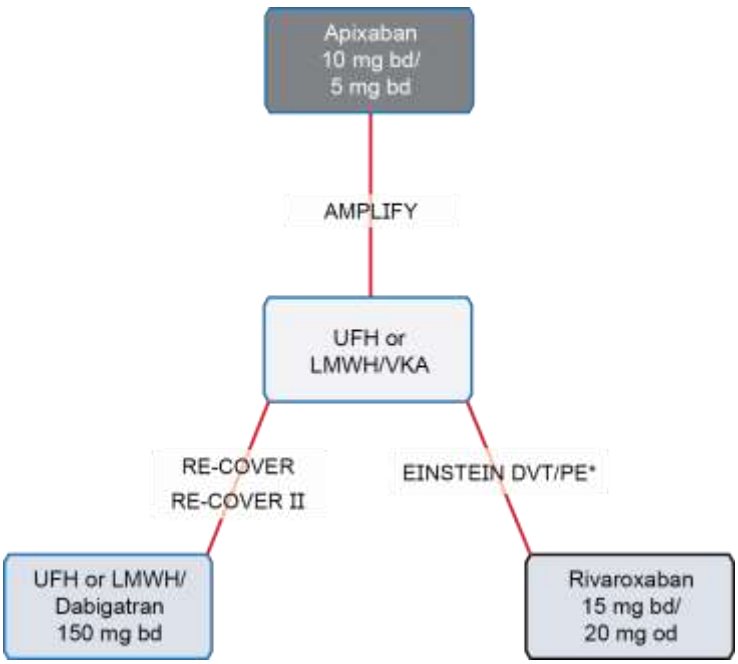
The EINSTEIN pooled analysis combined both EINSTEIN DVT and EINSTEIN PE trials, which were initially published separately. The pooled analysis was used in the primary and sensitivity analyses

as it applied to a general VTE population, rather than being specific to the primary VTE event of the patient. For RE-COVER and RE-COVER II, the primary analysis used trial-level data as both trials reported data based on a VTE population. For RE-COVER II, the data used were based on an abstract as the full publication was not available at the time of the analysis. Recently published pooled data for RE-COVER and RE-COVER II were used in a sensitivity analysis as there appeared to be some difference in the adjudication of events between the pooled analysis study and the RE-COVER study.(51) The results of the quality assessment of AMPLIFY are presented in Section 10.4 and those of all the other included trials are presented in Section 10.8.1.

Analyses were conducted using the ITT population (randomised to receive treatment) for the efficacy outcomes (i.e. recurrent VTE or VTE-related death, non-fatal PE, DVT, VTE-related death, all cause death, and overall discontinuation) where possible. However, the majority of trials in the NMA reported on the modified ITT (mITT) (for example, where patients with no outcome data were excluded from the analysis) as per trial publications. Due to the difficulty in obtaining trial specific raw data on those 'randomised to receive' the respective interventions, the mITT was used for the majority of trials in the network. The ITT analysis provides less biased and consistent treatment effects derived from the NMA.(74) In contrast, the evaluation of the safety outcomes across all trials was based on the safety (per protocol) population which only considered patients who fully adhered to the clinical study protocol, and therefore, received ≥1 dose of the study drug during the intended treatment period. This approach is recommended for the analysis of safety outcomes in clinical trials because it provides a true biological effect of the treatment.(74)

Comparisons between all treatments were made based on the network shown in Figure 10. This network represents all trials and will vary per outcome depending on the availability of data.

Figure 10: Network diagram for the treatment period network



bd: Twice daily; LMWH: Low molecular weight heparin; od: Once daily; UFH: Unfractionated heparin; VKA: Vitamin K antagonist
*EINSTEIN pooled analysis was used for the treatment period NMA

6.7.2.2 NMA 2: Prevention Period – overview of trials

NMA 2 was conducted based on prospective, RCTs, with open-label and double-blind study designs, comparing NOACs (apixaban, dabigatran and rivaroxaban), aspirin, VKA and placebo. The included

trials required patients to have at least 3 months prior anticoagulation. Eleven RCTs (reported in ten publications) were included in the analysis of the prevention of recurrent VTE (Table 31).

In the current prevention evidence network, low warfarin INR range is included as a treatment node (PREVENT (75) and ELATE (76) studies) as it provides an additional 'loop' of evidence increasing the reliability of the treatment effect estimates from the NMA. Additionally, a recent study by Dequen et al. (77) exploring the impact of extending networks on the relative treatment effects of NOACs in recurrent VTE demonstrated that the precision of results increased by using a larger network of studies, suggesting that removing this treatment node from the network may reduce the reliability of the results obtained.

Table 31: RCTs included in NMA 2 (Prevention Period)

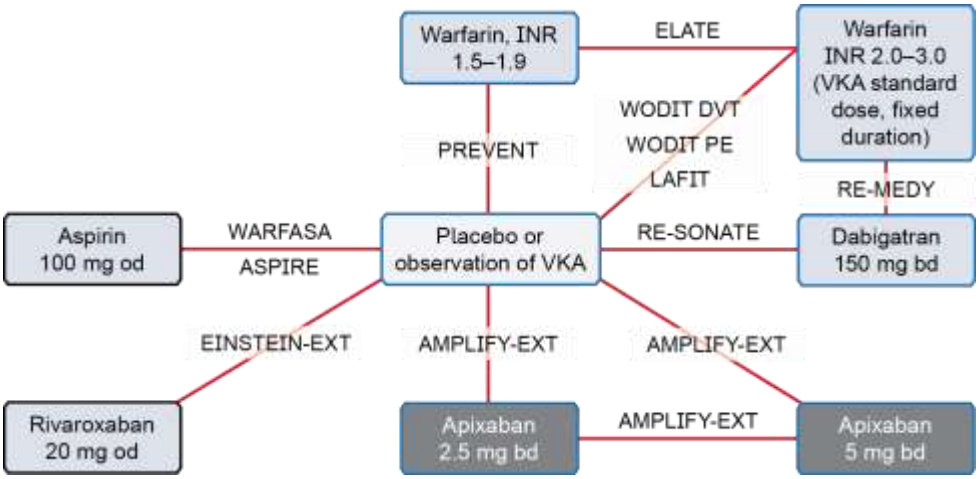
Trial	**Treatment** (as described in the trial)	**Comparator** (as described in the trial)
AMPLIFY-EXT (16)	Apixaban 2.5 mg bd/ 5 mg bd	Placebo
EINSTEIN-EXT (78)	Rivaroxaban 20 mg od	Placebo
WARFASA (54)	Aspirin 100 mg od	Placebo
RE-SONATE (79)	Dabigatran 150 mg bd	Placebo
RE-MEDY (79)	Dabigatran 150 mg bd	Warfarin (INR 2.0–3.0)
ASPIRE (55)	Aspirin 100 mg od	Placebo
LAFIT (80)	Warfarin (INR 2.0–3.0)	Placebo
ELATE (76)	Warfarin (INR 1.5–1.9)	Warfarin (INR 2.0–3.0)
WODIT DVT (81)	VKA continuation	VKA discontinuation/ observation
WODIT PE (82)	VKA continuation	VKA discontinuation/ observation
PREVENT (75)	Warfarin (INR 1.5–1.9)	Placebo

Bd: Twice daily; INR: International normalised ratio; od: Once daily; VKA: Vitamin K antagonist

Event data were captured so as to include all events occurring while patients were followed during the planned treatment period, as defined in the pre-specified protocol of each study. This was consistent with the approach adopted by Castellucci *et al.* (83) (who compared the efficacy and safety of various oral anticoagulants, including dabigatran, rivaroxaban, apixaban, VKA and aspirin, for the prevention of recurrent VTE) and was intended to minimise the level of bias in the network for trials that have extended follow-up periods as part of their trial design. The primary analyses used the outcome event data reported while patients were on treatment, with the exception of the ASPIRE and ELATE trials, where the outcome data were taken as that reported while the patients were in the follow-up period of the study, having stopped treatment because this was the pre-specified analysis plan of these trials.

The results of the quality assessments of the trials in the prevention network are presented in Section 10.8.2. The quality assessment of AMPLIFY-EXT is reported in Section 10.4. Comparisons between all treatments were made based on the network shown in Figure 11. This network represents all trials and varied per outcome depending on the availability of outcome data.

Figure 11: Network diagram for the prevention period network



bd: Twice daily; INR: International normalised ratio; od: Once daily; VKA: Vitamin K antagonist

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

The efficacy and safety outcomes analysed for NMA 1 and NMA 2 are described below. Data were extracted from the primary publications where available and from the clinical study reports (CSRs for AMPLIFY and AMPLIFY-EXT) where such data were not available from the primary publication. A full summary of the data used in NMA 1 and NMA 2 is presented in Section 10.9 and Section 10.10, respectively. Health-related quality of life (HRQL) outcomes were not measured in the trials identified, therefore a NMA for this outcome was not feasible.

In both NMA 1 and NMA 2 when a study contained a zero observation (e.g. no patients had the event), by default, a continuity correction of 0.5 was applied in order to calculate the study relative risk (i.e.obtain non-infinite estimates of treatment effects and non-infinite variance). This practice is identified in Section 16.9.2 of the Cochrane Handbook and the NICE DSU Technical Support Document.(74, 84)

6.7.3.1 NMA 1: Treatment Period – outcome data

The availability of outcome data for the base case analysis as reported by each trial, is summarised in Table 32. A full summary of the data used in the NMA is presented in Section 10.9.

The composite outcome of recurrent VTE or VTE-related death consisted of the sum of non-fatal PE, DVT and VTE-related death outcomes. Results of the component outcomes have been presented in Section 10.9.

Table 32: Outcome data as reported by trials in the treatment period network (NMA 1)

Outcome	AMPLIFY (14)	RE-COVER (72)	RE-COVER II (73)	EINSTEIN DVT/PE pooled (50)
Recurrent VTE or VTE-related	✓	✓	✓	✓
Non-fatal PE	✓	✓	✓	✓
DVT	✓	✓	✓	✓
VTE-related death	✓	✓	✓	✓
Major or CRNM bleeding	✓	✓	✓	✓
Major bleeding	✓	✓	✓	✓
CRNM bleeding	✓	✓	✓	✓
Intracranial bleeding	✓	✓	✓	✓
Other major bleeding	✓	✓	✓	✓
Other deaths (efficacy)	✓	✓	✓	✓
Overall treatment discontinuation	✓	✓	✓	✓
All-cause mortality	✓	✓	✓	✓

✓= data reported; CRNM: clinically relevant non-major; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism
*Recurrent VTE or VTE-related death outcome is composed of the sum of the incidences of non-fatal PE, DVT and VTE-related death

Data assumptions

For several outcomes and analyses, assumptions were required to calculate outcome event data, as described below:

- **VTE-related death:** Analysis of VTE-related death was based on efficacy outcome data. For the AMPLIFY and EINSTEIN DVT/EINSTEIN PE pooled analysis, it was calculated from the incidence of fatal PE, plus fatal events where PE could not be ruled out. For RE-COVER and RE-COVER II trials, it was taken as death related to VTE and death related to PE, respectively.

- **CRNM bleeding:** This outcome was not directly reported in the RE-COVER and RE-COVER II trials. To obtain event data for this outcome from the trials, the reported 'major bleeding' outcome data were subtracted from the reported 'major or CRNM bleeding' data.

- **Major or CRNM bleeding**: Event data for this outcome were not available for index DVT and index PE populations in some trials, such as AMPLIFY. Therefore, outcome data were calculated by adding the reported 'major bleeding' event data to the reported 'CRNM bleeding' event data. This was done for event data from all trials, where available.

- **Other major bleed**: Event data for this outcome were calculated by subtracting intracranial bleeding events from major bleeding events. This was done for event data from all trials, where available.

- **Other deaths**: Event data for this outcome were calculated by subtracting VTE or bleeding related deaths from all deaths. For the index DVT and index PE populations, this outcome was calculated by subtracting VTE and bleeding related deaths from all deaths.

- **All-cause mortality:** The publication of pooled data from EINSTEIN DVT/ EINSTEIN PE did not report data on all-cause mortality. Therefore, in the analysis of this outcome, event data were taken directly from the EINSTEIN DVT and EINSTEIN PE publications.

Sensitivity analyses

The following sensitivity analyses were conducted on NMA 1:

Modified intention-to-treat analysis (mITT)
The impact of using the modified ITT population on the treatment period network when analysing the efficacy outcomes from AMPLIFY was explored in a sensitivity analysis. The modified ITT population included a proportion of patients from the ITT population for whom the outcome status at 6 months was documented.(51)

Pooled RE-COVER/RE-COVER II data set
A sensitivity analysis was also conducted using published pooled data from the RE-COVER/RE-COVER II trials in place of the data from the individual trials that were used in the primary analysis, as there appeared to be some difference in the adjudication of events between the pooled analysis and the RE-COVER study.

Excluding dabigatran studies - RE-COVER and RE-RE-COVER II
A sensitivity analysis was conducted excluding dabigatran studies (RE-COVER and RE-COVER II). Dabigatran for the treatment and prevention of DVT and /or PE is currently being appraised by NICE with an anticipated published guidance date October 2014.(12) Additionally, it is used in routine clinical practice as an alternative to LMWH/warfarin, rivaroxaban and apixaban in other indications.(85, 86) Dabigatran, with initial therapy of LMWH, was not included as a comparator in the final scope. However, its inclusion reflected the consensus of stakeholders at the NICE apixaban scoping meeting for this appraisal.(7)

6.7.3.2 NMA 2: Prevention Period – outcome data

The availability of outcome data for the primary base case analysis for NMA 2 as reported by each trial is summarised in Table 33. A full summary of the data used in the NMA is contained in Section 10.10.

The composite outcome of recurrent VTE or VTE-related death consisted of the sum of non-fatal PE, DVT and VTE-related death outcomes. The results of these component outcomes have been presented in Section 10.10.

Data assumptions
Analyses were conducted using the intention-to-treat population as defined in each publication for the VTE outcomes (i.e. recurrent VTE and VTE-related death, DVT and VTE-related death), all-cause mortality and overall treatment discontinuations, and for all the bleeding related outcomes (i.e. Major bleeding, Major and/or CRNM bleeding, CRNM) the safety population was used.

For several outcomes and analyses, assumptions were required to calculate outcome event data, as described below:

- **VTE-related death**: For AMPLIFY-EXT (16) and EINSTEIN-EXT (78), data were calculated from fatal PE plus unexplained death where PE could not be ruled out. For all other studies events were reported as death due to PE [PREVENT (75), ELATE (76), LAFIT (80), ASPIRE (55), and RE-SONATE (79) or due to VTE [WODIT DVT (81) and RE-MEDY (79)].

- **CRNM bleeding**: This outcome was not directly reported in the RE-MEDY or RE-SONATE trials (46). To obtain event data for this outcome, the reported ‘major bleeding’ outcome data were subtracted from the reported ‘major or CRNM bleeding’ data.

- **Major or CRNM bleeding**: This outcome was not directly reported in the ASPIRE study (55). Event data for this outcome was obtained from addition of the reported 'major bleeding' event data and reported 'CRNM bleeding' event data.

Meta-regression
Meta-regression is a statistical technique which can be used to relate the size of treatment effect from a meta-analysis to certain covariates. Potential covariates of interest for meta-regression in the current analysis included the percentage of patients with an unprovoked VTE, and the percentages of patient with an index DVT, an index PE, and an index DVT or PE. Please note that a meta-regression was not performed due to insufficient reporting of the potential covariates across the trials in the network.

Subgroup analyses
Subgroup analyses were not explored in the prevention phase as there were too few studies reporting on appropriate patient subgroups (such as index DVT and index PE groups) within the evidence network.

Sensitivity analyses
The following sensitivity analyses were conducted on NMA 2:

Intention-to-treat analysis (ITT)
A conservative scenario was conducted to take into account all event data for randomised patients using the ITT principle with the aim of testing the robustness of the results of the primary efficacy outcomes against the missing data. This is in contrast to the base case NMA 2 which considered events that happened during the planned treatment period where patients received either study drugs, placebo or observation, which is based on the Castellucci et al approach.(83)

ITT (excluding WODIT DVT/PE studies)
A further sensitivity analysis using the ITT principle was undertaken, which excluded studies (WODIT DVT/PE) that had a significantly longer follow-up period (patients were off treatment) in which the majority of recurrent VTE and VTE related death events occurred.

Base case (excluding dabigatran studies - RE-SONATE and RE-MEDY)
A sensitivity analysis was conducted to explore the impact of excluding dabigatran from the prevention period network (exclusion of RE-SONATE and RE-MEDY) for the reasons outlined above in Section 6.7.3.1.

Table 33: Outcome data as reported by trials in the prevention period network (NMA 2)

Outcome	AMPLIFY -EXT (16)	EINSTEIN-EXT (78)	WARFASA (54)	RE-SONATE (79)	RE-MEDY (79)	ASPIRE (55)	LAFIT (80)	ELATE (76)	WODIT DVT (81)	WODIT PE (82)	PREVENT (75)
Recurrent VTE or VTE-related death	✓	✓	✓‡	✓	✓	✓	✓	✓	✓	×	✓
Non-fatal PE	✓	✓	×§	✓	✓	×	✓	✓	×†	×	×
DVT	✓	✓	×¶	✓	✓	✓	✓	✓	×	×	×
VTE-related death	✓	✓	×	✓†††	✓	✓	✓	✓	✓†††	×	✓
Major or CRNM bleeding	✓	✓	✓	✓	✓	✓††	×	×	×	×	×
Major bleeding	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CRNM bleeding	✓	✓	✓	✓§§	✓‡‡	✓	×	×	×	×	×
Overall treatment discontinuation	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓
All-cause mortality	✓	✓	×¶¶	×	✓	✓	✓	✓	×	×	✓

✓= data reported; ×=data not reported. CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism
†Data reported in Table 1 of publication for 'non-fatal PE'. These data are for a mean follow-up of 37.8 months (continued therapy group) or 37.2 months (discontinued therapy group). However, data for inclusion in the analysis were restricted to those reported for the nine month treatment period only.
‡Table 2 of the publication reports recurrent VTE events during the whole study follow-up in addition to events during treatment. The latter data have been used in the analysis.
§Table 2 of the publication reports number of recurrent PE events during entire study follow-up, not restricted to on-treatment phase only.
¶Table 2 of the publication reports number of recurrent DVT events during entire study follow-up, not restricted to on-treatment phase only.
††Calculated from the addition of 'major bleed' and 'CRNM bleed' as reported in Table 2 of the publication.
‡‡Calculated by subtracting major bleed from 'major or CRNM bleeding' as reported in Table 2 of the publication.
§§Calculated by subtracting major bleed (n=2) from 'major or CRNM bleeding' (n=36) as reported in Table 3 of the publication.
¶¶Table 2 of the publication reports number of deaths during entire study follow-up, not restricted to on-treatment phase only.
†††Excluded in the analysis where trials with zero events in all treatment arms were excluded.

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

The NMA was conducted under a Bayesian framework using the statistical software package WinBUGS. The full code used is detailed in an Appendix, Section 10.11.

6.7.4.1 NMA 1: Treatment Period – methodology

For the treatment period, the NMA was performed on trials of patients with an objectively confirmed symptomatic VTE (i.e. DVT and/or PE).

Due to the small number of studies in the treatment period network, the base case NMA was restricted to a fixed-effect model. Section 9.6.5.1 of the Cochrane Systematic Review Handbook states that “typical advice” for producing “useful findings” from calculations investigating heterogeneity would be based on at least ten studies.(74)

6.7.4.2 NMA 2: Prevention Period – methodology

For the prevention period NMA, the primary analyses were performed on trials of patients who had received prior treatment for an acute VTE event; the analyses combined studies with varying baseline risks of recurrent VTE. There were only two outcomes (recurrent VTE or VTE-related death and major bleeding) where event data were available from all the ten studies within the prevention network. Therefore, for these outcomes, both fixed-effect and random-effects meta-analyses were conducted, whereas the remaining outcomes were restricted to fixed-effects models only.

Random-effects analyses were performed using both a vague/non-informative prior, and using an informative prior. The prior represents the prior probability distribution; a vague prior contains no information about the parameters of interest, whereas an informative prior expresses specific information about the parameter of interest, (which can be based on an accumulation of previous evidence). The informative prior was used to inform the estimation of the variance parameter in the random-effects analysis, as in sparse networks with little data it can be difficult to estimate the heterogeneity parameter using the data alone.(87) The variance prior used was that corresponding to objective events (all-cause mortality in the Cochrane review) and pharmacological vs. placebo comparisons:

$$\sigma^2 \sim lognor(-4.06, 1.45^2)$$

Where σ^2 = between studies variance (heterogeneity parameter).

6.7.4.3 Model Fit

The model fit of the fixed-effect and random-effects models conducted for the recurrent VTE or VTE-related death and major bleeding outcomes was compared using the deviance information criterion (DIC) for the prevention period NMA. In comparing models, the fixed-effect model was considered to be the model of choice unless the DIC of the random-effects model was at least 3–5 points lower than that of the fixed-effects model, thereby providing enough of an improvement in model fit to justify the additional complexity of a random-effects model.(88)

6.7.4.4 Interpretation of the NMA results

The NMA results for each outcome (all are adverse outcomes) are presented as relative risks (RRs). These can be interpreted as follows:

- A RR of 1 indicates that there was no difference in risk between the active and control arms
- A RR<1 indicates that the treatment had a lower risk of the outcome than the comparator.
- A RR>1 indicates that treatment had a higher risk of the outcome than the comparator.

Statistical significance is referred to at the 5% level.

6.7.5 *Please present the results of the analysis.*

6.7.5.1 NMA 1: Treatment Period – results

Key results of the base case analysis for apixaban vs. LMWH/VKA, LMWH/dabigatran and rivaroxaban are presented in Table 34. The full results, including all comparisons not involving apixaban, are presented in the Appendices, see Section 10.12.

Efficacy Outcomes
There were no significant differences between apixaban and any of the other therapies in terms of the composite outcome of recurrent VTE or VTE-related death:

- Apixaban vs. LMWH/VKA [redacted]
- Apixaban vs. LMWH/dabigatran [RR 0.76; 95% CrI 0.46, 1.27] (89)
- Apixaban vs. rivaroxaban [RR 0.93 95% CrI 0.59, 1.46] (89)

There were no significant differences between apixaban and the relevant comparators for the additional efficacy outcomes of non-fatal PE, DVT and VTE-related death.

Safety Outcomes

The relative risks for all the bleeding related outcomes were significantly reduced for apixaban in comparison to LMWH/VKA in the base case analysis, with the exception of intracranial bleeds which did not reach statistical significance:

- Apixaban vs. LMWH/VKA, Major or CRNM bleeding [redacted]
- Apixaban vs. LMWH/VKA, Major bleeding [redacted]
- Apixaban vs. LMWH/VKA, CRNM bleeding [redacted]

Apixaban demonstrated a significantly lower rate of major or CRNM (composite) bleeding than dabigatran and rivaroxaban:

- Apixaban vs. LMWH/dabigatran [redacted]
- Apixaban vs. rivaroxaban [RR 0.47; 95% CrI 0.36, 0.61] (89)

Apixaban demonstrated a significantly lower rate of major bleeding vs. LMWH/dabigatran:

- Apixaban vs. LMWH/dabigatran [RR 0.40; 95% CrI 0.19, 0.81] (89)

Apixaban also demonstrated a significantly lower rate CRNM bleeding vs. rivaroxaban:

- Apixaban vs. rivaroxaban [RR 0.47; 95% CrI 0.36, 0.62] (89)

There were no significant differences in the incidence of CRNM bleeding when comparing apixaban with LMWH/dabigatran, and in major bleeding when comparing apixaban with rivaroxaban.

Table 34: Base case analysis for treatment period network (NMA 1) results – 6 month timepoint – fixed-effect model (statistically significant results are shown in bold)

Outcome	Apixaban vs. LMWH/VKA, RR (95% CrI)	Apixaban vs. LMWH/dabigatran, RR (95% CrI) (89)	Apixaban vs. rivaroxaban, RR (95% CrI) (89)
Recurrent VTE or VTE-related death*	[redacted]	0.76 (0.46, 1.27)	0.93 (0.59, 1.46)
Major or CRNM bleeding	[redacted]	**0.69 (0.51, 0.94)**	**0.47 (0.36, 0.61)**
Major bleeding	[redacted]	**0.40 (0.19, 0.81)**	0.55 (0.27, 1.09)
CRNM bleeding	[redacted]	0.80 (0.57, 1.12)	**0.47 (0.36, 0.62)**
Overall treatment discontinuation	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	0.79 (0.44, 1.41)	0.82 (0.50, 1.34)

CrI: Credible interval; CRNM: Clinically relevant non-major; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; RR: Relative risk; UFH: Unfractionated heparin; VTE: Venous thromboembolism
*VTE or VTE-related death outcome is composed of the sum of the incidences of non-fatal PE, DVT and VTE-related death

Sensitivity Analysis

Results of the sensitivity analysis for the primary efficacy outcome of recurrent VTE or VTE-related death for the modified ITT population were consistent with the base case results reported; the results for the primary efficacy outcome are presented in Table 35. Results for the safety outcomes are not affected in this scenario as they were analysed on the safety population, but are presented again here for consistency. The data used and the results of the modified ITT population sensitivity analysis for the primary efficacy outcomes, including comparisons not involving apixaban, are presented in Section 10.13.

The sensitivity analysis results for the primary efficacy outcome and the key safety outcomes of major bleeding, major or CRNM bleeding, and CRNM bleeding for the RE-COVER/RE-COVER II pooled analysis and for the exclusion of RE-COVER/RE-COVER II are also shown in Table 35. These analyses also demonstrated that the results were consistent with the primary base case analysis. The data used and results of the respective outcomes for this analysis are presented in Section 10.14.

Table 35: Analysis for Modified ITT population and RE-COVER/RE-COVER II pooled analysis. Sensitivity for treatment period network (NMA 1) results– 6 month timepoint – fixed-effect model (statistically significant results are shown in bold)

Outcome	Apixaban vs. LMWH/VKA, RR (95% CrI)	Apixaban vs. LMWH/dabigatran, RR (95% CrI)	Apixaban vs. rivaroxaban, RR (95% CrI)
Modified ITT population			
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]

Major bleeding*	[redacted]	[redacted]	[redacted]
Major and/or CRNM*	[redacted]	[redacted]	[redacted]
CRNM bleeding*	[redacted]	[redacted]	[redacted]
RE-COVER/RE-COVER II pooled analysis			
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]
Major or CRNM	[redacted]	[redacted]	[redacted]
CRNM bleeding	[redacted]	[redacted]	[redacted]
Exclusion of RE-COVER and RE-COVER II (Dabigatran studies)			
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]
Major or CRNM	[redacted]	[redacted]	[redacted]
CRNM bleeding	[redacted]	[redacted]	[redacted]

*Results do not change to base case, as safety population does not change under modified ITT assumptions
CrI: Credible interval; LMWH, Low molecular weight heparin; VKA, Vitamin K antagonist; RR, Relative risk; VTE, Venous thromboembolism; CRNM, Clinically relevant non-major

6.7.5.2 NMA 2: Prevention Period – results

Both fixed-effect and random-effects meta-analyses were conducted for recurrent VTE or VTE-related death and major bleeding outcomes as these were the only two outcomes where event data were available from all ten studies. The remaining outcomes were restricted to fixed-effect models due to the limited number of studies.(74) In all instances, the fixed-effect model was deemed to provide a better fit and was therefore used in the base case analysis (Table 36).

Table 36: DIC and residual deviance model fit statistics

Outcome	DIC		Total residual deviance		Number of data points in analysis
	FE	RE	FE Mean / Median (95% CrI)	RE Mean / Median (95% CrI)	
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DIC: Deviance information criterion; FE: Fixed effect; RE: Random effects; VTE: Venous thromboembolism
Random-effects models were conducted for the recurrent VTE or VTE-related death and major bleeding outcomes only, as the remaining outcomes were reported in a network of less than 10 trials

Results of the base case analysis for apixaban vs. comparators in the long-term prevention period are presented in Table 37. The full results, including all comparisons not involving apixaban, are presented in Section 10.15.

Efficacy Outcomes

There were no significant differences between treatments in terms of the composite outcome of recurrent VTE or VTE-related death for apixaban, dabigatran, rivaroxaban, or VKA:

- Apixaban vs. dabigatran [redacted]
- Apixaban vs. rivaroxaban [redacted]
- Apixaban vs. VKA (INR 2.0–3.0) [redacted]

However, apixaban was associated with a significantly lower rate of recurrent VTE or VTE-related death (composite) compared with aspirin and placebo [redacted] and [redacted], respectively).

Safety Outcomes

Apixaban demonstrated a significantly lower rate of major or CRNM (composite) bleeding than dabigatran, rivaroxaban and VKA:

- Apixaban vs. dabigatran [redacted]
- Apixaban vs. rivaroxaban [redacted]
- Apixaban vs. VKA (INR 2.0–3.0) [redacted]

Apixaban also demonstrated a significantly lower rate of major bleeding compared to rivaroxaban and VKA:

- Apixaban vs. rivaroxaban [redacted]
- Apixaban vs. VKA (INR 2.0–3.0) [redacted]

Apixaban also demonstrated a significantly lower rate of CRNM bleeding compared to rivaroxaban and VKA:

- Apixaban vs. rivaroxaban [redacted]
- Apixaban vs. VKA (INR 2.0–3.0) [redacted]

For both major bleeding and CRNM bleeding, there was no statistical difference between apixaban and dabigatran. There were no statistical differences for any of the safety outcomes between apixaban vs. aspirin and apixaban vs. placebo. However, the overall treatment discontinuation was significantly lower in the apixaban group compared to both comparators (Table 37).

The results of the random-effects analyses were performed using both a vague prior and informative prior for the recurrent VTE or VTE-related death and major bleeding outcomes. In all cases, the results from the random-effects models were consistent with those of the fixed-effect models (Section 10.16).

Table 37: Base case analysis for the prevention period NMA (NMA 2) – fixed-effect model (statistically significant results are shown in bold)

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
Recurrent VTE or VTE-related death*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bd: twice daily; CrI: Credible interval; CRNM: Clinically relevant non-major; DVT: Deep vein thrombosis; INR: International normalised ratio; PE: Pulmonary embolism; od: once daily; RR: Relative risk; VTE: Venous thromboembolism; VKA: Vitamin K antagonist
*Recurrent VTE or VTE-related death outcome is composed of the sum of the incidences of non-fatal PE, DVT and VTE-related death

The apixaban study AMPLIFY-EXT was powered for the composite efficacy endpoint (recurrent VTE or all cause death). Therefore when individual subcomponents of the composite are scrutinised, especially for the smallest component (recurrent PE), the play of chance due to under-powering is the most likely explanation for the difference, which is evidenced by the wider confidence intervals for these outcomes (e.g. non-fatal PE; apixaban vs. warfarin [redacted]). Importantly, the VTE-related mortality outcome, which reflects PE (as DVT is not fatal, unless it leads to a PE), was not significantly different between apixaban and the other therapies. Heterogeneity within the network may also have contributed to this difference.

Sensitivity Analysis

The key results of the sensitivity analyses conducted on the prevention period NMA are summarised in Table 38.

Intention-to-treat analysis (ITT)

The results from the ITT analysis using all event data recorded over the entire study period were broadly similar to the base case analysis.(83) However, the primary efficacy outcome of recurrent VTE or VTE-related death was significantly lower for apixaban compared with LMWH/VKA in the current analysis (RR 0.49; 95% CrI 0.24, 0.95) (Table 38). This outcome differed from the base case analysis as the base case analysis utilised outcome data reported during the intended treatment period whereas the ITT analysis included data from both the treatment and the follow-up period. For example, for WODIT DVT, the intended follow-up period was at least 2 years.(77) Therefore in the sensitivity analysis, outcome data for VTE recurrence at 3 years were used compared with 9 months (on treatment in the base case analysis). There were no differences between the base case and ITT networks for any of the safety outcomes (all safety outcomes were based on the safety population); the safety outcomes are therefore only presented below for completion. The data used to inform the network and the corresponding results, including comparisons not involving apixaban, for the primary efficacy outcome in this sensitivity analysis are reported in Section 10.17.

ITT scenario (excluding WODIT DVT and WODIT PE trials)

Similar results to the base case analysis were observed from the ITT analysis where the WODIT DVT and WODIT PE trials were excluded. The results for the primary efficacy outcome in this analysis are reported in Table 38. The data used and the full results for the primary efficacy analysis are included in Section 10.18.

Sensitivity analysis excluding Dabigatran trials (RE-MEDY and RE-SONATE)

On the exclusion of RE-MEDY and RE-SONATE from the base case network, the impact of not including dabigatran as a comparator was explored. Results for the primary efficacy outcome and key safety outcomes (Major or CRNM bleeding, Major bleeding, CRNM bleeding) are reported in Table 38. Due to the availability of data, some outcomes, such as CRNM bleeding and Major or CRNM bleeding for apixaban vs. VKA, were not possible. The results were largely similar to the base case analysis; however, the reduction in major bleeding for apixaban vs. VKA did not reach statistical significance. The data used to inform the network and the corresponding results, including comparisons not involving apixaban, for the primary efficacy outcome and key safety outcomes in this sensitivity analysis are reported in Section 10.19.

Table 38: Sensitivity analysis for prevention period network (NMA 2) results – fixed-effect model (statistically significant results are shown in bold)

Outcome	Apixaban 2.5 mg bd vs. dabigatran 150 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. rivaroxaban 20 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. VKA (INR 2.0–3.0), RR (95% CrI)	Apixaban 2.5 mg bd vs. aspirin 100 mg od, RR (95% CrI)	Apixaban 2.5 mg bd vs. placebo, RR (95% CrI)
ITT main analysis					
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major or CRNM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT analysis (exclusion of WODIT DVT and WODIT PE studies)					
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major or CRNM*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclusion of RE-MEDY and RE-SONATE (Dabigatran studies)					
Recurrent VTE or VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major or CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bd: twice daily; CrI: Credible interval; od: once daily; RR: Relative risk; VKA, Venous thromboembolism; VTE: Venous thromboembolism
*Lack of outcome data for major or CRNM bleeding and CRNM bleeding to allow for any analyses to be carried out

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

6.7.6.1 NMA 1: Treatment Period – assessment of heterogeneity

The potential variability in the intervention effects of studies (heterogeneity) in NMA 1 were identified in line with the baseline characteristics of the included studies, these are discussed below.

Potential sources of heterogeneity
The baseline characteristics of the included studies were discussed at an advisory board (see Section 7.3.5) in order to ascertain whether there were imbalances in important effect modifiers that could potentially lead to biased indirect comparisons (Table 39).(9, 90) The main differences between the included studies are summarised below:

Study designs

- In terms of study design, the network included a mixture of open label (EINSTEIN DVT/PE pooled) and double blinded studies (AMPLIFY, RE-COVER and RE-COVER II). In general, double blind studies are less prone to bias compared with open-label studies because the knowledge of concealment of treatment and on the reporting of study outcomes is preserved. However, a double-blind design is not always feasible particularly, in anticoagulation trials.(91) This is because a double-dummy design is often required to ensure that double-blinding is conserved and therefore, a certain number of tablets and/or injections would need to be taken by the patient. For example, in warfarin-controlled trials of the NOACs, it is essential to blind patients and investigators to INR values thus sham INR values need to be obtained from patients via a complicated algorithm which makes the recruitment of patients as well as administering of treatment challenging, hence the alternative is the open-label design. However, it was the view of the clinical experts consulted that the difference in RCT trial design would not bias the treatment effects derived from the NMA.(9)

Unprovoked VTE

- Of the studies that reported the proportion of patients with unprovoked VTE, AMPLIFY reported 89.8% of patients as having an unprovoked VTE, whereas EINSTEIN pooled analysis reported 63.5% of patients. AMPLIFY purposefully studied a greater proportion of patients with a higher risk of recurrence in line with American College of Chest Physicians (ACCP) recommendations for the treatment of DVT and PE.(92) It was the view of the clinical experts consulted that a difference in the proportion of unprovoked patients between trials would not affect the comparability of the results and if there was a difference, it would favour the study with a lower risk population.(9)

Time on treatment

- The EINSTEIN DVT and EINSTEIN PE trials had treatment periods ranging from 3, 6 or 12 months whereas the remaining trials had fixed treatment duration of 6 months. The treatment duration of either 3, 6 or 12 months for patients in the EINSTEIN trials was determined by the treating physician before randomisation. This was used as a proxy measure because the intent for treatment was influenced by the initial assessment of the risk-benefit of anticoagulation for each patient. The data on the treatment effect used in the NMA for the EINSTEIN trials was based on the whole trial population rather the individual treatment subgroups. It was the view of the clinical experts consulted that on average the treatment effect would be equivalent to the other NOAC trials included in the NMA.(9)

Statistical assessment of heterogeneity

The Cochrane Handbook suggests that a useful statistic for quantifying heterogeneity is the I^2 statistic.(74) The network contained broadly similar trials with minimal variance in study design and baseline characteristics. However, the I^2 test for heterogeneity was not feasible to conduct due to the limited number of trials in the treatment period network. It is important to note that investigations of heterogeneity may be of questionable value when there are few studies in the network.(74)

Table 39: Patient characteristics for included studies in the treatment period network (NMA 1)

Trial	Treatment	Mean age (SD)	Female, %	Unprovoked VTE, %	Unprovoked VTE (trial level), %	Patients with active cancer, %	Index DVT, %	Index PE, %	Index DVT/PE, %	Time on treatment
AMPLIFY (14, 61) Double-blind RCT	Apixaban 10 mg bd/ 5 mg bd[†] (n=2,691)	57.2 (16.0)	41.7	89.8	89.8	2.5	65.0	25.2	9.4	6 months
	Enoxaparin/ warfarin INR 2.0-3.0[‡] (n=2,704)	56.7 (16.0)	40.9	89.8		2.9	65.9	25.2	8.3	
RE-COVER (72) Double-blind RCT	UFH or LMWH/dabigatran 150 mg bd[§] (n=1,274)	55.0 (15.8)	42.0	NR	NR	5.0	69.1	21.2	9.5	6 months
	UFH or LMWH/warfarin INR 2.0-3.0[¶] (n=1,265)	54.4 (16.2)	41.1	NR		4.5	68.6	21.4	9.8	
RE-COVER II (70) Double-blind RCT	UFH or LMWH/dabigatran 150 mg bd[§§] (n=1,279)	54.7 (16.2)	39.0	NR	NR	3.9	68.5	23.3	8.1	6 months
	UFH or LMWH/warfarin INR 2.0-3.0[¶¶] (n=1,289)	55.1 (16.3)	39.8	NR		3.9	67.8	23.1	9.1	

Trial	Treatment	Mean age (SD)	Female, %	Unprovoked VTE, %	Unprovoked VTE (trial level), %	Patients with active cancer, %	Index DVT, %	Index PE, %	Index DVT/PE, %	Time on treatment
EINSTEIN DVT/ EINSTEIN PE pooled analysis (50) Open-label RCTs	Rivaroxaban 15 mg bd/ 20 mg od[††] (n=4,151)	57.0 (17.0)	44.5	63.1	63.5	5.6	NR (41.7[¶¶¶])	NR (58.3[¶¶¶])	NR	3, 6 or 12 months[†††]
	Enoxaparin/VKA INR 2.0-3.0[‡‡] (n=4,131)	57.0 (16.8)	46.4	63.8		4.8	NR (41.6[¶¶¶])	NR (58.4[¶¶¶])	NR	

bd, twice daily; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; NR, not reported; od, once daily; PE, pulmonary embolism; RCT, randomised controlled trial; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism

[†]Patients received 10 mg apixaban twice daily for the first 7 days, followed by 5 mg twice daily for 6 months.

[‡]Patients received enoxaparin 1mg/kg every 12 hours for ≥5 days and warfarin (adjusted to INR 2.0–3.0) begun concomitantly and continued for 6 months. Enoxaparin was discontinued when the INR was 2.0–3.0.

*Data are from the cancer case report forms as per the CSR (61)

[§]Patients received initial treatment with an approved parenteral anticoagulant (UFH, 11.3%; LMWH, 89.4%; fondaparinux, 3.9%) for a median of 6 days (interquartile range [IQR] 5–8) [continued for ≥5 days and until INR was 2.0–3.0] (single dummy phase). Patients then received dabigatran 150 mg twice daily for 6 months.

[¶]Patients received initial treatment with an approved parenteral anticoagulant (UFH, 13.0%; LMWH, 90.7%; fondaparinux, 2.8%) for a median of 6 days (IQR 5-8) [continued for ≥5 days and until INR was 2.0–3.0] (single dummy phase). Patients also received warfarin on the day of randomisation (adjusted to INR 2.0–3.0) for 6 months (double dummy phase).

[††]Patients received rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily.

[‡‡]Patients received enoxaparin 1mg/kg twice daily for ≥5 days and either warfarin or acenocoumarol (adjusted to INR 2.0–3.0), started ≤48 hours post randomisation. Enoxaparin was discontinued when the INR was ≥2.0 for ≥2 consecutive days.

[§§]Patients received initial treatment with an approved parenteral anticoagulant (UFH, 15.5%; LMWH, 88.5%; fondaparinux, 2.5%) for a mean of 6.8 days (SD 3.4) [continued for ≥5 days and until INR was 2.0–3.0] (single dummy phase). Patients then received dabigatran 150 mg twice daily for 6 months (double dummy phase).

[¶¶]Patients received initial treatment with an approved parenteral anticoagulant (UFH, 16.1%; LMWH, 89.1%; fondaparinux, 1.6%) for a median of 7.1 days (SD 3.7) [continued for ≥5 days and until INR was 2.0–3.0] (single dummy phase). Patients also received warfarin on the day of randomisation (adjusted to INR 2.0–3.0) for 6 months (double dummy phase).

[†††]The intended treatment duration (3, 6, or 12 months) was determined by the treating physician before randomisation.

[¶¶¶]Within the pooled analysis, 1,731/4,151 (41.7%) patients were from the EINSTEIN-DVT study and received rivaroxaban and 1,718/4,131 (41.6%) patients received enoxaparin/VKA.

6.7.6.2 NMA 2: Prevention Period – assessment of heterogeneity

An overview of the baseline characteristics of the included trials is presented in Table 41. The baseline characteristics were discussed with clinical experts during a recent advisory consultation in order to ascertain whether there were imbalances in important effect modifiers that could lead to biased indirect comparisons.(9) There was a consensus that there were imbalances in these effect modifiers that could have an impact on the NMA results. However, the experts felt that it was still important to conduct the NMA to inform decision making. Overall, the differences between-study variables may result in issues in the reliability of results with respect to the NMA.(74) The impact of these differences have been explored through sensitivity analyses where possible.

The potential sources of heterogeneity in NMA 2 and statistical assessment of these are discussed below.

Potential sources of heterogeneity
In contrast to NMA 1, additional potential sources of conceptual heterogeneity between the included studies were identified. These included the initial treatment duration, study treatment duration, and the proportion of enrolled patients with active cancer. The main differences between the included studies are summarised below:

- **Study designs**
  In terms of study design, the network included a mixture of open label and double-blind studies (Table 41). A summary of the discussion of the trial designs is presented in Section 6.7.6.1.

- **Patient populations**
  Of the studies that reported the proportion of patients with unprovoked VTE; AMPLIFY-EXT, WARFASA, LAFIT, ASPIRE, WODIT DVT, ELATE and PREVENT reported >90% of patients with unprovoked VTE (Table 41). EINSTEIN-EXT reported 73.7% of patients with unprovoked VTE. However, two studies (RE-SONATE and RE-MEDY) included in the network did not report on this parameter. Patients with an unprovoked VTE may have a higher risk of recurrence (9) which may result in variation in the baseline risk of VTE events between trials. It was the view of the clinical experts consulted that a difference in the proportion of unprovoked patients between trials would not affect the comparability of the results and if there was a difference, it would favour the study with a lower risk population (e.g. provoked patients).(9)

- **Patients with cancer**
  Of the included studies, only 3 trials reported on the proportion of patients with active cancer at baseline. AMPLIFY-EXT (1.1–2.2%) and ASPIRE (2%) reported a lower proportion of patients with active cancer compared with EINSTEIN-EXT (4.4–4.7%) and RE-MEDY (4.1–4.2%). Patients with active cancer are at an increased risk of developing VTE, particularly while receiving systemic chemotherapy.(93) All studies reported a small proportion of patients with active cancer and therefore, no major impact on the NMA results are expected.(9)

- **Clinical judgment regarding the need for continuation of therapy**
  Differences across trials with respect to the clinical judgment regarding the need for continuation of therapy may have resulted in some heterogeneity of patient risk characteristics across the trials in the NMA.(9) Not all trial publications directly discussed the clinical judgment regarding the need for continuation in the design of the trial. The Inclusion/exclusion criteria with respect to a need for continuation of treatment of the trials is reported in Appendix 7.

- **Prior treatment duration**
  Three months is the minimum time required to complete 'initial treatment' of VTE, with the decision to treat for longer periods/indefinitely influenced by the long-term risk of recurrence and the risk of bleeding.(94) Prior treatment duration of studies included in the NMA varied from a minimum of 3 months in the LAFIT, ELATE, WODIT DVT, WODIT PE, RE-MEDY and PREVENT trials, up to 6–18 months in the AMPLIFY- EXT, EINSTEIN-EXT, WARFASA and RE-SONATE trials and 24 months in the ASPIRE trial. The ASPIRE trial included 1% patients of patients receiving initial anticoagulation for ≤3 months in each arm however, the overall average duration of initial therapy was ≥6 months. This may suggest a potential variation in the baseline risk of VTE across trials attributable to differences in the timeframe since patients experienced an initial VTE event.

- **Study follow up**
  The study follow up is discussed with respect to time on treatment and follow up duration as presented below.

  <u>Time on treatment</u>
  Differences were also noted in the prevention period between the trials particularly, time on treatment ranged from 6 months (RE-SONATE) to 37.2 months (ASPIRE). This suggests a potential variation in the absolute risk of VTE recurrence across trials. However, despite this difference, the experts consulted suggested the focus should not unduly be on aligning different treatment and follow up durations as this would not significantly impact the relative treatment effect.(9)

  <u>Follow up duration</u>
  Data used in the meta-analyses for NMA2 included all events that occurred after randomisation and while patients were followed or under observation during the planned intervention period (as per study protocol) with the exception of the ASPIRE (55) and ELATE (76) RCTs. In the ASPIRE trial, patients were randomised to treatments for up to 4 years duration and therefore, data for events occurring after a median of 37.2 months were used in the analyses. In the ELATE trial, patients were randomised to treatments and followed over time (i.e. the investigators did not define a time point to stop the interventions) so the data available for the latest follow up period were used in the analyses. The data used in the analyses were collected from follow up durations ranging from 10 months to 37.2 months.

- **Definitions of outcomes**
  There may be important differences between definitions used for a particular outcome or the frequency of or the test used for outcome assessment. However, a robust comparison between studies was limited by the degree of reporting in the publications. Therefore, all analyses conducted are discussed in line with the pre-specified definitions of outcomes in the respective trials.

Statistical assessment of heterogeneity

The Cochrane Handbook (74) suggests that a useful statistic for quantifying heterogeneity is the I^2 statistic. Heterogeneity is dependent on more than one factor, and Cochrane suggests that specifying thresholds for the I^2 statistic can be misleading. However, Cochrane does suggest a rough guide that could be used for the interpretation of the I^2 statistics as follows:

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

*The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. p value from the chi-squared test, or a confidence interval for I^2).

An assessment of heterogeneity was possible for the following outcomes only (direct treatment comparisons with ≥ 2 studies):

- Recurrent VTE and VTE-related death [aspirin vs. placebo; warfarin INR 2.0–3.0 vs. placebo]
- Major or CRNM bleed [aspirin vs. placebo]
- Major bleed [aspirin vs. placebo; warfarin INR 2.0–3.0 vs. placebo]
- CRNM bleed [aspirin vs. placebo]
- Treatment discontinuations [aspirin vs. placebo]

Although data for two studies (LAFIT and WODIT-DVT) were included in the treatment comparison of warfarin INR 2.0–3.0 vs. placebo for the outcome of VTE-related death, zero events were reported in both arms of the WODIT-DVT study and therefore an assessment of heterogeneity was not feasible.(80, 81) As indicated in Table 40, there was little heterogeneity in the treatment comparisons examined. The forest plots for each analysis are presented by outcome in Figure 12 to Figure 16. Despite conceptual heterogeneity identified above, this did not translate in to observable statistical heterogeneity

Table 40: Summary of heterogeneity across studies included in the extended treatment network

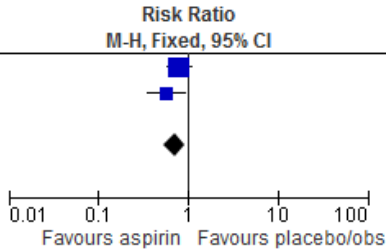
Outcome	No. of studies (citation)	I^2%	Forest Plot	Summary
Recurrent VTE and VTE-related death				
Aspirin vs. placebo/observation	2 (54, 55)	17%	Figure 12	Heterogeneity might not be important
Warfarin INR 2.0–3.0 vs. placebo/observation	2 (80, 81)	0%	Figure 12	Heterogeneity might not be important
Major or CRNM bleed				
Aspirin vs. placebo/observation	2 (54, 55)	0%	Figure 13	Heterogeneity might not be important
Major bleed				
Warfarin INR 2.0–3.0 vs. placebo/observation	3 (80-82)	0%	Figure 14	Heterogeneity might not be important
Aspirin vs. placebo/observation	2 (54, 55)	0%	Figure 14	Heterogeneity might not be important
CRNM bleed				
Aspirin vs. placebo/observation	2 (54, 55)	0%	Figure 15	Heterogeneity might not be important
Overall treatment discontinuation				
Aspirin vs. placebo/observation	2 (54, 55)	0%	Figure 16	Heterogeneity might not be important

CRNM: Clinically relevant non-major; VTE: Venous thromboembolism; INR: International normalised ratio

Figure 12: Forest plots – Recurrent VTE and VTE-related death

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo or observation Events	Placebo or observation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPIRE	57	411	73	411	64.7%	0.78 [0.57, 1.07]
WARFASA	23	205	39	197	35.3%	0.57 [0.35, 0.91]
Total (95% CI)		**616**		**608**	**100.0%**	**0.71 [0.54, 0.92]**
Total events	80		112			

Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² = 17%
Test for overall effect: Z = 2.59 (P = 0.010)



Study or Subgroup	Warfarin Events	Warfarin Total	Placebo or observation Events	Placebo or observation Total	Weight	Risk Ratio IV, Fixed, 95% CI
LAFIT	1	79	17	83	51.0%	0.06 [0.01, 0.45]
WODIT DVT	1	134	11	133	49.0%	0.09 [0.01, 0.69]
Total (95% CI)		**213**		**216**	**100.0%**	**0.07 [0.02, 0.31]**
Total events	2		28			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.58 (P = 0.0003)

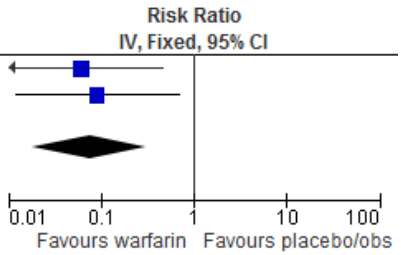
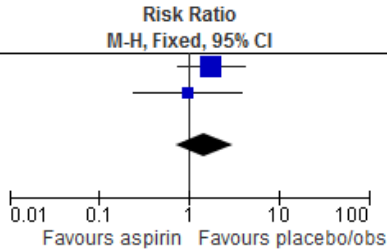


Figure 13: Forest plot – Major or CRNM bleed

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo or observation Events	Placebo or observation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPIRE	14	411	8	411	66.2%	1.75 [0.74, 4.13]
WARFASA	4	205	4	197	33.8%	0.96 [0.24, 3.79]
Total (95% CI)		**616**		**608**	**100.0%**	**1.48 [0.72, 3.05]**
Total events	18		12			

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)

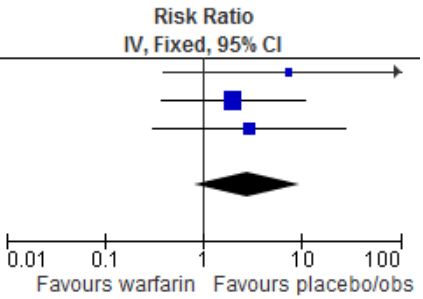


CRNM, clinically relevant non-major

Figure 14: Forest plots – Major bleed

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
LAFIT	3	79	0	83	17.3%	7.35 [0.39, 140.05]
WODIT DVT	4	134	2	133	53.2%	1.99 [0.37, 10.65]
WODIT PE	3	165	1	161	29.6%	2.93 [0.31, 27.85]
Total (95% CI)		**378**		**377**	**100.0%**	**2.79 [0.82, 9.50]**
Total events	10		3			

Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)



Study or Subgroup	Aspirin Events	Aspirin Total	Placebo or observation Events	Placebo or observation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ASPIRE	8	411	6	411	85.5%	1.33 [0.47, 3.81]
WARFASA	1	205	1	197	14.5%	0.96 [0.06, 15.26]
Total (95% CI)		**616**		**608**	**100.0%**	**1.28 [0.48, 3.41]**
Total events	9		7			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)

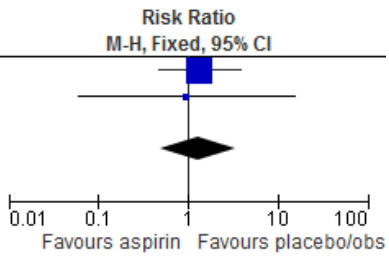
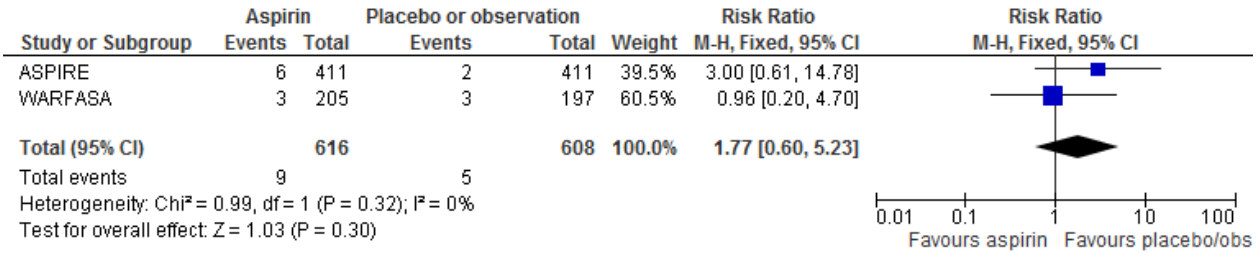
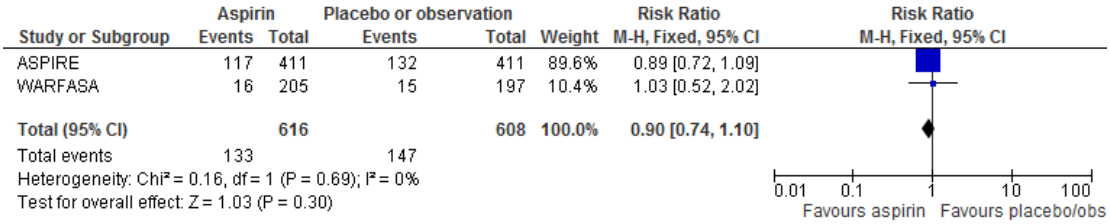


Figure 15: Forest plot – CRNM bleed



CRNM, clinically relevant non-major

Figure 16: Forest plot – Overall treatment discontinuation



The implications of between-study variability were explored through sensitivity analyses for a range of outcomes, where possible. The analyses demonstrated that the base case conclusions were broadly consistent regardless of changes to the network [excluding and/or including trials where applicable].

Although the scope of a systematic review should limit heterogeneity, there is always the potential for treatment effect modifiers to be present in trials however, these may be unrecognised.(95) Additionally, the Centre for Reviews and Dissemination (CRD) at the University of York conducted a review of the Castellucci network which was the same as our base case for the prevention period NMA.(96) The review concluded that although the reliability of the findings were moderate to low due to uncertainties inherent in the evidence base, the comparative effectiveness of apixaban compared to placebo or LMWH/VKA was likely to be reliable.(96)

Table 41: Baseline patient characteristics for included studies in the prevention period network (NMA 2)

Trial	Treatment (no. randomised)	Mean age (SD)	Female, %	Unprovoked VTE by trial %	Patients with active cancer, %	Index DVT, %	Index PE, %	Index DVT/PE, %	Prior treatment duration	Time on treatment
AMPLIFY-EXT (16) Double blind, superiority RCT Multinational[§]	Apixaban 2.5 mg bd (n=840)	56.6 (15.3)	42.0	91.7[†]	1.8	64.8	35.2	-	6-12 months[‡]	12 months
	Apixaban 5 mg bd (n=813)	56.4 (15.6)	42.3		1.1	64.8	35.2	-		
	Placebo (n=829)	57.1 (15.2)	43.5		2.2	66.5	33.5	-		
EINSTEIN-EXT (78) Open label, non-inferiority RCT Multinational[‡‡]	Rivaroxaban 20 mg od (n=602)	58.2 (15.6)	41.2	73.7[¶]	4.7	64.1	35.9	-	6-12 months	8.7 months[††]
	Placebo (n=595)	58.4 (16.0)	42.9		4.4	60.0	40.0	-		
WARFASA (54) Double blind RCT Austria, Italy	Aspirin 100 mg od (n=205)	61.9 (15.3)	34.2	100	NR	59.5	40.5	-	6-18 months	24.0 months[§§]
	Placebo (n=198)	62.1 (15.1)	38.1		NR	65.9	34.1	-		23.5 months[§§]
RE-SONATE (79) Double blind RCT Multinational[¶¶]	Dabigatran 150 mg bd (n=681)	56.1 (15.5)	44.1	NR	0*	63.3	26.9	6.9	6-18 months	6 months[§§§]
	Placebo (n=662)	55.5 (15.1)	45.0		0*	66.6	26.9	5.3		

RE-MEDY (79) Double blind RCT Multinational[†††]	Dabigatran 150 mg bd (n=1,430)	55.4 (15.0)	39.1	NR	4.2	65.6	22.7	11.7	3-12 months	18 months[‡‡‡]
	Warfarin INR 2.0-3.0 (n=1,426)	53.9 (15.3)	38.9		4.1	64.7	23.5	11.8		
ASPIRE (55) Double blind RCT Multinational[¶¶¶]	Aspirin 100 mg od (n=411)	55 (16.0)	45.0	95[††††]	2	57.4	27.3	14.4	<3 months, 1.1%; 3 to <6 months, 26.2%; 6 to <12 months, 63.8%; ≥12 months, 9.0%	37.2 months[§§]
	Placebo (n=411)	54 (15.8)	46.2			56.5	29.0	13.6		
LAFIT (80) Double blind RCT Canada, USA	Warfarin INR 2.0-3.0 (n=79)	59 (16)	31.6	100[‡‡‡‡]	0[§§§§]	75.9	24.1	-	3 months	10 months[¶¶¶¶]
	Placebo (n=83)	58 (16)	47.0			73.5	26.5	-		
ELATE (76) Double blind RCT Canada, USA	Warfarin INR 1.5-1.9 (n=369)	57 (16)	42.5	100	NR[†††††]	68.3	31.7	-	≥3 months	2.2 years[‡‡‡‡‡]
	Warfarin INR 2.0-3.0 (n=369)	57 (16)	47.4			61.5	38.5	-		

WODIT DVT (81) Open-label RCT Italy	VKA continuation §§§§§ (n=134)	66.8 (6.7)	45.5	100††††††	NR¶¶¶¶¶	100††††††	0	-	3 months	37 months‡‡‡‡ ‡‡
	VKA discontinuation /observation§§§§§ (n=133)	67.7 (7.3)	38.8				0	-		
WODIT PE (82) Open-label RCT Italy	VKA/ continuation*** (n=165)	62.9 (16.3)	60.6	55.9	NR¶¶¶¶¶	0	44.8**	55.2	3 months	33.8 months
	VKA discontinuation/ observation (n=161)	61.0 (15.5)	58.4	56.5		0	44.7**	55.3		
PREVENT (75) Double blind RCT Canada, USA, Switzerland	Warfarin INR 1.5-1.9 (n=255)	53 (NR)	47.1	100	NR§§§§§§	NR	NR	NR	6.5 months§§	2.1 years¶¶¶¶¶¶
	Placebo (n=253)	53 (NR)	47.4			NR	NR	NR		

bd, twice daily; INR, international normalised ratio; od, once daily; NR, not reported in the publication; VKA, vitamin K antagonist; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; od, once daily; RCT, randomised controlled trial; SD, standard deviation

†Apixaban 2.5 mg, 93.2%; 5 mg, 90.7%; placebo, 91.1%

‡Patients were eligible for inclusion if they had been treated for 6 to 12 months with standard anticoagulant therapy [12/2482 (0.5%) patients were treated <6 months and 34/2482 (1.4%) patients >12 months prior to randomisation].

§Argentina, Australia, Austria, Brazil, Canada, Czech Republic, Denmark, France, Germany, India, Israel, Italy, Norway, Poland, Portugal, Russia, Spain, UK, Ukraine, USA

¶Rivaroxaban, 73.1%; placebo, 74.2%

††Duration of treatment: (i) rivaroxaban-treated patients randomised to 6 month intended treatment, 181 days (IQR 177-183) [converted to 6.0 months]; (ii) rivaroxaban-treated patients randomised to 12 month intended treatment, 264 days (IQR 166-354) [converted to 8.7 months]; (iii) placebo-treated patients randomised to 12 month intended treatment, 265 days (IQR 166-354) [converted to 8.7 months].

‡‡Australia (n=129), Austria (n=57), Belgium (n=24), Brazil (n=14); China (n=31); Czech republic (n=62); Denmark (n=12); France (n=135); Germany (n=35); Hungary (n=56); India (n=19); Indonesia (n=2); Israel (n=46); Italy (n=76); Malaysia (n=5); Netherlands (n=96); Norway (n=17); Philippines (n=6); Poland (n=43); Singapore (n=19); South Africa (n=42); Spain (n=44); Sweden (n=123); Switzerland (n=5); Thailand (n=9); UK (n=7); USA (n=29).

§§Median duration

¶¶Australia, Austria, Belgium, Canada, Czech Republic, Estonia, Germany, Italy, Korea, Lithuania, Latvia, Netherlands, New Zealand, Poland, Russia, Singapore, Sweden, Switzerland, South Africa, Thailand, USA.
†††Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Great Britain, Greece, Hungary India, Israel, Italy, Mexico, Netherlands, New Zealand, Poland, Portugal, Russia, Slovakia, South Africa, Spain, Sweden, Turkey, Ukraine, USA.
‡‡‡RE-MEDY was initially designed for 18 months of treatment. However, because of a lower than projected event rate, the protocol was amended to increase the sample size and extend the planned treatment period for patients already enrolled who consented to the extension, with the resulting planned study treatment ranging from 6 to 36 months.
§§§Patients were assessed at 15 and 30 days after randomisation, then monthly until day 180.
¶¶¶Australia, New Zealand, Singapore, India, Argentina
††††5% of patients had a prior provoked VTE, although inclusion criteria states enrolled patients “had had a first-ever unprovoked VTE”.
‡‡‡‡Eligible patients were restricted to those with a first episode of idiopathic VTE, defined as objectively confirmed, symptomatic DVT or PE that occurred in the absence of a major thrombogenic risk factor.
§§§§Presence of cancer in the previous five years was an exclusion criterion. In addition p.903 of the publication states that 9 of the enrolled patients were excluded prior to randomisation due to evidence of cancer since diagnosis suggesting that none of the randomised patients had a cancer diagnosis.
¶¶¶¶Mean duration of follow-up was 12 months for patients assigned to warfarin and 9 months for those assigned to placebo.
†††††Patients who had active cancer within the last 2 years were excluded as this was considered to be a major risk factor for thrombosis.
‡‡‡‡‡Mean duration of follow-up. The mean period during which patients received double-blind treatment was 2.1 years in the low-intensity-therapy group and 2.2 years in the conventional-intensity-therapy group.
§§§§§Patients had received three months of therapy with warfarin (97% of patients) or acenocoumarol prior to randomisation to continued treatment or discontinuation of treatment.
¶¶¶¶¶Although patients with known permanent or temporary risk factors were excluded from the study; systematic screening for thrombophilia and cancer was not performed.
††††††Patients with a first episode of symptomatic idiopathic proximal DVT were eligible for inclusion.
‡‡‡‡‡‡Publication reports mean follow-up: (i) patients randomised to continue therapy, 37.8 months; (ii) patients randomised to discontinue therapy, 37.2 months. Publication also reports an ITT analysis reporting the risk of recurrence during the first nine months of follow-up.
§§§§§§Patients were ineligible if they had a history of metastatic cancer.
¶¶¶¶¶¶Mean duration of follow-up. Maximum duration of treatment was 4.3 years.
*Active cancer was an exclusion criterion. However, a single patient in the dabigatran arm and two patients in the placebo arm had active cancer and represented protocol violations.
**Patients with a first episode of symptomatic, objectively confirmed PE were included in the study. This value is calculated using the percentage of patients with concomitant DVT which is reported in the publication.
***Patients were randomised to continue treatment for 3 additional months (PE associated with transient risk factors, n=75) or an additional 9 months (idiopathic PE, n=90). The dose of warfarin or acenocumarol was adjusted to INR 2.0–3.0.

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

Results of sensitivity analyses exploring the impact of excluding WODIT PE/DVT trials and RE-SONATE/RE-MEDY trials are presented in Section 6.7.5.2 for the prevention period network (NMA 2).

Exclusion of WODIT DVT/PE trials were investigated as these trials had a significantly longer follow-up period (where patients were off treatment) than other trials, in which period the majority of recurrent VTE or VTE-related death events occurred.

Exclusion of the dabigatran trials (RE-SONATE and RE-MEDY) was explored as dabigatran is not included as a comparator within the NICE final scope (Section 6.7.5.2).

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

Bucher tests for inconsistency were performed for each loop of the evidence network.(84) There was no statistical evidence of inconsistency identified in this analysis (Figure 17 and Figure 18).

In addition to the statistical test for inconsistency, an informal assessment of inconsistency was made by comparing the point estimates of both direct and indirect evidence informing the same comparison. This confirmed that the evidence within the loops was also consistent (Figure 17 and Figure 18).

Figure 17: Consistency within a closed loop – Recurrent VTE or VTE-related death (Warfarin INR 2.0–3.0, dabigatran and placebo/observation of VKA)

[redacted]

INR: International normalised ratio; VKA: Vitamin K antagonist; BD: Twice daily; OR: Odds ratio

Figure 18: Consistency within a closed loop – Recurrent VTE or VTE-related death (Warfarin INR 2.0–3.0, warfarin INR 1.5-1.9 and placebo)

[redacted]

INR: International normalised ratio; VKA: Vitamin K antagonist; BD: Twice daily; OR: Odds ratio

6.8 Non-RCT evidence

6.8.1 *If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results*

No non-RCT evidence was identified for apixaban in the indication under review.

6.9 Adverse events

6.9.1 ***If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event).***

The search strategies as described previously in Section 6.1 were used to identify trials assessing adverse events. There were no additional trials identified.

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

AMPLIFY

Summary

- Apixaban was statistically superior to enoxaparin/warfarin with respect to the primary safety outcome of adjudicated major bleeding.
  - Major bleeding occurred in 15 patients in the apixaban group (0.6%), compared with 49 patients in the enoxaparin/warfarin group (1.8%) (RR 0.31; 95% CI 0.17, 0.55; p<0.001, for superiority).
- Apixaban had an improved bleeding risk profile compared to enoxaparin/warfarin and this was consistent across all bleeding related outcomes.
  - Composite of major or CRNM bleeding (RR 0.44; 95% CI 0.36, 0.55; p<0.001)
  - CRNM bleeding (RR 0.48; 95% CI 0.38, 0.60; [redacted])
  - Gastrointestinal major bleeds (7 [0.3%] of apixaban patients vs. 18 [0.7%] of enoxaparin/warfarin patients)
- The incidence of adverse events (AEs), serious adverse events (SAEs) and discontinuations due to AEs for apixaban were similar to that of enoxaparin/warfarin.
- The overall safety profile of apixaban during treatment was consistent for patients stratified by their index event (DVT or PE).

6.9.2.1 Data sets analysed

Safety endpoints and adverse events are reported for the treated population for apixaban (n=2676) and enoxaparin/warfarin (n=2689).

6.9.2.2 Primary Safety Outcome

Apixaban was superior to enoxaparin/warfarin for the primary safety outcome of adjudicated major bleeding during the treatment period (Table 42). Major bleeding occurred in 15 (0.6%) patients in the apixaban group, as compared with 49 (1.8%) patients in the enoxaparin/warfarin group (RR 0.31; 95% CI 0.17, 0.55; p<0.001).(14, 61) A numerically higher incidence of fatal and non-fatal major bleeding at critical sites were also observed in the enoxaparin/warfarin treatment arm (Table 43).

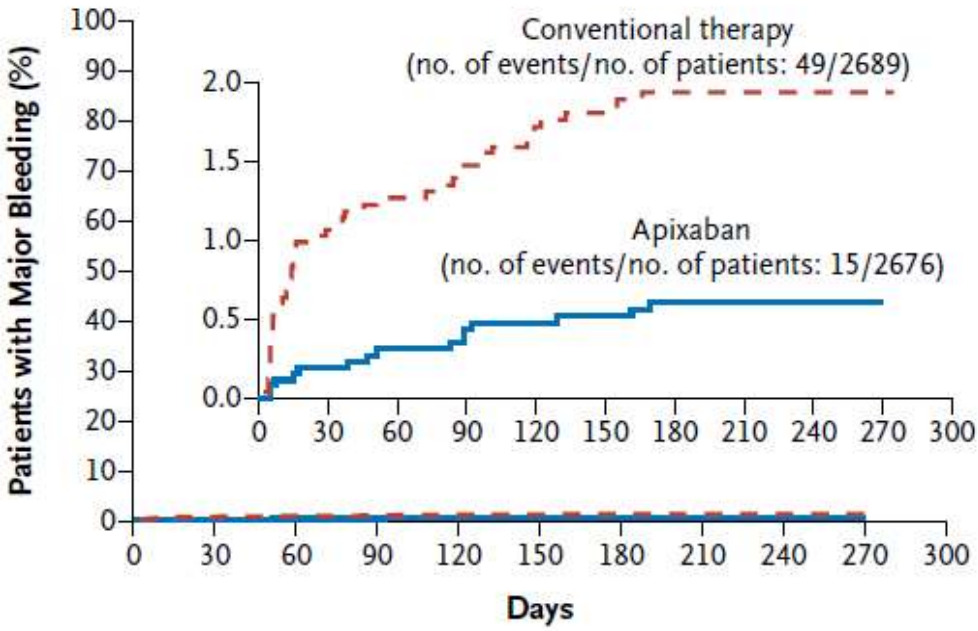
Table 42: Summary of primary safety outcome (AMPLIFY, treated patients) (14)

	Apixaban N=2676	**Enoxaparin/ warfarin N=2689**	**Relative risk (95% CI)**	**p-value (for superiority)**
Primary safety outcome, n (%) – safety population (treated patients)				
Major bleeding	15 (0.6)	49 (1.8)	0.31 (0.17-0.55)	<0.001

CI: Confidence interval
All safety analyses included data obtained from patients during study treatment, defined as the time from the administration of the first dose until 48 hours after the last dose was administered.
The definition of major bleeding was adapted from the International Society on Thrombosis and Haemostasis (ISTH) definition (66)

The cumulative event rate for the primary safety outcome is presented in Figure 19.

Figure 19: Kaplan–Meier cumulative event rates for the first episode of major bleeding (AMPLIFY, treated patients) (14)



No. at Risk											
Apixaban	2676	2519	2460	2409	2373	2339	61	4	1	0	0
Conventional therapy	2689	2488	2426	2383	2339	2310	43	3	1	1	0

Conventional therapy refers to enoxaparin/warfarin. The inset shows the same data on an enlarged y-axis

6.9.2.3 Location of Adjudicated Major Bleeding

The frequencies of adjudicated major bleeding into critical sites for all anatomical locations were numerically lower in the apixaban group compared with the enoxaparin/warfarin group. Of particular note is the lower number of major gastrointestinal bleeds experienced by patients on apixaban (n=7, 0.3%) compared with those on enoxaparin/warfarin (n=18, 0.7%) (Table 43).(60)

Table 43: Summary of major bleeding characteristics (AMPLIFY, treated subjects) (14)

	Apixaban N=2676	Enoxaparin/warfarin N=2689
Bleeding characteristics, n (%)		
Major Bleeding	15 (0.6)	49 (1.8)
Fatal bleeding (by primary site of bleeding)	1 (<0.1)	2 (0.1)
Non-fatal major bleeding at critical site		
Intracranial	3 (0.1)	6 (0.2)
Retroperitoneal	1 (<0.1)	3 (0.1)
Intraocular	0	2 (0.1)
Intra-articular	0	2 (0.1)
Intrathoracic	0	1 (<0.1)
Other non-fatal major bleeding		
Gastrointestinal	7 (0.3)	18 (0.7)
Intramuscular bleeding	0	5 (0.2)
Epistaxis	1 (<0.1)	1 (<0.1)
Urogenital bleeding	1 (<0.1)	3 (0.1)
Subcutaneous haematoma	1 (<0.1)	6 (0.2)

6.9.2.4 Secondary Safety Outcomes

In AMPLIFY, apixaban was associated with a statistically significant reduction in the rate of bleeding across all components of bleeding; major/CRNM bleeding, CRNM bleeding, minor bleeding, and total bleeding compared with enoxaparin/warfarin ([redacted]) (Table 44). The adjudicated composite of major/CRNM bleeding was observed in 115 patients (4.3%) in the apixaban group compared with 261 patients (9.7%) in the enoxaparin/warfarin group (RR 0.44; 95% CI 0.36, 0.55; p<0.001). A summary of the event rates for the secondary safety outcomes are presented in [redacted].

Table 44: Summary of secondary safety outcomes (AMPLIFY, safety population) (14, 61)

	Apixaban N=2676	Enoxaparin/ warfarin N=2689	Relative risk (95% CI)	p-value
Secondary safety outcomes, n (%) – safety population (treated patients)				
Major/CRNM bleeding	115 (4.3)	261 (9.7)	0.44 (0.36, 0.55)	<0.001
CRNM bleeding	103 (3.8)	215 (8.0)	0.48 (0.38, 0.60)	[redacted]
Minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Total bleeding	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence interval; CRNM: Clinically relevant non major

Figure 20: Summary of event rates for the secondary safety outcomes (AMPLIFY, safety population: Apixaban N=2676; Enoxaparin/warfarin N=2689) (61)

[redacted]

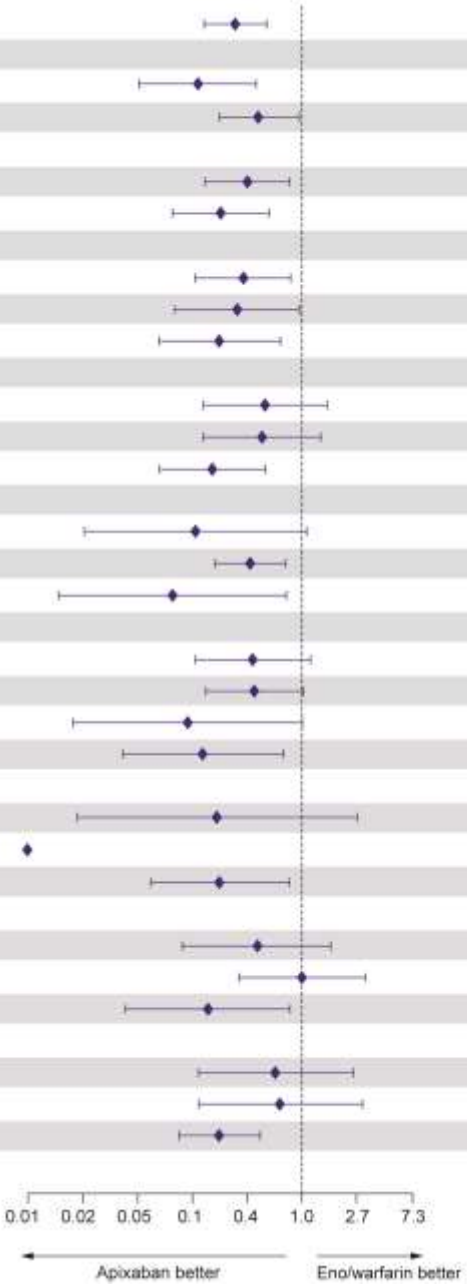
CI: Confidence interval; CRNMB: Clinically relevant non-major bleeding; MB: Major bleeding

6.9.2.5 Subgroup Analysis

Analyses for the primary safety outcome were performed for a large number of subgroups, both pre-specified and post-hoc (Figure 21). Treatment by subgroup interactions with a p-value <0.10 were investigated further; however, no clinically important observations were noted. Tabulated results for the primary safety outcome for all pre-specified subgroups are presented in the Appendices, Section 10.26.

Figure 21: Relative risk of the primary safety outcome (adjudicated major bleeding) according to pre-specified subgroups (AMPLIFY, safety population) (60)

Subgroup	Apixaban no. of events	Apixaban no. of patients	Eno/warfarin no. of events	Eno/warfarin no. of patients	P Value for Interaction
Overall	15	2676	49	2689	
Index event					0.0869
PE (with or without DVT)	4	928	25	902	
DVT only	11	1738	24	1773	
Sex					0.4168
Male	9	1561	24	1591	
Female	6	1115	25	1098	
Age					0.8174
<65 years	7	1725	20	1753	
65 to <75 years	4	553	13	566	
≥75 years	4	398	16	370	
Level of renal impairment					0.3606
Severe or moderate	5	175	9	163	
Mild	5	549	10	544	
Normal renal function	5	1720	25	1756	
Weight					0.3210
≤60 kg	1	230	7	243	
>60 kg to <100 kg	13	1920	32	1924	
≥100 kg	1	521	10	518	
BMI					0.4773
≤25 kg/m²	5	725	12	711	
>25 to 30 kg/m²	7	999	17	1029	
>30 to 35 kg/m²	1	575	8	587	
>35 kg/m²	2	362	12	343	
Anatomical extent of index PE					NE
Limited	1	79	4	88	
Intermediate	0	391	7	394	
Extensive	3	356	12	325	
Anatomical extent of index DVT					0.1937
Popliteal vein	3	423	7	440	
Femoral vein	6	569	6	580	
Iliac or common femoral	2	746	11	750	
Use of LMWH/UFH					0.2432
No LMWH/UFH use	3	353	5	379	
>0 to 12 hours	3	370	4	340	
>12 hours	9	1949	40	1966	



BMI: Body mass index; CI: Confidence interval; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; UFH: Unfractionated heparin; NE, Not evaluable

6.9.2.6 Primary Safety Outcome by Index Event Type

The primary safety outcome of adjudicated major bleeding during the treatment period was consistent across DVT and PE (with or without DVT) index event subgroups (Table 45). Among patients who had DVT at enrolment, major bleeding occurred in 11 of 1738 patients (0.6%) in the apixaban group and in 24 of 1773 (1.4%) in the enoxaparin/warfarin group.(14) Similarly, among patients who had PE(with or without DVT) at enrolment, major bleeding occurred in 4 of 928 patients (0.4%) in the apixaban group and in 25 of 902 patients (2.8%) in the enoxaparin/warfarin group.(14)

Table 45: Summary of the primary safety outcome for DVT/PE subgroups indexed by event type (AMPLIFY, safety population) (14, 61)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)
Primary safety outcome: Major bleeding, n/N (%) – treated patients			
PE (with or without DVT) subgroup	4/928 (0.4)	25/902 (2.8)	[redacted]
DVT subgroup	11/1738 (0.6)	24/1773 (1.4)	[redacted]

CI: Confidence interval; DVT: Deep vein thrombosis; PE: Pulmonary embolism

6.9.2.1 Safety Outcomes in Cancer Patients

One of the pre-specified subgroups in AMPLIFY was on patients with active cancer at baseline; the safety results are presented in Table 22. Although the number of cancer patients was small, the results in this pre-specified, high risk subgroup are consistent with the overall AMPLIFY findings.(61) Additional studies are warranted to compare the efficacy and safety of apixaban and extended LMWH, the recommended therapy for VTE treatment in many cancer patients.

Table 46: Safety results in the pre-specified subgroup of patients with active cancer at baseline (AMPLIFY, safety population) (61)

	Apixaban	Enoxaparin/ warfarin	Relative risk (95% CI)	Treatment interaction p value
Primary safety outcome: major bleeding, n/N (%)				
Active cancer at baseline	[redacted]	[redacted]	[redacted]	[redacted]
No active cancer at baseline	[redacted]	[redacted]	[redacted]	

6.9.2.2 Post-hoc Analysis of Major Bleeding and CRNM Bleeding at 3 Months

A post-hoc analysis was performed to assess the time-dependent risk of the primary safety outcome of major bleeding and of CRNM bleeding at 3 months. At this early timepoint, apixaban resulted in a statistically significant lower risk of major bleeding compared with enoxaparin/warfarin (p=0.0001; Table 47).

Table 47: Post-hoc analysis of major and CRNM bleeding at 3 month timepoint (AMPLIFY, safety population) (97)

	Apixaban N=2676	Enoxaparin/ warfarin N=2689	Relative risk (95% CI)	p-value
Safety outcome, n (%) – treated patients				
Major bleeding at 3 months	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding at 3 months	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence interval; CRNM: Clinically relevant non-major

6.9.2.3 Other Safety Outcomes

The proportions of patients reporting AEs and SAEs were comparable in both treatment groups (Table 48). Overall, 1795 patients (67.1%) in the apixaban treatment group and 1923 patients (71.5%) in the enoxaparin/warfarin treatment group experienced at least one AE.(14) Additionally, 417 patients (15.6%) in the apixaban treatment group and 410 patients (15.2%) in the enoxaparin/warfarin treatment group had at least one SAE.(14)

Bleeding AEs were reported by fewer patients in the apixaban treatment group than in the enoxaparin/warfarin treatment group (415 patients [15.5%] vs. 695 patients [25.8%])) (Table 48).(14) [redacted]

A similar proportion of patients discontinued due to an AE in the apixaban and enoxaparin/warfarin groups (6.1% vs. 7.4%, respectively). Of these discontinuations, 0.7% were due to a bleeding-related event in the apixaban group compared with 1.7% in the enoxaparin/warfarin group. Deaths were recorded for [redacted] in the apixaban treatment group and [redacted] in the enoxaparin/warfarin treatment group, based on the safety population.(14, 61)

Overall, no safety concerns were noted in the analysis of AEs, SAEs, discontinuations due to AEs, or the incidence of deaths.

Table 48: Summary of adverse events during the treatment period (AMPLIFY, safety population) (14, 61)

	Apixaban N=2676	Enoxaparin/warfarin N=2689
Adverse events, n (%) – safety population (treated patients)		
AE	1795 (67.1)	1923 (71.5)
SAE	417 (15.6)	410 (15.2)

Bleeding AE	415 (15.5)	695 (25.8)
Discontinuations due to AE	162 (6.1)	199 (7.4)
Deaths	[redacted]	[redacted]
AEs occurring in ≥5% of patients in either arm [redacted]	[redacted] [redacted]	[redacted] [redacted]

AE: Adverse event; SAE: Serious adverse event

Due to historical concern regarding hepatic safety of anticoagulant therapy, characterisation of the liver-related safety profile is an important aspect of an evaluation of novel oral anticoagulants.(98) There were no clinical concerns with the results of the liver safety assessments of apixaban for the treatment and prevention of recurrent VTE (Section 10.27).

AMPLIFY-EXT

Summary

- The number of major bleeding events (primary safety outcome) was low and similar across the apixaban 2.5 mg and placebo groups (2 patients [0.2%] in apixaban arm, 4 patients [0.5%] in placebo arm; RR 0.49; 95% CI 0.09, 2.64; [redacted]).
- There were no statistically significant differences between apixaban 2.5 mg and placebo in any adjudicated bleeding category.
  - Composite of major/CRNM bleeding (RR 1.20; 95% CI 0.69, 2.10; [redacted]).
  - CRNM bleeding (RR 1.29; 95% CI 0.72, 2.33; [redacted]).
- The safety profile of apixaban was similar to that of placebo based on the incidence of AEs and SAEs.
- There was twice the rate of discontinuations due to AEs in the placebo group (16.2%) compared to apixaban 2.5 mg (8%), which was primarily driven by the higher rate of recurrent DVT and PE in the placebo group.
- The overall safety profile during treatment was consistent for patients across all subgroups, including when split by their index event (DVT or PE).

6.9.2.4 Data sets analysed

Safety outcomes and adverse events are reported for the treated population for apixaban 2.5 mg bd (n=840) and placebo (n=826). Results of the primary and secondary safety outcomes for apixaban 5 mg bd are presented in the Appendices, Section 10.30.

6.9.2.5 Primary Safety Outcome

The number of major bleeding events was low in both the apixaban and placebo groups, with 2 events [redacted] in the apixaban 2.5 mg treatment group, and 4 events [redacted] in the placebo group (Table 49).(16, 64) The Hochberg adjusted p-value for superiority vs. placebo was [redacted] indicating that apixaban was not significantly different to placebo on the primary safety outcome.

Table 49: Summary of primary safety outcome (AMPLIFY-EXT, safety population) (16, 64)

	Apixaban 2.5 mg N=840	Placebo N=826	Relative risk (95% CI)	p-value (for superiority)
Primary safety outcome, n (%) – treated patients				
Major bleeding	2 (0.2)	4 (0.5)	0.49 (0.09-2.64)	[redacted]

CI: Confidence interval
The definition of major bleeding was adapted from the International Society on Thrombosis and Haemostasis definition.(66)

6.9.2.6 Secondary Safety Outcomes

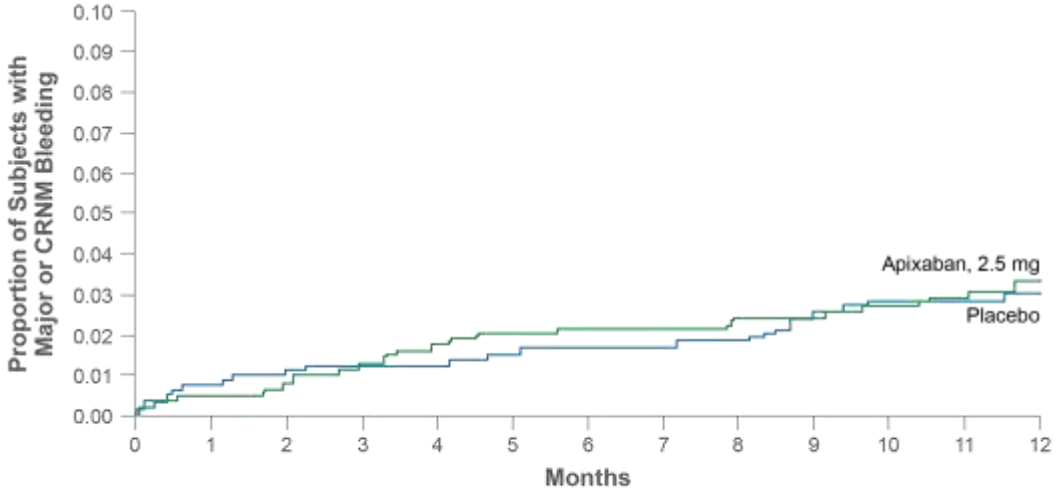
The secondary adjudicated bleeding outcomes for apixaban were not significantly different from placebo across all bleeding outcomes; see Table 50 and Figure 22.(16, 64) The adjudicated composite of major/CRNM bleeding was low in both treatment arms, observed in 27 patients (3.2%) in the apixaban group and 22 patients (2.7%) in the placebo group (RR 1.20; 95% CI 0.69, 2.10; p=0.5148). Event rates for all secondary safety outcomes are presented in [redacted].

Table 50: Summary of secondary safety outcomes (AMPLIFY-EXT, safety population) (16, 64)

	Apixaban 2.5 mg N=840	Placebo N=826	Relative risk (95% CI)	p-value
Secondary safety outcomes, n (%) – treated patients				
Major/CRNM bleeding	27 (3.2)	22 (2.7)	1.20 (0.69, 2.10)	[redacted]
CRNM bleeding	25 (3.0)	19 (2.3)	1.29 (0.72, 2.33)	[redacted]
Minor bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Total bleeding	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence interval; CRNM: Clinically relevant non-major
*Hochberg adjusted p-value for superiority

Figure 22: Kaplan–Meier cumulative event rates for the first episode of the composite of major or CRNM bleeding (AMPLIFY-EXT, safety population) (16)

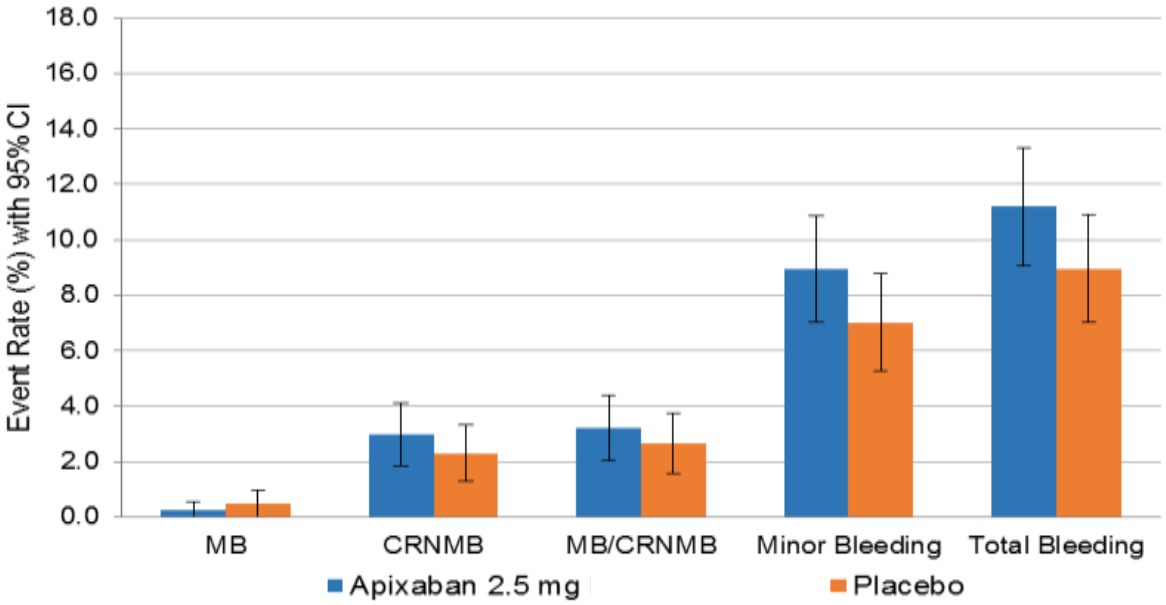


No. at Risk					
Apixaban 2.5 mg	840	786	759	737	354
Placebo	826	749	687	651	298

[redacted]

CRNM: Clinically relevant non-major bleeding

[redacted]



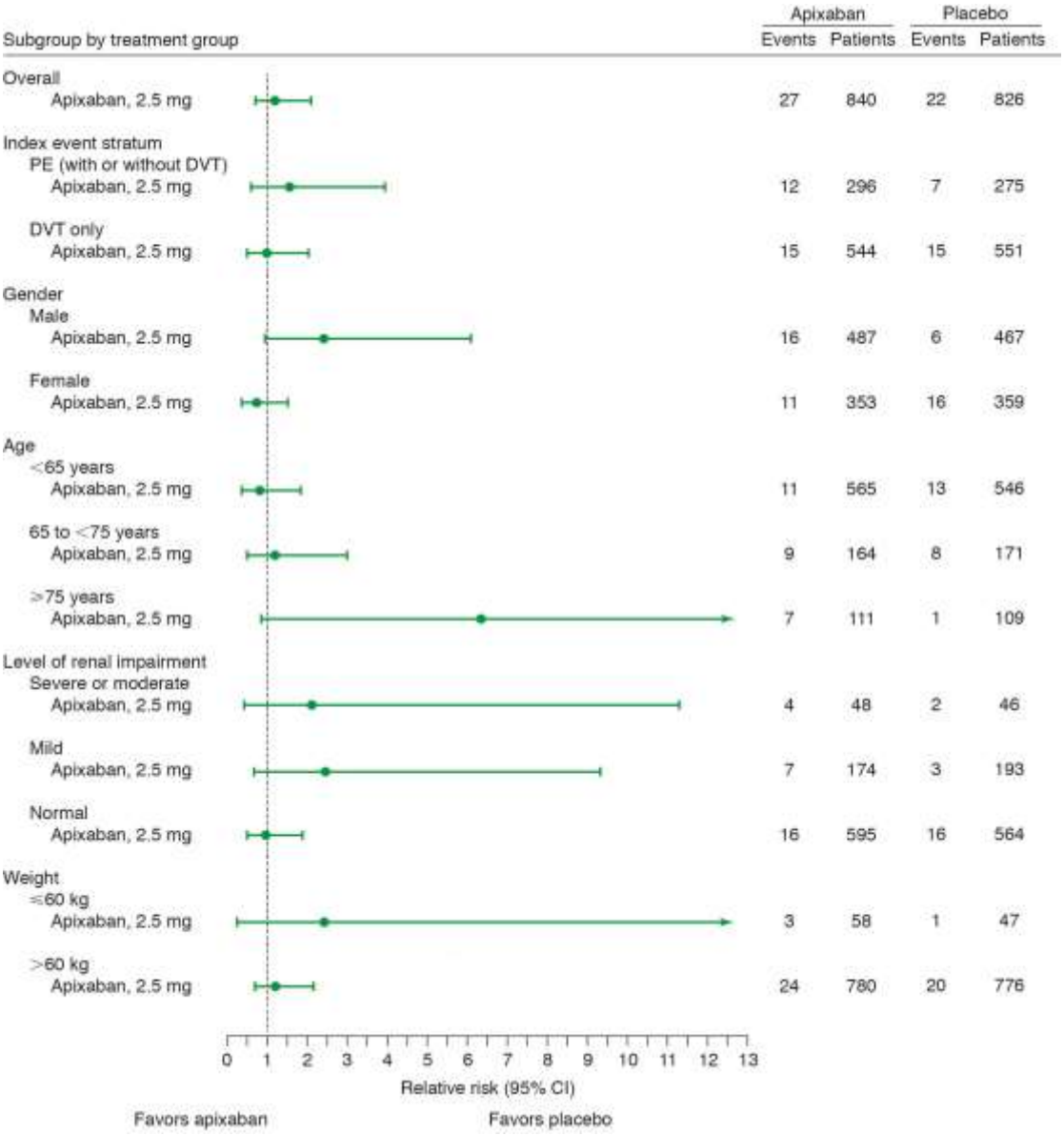
CRNMB: Clinically relevant non-major bleeding; MB: Major bleeding

6.9.2.7 Subgroup Analysis

Subgroup analyses specified for the primary safety outcome (major bleeding) were conducted on the secondary safety outcome of the composite of major or CRNM bleeding due to the small number of adjudicated major bleeding events (6 events) across the 2 treatment arms. Therefore, the combination of major or CRNM bleeding allowed for a more robust comparison across subgroups.

Analysis of the results showed that there were no clinically important differences between apixaban 2.5 mg and placebo for the composite safety outcome of major/CRNM bleeding for any of the subgroups investigated (Figure 24) (Section 10.28).

Figure 24: Summary of the relative safety for the composite outcome of major/CRNM bleeding across pre-specified subgroups (AMPLIFY-EXT, safety population) (16)



CI: Confidence interval; DVT: Deep vein thrombosis; PE: Pulmonary embolism

6.9.2.8 Other Safety Outcomes

The proportion of patients reporting AEs was similar across the treatment groups (Table 51). Overall, 596 patients (71.0%) in the apixaban 2.5 mg treatment group and 606 patients (73.4%) in the placebo group experienced at least 1 AE.(16) SAEs were reported in a numerically greater proportion of patients in the placebo group compared to the apixaban 2.5 mg treatment group (19.1% of patients in the placebo group and 13.3% of patients in the apixaban 2.5 mg treatment group), although no statistical tests were performed on these outcomes.(16) Vascular disorders (DVT, and venous thrombosis) accounted for the higher incidences of SAEs in the placebo group. [redacted] (Table 51).

[redacted]

Discontinuations due to AEs were higher in the placebo group than in the apixaban treatment group (134 patients [16.2%] in the placebo group, and 67 patients [8.0%] in the apixaban 2.5 mg treatment group).(16) The difference in discontinuation was primarily driven by higher numbers of recurrent VTE events in the placebo groups compared to apixaban [redacted].(16, 64)

Deaths (from any cause) were reported for 7 patients (0.8%) in the apixaban 2.5 mg treatment group and 14 patients (1.7%) in the placebo group.(16)

Overall, no new safety concerns were noted in the analysis of AEs, SAEs, discontinuations due to AEs, or the incidence of deaths. Furthermore, results of the liver safety assessments did not highlight any safety concerns associated with apixaban for the treatment and prevention of recurrent VTE (Section 10.29).

Table 51: Summary of adverse events during the treatment period (AMPLIFY-EXT, safety population) (16)

	Apixaban 2.5 mg N=840	Placebo N=826
Adverse events, n (%) – treated patients		
AE	596 (71.0)	606 (73.4)
SAE	112 (13.3)	158 (19.1)
Discontinuations due to AE	67 (8.0)	134 (16.2)
AEs occurring in ≥5% of patients in either arm		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Adverse events, n/N (%) – ITT population		
Deaths, through to end of intended treatment period	7/840 (0.8)	14/829 (1.7)

AE: Adverse event; DVT: Deep vein thrombosis; ITT: intention-to-treat; SAE: Serious adverse event

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

Bleeding

In the treatment phase (AMPLIFY), apixaban was statistically superior to enoxaparin/warfarin with respect to the primary safety outcome of the incidence of major bleeding. In addition, apixaban was associated with a significant reduction compared to enoxaparin/warfarin in the secondary bleeding outcomes of the incidence of CRNM bleeding and the composite of major or CRNM bleeding.(14)

For long-term prevention of VTE recurrence (AMPLIFY-EXT), the incidence of all bleeding endpoints was low and similar for apixaban and placebo.(16)

Other AEs

The overall safety profile of apixaban was similar to that of enoxaparin/warfarin over the first 6 months of treatment, based on the incidence of deaths, AEs, SAEs, and AEs leading to discontinuation.(14) For long-term preventation of VTE recurrence, AE event rates for apixaban were similar to placebo, while SAEs, discontinuations due to AEs and deaths were more common for placebo than for apixaban.(16)

6.10 Interpretation of clinical evidence

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

Overall statement: Apixaban is similarly effective as LMWH/VKA, rivaroxaban and LMWH/dabigatran for the treatment of VTE and long-term prevention of recurrent VTE, and causes fewer major or CRNM bleeds. Apixaban is superior to placebo in the prevention of recurrent VTE or all-cause mortality and has a similar safety profile to placebo.

Apixaban has been studied in two phase III, double-blind, randomised controlled trials, AMPLIFY and AMPLIFY-EXT. AMPLIFY compared apixaban with LMWH (enoxaparin)/warfarin over 6 months in 5,395 patients with confirmed symptomatic DVT or PE. AMPLIFY-EXT investigated apixaban 2.5 mg and 5 mg or placebo for the prevention of recurrent VTE in 2,482 patients who had previously received anticoagulation for 6 to 12 months for the treatment of DVT and/or PE.

AMPLIFY demonstrated that, for the treatment of DVT or PE:

- Apixaban was non-inferior compared to enoxaparin/warfarin at preventing the primary outcome of recurrent symptomatic VTE or VTE-related death (RR 0.84; 95% confidence interval [CI], 0.60, 1.18; p<0.001).
- The adjudicated composite secondary outcomes of recurrent VTE or all-cause death and of recurrent VTE or CV-related death was RR 0.82, 95% CI 0.61, 1.08 and RR 0.80, 95% CI 0.57, 1.11 in the apixaban group compared to the enoxaparin/warfarin comparator, although the difference between groups did not reach statistical significance for superiority (p=0.16 and p=0.18, respectively).
- Apixaban was statistically superior to enoxaparin/warfarin with respect to the primary safety outcome of adjudicated major bleeding.
    - Major bleeding occurred in 15 patients in the apixaban group (0.6%), compared with 49 patients in the enoxaparin/warfarin group (1.8%) (RR 0.31; 95% CI 0.17, 0.55; p<0.001, for superiority).
- Apixaban had an improved bleeding risk profile compared to enoxaparin/warfarin, which was consistent across all bleeding related outcomes.
    - Composite of major or CRNM bleeding (RR 0.44; 95% CI 0.36, 0.55; p<0.001)
    - CRNM bleeding (RR 0.48; 95% CI 0.38, 0.60; p<0.0001)
    - Gastrointestinal major bleeds (7 [0.3%] of apixaban patients vs. 18 [0.7%] of enoxaparin/warfarin patients)
- The event rate of adverse events (AEs), serious adverse events (SAEs) and discontinuations due to AEs for apixaban was similar to that of enoxaparin/warfarin. [redacted]
- Comparable overall discontinuation rates between apixaban and enoxaparin/warfarin were observed in AMPLIFY (14.0% vs. 15.3%, respectively).
- Apixaban significantly reduced all-cause hospitalisations during the 6 month intended treatment period, compared to enoxaparin/warfarin (p=0.048).

AMPLIFY-EXT showed that in patients receiving treatment for the prevention of recurrent VTE:

- Apixaban 2.5 mg was superior to placebo in preventing the primary outcome of recurrent VTE or all-cause death (RR 0.33; 95% CI 0.22, 0.48; p<0.0001).
- The incidence of the composite secondary outcomes of recurrent VTE or VTE-related death and of recurrent VTE or CV-related death were significantly reduced in the apixaban 2.5 mg arm compared to placebo RR 0.19, 95% CI 0.11, 0.33 and [redacted], respectively; [redacted] for superiority for both outcomes).
- The number of major bleeding events (primary safety outcome) was low and similar across the apixaban 2.5 mg and placebo groups (2 patients [0.2%] in apixaban arm, 4 patients [0.5%] in placebo arm; RR 0.49; 95% CI 0.09, 2.64; p=0.3925).
- There were no statistically significant differences between apixaban 2.5 mg and placebo in any adjudicated bleeding category.
    - Composite of major/CRNM bleeding (RR 1.20; 95% CI 0.69, 2.10; p=0.5148).
    - CRNM bleeds (RR 1.29; 95% CI 0.72, 2.33; p=0.3932).
- The safety profile of apixaban was similar to that of placebo based on the incidence of AEs and SAEs. [redacted]
- Apixaban 2.5 mg had a lower rate of overall discontinuation compared to placebo (13.6% vs. 22.7%, respectively), which was primarily driven by the higher rate of recurrent DVT and PE in the placebo group.
- Apixaban significantly reduced all-cause hospitalisations during the 12 month intended treatment period, compared to placebo (p=0.030).

In both AMPLIFY and AMPLIFY-EXT, the primary efficacy and safety results were consistent across all pre-specified subgroups, including when patients were grouped by their index event, DVT or PE (with or without DVT).

In the absence of head-to-head RCT evidence, network meta-analyses were conducted to determine the relative efficacy and safety of apixaban compared to other NOACs for VTE in the treatment and prevention periods, and additionally to VKA and aspirin in the prevention period.

In the **treatment period (NMA 1)**:

- There were no significant differences between therapies for the composite outcome of recurrent VTE or VTE-related death.
- Apixaban demonstrated a significantly lower rate for the composite outcome of major or CRNM bleeding than dabigatran and rivaroxaban.
- Apixaban also demonstrated a significantly lower rate of major bleeding vs. dabigatran, and of CRNM bleeding vs. rivaroxaban.

In the **prevention period (NMA 2):**

- There were no significant differences in terms of the composite outcome of recurrent VTE or VTE-related death for apixaban 2.5 mg, dabigatran, rivaroxaban, or VKA.
- Apixaban demonstrated a significantly lower rate of major or CRNM (composite) bleeding than dabigatran, rivaroxaban and VKA.
- Apixaban also demonstrated a significantly lower rate of major bleeding and of CRNM bleeding compared to rivaroxaban and VKA.
- Apixaban was associated with a significantly lower rate of recurrent VTE or VTE-related death compared with aspirin and there were no statistical differences for any of the other outcomes.

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

The clinical evidence base consisted of two RCTs (AMPLIFY and AMPLIFY EXT) and, in the absence of head-to-head studies against the comparators, two NMAs were conducted.

Strengths of AMPLIFY and AMPLIFY-EXT

The strengths of both these studies included the minimisation of bias with the randomised, double-blind design, identical follow-up of all patients, and independent adjudication of all outcome events. The execution of the studies was rigorous, with minimal loss to follow-up, few patients withdrawing consent and good adherence to study medication. Discontinuations of study medication were low with few discontinuations due to adverse events.

AMPLIFY

The results of the study are likely to be applicable to the general UK population with VTE; demographics from the Clinical Practice Research Database (CPRD) study are summarised in Appendix 9f.(44) The efficacy and safety results were maintained across subgroups (see Sections 6.5.1.4 and 6.9.2.5) including a post-hoc analysis at 3 months (see Sections 6.5.1.8 and 6.9.2.1). AMPLIFY demonstrated efficacy and safety of apixaban at both 3 and 6 months which is consistent with current clinical practice.

For the comparator arm patients on warfarin were generally well managed. The proportion of time that patients' INR was in the target therapeutic range (TTR, INR of 2-3) was 61% which was similar to the benchmark reported in a recent systematic review and meta-analysis by Erkens et al (99) (see Section 6.10.4).

The efficacy and safety results were maintained across index event, DVT and PE (see Section 6.5.1.4 and 6.9.2.5).

AMPLIFY-EXT

The results of the study are likely to be applicable to the general UK population due to the broad spectrum of patients recruited and given that a proportion of the patients were from 7 UK centres. Patients enrolled in this study were those who had already had 6–12 months of anticoagulation therapy and for whom there was uncertainty about the benefits and risks of continued anticoagulation. AMPLIFY-EXT used placebo as a comparator in patients with ongoing risk of VTE who may currently receive 'no treatment' due to their risk of bleeding. The results of this study provided evidence to support the continued use of apixaban for long term prevention of VTE recurrence. In circumstances where warfarin is discontinued, the risk of recurrent VTE is estimated to be 6% to 10% per year in patients without reversible risk factors.(54, 71, 100, 101) Therefore, given that the proportion of patients with recurrent thromboembolism (fatal or non-fatal) in the placebo group was 8.8%, it is evident that the study entry criteria identified patients with an appreciable risk of recurrence.

The efficacy and safety results were maintained across a broad range of subgroups including when grouped by index event, DVT and PE (see Sections 6.5.1.13 and 6.9.2.7).

Limitations of AMPLIFY and AMPLIFY-EXT

In AMPLIFY and AMPLIFY-EXT, patients with active cancer requiring 6 months or more of LMWH were excluded from the studies and therefore only a small percentage of patients with active cancer were included and treated with apixaban (2.9% in AMPLIFY, 1.8% in AMPLIFY-EXT [2.5 mg arm]). The efficacy and safety of apixaban is not established in patients with active cancer.

Another limitation was that it was not possible to derive health-related quality of life (HRQL) from either AMPLIFY or AMPLIFY-EXT as the studies did not report on HRQL outcome measures.

AMPLIFY

Dosing of enoxaparin (1 mg/kg bd) was a US licensed dose. Although this is different to the UK licensed dose for treatment (1.5 mg/kg od), Merli et al. (102) suggests this difference in dosing does not affect outcomes and has been used in other recent trials of anticoagulants.(70, 71) NICE has previous accepted that differences in dosage did not appear to be clinically significant during the rivaroxaban appraisal.(16)

AMPLIFY-EXT

In AMPLIFY-EXT the patients were treated for only 12 months. However the trial duration was sufficiently long enough to power the study for the primary outcomes. A subgroup of patients was treated for up to 18 months.

Strengths and limitations of the NMAs

The strengths and limitations of both the treatment and prevention period NMAs are presented below.

Strengths

The NMAs were based on prospective RCTs, with either open-label or double-blind study designs. Additionally, the studies across both NMA 1 (treatment period) and NMA 2 (prevention period) were relatively similar in terms of the population, interventions, outcomes and study designs allowing for meaningful comparisons to be made between treatments.

The NMAs were based on both direct and indirect comparisons of differences between randomised treatment allocations and thus biases inherent with naïve comparisons of outcomes in individual arms were minimised. Therefore, the NMAs give more precise estimates of treatment effect and reflect the full range of estimates from the literature, taking account of inconsistencies and heterogeneity. This is a practice endorsed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for the purpose of using indirect and direct evidence for decision making.(103)

The NMAs were restricted to fixed-effects models predominantly due to the small number of studies (particularly NMA1). Treatment effects were estimated directly from the trial data and therefore,

meaningful conclusions can be drawn from the analysis. Furthermore, Section 9.6.5.1 of the Cochrane Systematic Review Handbook states that “typical advice” for producing “useful findings” from calculations investigating heterogeneity should be based on a sufficient number of studies.(74)

Pairwise indirect comparisons using the Bucher method (104) for outcomes where an NMA was not possible were conducted for the subgroup index event analysis, preserving the strength of the randomised trials.

Limitations

For the treatment period NMA (NMA 1), assessment of heterogeneity was not possible due to the limited number of studies.(74) However, the studies included in the NMA were broadly similar in terms of the population, outcomes and study design.

For the prevention period NMA (NMA 2), conceptual heterogeneity within the network was identified (Section 6.7.6). However, this was investigated through sensitivity analyses where appropriate, with a general trend of comparable results across sensitivity analysis on a range of outcomes. Furthermore tests of inconsistency and heterogeneity were undertaken and did not demonstrate any apparent statistical biases within the network.

Additionally it was not possible to derive health-related quality of life (HRQL) from the NMA as neither the apixaban studies nor any of the relative comparator studies included HRQL outcome measures.

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

Relevance of the evidence base to the decision problem

Population with DVT and/or PE for whom a VKA is suitable

Both AMPLIFY and AMPLIFY-EXT trials included patients with DVT and/or PE, as specified in the decision problem. The proportion of the DVT and/or PE in the trials was consistent with that seen in the UK clinical population.(44) The outcomes of the trials in terms of efficacy and safety were consistent by index DVT or PE (with or without DVT) events. Additionally, AMPLIFY provides evidence of the clinical efficacy and safety of apixaban compared with LMWH/VKA, which is the current standard of care for VTE.

Population with DVT and/or PE in whom a VKA is unsuitable

AMPLIFY was a randomised controlled trial against LWMH/VKA and therefore it did not include patients who were unsuitable for VKA treatment as an explicit inclusion/exclusion criteria. AMPLIFY-EXT included patients who had 6–12 months previous anticoagulation treatment, primarily with warfarin, or were included from the AMPLIFY trial. Moreover for those patients who did not receive warfarin previously it was not recorded whether they were unsuitable for warfarin treatment. No evidence was found in the systematic review (see Section 6.7.2) for patients in an ‘unsuitable for VKA’ population not including active cancer patients. The safety and efficacy of apixaban is not established in patients with active cancer. The NMA did, however, provide estimates of the relative

treatment effect for comparators (for example rivaroxaban) that would be considered for patients who were unsuitable for VKA.

Population listed under 'other considerations'

Data from AMPLIFY and AMPLIFY-EXT allowed for subgroup analysis by index event type, DVT or PE (with or without DVT), to be carried out on both efficacy and safety outcomes.

In patients for whom the benefit/risk of long-term anticoagulation is uncertain, AMPLIFY-EXT provides direct evidence for longer-term apixaban use versus placebo (which is representative of 'no preventative treatment'). Furthermore, NMA 2 allowed for the indirect comparison of apixaban with aspirin for the long-term prevention period for patients in whom the benefit/risk of anticoagulation is uncertain.

Relevance of outcomes to patients in practice

The objective of anticoagulation therapy in patients with DVTs and/or PEs is to treat the original thrombus and to prevent recurrence, whilst reducing death related to VTE. In addition, it is important to maximise efficacy whilst minimising the risks to patients in terms of bleeding.

In line with the decision problem and routine clinical practice, AMPLIFY and AMPLIFY-EXT investigated outcomes of clinical relevance to patients in practice including death, VTE recurrence, complications associated with VTE, and adverse events associated with treatment, specifically bleeding.

Bleeding is a serious and costly complication of anticoagulation, leading to under-treatment and an increased risk of recurrent VTE (10, 105). AMPLIFY demonstrated a lower rate of bleeding (composite of major or CRNM as well as major bleeding) compared to warfarin whilst maintaining comparable efficacy. AMPLIFY-EXT demonstrated a comparable rate of bleeding (composite of major or CRNM as well as major bleeding) compared to placebo whilst significantly reducing the rate of recurrent VTE.

Hospitalisation of VTE patients has important resource implications for the NHS.(4) Apixaban as an oral therapy, does not require INR monitoring or dose adjustments and removes the need for patients to receive parenteral LMWH treatment in hospital, inpatient stays to stabilise treatment, and clinic visits for blood monitoring . Furthermore, in AMPLIFY and AMPLIFY-EXT, apixaban significantly reduced all cause hospitalisation compared with warfarin and placebo and increased time to first hospitalisation.

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

The factors that may influence the external validity include trial and licensed dosing, time in therapeutic range, patients eligible for treatment, demographics of the trial population, enoxaparin regime, and treatment compliance.

Baseline characteristics of the trial population

Detailed summaries of the baseline characteristics of the trial populations in AMPLIFY and AMPLIFY-EXT are presented in Section 6.3.4.

For broader generalisability, the mean age (±SD) at baseline of patients enrolled in both with AMPLIFY and AMPLIFY-EXT was 57 (±16) years which is in line with the clinical presentation of VTE.(44) Additionally, the trials comprised two-thirds DVT patients and one-third PE patients which is similar to the distribution found in the UK general population; demographics from the CPRD study are summarised in Appendix 9f.

Patients eligible for treatment

Apixaban is licensed for the use in patients with DVT/PE and has few contraindications.(20) The AMPLIFY and AMPLIFY-EXT trials evaluated adult patients with confirmed VTE with the exception of those with active bleeding or at high risk of bleeding with LMWH or a VKA, renal impairment (creatinine clearance <25 mL/min) or who had received thrombectomy, insertion of vena cava filter or fibronolytic agent for the current episode of thrombosis.

In the apixaban SPC,(20) caution is recommended in patients with CrCl 15–29 ml/min; it is not recommended in patients with CrCl <15 ml/min; and it is contraindicated in patients with active clinically significant bleeding. Apixaban is not recommended as an alternative to UFH in patients with pulmonary embolism who are haemodynamically unstable or who receive thrombolysis or pulmonary embolectomy. Caution is also recommended in patients with mild or moderate hepatic impairment and it is not recommended in patients with severe hepatic impairment.

Although the AMPLIFY trials included a small number of patients with active cancer, patients who required LMWH for 6 months or more were excluded and the apixaban SPC states that the safety and efficacy of apixaban has not been established in patients with active cancer.

Therefore, the AMPLIFY and AMPLIFY-EXT trial regimen and the apixaban SPC (20) is in line with the NICE clinical guideline on the treatment and management of patients with VTE in England and Wales.(8)

Apixaban Dosing

The dosing of apixaban in the AMPLIFY trial is consistent with the dosing regimen for the treatment of DVT and PE in the SPC: 10 mg bd for first 7 days followed by 5 mg bd. For longer term prevention of recurrent VTE, AMPLIFY-EXT provides data for the licensed dose of 2.5 mg bd dose after at least 6 months of treatment.

INR control in AMPLIFY

Guidelines from the National Patient Safety Agency and the Scottish Executive Health department recommend a TTR of at least 60%, which was accepted by the NICE Appraisal Committee in TA287(40). For patients receiving warfarin in the AMPLIFY trial, the TTR was on average 60.9%. As such, the TTR in AMPLIFY was within the range expected in UK clinical practice. Furthermore, warfarin control was consistent with other relevant VTE clinical trials that reported a TTR of 58% (EINSTEIN DVT), 60% (RE-COVER), and 62.7% (EINSTEIN PE) studies.(70-72)

Placebo comparator in AMPLIFY-EXT

NICE CG144 supports extending anticoagulant therapy in some patients until the risk of recurrent VTE no longer outweighs the risk of bleeding, or until the patient wishes to stop treatment (even if the patient's risk of recurrence outweighs the increased risk of bleeding).(8) The increased risk of bleeding with currently available anticoagulants is a barrier to therapy and some patients may not routinely receive any pharmacological therapy, so there remains an unmet medical need for a treatment option in this patient population.

At the time of the AMPLIFY-EXT trial, VKA (warfarin) was the only available anticoagulant for the treatment of recurrent VTE beyond the initial 6–12 months. Patients enrolled in AMPLIFY-EXT faced uncertainty as to whether to continue treatment with warfarin or stop treatment due to the risk of bleeding. Clinicians in England and Wales are presented with a similar dilemma in assessing the benefit of continued anticoagulant treatment against the risk of bleeding. Therefore, placebo ('no treatment') was considered the appropriate comparator in AMPLIFY-EXT and hence these data are applicable to the UK population with recurrent VTE. The rate of recurrent VTE in the placebo group of AMPLIFY-EXT (8.8%) confirms that these patients were at a continued risk of recurrent VTE.

Compliance

Treatment compliance in AMPLIFY was [redacted]% for apixaban 5 mg and in AMPLIFY-EXT was [redacted]% for apixaban 2.5 mg. The high levels of treatment compliance are discussed in Section 6.3.5 and reflect the simple and convenient dosing of apixaban, which could be expected to improve patient adherence to treatment. High levels of compliance also confirm that these were well-conducted trials.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Summary of Cost-Effectiveness Results

- A Markov state transition model was used to assess the clinical and economic implications of the treatment of an index VTE and the prevention of recurrent VTE with apixaban compared to the current standard of care (LMWH/VKA) and other NOACs from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective.
- In the base case, apixaban was cost-effective versus LMWH/VKA for the 6-month treatment duration, with an ICER of £2,406 per QALY gained. Apixaban was dominant (more effective, less costly) compared to rivaroxaban and LMWH/dabigatran for the 6-month treatment duration.
    - In addition, over a 3-month treatment duration, apixaban was shown to be dominant vs. all comparators (LMWH/VKA, rivaroxaban and LMWH/dabigatran).
- For the lifelong treatment duration, apixaban was cost-effective vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran with ICERs of £16,676, £809 and £5,058 per QALY gained, respectively.
    - In the incremental analysis rivaroxaban was dominated by LMWH/VKA, LMWH/dabigatran was extendedly dominated by apixaban and apixaban had an ICER of £16,676 per QALY gained compared to LWMH/VKA.
- In a conservative scenario where lifelong treatment with apixaban was compared with 6 months of treatment with LMWH/VKA followed by no treatment, apixaban had an ICER of £17,917 per QALY gained.
- Apixaban is therefore cost-effective at a willingness-to-pay (WTP) of £20,000 per QALY gained for patients who would benefit from lifelong anticoagulation, but who are currently not being treated. It is likely that these are patients at risk of recurrent VTE who have a high unmet need.
- In a scenario where lifelong treatment with apixaban was compared with 6 months of treatment with LMWH/VKA followed by lifelong treatment with aspirin, apixaban had an ICER of £22,595 per QALY gained.
- The model is robust to changes in the model parameters, as varied in the deterministic sensitivity analysis. The main drivers of the cost-effectiveness model were the :
    - Relative risks of major bleed for patients on LMWH/VKA for the lifelong treatment duration and for rivaroxaban or LMWH/dabigatran for the 6-month and lifelong treatment durations;
    - Relative risks of treatment discontinuation for rivaroxaban or LMWH/dabigatran for the lifelong treatment duration
    - Relative risks of recurrent VTE for patients on LMWH/VKA, rivaroxaban or LMWH/dabigatran for the 6-month treatment duration; and
    - Risk of major bleed for patients treated with apixaban for the 6-month and lifelong treatment durations.

- The probabilistic sensitivity analysis (PSA) showed that for the 6-month treatment duration there was a 100% probability that apixaban would be cost-effective vs. LMWH/VKA, an 85% probability vs. rivaroxaban and a 98% probability vs. LMWH/dabigatran at a WTP threshold of £20,000 per QALY.
- For the lifelong treatment duration there was a 54%, 96% and 86% probability that apixaban would be cost-effective vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran, respectively at a WTP threshold of £20,000 per QALY.

Identification of studies

7.1.1 ***Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.***

An update of the existing systematic review conducted for the rivaroxaban NICE submission was carried out to identify published economic evaluations.(11) Full details of the methodology used to update the existing systematic review are presented in Appendix 10.

The existing rivaroxaban systematic review was conducted on 25th October 2012 and the review update was carried out on 15th July 2014.

The following databases were searched from 25th October 2012 to15th July 2014:

- MEDLINE(Ovid)
- MEDLINE In-Process Citations and Daily Update (Ovid)
- EMBASE (Ovid)
- EconLit (EBSCO)
- The Cochrane Library (incorporating the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database)

In order to retrieve literature not identified through the electronic database search, reference lists of included papers were scanned and searches for grey literature and completed and on-going studies were also carried out. Furthermore, the NICE website was searched for manufacturer and Evidence Review Group (ERG) economic models for potentially relevant literature.

The inclusion and exclusion criteria used to identify potentially relevant articles in the review update are summarised in Table 52. These are the same eligibility criteria used in the exisiting rivaroxaban systematic review.

Table 52: Inclusion and exclusion criteria for the economic evaluation reviews

Category	Inclusion Criteria	Exclusion Criteria	Rationale
Study type	Relevant economic study design: • Cost-utility analysis • Cost-benefit analysis • Cost-effectiveness analysis • Cost-consequence analysis • Comparative cost analysis.	-	The review aimed to identify all types of relevant economic evaluations. These criteria were the same as those used in the previous rivaroxaban NICE submission.
Outcomes	• Costs • Quality adjusted life years (QALYs) • Incremental costs and QALYs • Any other measure of effectiveness reported together with costs.	-	The objective was to include studies reporting on costs or QALYs. QALYs are the preferred clinical outcome of economic evaluations under the NICE reference case
Population	Patients with suspected or confirmed PE or DVT.	-	This is the patient population under consideration for this appraisal.
Interventions	Any pharmaceutical for the treatment of VTE.	-	Devices or other non-pharmaceutical interventions were not relevant to this appraisal. VTE is the indication under review in this appraisal.
Publication type	-	• Unpublished reports • Abstract-only studies at full paper screening • Letters • Editorials • Reviews of economic evaluations (although reference lists of these will be checked).	Primary study articles reporting on the relevant data were required.
Language	-	Non-English language articles.	-

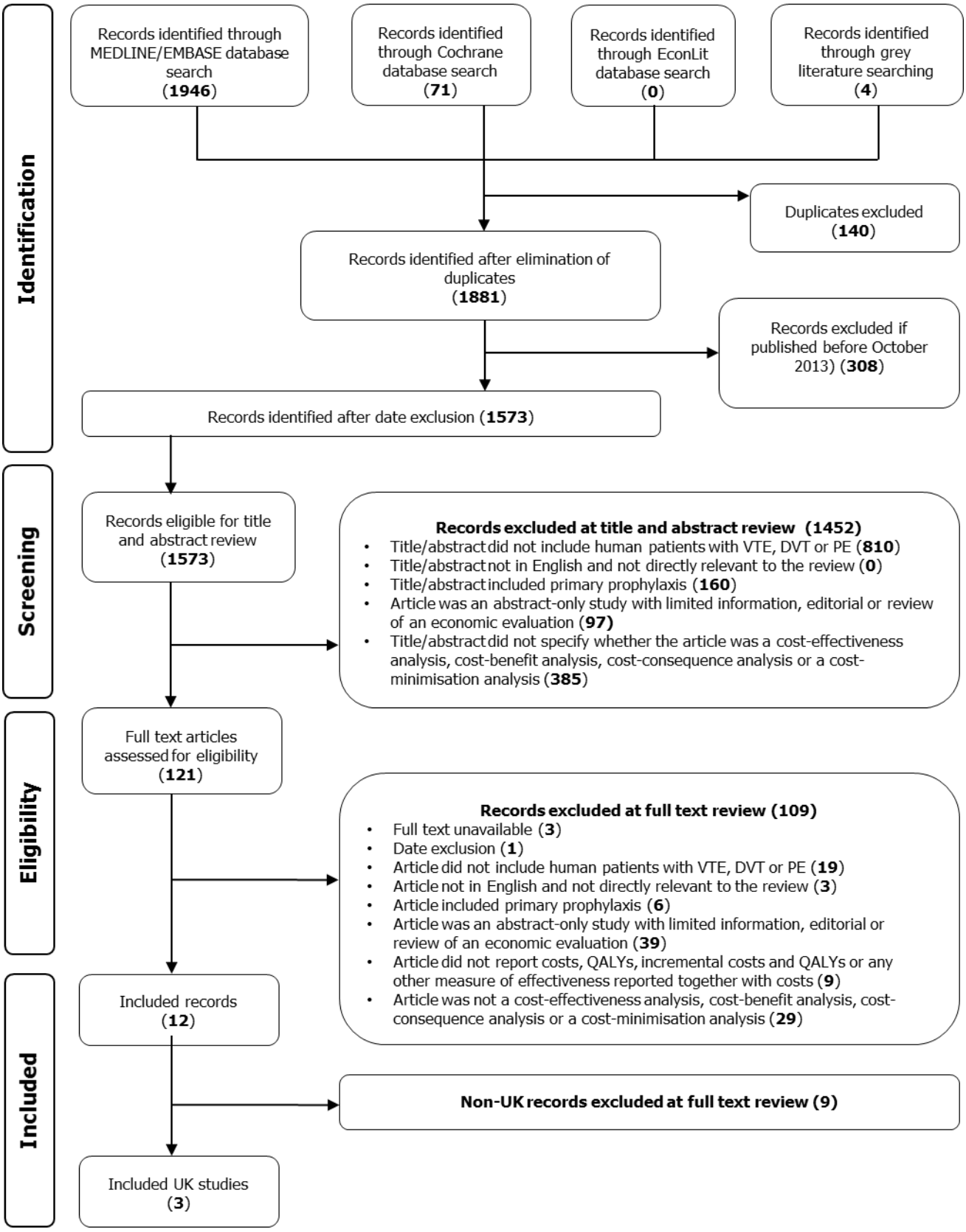
The existing rivaroxaban systematic review identified 7 cost-effectiveness studies, over half of which (4 studies) were conducted in the USA. One study was conducted from a Canadian healthcare perspective, and the remaining two studies were conducted in Italy and Germany. No UK-based

studies, nor any pertaining to apixaban, were identified in this review. Details of the 7 studies included in the exisiting rivaroxaban review are presented in Appendix 14, Section 10.33.

The electronic database search identified 2,017 articles while grey literature searching yielded 4 additional potentially relevant articles (Figure 25). Following deduplication and date restriction (25th October 2012 to 15th July 2014), 1,573 articles were screened based on title ± abstract. On the reapplication of the inclusion criteria, 1,452 title ± abstracts were excluded. Therefore 121 full text papers were further screened for inclusion, of which 109 were excluded. Therefore,12 economic studies in VTE were included in the updated systematic review (Figure 25). However, none of the economic evaluations evaluated apixaban.

Of the 12 economic studies that were identified in the the systematic review, 3 studies were UK cost utility studies that evaluated currently available pharmacological interventions in an active comparator setting and reported an ICER, and therefore were deemed relevant to this submission. A summary of the UK studies and quality assessment is presented in Table 83 and Table 85 to Table 87 in the Appendices, Section 10.33. A brief description of the 9 non-UK studies is also provided in Table 84.

Figure 25: PRISMA flow diagram of number of journal articles identified and included at each stage of the cost-effectiveness review update



Description of identified studies

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

No studies were identified that were directly relevant to the decision problem (i.e. evaluated apixaban) as described in Section 5. Summaries of the results from the exisiting rivaroxaban NICE submission and the UK cost-utility studies identified in the updated systematic review are provided in Table 82 and Table 83 in the Appendices, Section 10.33. The most informative models identified were the two rivaroxaban models that were presented in the manufacturer submissions for TA261 (rivaroxaban for treatment of DVT) and TA287 (rivaroxaban for the treatment of PE).(18, 19) The other UK cost-utility study identified by the updated systematic review was only published in poster format and was therefore less informative due to the insufficient reporting on the relevant data.(106)

7.1.3 ***Please provide a complete quality assessment for each cost-effectiveness study identified.***

A quality assessment was performed for the UK cost-utility studies included in the updated systematic review using an evaluation form adapted from the British Medical Journal Economic Evaluation Working Party Quality Assurance. Results for the UK studies are presented in Table 85 to Table 87 Appendix 15, Section 10.34. The quality of the reports for the two rivaroxaban models produced for the NICE technology appraisal was high; therefore a low risk of bias in the results was expected. Although the dabigatran model reported in Wolowacz et al. (2013) was only available as a congress poster, sufficient data were reported to allow for a meaningful quality assessment to be carried out.

7.2 De novo analysis

Patients

7.2.1 ***What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.***

The base case population used in the economic evaluation reflected the population apixaban is licensed for; patients who require anticoagulation for treatment of an index VTE event up to 6 months and subsequent lifelong therapy for the prevention of recurrent VTE events.(20) This also reflects CG144 for the management of VTE in the UK. Baseline characteristics for patients in the base case analysis are shown in Table 53 and are based on the trial population of the AMPLIFY study, which was considered to be broadly applicable and generalisable to the VTE population in the UK.
A sensitivity analysis using data from the UK CPRD, formerly the General Practice Research Database (GPRD) was also conducted. (Section 7.6). There are some limitations associated with using the CPRD data. The data contains only patients in general practice and includes all instances of VTE (including post-surgical patients, patients with active cancer, and patients where no defined diagnosis criteria are presented). Accordingly, the AMPLIFY data was used in preference to the CPRD data in the basecase. Nevertheless, patient characteristics were broadly similar between

AMPLIFY and the CPRD analysis (Appendix 13f, Section 10.31) with the main differences being a higher mean age in CPRD than in AMPLIFY (64.66 years versus 56.9 years) and a slightly higher proportion of female patients (51.52% versus 41.29% respectively).

Table 53: Patient characteristics employed in base case analysis

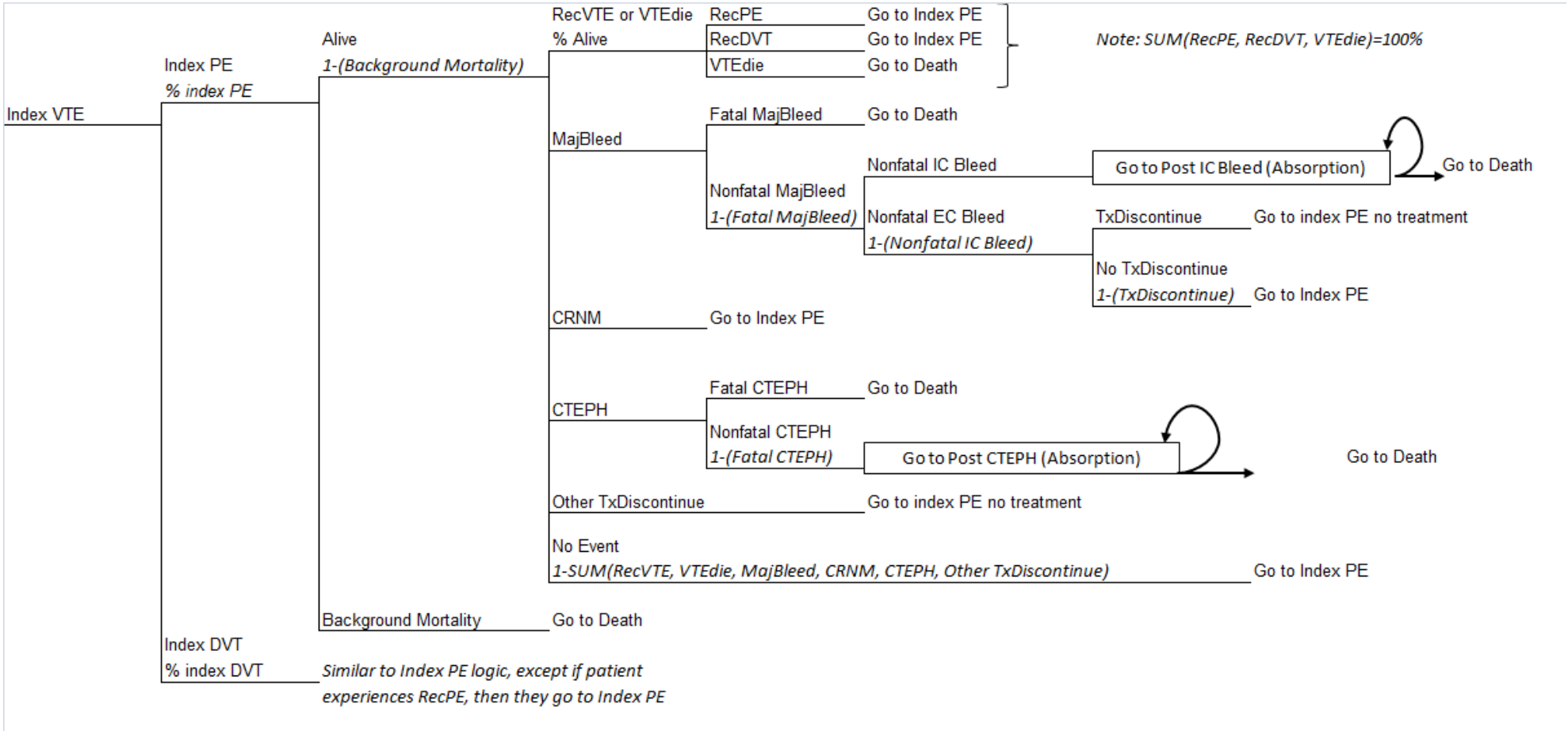
	Value/Mean
Female	[redacted]
Mean age (years)	[redacted]
Weight (kg)	84.6[b]
Source: [a]AMPLIFY clinical study report, Table 14.1.2.1.1 p16 (61); [b] AMPLIFY (14)	

Two subgroup analyses were carried out as part of the sensitivity analyses to investigate patients with index DVT and index PE, respectively, as requested in the NICE scope (see Section 5).

Model structure

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

Figure 26: Model diagram



CRNMbleed; clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; IC, intracranial; MajBleed, major bleed; PE, pulmonary embolism; RecDVT, recurrent deep vein thrombosis; RecPE, recurrent pulmonary embolism; RecVTE, recurrent venous thromboembolism; TxDiscontinue, treatment discontinuation; VTE, venous thromboembolism; VTEdie, death from venous thromboembolis

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

A Markov state transition model was developed in Microsoft Excel® to assess the clinical and economic implications of treatment of an index VTE and the prevention of VTE recurrence after an initial event with apixaban as compared to treatment with the current standard of care (LMWH/VKA) as well as rivaroxaban and LMWH/dabigatran in the basecase. The model structure was developed based on models from the literature and models previously accepted by NICE for this disease area.(18, 19, 106)

Thirteen health states were included in the model (Figure 26). These were index PE, index DVT, recurrent PE, recurrent DVT, CTEPH, intracranial (IC) bleed, non-IC major bleed, CRNM bleed, PE off treatment, DVT off treatment and death (Figure 26). PE second-line treatment and DVT second-line treatment health states were used in a sensitivity analysis . PTS was not modelled as a health state, but as an accrual of costs and utility decrements in the background. The model considered first index DVT or PE as separate health states to recurrent DVT or PE events that occur subsequently.

The model is consistent with the clinical pathway of care identified in Section 2.5. A Markov model was considered appropriate for modelling VTE as it is a chronic condition and patients' health status may change over time. This was also consistent with the approach adopted in the rivaroxaban HTA submissions.(40, 41) Furthermore VTE can be defined by a set of mutually exclusive and exhaustive health states. The relevance of the health states included in the model was validated by clinical experts.(9, 107)

A lifelong time horizon was used to fully capture the long-term consequences of VTE. This was defined at the point where 99.9% of the patients die and the maximum age allowed in the model was 100 years. A 3-month cycle length was chosen because it was considered sufficiently long to capture the implications of a VTE event fully and sufficiently short to include only a single event within a cycle. This approach is consistent with previous models for rivaroxaban.(40, 41, 108) It also reflects treatment durations recommended in clinical practice and NICE CG144.(8) Only one event was allowed to occur within each cycle due to the Markov structure.

The model time horizon is distinct from the allowed durations of treatment in the model, with treatment durations being divided into treatment and prevention periods but the analysis being run with a lifetime time horizon in all cases. The therapy periods included in the base case were:

- **Treatment –** 6-month VTE treatment duration (3 months investigated in scenario analysis)
- **Prevention –** Treatment of VTE beyond 6 months that continues lifelong (in the economic section 'lifelong treatment duration ' has been used to describe this therapy period)

These treatment durations were chosen on the basis of NICE CG144, which recommends that patients with a first episode of DVT or PE should receive anticoagulation for at least 3 months, with patients at a high risk of VTE recurrence being considered for long-term treatment.(8) However, in clinical practice, as per the advice of clinical experts at a recent advisory board meeting, patients may receive between 3–6 months of treatment because of the delay in stabilising patients on warfarin or because there may be a delay in patients being seen by their GP or anticoagulation service. Therefore, these experts supported the choice of a 6-month treatment duration for the base case.(9) A 6-month treatment duration was also used in the base case as the majority of NOAC trials report at this time point.(14, 70, 72, 73, 109) However, as some patients may only require 3 months of treatment, the cost-effectiveness of apixaban at 3 months of treatment, was assessed as a scenario analysis.(9, 22)

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

The Markov model included the following 13 health states:

Table 54: Markov model health states

Health state	Description
Index PE	Patients who enter the model having experienced an index PE event or who entered with an index DVT event and subsequently experienced a recurrent symptomatic PE event.
Index DVT	Patients who enter the model having experienced an index DVT event
Recurrent PE	Patients who experience a non-fatal recurrent symptomatic PE enter this state for one cycle length before moving to the index PE health state.
Recurrent DVT	Patients who experience a non-fatal recurrent symptomatic DVT enter this state for one cycle length before moving back to the index VTE health state they were in before the recurrent event.
CTEPH	Patients who experience non-fatal CTEPH transition to a semi-absorbing post CTEPH health state and remain in this state unless they die.
IC bleed	Patients who experience a non-fatal IC bleed transition to a semi-absorbing post IC bleed health state and remain in this state unless they die.
Non-IC major bleed	Patients who experience a non-fatal non-IC major bleed transition to this transient health state, where they incur a disutility and acute care costs. Patients remaining on their current anticoagulation return to the index VTE health state. Patients discontinuing treatment transition to either the second-line VTE health state (sensitivity analysis) or the off treatment VTE health state (base case analysis).
CRNM bleed	Patients who experience a CRNM bleed transition to this transient health state, incurring a disutility and acute care costs. Patients transition back to the index VTE health state.
PE second-line treatment	In the base case, patients who discontinue first-line treatment move directly to the off treatment health states. In sensitivity analyses patients who discontinue first-line treatment are able to move to the second-line treatment health states. The events modelled in the second-line treatment health states are identical to those in the first-line health states.
DVT second-line treatment	
PE off treatment	Patients originating from the index PE health state enter this health state after permanently discontinuing treatment. The events modelled in this health state are identical to the first- and second-line treatment health states without the option for further treatment switching.
DVT off treatment	Patients originating from the index DVT health state enter this health state after permanently discontinuing treatment. The events modelled in this health state are identical to the first- and second-line treatment health states without the option for further treatment switching.
Death	Patients enter the death state due to background mortality, death due to a recurrent symptomatic VTE event, fatal major bleeding, or fatal CTEPH.

CRNM: Clinically relevant non-major; CTEPH: Chronic thromboembolic pulmonary hypertension; DVT: Deep vein thrombosis; IC: Intracranial; PE: Pulmonary embolism; VTE: Venous thromboembolism

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

VTE is a condition in which a blood clot (thrombus) forms in a vein. DVT (clot formation in the lower limb) and PE (clot formation in the lung) are manifestations of the same disease with serious and potentially fatal outcomes such as CTEPH and PTS (see Section 2.1). Anticoagulation is associated with both a reduction in recurrent VTEs and the potential for an increased bleeding risk compared to no treatment. The model structure captures both the man aspects of the condition and adverse events arising from the use of anticoagulation.

In the model, PE and DVT were considered using separate health states due to the different risks of events, such as CTEPH and PTS, associated with these states.(36, 37) Patients entered the model having experienced either an index PE ([redacted]) or index DVT ([redacted]).(61) These proportions were derived from the AMPLIFY CSR, with patients experiencing both PE and DVT included in the index PE group as this is the more severe event.(61) At each cycle in the model, patients were at risk of experiencing a recurrent DVT or PE event, IC bleed, non-IC major bleed, CRNM bleed, CTEPH, treatment discontinuation or other death. A constant proportion of patients were assumed to experience PTS within the DVT health states due to limitations with the Markov structure.

Recurrent DVT or PE

In the model, recurrent VTE events were divided into VTE-related death, non-fatal recurrent PE, or non-fatal recurrent DVT due to the different effects on mortality, costs, and utilities.

Recurrent VTE events other than VTE-related death were modelled as tunnel states.[2] Patients who survived a non-fatal recurrent PE or who experienced a recurrent DVT after an initial PE transitioned to one of the “index PE” health states (including PE-related mortality, risk of CTEPH) after the cycle ended.(107) Patients who experienced a non-fatal recurrent DVT transitioned to one of the “index DVT” health states after the cycle ended (Figure 26).

Upon the occurrence of a recurrent PE or recurrent DVT in the model, it was assumed that patients would receive 6 months of treatment with LMWH/VKA, beyond the intended treatment duration of the currently assigned treatment, as has been implemented in previous models.(18, 19) This change affected only costs and utilities, because the Markov structure did not alter subsequent transition risks. After 6 months, patients returned to the index state and continued treatment for the remainder of the model treatment period.

IC and non-IC bleeding

Major bleeding events in the model could be fatal or non-fatal. Patients experiencing a non-fatal major bleed transitioned to either the semi-absorbing “non-fatal IC bleed” state or the transient “non-fatal non-IC major bleed” state.

It was assumed that patients who experienced an IC bleed discontinued anticoagulant treatment permanently; this assumption was based on previous submissions and validated with clinical experts.(9, 18, 19, 107)

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[2] When an event is modelled as a tunnel state, the model processes the event in such a way that: 1) An event cost is applied based on a per-episode basis (ie., a one-time fixed cost); 2) A utility decrement is applied for a user-defined duration; and 3) Patients cycle back to their previous health state after the event is processed (ie., the model assumes no impact on subsequent event risks and the treatment that follows).

Patients who survived a non-IC major bleed stayed on their current anticoagulant or discontinued treatment in proportions based on data from AMPLIFY.(14) Those who stayed on their current anticoagulant moved back to the index VTE health states and continued treatment for the remainder of their intended treatment duration. Those discontinuing treatment moved to the "VTE No treatment" health state in the base case. In scenario analyses, patients could also move to the "VTE second-line treatment" health states after discontinuing first-line treatment (Section 7.7.9).

CRNM bleeding

Being less severe than an IC or non-IC bleed, a CRNM bleed was not considered to affect the patient's risk of mortality. All patients experiencing CRNM bleeds experienced a disutility for 2 days and incurred acute costs of care. It was assumed that a CRNM bleed did not affect discontinuation and that patients remained on their current anticoagulant for the remainder of their intended treatment duration after a 2 day interruption of treatment (verified by expert opinion).(9, 110) These patients would no longer incur anticoagulant costs, administration costs, and monitoring costs, nor would they receive a utility decrement for being on an anticoagulant during the period of interruption.

CTEPH

Only patients in the PE health state were exposed to the risk of CTEPH.(36, 37) Upon the occurrence of CTEPH, patients transitioned to the semi-absorbing "post-CTEPH" health state, in which they were assigned expected costs, a utility decrement, and the higher mortality rates associated with patients with CTEPH or a history of CTEPH.(18, 19, 111-113)

PTS

PTS was modelled as a function of recurrent DVT (rather than as a separate health state) for patients in the "PE treatment" health states and for all patients in the DVT health states.(18, 19) The model accounted only for severe PTS, as it was found that mild or moderate PTS had little effect on patients' costs and utilities.(53, 114)

Given the limitations of a Markov structure, a time-varying incidence of PTS could not be applied, nor could the incidence of PTS be dependent on previous clinical events experienced. Instead, a simplified approach was used where it was assumed that a constant proportion of patients would experience PTS within the DVT health states, similar to the approach used in previous rivaroxaban submissions.(18, 19) To take into account patients in the PE health states who experienced DVT, the total number of recurrent DVTs experienced within the PE health states was used after subtracting transition risks due to death from the cumulative total in each cycle as these patients leave the VTE health states. Similarly, the total number of recurrent PEs experienced within the DVT health states was considered to take into account patients who transitioned to the PE states with a history of DVT. PTS costs and utility decrements were applied to the cumulative proportion of patients in DVT health states or with DVT within the PE health states in each cycle.

Treatment Discontinuation

Treatment discontinuation unrelated to recurrent VTE and bleeding events ('other' treatment discontinuation) was modelled explicitly. In the base case, patients who discontinued treatment for reasons other than recurrent VTE or bleeding moved permanently to the "VTE No treatment" health state, and their risks were updated accordingly. In a scenario analysis patients could also move to the "VTE second-line treatment" health states where they received VKA after discontinuing first-line treatment.

The "VTE No treatment" health state was segregated into patients with an index PE and patients with an index DVT. In the no treatment health states, events were modelled identically to those in the VTE first-line and second-line treatment health states, but with no further switching to different treatment health states. If a patient on no treatment experienced a VTE, they were modelled to

receive 6 months of LMWH/VKA therapy, which affects costs and utilities only and not future event risks. The untreated risk of recurrent VTE in these health states was independent of prior treatment.

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

Table 55: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifelong	The model time horizon includes both the index event being treated as well as long-term prevention of a recurrent event. A lifetime time horizon was chosen to consider the long-term consequences of treatment given that lifelong treatment is appropriate for a proportion of patients with VTE, and based on the NICE reference case.	NICE reference case (115)
Cycle length	3 months	A 3-month cycle length was chosen because it was considered sufficiently long to capture fully the implications of a VTE event and sufficiently short to include only a single event within a cycle, and for consistency with previous models for rivaroxaban.	NICE TA261 and NICE TA287 (18, 19)
Half-cycle correction	Yes	The model used the life-table approach to account for half-cycle corrections where state membership at the end of each cycle x (Lx) was accounted for as follows: $\rightarrow L_x = 0.5l_x - 0.5l_{x-1}$;	Barendregt 2014 (116)
Were health effects measured in QALYs; if not, what was used?	QALY	The NICE reference case states that the preferred form of health effects is in terms of quality-adjusted life years (QALYs).	NICE reference case (115)
Discount of 3.5% for utilities and costs	3.5%	The annual discount rate recommended in the NICE reference case for both costs and benefits is 3.5%.	NICE reference case (115)
Perspective (NHS/PSS)	UK NHS and PSS perspective	NICE reference case	NICE reference case (115)
NHS, National Health Service; PSS, Personal social services; QALYs, quality-adjusted life years; VTE: Venous thromboembolism			

Technology

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

Apixaban was compared against the following:

- **6-month treatment duration (base case) –** LMWH/VKA, rivaroxaban and LMWH/dabigatran.
- **Lifelong treatment duration (base case) –** LMWH/VKA, rivaroxaban, LMWH/dabigatran.

In addition, lifelong treatment with apixaban was compared against treatment with LMWH/VKA for 6 months followed by no treatment.

Aspirin was considered as a comparator in a scenario analysis for the prevention period after treatment with LMWH/VKA for 6 months. Scenario analyses were also conducted comparing apixaban against LMWH monotherapy for the 6-month and lifelong treamtment durations, as well as for lifelong apixaban versus LMWH monotherapy for 6 months followed by no treatment.

Apixaban and other comparators are included in the model according to their UK marketing authorisations and doses (Section 7.5.5, Table 69).

Enoxaparin is the most widely used LMWH in England and Wales for VTE treatment and was used as the parenteral therapy for both VKA and dabigatran in the model. The recommended dose for enoxaparin (1.5 mg/kg) in the UK was used in the economic evaluation. This is a lower dose than was used in the AMPLIFY trial (2 mg/kg). The UK dose has a lower drug acquisition and treatment administration cost and is therefore a conservative assumption.

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

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

No explicit treatment continuation rules are recommended in CG144 for VTE recurrences or bleeding.(8) No continuation rules are therefore considered in the model.

The model considers two base case scenarios reflecting the need for anticoagulation up to 6 months or for lifelong treatment based on clinical judgement and recommendations as in CG144 (see Section 2.4.1).

The model considers treatment discontinuation due to non-fatal IC bleeds, non-fatal non-IC bleeds, recurrent VTE or other reasons.

7.3 Clinical parameters and variables

7.3.1 ***Please demonstrate how the clinical data were implemented into the model.***

Risks of clinical events for patients treated with apixaban or LMWH/VKA in the first 6 months were derived from AMPLIFY, and for patients treated with apixaban or no treatment after this period from AMPLIFY-EXT.(14, 16) In the base case analysis, absolute risks derived from AMPLIFY and AMPLIFY-EXT were used. Risks for all efficacy endpoints were based on the ITT subjects, while all risks for safety endpoints (bleeding) were based on treated subjects (Section 6.5).

Event rates for other NOACs were based on the NMA, which carried out indirect comparisons between apixaban and rivaroxaban and LMWH/dabigatran, as well as VKA and aspirin for the prevention period (See Section 6.7).

Relative risks for efficacy and adverse events from the NMA were used in the economic model for comparators and were applied to the absolute event risks from the trials (Section 6.7.5).

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

The clinical event rates in the model were obtained from the apixaban clinical trials (i.e., AMPLIFY and AMPLIFY-EXT) and the network meta-analysis presented in Section 7.3.6. Risks of recurrent VTE, major bleeding and CRNM bleeds up to six months were taken from AMPLIFY and risks of recurrent VTE beyond six months were taken from AMPLIFY-EXT. These risks were expressed in time-dependent three-month intervals and were applied directly into the three-month model cycles. Six-month rates for treatment discontinuation up to six months were taken from AMPLIFY, while twelve-month rates for treatment discontinuation, CRNM bleeds and major bleeds beyond six months were taken from AMPLIFY-EXT. Rates were converted into three-month risks (model cycle length) using the following formula where r denotes the rate and t denotes time:

Risk per cycle = 1- e-(rt)

Note that for six-month rates derived from AMPLIFY, t was equal to three months (model cycle length) divided by six months (duration of AMPLIFY trial). For twelve-month rates derived from AMPLIFY-EXT, t was equal to three months divided by twelve months (duration of AMPLIFY-EXT trial). Using the formula above, rates were converted into three-month probabilities. Table 94 in the appendices, Section 10.37, presents specific details on how each type of input was obtained as well as transformations applied.

The probability of experiencing an event for treatments other than those in the apixaban clinical trials were calculated by multiplying the risk of event with apixaban by the relative risk of each respective treatment versus apixaban. Relative risks were obtained from the network meta-analysis.

All risks are time-dependent (from time-point of the index VTE) and treatment dependent. Table 95 in Appendix 19a presents an example of the transition probabilities by cycle for a patient with index PE on treatment. Please note that this example does not show how patients can transition to the index PE health state from the index DVT health state for the purposes of simplicity.

7.3.3 *Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

Risks of recurrent VTE and VTE-related death gradually decrease over time.(34, 35) This was captured in the model through incorporating time-dependent risks derived from secondary analysis of AMPLIFY for apixaban and LMWH/VKA for 6 months and AMPLIFY-EXT for apixaban and no treatment from 6 to 18 months.(97, 117) The relative risks for other comparators were taken from the NMAs 1 and 2. For apixaban, the risk of recurrent VTE and VTE-related death beyond 18 months was derived by applying the relative risk for apixaban versus placebo from AMPLIFY-EXT, and for other comparators using relative risks derived from NMA 2.

In the lifelong duration scenario, the risk of recurrent VTE and VTE-related death for no treatment after 18 months, was derived from a prospective cohort study of 1,626 VTE patients over 10

years.(3) Note for the treatment duration scenario, data from AMPLIFY-EXT was not used; however, data were used from the prospective cohort to model the risk of recurrent VTE for patients not on treatment.

In the model, risks of major and CRNM bleeds vary over time for the first six months, as is evident from secondary analysis of AMPLIFY,(97) but are time-independent after 6 months due to the small number of events observed in AMPLIFY-EXT. In the base case, risks of bleeding events were unadjusted for ageing. This was a conservative assumption given that the risk of bleeding is lower for apixaban compared to other comparators, and would be expected to increase with age,(118) thus magnifying the reduced bleeding risk with apixaban. However, bleeding risks were adjusted over time to take into account the increased risks with aging in a scenario analysis. Bleeding risks (major bleed, CRNM bleed) were increased by a factor of 1.97 per decade,(118) similar to adjustments made to the risks of bleeding in earlier models assessing anticoagulants in other indications.(39, 110, 119) The adjustments were made after a period of 18 months from the index event (ie., beyond the period for which trial data were available).

A constant risk of CTEPH was applied in the model following a PE event and was validated by a clinical expert.(37, 107) The model also assumes a constant prevalence of severe PTS of 8.1% (95% CI: 5.8%–10.4%) amongst patients with DVT.(31) This assumption is a simplified approach similar to that used in the rivaroxaban model, based on the cumulative risk and is likely to underestimate the risk in the first 5 years but overestimate it thereafter.

7.3.4 *Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

Intermediate outcome measures were not used in the model.

7.3.5 ***If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:***

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

Expert opinion was sought to inform and validate assumptions and to gain feedback on the clinical validity of the structure of the model. An advisory board was held with three medical experts (a haematologist, a cardiologist and a GP) and three health economists to reach a consensus on inputs and assumptions used in the model.(9) All experts received honoraria to attend the advisory board. Criteria for selecting clinical experts included being a practising clinician in the disease area and being familiar with HTA methods, including NMAs and economic modelling.

Expert opinion was also sought from a consultant in vascular medicine during the development of the NMA and economic model in the form of telephone and direct interviews.(107)

The clinical experts agreed that the model structure had clinical validity and was appropriate and generalisable to VTE.

Summary of selected values

7.3.6 ***Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.***

Index PE and DVT

In the base case analysis, the risks of recurrent VTE and bleeding events were the same for both PE and DVT health states, as the AMPLIFY and AMPLIFY-EXT trials showed no significant differences between the two subgroups.(14, 16) This allowed effects from the whole population to be included in the study, and increased the power of the analysis. Scenario analyses varying the risks of recurrent VTE and bleeding events were performed (see Section 7.6.1). The PE and DVT health states are compared in Table 56.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 56: Comparison of health states relating to PE and DVT (base case)

Category	Index PE and Recurrent PE	Index DVT and Recurrent DVT
VTE	At risk of recurrent VTE (either DVT or PE)*	
Bleeds	At risk of bleeds	
CTEPH	At risk of CTEPH	No risk of CTEPH
PTS	No risk of PTS (excluding those with a recurrent DVT post-PE)	At risk of PTS
Category	**Recurrent PE**	**Recurrent DVT**
Mortality	Long-term effect of PE on mortality applied using increased hazard ratios for death, excluding mortality due to the modelled events	Long-term effect of DVT on mortality applied using increased hazard ratios for death, excluding mortality due to the modelled events
Quality of life	PE-associated utility	DVT-associated utility
Resource use (costs)	Treatment, monitoring, and routine care costs associated with PE	Treatment, monitoring, and routine care costs associated with DVT

*Index VTE events are divided into DVT or PE. Patients experiencing DVT or PE are tracked separately after the event.

CTEPH: Chronic Thromboembolic Pulmonary Hypertension; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; PTS: Post-Thrombotic Syndrome; VTE: Venous Thromboembolism

Recurrent VTE and VTE-related death

Different risks of recurrent VTE and VTE-related death were applied to the model for the first 6 months of treatment and treatment beyond 6 months (Table 57). The risks of these events were calculated by partitioning the risk of the composite recurrent VTE and VTE-related death endpoint according to the distribution of the individual events. In the base case analysis, these risks were derived from the apixaban and LMWH/VKA arms in AMPLIFY for the first 6 months of treatment, and from the apixaban and placebo arms in AMPLIFY-EXT for treatment beyond 6 months. Baseline risks of recurrent VTE for other comparators in the model were derived by applying relative risks (RRs) (ie., vs. apixaban) obtained from the NMA, as displayed in Table 58.

Table 57: Absolute risk of recurrent VTE and VTE-related death

6-month treatment duration	Apixaban	LMWH/VKA
0–3 months	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]
Source: Secondary analysis of AMPLIFY data.(97)		
Lifelong treatment duration	**Apixaban**	**Placebo**
6–9 months	[redacted]	[redacted]
9–12 months	[redacted]	[redacted]
12–15 months	[redacted]	[redacted]

15–18 months	[redacted]	[redacted]

Time-dependent risks were computed using the ITT principle.

LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist

Source: Secondary analysis of AMPLIFY-EXT data.(117)

Table 58: Relative risks of recurrent VTE or VTE-related death based on the NMA

	6-month treatment duration		Lifelong treatment duration	
	RR vs. apixaban	95% CI	RR vs. apixaban	95% CI
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	1.08†	0.69-1.69†	[redacted]	[redacted]
LMWH/dabigatran	1.31†	0.79-2.16†	[redacted]	[redacted]
No treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin*	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence Interval; LMWH: Low Molecular Weight Heparin; RR: Relative Risk; VKA: Vitamin K Antagonist

*6-month relative risk used only for second-line treatment

Source:

a) NMA for treatment period (Section 6.7.5). The treatment network NMA was assumed to be generalisable to the 6 month timepoint, as most trials reported results at 6 months. Only the rivaroxaban EINSTEIN trials reported results for patients who had received 3, 6 or 12 months treatment.
b) NMA for prevention period (Section 6.7.5). The prevention network NMA was assumed to be generalisable to the lifelong treatment duration.

†Cohen et al. 2014 {Cohen, Presented at European Society of Cardiology Congress 2014`, 2nd September`, presentation no. 6037 #687}

Distribution of recurrent VTE events (base case)

In the base case analysis, it was assumed that the distribution of patients across recurrent VTEs and VTE-related death was equal for the different treatments, based on insufficient evidence to demonstrate differences between treatments and consistency with previous models.(18, 19) Expert opinion was that there was no reason to believe the distributions of recurrent VTE would be different as a result of using a different anticoagulant.(9, 107) Scenario analyses were carried out to evaluate differing treatment effects on the distribution of recurrent VTE events. The distribution of recurrent VTEs and VTE-related death was based on pooled estimates from the apixaban and LMWH/VKA arms of AMPLIFY for the first 6 months of treatment and pooled estimates from the apixaban and placebo arms of AMPLIFY-EXT for treatment beyond 6 months (Table 59). The estimates from an earlier systematic review of RCTs were not used due to the lack of validity in the attribution of cause of death in some of the studies included in this NMA.(120) This is consistent with the approach followed in the rivaroxaban DVT model (TA261).(18)

Table 59: Distribution of recurrent PE, recurrent DVT and VTE-related death

	VTE-related death		Non-fatal recurrent PE		Non-fatal recurrent DVT	
	N	%	N	%	N	%
0–6 months[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>6 months[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; VTE: Venous Thromboembolism

Source:

a) Secondary analysis of AMPLIFY data (pooled apixaban and LMWH/VKA).(97)
b) Secondary analysis of AMPLIFY-EXT data.(117)

Major bleeding

Risks for major bleeds were specific to each anticoagulant treatment. The risks of major bleeding were time-dependent for the first 6 months within the analysis, but were not time-dependent for the prevention period in the model due to the small number of events observed. Baseline risks for apixaban and LMWH/VKA for the first 6 months of treatment were derived from AMPLIFY, and from AMPLIFY-EXT for apixaban and placebo (no treatment) beyond 6 months (Table 60).

Table 60: Event rates of major bleeding

6-month treatment duration	Apixaban	LMWH/VKA
Event rate (95% CI)		
0–3 months	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]
Source: Secondary analysis of AMPLIFY data.(97)		
Lifelong treatment duration	**Apixaban**	**Placebo**
>6 months	[redacted]	[redacted]

Time-dependent risks were computed using the safety population, including data from patients during study treatment (time from the administration of the first dose until 48 hours after the last dose was administered)

CI: Confidence Interval; LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist

Source: Secondary analysis of AMPLIFY-EXT data.(117)

Baseline risks of major bleeding for other comparators in the model were derived by applying RRs (vs. apixaban) obtained from the NMA as displayed in Table 61.

Table 61: Relative risks of major bleeding as based on the NMA*

	6-month treatment duration[a]		Lifelong treatment duration[b]	
	RR vs. apixaban	(95% CI)	RR vs. apixaban	(95% CI)
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	1.83[†]	0.92-3.76[†]	[redacted]	[redacted]
LMWH/dabigatran	2.51[†]	1.23-5.34[†]	[redacted]	[redacted]
No treatment*	[redacted]	[redacted]	[redacted]	[redacted]

Aspirin*	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence Interval; LMWH: Low Molecular Weight Heparin; RR: Relative Risk; VKA: Vitamin K Antagonist

*6-month relative risk used only for second-line treatment

Source:

a) NMA for treatment period (Section 6.7.5). The treatment network NMA was assumed to be generalisable to the 6 month timepoint, as most trials reported results at 6 months. Only the rivaroxaban EINSTEIN trials reported results for patients who had received 3, 6 or 12 months treatment.
b) NMA for prevention period (Section 6.7.5). The prevention network NMA was assumed to be generalisable to the lifelong treatment duration.

†Cohen et al. 2014 {Cohen, Presented at European Society of Cardiology Congress 2014`, 2nd September`, presentation no. 6037 #687}

Nature of major bleeding events

In the base case analysis, the case-fatality rate associated with major bleeding events and the nature of non-fatal events (IC or non-IC) was assumed to be independent of treatment and based on a pooled analysis of randomised trials of patients who received anticoagulant therapy for a minimum of 6 months.(121) This study was used due to the small number of events observed in each trial (hence AMPLIFY and AMPLIFY-EXT could not be used alone), and on expert advice that the nature of the major bleed event was not expected to vary by treatment.(9, 107)

In the base case analysis it was assumed that 13.46% (118/877) of major bleeds would be fatal and, of the remaining non-fatal bleeds, 13.97% (106/759) would be IC bleeds.(121) The proportion of non-IC major bleeds was calculated as the remainder of non-fatal major bleeds that were not IC bleeds.

CRNM bleeding

The risks for CRNM bleeds were specific to each anticoagulant treatment and were time-dependent for the first 6 months of the model. Table 62 describes these time-dependent risks for apixaban and LMWH/VKA used for the first 6 months of treatment and the risks for apixaban and placebo used beyond the first 6 months of treatment; these latter risks were not time-dependent due to the small number of events observed.

Table 62: Absolute risk of CRNM bleeding

6-month treatment duration	Apixaban	LMWH/VKA
0–3 months	[redacted]	[redacted]
3–6 months	[redacted]	[redacted]

Time-dependent risks were computed using a modified ITT population, including data from patients during study treatment (time from the administration of the first dose until 48 hours after the last dose was administered)

Source: Secondary analysis of AMPLIFY data.(97)

Lifelong treatment duration	Apixaban	Placebo
>6 months	[redacted]	[redacted]

LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist

Source: Secondary analysis of AMPLIFY-EXT data.(117)

Baseline risks of CRNM bleeding for other comparators in the model were derived by applying RRs (ie., vs. apixaban) obtained from the NMA as displayed in Table 63.

Table 63: Relative risks of CRNM bleeding based on the NMA

	6-month treatment duration[a]		Lifelong treatment duration[b]	
	RR	(95% CI)	RR	(95% CI)
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	2.12†	1.62-2.80†	[redacted]	[redacted]
LMWH/dabigatran	1.25†	0.89-1.75†	[redacted]	[redacted]
No treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin*	[redacted]	[redacted]	[redacted]	[redacted]

CI: Confidence Interval; LMWH: Low Molecular Weight Heparin; RR: Relative Risk; VKA: Vitamin K Antagonist

*6-month relative risk used only for second-line treatment

Source:

a) NMA for treatment period (Section 6.7.5). The treatment network NMA was assumed to be generalisable to the 6 month timepoint, as most trials reported results at 6 months. Only the rivaroxaban EINSTEIN trials reported results for patients who had received 3, 6 or 12 months treatment.
b) NMA for prevention period (Section 6.7.5). The prevention network NMA was assumed to be generalisable to the lifelong treatment duration.

†Cohen et al. 2014 {Cohen, Presented at European Society of Cardiology Congress 2014`, 2nd September`, presentation no. 6037 #687}

CTEPH

The risk of CTEPH was assumed to be equal across treatments as no evidence was otherwise identified, with any differences among treatments produced by the model arising from different numbers of patients experiencing PE or changes in life expectancy (and thus the duration for which patients are at risk of CTEPH). The rate of CTEPH amongst patients with PE was 1.25% (95% CI 0.03% to 2.46%) expressed over a period of 2.1 years, as obtained from a prospective study that followed up 320 patients with PE.(33) The same source was identified by a systematic review carried out in the NICE rivaroxaban submissions.(18, 19)

The per-cycle probability of CTEPH was calculated as follows:

Risk of CTEPH =1-(1-Rate of CTEPH within 2.1 years (1.25%))(number of years in cycle (0.25) / (2.1 years))=0.1496%*

Severe PTS

For patients starting in the DVT health states or in the PE health states having experienced a DVT, a constant risk of developing severe PTS was applied as obtained from a prospective study, identified in a systematic review carried out in the NICE rivaroxaban submissions.(18, 19, 31) Similarly to CTEPH, the risk of PTS was the same for all treatments as there is no evidence to assume otherwise, and any differences among treatments from the model resulted from different numbers of patients experiencing DVT events in the PE health states or from changes in life expectancy that would alter the exposure to the risk of PTS.

It has been reported that the incidence of PTS varies over time, with the source study reporting that the cumulative incidence of PTS was 2.7% after 1 year and 8.1% after 5 years in 528 patients.(31) However, given the limitations of using a Markov structure, the model assumed a constant prevalence of severe PTS of 8.1% (95% CI: 5.8%–10.4%) amongst patients with DVT. This figure is applied to the number of patients who are alive and who are in the index DVT health state and to those patients in the index PE health state who have had a recurrent DVT or have

transitioned from the index DVT health state due to recurrent PE. In order to calculate the proportion of patients in the PE health state who would be exposed to the risk of PTS the sum of recurrent PE events within the DVT health state (ie. those who transitioned from the DVT health state) plus the sum of recurrent DVT events within the PE health state is multiplied by the proportion of patients alive. This approach is subject to double-counting, potentially overestimating the number of patients with PTS as patients could have multiple DVT recurrences. This assumption was used as the Markov structure did not allow for tracking and was considered to be unfavourable to treatments with longer life-expectancy and higher risk of recurrence.

Treatment discontinuation

Treatment discontinuation after bleeding events

After the occurrence of a CRNM bleed, all patients interrupted treatment for 2 days, while after occurrence of an IC bleed, all patients discontinued treatment permanently. This assumption was based on expert opinion and previous NICE submission.(9, 18, 19, 107)

On the occurrence of a non-IC major bleed, [redacted] of patients discontinued treatment permanently whilst the remainder interrupted treatment for a duration of 14 days. The proportion discontinuing was based upon AMPLIFY secondary analysis of pooled discontinuation due to non-IC major bleeds for apixaban and VKA.(97) The duration of interruption was informed by clinical experts.(9, 107)

“Post-CTEPH” and “Post-IC” bleed health states

“Post-CTEPH” and “post-IC” bleed health states were semi-absorbing states, with patients entering these states only able to transition to the death state. The choice to model these health states as semi-absorbing was based on the fact that these conditions are considered to be more severe than the VTE health states with respect to mortality, costs, and disutilities.(11, 18, 19, 41, 122, 123) Patients in these states were assigned expected costs, utility, and survival associated with patients with a history of these diseases/events.These values implicitly accounted for future health problems, so no further events (other than death) were recorded for these patients. Increased mortality in these health states was implemented by applying a constant (time-independent) HR to mortality.

Other treatment discontinuation

In the base case, the event rate for treatment discontinuation unrelated to the modelled events was obtained from AMPLIFY and AMPLIFY-EXT for apixaban and LMWH/VKA (Table 64). Discontinuation unrelated to modelled events was not reported in detail in the other trials for the other comparators, therefore the treatment effect on overall treatment discontinuation from the NMA was used for these comparators (Table 65). As there were no significant differences between the rates for the different treatments, the risk of discontinuation unrelated to modelled events was set equal to apixaban for all treatments in a sensitivity analysis. A further sensitivity analysis was performed where the risk of ‘other’ treatment discontinuation was set to zero for all treatments (see Section 7.6.1).

Table 64: Event rates of other treatment discontinuation

6-month treatment duration	Apixaban	LMWH/VKA	RR (95% CI)
0–6 months event rate (95% CI)	[redacted]	[redacted]	[redacted]
Source: Secondary analysis of AMPLIFY data.(97)			
Lifelong treatment duration	**Apixaban**		
>6 months event rate (95% CI)	[redacted]		
CI: Confidence Interval; LMWH: Low molecular weight heparin; VKA: Vitamin K antagonist Source: Secondary analysis of AMPLIFY-EXT data.(117)			

Baseline risks of other treatment discontinuation for other comparators in the model were derived by applying RRs (vs. apixaban) obtained from the NMA for all-cause discontinuation as shown in Table 65.

Table 65: Relative risks of overall treatment discontinuation from the NMA

	6-month treatment duration[a]		Lifelong treatment duration[b]	
	RR	95% CI	RR	95% CI
LMWH/VKA	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/Dabigatran	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin*	[redacted]	[redacted]	[redacted]	[redacted]
CI, Confidence interval, LMWH, Low molecular weight heparin, NMA, Network meta-analysis, RR, Relative risk, VKA, Vitamin K antagonist *6-month relative risk used only for second-line treatment Source: a) Network meta-analysis of acute studies (Section 6.7.5) b) Network meta-analysis of extended studies (Section 6.7.5)				

Risk of recurrent VTE post treatment discontinuation

Risks of recurrent VTE events for patients in the “no treatment” health states were based on real-world data and were time-dependent.(31)

For the lifelong treatment duration, the risk of recurrent VTE used in patients discontinuing for the period of 6–18 months was based on the placebo arm from AMPLIFY-EXT to enable a fair comparison between the treatment arms evaluated in the model (see Table 57).

The risks beyond the end of AMPLIFY-EXT or in the treatment duration scenario beyond the end of AMPLIFY were based on a prospective cohort study,(31) identified as the most appropriate source in systematic reviews conducted in the NICE rivaroxaban submissions,(18, 19) following 1,626 VTE patients over 10 years after treatment cessation.(3) The study reported the cumulative incidence of recurrent VTE as 11.0% (95% CI, 9.5–12.5) after 1 year, 19.6% (17.5–21.7) after 3 years, 29.1% (26.3–31.9) after 5 years, and 39.9% (35.4–44.4) after 10 years.(3)

The absolute difference between the cumulative incidences at each time point was used to calculate a per-cycle probability of the risk of recurrent VTE after treatment discontinuation for each time point in the model. Please see Appendix 19, Section 10.37, for information on how these calculations were performed.

Risk of bleeding events post treatment discontinuation

Risks of bleeding events for patients in the “no treatment” health states were based on the placebo arm of AMPLIFY-EXT (see Table 60), due to the absence of long-term real-world studies to inform bleeding risks on untreated patients with prior VTE. In one sensitivity analysis, the risk of major bleeding for “no treatment” and apixaban was set equal. In another sensitivity analysis, the risks of major bleeds were adjusted over time to reflect an increase in risk due to ageing (see Section 7.6.1 below).(118)

Other deaths

In the model, “other deaths” represented deaths from causes unrelated to VTE recurrences, VTE complications, or bleeding. In the base case analyses, other deaths were modelled as age- and sex-dependent background general mortality rates based on data from the Office of National Statistics (ONS) 2010-2012.(124) The background mortality rates were adjusted by a hazard ratio to reflect excess mortality associated with patients diagnosed with VTE. The hazard ratio was derived by adjusting survival rates from a study of VTE patients by Flinterman et al. (125) to exclude death due to VTE or bleeding events and comparing these with a control population from the same study, representing general population survival. The resulting estimated hazard ratio was 4.41 (3.63–5.36). Mortality due to VTE and bleeding events were excluded to avoid double-counting since this was considered explicitly in the model. In the base case analysis, the risk of other death was assumed to be equal across treatments, consistent with earlier models and based on advice from clinical experts who suggested that mortality benefits observed from anticoagulant treatment would be a result of reducing recurrent VTE or bleeding events.(9, 18, 19, 41, 107, 126) In a scenario analysis, different risks associated with other mortality were tested (Section 7.7.9).

Excess Mortality in Patients Experiencing IC bleeds and CTEPH

Patients entering the non-fatal IC bleed and CTEPH semi-absorbing health states were modelled as having a higher risk of mortality. Excess mortality in patients in these states was expressed as the excess mortality relative to patients with VTE who did not experience any events. For patients experiencing an IC bleed, an HR of 2.6 (2.2–3.0) was used. This estimate was based on the observed excess mortality in patients with VTE receiving conventional anticoagulation who had experienced a major bleed versus patients with VTE who had not bled at a 3-month follow-up of patients in the large RIETE registry (n=29,903), a multicentre registry of patients with VTE.(112) This estimate excludes initial fatal events from the cohort of patients who had bled and was adjusted for baseline characteristics. .

For patients with CTEPH, an HR for mortality of 1.3 (0.98–1.73) was assumed, in relation to patients with PE who had not experienced any events and who had a median follow-up of 3.8 years.(113) This estimate was calculated for patients with chronic pulmonary disease from a large retrospective analysis of 1023 patients with PE who were followed up for 3.8 years and was preferred to the constant probability of mortality approach which was assumed in earlier models.(18, 19) If a constant risk of mortality equivalent to 9.5% annually had been assumed as in earlier models,(127) this would suggest that, after the age of 72, patients would benefit from being in the CTEPH state, as they would have a lower mortality than the overall VTE population at that age (estimated by applying the HR of VTE to general population UK life-tables).

7.3.7 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.*

Time-dependent relative risks of recurrent VTE events for apixaban and no treatment in the model were available from AMPLIFY and AMPLIFY-EXT up to 18 months. Beyond this point a constant risk was applied for the remainder of the model time horizon, based on a large prospective cohort study by Prandoni et al. which followed 1,626 VTE patients over 10 years.(3) The relative risk of apixaban versus placebo from AMPLIFY-EXT and versus other comparators from the NMA were applied to this risk to derive the risk of recurrent VTE beyond 18 months. The relative effect observed from AMPLIFY-EXT and the NMA were assumed to continue in the model, on the basis that there were no long-term data to suggest otherwise. Relative risks and event rates derived from AMPLIFY-EXT for major bleeding, CRNM bleeding and other treatment discontinuation were applied as constant rates from 6 months until the end of the model time horizon, on the assumption that the number of events occurring beyond 6 months would be small, based on the available clinical trial data.(16, 54, 55, 75, 76, 78-82)

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

A summary of the assumptions made in the economic analysis is presented in Table 66.

Table 66: Assumptions in the economic analysis

Assumption	Rationale
As a result of the Markovian assumption, we did not track or model any further VTE recurrences after IC bleeds, nor did we account for an increased risk of additional recurrent VTEs once patients experienced a recurrent event.	These assumptions are likely to be unfavourable to apixaban given the reductions observed in recurrent VTE events seen with apixaban treatment. Had we modelled additional exposure to the risk of a recurrent VTE after an IC bleed and/or an increased risk of recurrent VTE following a first recurrence, this would result in a larger reduction in events for patients treated with apixaban and more favourable results, given the relative bleeding effect for apixaban when compared to other therapies.
We did not account for permanent treatment changes following a recurrent VTE. We also assumed that mortality due to causes unrelated with VTE were independent of treatment.	This assumption was necessary due to the Markovian assumption which restricts the ability to track a patient's history following a recurrent VTE event. There is evidence to suggest patients who experience a recurrent VTE would remain on treatment for their remaining lifetime.(128, 129)
In our analysis, we assumed that the nature of recurrent VTEs (the distribution among non-fatal PE, non-fatal DVT, and VTE-related death) and major bleeding events (case-fatality of major bleeds as well as the proportion of non-fatal bleeds that were intracranial) were independent of treatment.	This assumption is similar to that used in earlier models (108, 125, 130, 131) and is appropriate given that the trials were not sufficiently powered to determine differences in the individual end-points.(14, 16) This assumption was tested in a scenario analysis (Section 7.6.1).

Assumption	Rationale
The distribution of recurrent VTE events was obtained from AMPLIFY and AMPLIFY-EXT by pooling the two arms included in each trial	This is consistent with the approach used in earlier models,(11, 18, 19, 41, 125, 131) and whilst the distribution of recurrent events could have been informed by an earlier meta-analysis,(120) use of data from AMPLIFY was considered to be more suitable and reflective of the population due to lack of validity in the attribution of cause of death in some of the studies included in the meta-analysis. This was also supported by clinical experts.(9, 107) This assumption was tested in a scenario analysis using data from the NMA (Section 7.6.1).
The distribution of recurrent VTE events was assumed to be constant in the acute period and constant in the extended period based on the observed data.	This approach is similar to that utilized in earlier models.(18, 19) Though the distribution of recurrent VTE events may vary over time, the trial data were not sufficiently powered to detect such differences. In addition, the earlier meta-analyses published by Carrier et al. suggested negligible differences in the distribution of recurrent events between patients treated for 3 or 6 months.(120)
For the nature of major bleeding events, data from the literature was used, although an inherent limitation is that the source used is not specific to a VTE population.	AMPLIFY and AMPLIFY-EXT were not used due to the fact that the number of events observed was small. Furthermore, the source study found that the indication for oral anticoagulant therapy had a limited influence on the proportion of major bleeds that are intracranial or fatal; this finding was backed up by clinical opinion.(9, 107, 121) However alternative estimates for the proportion of fatal and non-intracranial bleeding events based on the VTE population were tested in scenario analysis.
It was assumed that the risk of bleeding did not increase due to ageing.	This was a conservative assumption that favours the other comparators over apixaban, due to the lower risk of bleeding associated with apixaban. This assumption was tested in a scenario analysis by including an adjustment factor for ageing.
The risk of treatment discontinuation beyond that attributed to VTE and bleeding events (“other” treatment discontinuation) was assumed to remain constant over time.	This was consistent with the previous rivaroxaban submissions.(18, 19) To test the impact of this assumption the risk of treatment discontinuation was set to 0 in scenario analysis.
Overall treatment discontinuation was used as a proxy for “other” treatment discontinuation for comparators, potentially resulting in double-counting	This was due to the lack of head-to-head data for comparators for this outcome. This was tested in scenario analysis by setting the risk of other treatment discontinuation to be equal for al treatments
Utilities were derived from a number of different sources, and some values may not be specific to a UK population.	This was a result of insufficient data in the published literature. Alternative utility estimates derived from a standard gamble were tested in scenario analysis
We assumed the same utility decrement would apply to patients treated with NOACs as that observed in patients treated with aspirin.	A conservative assumption was made in the absence of relevant evidence that NOACs are associated with a small utility decrement equivalent to that reported for aspirin (132). This approach was taken in the previous submission to NICE for apixaban for non-valvular atrial fibrillation(133), but was not taken in the previous rivaroxaban NICE submissions for DVT and PE.(18, 19) A scenario was examined where no disutility was applied for all treatments.
It was assumed that the cost of LMWH for the LMWH/VKA and LMWH/dabigatran arms would be equivalent to the recommended UK enoxaparin dose of 1.5 mg/kg, whereas in AMPLIFY a dose of 2 mg/kg was used.	The UK dose has a lower drug acquisition and treatment administration cost and is therefore a conservative assumption. A weighted average of LMWH treatment costs was used in a sensitivity analysis based on market share data.

Assumption	Rationale
We assumed the continuation of relative treatment effects from the NMA past the trial endpoints.	This assumption was made on the basis that there is a lack of long-term evidence beyond the trial endpoints to model these effects.
INR monitoring visits were assumed to be undertaken in primary care in 66.45% of cases, with the remainder (33.55%) undertaken in secondary care This distribution was tested in scenario analysis by setting monitoring to 100% for each setting.	Based on a national survey that included 78 Primary Care Trusts (PCTs) in England, three local health boards in Wales, and health board in Scotland, and validated by clinical experts as being reasonable.(9, 18, 19)
It was assumed that 50% of the first INR monitoring visits conducted in primary care were delivered by a GP with the remainder delivered by a nurse.	This was similar to assumptions used in earlier NICE submissions.(18, 19)
It was assumed that 6 monitoring visits would be required in the first 3 months followed by 3 visits every 3 months.(134)	This is a more conservative rate than that used in the previous rivaroxaban NICE technology appraisals, where patients were assumed to require 9 visits in the first three months followed by 5 visits every 3 months.(18, 19)
DVT: Deep vein thrombosis; IC: Intracranial; LMWH: Low molecular weight heparin; NMA: Network meta-analysis; NOAC: Novel oral anticoagulant; PE: Pulmonary embolism; VKA: Vitamin K antagonist; VTE: Venous thromboembolism	

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 *Please outline the aspects of the condition that most affect patients' quality of life.*

The aspects of the condition deemed most likely to affect the patient are as follows:

- The occurrence of VTE has been shown to have a negative impact on the quality of life of patients across physical, social and psychological domains.(135, 136) In particular, PE is considered to have a greater impact on quality of life than DVT.(137)
- Long-term morbidity can arise due to the development of CTEPH after a PE.(111)
- Similarly, the occurrence of PTS is a significant determinant of quality of life in DVT patients.(138)

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

On the occurrence of a PE or DVT, patients would experience a decrease in HRQL, expected to last for 30 days as symptoms of the event are commonly resolved within a period of less than 2 months.(139)

In addition to utility decrements associated with the index VTE event itself, a small treatment dependent decrease in HRQL for VKA, aspirin or NOACs would also be expected due to reasons such as the inconvenience of taking medication.(39) This would persist for the duration of treatment.(132)

Finally, the occurrence of adverse events such as CTEPH, PTS, or bleeding as a result of anticoagulation would also be expected to adversely affect a patient's HRQL. Non-IC major bleeds and CRNM bleeds would cause a temporary reduction in HRQL,(9, 110) as they are not associated with long-term consequences, whereas the adverse effects of PTS, CTEPH, and IC major bleeds

are expected to last for the remainder of a patient's lifetime due to the severity of these events.(111, 138, 140)

HRQL data derived from clinical trials

7.4.3 ***If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.***

- ***Method of elicitation.***
- ***Method of valuation.***
- ***Point when measurements were made.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***

No HRQL data were collected in the clinical trials.

Mapping

7.4.4 ***If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.***

- ***Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.***
- ***Details of the methodology used.***
- ***Details of validation of the mapping technique.***

No mapping was conducted.

HRQL studies

7.4.5 ***Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 16.***

An update was carried out to the existing systematic review conducted for the rivaroxaban NICE submission to identify potentially relevant studies reporting utilities.(11) Full details of the methodology used to update the rivaroxaban systematic review are provided in Appendix 16, Section 10.35.

The exisiting systematic review for HRQL studies used in the rivaroxaban appraisal was conducted on 1st May 2012 and the update was conducted on the 15th July 2014.

The following databases were searched 1st May 2012 to 15th July 2014:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations and Daly Update (Ovid)
- EMBASE (Ovid)
- EconLit (EBSCO)

- Cochrane Library (incorporating the NHS Economic Evaluations Database (NHS EED), and the Health Technology Assessment (HTA) database)

In order to retrieve further literature not identified through the electronic database search, reference lists of included papers were scanned and searches for grey literature, completed and on-going studies were also carried out. A separate search for conferences was not carried out because the pre-specified conferences were identified through the electronic database search. Furthernore, the NICE website was searched for manufacturer and Evidence Review Group (ERG) economic models for potentially relevant literature.

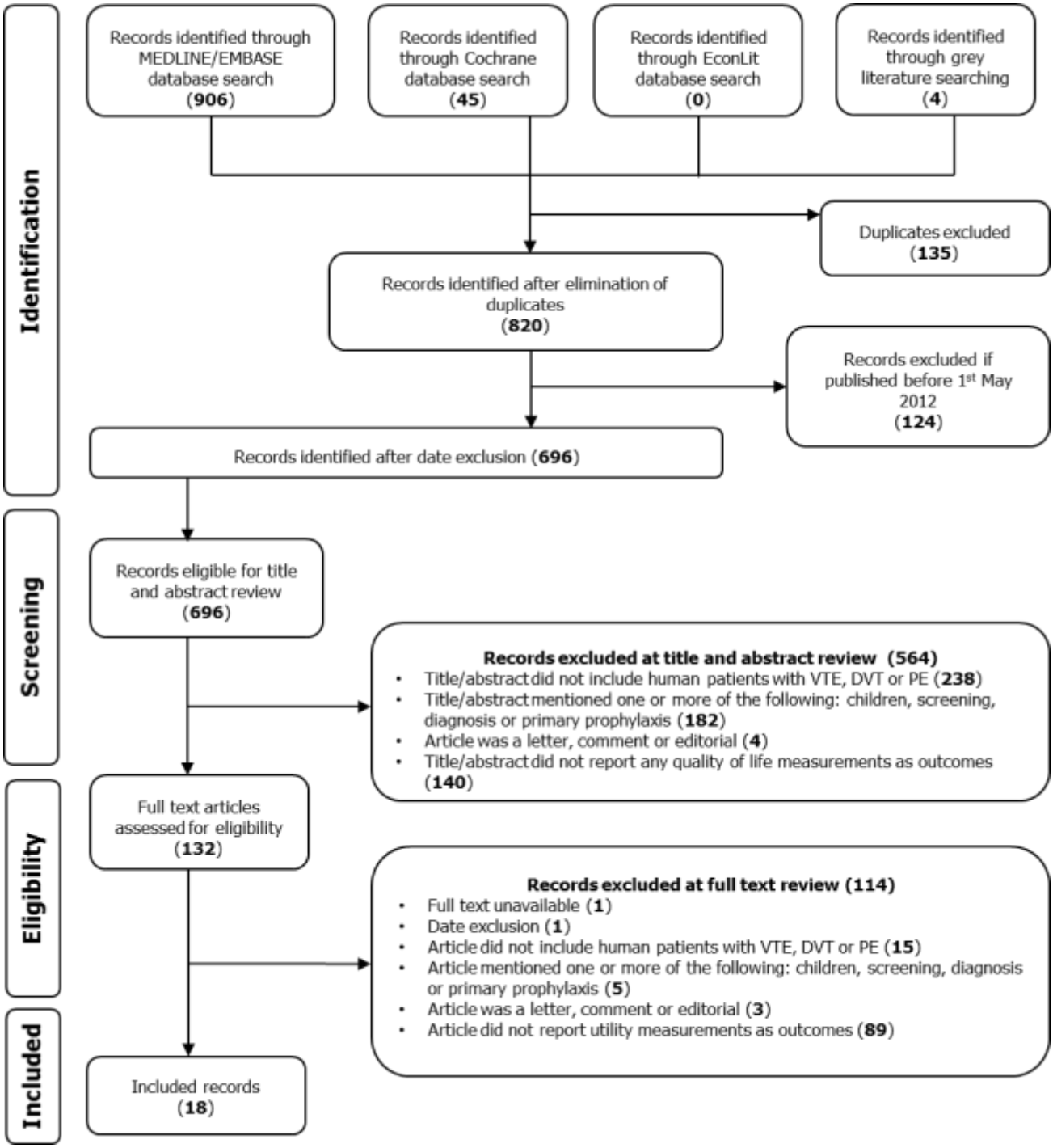
The inclusion and exclusion criteria used to identify relevant articles in the review update are summarised in Table 88 in the appendices Section 10.35.6. These are the same eligibility criteria applied in the existing rivaroxaban systematic review for the NICE submission

The existing rivaroxaban systematic conducted by Bayer identified 7 studies reporting relevant utility values. Full details of the 7 studies included in the existing rivaroxaban systematic review are presented in Table 89 in Appendix 16, Section 10.35.

The electronic database search identified 951 articles, while grey literature searching yielded 4 additional potentially relevant articles (Figure 27). Following deduplication and date restriction (1st May 2012 to 15th July 2014), 696 articles were screened based on title ± abstract.

On the reapplication of the inclusion criteria, 564 title ± abstracts were excluded. Therefore 132 full text papers were further screened for inclusion, of which 114 were excluded. Therefore, 18 studies were included in the updated systematic review. The list of all included studies is presented in Table 90 in the Appendices, Section 10.35.

Figure 27: PRISMA flow diagram of number of journal articles identified and included at each stage of the Health Utilities Review Update



7.4.6 ***Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.***

- ***Population in which health effects were measured.***
- ***Information on recruitment.***
- ***Interventions and comparators.***
- ***Sample size.***
- ***Response rates.***
- ***Description of health states.***
- ***Adverse events.***
- ***Appropriateness of health states given condition and treatment pathway.***
- ***Method of elicitation.***
- ***Method of valuation.***
- ***Mapping.***
- ***Uncertainty around values.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***
- ***Appropriateness of the study for cost-effectiveness analysis.***

Details of the 7 utility studies identified by the existing rivaroxaban systematic review performed by Bayer are presented in Table 89 in Appendix 16, Section 10.35. The EQ-5D, SG, and TTO were used to elicit utility values in 2 studies each, whereas the CAMPHOR scores and utility index was used in 1 study.

Among the 18 studies assessing health utilities identified in the updated systematic review , a range of elicitation methods were used. Utilities were derived using the EuroQol 5 Dimension (EQ-5D) in 6 studies, the Standard Gamble (SG) in 6 studies, the Time Trade-Off (TTO) in 5 studies and the Visual Analogue Scale (VAS) in 3 study. The two NICE rivaroxaban appraisals identified reported utilities derived using all four methods of elicitation described above and the method of elicitation was not reported in 3 studies. Table 90 in the Appendix 16, Section 10.35. provides a summary of the studies reporting utilities identified by the updated systematic review.

Of the additional 6 studies that reported EQ-5D utility values, the preferred method in the NICE reference case,

- 4 reported utilities derived from Norwegian populations.(141-144) Three of these reported from the CaVenT RCT, but did not provide utilities relevant to the model health states. The other study was a small case control study (N=208 PE cases, 114 matched controls), but was only available in abstract form and so the quality of the study, methods and relevance to the population with PE in the model were unclear.
- 1 was a multi-national study by Ghofrani et al. (26 countries) and reported on CTEPH; this was used in the economic model for the CTEPH health state. (111)
- 1 was a secondary source (108) that reported on a post-IC bleed utility of 0.69, which was extracted from a study of stroke patients by Xie et al.(145) The study used EQ-5D United States preference based weights.

7.4.7 *Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.*

No HRQL data were collected in any of the included clinical trials.

Adverse events

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

Bleeding events are the main adverse events related to anticoagulation. Three types of bleeding events were considered in the model: major IC bleed, major non-IC bleed and CRNM bleed. On the occurrence of fatal major bleeds, patients transitioned to the “Death” health state and were assigned a utility of 0. Patients experiencing a non-fatal IC bleed were assigned an updated utility value for a period of 91 days.(137, 140) On the occurrence of a non-fatal non-IC major bleed or a CRNM bleed, utility decrements were applied additively to the baseline utility for durations specific to each event. All patients experiencing CRNM bleeds experienced a disutility for 2 days,(110) (146) and patients with a non-IC major bleed were assigned a utility decrement for 30 days.(9, 137)

Patients were also at risk of developing CTEPH or PTS. Patients who died as a result of CTEPH transitioned to the “Death” health state and were assigned a utility of 0. Those who survived were assigned an updated utility value for their remaining lifetime.(111) Patients developing PTS were assigned an associated utility decrement throughout the model.(114)

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

7.4.9 *Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.*

The utility values used in the cost-effectiveness analysis are summarised in Table 67. Utilities were updated upon the occurrence of an IC bleed and CTEPH, which result in permanent health state changes. Utility decrements were applied additively to the baseline utility upon the occurrence of a PE, DVT, non-IC major bleed, CRNM bleed, or severe PTS for durations specific to each transient event. These duration inputs were based on the literature, and for non-IC bleeds on expert opinion (Table 67). The use of age-specific utilities was explored in a sensitivity analysis (Section 7.6.1).

Baseline utility
A baseline utility was applied to all patients, based on a UK population-average score from Kind et al. (Table 67).(147) This study was reported by NICE as a landmark national EQ-5D survey, and was used in the present model for consistency with the previous rivaroxaban NICE submissions.(18, 19) In scenario analysis the baseline utility was also varied by age (Section 7.6.1).

PE and DVT
Utility decrements associated with PE and DVT were derived from a study by Locadia et al., in line with the previous rivaroxaban NICE submissions.(18, 19, 137) A study by Hogg et al. was also identified in the systematic review, however as this study used the standard gamble method to elicit utility values, whereas the Locadia et al. study used the time trade-off method, which is preferred in the NICE methods guide (115), the Locadia utility was used in the base case, and utilities from Hogg are tested within a scenario analysis (Section 7.6.1).

IC bleeds
Changes in quality of life associated with IC bleeds were modelled using updated utility values derived from studies by Locadia et al. (137) and Pickard et al.(140) This approach was similar to that used in the rivaroxaban NICE submissions and the conservative approach employed by the ERG in TA287,(18, 19) and was replicated as these studies were identified as the best available evidence for

utilities associated with IC bleeds. Pickard et al. was preferred to Xie et al. (145) for the post-acute IC bleeds due to the use of UK rather than USA preference based weights.

Major non-IC bleeds
Locadia et al. was selected in line with previous rivaroxaban NICE submissions (18, 19, 137), on the basis that in the absence of EQ-5D values, utility values derived through time trade off are deemed more suitable than those by other means such as standard gamble.(115)

CRNM bleeds
A utility decrement associated with CRNM bleeds was obtained from a study by Sullivan et al. identified through grey literature searches outside of the systematic review update.(146) While this study was not specific to patients with VTE, EQ-5D was used as the method of elicitation, as preferred by NICE (115), and no alternative studies were identified.

CTEPH
A utility value for CTEPH was derived from the Ghofrani et al. study by averaging the utilities reported for the riociguat and placebo arms.(111) This study was considered the most suitable for modelling this health state as it used the EQ-5D method of elicitation, which is preferred by NICE.(115)

Severe PTS
The model considered only severe forms of PTS, therefore the utility decrement described by Lenert et al. was the most appropriate value identified.(19, 114) While the Enden et al. study reported utility values for both mild and severe PTS, these were derived from patients with venous ulcers rather than in patients with VTE or PTS specifically.(142)

Anticoagulation
Utility decrements associated with use of VKA and aspirin were obtained from a study by Gage et al., which was the only study identified that provided a disutility for aspirin as well as VKA.(132) In the absence of relevant evidence, use of NOACs was assumed to have the same impact on quality of life as aspirin. This is a more conservative assumption than has been used in previous models where only warfarin disutilities have been applied.(11, 41) A scenario was examined where no disutility was applied for all treatments (Section 7.6.1).

While the Marchetti 2001 study was also identified by the systematic review as providing a treatment-related disutility for warfarin (148) and has been used in previous rivaroxaban submissions,(18, 19) the disutility reported by Gage et al. was used as it was more conservative, giving a smaller difference between warfarin and the other comparators.

Table 67: Summary of quality of life values for the cost-effectiveness analysis

Utility scores for baseline, IC bleed, and CTEPH	Utility score	Utility measurement	Source	Duration	Source
Baseline Utility	0.8224	EQ-5D	Kind et al. 1998 (147) (NICE TA261(18); NICE TA287 (19))	-	-
IC Bleed					
Acute care period	0.33	TTO	Locadia et al. 2004 (137) (NICE TA261(18); NICE TA287 (19))	91 days	Locadia et al. 2004 (137)
Post-acute care	0.61	EQ-5D	Pickard et al. 2004 (140) NICE TA287 (19))	Beyond 91 days	
CTEPH					
Acute care period	0.65	EQ-5D	Ghofrani et al. 2013 (111)	30 days	Ghofrani et al. 2013 (111)
Post-acute care	0.65			Beyond 30 days	
Utility decrements associated with clinical events and use of ACs	**Utility decrement**	**Utility measurement**	**Source**	**Duration**	**Source**
PE	-0.32	TTO	Locadia et al. 2004 (137)(NICE TA261(18); NICE TA287 (19))	30 days	Hogg et al. 2013 (139)
DVT	-0.11				
Bleeding					
Major non-IC bleed	-0.30	TTO	Locadia et al. 2004 (137) (NICE TA261(18); NICE TA287 (19))	30 days	Expert opinion (9)
CRNM bleed	-0.0054	EQ-5D	Sullivan et al. 2011 (146)	2 days	Dorian et al. 2014 (110)
Severe PTS	-0.07	SG	Lenert et al. 1997 (114) (NICE TA261(18); NICE TA287 (19))	Throughout	Lenert et al. 1997 (114)

Anticoagulation					
Apixaban	-0.002	TTO	Gage et al. 1996 (132)	Whilst on treatment	Gage et al. 1996 (132)
Rivaroxaban	-0.002				
LMWH/dabigatran	-0.002				
LMWH/VKA	-0.013				
Aspirin	-0.002				
AC: Anticoagulant; CRNM: Clinically Relevant Non-Major; CTEPH: Chronic Thromboembolic Pulmonary Hypertension; DVT: Deep Vein Thrombosis; IC: Intracranial; LMWH: Low Molecular Weight Heparin; PE: Pulmonary Embolism; PTS: Post-Thrombotic Syndrome; SG: Standard gamble; TTO: Time trade-off; VKA: Vitamin K Antagonist					

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

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

Expert opinion was sought to inform and validate assumptions and to gain feedback on the clinical validity of the structure of the model. An advisory board was held with three medical experts (a haematologist, a cardiologist and a GP) and three health economists to reach a consensus on inputs and assumptions used in the model.(9) All experts received honoraria to attend the advisory board. Criteria for selecting clinical experts included being a practicing clinician in the disease area and being familiar with HTA methods including NMAs and economic modelling.

Expert opinion was also sought from a consultant in vascular medicine during the development of the NMA and economic model in the form of telephone and direct interviews.(107)

Utilities were taken from the literature identified through the Quality of Life and Health Utilities systematic review. The clinical experts agreed that the chosen utilities had face validity.

[iv] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.11 *Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?*

The utility scores and decrements associated with each health state are presented in Section 7.4.9, Table 67.

The utility values are subject to variation between patients, for example due to differences in age. This is accounted for by varying the utility scores and decrements in the deterministic sensitivity analysis (Section 7.6.2), PSA (Section 7.6.3), and scenario analyses (Section 7.6.1).

7.4.12 *Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?*

A list of utility values identified in the systematic review, and their reasons for inclusion or exclusion are summarised in Section 7.4.6.

7.4.13 *If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?*

A baseline utility of 0.825 was applied to all patients, based on a population-average score from Kind et al.(147) The baseline utility was updated on the occurrence of an IC bleed or CTEPH, and utility decrements were applied to the baseline utility upon the occurrence of a PE, DVT, non-IC major bleed, CRNM bleed, or severe PTS for durations specific to each event (Section 7.4.9, Table 67).

7.4.14 *Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.*

HRQL was assumed to vary as patients experienced different events within the model, as described in Section 7.4.9, Table 67. Within each health state, HRQL was assumed to be constant over time.

7.4.15 *Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.*

No further amendments have been undertaken.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 ***Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.***

Clinical management of VTE is conducted across both primary and secondary care. Patients receive initial treatment for a VTE, treatment-related bleed or CTEPH in hospital, while longer term monitoring and post-acute care is more frequently conducted in primary care.

Hospital costs were calculated using 2012/2013 NHS reference costs where relevant HRG procedure codes were available.(149) Unit costs associated with primary care were calculated from the Personal Social Services Research Unit (PSSRU) 2013.(150) Where costs could not be identified from these sources, such as for post-acute care of IC bleeds, unit costs were obtained from the published literature.

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

Where possible, UK National Reference costs were used. If UK NHS reference costs were not available, other sources were used as stated in Section 7.5.1.

Scenario analysis was carried out using PbR tariffs in place of NHS reference costs.

Resource identification, measurement and valuation studies

7.5.3 ***Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in appendix 17. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:***

- ***country of study***
- ***date of study***
- ***applicability to UK clinical practice***
- ***cost valuations used in study***
- ***costs for use in economic analysis***
- ***technology costs.***

An update of the existing systematic review for costs and resource use conducted for the rivaroxaban NICE submission was carried out to identify potentially identify relevant studies reporting costs and resource use.(11) Full details of the methodology used to update the existing systematic review are presented Appendix 17, Section 10.36.

The existing rivaroxaban systematic review review was conducted on 3rd October 2012. The review update was conducted on the 15th July 2014.

The following databases were searched from 3rd October 2012 to 15th July 2014::

- MEDLINE (Ovid)

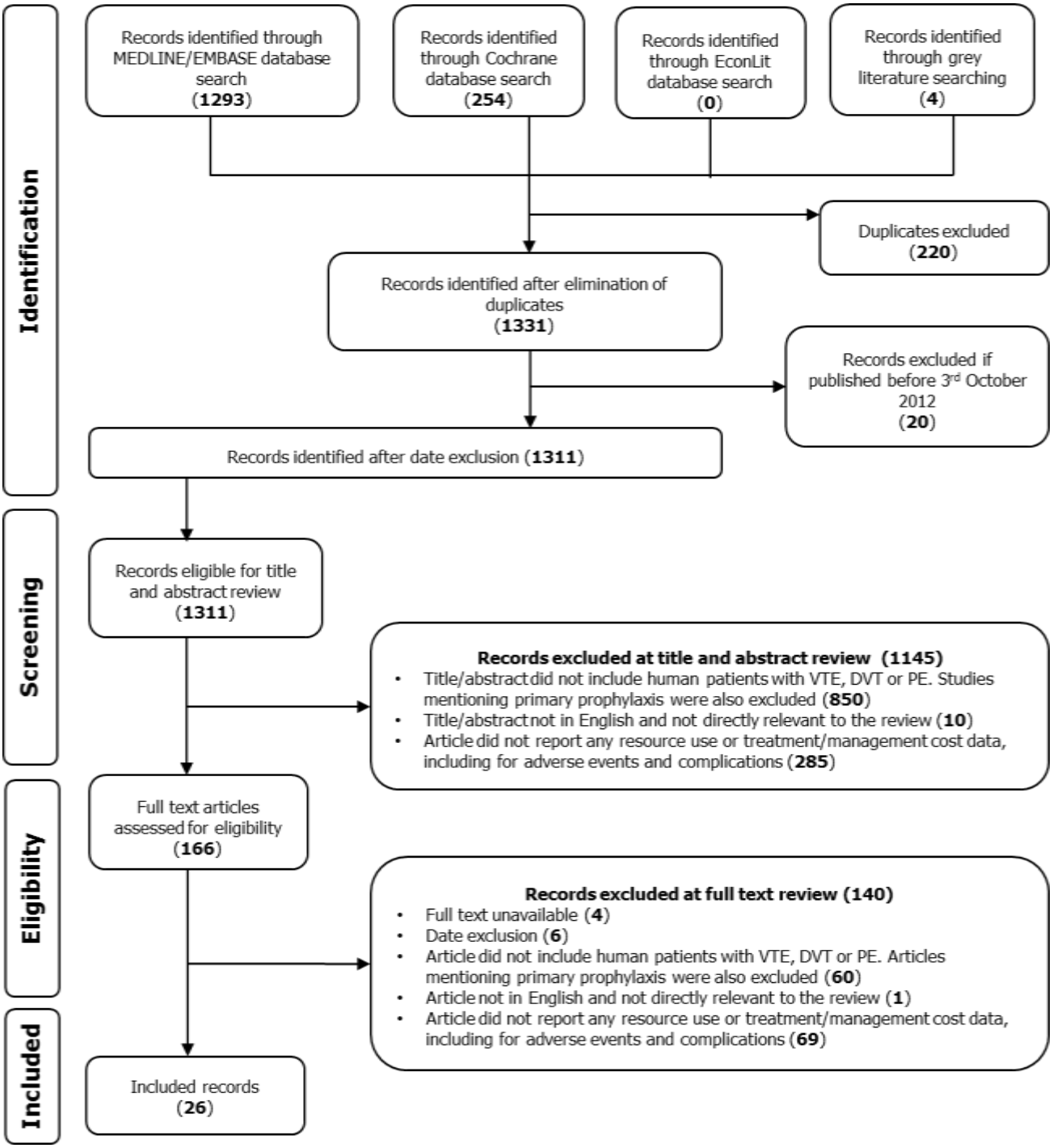
- MEDLINE In-Process Citations and Daily Update (Ovid)
- EMBASE electronic (Ovid)
- EconLit (EBSCO)
- Cochrane Library (incorporating the NHS Economic Evaluations Database (NHS EED), and the Health Technology Assessment (HTA) database)

In order to retrieve further literature not identified through the electronic database search, reference lists of included papers were scanned and searches for grey literature were carried out. A separate search for conferences was not carried out because the pre-specified conferences were identified through the electronic database search. Furthermore, the NICE website was searched for manufacturer and Evidence Review Group (ERG) economic models for potentially relevant literature.

Inclusion and exclusion criteria used to identify potentially relevant articles in the review update are summarised in Table 91 in the appendices Section 10.36.6. These are the same eligibility criteria that were applied in the exisiting rivaroxaban systematic review.

The electronic database search identified 1,547 articles while grey literature searching yielded 4 additional potentially relevant articles (Figure 27). Following deduplication and date restriction (3rd October 2012 to 15th July 2014),1,311 were screened based on title ± abstract. On the reapplication of the inclusion criteria, 1,145 title ± abstracts were excluded and therefore166 full text papers were further screened for inclusion, of which 140 were excluded. Therefore, 26 studies were included in the updated systematic review. Of the included studies, only two UK based studes were found to be relevant, the rivaroxaban NICE submissions.(18, 19) The list of all included studies is presented in Table 93 in the Appendices, Section 10.36.

Figure 28: PRISMA flow diagram of number of journal articles identified and included at each stage of the Cost and Resource Use Review Update



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

- ***the criteria for selecting the experts***

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[v] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

Expert opinion was sought to inform and validate assumptions and to gain feedback on the clinical validity of the structure of the model. An advisory board was held with three medical experts (a haematologist, a cardiologist and a GP) and three health economists to reach a consensus on inputs and assumptions used in the model.(9) All experts received honoraria to attend the advisory board. Criteria for selecting clinical experts included being a practicing clinician in the disease area and being familiar with HTA methods such as evidence synthesis including NMAs and economic modelling.

Expert opinion was also sought from a consultant in vascular medicine during the development of the NMA and economic model in the form of telephone and direct interviews.(107)

Costs and resource use associated with anticoagulation, VTE and VTE-related death, as well as adverse events were validated by the clinical experts as a sufficient representation of clinical practice. In particular, experts were asked to validate costs and resource use associated with LMWH therapy, INR monitoring, CTEPH, PTS, treatment interruption following a CRNM bleed, treatment patterns following a recurrent VTE.

Intervention and comparators' costs

7.5.5 ***Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.***

Drug acquisition costs for were obtained from the British National Formulary (BNF) and the electronic Market Information Tool (eMIT) as detailed in Table 68.(151-153)

Table 68: Drug acquisition costs

Therapy	Detail	Price per Unit
LMWH[a]	Enoxaparin sodium 300 mg/1 ml solution for injection pre-filled syringes	£21.33
VKA[b]	VKA 6 mg (calculated VKA 1 mg pack size 28 + 5 mg pack size 28)	£0.009
Apixaban[a]	Apixaban 2.5 mg tablets	£1.10
	Apixaban 5 mg tablets	£1.10

Rivaroxaban[a]	Rivaroxaban 15 mg tablets	£2.10
	Rivaroxaban 20 mg tablets	£2.10
Dabigatran[a]	Dabigatran 150 mg tablets	£1.10
Aspirin[b]	Aspirin 75 mg gastro-resistant tablets (pack size 56)	£0.004

LMWH: Low Molecular Weight Heparin; VKA: Vitamin K antagonist

Source:

a) BNF September 2014.(151)

b) eMIT February 2014.(152)

In the NOAC trials, the dose of enoxaparin assigned to patients was 1 mg/kg bd.(14, 73, 109) However, the SPC approved by the European Medicines Agency recommends a dose of 1.5 mg/kg qd.(154) The approved European dose was used to cost LMWH in the model. Since the European licensed dose leads to a lower cost for LMWH, this assumption is considered to be conservative. The administration schedule for each treatment regimen was obtained from the respective summary of product characteristics (SPC) as detailed in Table 69. For prevention, treatment was assumed to continue indefinitely until discontinuation or death. The induction length for LMWH was obtained from secondary analysis of the AMPLIFY trial and was 7.64 days for LMWH/warfarin.(97) The LMWH induction for dabigatran was 5 days in the model based on dabigatran's SPC and, unlike warfarin, there is no need to remain on LMWH until TTR is in range.

The BNF suggests a loading dose of warfarin of 5–10 mg and maintenance doses of 3–9 mg to achieve an INR between 2 and 3, as prescribed in the trials.(14, 73, 109) As a conservative assumption, an average daily dose of 6 mg was used as the mid-point of the maintenance dose range and toward the lower end of the loading dose range, similar to assumptions used in earlier NICE submissions.(11, 41)

Conservatively, no costs were assumed for "no treatment".

Table 69: Administration schedule

Treatment arm	Treatment	Induction Dose	Induction Length	Maintenance Dose	Maintenance Length	Prevention Dose (daily)
LMWH/VKA	LMWH[a]	1.5 mg/kg od (120 mg syringe)	7.64 days	-	-	-
	Warfarin[b]	6 mg	5 days	6 mg (1 mg & 5 mg tablets)	-	6 mg
Apixaban	Apixaban[c]	10 mg bd	7 days	5 mg bd	6 months	2.5 mg bd
Rivaroxaban	Rivaroxaban[d]	15 mg bd	21 days	20 mg od	-	20 mg od
LMWH/ dabigatran	LMWH[a]	1.5 mg/kg od (120 mg syringe)	5 days	-	-	-
	Dabigatran[e]	-	-	150 mg bd	-	150 mg bd
LMWH/VKA followed by no treatment	LMWH[a]	1.5 mg/kg od (120 mg syringe)	7.64 days	-	-	-
	Warfarin[b]	6 mg	5 days	6 mg (1 mg & 5 mg tablets)	6 months	-

Aspirin	LMWH[a]	1.5 mg/kg od (120 mg syringe)	7.64 days	-	-	-
	Warfarin[b]	6 mg	5 days	6 mg (1 mg & 5 mg tablets)	6 months	-
	Aspirin[f]	-	-	-	-	100 mg od

bd: Twice daily; LMWH: Low Molecular Weight Heparin; od: Once daily; VKA: Vitamin K Antagonist

Sources:
a) Clexane SPC 2013 (154)
b) Warfarin SPC 2014 (155)
c) Eliquis SPC 2014 (20)
d) Xarelto SPC 2014 (156)
e) Pradaxa SPC 2014 (157)
f) Aspirin SPC 2013 (158)

Based on the drug acquisition costs and recommended daily doses, the daily price for each drug in each treatment phase was calculated (Table 70).

Table 70: Daily drug costs

Treatment	Detail	Daily Price Induction	Daily Price Maintenance	Daily Price Prevention
LMWH/VKA[a,b]	1 x 1 mg and 1 x 5 mg VKA Enoxaparin sodium 300 mg/1 ml solution for injection pre-filled syringes (7.64 days induction)	LMWH: £9.02 VKA: £0.009	VKA: £0.009	VKA: £0.009
Apixaban[a]	4 x 5 mg (induction) 2 x 5 mg (maintenance) 2 x 2.5 mg (maintenance and prevention)	£4.40	£2.20	£2.20
Rivaroxaban[a]	2 x 15 mg (induction) 1 x 20 mg (maintenance and prevention)	£4.20	£2.10	£2.10
LMWH/dabigatran[a]	22 x 150 mg dabigatran (maintenance and prevention) Enoxaparin sodium 300 mg/1 ml solution for injection pre-filled syringes (5 days)	LMWH: £9.02	Dabigatran: £2.20	Dabigatran: £2.20
Aspirin[b]	1.33 x 75 mg	-	-	£0.005

LMWH: Low Molecular Weight Heparin; VKA: Vitamin K Antagonist
Source:

a) BNF September 2014.(151)

b) eMIT February 2014.(152)

Administration and monitoring costs of LMWH/VKA

Unit costs associated with administering LMWH are outlined in Table 71. It was assumed that 92% of patients taking LMWH would self-inject and the remainder would require administration of the injection by health professionals, based on previous assumptions from the rivaroxaban NICE submissions.(18, 19) All patients initiating LMWH were assigned a one-off training cost, calculated by assuming half an hour spent with a nurse at a GP practice based on the average time per contact from the PSSRU and consistent with the rivaroxaban NICE submissions.(11, 18, 19, 41, 150) For the

proportion of patients who required professional administration of the injection, a cost equivalent to 15.5 minutes contact with a nurse at a GP practice was applied, the average per surgery consultation.(150) Administration costs were applied only to the proportion of patients treated as outpatients for the index and recurrent events to avoid double-counting (assuming that administration costs for inpatients would be included in their hospital charges). The same administration assumptions were also used for the LMWH induction of dabigatran in the model.

Table 71: Unit costs and resource use associated with LMWH administration

Item	% patients	Unit cost	Rationale
One-off training cost	100%	£17.00	30 minute nurse visit at GP practice at £34 per hour[a]
Professional administration of LMWH injection	8%[b]	£8.78	15.5 minute contact with a nurse at a GP practice[a]

Sources:
a) PSSRU Unit Costs of Health and Social Care 2013 (150)
b) NICE TA261 – Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism 2012 (41)

Unit costs associated with INR monitoring during treatment with VKA are given in Table 72. Service codes used to cost secondary care monitoring visits are given in Table 97 and Table 98 in the appendices, Section 10.38.

Table 72: Unit costs associated with INR monitoring

Item	Unit cost	Rationale
First visit in secondary care	£21.55	NHS reference costs weighted by consultant-led and non-consultant-led activity[a]
Subsequent visit in secondary care	£24.96	
GP visit in primary care	£37.00	Cost per patient contact with GP lasting 11.7 minutes[b]
Nurse visit in primary care	£8.78	15.5 minute contact with a nurse at a GP practice[b]
INR test in primary care	£3.23	Cost used in NICE TA261, inflated to 2012/2013 costs using PSSRU inflation indices[b,c]

Sources:
a) NHS reference costs 2012/2013, Outpatient procedures; 324 Anticoagulant Service (149)
b) PSSRU Unit Costs of Health and Social Care 2013 (150)
c) NICE TA261 – Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism 2012 (41)

Resource use related to INR monitoring visits is summarised in Table 73. INR monitoring visits were assumed to be undertaken in primary care in 66.45% of cases, with the remainder (33.55%) undertaken in secondary care based on a national survey that included 78 Primary Care Trusts (PCTs) in England, three local health boards in Wales, and health board in Scotland, and validated by clinical experts as being reasonable.(9, 18, 19) This distribution was tested in scenario analysis by setting monitoring to 100% for each setting.

It was assumed that 50% of the first INR monitoring visits conducted in primary care were delivered by a GP with the remainder delivered by a nurse, similar to assumptions used in earlier NICE submissions.(18, 19) For subsequent INR monitoring visits, a 25/75% distribution between GPs and nurses was assumed.(134)

It was assumed that 6 monitoring visits would be required in the first 3 months followed by 3 visits every 3 months.(134) This is a more conservative rate than that used in the previous rivaroxaban NICE technology appraisals, where patients were assumed to require 9 visits in the first three months followed by 5 visits every 3 months.(18, 19) The resulting annual cost of monitoring in the first year of the model was therefore £319.19, and in subsequent years the cost was £252.52.

Table 73: Resource use associated with INR monitoring

Resource use	First visit	Subsequent visit
Number of visits in first 3 months	1[a]	5[a]
Number of visits per 3 months thereafter	0[a]	3[a]
Proportion of monitoring visits in secondary care	33.55%[b,c]	33.55%[b,c]
Proportion of monitoring visits in primary care	66.45%[b,c]	66.45%[b,c]
Proportion with GP	50%[b,c]	25%[a]
Proportion with nurse	50%[b,c]	75%[a]

Sources:
a) Copley et al. 2013 (134)
b) NICE TA261 – Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (18)
c) NICE TA287 – Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (19)

Health-state costs

7.5.6 ***Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.***

Treatment of VTE

As per the rivaroxaban NICE submissions, VTE events were assumed to be treated in outpatient settings for 69% of DVT patients and 17% of PE patients, the remainder being treated in an inpatient setting.(18, 19) These estimates were maintained in the base case analysis but varied in the probabilistic and scenario analysis.

The cost of inpatient treatment was obtained from 2012/2013 NHS reference costs as detailed in Table 74.(149) Service codes used to derive these costs are presented in Table 99 and Table 100 of Appendix 19, Section 10.38.

Table 74: Inpatient treatment costs of VTE

Acute Inpatient Cost	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
PE	£1,525.72[a]	£1,141.53	£1,787.63
DVT	£747.18[b]	£536.69	£883.28

DVT: Deep vein thrombosis; PE: Pulmonary embolism

Source: National Schedule of Reference Costs Year: 2012-13 (149)

a) Codes DZ09D-DZ09H. Includes all short-stay, long-stay, average elective and non-elective

activities, day cases, regular day or night admissions. Procedures in outpatients were excluded as outpatient cost is counted separately.

b) Codes QZ20A-QZ20E. Includes all short-stay, long-stay, average elective and non-elective activities, day cases, regular day or night admissions. Procedures in outpatients and directly accessed services were excluded as outpatient cost is counted separately.

Treatment of a DVT event in an outpatient setting was assumed to comprise of one Doppler ultrasound, a D-dimer test, and one emergency room admission (total £194.93). Treatment of a PE event in an outpatient setting was assumed to comprise a computer tomography pulmonary angiogram (CTPA), a chest X-ray, one echocardiogram, a D-dimer test, and one emergency room admission (total £323.94). These resource use estimates associated with outpatient treatments were obtained from earlier economic evaluations based on NICE clinical guideline 92.(18, 19, 23) The unit costs for each of these tests are displayed in Table 75. The cost of a D-dimer test was obtained from rivaroxaban NICE submission TA287 (£13.11).(40)

Table 75: Unit costs for items associated with outpatient treatment

Resource Use Item	Currency Code	Currency Description	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
Doppler ultrasound	RA24Z	Ultrasound Scan, 20 minutes and over	£64.94	£45.69	£72.59
CT angiography	RA08A	Computerised Tomography Scan, one area, no contrast, 19 years and over	£89.71	£66.24	£105.88
Echocardiogram	RA60A	Simple Echocardiogram, 19 years and over	£75.96	£58.46	£87.50
Chest X-ray	DAPF	Direct Access Plain Film	£28.28	£22.00	£34.59
D-Dimer test[a]	-	-	£13.11	£9.18	£17.04
Emergency admission	180	Accident & Emergency	£116.88	£55.61	£150.14

Source (for all except D-Dimer test): National Schedule of Reference Costs Year : 2012-13 - All NHS trusts and NHS foundation trusts - HRG Data(149)

a) National Institute of Clinical Excellence (NICE), Pulmonary embolism (acute treatment, VTE prevention) - rivaroxaban: evaluation report; 02 - Submission from the technology manufacturer – Bayer; 19 April 2013. TA287 (11, 41) Inflated to 2012/2013 costs using the PSSRU inflation indices.(150)

Adverse-event costs

7.5.7 ***Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.***

In addition to drug acquisition, routine care, and monitoring costs, the model accrued costs associated with the incidence of bleeding events (Table 76). Acute care costs for each of the events were obtained from NHS Reference Costs 2012/2013 (Appendix 19, Section 10.38; Table 101 to Table 105).(149) The acute cost of CTEPH in the base case was assumed to include the cost of a chest x-ray, lung function test, walk test, ECG, echocardiogram, blood tests, CT lung can and right-heart catheter study.(159) In addition, the cost for pulmonary endarterectomy (PEA) was applied for 9.6% of patients, validated by expert opinion.(160, 161) The calculations performed to derive the acute cost of CTEPH are explained in Appendix 19, Section 10.38.

Table 76: Acute event costs per episode

	Cost	Lower Interval	Upper Interval
Semi-absorbing health states			
IC bleed[a]	£2,589.48	£1,689.11	£3,154.86
CTEPH[a,b]	£1,251.46	£1,009.08	£1,426.56
Transient health states			
Non-IC major bleed[c]	£1,064.08	£802.21	£1,239.77
CRNM bleed[d]	£137.81	£119.17	£152.66
Fatal events			
Fatal major bleed[a]	£2,589.48	£1,689.11	£3,154.86
Fatal CTEPH[e]	£1,251.46	£1,009.08	£1,426.56
VTE-related death[f]	£1,525.72	£1,141.53	£1,787.63

CRNM: Clinically Relevant Non-Major; CTEPH: Chronic Thromboembolic Pulmonary Hypertension; IC: Intracranial; VTE: Venous Thromboembolism
Source: National Schedule of Reference Costs Year 2012-2013 (149)

a. Codes AA23C-AA23G. Elective, non-elective, regular day or night admissions, day cases
b. Codes DAPF, DZ45Z, DZ32Z, EA47Z, RA60A, DAPS05, RA10Z, EA36H, REHABL1-3 admitted patient care and other
c. Codes FZ38G-H, FZ38J-N, FZ38P, FZ24G-H and FZ24J
d. Code VB07Z
e. Assumed to be the same as CTEPH
f. Assumed to be the same as non-fatal pulmonary embolism event (Table 74)

For the semi-absorbing health states of non-fatal IC bleeds and CTEPH, patients accumulated maintenance costs following the acute care period until death (Table 77). Two different maintenance costs were specified for IC bleed, one for the first 3 months after the acute event and one for subsequent 3-month periods.

For patients experiencing an IC bleed, it was assumed that the maintenance costs for the first 3 months after the acute care period would reflect 14 days of stroke rehabilitation as obtained from NHS Reference Costs 2012/2013.(149) This assumption is consistent with earlier submissions as advised by experts.(18, 19, 161) Following the 3-month period after the initial IC bleed, the maintenance and rehabilitation cost was obtained from a population-based study using OXVASC that assessed the costs of post-stroke events at 5 years (Table 77).(128) Costs included accident and emergency visits, emergency transport, outpatient care visits, day case admissions, and hospitalisations.

The cost of management of patients with CTEPH was taken from NICE CG92 and inflated using PSSRU indices (Appendix 19, Section 10.38; Table 96).(18, 19, 23) In the rivaroxaban NICE submission TA261, the cost of severe PTS was assumed to comprise three vascular surgery

outpatient visits in the first year of the model and two GP visits annually thereafter.(162) In the present model, both DVT and PE are included, with PTS having the potential to occur in PE patients who have a recurrent DVT. Due to the limitations of the memoryless Markov structure, it was not possible to track the first year of PTS in PE patients experiencing recurrent DVT. Furthermore, the model results were robust to varying the cost of PTS in one-way sensitivity analyses.

Table 77: Maintenance costs

	Mean Cost	Lower Interval	Upper Interval
First 3-month cycle following acute care			
IC bleed[a]	£4,692.13	£3,914.32	£5,565.39
CTEPH[b]	£4,232.34	£2,962.64	£5,502.04
Long term (per 3-month cycle)			
IC bleed[c]	£680.53	£478.64	£905.58
CTEPH[d]	£4,232.34	£2,962.64	£5,502.04
PTS[e]	£188.92	£132.24	£245.60

CTEPH: Chronic Thromboembolic Pulmonary Hypertension; IC: Intracranial; PTS: Post-Thrombotic Syndrome

Source:

a) National Schedule of Reference Costs Year 2012-2013; VC04Z, RH Assumed 14 days of stroke rehabilitation similarly to TA261.(149)
b) Advised by experts that the long term maintenance costs would be also be applied in the first 3 months, NICE CG92 inflated using PSSRU indices.(23, 161)
c) Luengo Fernandez et al 2012.(128), inflated using PSSRU indices and an exchange rate of 0.64 to convert from US dollars.(150)
d) NICE CG92 inflated using PSSRU indices.(23)
e) NICE CG92, as advised by experts.(23, 161)

Miscellaneous costs

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

No additional costs were included in the model.

7.6 Sensitivity analysis

7.6.1 *Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.*

Scenario analysis was conducted to determine the effect of structural and input assumptions not included in the one-way sensitivity analysis. The inputs for all scenario analyses can be found in Appendix 20a, Section 10.39. The following scenarios were tested:

1. Use of PbR tariffs in place of NHS reference costs
2. Age-varying baseline utilities
3. Inclusion of adjustment factors due to ageing for increased baseline bleeding risk over time
4. Extending current treatment duration for 6 months on occurrence of recurrent VTE instead of receiving 6 months treatment with LMWH/VKA
5. Treatment dependent distributions of recurrent VTE (VTE-related death, non-fatal PE and DVT) fatal major bleeding and non-fatal IC and other cause mortality based on NMA data
6. Background mortality set equal to general population
7. Inclusion of VKA as a second-line treatment option (see below for further details)
8. Only inpatient treatment of VTE
9. Only outpatient treatment of VTE
10. Utility decrement for all treatments set equal to VKA
11. Alternative set of utility values for PE, DVT, IC and non IC major bleeds (standard gamble, Hogg et al 2013 (139))
12. Setting treatment discontinuation to be 0 across all treatments
13. Setting treatment discontinuation to be equal across all treatments
14. Inclusion of anticoagulant cost and utility decrement for patients who experience recurrent VTE for a period of 13 years (average life expectancy in model; affects costs and utilities only; see below for further details)
15. Higher baseline risk of recurrent VTE for no treatment (see below for further details)
16. Lower baseline risk of recurrent VTE for no treatment (see below for further details)
17. INR monitoring costs set equal to TA261/TA281 and previous rivaroxaban SMC submissions (more frequent INR monitoring visits)
18. INR monitoring assumed to be 100% in primary care
19. INR monitoring assumed to be 100% in secondary care
20. Lower INR monitoring resource use (4 visits on initiation, 1 visit subsequently)
21. All non-consultant led monitoring takes place in secondary care
22. Treatment period pooled RE-COVER I and II data NMA
23. Prevention period ITT analysis using NMA data
24. Prevention period ITT analysis using NMA data excluding WODIT DVT and PE studies
25. Prevention period NMA analysis excluding dabigatran
26. Treatment duration of 3 months (see below for further details)
27. Treatment duration of 18 months (see below for further details)
28. Baseline demographics from the CPRD study (see below for further details)
29. Excluding the cost of LMWH
30. Dalteparin unit cost for LMWH
31. Alternative distribution of fatal major bleeds and non-fatal IC bleeds
32. Alternative distribution of recurrent VTE events
33. Major bleeding rates set equal for apixaban and placebo for the extended period
34. LMWH monotherapy as a comparator (see below for further details)

35. LMWH/VKA followed by aspirin as a comparator
36. Inclusion of renal function test for dabigatran

VTE second-line treatment

Upon discontinuation of first-line treatment, the base case analysis assumed permanent discontinuation of treatment. However, in scenario analyses, the model allowed for patients to be treated with second-line treatment.

The VTE second-line treatment health states were segregated into patients with index PE and patients with index DVT. These health states are modelled identically to the first-line health states, with the exception that patients discontinuing second-line treatment would receive no further treatment. When patients received second-line treatment, the efficacy of the chosen second-line drug was assumed to be the same as the efficacy observed with the drug when used as first-line treatment.

Additional anticoagulant costs and utility decrements for a period of 13 years for patients experiencing recurrent VTE

There have been suggestions that patients who experience a recurrent VTE would remain on treatment for their remaining lifetime.(128, 129) We therefore examined a scenario in which any patients experiencing a VTE event would be assigned 13 years of treatment costs (average life-expectancy in the model). The assigned treatment costs would reflect the treatment patients were on at the time of the recurrent VTE event. That is, patients on apixaban would receive costs for 13 years of apixaban whereas patients experiencing a recurrent VTE event whilst on LMWH/VKA would receive costs for 13 years of LMWH/VKA. It is important to note that this scenario is prone to imprecise estimates as a simplistic calculation was employed in assigning additional costs to each recurrent event based on treatment. For example, this scenario would result in a patient who experiences a VTE event at age 99 receiving 13 years of additional anticoagulation costs. Furthermore neither discounting nor the additional benefit received from anticoagulant treatment is considered.

Higher and lower baseline risk of recurrent VTE for no treatment

The risk of recurrent VTE in AMPLIFY-EXT reflects the risk in patients where the benefits of continued anticoagulation is uncertain. As patients at high risk of recurrent VTE were explicitly excluded, a scenario was examined where the risk of recurrent VTE was higher than that observed in AMPLIFY-EXT. A scenario examining patients at lower risk of recurrence was also carried out for completeness.

This analysis was conducted by increasing/decreasing the risks of recurrent VTE for the placebo arm beyond the first 6 months of treatment and calculating apixaban risks based on the relative treatment effect observed in AMPLIFY-EXT.

3-month treatment duration

A scenario analysis was carried out using 3-month data for apixaban and LWMH/warfarin with the 6-month treatment period NMA RR for comparators. (Section 6.7.5).

18-month treatment duration

A scenario analysis was carried out over an 18-month treatment duration to reflect the minimum combined trial length of AMPLIFY and AMPLIFY-EXT.

CPRD analysis

We included a scenario using patient characteristics reported in a cohort study of VTE treatment patients from the UK CPRD. As discussed previously in Section 7.2.1, there are a number of limitations with using these data in that only patients from general practice are included and VTE events are not characterised by cause, for example post-surgical VTE.

Demographics from the CPRD study are summarised in Appendix 13f, Section 10.31.

LMWH/VKA followed by aspirin as a comparator

An exploratory scenario comparing lifelong apixaban with 6 months of treatment with LMWH/VKA followed by aspirin was carried out as aspirin is used in clinical practice as an alternative to no preventative therapy.(30)

LMWH monotherapy as a comparator

No evidence from the systematic review was identified on the use of LMWH monotherapy in a population with DVT and/or PE for whom a VKA is unsuitable. However, a recent NMA has been published that presents relative efficacy for apixaban versus LMWH monotherapy in a population for whom a VKA is suitable.(163) An exploratory analysis was therefore carried out to estimate the relative cost-effectiveness of apixaban against LMWH for a population with DVT and/or PE for whom a VKA is suitable.

7.6.2 *Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.*

Univariate deterministic sensitivity analysis was performed where each parameter was varied according to the 95% confidence intervals and standard deviations where applicable while holding all other parameters constant. Unit costs of treatment were not varied, as these are fixed inputs. The results are defined in terms of incremental cost per QALY gained or incremental costs and QALYs where dominance was observed.

7.6.3 *Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).*

PSA was carried out to test the variability in outcomes due to statistical uncertainty in the model inputs. For the base case the PSA was run for 2,000 replications where repeated samples were drawn from probability distributions to determine an empirical distribution for costs and QALYs to construct a range of cost-effectiveness ratios. Event rates, relative risks, costs and utilities were varied simultaneously and independently of each other from replication to replication by sampling from probability distributions to generate cost-effectiveness acceptability curves (CEACs). The number of simulations was chosen by running the probabilistic analysis over 10,000 simulations and examining where the CEACs converged to a constant value. Time horizon, population characteristics, model settings and treatment unit costs were kept constant.

A number of probability distributions were employed including the beta, log-normal, gamma, and Dirichlet distributions (Appendix 20b, Table 111). Gamma or beta distributions were used for event rates. Probabilities used to describe the distribution of patients amongst a number of different components (e.g. distribution of patients who experienced recurrent VTE by the proportions that were VTE-related death, non-fatal PE and DVT) were varied using a Dirichlet distribution. Other probabilities were varied using a beta distribution. Relative risks were varied using a log-normal distribution, gamma or log-normal distributions were used for costs, and a beta distribution was used for utilities. Where data was missing, which was only the case for some unit costs, a 30% variation from the mean was assumed and a gamma distribution used.

7.7 Results

Clinical outcomes from the model

7.7.1 ***For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.***

Predictive validity was checked by comparing key outcomes to the source data (Table 78). In performing this, the model was set to the settings of AMPLIFY and AMPLIFY-EXT (ie., number of patients, duration of follow-up) and the key event rates were compared.

Event counts and relative risks were comparable to the outcomes reported from the trials, with the exception of all-cause mortality and treatment discontinuation. Data to inform case fatality was neither treatment dependent nor based on trial data for major bleeding events. The number of deaths predicted for the VKA arm matched those observed in the trial, thus providing validation to current inputs used to model mortality. A slightly higher number of deaths was observed in the apixaban arm. When evaluating all-cause mortality excluding events modelled in AMPLIFY, apixaban had a benefit vs. VKA in the trial beyond the mortality benefit observed due to reduction in VTE and bleeding events. This is not included when assuming the same background mortality resulting in a less favourable but conservative model prediction for apixaban. Treatment discontinuation reported in the model was that related to discontinuation due to non-IC major bleeds and discontinuation unrelated to the events modelled. The lower number of discontinuations observed can be attributed to patients discontinuing treatment on the occurrence of VTE or CRNM bleeds in the trial, whereas in the model we allowed for these patients to remain on treatment.

Table 78: Summary of model results compared with clinical data

	AMPLIFY			**Model Results**		
	Apixaban	**VKA**	**RR**	**Apixaban**	**VKA**	**RR**
Recurrent VTE and VTE-related death	59	71	0.84	60	72	0.84
Major bleeds	15	49	0.31	15	49	0.31
CRNM bleed	103	215	0.48	102	213	0.48
Treatment discontinuation	162	199	0.82	131	150	0.87
All- cause death	41	52	0.79	46	53	0.87
Model settings: • Number of patients in each treatment group: Apixaban (N = 2691), VKA (N = 2704) • Treatment duration and time horizon = 6 months						
	AMPLIFY-EXT			**Model Results**		
	Apixaban	**Placebo**	**RR**	**Apixaban**	**Placebo**	**RR**
Recurrent VTE and VTE-related death	14	73	0.19	13	72	0.19
Major bleeds	2	4	0.49	2	4	0.51

CRNM bleeds	25	19	1.29	24	19	1.30
Recurrent VTE or death from any cause	32	96	0.33	32	91	0.36
Model settings: • Number of patients in each treatment group = Apixaban 2.5 mg (N = 804), placebo (N = 829) • Treatment duration and time horizon = 12 months						

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

Markov traces summarising the proportion of patients in the cohort in each health state over time are presented in Appendix 21, Section 10.41.

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

A summary of QALYs accrued in each health state across the model time horizon is presented in Appendix 22, Section 10.42.

7.7.4 ***Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:***

Costs and QALYs for each health state/clinical outcome are presented in the Appendices, Sections 10.43 and 10.44.

7.7.5 ***Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.***

Disaggregated QALYs – 6-month treatment duration and lifelong treatment duration

Disaggregated incremental QALY gains for 6-month and lifelong treatment duration by health state are presented in the Appendices, Section 10.43.

Disaggregated Costs – 6-month treatment duration and lifelong treatment duration

Disaggregated incremental costs by health state are presented in the Appendices, Section 10.44.

Base-case analysis

7.7.6 ***Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.***

Base case results – 6-month treatment duration

The numbers of clinical events occurring in the model per 1,000 patients for the 6-month treatment duration are presented in Table 79 below.

Table 79: Number of clinical events predicted among 1,000 patients with index VTE over a 6 month treatment duration

Number of Events (Total Population)	Apixaban	LMWH/VKA	Rivaroxaban	LMWH/dabigatran
Recurrent VTE and VTE related death				
VTE-related death	74	74	74	75
Non-fatal recurrent PE	152	153	152	154
Non-fatal recurrent DVT	376	376	376	377
Total	601	603	602	606
Major bleeds				
Fatal	9	11	10	10
Non-fatal IC bleeds	8	10	9	9
Non-fatal non-IC major bleeds	50	59	53	56
Total	67	79	72	75
Clinically relevant non-major bleed	332	372	374	340
Chronic thromboembolic pulmonary hypertension	32	32	32	32

Number of Events (Total Population)	Apixaban	LMWH/VKA	Rivaroxaban	LMWH/dabigatran
Other treatment discontinuation				
Event related (non-fatal non-IC major bleeding)	2	6	3	4
Other treatment discontinuation	47	50	43	55
Total	49	56	46	59
Death				
Event related (acute)	83	85	83	85
Long-term event related (death due to CTEPH, IC bleed absorbing health states)	40	41	40	41
Background death	878	874	876	874
Total	1,000	1,000	1,000	1,000
CTEPH: Chronic thromboembolic pulmonary hypertension; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; IC: Intracranial; PE: Pulmonary embolism; VKA: Vitamin K antagonist; VTE: Venous thromboembolism				

ICERs resulting from the costs and health outcomes at six months presented above are summarised in Table 80 for LMWH/VKA, rivaroxaban and LMWH/dabigatran versus apixaban. Results from incremental analysis are presented in Table 81.

Apixaban was cost-effective vs. LMWH/VKA for the 6-month treatment duration, with an ICER of £2,406 per QALY gained. Apixaban was dominant vs. rivaroxaban and LMWH/dabigatran for this treatment duration.

The economic results are consistent with NMA 1 (Section 6.7.5.1) demonstrating that apixaban has comparable efficacy to alternative therapies, but with a lower bleeding risk for patients treated for a 6-month duration (Table 79). Apixaban was associated with lower total costs compared to rivaroxaban due to a shorter initiation period (7 days vs. 21 days) and dabigatran which requires initial parenteral anticoagulant injections. In patients treated with LMWH/VKA, the high cost of LMWH and the cost of VKA monitoring are the main contributors to the cost of treatment vs. apixaban.

Table 80: Base case results – 6-month treatment duration

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) apixaban versus comparator (LYG)	ICER (£) apixaban versus comparator (QALYs)
Apixaban	£5,034.96	10.323	8.422	-	-	-	-	-
LMWH/VKA	£4,954.94	10.292	8.389	£80.02	0.031	0.033	£2,570	£2,406
Rivaroxaban	£5,069.16	10.311	8.412	-£34.20	0.012	0.010	Dominant	Dominant
LMWH/ dabigatran	£5,100.37	10.293	8.396	-£65.41	0.030	0.026	Dominant	Dominant
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; LYG: Life years gained; QALYs: Quality-adjusted life years; VKA: Vitamin K antagonist								

Table 81: Base case incremental analysis – 6-month treatment duration

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) Comparator vs. LMWH/VKA	Incremental analysis
LMWH/VKA	£4,954.94	8.389	-	-	-	-
Apixaban	£5,034.96	8.422	£80.02	0.033	£2,405.53	£2,405.53
Rivaroxaban	£5,069.16	8.412	£114.22	0.023	£5,016.99	Dominated
LMWH/ dabigatran	£5,100.37	8.396	£145.43	0.007	£19,782.46	Dominated
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; QALYs: Quality-adjusted life years; VKA: Vitamin K antagonist						

Base case results – Lifelong treatment duration

The numbers of clinical events occurring in the model per 1,000 patients for the lifelong treatment duration are presented in Table 82 below.

Table 82: Number of clinical events predicted among 1,000 patients with index VTE over a lifelong treatment duration

Number of Events (Total Population)	Apixaban	LMWH/ VKA	Rivaroxaban	LMWH/ dabigatran
Recurrent VTE and VTE related death				
VTE-related death	37	38	42	39
Non-fatal recurrent PE	76	78	86	79
Non-fatal recurrent DVT	183	184	208	186
Total	296	299	336	304
Major bleeds				
Fatal	7	22	67	15
Non-fatal IC bleeds	6	20	61	14
Non-fatal non-IC major bleeds	38	123	373	83
Total	51	166	500	112
Clinically relevant non-major bleed	396	949	756	615
Chronic thromboembolic pulmonary hypertension	30	29	27	29
Other treatment discontinuation				
Event related (non-fatal non-IC major bleeding)	9	52	183	31
Other treatment discontinuation	554	598	479	606
Total	563	650	662	637
Death				
Event related (acute)	44	60	110	54

Number of Events (Total Population)	Apixaban	LMWH/ VKA	Rivaroxaban	LMWH/ dabigatran
Long-term event related (death due to CTEPH, IC bleed absorbing health states)	36	49	88	43
Background death	920	891	803	903
Total	1,000	1,000	1,000	1,000
CTEPH: Chronic thromboembolic pulmonary hypertension; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; IC: Intracranial; PE: Pulmonary embolism; VKA: Vitamin K antagonist; VTE: Venous thromboembolism				

ICERs resulting from the costs and health outcomes for the lifelong treatment duration are summarised in Table 83 for LMWH/VKA, rivaroxaban and LMWH/dabigatran versus apixaban. Results from incremental analysis are presented in Table 84.

For the lifelong treatment duration, apixaban was cost-effective vs. LMWH/VKA, with an ICER of £16,676 per QALY gained. Apixaban was cost-effective vs. rivaroxaban and LMWH/dabigatran with ICERs of £809 and £5,058 per QALY gained, respectively. Acquisition and administration costs were lower for rivaroxaban than for either LMWH/dabigatran or apixaban as a result of the higher rate of treatment discontinuation seen for this intervention (Table 82 and Appendix Section 10.44, Table 146 and Table 147).

Although there are numerical differences in NMA 2 (Section 6.7.5.2) in favour of warfarin and dabigatran for VTE or VTE related death, these are reversed once a holistic approach to modelling is used over life time treatment duration. As demonstrated in NMA 2 patients treated with apixaban have a lower risk of bleeding and so fewer patients are projected to discontinue treatment in comparison to other anticoagulants. Consequently patients remain on treatment for a longer period of time gaining the prevention benefit against recurrent VTE, which in turn results in a reduced number of VTE events over a lifetime time-horizon compared to the other therapies. However patients treated with apixaban incur additional costs compared to the other therapies due to the longer time on treatment.

Table 83: Base case results – Lifelong treatment duration

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) apixaban versus comparator (LYG)	ICER (£) apixaban versus comparator (QALYs)
Apixaban	£9,497.37	10.635	8.673	-	-	-	-	-
LMWH/VKA	£6,136.28	10.481	8.472	£3,361.09	0.154	0.201	£21,803	£16,676
Rivaroxaban	£9,013.16	9.981	8.075	£484.21	0.654	0.598	£741	£809
LMWH/ dabigatran	£9,083.28	10.544	8.591	£414.09	0.091	0.082	£4,540	£5,058
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; LYG: Life years gained; QALYs: Quality-adjusted life years; VKA: Vitamin K antagonist								

Table 84: Base case incremental analysis – Lifelong treatment duration

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) Comparator vs. LMWH/VKA	Incremental analysis
LMWH/VKA	£6,136.28	8.472	-	-	-	-

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) Comparator vs. LMWH/VKA	Incremental analysis
Rivaroxaban	£9,013.16	8.075	£2,876.88	-0.397	Dominated	Dominated
LMWH/ dabigatran	£9,083.28	8.591	£2,947.00	0.120	£24,621.57	Extendedly dominated
Apixaban	£9,497.37	8.673	£3,361.09	0.202	£16,675.53	£16,675.53
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; QALYs: Quality-adjusted life years; VKA: Vitamin K antagonist						

In the comparison against LMWH/VKA followed by no treatment, apixaban had an ICER of £17,917 per QALY gained (Table 85). This was a conservative analysis as patients in the LMWH/VKA arm received treatment only for the first 6 months whereas in the apixaban arm, patients received lifelong treatment. Thus anticoagulation and administration costs, as well as the rate of treatment duration are substantially lower for the comparator arm than for apixaban. Nevertheless this scenario demonstrated that apixaban is cost-effective at a willingness to pay threshold of £20,000 per QALY gained and may be a beneficial treatment for a subgroup of patients that would benefit from lifelong anticoagulation, but who may not currently be receiving treatment, for example, due to bleeding risk. These patients currently have no therapeutic option and therefore a higher willingness to pay may be appropriate.

Table 85: Deterministic results, apixaban vs. LMWH/VKA for 6 months followed by no treatment – Lifelong treatment duration

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) apixaban versus comparator (LYG)	ICER (£) apixaban versus comparator (QALYs)
LMWH/VKA/no treatment	£4,891.62	10.323	8.416	£4,605.75	0.312	0.257	£14,733	£17,917
Apixaban	£9,497.37	10.635	8.673	-	-	-	-	-
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; LYG: Life years gained; QALYs: Quality-adjusted life years; VKA: Vitamin K antagonist								

Sensitivity analyses

7.7.7 *Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.*

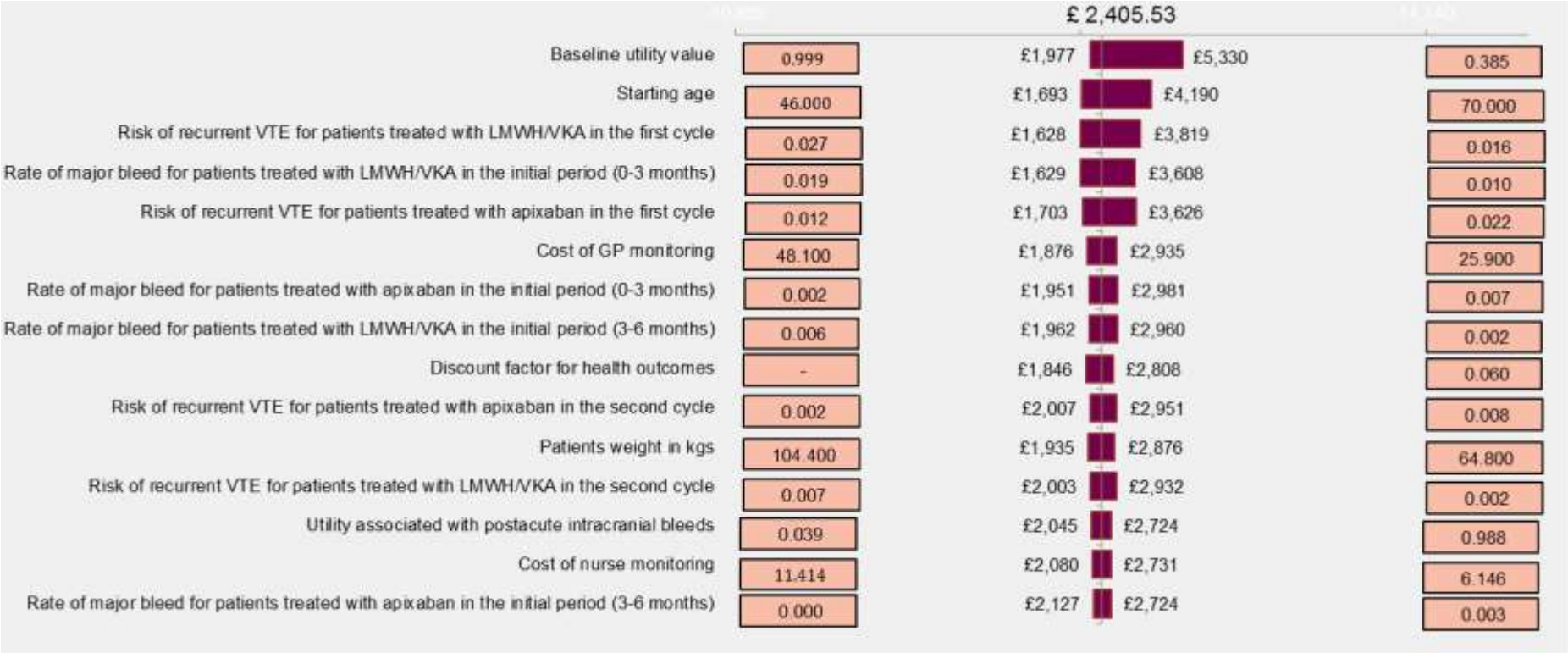
Univariate sensitivity analysis – 6-month treatment duration

Univariate deterministic sensitivity analysis was performed by varying each parameter according to the 95% confidence intervals and standard deviations where applicable, while holding all other parameters constant. Tornado diagrams for apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran are presented below.

Apixaban vs. LMWH/VKA

Incremental costs for apixaban vs. LMWH/VKA varied between £62 and £98 whilst incremental QALYs varied between 0.015 and 0.043.The ICER of apixaban vs. LMWH/VKA varied between £1,628 and £5,330 per QALY gained, indicating that the results are robust to changes in the parameters.

Figure 29: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/VKA (index VTE, 6-Month treatment duration)



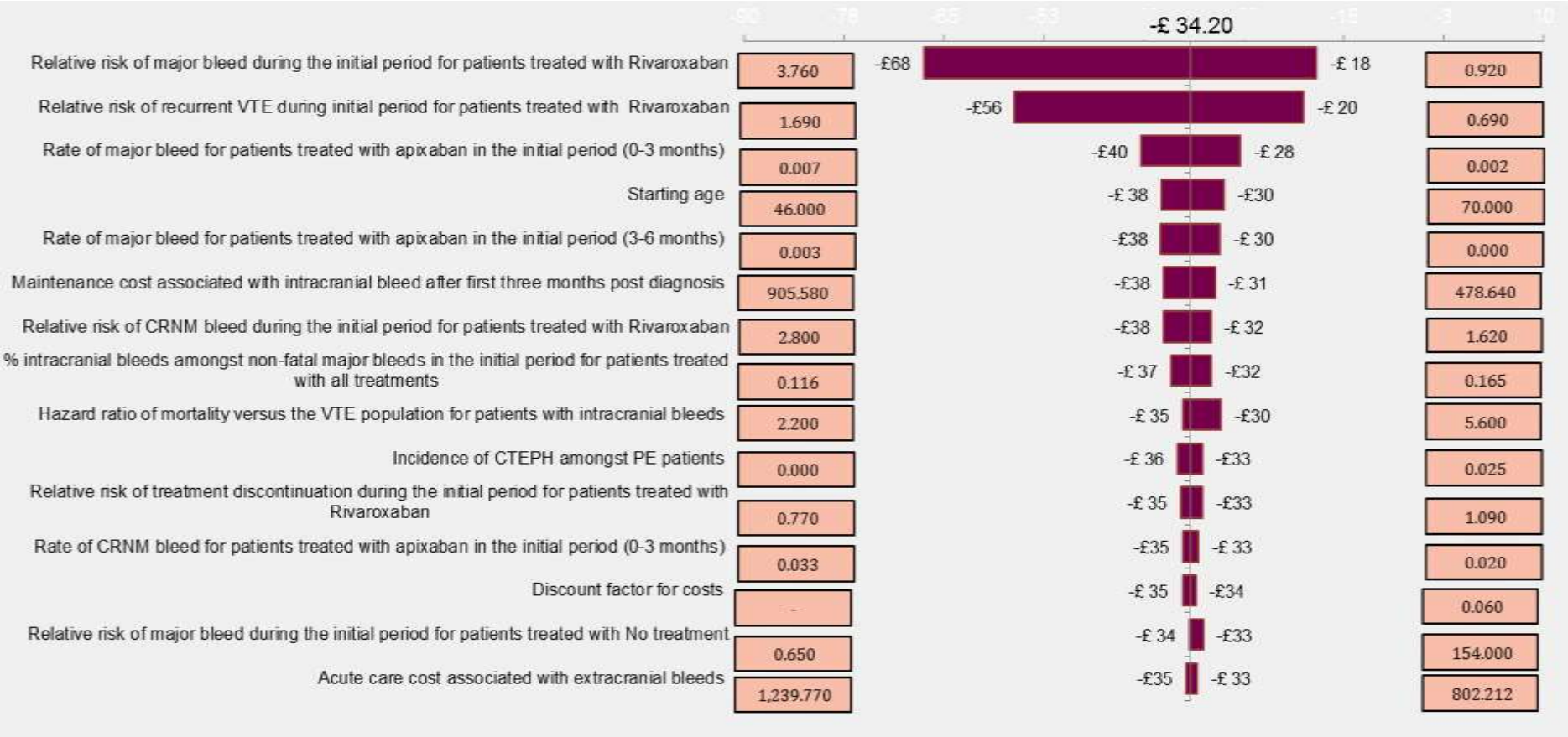
LMWH: Low molecular weight heparin; VKA: Vitamin K antagonist; VTE: Venous thromboembolism

Apixaban vs. rivaroxaban

Incremental costs for apixaban vs. rivaroxaban varied between -£68 and -£13 whilst incremental QALYs varied between -0.005 and 0.059. The ICER of apixaban vs. rivaroxaban varied between being dominant and less costly, less effective.

Apixaban was less costly than rivaroxaban in all scenarios, and only one scenario resulted in apixaban being less effective than rivaroxaban in terms of QALY gains; reducing the relative risk of recurrent VTE for rivaroxaban vs. apixaban to 0.69 (1.08 in the base case).

Figure 30: Tornado diagram illustrating results from univariate sensitivity analysis for incremental costs vs. rivaroxaban (index VTE, 6-month treatment duration)



CRNM: Clinically relevant non-major; CTEPH: Chronic thromboembolic pulmonary hypertension; PE: Pulmonary embolism; VTE: Venous thromboembolism

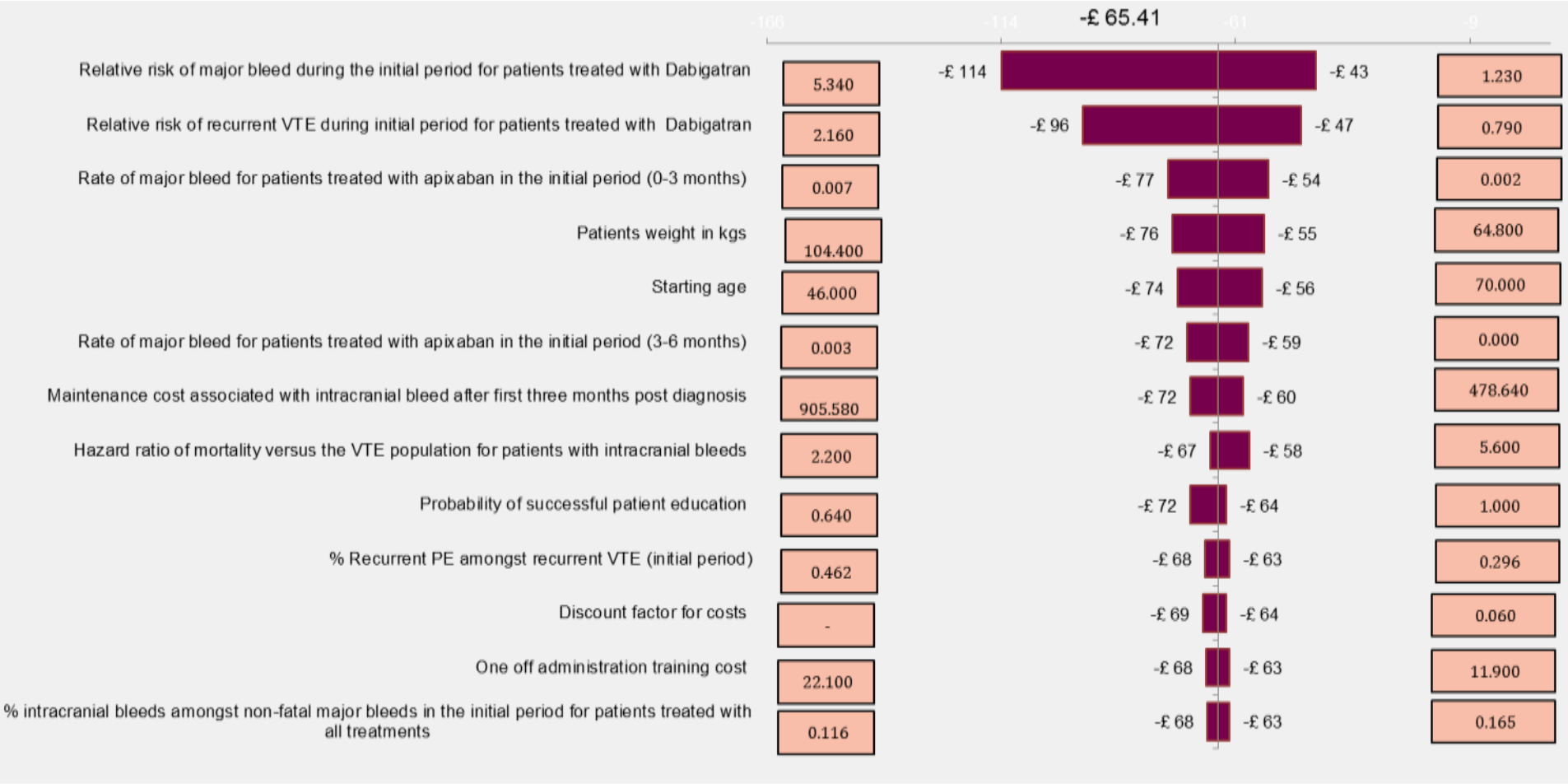
Figure 31: Tornado diagram illustrating results from univariate sensitivity analysis for incremental QALYs vs. rivaroxaban (index VTE, 6-month treatment duration)

DVT: Deep vein thrombosis; VTE: Venous thromboembolism

Apixaban vs. LMWH/dabigatran

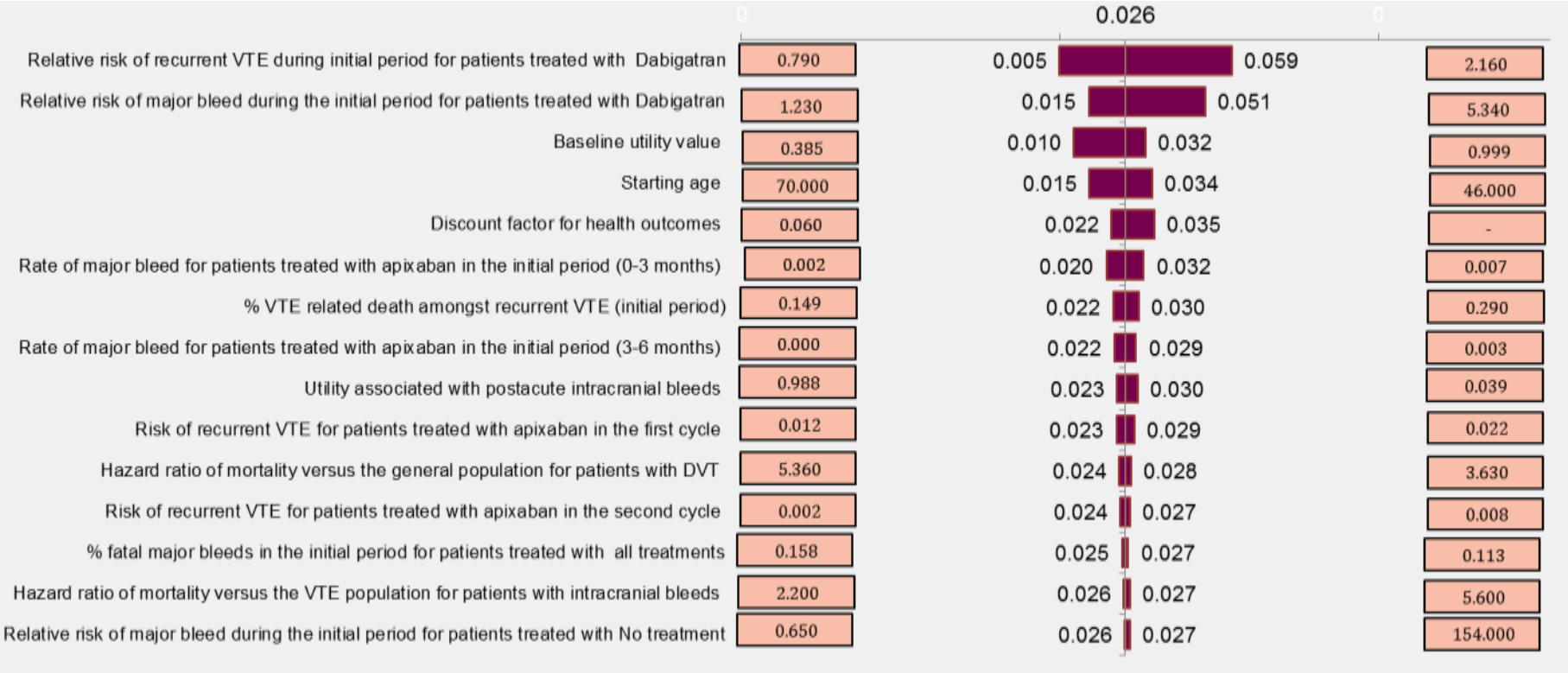
Incremental costs for apixaban vs. LMWH/dabigatran varied between -£114 and -£43 whilst incremental QALYs varied between 0.005 and 0.059. The ICER of apixaban vs. LMWH/dabigatran was dominant and for all scenarios.

Figure 32: Tornado diagram illustrating results from univariate sensitivity analysis for incremental costs vs. LMWH/dabigatran (index VTE, 6-month treatment duration)



PE: Pulmonary embolism; VTE: Venous thromboembolism

Figure 33: Tornado diagram illustrating results from univariate sensitivity analysis for incremental QALYs vs. LMWH/dabigatran (index VTE, 6-month treatment duration)



DVT: Deep vein thrombosis; VTE: Venous thromboembolism

Univariate sensitivity analysis – Lifelong treatment duration

Univariate deterministic sensitivity analysis was performed by varying each parameter according to the 95% confidence intervals and standard deviations where applicable, while holding all other parameters constant. Tornado diagrams for apixaban vs. LMWH/VKA, rivaroxaban, LMWH/dabigatran and LMWH/VKA followed by no treatment are presented below.

Apixaban vs. LMWH/VKA

Incremental costs for apixaban vs. LMWH/VKA varied between £2,133 and £4,230 whilst incremental QALYs varied between 0.086 and 0.989. The ICER of apixaban vs. LMWH/VKA varied between £2,157 and £41,394 per QALY gained.

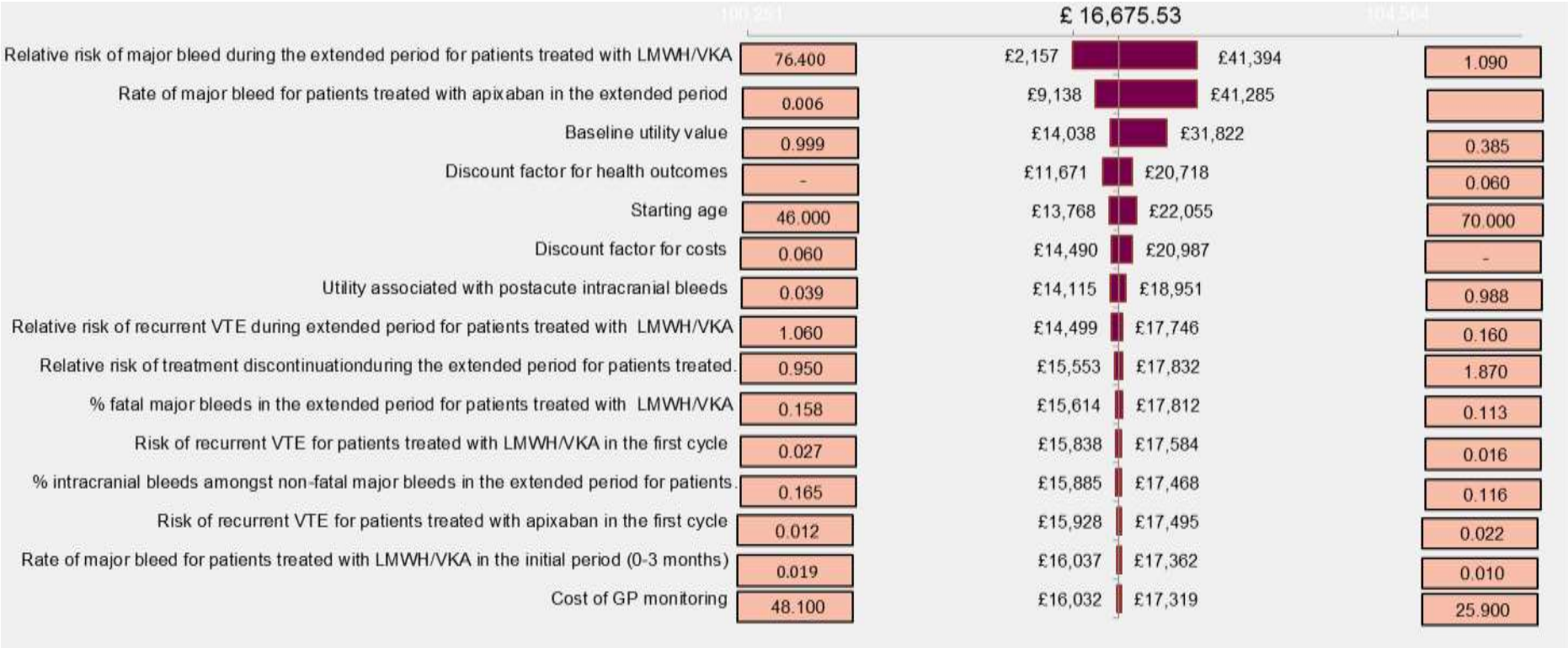
Three scenarios resulted in an ICER above £30,000 per QALY gained:

- Reducing the relative risk of major bleeding for LMWH/VKA vs. apixaban to 1.09 (7.7 in the base case)
- Setting the risk of major bleeding for apixaban to 0, thereby causing no differences between the two drugs in major bleeding outcomes despite evidence of a significant difference in the NMA
- Reducing the baseline utility value of patients entering the model to 0.385; the lower confidence interval of the utility value which is well below the average utility value found for even a population of 90-year olds, thereby decreasing QALY gains substantially.

Three further scenarios resulted in an ICER above £20,000 per QALY gained:

- Increasing the discount factor for QALYs to 6%
- Increasing the starting age to 70, subsequently decreasing life expectancy and QALY gains
- Decreasing the discount factor of costs to 0%

Figure 34: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/VKA (index VTE, lifelong treatment duration)



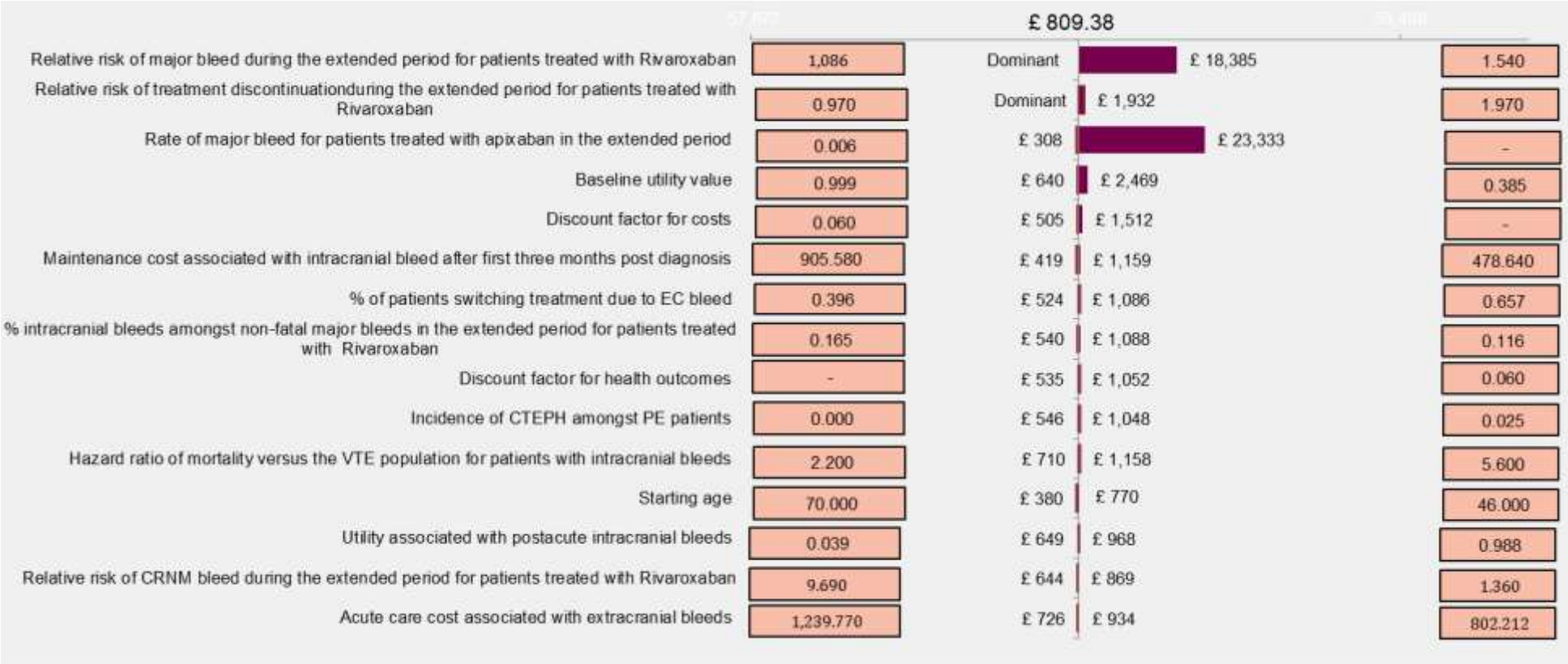
GP: General practitioner; LMWH: Low molecular weight heparin; VKA: Vitamin K antagonist; VTE: Venous thromboembolism

Apixaban vs. rivaroxaban

Incremental costs for apixaban vs. rivaroxaban varied between -£41 and £1,059 whilst incremental QALYs varied between 0.013 and 2.278. The ICER of apixaban vs. rivaroxaban varied between being dominant and £23,333 per QALY gained.

Only one scenario resulted in an ICER above £20,000 per QALY gained: setting the risk of major bleeding for apixaban to 0, thereby resulting in no differences between the two drugs in major bleeding outcomes despite evidence of there being a significant difference from the NMA.

Figure 35: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. rivaroxaban (index VTE, lifelong treatment duration)



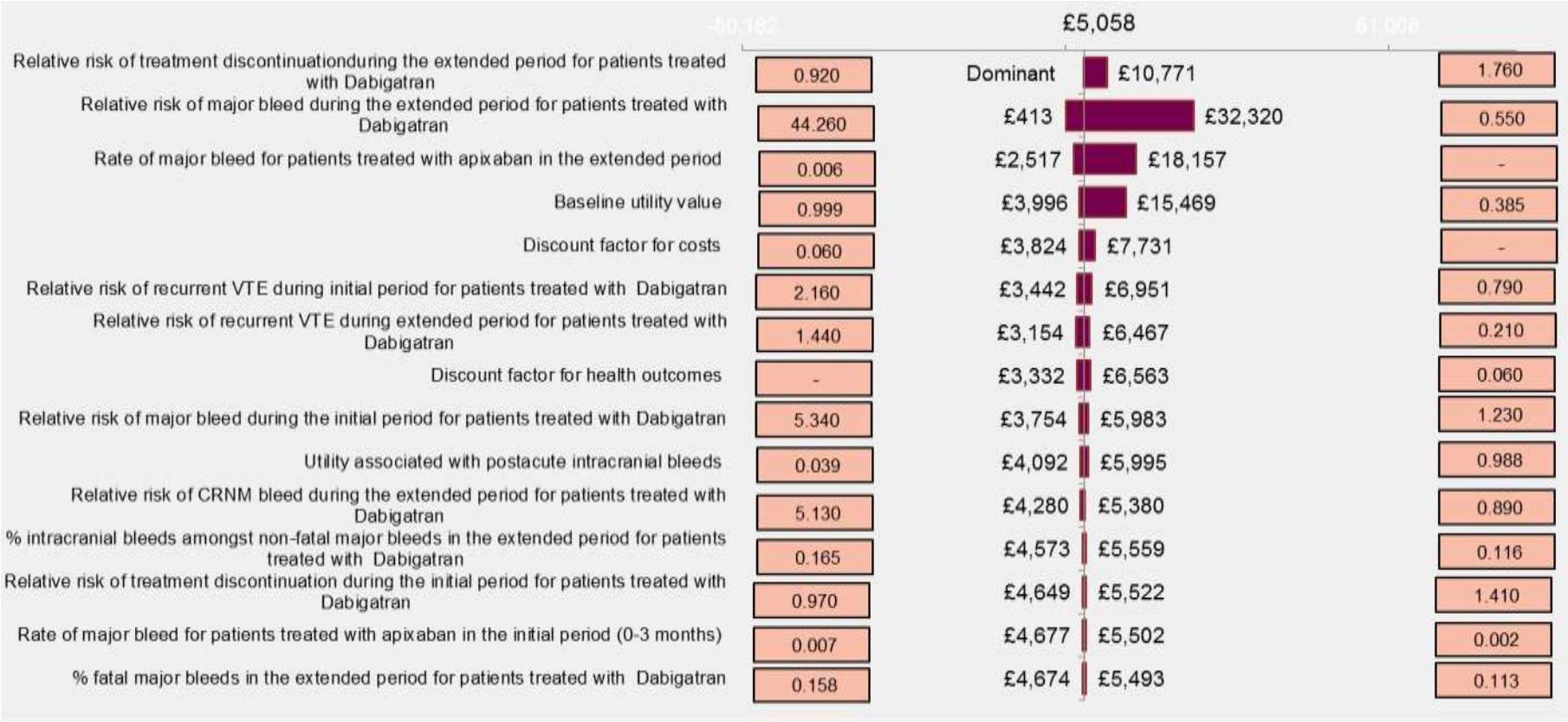
CRNM: Clinically relevant non-major; CTEPH: Chronic thromboembolic pulmonary hypertension; EC: Extracranial; PE: Pulmonary embolism; VTE: Venous thromboembolism

Apixaban vs. LMWH/dabigatran

Incremental costs for apixaban vs. LMWH/dabigatran varied between -£157 and £1,035 whilst incremental QALYs varied between 0.013 and 0.989. The ICER of apixaban vs. LMWH/dabigatran varied between being dominant and £32,320 per QALY gained.

Only one scenario resulted in an ICER above £20,000 per QALY gained: reducing the relative risk of major bleeding for dabigatran versus apixaban to 0.55 (4.21 in the base case).

Figure 36: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/dabigatran (index VTE, lifelong treatment duration)

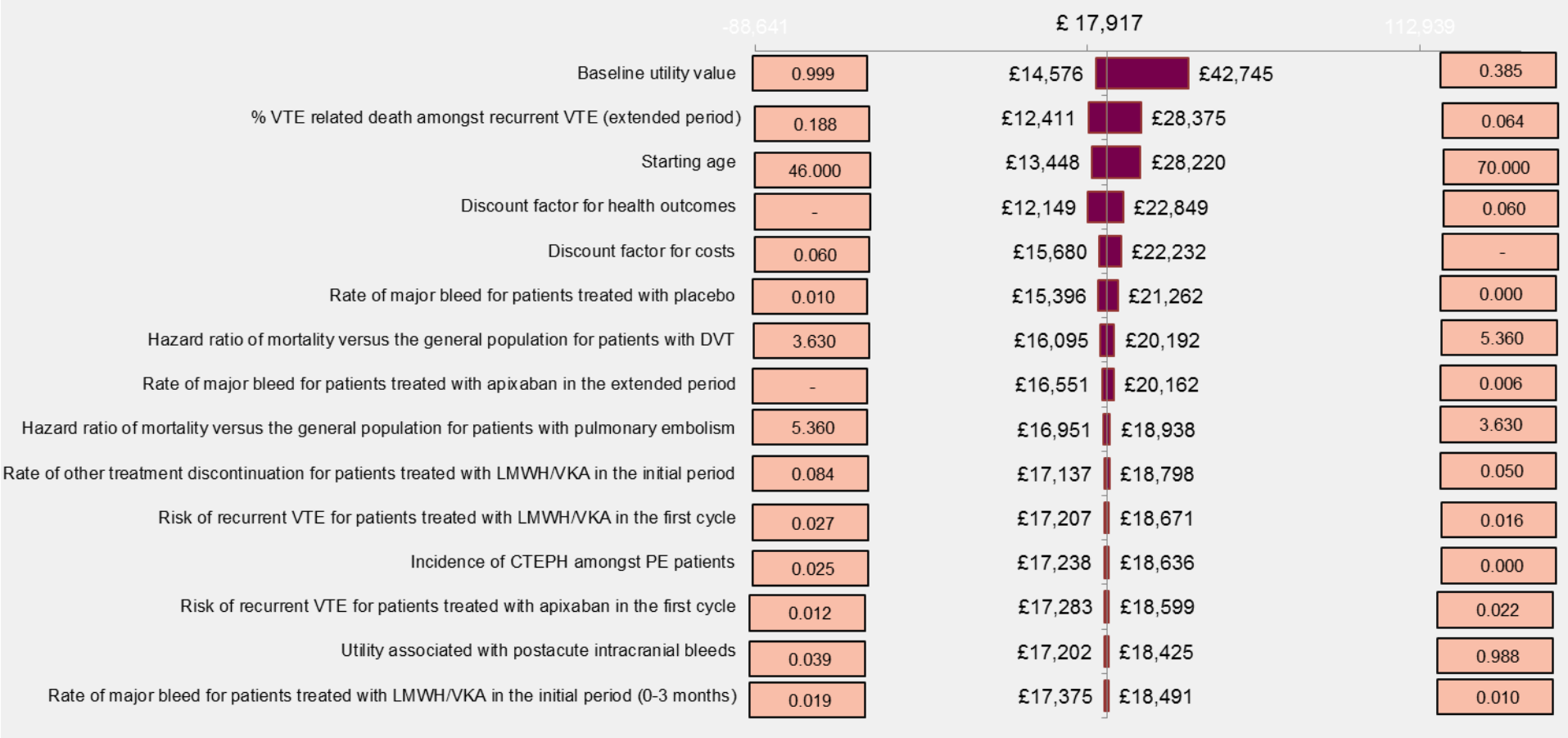


CRNM: Clinically relevant non-major; VTE: Venous thromboembolism

Apixaban vs. LMWH/VKA followed by no treatment

Incremental costs for apixaban vs. LMWH/VKA followed by no treatment varied between £2,999 and £5,715 whilst incremental QALYs varied between 0.106 and 0.401. The ICER for apixaban vs. LMWH/VKA followed by no treatment varied between £12,149 and £42,745 per QALY gained. The ICER for apixaban versus LMWH/VKA followed by no treatment remained under £30,000 for the majority of cases, and in only one case when the baseline utility value is changed to a value well below the population average, does the ICER rise above £30,000.

Figure 37: Tornado diagram illustrating results from univariate sensitivity analysis for incremental cost per QALY gained vs. LMWH/VKA followed by no treatment (index VTE, lifelong treatment duration)



CTEPH: Chronic thromboembolic pulmonary hypertension; DVT: Deep vein thrombosis; LMWH: Low molecular weight heparin; PE: Pulmonary embolism; VKA: Vitamin K antagonist; VTE: Venous thromboembolism

7.7.8 *Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.*

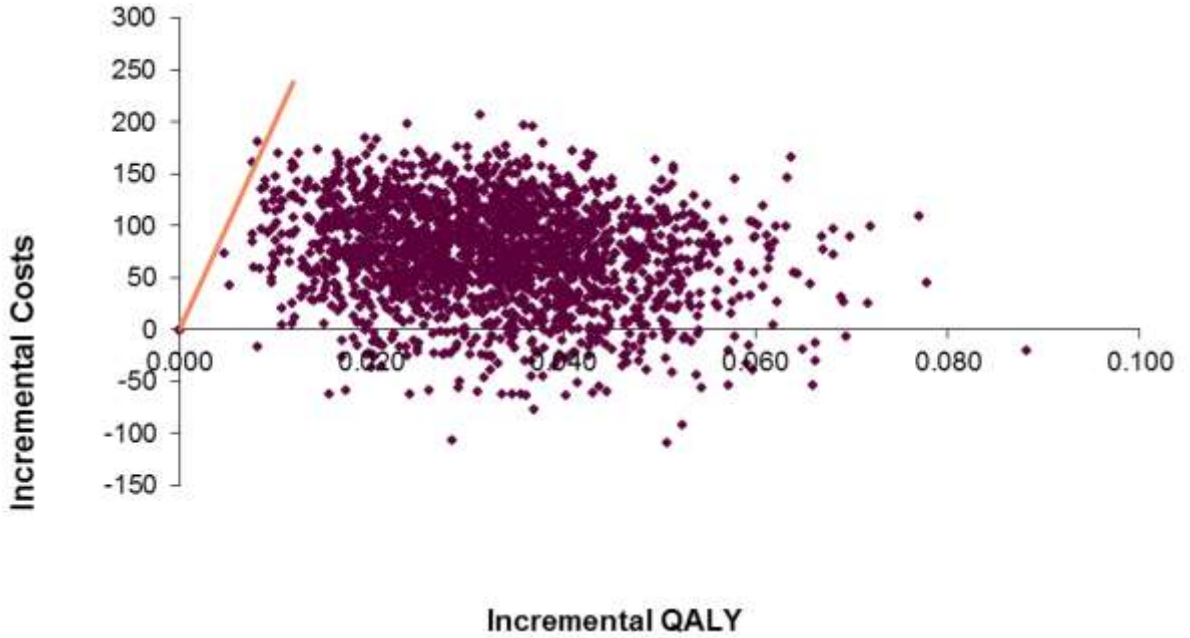
Probabilistic sensitivity analyses – 6-month treatment duration

The incremental outcomes in terms of QALYs gained are plotted against incremental costs for apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran on cost-effectiveness planes below.

In the comparison to LMWH/VKA, 100% of runs resulted in an ICER of less than £20,000 per QALY. In comparison to rivaroxaban, approximately 85% of the runs in the analysis resulted in apixaban being dominant and having an ICER of less than £20,000 per QALY. In comparison to LMWH/dabigatran, apixaban was dominant and had an ICER of less than £20,000 per QALY gained in approximately 98% of simulations.

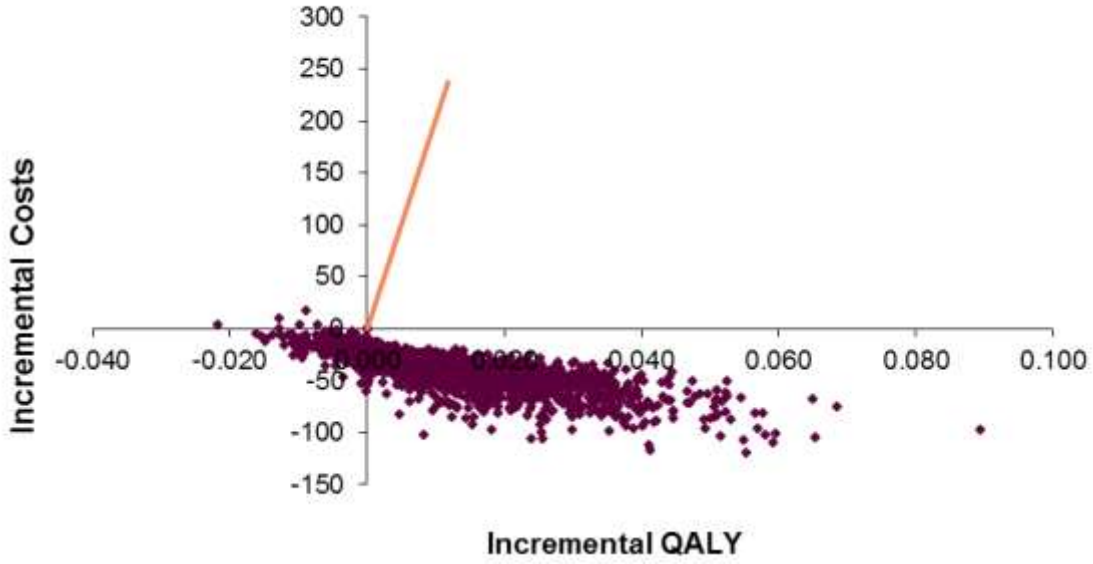
The proportion of simulations in which apixaban was cost-effective at a threshold of £20,000 per QALY gained was the same as the proportion at a cost-effectiveness threshold of £30,000 per QALY gained.

Figure 38: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. LMWH/VKA, cost per QALY, index VTE, 6-month treatment duration



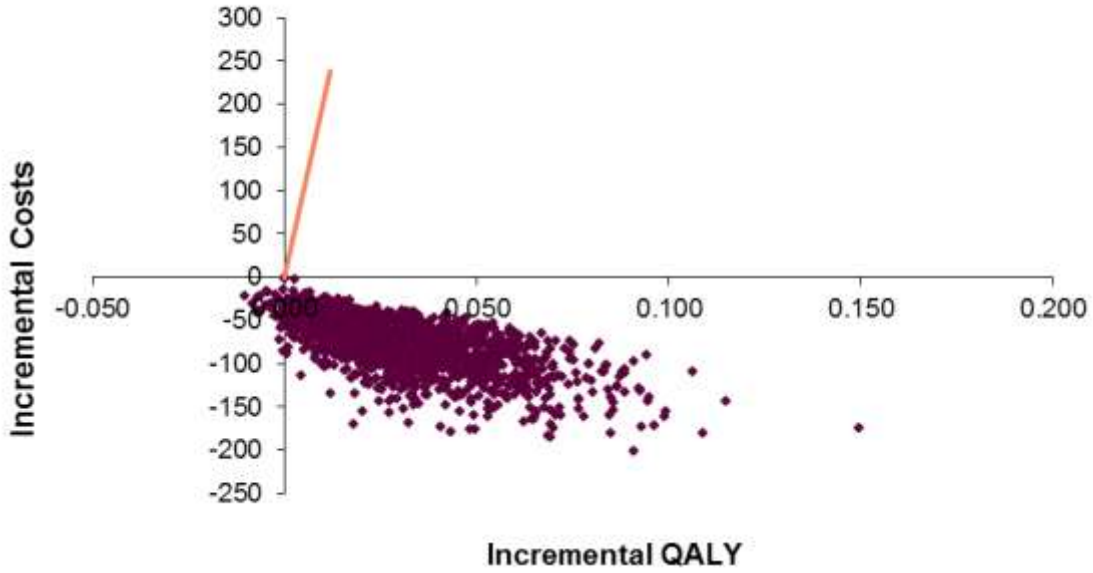
QALY: Quality adjusted life year

Figure 39: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. rivaroxaban, cost per QALY, 6-month treatment duration index VTE



QALY: Quality adjusted life year

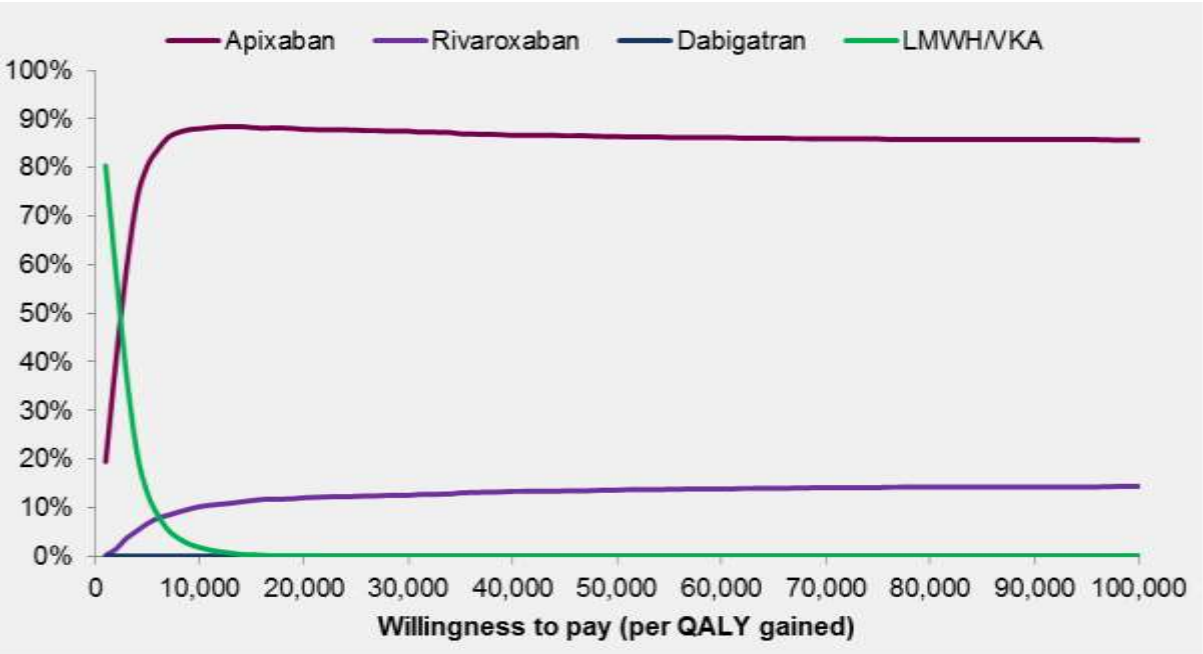
Figure 40: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. LMWH/dabigatran, cost per QALY, index VTE, 6-month treatment duration



QALY: Quality adjusted life year

The cost-effectiveness acceptability curve (CEAC) highlights that apixaban is the optimal treatment choice at a willingness to pay above £3,000 per QALY compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran.

Figure 41: Multi-way cost-effectiveness acceptability curve, index VTE, 6-month treatment duration



LMWH: Low molecular weight heparin; QALY: Quality adjusted life year; VKA: Vitamin K antagonist

Probabilistic sensitivity analyses – Lifelong treatment duration

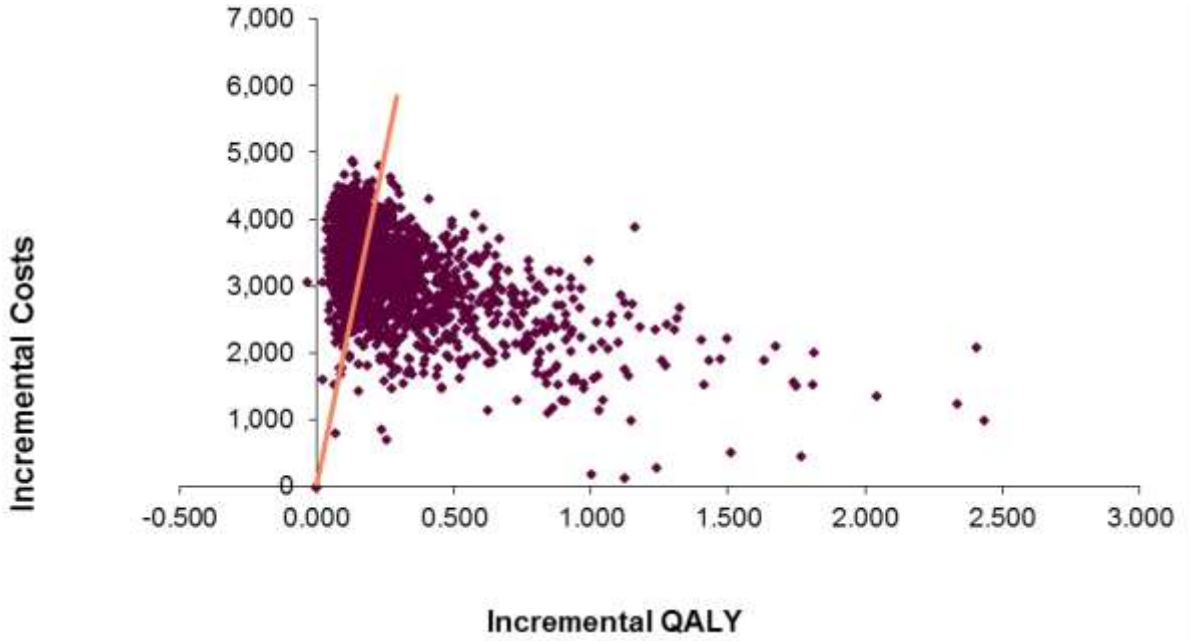
The incremental outcomes in terms of QALYs gained are plotted against incremental costs for apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran on cost-effectiveness planes below.

In the comparison to LMWH/VKA, approximately 54% and 77% of the runs in the analysis resulted in apixaban having an ICER of less than £20,000 and £30,000 per QALY, respectively (Figure 42; Figure 45).

In the comparison to rivaroxaban, approximately 96% and 98% of runs resulted in an ICER of less than £20,000 and £30,000 per QALY, respectively (Figure 43; Figure 45).

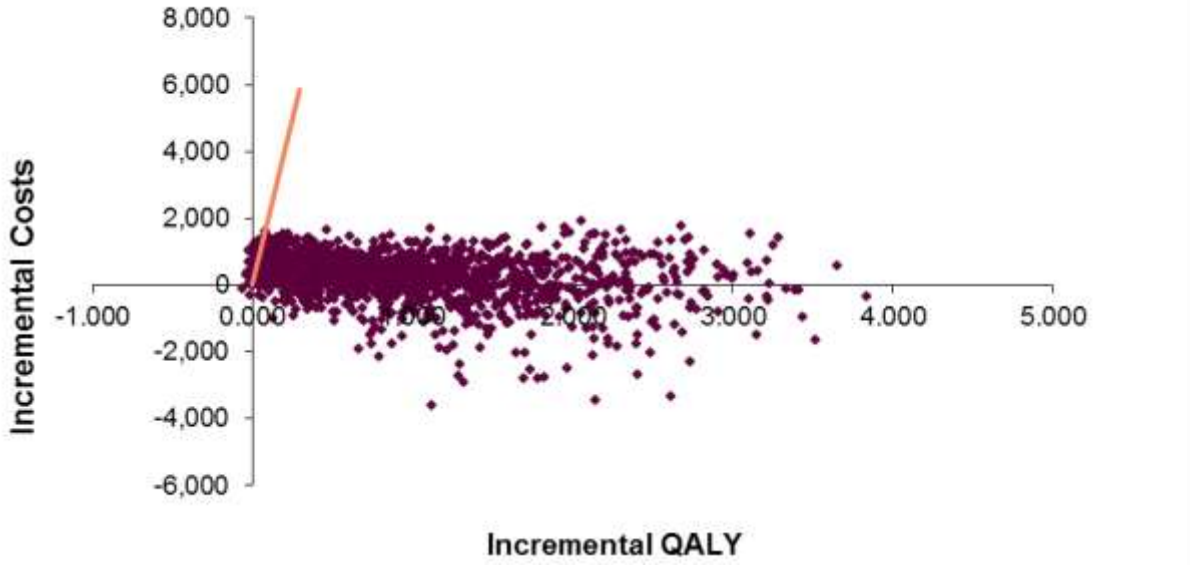
In the comparison to LMWH/dabigatran, approximately 86% and 89% of runs resulted in an ICER of less than £20,000 and £30,000 per QALY, respectively (Figure 44; Figure 45).

Figure 42: Probabilistic analysis - results on the cost-effectiveness plane, apixaban vs. LMWH/VKA, cost per QALY, index VTE, lifelong treatment duration



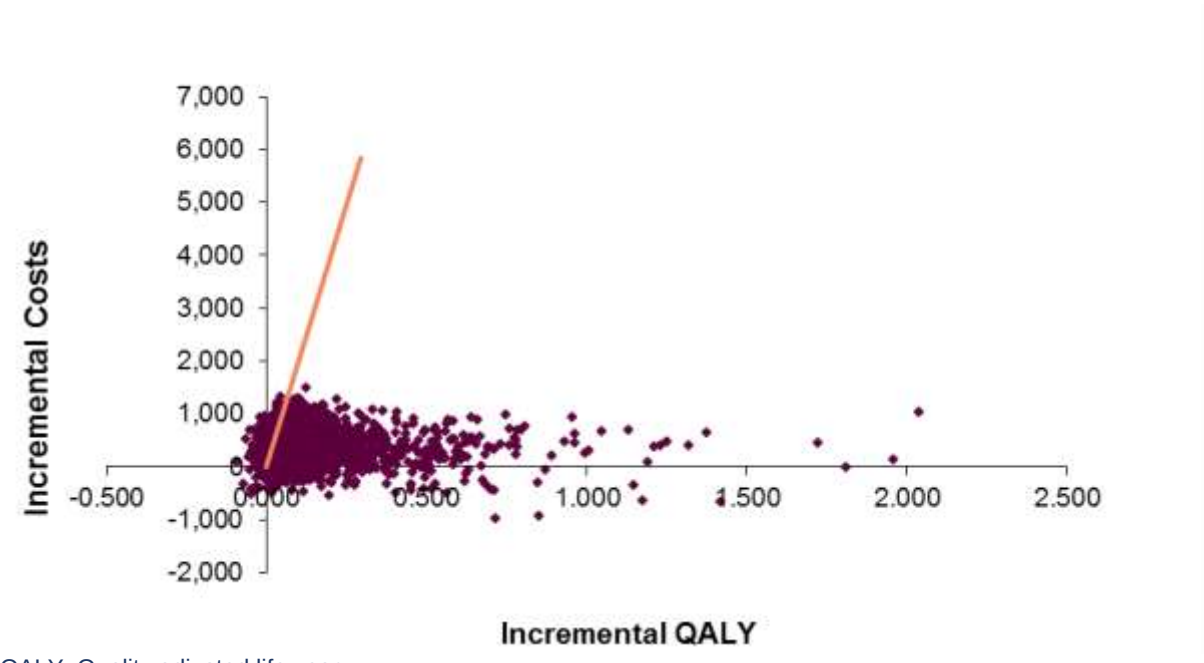
QALY: Quality adjusted life year

Figure 43: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. rivaroxaban, cost per QALY, lifelong treatment duration index VTE



QALY: Quality adjusted life year

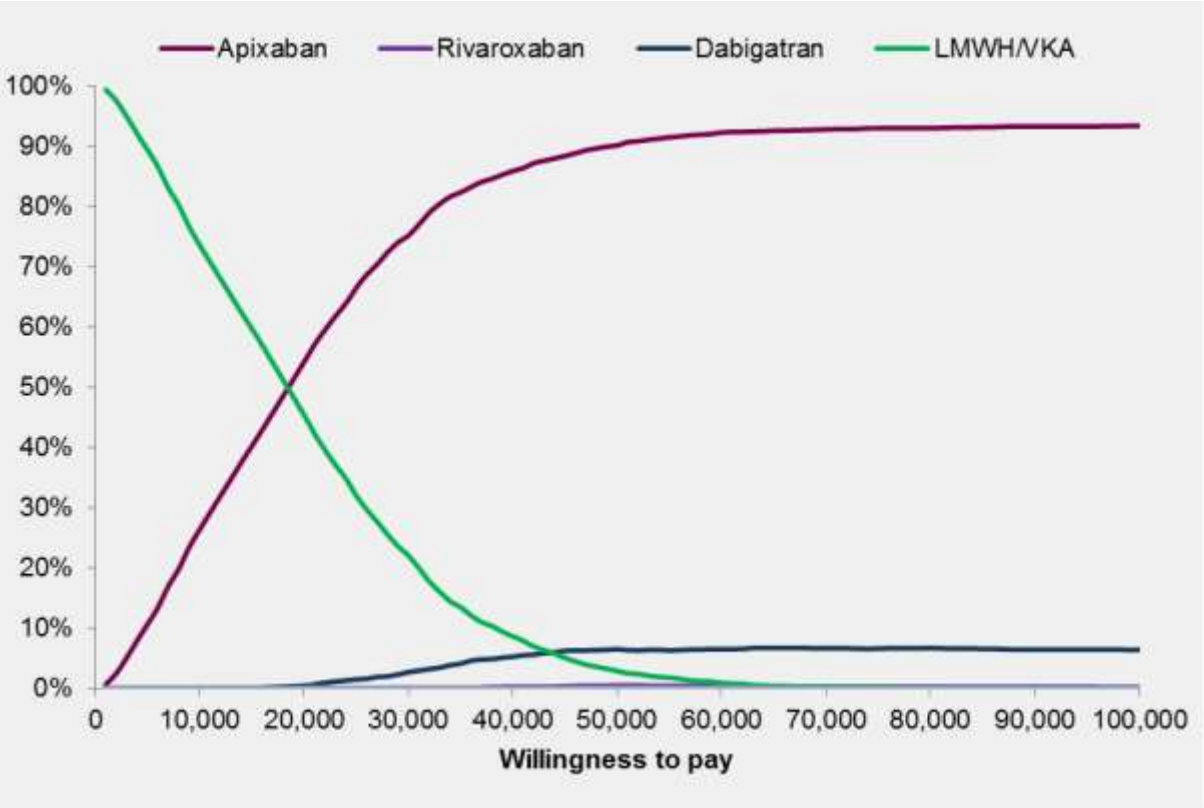
Figure 44: Probabilistic analysis - Results on the cost-effectiveness plane, apixaban vs. LMWH/dabigatran, cost per QALY, index VTE, lifelong treatment duration



QALY: Quality adjusted life year

The CEAC highlights that apixaban is the optimal treatment choice at a willingness to pay above £16,000 per QALY compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran.

Figure 45: Multi-way cost-effectiveness acceptability curve, index VTE, lifelong treatment duration



LMWH: Low molecular weight heparin; QALY: Quality adjusted life year; VKA: Vitamin K antagonist

7.7.9 *Please present the results of scenario analysis. Include details of structural sensitivity analysis*

Scenario analysis – 3-month treatment duration

For the 3-month treatment duration, apixaban was dominant vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran.

Table 86: Deterministic results, apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran (index VTE, 3-month treatment duration)

	LMWH/VKA	Rivaroxaban	LMWH/ dabigatran
Incremental QALYs	0.031	0.010	0.023
Incremental costs	-£49	-£42	-£66
ICER (£ per QALY gained)	Dominant	Dominant	Dominant
ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life years; VKA, vitamin K antagonist			

Scenario analyses – 6-month treatment duration

In comparison to LMWH/VKA, apixaban was dominant for the scenario using higher INR monitoring costs. In all other scenarios, apixaban was cost-effective with an ICER that ranged from £1,485 to £4,796 per QALY gained. Apixaban was dominant compared to rivaroxaban and LMWH/dabigatran for all scenarios tested.

Table 87: Scenario analysis apixaban vs. LMWH/VKA, rivaroxaban, and LMWH/dabigatran (index VTE, 6-month treatment duration)

	LMWH/VKA			Rivaroxaban			LMWH/dabigatran		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£80	0.033	£2,406	-£34	0.010	Dominant	-£65	0.026	Dominant
Anticoagulant dependent distribution of VTE, bleeding and other death	£115	0.043	£2,689	£0	0.022	Dominant	-£7	0.042	Dominant
Adjustment factors for bleeding	£80	0.033	£2,428	-£34	0.01	Dominant	-£65	0.026	Dominant
Background mortality set to equal general population	£67	0.045	£1,485	-£40	0.015	Dominant	-£79	0.037	Dominant
Utility decrement for all treatments set equal to VKA	£80	0.028	£2,855	-£34	0.01	Dominant	-£65	0.026	Dominant
Utility values by Hogg et al 2013	£80	0.038	£2,095	-£34	0.012	Dominant	-£65	0.029	Dominant
Set treatment discontinuation to be equal amongst treatments	£80	0.033	£2,402	-£33	0.011	Dominant	-£67	0.026	Dominant
Set treatment discontinuation to 0	£84	0.033	£2,525	-£34	0.011	Dominant	-£67	0.026	Dominant
Extend treatment lifelong on VTE recurrence (costs and utilities added only)	£75	0.034	£2,223	-£36	0.011	Dominant	-£78	0.027	Dominant
Extend duration of current treatment	£82	0.033	£2,464	-£35	0.01	Dominant	-£67	0.026	Dominant
Higher baseline risk of recurrent VTE for placebo	£82	0.033	£2,508	-£34	0.01	Dominant	-£64	0.025	Dominant
Lower baseline risk of recurrent VTE for placebo	£80	0.033	£2,375	-£34	0.011	Dominant	-£66	0.026	Dominant
Exclude cost of LMWH	£158	0.033	£4,749	-£34	0.01	Dominant	-£11	0.026	Dominant

	LMWH/VKA			Rivaroxaban			LMWH/dabigatran		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
INR monitoring costs set equal to TA261/TA287 higher limit	-£20	0.033	Dominant	-£34	0.01	Dominant	-£66	0.026	Dominant
Only inpatient treatment of VTE	£91	0.033	£2,726	-£34	0.01	Dominant	-£56	0.026	Dominant
Only outpatient treatment of VTE	£70	0.031	£2,262	-£34	0.01	Dominant	-£75	0.022	Dominant
Alternative distribution of recurrent VTE events	£80	0.033	£2,406	-£34	0.01	Dominant	-£65	0.026	Dominant
Alternative distribution of fatal major bleeds and non-fatal IC bleeds	£96	0.025	£3,835	-£28	0.007	Dominant	-£55	0.02	Dominant
PbR tariffs	£71	0.033	£2,147	-£37	0.01	Dominant	-£72	0.026	Dominant
Age varying utilities	£80	0.032	£2,505	-£34	0.01	Dominant	-£65	0.025	Dominant
VKA as a second-line treatment	£79	0.033	£2,379	-£34	0.011	Dominant	-£66	0.026	Dominant
All monitoring conducted in primary care	£94	0.033	£2,813	-£34	0.01	Dominant	-£65	0.026	Dominant
All monitoring conducted in secondary care	£53	0.033	£1,598	-£34	0.01	Dominant	-£66	0.026	Dominant
Lower monitoring resource use (4 visits on initiation, 1 subsequent)	£160	0.033	£4,796	-£34	0.01	Dominant	-£65	0.026	Dominant
All non-consultant led monitoring in secondary care	£96	0.033	£2,880	-£34	0.01	Dominant	-£65	0.026	Dominant
Dalteparin unit cost	£84	0.033	£2,528	-£34	0.01	Dominant	-£63	0.026	Dominant
CPRD population characteristics	£89	0.027	£3,328	-£31	0.008	Dominant	-£57	0.02	Dominant
Placebo risk for major bleeding same as apixaban	£80	0.033	£2,388	-£34	0.011	Dominant	-£66	0.026	Dominant
RE-COVER pooled NMA	£79	0.034	£2,352	-£34	0.010	Dominant	-£63	0.025	Dominant
Acute period: Exclude dabigatran	£79	0.034	£2,317	-£34	0.010	Dominant	-	-	-
Inclusion of renal function test for dabigatran	-	-	-	-	-	-	-£74	0.026	Dominant

	LMWH/VKA			Rivaroxaban			LMWH/dabigatran		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
CPRD: Clinical Practice Research Datalink; IC, Intracranial; ICER, Incremental cost-effectiveness ratio; INR: International normalised ratio; LMWH, Low molecular weight heparin; NMA: Network meta-analysis; PbR: Payment by Results; QALY, Quality-adjusted life-year; VKA, Vitamin K antagonist; VTE, Venous thromboembolism; Incr., Incremental									

Scenario analysis – 18-month treatment duration

For the 18-month treatment duration scenario analysis, apixaban was cost-effective vs. LMWH/VKA with an ICER of £8,823 per QALY gained and dominant vs. rivaroxaban and LMWH/dabigatran.

Table 88: Deterministic results, apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran (index VTE, 18-month treatment duration)

	LMWH/VKA	Rivaroxaban	LMWH/ dabigatran
Incremental QALYs	0.058	0.137	0.032
Incremental costs	£511	-£244	-£67
ICER (£ per QALY gained)	£8,823	Dominant	Dominant
ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life years; VKA, vitamin K antagonist			

Scenario analyses – Lifelong treatment duration

In scenario analyses comparing apixaban to LMWH/VKA over a lifelong treatment duration, ICERs ranged from £11,949 to £25,999 per QALY gained. Apixaban was cost-effective compared to LMWH/VKA at a willingness to pay threshold of £20,000 per QALY gained for all but three scenarios:

- Setting utility decrements for all treatments to equal those of VKA
- Using a lower distribution of fatal bleeds and non-fatal IC bleeds compared to the base case
- Using lower INR monitoring resource use estimates (4 visits on initiation and 1 visit subsequently)

In comparison to rivaroxaban and LMWH/dabigatran, apixaban was dominant or cost-effective at a £20,000 per QALY gained threshold for all scenarios.

Table 89: Scenario analysis apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran (index VTE, lifelong treatment duration)

	LMWH/VKA			Rivaroxaban			LMWH/dabigatran		
	Incremental Costs	Incremental QALYs	ICER	Incremental Costs	Incremental QALYs	ICER	Incremental Costs	Incremental QALYs	ICER
Base Case	£3,361	0.202	£16,676	£484	0.598	£809	£414	0.082	£5,058
Anticoagulant dependent distribution of VTE bleeding and other death	£3,563	0.21	£16,967	£925	0.343	£2,694	£678	0.128	£5,314
Adjustment factors for bleeding	£3,268	0.233	£14,020	£433	0.682	£635	£391	0.1	£3,909
Background mortality set to equal general population	£4,219	0.324	£13,042	£724	1.023	£708	£674	0.147	£4,586
Utility decrement for all treatments set equal to VKA	£3,361	0.129	£25,999	£484	0.575	£842	£414	0.073	£5,665
Utility values by Hogg et al 2013	£3,361	0.233	£14,435	£484	0.725	£668	£414	0.098	£4,210
Set treatment discontinuation to be equal amongst treatments	£3,190	0.203	£15,713	£35	0.637	£55	-£55	0.071	Dominant
Set treatment discontinuation to 0	£5,226	0.298	£17,552	£831	0.899	£925	£20	0.097	£206
Extend duration of current treatment	£3,362	0.202	£16,664	£484	0.598	£808	£413	0.082	£5,043

	LMWH/VKA			Rivaroxaban			LMWH/dabigatran		
	Incremental Costs	Incremental QALYs	ICER	Incremental Costs	Incremental QALYs	ICER	Incremental Costs	Incremental QALYs	ICER
Higher baseline risk of recurrent VTE for no treatment	£3,347	0.196	£17,110	£460	0.609	£755	£406	0.078	£5,200
Lower baseline risk for recurrent VTE for no treatment	£3,365	0.204	£16,492	£492	0.595	£826	£416	0.083	£4,989
Exclude cost of LMWH	£3,439	0.202	£17,061	£486	0.598	£813	£468	0.082	£5,719
INR monitoring costs set equal to TA261/TA287 higher limit	£2,408	0.202	£11,949	£482	0.598	£806	£414	0.082	£5,055
Only inpatient treatment of VTE	£3,373	0.202	£16,732	£476	0.598	£795	£423	0.082	£5,171
Only outpatient treatment of VTE	£3,365	0.201	£16,703	£496	0.592	£838	£409	0.079	£5,192
Alternative distribution of recurrent VTE events	£3,361	0.202	£16,676	£484	0.598	£809	£414	0.082	£5,058
Alternative distribution of fatal major bleeds and non-fatal IC bleeds	£3,469	0.144	£24,038	£854	0.371	£2,303	£462	0.051	£8,999
PbR tariffs	£3,300	0.202	£16,374	£240	0.598	£401	£381	0.082	£4,649
Age varying utilities	£3,361	0.192	£17,466	£484	0.561	£864	£414	0.077	£5,401
VKA as a second line treatment	£3,144	0.204	£15,436	£169	0.601	£281	£235	0.083	£2,817
All monitoring conducted in primary care	£3,495	0.202	£17,339	£484	0.598	£810	£414	0.082	£5,058
All monitoring conducted in secondary care	£3,096	0.202	£15,361	£484	0.598	£809	£414	0.082	£5,057
Prevention period: ITT analysis	£3,269	0.273	£11,971	£482	0.599	£805	£376	0.131	£2,870
Prevention period: ITT exclusion of WODIT	£3,267	0.260	£12,555	£479	0.609	£786	£404	0.114	£3,538
Prevention period: Exclude dabigatran	£3,356	0.205	£16,346	£468	0.646	£724	-	-	-

	LMWH/VKA			Rivaroxaban			LMWH/dabigatran		
	Incremental Costs	**Incremental QALYs**	**ICER**	**Incremental Costs**	**Incremental QALYs**	**ICER**	**Incremental Costs**	**Incremental QALYs**	**ICER**
Lower monitoring resource use (4 visits on initiation, 1 subsequent)	£4,293	0.202	£21,301	£485	0.598	£811	£414	0.082	£5,060
All non-consultant led monitoring in secondary care	£3,481	0.202	£17,271	£485	0.598	£810	£414	0.082	£5,059
Dalteparin unit cost	£3,365	0.202	£16,696	£484	0.598	£810	£417	0.082	£5,091
CPRD population characteristics	£2,744	0.141	£19,458	£285	0.385	£741	£264	0.052	£5,054
Placebo risk for major bleeding same as apixaban	£3,367	0.199	£16,896	£492	0.595	£828	£419	0.08	£5,236
Inclusion of renal function test for dabigatran	-	-	-	-	-	-	£405	0.082	£4,951

CPRD: Clinical Practice Research Datalink; IC, Intracranial; ICER, Incremental cost-effectiveness ratio; INR: International normalised ratio; ITT: Intention-to-treat; LMWH, Low molecular weight heparin; PbR: Payment by Results; QALY, Quality-adjusted life-year; VKA, Vitamin K antagonist; VTE, Venous thromboembolism

Scenario analyses – Apixaban vs. LMWH/VKA/no treatment, lifelong treatment duration

For scenarios in which lifelong treatment with apixaban was compared to 6-month treatment with LMWH/VKA followed by no treatment, ICERs ranged from £11,902 to £24,927 per QALY gained (Table 90).

Table 90: Scenario analysis apixaban vs. LMWH/VKA for 6 months followed by no treatment (index VTE, lifelong treatment duration)

	Incremental Costs	Incremental QALYs	ICER
Base Case	£4,606	0.257	£17,917
Anticoagulant dependent distribution of VTE bleeding and other death	£4,804	0.217	£22,125
Adjustment factors for bleeding	£4,580	0.261	£17,518
Background mortality set to equal general population	£5,616	0.456	£12,324
Utility decrement for all treatments set equal to VKA	£4,606	0.185	£24,927
Utility values by Hogg et al 2013	£4,606	0.264	£17,461
Set treatment discontinuation to be equal amongst treatments	£4,605	0.258	£17,883
Set treatment discontinuation to 0	£7,559	0.34	£22,213
Extend duration of current treatment	£4,609	0.257	£17,918
Higher baseline risk of recurrent VTE for no treatment	£4,419	0.371	£11,902
Lower baseline risk for recurrent VTE for no treatment	£4,684	0.209	£22,361
Exclude cost of LMWH	£4,701	0.257	£18,286
INR monitoring costs set equal to TA261/TA287 higher limit	£4,493	0.257	£17,478
Only inpatient treatment of VTE	£4,550	0.257	£17,700
Only outpatient treatment of VTE	£4,667	0.19	£24,542
Alternative distribution of recurrent VTE events	£4,606	0.257	£17,917
Alternative distribution of fatal major bleeds and non-fatal IC bleeds	£4,641	0.241	£19,251
PbR tariffs	£4,551	0.257	£17,705
Age varying utilities	£4,606	0.243	£18,929
VKA as a second line treatment	£5,454	0.239	£22,793
All monitoring conducted in primary care	£4,621	0.257	£17,977
All monitoring conducted in secondary	£4,575	0.257	£17,800

care			
Prevention period: ITT analysis	£4,595	0.262	£17,533
Prevention period: ITT exclusion of WODIT	£4,595	0.262	£17,561
Prevention period: Exclude dabigatran	£ 4,606	0.257	£ 17,937
Lower monitoring resource use (4 visits on initiation, 1 subsequent)	£4,694	0.257	£18,261
All non-consultant led monitoring in secondary care	£4,624	0.257	£17,988
Dalteparin unit cost	£4,611	0.257	£17,937
CPRD population characteristics	£3,817	0.167	£22,832
Placebo risk for major bleeding same as apixaban	£4,648	0.238	£19,490
CPRD: Clinical Practice Research Datalink; IC, Intracranial; ICER, Incremental cost-effectiveness ratio; INR: International normalised ratio; ITT: Intention-to-treat; LMWH, Low molecular weight heparin; PbR: Payment by Results; QALY, Quality-adjusted life-year; VKA, Vitamin K antagonist; VTE, Venous thromboembolism			

Scenario analyses – Apixaban vs. LMWH/VKA/aspirin, lifelong treatment duration

For the scenario versus LMWH/VKA for 6 months followed by aspirin for lifelong treatment, apixaban had incremental costs of £4,663, and an incremental gain of 0.206 QALYs, giving an ICER of £22,595 per QALY gained (Table 91).

Table 91: Scenario analysis apixaban vs. LMWH/VKA for 6 months followed by aspirin (index VTE, lifelong treatment duration)

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Aspirin followed by LMWH/VKA	£4,835	8.467	£4,663	0.206	£22,595
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; QALY: Quality adjusted life year; VKA: Vitamin K antagonist					

Scenario analyses – Apixaban vs. LMWH monotherapy, 6-month treatment duration

For the scenario versus LMWH monotherapy for 6 months, apixaban was dominant with incremental costs of -£1,473, and an incremental gain of 0.024 QALYs (Table 92).

Table 92: Scenario analysis apixaban vs. LMWH monotherapy (index VTE, 6-month treatment duration)

	Incremental Costs	Incremental QALYs	ICER
LMWH monotherapy as a comparator	-£1,473	0.024	Dominant
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; QALY: Quality adjusted life year			

Scenario analyses – Apixaban vs. LMWH monotherapy, lifelong treatment duration

Apixaban was dominant in the scenario comparing lifelong apixaban versus lifelong LMWH monotherapy and apixaban was cost-effective versus LMWH monotherapy for 6 months followed by no treatment, with an ICER of £12,318 per QALY gained (Table 93).

Table 93: Scenario analysis apixaban vs. LMWH monotherapy (index VTE, 6-month treatment duration)

	Incremental Costs	Incremental QALYs	ICER
Lifelong LMWH monotherapy	-£19,270	0.092	Dominant
6-month LMWH monotherapy followed by no treatment	£3,052	0.248	£12,318
ICER: Incremental cost-effectiveness ratio; LMWH: Low molecular weight heparin; QALY: Quality adjusted life year			

7.7.10 *What were the main findings of each of the sensitivity analyses?*

Results from the sensitivity analyses indicate that the model results and conclusions are robust to changes in the model inputs.

In deterministic sensitivity analysis, for a 6-month treatment duration the ICERs for apixaban vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran did not exceed a willingness to pay threshold of £20,000 for any parameters. For a lifelong treatment duration, the ICER showed more variation. The changes in parameters that produced an ICER over £30,000 included reducing the baseline utility for the population, and removing the differences in major bleeding between apixaban and comparators despite evidence of differences from the NMAs.

Results from the PSA suggest that for the 6-month and lifelong treatment durations, apixaban had the highest probability of being cost-effective compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran at willingness to pay thresholds of £3,000 and £16,000 per QALY gained, respectively.

For all scenario analyses conducted with a treatment duration of 3, 6 or 18 months, apixaban was dominant or cost-effective at a willingness to pay threshold of £20,000 per QALY gained compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran.

For scenario analyses conducted with a lifelong treatment duration, apixaban was cost-effective at a willingness to pay threshold of £20,000 per QALY gained vs. LMWH/VKA in all but three scenarios: one in which utility decrements for all treatments were set to equal those of VKA, one using a treatment dependent distribution of fatal bleeds and non-fatal IC bleeds and one using lower INR monitoring resource use. Apixaban was dominant or cost-effective at a willingness to pay threshold of £20,000 per QALY gained in all other scenarios compared to LMWH/VKA, rivaroxaban and LMWH/dabigatran.

7.7.11 *What are the key drivers of the cost-effectiveness results?*

From the deterministic sensitivity analysis, the cost-effectiveness of apixaban was most sensitive to the following parameters:

- The relative risks of major bleeding for patients treated with rivaroxaban or LMWH/dabigatran for both the 6-month and lifelong treatment durations and for LMWH/VKA for the lifelong treatment duration
- The rate of major bleeds for patients treated with apixaban for 0-3 months, and for the lifelong treatment duration
- The relative risks of recurrent VTE for patients treated with LMWH/VKA, rivaroxaban or LMWH/dabigatran for the 6-month treatment duration
- Baseline utility value and starting age for the 6-month and lifelong treatment durations

- The relative risks of treatment discontinuation for patients treated with rivaroxaban or LMWH/dabigatran for the lifelong treatment duration

The model is driven by the risks of major bleeds as this is the most important differentiation between apixaban and the other anticoagulants (see Section 6.7.5). This indicates that the model is reflecting important clinical differences between the therapies and is not being driven by illogical parameters.

7.8 Validation

7.8.1 *Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.*

Face validity

Face validity of the model was established by presenting the initial model concept, the Markov diagram, and final model structure to KOLs in an advisory board format.(9) The purpose of the review was to ensure that all models were designed correctly and rigorously from the perspective of clinical face validity as well as modelling standpoints. Technical accuracy was determined by performing extreme-value sensitivity analyses to check for logical consistency. Upon the completion of the model, a comprehensive and rigorous quality check was performed by two independent external experts, which included validating the logical structure of the model, mathematical formulas and sequences of calculations, and the values of numbers supplied as model inputs.

Predictive validity

Predictive validity was checked by comparing key outcomes to the source data. In performing this, the model was set to the settings of AMPLIFY and AMPLIFY-EXT (ie., number of patients, duration of follow-up) and the key event rates were compared. The results from the predictive validation against the AMPLIFY and the AMPLIFY-EXT trials are shown in Section 7.7.1.

7.9 Subgroup analysis

7.9.1 *Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.*

Deterministic results assessed two subgroups: patients with index PE, and patients with index DVT.

7.9.2 *Please clearly define the characteristics of patients in the subgroup.*

The model structure and majority of inputs (costs, utilities, risk of PTS, risk of CTEPH) remained unaltered for the PE and DVT subgroups, however the baseline risks of recurrent VTE, bleeding and discontinuation events were altered to reflect the PE and DVT populations specifically. The relative risks were adjusted where data permitted for the treatment period. If treatment effects for NOACs were not available, the same treatment effects observed in the overall population were used. Data from the overall population were used beyond the first 6 months of treatment (both risks and RRs). Inputs used in the subgroup analyses are presented in Appendix 19.

7.9.3 *Please describe how the statistical analysis was undertaken.*

A full set of analysis was not conducted for the subgroups as the primary population of interest was overall patients with VTE and because AMPLIFY and AMPLIFY-EXT were not powered to account for these subgroups. The model accounted for both index and DVT in the base case by considering a proportion of VTE events to be PEs and the remaining proportion DVTs, based on the trial data.

7.9.4 *What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).*

Base case results for the index PE and index DVT subgroups are presented in Table 94 and Table 95 below for the 6-month treatment duration, and in Table 96 and Table 97 for the lifelong treatment duration, respectively.

For the 6-month treatment duration, apixaban had ICERs of £1,713 and £3,350 per QALY gained vs. LMWH/VKA for the index PE and index DVT subgroups, respectively. Apixaban was dominant vs. LMWH/dabigatran for both subgroups and vs. rivaroxaban in the index PE subgroup. In the DVT subgroup, apixaban was less costly and equally effective compared to rivaroxaban.

For the lifelong treatment duration, apixaban was cost-effective vs. LMWH/VKA, rivaroxaban and LMWH/dabigatran at a willingness to pay threshold of £20,000 per QALY gained for both subgroups. In the conservative comparison of lifelong treatment with apixaban vs. 6 months of treatment with LMWH/VKA followed by no treatment, apixaban had ICERs of £17,691 and £18,018 per QALY gained, respectively, for the index PE and DVT subgroups.

Table 94: Base case results – 6-month treatment duration (index PE)

	Apixaban	LMWH/VKA	Rivaroxaban	LMWH/dabigatran
Total QALYs	8.390	8.341	8.359	8.381
Total costs	£9,632.23	£9,548.76	£9,659.95	£9,667.35
Incremental QALYs (apixaban vs. comparator)	-	0.049	0.031	0.009
Incremental costs (apixaban vs. comparator)	-	£83	-£28	-£35
ICER (£ per QALY gained) (apixaban vs. comparator)	-	£1,713	Dominant	Dominant

ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life years; VKA, vitamin K antagonist

Table 95: Base case results – 6-month treatment duration (index DVT)

	Apixaban	LMWH/VKA	Rivaroxaban	LMWH/dabigatran
Total QALYs	8.431	8.405	8.431	8.396
Total costs	£2,640.80	£2,555.17	£2,656.15	£2,736.76
Incremental QALYs (apixaban vs. comparator)	-	0.026	0.000	0.035
Incremental costs (apixaban vs. comparator)	-	£86	-£15	-£96
ICER (£ per QALY gained) (apixaban vs. comparator)	-	£3,350	Less costly, equally effective	Dominant
ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life years; VKA, vitamin K antagonist				

Table 96: Base case results – Lifelong treatment duration (index PE)

	Apixaban	LMWH/VKA	Rivaroxaban	LMWH/dabigatran	LMWH/VKA/no treatment
Total QALYs	8.635	8.423	8.045	8.572	8.635
Total costs	£14,244.65	£10,920.08	£13,311.71	£13,804.35	£14,244.65
Incremental QALYs (apixaban vs. comparator)	-	0.212	0.590	0.063	0.267
Incremental costs (apixaban vs. comparator)	-	£3,325	£933	£440	£4,728
ICER (£ per QALY gained) (apixaban vs. comparator)	-	£15,661	£1,582	£7,022	£17,691
ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life years; VKA, vitamin K antagonist					

Table 97: Base case results – Lifelong treatment duration (index DVT)

	Apixaban	LMWH/VKA	Rivaroxaban	LMWH/dabigatran	LMWH/VKA/no treatment
Total QALYs	8.684	8.488	8.096	8.593	8.684
Total costs	£7,014.54	£3,631.35	£6,601.63	£6,629.72	£7,014.54
Incremental QALYs (apixaban vs. comparator)	-	0.196	0.588	0.092	0.252
Incremental costs (apixaban vs. comparator)	-	£3,383	£413	£4,197	£4,539
ICER (£ per QALY gained) (apixaban vs. comparator)	-	£17,257	£702	£7,005	£18,018

ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; QALY, quality adjusted life years; VKA, vitamin K antagonist

7.9.5 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.*

The decision problem identified patients with active cancer as a separate population (Section 5). As the efficacy and safety of apixaban is not established for the treatment of patients with active cancer, these patients were not considered in a separate subgroup analysis.(20) An exploratory analysis was performed to compare apixaban with LMWH monotherapy (commonly used for cancer patients) in the VKA suitable population (Section 7.6).

7.10 Interpretation of economic evidence

7.10.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

The systematic review discussed in Section 7.1 did not identify any economic evaluations which estimated the cost-effectiveness or cost-utility of apixaban in VTE.

The present model was designed with a similar structure to earlier cost-effectiveness analyses modelling VTE, bleeding events and the impact of anticoagulant treatment over different treatment durations.(18, 19)

7.10.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?*

The economic evaluation is relevant to all patients that could potentially use the technology as identified in the decision problem.

7.10.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

The main strengths of the evaluation are:

- The extensive sensitivity and subgroup analyses that provide an overall picture of the impact of apixaban's entry into the market across different treatment durations and patient groups.
- The use of conservative inputs (18, 19) that favoured other comparators, notably LMWH/VKA; for example an increased risk of bleeding over time and with age, or less frequent INR monitoring visits than assumed in earlier submissions and recommended by the NICE Appraisal Committee.(164, 165) Had the same monitoring assumptions been used in the present model, apixaban would be dominant vs. LMWH/VKA for the 6-month treatment duration and the ICER for the lifelong treatment duration would be £11,797 per QALY.
- The mortality estimates used in this analysis improve upon earlier models that assumed that patients with VTE, who do not experience any other events, will follow the mortality patterns of the general population.(18, 19, 108, 130) This assumption is at odds to evidence from retrospective studies.(31, 93, 125) In addition, earlier models assumed no long-term impact of IC bleeds on mortality, only an acute impact. (18, 19, 108, 130) This assumption is again at odds to long-term population-based studies that suggest a longer term impact on mortality for IC bleeds.(123) Therefore, the present model accounted for the long-term impact on mortality after IC bleeds occurred as well as increased mortality in VTE patients who did not experience any other events, thus providing more accurate model of the costs and QALYs likely to be incurred over a lifetime horizon.

The main weaknesses of the evaluation are:

- There was some uncertainty in the NMA for the prevention period due to heterogeneity between included studies; there were large confidence intervals for some comparisons, such as the comparison of apixaban versus rivaroxaban for major bleeding. Nevertheless, when testing alternative NMA networks in scenario analyses apixaban remained robustly cost-effective regardless of the NMA network chosen.
- Estimates of increased mortality in the model did not exclude mortality due to CTEPH or non-IC major bleeds and thus may have double-counted these events; however, as the number of these events was small the impact was therefore considered negligible. Scenario analyses that set the background mortality of VTE patients to be equal to that of the general population resulted in more favourable results for apixaban across all comparisons and treatments, with higher QALY gains and cost savings in cases in which apixaban was dominant and lower ICERs when apixaban was cost-effective. Consequently, any bias associated with this assumption is unfavourable to apixaban.
- Clinical evidence from AMPLIFY and AMPLIFY-EXT indicates that there are differences in rates of hospitalisation in favour of apixaban compared to LMWH, VKA, and placebo (no treatment). This evaluation has not specifically included these differences to avoid double-counting hospitalisations associated with clinical events in the model and therefore this may be a bias against apixaban.

7.10.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

Earlier evidence review groups have suggested that an area of uncertainty with regards to the economic value of NOACs is bleed reversal.(128, 166) In the present analysis we did not include a cost for bleed reversal as there is currently no approved bleed reversal agent for NOACs. The cost of reversal could be reflected as an increased acute event cost for major bleeds associated with the NOACs compared to LMWH/VKA, aspirin or no treatment. Due to apixaban's favourable bleeding profile, inclusion of bleed reversal costs would be expected to result in more favourable results for apixaban compared to the other NOACs; therefore, inclusion of such attributes would not alter the conclusions of the present analyses.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

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

The number of patients eligible for treatment with apixaban is estimated based on the population of England and Wales and epidemiological data from published studies.

Table 98 below outlines the eligible population from 2015 to 2019 for treatment and prevention of VTE.

Table 98: Eligible patient population

	2015	2016	2017	2018	2019	Reference Sources
Population of England	54,613,417	55,019,793	55,414,470	55,811,753	56,198,276	2012-based National Population Projections. Published by the Office for National Statistics (167)
Population of Wales	3,107,165	3,119,426	3,131,869	3,144,270	3,156,630	
Total Population	57,720,582	58,139,219	58,546,339	58,956,023	59,354,906	Calculated
Annual incidence of VTE per 10,000	13.2	13.2	13.2	13.2	13.2	13.2(6) per 10,000
Incidence	75,903	76,453	76,988	77,527	78,052	Calculated
Percentage incident events that are fatal prior to treatment	21.5%	21.5%	21.5%	21.5%	21.5%	AMPLIFY Secondary analysis (97)
Percentage contraindicated for anticoagulant therapy	2%	2%	2%	2%	2%	NICE costing template for rivaroxaban in DVT (168)
Patients starting treatment	58,392	58,815	59,227	59,642	60,045	Calculated

8.1.2 *What assumption(s) were made about current treatment options and uptake of technologies?*

Table 99 outlines the current treatment options for VTE and their projected market share over 5 years.(169) Table 100 illustrates the projected 5-year uptake of apixaban for the treatment and prevention of VTE in England and Wales across this group of patients.

Table 99: Projected market share without apixaban (169)

	Apixaban	Rivaroxaban	LMWH-dabigatran	LMWH-warfarin
2015	[redacted]	[redacted]	[redacted]	[redacted]
2016	[redacted]	[redacted]	[redacted]	[redacted]
2017	[redacted]	[redacted]	[redacted]	[redacted]
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]

Table 100: Projected market share with apixaban (169)

	Apixaban	Rivaroxaban	LMWH-dabigatran	LMWH-warfarin
2015	[redacted]	[redacted]	[redacted]	[redacted]
2016	[redacted]	[redacted]	[redacted]	[redacted]
2017	[redacted]	[redacted]	[redacted]	[redacted]
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]

Table 101 outlines the assumptions made around treatment duration. For those patients assigned lifelong treatment it was assumed that 14.46% would discontinue annually from all causes. This was calculated from the all-cause discontinuation from the 2.5 mg apixaban arm of AMPLIFY-EXT (114 out of 840) and the background mortality rate for England and Wales weighted by the ratio of male to female in the AMPLIFY study.(16, 64) No disease-specific mortality from recurrence was modelled, which is a conservative assumption in this budget impact model. The market share inputs apply to newly incident patients only. Prevalent patients are assumed to not switch treatment, and thus are not eligible for apixaban.

Table 101: Assumed treatment durations

	3 months	6 months	Lifetime
Apixaban	41.5%	43.5%	15%
Rivaroxaban	41.5%	43.5%	15%
LMWH-dabigatran	41.5%	43.5%	15%
LMWH-warfarin	41.5%	43.5%	15%

8.1.3 *What assumption(s) were made about market share (when relevant)?*

See Section 8.1.2 above.

8.1.4 *In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).*

The cost of INR monitoring was assumed to be £24.59 for the first visit and £21.04 per visit thereafter, with 6 visits in the first three months and monthly visits thereafter (Section 7.5.6). Table 102 presents the results of applying these costs to the patient numbers estimated.

Table 102: Costs of INR monitoring with and without apixaban

	2015	2016	2017	2018	2019
Without Apixaban	£ 8,815,277	£ 9,981,792	£ 10,896,015	£ 11,631,853	£ 12,276,644
With Apixaban	£ 8,329,575	£ 9,200,327	£ 9,781,516	£ 10,266,517	£ 10,652,080
Total net cost with Apixaban	-£ 485,702	-£ 781,465	-£ 1,114,500	-£ 1,365,336	-£ 1,624,564

The cost of training on LMWH administration was assumed to be £17 for each patient treated. The cost of administering LMWH for those unable to self-administer was assumed to be £8.78 per dose (and thus per day). It was assumed that 8% of patients would be unable to self-administer (Section 7.5.6).

Table 103 presents the results of applying these costs to the patient numbers estimated.

Table 103: Costs of training and administration for LMWH treatment with and without apixaban

	2015	2016	2017	2018	2019
Without Apixaban	£ 1,094,817	£ 1,103,489	£ 1,077,860	£ 1,057,492	£ 1,047,616
With Apixaban	£ 1,069,020	£ 1,012,436	£ 955,431	£ 917,183	£ 888,426
Total net cost with Apixaban	-£ 25,797	-£ 91,054	-£ 122,429	-£ 140,308	-£ 159,190

8.1.5 *What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?*

The unit costs assumed in the budget impact calculations, which are the same as those assumed in Section 7.5, are presented in Table 104 (induction), Table 105 (concomitant LMWH), Table 106 (up to 6 months) and Table 107 (after 6 months). The total treatment costs with and without apixaban are presented in Table 108.

Table 104: Unit costs assumed in budget impact calculations (induction)

	Unit size	Unit cost	Induction Dose	Induction Length
Apixaban	5 mg	£1.10*	2 × 5 mg bd	7
Rivaroxaban	15 mg	£2.10†	15 mg bd	21
LMWH-dabigatran#	N/A	N/A	N/A	N/A
LMWH-warfarin	6 mg‡	£0.009#	6 mg od‡	7.64

*BMS/Pfizer
†Electronic Drug Tariff, August 2014, Department of Health by the NHS Business Services Authority, NHS Prescription Services, http://www.ppa.org.uk/ppa/edt_intro.htm (170)
#The dose of dabigatran does not change during the concomitant LMWH induction period
eMIT February 2014.(152) ‡Assumed average warfarin dose

Table 105: Unit costs assumed in budget impact calculations (concomitant LMWH)

	Concomitant LMWH Length (days)	Concomitant LMWH Cost (per day)
Apixaban	N/A	N/A
Rivaroxaban	N/A	N/A
LMWH-dabigatran	5	£9.77*
LMWH-warfarin	7.64	£9.77*

*enoxaparin pre-filled syringe 120 mg; Electronic Drug Tariff, August 2014, Department of Health by the NHS Business Services Authority, NHS Prescription Services, http://www.ppa.org.uk/ppa/edt_intro.htm (170)

Table 106: Unit costs assumed in budget impact calculations (up to 6 months)

	Unit size	Unit cost	Dose
Apixaban	5 mg	£1.10*	5 mg bd
Rivaroxaban	20 mg	£2.10†	20 mg od
LMWH-dabigatran	150 mg	£1.10†	150 mg bd
LMWH-warfarin	6 mg	£0.009[#]	6 mg od‡

*BMS/Pfizer
†Electronic Drug Tariff, August 2014, Department of Health by the NHS Business Services Authority, NHS Prescription Services, http://www.ppa.org.uk/ppa/edt_intro.htm (170)
[#] eMIT February 2014.(152)
‡Assumed average warfarin dose

Table 107: Unit costs assumed in budget impact calculations (after 6 months)

	Unit size	Unit cost	Dose
Apixaban	2.5 mg	£1.10*	2.5 mg bd
Rivaroxaban	20 mg	£2.10[†]	20 mg od
LMWH-dabigatran	150 mg	£1.10[†]	150 mg bd
LMWH-warfarin	6 mg	£0.009[#]	6 mg od[‡]

*BMS/Pfizer
†Electronic Drug Tariff, August 2014, Department of Health by the NHS Business Services Authority, NHS Prescription Services, http://www.ppa.org.uk/ppa/edt_intro.htm (170)
[#] eMIT February 2014.(152)
‡Assumed average warfarin dose

Table 108: Treatment costs with and without apixaban

	2015	2016	2017	2018	2019
Without apixaban					
Apixaban	N/A	N/A	N/A	N/A	N/A
Rivaroxaban	£ 3,054,841	£ 4,445,635	£ 5,844,577	£ 7,183,094	£ 8,340,462
LMWH-dabigatran	£ 1,395,510	£ 2,084,369	£ 2,768,162	£ 3,428,980	£ 4,056,769
LMWH-warfarin	£ 3,345,418	£ 3,224,352	£ 3,112,838	£ 3,021,457	£ 2,966,737
Total	£ 7,795,769	£ 9,754,356	£ 11,725,576	£ 13,633,532	£ 15,363,967
With apixaban					
Apixaban	£ 1,267,859	£ 2,241,503	£ 3,432,428	£ 4,479,655	£ 5,578,026
Rivaroxaban	£ 2,886,707	£ 4,099,520	£ 5,245,583	£ 6,332,398	£ 7,219,925
LMWH-dabigatran	£ 1,318,383	£ 1,921,870	£ 2,483,661	£ 3,021,007	£ 3,510,980
LMWH-warfarin	£ 3,161,093	£ 2,958,846	£ 2,761,009	£ 2,623,014	£ 2,519,034
Total	£ 8,634,041	£ 11,221,739	£ 13,922,682	£ 16,456,075	£ 18,827,965
Total net cost with apixaban					

	£ 838,272	£ 1,467,383	£ 2,197,105	£ 2,822,543	£ 3,463,998

8.1.6 *Were there any estimates of resource savings? If so, what were they?*

Resource savings associated with INR monitoring costs and LMWH training and administration were identified and detailed in Section 8.1.4.

8.1.7 *What is the estimated annual budget impact for the NHS in England and Wales?*

Table 109 presents budget impact estimates for 2015 to 2019. Apixaban is estimated to be associated with a budget impact of £326,773 in the first year, rising to £1,680,244 in 2019.

Table 109: Budget impact

	2015	2016	2017	2018	2019	Total (cumulative)
Treatment	£ 635,344	£ 1,169,676	£ 1,797,392	£ 2,363,057	£ 2,941,733	£ 8,907,202
INR Monitoring	-£ 485,702	-£ 781,465	-£ 1,114,500	-£ 1,365,336	-£ 1,624,564	-£ 5,371,568
Training and administration (LMWH)	-£ 25,797	-£ 91,054	-£ 122,429	-£ 140,308	-£ 159,190	-£ 538,777
Annual Net	£ 326,773	£ 594,864	£ 960,177	£ 1,316,899	£ 1,680,244	£ 4,878,956

8.1.8 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

The budget impact model conservatively underestimates the cost savings with apixaban, as it does not account for the savings from events avoided through the reduced incidence of bleeding associated with apixaban.

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

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10 Appendices

The appendices have been supplied as a separate document.