Changes to the original text deriving from an update of the health economic model have been highlighted in blue in the table of contents and in blue boxes in the relevant sections.
At consultation, stakeholders are invited to comment on these updated sections only.

Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis

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Bayer, Leo Pharmaceuticals, and Bristol Myers Squib. She has also provided the patient perspective for the submissions for the technology appraisals for the NOACS and Diagnostic Guidance for Coagulometers. Other authors have no potential conflicts of interest to declare. This project was funded by NIHR HTA grant 11/92/17. All available data are included as an appendix to the report.

Keywords: atrial fibrillation, venous thromboembolic disease, deep vein thrombosis, pulmonary embolism, knee surgery, hip surgery, cancer, anticoagulation, novel oral anticoagulant, direct-acting oral anticoagulant, warfarin, vitamin K antagonist, coumarin, heparin, low molecular weight heparin, stroke, ischaemic stroke, haemorrhagic stroke, intracranial haemorrhage, myocardial infarction, mortality, bleeding, systematic review, meta-analysis, network meta-analysis, cost-effectiveness, adverse effects

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Abstract

Background: Warfarin is effective for stroke prevention in atrial fibrillation (AF), but anticoagulation is underused in clinical care. The risk of venous thromboembolic (VTE) disease during hospitalisation can be reduced by low molecular weight heparin (LMWH): warfarin is the most frequently prescribed anticoagulant for treatment and secondary prevention of VTE. Warfarin-related bleeding is a major reason for hospitalisation for adverse drug effects. Warfarin is cheap but therapeutic monitoring increases treatment costs. Novel oral anticoagulants (NOACs) have more rapid onset and offset of action than warfarin and more predictable dosing requirements.

Objectives: Determine the best oral anticoagulant/s for prevention of stroke in AF and for primary prevention, treatment and secondary prevention of VTE.

Design: Four systematic reviews, network meta-analyses and cost-effectiveness analyses of randomised controlled trials.

Setting: Hospital (VTE primary prevention and acute treatment) and primary care/anticoagulation clinics (AF and VTE secondary prevention).

Participants: Patients eligible for anticoagulation with warfarin (stroke prevention in AF, acute treatment or secondary prevention of VTE) or LMWH (primary prevention of VTE).

Interventions: NOACs, warfarin and LMWH together with other interventions (antiplatelet therapy, placebo) evaluated in the evidence network.

Main outcome measures: Efficacy: stroke, symptomatic VTE, symptomatic deep vein thrombosis and symptomatic pulmonary embolism. Safety: major bleeding, clinically relevant bleeding and intracranial haemorrhage. We also considered myocardial infarction and all-cause mortality and evaluated cost-effectiveness.

Data sources: Medline and Premedline, Embase and the Cochrane Library, reference lists of published network meta-analyses, trial registries.

Review methods: Two reviewers screened search results, extracted and checked data, and assessed risk of bias. For each outcome we conducted standard meta-analysis and network meta-analysis. We evaluated cost-effectivenes using discrete-time Markov models.

Results: Apixaban (5mg bd) was ranked as among the best interventions for stroke prevention in AF, and had the highest expected net benefit. Edoxaban (60mg od) was ranked second for major bleeding and all cause mortality. Neither the clinical nor cost

effectiveness analysis provided strong evidence that NOACs should replace post-operative LMWH in primary prevention of VTE. For acute treatment and secondary prevention of VTE we found little evidence that NOACs offer an efficacy advantage over warfarin, but risk of bleeding complications was lower for some NOACs than for warfarin. For willingness to pay threshold >£5000, apixaban (5mg bd) had the highest expected net benefit for acute treatment of VTE. Aspirin or no pharmacotherapy were likely to be the most cost-effective interventions for secondary prevention of VTE: our results suggest it is not cost effective to prescribe NOACs or warfarin for this indication.

Conclusions: NOACs have advantages over warfarin in patients with AF, but we found no strong evidence that they should replace warfarin or LMWH in primary prevention, treatment or secondary prevention of VTE.

Limitations relate mainly to shortfalls in the primary data: in particular there were no head-to-head comparisons between different NOAC drugs.

Future work: calculate Expected Value of Sample Information to clarify whether it would be justifiable to fund one or more head-to-head trials.

Study registration: PROSPERO CRD42013005324, CRD42013005331 and CRD42013005330.

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Word count 530

List of abbreviations/glossary

AE	adverse event
AF	atrial fibrillation
AIC	Akaike Information Criterion
bd	twice daily
BMI	body mass index
CEA	cost effectiveness analysis
CEACs	cost-effectiveness acceptability curves
CEAF	cost-effectiveness acceptability frontier
$CHADS_2$	a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF)
$CHADS_2VASC$	a modified clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF)
CI	confidence interval
CRB	clinically relevant bleeding
CRD	centre for reviews and dissemination
CTPH	chronic thromboembolic pulmonary hypertension
DVT	deep vein thrombosis
ECG	electrocardiogram
ECH	extracranial haemorrhage
EED	economic evaluation database
EVI	expected value of information
EVPI	expected value of perfect information
EVPPI	expected value of perfect partial information
EVSI	expected value of sample information
GI	gastrointestinal
GP	general practice
HAS-BLED	hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly: this estimates risk of major bleeding for patients on anticoagulation for atrial fibrillation
HR	hazard ratio
HRG	healthcare resource group
ICER	incremental cost-effectiveness ratio
ICH	intracranial haemorrhage
INB	incremental net benefit
INR	international normalized ratio
IS	ischaemic stroke
IU	International unit
KM	Kaplan-Meier
LMWH	low molecular weight heparin
MCMC	Markov Chain Monte Carlo
MI	myocardial infarction
n	sample size
NHS	national health service
NICE	national institute for health and care excellence
NIHR	national institute for health research
NMAs	network meta-analyses
NOAC	novel oral anticoagulant
NR	not reported
NVAF	non-valvular atrial fibrillation
od	once daily
OR	odds ratio
PE	pulmonary embolism
PGfAR	programme grants for applied research
post-op	post-operative
pre-op	pre-operative

PROSPERO	international prospective register of systematic reviews
PTS	post thrombotic syndrome
QALY	quality adjusted life year
RCT	randomised controlled trial
RIND	reversible ischaemic neurological deficit
SAVI	Sheffield Accelerated Value of Information
SD	standard deviation
SE	systemic embolism
THR	total hip replacement
TIA	transient ischaemic attack
TKR	total knee replacement
TTR	time in therapeutic range
VKA	vitamin K antagonist
VTE	venous thromboembolism

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Changes made for NICE AF Clinical Guidelines

To address the needs of the the NICE AF Clinical Guidelines, several changes were made ot the AF economic model. These are listed below, with references to edits made to the main report. All changes are restricted to the methods in Chapter 4 and results in Chapter 6. No changes were made to the VTE models.

Primary change was to model stroke risk across the states through CHA_2DS_2-VASc score. We used estimated stroke rates by CHA_2DS_2-VASc score from the Aspberg 2016 Swedish cohort study [1]. In the model, MI and stroke history increase the CHA_2DS_2-VASc score, as do increasing age and female gender. This is described in Section 6.2.2. Note that we assume no impact of bleed or ICH on future stroke risk as they are not included in CHADS2VASC2. The initial distribution of CHA_2DS_2-VASc score was defined through a mixture of the Asperb 2016 study and a meta-analysis of studies on CHA_2DS_2-VASc score in screen-detected AF. This is described in Section 6.3. We explore scenario analyses by age, gender, and initial CHA_2DS_2-VASc score, as described in Section 6.3.1. Results of these scenario analyses are presented in Section 6.8.

We updated the long-term annual costs of managing sequelae of major intracranial bleed (i.e. intracranial haemorrhage (ICH)) to follow the approach of the VTE guidelies, which are based on costs and proportions dependent and independent following ICH. This is described in Section 4.8.3.

We added no treatment as a decision option and assumed no costs to be associated with it.

We inflated all event and state costs (other than NOAC/warfarin costs and ICH costs which were separately updated). We updated from 2013-14 prices to 2019 prices so we used the latest month from the consumer price index for which we had data, which was August 2019. For starting year we used the value for 2014, rather than 2013. We used the DKC3 filed for medical services, as in the original DOACs model. This gave an inflation factor of 1.17 (=114.2/97.6). This inflation is noted whenever it was performed.

We updated annual cost of warfarin to £282.62 (141.31, 423.93). This corresponded to a 3-month cost of £70.66 (35.33, 105.98). This is from the cost impact analysis/costing template of the last guideline which quotes £241.54 per year for the anticoagulation clinic (no other reference provided) [2]. We assumed an upper and lower bound of 50% and 150% of this mean. We inflated from 2014 to August 2019 prices.

We updated NOAC costs to those relevant to 2019 from the British National Formulary.

CHADSVASC2 includes TIA and thromboembolism along with stroke. We've assumed that they have no impact on CHADSVASC in the model. Implemented sensitivity where TIA or SE move patients to the stroke state, as described in Section 6.4 with results in Section 6.9.

Included cost of reversal agent following extracranial and intracranial bleed (coded as bleed and ICH in the model, respectively) in a sensitivity analyses. We also explored the impact of Andexanet alfa as reversal agent for apixaban and rivaroxaban. The methods for these sensitivities are described in Section 6.5 and results in Section 6.10.

We checked in acute and management costs for ICH and bleed included reversal agents. NHS reference costs were used for acute costs of extracranial bleed and it as not possible to tell if these included reversal agents. Luengo-Fernandez (acute cost for ICH) did not specify if drug/reversal agents contributed to the costs [3].

To aid communication of the large number of sensitivity and scenario analyses, we have included in Table 66 a summary of conclusions under the various settings.

Scientific summary

Background

Warfarin is an effective oral anticoagulant for stroke prevention in atrial fibrillation (AF), but anticoagulation is underused in clinical care. The risk of venous thromboembolic (VTE) disease during hospitalisation can be reduced by low molecular weight heparin (LMWH): warfarin is the most frequently prescribed anticoagulant for treatment and secondary prevention of VTE. Warfarin-related bleeding is a major reason for hospitalisation for adverse drug effects. The cost of warfarin is low but therapeutic monitoring increases treatment costs. Novel oral anticoagulants (NOACs) have a more rapid onset and offset of action than warfarin and more predictable dosing requirements.

Objectives

To identify the most effective, safe and cost-effective anticoagulant for stroke prevention in AF, and for primary prevention, treatment and secondary prevention of VTE.

Methods

We conducted four systematic reviews, with network meta-analyses, of randomised controlled trials addressing (1) stroke prevention in AF, (2) primary prevention of VTE, (3) acute treatment of VTE and (4) secondary prevention of VTE. We extracted data on clinically relevant efficacy outcomes (stroke, symptomatic VTE, symptomatic deep vein thrombosis and symptomatic pulmonary embolism) and safety outcomes (major bleeding, clinically relevant bleeding and intracranial haemorrhage) as well as myocardial infarction and all-cause mortality. We searched Medline and Premedline, Embase and the Cochrane Library, reference lists of published network meta-analyses, and trial registries. Two reviewers screened search results, extracted and checked data, and assessed risk of bias. For each outcome we analysed each direct pair-wise comparison and performed network meta-analyses to compare all interventions simultaneously.

We constructed discrete-time Markov models to evaluate cost-effectiveness of the different interventions included in the four networks. These synthesized evidence on

a number of parameters (e.g. incidence of VTE and ischaemic stroke, relative treatment efficacy, adverse events, costs) to estimate the relative cost-effectiveness of treatment options. Model inputs were based on a variety of evidence sources including routine data on drug costs and observational studies of long term costs of and quality of life AF and VTE. Model inputs on relative treatment efficacy and safety of anticoagulants were derived from the results of the network meta-analyses.

Results

For stroke prevention in AF, apixaban (5mg bd) was ranked as being among the best interventions for a wide range of the outcomes evaluated including stroke or systemic embolism, MI, major bleeding, and all-cause mortality. Edoxaban (60mg od) was ranked second for major bleeding and all cause mortality. Except for all-cause mortality, outcomes for rivaroxaban (20mg od) were ranked less highly than several other NOACs. The non-NOAC interventions (warfarin (INR 2-3) and antiplatelet therapy (aspirin/clopidogrel≥150mg od)) were ranked worst for stroke or systemic embolism and were not among the best three interventions for any of the outcomes.

At a willingness to pay threshold of £20,000 per QALY, all NOACs had positive expected incremental net benefit compared to warfarin (INR 2-3), suggesting that their use in AF may be a cost effective use of NHS resources. Apixaban (5mg bd) had the highest expected incremental net benefit (£7533), followed by rivaroxaban (20mg od) (£6365), edoxaban (£5279) and dabigatran (£5279). Apixaban (5mg bd) was the only NOAC for which the 95% confidence interval around incremental net benefit was positive, suggesting that it is cost-effective compared with warfarin.

For primary prevention of VTE, we found little evidence that risk of symptomatic VTE, symptomatic deep vein thrombosis (DVT) or symptomatic PE were lower for NOACs than for LMWH. We also found little evidence that risk of major bleeding or clinically relevant bleeding is lower for NOACs than for LMWH. Warfarin was ranked with high probability as the best intervention for major bleeding events and LMWH (post-op, standard dose) was ranked with high probability as best or second-best intervention for clinically relevant bleeding. Neither the clinical nor cost effectiveness analysis provided strong evidence that NOACs should replace post-operative LMWH in primary prevention of VTE in patients undergoing hip or knee surgery.

For acute treatment of VTE, we found little evidence that NOACs reduced risk of symptomatic VTE, symptomatic DVT or symptomatic PE compared with warfarin, nor that the risk of any of these outcomes differed between licensed doses of NOACs. However there was evidence that risk of major bleeding and clinically relevant bleeding was lower with apixaban (5 mg bd) and rivaroxaban (15mg bd then 20mg od) than with warfarin (INR 2-3). There was a high probability that warfarin (INR 2-3) was ranked worst for major bleeding and clinically relevant bleeding. There was a high probability that apixaban 5mg bd was ranked best for major bleeding and clinically relevant bleeding, and this intervention also had a high probability of being ranked best or second best for symptomatic DVT, symptomatic VTE and all-cause mortality. For a willingness to pay threshold of >£5000, apixaban 5mg bd was the most cost effective alternative to warfarin.

For secondary prevention of VTE, risk of symptomatic VTE and risk of symptomatic DVT were lower for all NOACS (at the doses included in the network), compared with placebo and with aspirin. However there was no clear evidence that risk of these outcomes differed between the NOAC interventions and warfarin. Risk of major bleeding and clinically relevant bleeding was higher with warfarin and some NOAC interventions compared with placebo, but there was evidence that risk of these outcomes is lower with apixaban (2.5mg or 5mg bd) and dabigatran (150mg bd) compared with warfarin. Aspirin had the highest expected net benefit for secondary prevention of VTE at a willingness to pay per QALY threshold of £20,000 and £30,000. By contrast, All NOAC interventions had negative expected incremental net benefits at the £20,000 and £30,000 thresholds, indicating that they are not cost-effective compared with no pharmacotherapy.

Conclusions

NOACs have advantages over warfarin in patients with AF. Of the available NOACs, apixaban 5mg bd offers the best balance between efficacy and safety and has the highest probability of being most cost-effective. NOACs offer no efficacy advantage over warfarin in the acute treatment of VTE, but have a lower rate of bleeding complications albeit at a higher cost. For a willingness to pay threshold of >£5000, apixaban 5mg bd emerges as the most cost effective alternative to warfarin. Neither

the clinical nor cost effectiveness analysis provided strong evidence that NOACs should replace post-operative LMWH in primary prevention of VTE in patients undergoing hip or knee surgery. If secondary prevention after 3-6 months of anticoagulation for a first episode of VTE is to be considered (this is not currently established practice), NOACs provide no advantage over aspirin 100mg od.

The research needs identified by this review are: (1) for calculations of the Expected Value of Sample Information, in order to clarify whether it would be justifiable to fund one more trials making direct comparisons between the most promising NOACs and NOAC doses, in situations typical of NHS clinical practice; (2) for information on long-term rates of the main efficacy and safety outcomes among patients receiving anticoagulants for AF e.g. from registries or health record data; (3) for information on the role (if any) of therapeutic monitoring to enhance the safety and efficacy of NOACs; and (4) for information on long-term adherence rates in patients receiving NOACs for AF.

Study registration

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Funding details

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Plain English summary

Blood clots, which can occur in both arteries and veins, sometimes break loose and move to other organs where they cause serious health problems. Venous thromboembolism includes clots in deep veins of legs or pelvis and their displacement to the artery from the heart to the lungs. Atrial fibrillation is a form of irregular heartbeat that is associated with an increased risk of stroke. The NHS tries to reduce these problems in high risk patients through anticoagulant drugs, which lower risk of blood clots but increase risk of bleeding. New oral anticoagulant drugs (NOACs) offer potential advantages compared to warfarin and low molecular weight heparin, the current standard treatments. They cost more, but this might be offset by reduced need for anticoagulation services, better effectiveness, or improved safety. We compared the clinical- and cost-effectiveness of these treatments in people with atrial fibrilation, and people with or at risk of venous thromboembolism. We searched for relevant randomised trials, and compared all the treatments that had been evaluated. One of the NOACs, apixaban, was among the best treatments for stroke prevention in atrial fibrilation, and was the most cost-effective. We found little evidence, in terms of clinical or cost effectiveness, that NOACs should replace low molecular weight heparin for prevention of venous thromboembolism after hip or knee surgery. For treatment of venous thromboembolism, and for preventing repeat venous thromboembolisms, risk of complications due to bleeding was lower for some NOACs than for warfarin. Apixaban was the most cost-effective treatment for venous thromboembolism, but it is not cost effective to prescribe NOACs or warfarin for preventing recurrence of venous thromboembolism.

Word count 267

1. Background

1.1 Description of health problem

1.1.1 Atrial fibrillation, stroke and myocardial infarction

Atrial fibrillation (AF) is the most common cardiac arrhythmia.[4] The prevalence of AF roughly doubles with each decade of age, rising to almost 9% at age 80-90 years[5]. AF substantially increases (by up to 5 times) the risk of thromboembolic stroke (annual incidence 114 per 100,000) due to blood pooling in the left atrium and systemic embolisation to the brain. More than 20% of the 130,000 annual strokes in England and Wales are attributed to AF. Approximately 1/3 of stroke patients die in the first ten days, 1/3 recover in 1 month and 1/3 have disabilities needing rehabilitation making stroke the leading cause of adult disability. Patients with thromboembolic stroke from AF have higher mortality, morbidity and hospital stay than patients with other stroke subtypes. Warfarin is an effective oral anticoagulant for the prevention of stroke in patients with AF.[6] Although the incidence and mortality of stroke continue to fall in the UK, the underutilisation of anticoagulation in patients with AF at high-risk of stroke is a major gap in clinical care.[7] In patients with atrial fibrillation, antiplatelet and anticoagulant therapies are generally considered from the perspective of mitigation of stroke risk. However, the presence of atrial fibrillation is also associated with an approximately two-fold higher risk of future acute myocardial infarction[8], whose annual incidence in England (130 and 55.9 per 100,000 for men and women respectively)[9] is higher than that for stroke.

1.1.2 Venous thromboembolic disease

The annual incidence of venous thromboembolic (VTE) disease from a study conducted in Europe is 183 per 100,000.[10] It encompasses clot formation in deep veins of the legs or pelvis (deep vein thrombosis, or DVT); annual incidence 124 per 100,000), and their displacement to pulmonary arteries (pulmonary embolism, or PE); annual incidence 60 per 100,000). Important risk factors for VTE include major surgery, particularly lower limb orthopaedic surgery and surgery for cancer, as well as hospitalisation in acutely ill general medical patients (approximate incidence 15%). VTE costs the NHS £640 million and is responsible for approximately 30,000 deaths each year in hospitals in England. DVT is an important cause of long-term morbidity, being a risk factor for chronic leg ulceration. PE may also lead to long-term morbidity

due to pulmonary hypertension. There is an approximately 30% risk of recurrence of VTE within eight years.

The risk of VTE during hospitalisation for surgical or medical treatment can be reduced by low molecular weight heparin (LMWH), fonaparinux or unfractionated heparin.[11] Warfarin is the most frequently prescribed anticoagulant for the initial treatment and for the long-term secondary prevention of VTE in those deemed to be at high risk of recurrence.

1.2 Current usage and cost of warfarin in the National Health Service

A 2007 *Health Technology Assessment* report stated that approximately 950,000 people (2% of the GP population) in the UK are prescribed warfarin; increasing by about 10% per year.[12] Warfarin-related bleeding is one of the top five reasons for hospitalisation for adverse drug effects in England[13] because of the narrow therapeutic index and numerous drug/dietary interactions. Although the approximate acquisition cost of warfarin is only £10 per patient per year, the requirement for therapeutic monitoring to ensure optimal efficacy and to reduce the risk of bleeding, through hospital-, primary care-, or pharmacist-based anticoagulation clinics, or by home-monitoring with anticoagulant clinic support, increases the cost of warfarin treatment. The estimated annual cost of managing patients on warfarin in the NHS in England and Wales is approximately £90 million.[14] A 2006 NICE report estimated that 46% of patients who should be on warfarin are not receiving it, and that many receiving anticoagulation are not in optimal therapeutic range[14], perhaps because of concern about the risk and inconvenience of warfarin treatment.

1.3 Description of interventions under assessment: new oral anticoagulants

The class of novel (or non-vitamin K antgonist) oral anticoagulants (NOACs), sometimes called direct acting oral antocagulants (DOACs), includes dabigatran (a direct inhibitor of clotting factor II) and rivaroxaban, apixaban, edoxaban, otamixaban and betrixaban (which are factor X inhibitors). These agents have a more rapid onset and offset of action than warfarin, and are considered to have more predictable dosing

requirements than warfarin, possibly reducing the need for therapeutic drug monitoring, increasing convenience and reducing overall cost.[15] However, the safety and efficacy of at least one of the NOACs (dabigatran) may vary according to achieved plasma concentration, which may differ between individuals receiving the same dose[16], suggesting a potential benefit from therapeutic drug monitoring. If this proved to be the case, the corollary would be an increase in the overall cost of treatment.

These drugs have been evaluated in clinical trials as an alternative to warfarin for the prevention of stroke in patients with AF (for which warfarin is given lifelong); as an alternative to LMWH for prevention of VTE in high-risk patients undergoing major orthopaedic surgery as well as those being hospitalised with acute medical conditions (for which LMWH is given to cover the high-risk period); as an alternative to a period of LMWH and then warfarin for acute treatment of a first VTE (usually for 6 months); as well as for secondary prevention after a first episode of VTE, for which there is currently no widely used treatment.

The estimated annual acquisition cost per patient of new anticoagulants is substantially higher than that of warfarin and will remain so until patent expiry (for example, 2020 for rivaroxaban). However, the higher acquisition cost could be offset by the reduced need for therapeutic monitoring through anticoagulation services, by increased effectiveness, or by improved safety. Potential limitations of NOACs include class- and drug-specific cautions/contraindications, potential for sub-therapeutic dosing, reduced adherence due to lack of regular monitoring, absence of, or limited experience with antidotes, as well as the added cost of maintaining stocks of numerous different anticoagulants and the potential for prescribing errors due to unfamiliarity.

1.4 Rationale for undertaking this evidence review

Limitations of the previous evidence base (and shortfalls in previous attempts at evidence synthesis) make rational selection from the now wide range of available oral anticoagulants difficult for NHS commissioners, doctors and patients. Much of the existing NICE guidance in this area is limited to technology appraisals of the individual agents.

Clinical trials in this area have the following limitations:

- Few, if any, trials have made direct comparisons of NOAC drugs with one another. This limitation can be addressed through the use of network-meta-analysis to estimate the comparative efficacy and safety of agents, which have been tested against a common comparator, e.g. warfarin.
- Different rates of sub-therapeutic anticoagulation with warfarin within trials (as measured by the time spent in the therapeutic range) may have artificially inflated the apparent efficacy of newer agents. This limitation can be addressed to some extent by investigating the relation of average time in therapeutic range with efficacy, within the network meta-analysis framework.

Prior synthesis research in this area has the following limitations:

- Some meta-analyses preceded recently published, potentially influential trials.
- Failure to fully incorporate evidence on the adverse effects of oral anticoagulants by including data from all trials, regardless of indication, to maximise power and provide the most robust evidence on the balance between benefit and harm.
- The lack of cost-effectiveness analyses relevant to England and Wales.

Thus, there is a need for an up-to-date comprehensive evidence synthesis of all competing treatments to inform the rational choice of a minimum set of oral anticoagulants needed by NHS hospitals for the main therapeutic indications to avoiding unnecessary over-stocking and to reduce the risk of prescription error due to unfamiliarity.

2. Research questions

2.1 Aim

We set out to determine what is/are the best oral anticoagulant/s for prevention of stroke in atrial fibrillation; and for primary prevention, treatment and secondary prevention of venous thromboembolic disease.

2.2 Objectives of evidence review

Our specific objectives were:

- To identify the most effective, safe and cost-effective anticoagulant for stroke prevention in atrial fibrillation, and consider whether the evidence is consistent across important patient subgroups (for example presence of comorbidities, age).
- To identify the most effective, safe and cost-effective oral anticoagulant for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and consider whether the evidence is consistent for both prevention and treatment, and across important patient subgroups (for example cancer surgery, hip and knee replacement, and hospital admission for acute medical illness).
- To identify optimal anticoagulation strategies for use by Trust Drugs and Therapeutics Committees, based on the best drug(s) for each of the main therapeutic indications.
- To estimate the value of conducting further research on the cost-effectiveness of these drugs, for example by conducting a head-to-head trial of two or more new anticoagulants.

3. Review methods (1): Assessment of clinical effectiveness and safety

3.1 Introduction

We conducted four systematic reviews, with network meta-analyses, of randomised controlled trials addressing questions relevant to the study objectives:

1. Effectiveness and safety of oral anticoagulants for prevention of stroke in non-valvular atrial fibrillation.
2. Effectiveness and safety of oral anticoagulants for primary prevention of venous thromboembolic disease.
3. Effectiveness and safety of oral anticoagulants for acute treatment of venous thromboembolic disease.
4. Effectiveness and safety of oral anticoagulants for secondary prevention of venous thromboembolic disease.

We undertook these reviews in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews[17], and the *Cochrane Handbook for Systematic Reviews of Interventions*[18] (as updated online during 2011: see www.cochrane-handbook.org). We prospectively registered the reviews in the PROSPERO database (http://www.crd.york.ac.uk/prospero), with registration numbers CRD42013005324, CRD42013005331 and CRD42013005330.

3.2 Eligibility criteria

3.2.1 Study designs

In all reviews we included phase II or phase III randomised controlled trials using either a superiority or non-inferiority design.

3.2.2 Participants

In all reviews we included adults (≥18 years) eligible for oral anticoagulation or (antithrombotic) treatment. Trials in participants only eligible for parenteral (injected) anticoagulation were excluded. Unless otherwise specified, anticoagulation services may have been delivered in hospital-, primary care-, pharmacy-based clinics or

through home monitoring and telephone support. The review was not limited to NHS anticoagulation services.

Specific criteria for inclusion in the four reviews were as follows.

1. *Stroke prevention in AF*: Adults with non-valvular AF.
2. *Primary prevention of VTE*: Adults admitted to hospital who were considered to be at high risk of VTE, including those with a medical condition (e.g. cancer, major trauma, stroke), or undergoing a surgical procedure (e.g. total knee or hip arthroplasty, hip fracture surgery) that carries a high risk of VTE.
3. *Acute treatment of VTE*: Adults who have received a new or recurrent objectively-confirmed diagnosis of acute symptomatic VTE.
4. *Secondary prevention of VTE*: Adults who have completed a minimum of three months of anticoagulant treatment for objectively-confirmed first VTE without recurrence (secondary prevention).

3.2.3 Interventions and comparators

Five NOACs were the focus of all reviews: dabigatran, apixaban, edoxaban, betrixaban, rivaroxaban. NOACs not considered were eribaxaban (the current stage of development was unclear); ximelagatran (withdrawn due to liver toxicity); darexaban (YM150) and AZD0837 (both discontinued), LY517717 and letaxaban (TAK442) (no available information on any further clinical development for both); and otamixaban (parenteral administration).

As the reviews were conducted to inform network meta-analyses, we determined the comparator interventions to ensure they would provide information on the relative effectiveness of the interventions of interest. We constructed preliminary networks of available treatment comparisons from trials included in previously published network meta-analyses (irrespective of the outcome data available from them). Comparators were chosen based on the possibility of informing indirect evidence on the relative effectiveness of oral anticoagulants; and on the 'distance' of these comparators from our interventions of interest in the network, which relates to the likely increase in precision in the estimates of relative effectiveness of the oral anticoagulants.

Specific comparators in the four reviews were as follows

1. *Stroke prevention in AF*: therapeutic doses of warfarin or other vitamin K antagonist (with optimal INR range 2-4); aspirin; clopidogrel.
2. *Primary prevention of VTE*: standard dose LMWH; therapeutic doses of warfarin or other vitamin K antagonist (with optimal INR range 2-4); placebo.
3. *Acute treatment of VTE*: therapeutic doses of warfarin or other vitamin K antagonist (with optimal INR range 2-4).
4. *Secondary prevention of VTE*: therapeutic doses of warfarin or other vitamin K antagonist (with optimal INR range 2-4); placebo; no treatment

Studies evaluating fixed dose administration of warfarin were excluded. Studies evaluating warfarin with suboptimal target INR compared with UK guidelines were excluded from the main analyses but combined with studies evaluating warfarin with standard target INR in sensitivity analyses. Unfractionated heparin and fondaparinux were excluded from the primary prevention of VTE review as they would be distant from the NOACs in the network and hence contribute very little information. Non-standard doses of LMWH that were excluded from this review included enoxaparin at 20mg twice daily, ardeparin at 25 anti-X U/kg twice daily or 35 anti-X U/kg twice daily and nadroparin 3800IU anti-Xa once daily.

3.3 Outcomes of interest

3.3.1 Prevention of stroke in atrial fibriliation

We sought data on the following outcomes:

- stroke or systemic embolism*
- all stroke
- ischaemic stroke (major ischemic stroke or minor ischaemic stroke)*
- fatal stroke
- non-fatal stroke
- haemorrhagic stroke (major haemorrhagic stroke or minor haemorrhagic stroke)
- any bleeding
- minor bleeding
- major bleeding*

- clinically relevant non-major bleeding
- clinically relevant bleeding* (defined as clinically relevant non-major bleeding or major bleeding)
- intracranial bleeding*
- extra-cranial major bleeding
- extra-cranial minor bleeding
- fatal bleeding
- bleeding from surgical site
- thrombocytopenia
- myocardial infarction*
- transient ischaemic attack
- arterial event
- quality of life outcomes
- hospital admission
- death (cardiovascular)
- all-cause mortality*

The outcomes addressed in network meta-analyses are marked with an asterisk in the list above. These were chosen based on three considerations: (1) their clinical importance; (2) the consistency of reporting across studies included in the network and (3) the amount of data available for inclusion in network meta-analyses.

3.3.2 Venous thromboembolism

For all VTE reviews we sought data on the following outcomes:

Efficacy:

- symptomatic VTE*
- non-symptomatic VTE
- major VTE (defined as symptomatic or asymptomatic proximal DVT, non-fatal PE, and VTE -related death)
- fatal VTE
- symptomatic DVT*
- non-symptomatic DVT
- distal DVT

- symptomatic distal DVT
- proximal DVT
- symptomatic proximal DVT
- PE
- symptomatic PE*
- non-symptomatic PE
- fatal PE
- non-fatal PE
- symptomatic non-fatal PE

Safety:

- any bleeding
- minor bleeding
- major bleeding*
- clinically relevant non-major bleeding
- clinically relevant bleeding* (defined as clinically relevant non-major bleeding or major bleeding)
- intracranial bleeding
- extra-cranial major bleeding
- extra-cranial minor bleeding
- fatal bleeding
- bleeding from surgical site
- thrombocytopenia

Other:

- myocardial infarction*
- transient ischaemic attack
- arterial event
- quality of life outcomes
- hospital admission
- cardiovascular mortality
- all-cause mortality*

The outcomes addressed in network meta-analyses are marked with an asterisk in the list above. These were chosen based three considerations: (1) their clinical importance; (2) the consistency of reporting across studies included in the network and (3) the amount of data available for inclusion in network meta-analyses.

3.4 Identification of evidence

3.4.1 Search strategy

Scoping searches conducted during protocol development identified some previously published network meta-analyses of oral anticoagulants. We rescreened the studies included in these network meta-analyses against our eligibility criteria and developed searches to identify any additional studies published beyond the search dates of the most recent network meta-analyses in each population.[11,19-21]

We used two separate search strategies, one for the review of stroke prevention in AF and one for the three reviews in VTE. In each search strategy we combined terms for either AF or VTE with terms for the interventions and comparators of interest and added a filter to focus the search on randomised controlled trials. We searched Medline and Premedline, Embase and the Cochrane Library. The stroke prevention in AF review search was run on the 12th March 2014, updated on the 15th September 2014 and covered the period 2010 to September 2014. The search for the three reviews in VTE was run on the 19th March 2014, updated on the 15th September 2014 and covered the period 2008 to September 2014. We applied no restrictions on language. The principal search strategy is included in Appendix 1. We removed duplicate records identified by title, authors, journal citation and date published.

We sought information on studies in progress, unpublished research or research reported in the grey literature from www.clinicaltrials.gov (to September 2012). We screened reference lists of retrieved studies and relevant review articles. We also searched NHS EED and NICE Technology Appraisals.

3.4.2 Assessing relevance and inclusion

Two reviewers independently screened the results of the searches by title and abstract. We resolved disagreements through consensus or referral to a third reviewer

where necessary. We obtained full texts of all potentially relevant reports and two reviewers assessed these independently against the eligibility criteria, with disagreements resolved by a third reviewer. We collated multiple reports of the same study mapped them to unique studies.

3.5 Data extraction

We developed data extraction forms and piloted them on a small selection of studies. Data were extracted from the trial reports by one reviewer and checked by a second. Disagreements were resolved through consensus or by referral to a third reviewer where necessary. We extracted data on the following: study details (identifier, study design, location, year, length of follow up, industry sponsorship); participant details (number of participants, age, gender); intervention details (drug name, dose, timing); comparator details; details relevant to risk of bias assessment (including adherence to and withdrawal from randomised allocation); and effect modifiers. Multiple reports from a study informed a single data extraction form. We extracted and managed data using Microsoft Access software.

We extracted dichotomous data based on the full randomised samples as number of events in intervention and control groups and numbers of participants, and we sought details of follow-up time (e.g. participant-years in each treatment group). We also extracted estimates of hazard ratios and their confidence intervals where available.

3.6 Assessment of risk of bias in included trials

We assessed studies using the Cochrane risk of bias tool.[22] This assigns a judgement of high, low or unclear risk of bias for each of the following domains: selection bias (randomisation sequence and allocation concealment), performance bias (blinding of participants and carers), detection bias (blinding of outcome assessment), attrition bias (due to drop outs and exclusions), and reporting bias (selective outcome reporting). Assessments were carried out by one reviewer and checked by a second. We resolved disagreements through consensus or by referral to a third reviewer where necessary.

3.7 Selection of data for analysis

3.7.1 Choice of interventions

To perform network meta-analyses we had to allocate each intervention group in each trial to a category, with each intervention category forming a 'node' in the network. We kept different doses or frequencies of administration (i.e. once daily (od) or twice daily (bd)) of oral anticoagulants in separate nodes. We assigned different vitamin K antagonists to one node (named 'Warfarin'), but separated intended INR range 2-3 from intended INR range 3-4 and from other ranges. For LMWH interventions in the review of primary prevention of VTE, we separated pre-operative LMWH from post-operative LMWH. The intervention categories (or network nodes) are labelled throughout the report using drug, frequency and dose or INR range, as appropriate.

3.7.2 Choice of time points

Where outcome data were presented for multiple time points we took the longest period of follow up, except for bleeding events in the review of primary prevention of VTE, which we assessed at the end of the treatment period.

3.7.3 Choice of outcomes

Where outcome data were not presented directly, we computed or substituted them, using data for other outcomes, making assumptions we considered to be reasonable. Where we could not extract data for the outcome 'stroke or systemic embolism' in the review of stroke prevention in AF, we used all stroke. When clinically relevant bleeding was not reported but both major bleeding and clinically relevant non-major bleeding events were, we used the total number of events across these two categories. If symptomatic PE was not reported in any of the three VTE reviews, we used symptomatic non-fatal PE if available, or the sum of fatal PE and non-fatal PE. Additionally, in the review of primary prevention of VTE, where symptomatic VTE was not reported we added across symptomatic DVT and symptomatic PE, if available.

3.8 Quantitative synthesis (including network meta-analysis)

For each analysed outcome in each review (see section 3.7.3), we undertook both standard meta-analyses of "direct evidence" (evidence based on head to head

comparisons between interventions made within studies) and a network meta-analysis. Results of the individual studies are available in forest plots, arranged within each possible pair-wise analysis. The comparisons displayed on the forest plots were computed from the raw data reported in the studies, and we calculated effect estimates using standard frequentist techniques.

Network meta-analysis is a method of synthesising information from a collection of studies by combining evidence from all intervention comparisons that have been made among the studies. The results it produces for each pair-wise comparison combine all the "direct evidence" (evidence based on head-to-head comparisons between interventions made within individual studies), with all the "indirect evidence" (comparisons between interventions inferred from the network via common comparator interventions)[23,24]. For example, indirect evidence comparing the effect of interventions A and B can be inferred from the direct evidence provided by a trial comparing A with C and a trial comparing B with C. Network meta-analysis thus enables estimation of relative intervention effect estimates for every pair of interventions, regardless of whether or not they have been compared directly in a randomised controlled trial. It also enables the ranking of treatments according to the probability that each is the best, or worst, for a given outcome.

We plotted the networks to illustrate the data structure for each review and outcome. In these plots, the size of the node for each intervention is proportional to the number of patients randomised to that intervention. When direct evidence comparing two interventions was available, these two interventions are connected by an edge (line) whose thickness is proportional to the number of patients that contributed to the comparison. The intervention labels are formatted as follows:

- Licensed doses of NOACs are written in bold typeface; these are interventions of primary interest.
- Interventions that were excluded from the primary analysis labels are presented in square brackets. Such exclusions are because (i) they were not considered to be of interest to inform health decisions in the UK (e.g., warfarin interventions using subtherapeutic INR ranges), or (ii) the total number of events was zero so they are uninformative, or (iii) they do not connect with the other trials in the network.

- Excluded interventions that were included in sensitivity analyses are marked with an asterisk.

We had planned to take a random-effects approach to the meta-analyses, assuming a common heterogeneity variance across all comparisons.[23] In most networks there was insufficient replication of intervention comparisons to allow estimation of the heterogeneity variance. All of our analyses are therefore based on fixed-effect models.

The primary network meta-analyses treat the data as binomial, modelling the number of events out of the total number of participants using a logistic model. Where there were no events in either arm of a trial, it was omitted from the analysis. Where there were events in at least one arm of a trial, but no events in at least one other arm, we added 0.5 events to all intervention arms in the trial. In supplementary analyses for some outcomes we modelled hazard ratios rather than odds ratios. For this we used a complementary log-log link to account for differential follow-up times (thereby assuming a constant hazard of the outcome over time), or modelled possibly-repeated events as rate data, or included hazard ratios extracted directly from trial reports. Some of these analyses were used in the economic models (see section 4).

All meta-analyses were performed within a Bayesian framework, using freely-available WinBUGS software (version 1.4.3) and code.[25] We assessed convergence of the Markov chains using the potential scale reduction factor as well as visual examination of history and autocorrelation plots for each estimated parameter. We assessed goodness of fit by calculating the posterior mean residual deviance. This is defined as the difference between the deviance for the fitted model and the saturated model, where the deviance measures the fit of the model using the likelihood function. Comparisons of models were made using the deviance information criterion, which is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters.[26] The deviance information criterion penalises the posterior mean residual deviance (a measure of model fit) by the effective number of parameters in the model (as measure of complexity) and can therefore be viewed as a trade-off between the fit and complexity of the model.

3.8.1 Investigation of heterogeneity

We had planned to use subgroup and meta-regression[27] analyses to examine the extent to which patient-level and study-level characteristics explain between-study heterogeneity. We pre-specified important characteristics to be age, gender, ethnicity/race, body mass index or weight, renal status or creatinine clearance, blood pressure, diabetes mellitus, hypertension, previous thrombotic event, liver disease, chronic heart failure, cancer, pregnancy, intervention dose, average time in therapeutic range in the warfarin group and summary assessment of risk of bias for each outcome. Additional factors for AF trials were $CHADS_2$, $CHADS_2VASC$, HAS-BLED, history of previous stroke or transient ischaemic attack and previous myocardial infarction. Additional factors for primary prevention of VTE were general versus orthopaedic surgery, elective versus non-elective/emergency surgery, and medical versus surgical trials An additional factor for acute treatment or secondary prevention of VTE was the nature of the index event (whether PE or deep venous thrombosis). Where available, inferences about subgroup effects would be based on within-trial subgroup analyses (for example, comparing relative intervention effects in older and younger participants). Investigation of between-study variation using these characteristics could not be studied in most cases, due to the lack of multiple trials of the same pair-wise comparison, although we conducted some sensitivity analyses for the review of stroke prevention in AF patients. Specifically, we performed several meta-regressions using the average time in therapeutic range in the warfarin group as a covariate.

3.8.2 Investigation of inconsistency

The validity of a network meta-analysis depends on the assumption that there is no effect modification of the pairwise intervention effects or, that the prevalence of effect modifiers is similar in the different studies. This key assumption has been referred to variously as exchangeability,[25] transitivity,[28] similarity[29] and consistency[30,31]. For a clinical and epidemiological judgement of the plausibility of this assumption we examined whether the trials were similar in ways that might modify treatment effect, based on the prespecified list of potential effect modifiers in section 3.8.1.

"Evidence inconsistency" can be considered an additional layer of heterogeneity that occurs in networks of evidence when there is a discrepancy between the direct and indirect estimates of relative intervention effects. Therefore inconsistency is a property of 'closed loops' of evidence, in which both direct and indirect evidence are available for each comparison. We visually inspected the network diagrams to identify potential for inconsistency (closed loops), and used model fit and selection statistics to informally assess whether it was evident. Where there was potential for inconsistency, we compared the residual deviance from the consistency model (providing network meta-analysis evidence) with the residual deviance from an 'inconsistency model', without consistency constraints (in which only direct evidence is analysed for each comparison). Where both direct and indirect evidence was available and the direct evidence had a standard error that differed (beyond the second decimal place) from the network meta-analysis estimate, we used results from these two analyses to back-compute the indirect estimates, on the basis that the network meta-analysis estimates (from the consistency model) would be equivalent to a weighted average of the direct estimate (from the inconsistency model) and the indirect estimate. In the results tables we present all three of these estimates. The extent of the disagreement between the direct and indirect estimates can be used as a local measure of inconsistency for that comparison. Note that for the vast majority of comparisons there was either only direct evidence or only indirect evidence, so that the network meta-analysis estimates correspond to one of these.

4. Review methods (2): Cost effectiveness analysis

4.1 Introduction

This chapter describes the structure of the decision analysis models that we developed to assess the cost-effectiveness of NOACs in the primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of ischaemic stroke in atrial fibrillation. We also provide a brief overview of previous cost-effectiveness models which we identified and used to inform the development of our models.

Our models synthesize evidence on a number of parameters (e.g. incidence of VTE or ischaemic stroke, relative treatment efficacy, adverse events, costs etc.) in order to estimate the relative cost-effectiveness of treatment options. The 'model inputs' are based on a variety of evidence sources. These include routine data on drug costs and observational studies of the long term costs and quality of life (i.e. utilities) in AF and VTE. Many of these model inputs are shared between the AF and VTE cost-effectiveness models and we summarise them in this chapter. However, other model inputs, for example on relative treatment efficacy and safety of anticoagulants, are derived from the results of meta-analyses of RCTs identified in our systematic review. We summarise these efficacy and safety model inputs in chapters 6 and 11 which present the results of the cost-effectiveness models for AF and VTE, respectively.

The VTE secondary prevention, acute treatment and primary prevention models were constructed in MS Excel and the AF model was constructed in R (v 3.02)[32]. All (network) meta-analyses were conducted in WinBUGS[33] (v 1.4).

4.2 Decision questions

The questions we addressed were:

1. What is the most cost-effective first line anticoagulant in the prevention of ischaemic stroke for patients with AF?
2. What is the most cost-effective first line strategy for the secondary prevention of VTE after an initial PE or DVT?
3. What is the most cost-effective first line anticoagulant for the acute treatment of symptomatic VTE?

4. What is the most cost-effective first line anticoagulant for primary prevention of VTE following two types of elective surgery (a. total hip replacement or b. total knee replacement)?

In each case, we evaluated cost-effectiveness from a NHS perspective. We modelled costs and outcomes over the expected lifetime of patients. In the next section, we give a brief overview of previous cost-effectiveness models addressing these decision questions. We then describe the patients, interventions, outcomes, model structure and shared model inputs for each of the four decision questions.

4.3 Previous economic models

We performed an informal search of the literature, including NICE technology appraisals, for previous model-based cost-effectiveness analyses addressing one of the four decision questions. Our literature search was not intended to be exhaustive, but we aimed to identify a representative sample of existing modelling methods and structures to inform our models. We developed the structure of our models from a critical appraisal of these previous models together with discussions with clinical experts and patient group representatives on the project team.

For prevention of ischaemic stroke in AF, we identified eighteen previous models, summarised in Table 1 and discussed in detail in Appendix 6. A recently published systematic review[34] identified 30 models on prevention of stroke in AF, however the main model structures identified in that review were covered by the 12 studies we found. For the prevention and treatment of VTE, we identified sixteen previous models, two acute treatment models (Table 2) and fourteen primary prevention models post orthopaedic surgery (Table 3).

Table 1 Summary of sample of 18 previous economic models of anticoagulation for AF

Author, year	Setting	Model type	Interventions	Events	Health states	Time horizon
Gage, 1995 [35]	USA	Markov	Warfarin, Aspirin	TIA, stroke, haemorrrhage, death	Well, RIND, Mild stroke, Moderate-severe stroke, Second stroke, Mild ICH, Moderate-severe ICH, RIND and ICH, Stroke and ICH, Dead	10 years
Lightowlers, 1998[36]	UK	Decision tree	Warfarin (several monitoring strategies), no treatment	Bleed, stroke	NA	10 years
Bayer, 2011 [37]	UK	Markov	Rivaroxaban, Dabigatran, Warfarin, Aspirin, no treatment	Minor stroke, major stroke, minor bleed, major bleed, MI, ICH, SE, death	On and off treatment for AF stable and post event states for minor stroke, major stroke, minor bleed, major bleed, MI, and ICH. Dead.	Lifetime
Shah, 2011 [38]	USA	Markov	Dabigatran, Warfarin, Aspirin	MI, TIA, stroke (4 severities), minor bleed, major bleed, dyspepsia, death	Well, TIA, Mild Stroke, Major Stroke, Second Stroke, ICH, Stroke and ICH, Dead	Lifetime
Freeman, 2011 [39]	USA	Markov	Dabigatran, Warfarin	TIA, stroke, ICH, extracranial haemorrhage, MI, death	Well, RIND, Mild stroke, moderate-severe stroke, Mild ICH, moderate-severe ICH, MI, Dead	Lifetime
Lee, 2012 [40]	USA	Markov	Apixaban, Warfarin	Stroke, bleed, MI, ICH, death	Well, RIND, minor ischaemic stroke, major ischaemic stroke, MI, minor ICH, major ICH, ischaemic stroke and ICH, death	Lifetime
Lee, 2012 [41]	USA	Markov	Rivaroxaban, Warfarin	RIND, minor stroke, major stroke, minor ICH, major ICH, stroke and ICH, ECH, MI, death	Well, minor stroke, major stroke, minor ICH, major ICH, MI, Dead	Lifetime
Harrington, 2013 [42]	USA	Markov	Apixaban, dabigatran, rivaroxaban, Warfarin	Minor ischaemic stroke, major ischaemic stroke, ICH, MI, Death	Well, Post minor ischaemic stroke, post major ischaemic stroke, post ICH minor disability, post ICH major disability, post MI, dead	30 years
Kamel, 2012 [43]	USA	Markov	Apixaban, Warfarin	TIA, ECH, MI, mild ischaemic stroke, moderate-severe ischaemic stroke, mild ICH, moderate-severe ICH, death	AF and history of stroke/TIA, mild ischaemic stroke, moderate-severe ischaemic stroke, mild ICH, moderate-severe ICH, recurrent ischaemic stroke or combined stroke and ICH, dead	20 years

CADTH - Wells, 2012[44]	Canada	Markov	Apixaban, dabigatran, rivaroxaban, warfarin	Minor stroke, major stroke, fatal stroke, non-fatal MI, fatal MI, TIA, non-fatal PE, fatal PE, ICH, major bleed, minor bleed, fatal bleed, no-event death	Well, previous TIA, previous minor stroke, previous major stroke, previous MI	40 years
Wisloff, 2013 [45]	Norway	Markov	Apixaban, Dabigatran, rivaroxaba, warfarin	Gastrointestinal bleed, ischaemic stroke, ICH, acute MI, heart failure death	Well, previous bleed, previous stroke, moderate stroke sequelae, severe stroke sequelae, previous MI, death	Lifetime
Kansal, 2012 [46]	UK	Markov	Dabigatran, warfarin	Ischaemic stroke, haemorrhagic stroke, TIA, SE, MI, minor bleed, ICH, ECH, death.	8 states combining stoke history/no stroke history with no disability and mild, moderate and severe disability. Death.	Lifetime
Canestaro, 2013[47]	US	Markov	Dabigatran, Apixaban, Rivaroxaban, Warfarin	Ischemic stroke, MI, SE, ICH, extracranial haemorrhage, other cause death	Well, post-MI, and death states as well as 3 severities of each of post-ischemic stroke, post-ischemic stroke and MI, post-ICH, post-ICH and MI, post-ICH and ischemic stroke, post-ICH ischemic stroke and MI. 21 states in total.	Lifetime
Nshimyumukiza, 2013[48]	Canada	Markov	Dabigatran, warfarin	ICH, ECH, stroke, MI, deep vein thrombosis, PE, death	Daily cycles over 4 states: No event, Major bleeding event, Major thromboembolism event, Mild/Severe deficit	5 years
Krejczy,2014[49]	German	Markov	Dabigatran, Apixaban, Rivaroxaban, Warfarin	TIA, ischemic stroke (fatal, moderate to severe, mild), haemorrhage (fatal, moderate to severe intracranial, mild intracranial, major non-cerebral, minor non-cerebral), MI, and death.	Healthy with non-valvular AF, TIA, ischemic stroke (fatal, moderate to severe, mild), haemorrhage (fatal, moderate to severe intracranial, mild intracranial, major non-cerebral, minor non-cerebral), MI, and death. Combinations of these events were included.	20 years
Pink, 2011[50]	UK	Discrete Event Simulation	Dabigatran, Warfarin	Stroke, PE, TIA, congestive heart failure, fatal stroke, fatal PE, other vascular death, ICH, other major bleed, minor bleed, non-	Recorded patient characteristics were hypertension, diabetes mellitus, congestive heart failure, previous stroke, previous TIA, previous MI, previous ICH	Lifetime

				bleed adverse events, MI, treatment discontinuation		
Lip, 2014[51]	UK	Markov	Dabigatran, Apixaban, Rivaroxaban	Ischemic stroke, ICH, gastrointestinal major bleed, other major bleed, clinically relevant non-major bleed, MI, SE, other cardiovascular hospitalization, death	Healthy with non-valvular AF, ischemic stroke, ICH, gastrointestinal major bleed, other major bleed, clinically relevant non-major bleed, MI, SE, other cardiovascular hospitalization, death, non-valvular AF on aspirin.	Lifetime
Rognoni 2014[52]	Italy	Markov	Dabigatran, Apixaban, Rivaroxaban, Warfarin	Temporary/mild/moderate-severe ischemic stroke, temporary/mild/moderate-severe ICH, MI, minor extracranial bleeding, major extracranial bleeding, death	Non-valvular AF only, temporary/mild/moderate-severe ischemic stroke, temporary/mild/moderate-severe ICH, MI, minor extracranial bleeding, major extracranial bleeding, death	Lifetime

*RIND=Reversible ischaemic neurological deficit, ICH=Intracranial haemorrhage, ECH=Extracranial haemorrhage, TIA=Transient ischaemic attack, MI=myocardial infarction, PE=Pulmonary embolism, SE=Systemic embolism.

Table 2 Summary of Previous economic models for acute treatment of VTE

Author, year	Setting	Population	Model type	Interventions	Events	Health states	Time horizon
Bayer TA261 2012[53]	UK	Adults receiving acute treatment for DVT	Markov model	Rivaroxaban and dual therapy (LMWH & VKA).	Mortality, VTE recurrence, CTPH, PTS, clinically relevant bleeding	On treatment, Major bleed – IC, Major bleed – EC, CRNM bleed, recurrent DVT, recurrent PE, CTEPH, post IC bleed, long term CTEPD, PTS mild/moderate and severe, off treatment and dead	40 years
Bayer TA287 2013[54]	UK	Adults that receiving acute treatment for PE	Markov model	Rivaroxaban, LMWH or fondaparinux with continued therapy as follows vitamin K antagonist or LMW for people for whom a vitamin K antagonist is not considered an appropriate treatment	Mortality, VTE recurrence, CTPH, PTS, clinically relevant bleeding	On treatment, major bleed – IC, major bleed – EC, CRNM bleed, recurrent DVT, recurrent PE+-DVT, PE post DVT, CTEPH, post IC bleed, long term CTEPH, severe PTS, off treatment post PE, off treatment post DVT and dead	40 years

EC: extra cranial haemorrhage, CRNM bleed: clinically relevant non-major bleed

Table 3 Summary of previous economic models for primary prevention of VTE

Author, year	Setting	Population	Model type	Interventions	Events	Health states	Time horizon
Boehringer Ingelheim TA157 2008 [55]	UK	Adults undergoing elective THR or TKR (model parameters and time on treatment differs between populations)	Decision tree and Markov model	Dabigatran, LMWH and fondaparinux	Mortality, incidence of DVT, incidence of PE, post DVT complications including post thrombotic syndrome, health-related quality of life, adverse effects of treatment including bleeding events (minor and major) and joint outcomes (medium and long-term) including joint infection.	Based on the structure by Botteman ([56]).	60 years
Bayer TA170 2012[57]	UK	Adults undergoing elective THR or TKR (model parameters and time on treatment differs between populations)	Decision tree and Markov model	Rivaroxaban, and LMWH.	VTE, symptomatic VTE, non-fatal PE, fatal PE and prophylaxis related bleeding	Text and model schematic has been blanked out	Lifetime
Bristol-Myers Squibb TA245 2012[58]	UK	Adults undergoing elective THR or TKR (model parameters and time on treatment differs between populations).	Decision tree and Markov model	Apixaban, LMWH, fondaparinux, rivaroxaban and dabigatran	Mortality, VTE, PTS syndrome and treatment related bleeding events	Well, untreated VTE, treated VTE, disabled, mild to moderate PTS year 1, mild to moderate PTS year 2+, severe PTS year 1, severe PTS year 2+, DVTt, PE, dead	35 years
Botteman 2002[56]	USA	Adults undergoing elective THR	Decision tree and Markov model	LMWH and warfarin	DVT, PE, , PTS and mortality	Surgery, DVT, DVT death, DVT survivor, post DVT, mild/moderate PTS year 1, mild/moderate PTS year 2+, severe PTS	Lifetime

Author, year	Setting	Population	Model type	Interventions	Events	Health states	Time horizon
						year 1, severe PTS year 2+, death	
Dranitsaris 2009[59]	Canada	Adults undergoing elective THR, TKR or hip fracture surgery	Decision tree	Dalteparin 10 days, dalterparin 35 days and warfarin	Major bleed, symptomatic DVT at discharge, symptomatic DVT by day 35	NA	Three months
Duran 2012[60] and Monreal 2013[61]	USA, France, Italy and Spain	Adults undergoing elective THR or TKR	Decision tree and Markov model	Rivaroxaban, enoxaparin and dabigatran	Symptomatic VTE, non-fatal PE, fatal PE, prophylaxis related bleeding	No PTS, PTS, death	Five years
Mahmoudi 2013[62]	USA	Adults undergoing elective THR or TKR	Decision tree	Xa inhibitors and LMWH	Distal DVT, proximal DVT, fatal PE, non-fatal PE major bleed, stroke	NA	Six months
McCullagh 2009[63]	Ireland	Adults undergoing elective hip or knee replacement surgery	Decision tree	Rivaroxaban and dabigatran	Distal DVT, proximal DVT, symptomatic PE, fatal PE, major bleed and fatal bleed	NA	180 days
McCullagh 2012[64]	Ireland	Adults undergoing elective hip replacement	Decision tree and Markov model	Rivaroxaban, dabigatran and enoxaparin sodium	Distal DVT, proximal DVT, symptomatic PE, fatal PE, major bleed and fatal bleed	No VTE, treated VTE, untreated VTE, PTS year 1, PTS maintenance, stroke and dead	Life time
Lundkvist 2007[65]	Sweden	Patients following hip fracture surgery	Decision tree	Fondaparinux and enoxaparin	Symptomatic VTE events, fatal and non-fatal recurrent VTE events and PTS	NA (model closes follows the structure of Gordois *et al*. and Sullivan *et al*,)	Five years
Gordois 2003[66]	England and Wales	Adults following major orthopaedic surgery	Decision tree	Fondaparinux and enoxaparin	Clinical VTE and VTE-related deaths	NA	Five years
Pishko 2012[67]	USA	Ambulatory cancer patients	Decision tree and Markov model	LMWH and no intervention	Major bleed, minor bleed, post bleed, VTE	Malignancy, major bleed, minor bleed, post bleed, VTE, post VTE	Two years
Sullivan 2004[68]	USA	Adults following major orthopaedic surgery	Decision tree	Fondaparinux and enoxaparin	Rates of symptomatic thromboembolic events	NA	Five years

Author, year	Setting	Population	Model type	Interventions	Events	Health states	Time horizon
Zindel 2012[69]	Germany	Adults undergoing elective THR or TKR	Decision tree	Rivaroxaban and enoxaparin sodium	DVT, fatal PE, non-fatal PE major bleed,	NA	Three months

4.4 Atrial fibrillation patients and interventions

4.4.1 Atrial fibrillation patient population

We considered patients with non-valvular AF who were eligible for anti-coagulation. We made no distinction between paroxysmal, persistent and permanent AF. The RCTs identified in the systematic review did not distinguish between AF type, but paroxysmal AF patients are less likely to be included in the RCTs than other AF types, therefore our results are most applicable to persistent and permanent AF patients. We consider a cohort of patients receiving first line anticoagulation at age 70, based on the mean age observed in the RCTs identified in the systematic review (mean age 70, standard deviation 8), and consider costs and benefits over a lifetime. We assume a 60/40 split in favour of males, similar to that observed in the RCTs. The distribution over CHA_2DS_2-VASc categories is based on a meta-analysis of scores for screen detected AF and Swedish cohort study, with details provided in Section 6.3.

4.4.2 Atrial fibrillation interventions

The first line treatments for AF included in the cost-effectiveness analysis, alongside their standard or licensed doses, are listed in Table **4**. We only consider licensed treatments and doses in our analysis. Although a few small RCTs have compared betrixaban to warfarin in atrial fibrillatin, there was not enough evidence to include it in the economic model. Standard care for AF patients, before the introduction of NOACs, was Warfarin [70]. No treatment is included as an option but is only realistic for patients with low CHA_2DS_2-VASc.

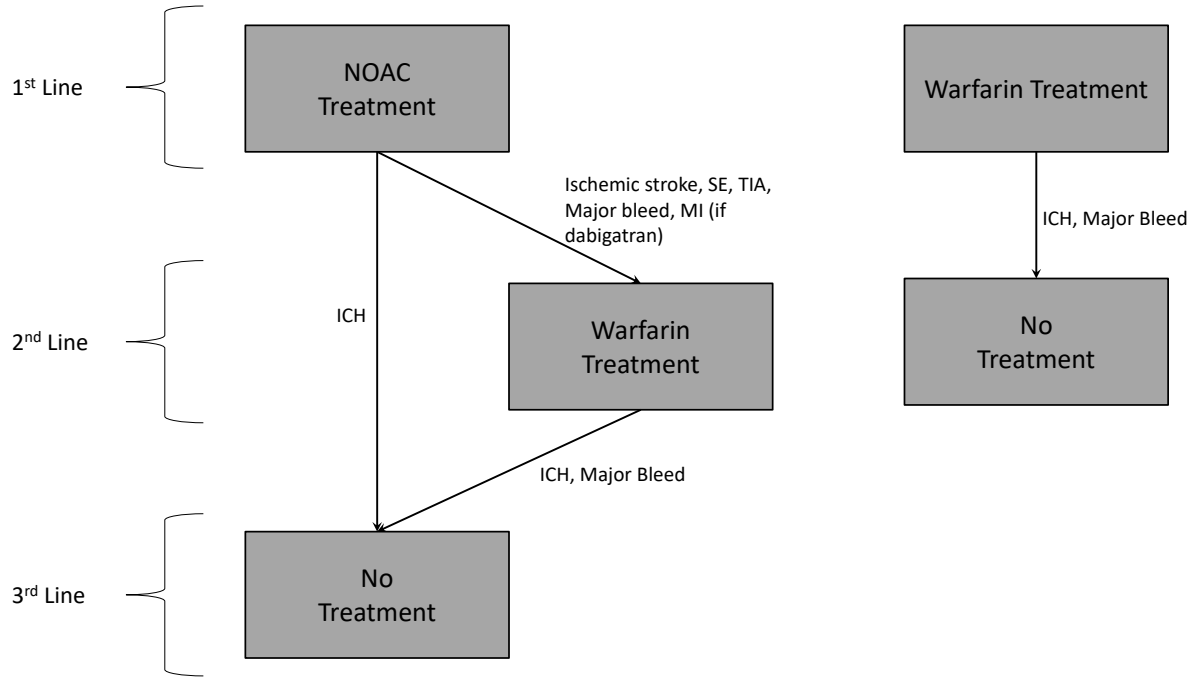
Treatment switching may occur as a result of treatment failure, indicated by ischaemic stroke, or serious adverse events such as intracranial haemorrhage. For patients on Warfarin first line treatment, the only second line intervention available was assumed to be no treatment. For patients on a NOAC first line treatment, second line treatment may be either warfarin or no treatment. No treatment is the only third line treatment. These rules are illustrated in Figure 1 where the events that may lead to treatment switching are indicated.

Table 4 First line anticoagulants and dose compared in the cost-effectiveness analysis

Intervention	Dose / target INR	Time on treatment
Apixaban	2.5mg twice daily (elderly)	Lifetime
Apixaban	5mg twice daily	Lifetime
Dabigatran	110mg twice daily (elderly)	Lifetime
Dabigatran	150mg twice daily	Lifetime
Rivaroxaban	20mg once daily	Lifetime
Warfarin	INR 2-3	Lifetime

*source BNF[71] or trial based

Figure 1 Illustration of treatment strategies and switching/discontinuation rules. The events that may lead to treatment switching are indicated next to the arrows between treatments.



4.5 VTE patients and interventions

4.5.1 VTE patient populations

For primary prevention, we estimated cost-effectiveness in two distinct subpopulations; patients undergoing elective total hip replacement (THR) or total knee replacement (TKR). We considered including other populations (e.g. patients hospitalised for medical treatment) but there was not enough evidence identified in the literature review to inform a model.

After a confirmed VTE event patients receive acute treatment. The population of patients in the acute treatment model includes those where a non-fatal symptomatic VTE event (DVT or PE) followed a THR or TKR as well as patients with a symptomatic VTE from other causes. Patients who completed at least three months of anticoagulant treatment for symptomatic VTE without recurrence are included in the secondary prevention model.

We assumed an average age of subjects entering the primary prevention model is 68.7 years (11.4 SD) and the split between males and females of 40/60, based on estimates from the National Joint Registry[72]. The assumed age is in line with the median of the mean age of patients enrolled in the primary prevention RCTs (median 64.6 years). The starting age in the acute and secondary prevention populations was 57.35 years; the median (across RCTs) of the mean age of patients enrolled in the acute treatment and secondary prevention RCTs. We assumed that the index VTE event on entry to the acute treatment and secondary prevention models was split between DVT and based on the proportion of non-fatal PE and DVT in the acute treatment population.

4.5.2 VTE interventions

For each indication we compared first line treatments for which we have sufficient evidence to estimate model parameters. There are seven comparators evaluated in the secondary prevention model (Table 5), four in the acute treatment model (Table 6), and four in each of the two primary prevention subpopulations (Table 7). Before the introduction of NOACs, standard practice[73] for primary prevention was LMWH, and for acute treatment was LMWH and warfarin for at least five days, then continue with

warfarin only. In secondary prevention, NICE guidance recommends that clinicians, after discussion with patients, consider extending warfarin therapy beyond three months if the risk of VTE recurrence is high and there is no additional risk of major bleeding[74]. However, NICE also acknowledged the need for further research to establish the cost-effectiveness of long-term anticoagulation after unprovoked VTE. In clinical practice, patients may be offered long-term anticoagulation after a second VTE event. Due to this uncertainty about best practice, we compared all anticoagulants to a 'no pharmacotherapy' secondary prevention strategy in the base-case model. In a sensitivity analysis, we assumed patients in this reference group would receive warfarin after a second VTE event. We assumed that all treatment will be stopped for subjects that have an intracranial haemorrhage and that no other treatment switching occurs. This assumption differs from the AF population where treatment can be stopped or switched for other reasons (section 4.4.2).

Table 5 Secondary prevention comparators

Intervention	Dose / Target INR	Time on treatment
Apixaban	2.5mg twice daily	Lifetime
Apixaban	5mg twice daily	Lifetime
Aspirin	75mg once daily	Lifetime
Dabigatran	150mg twice daily	Lifetime
Rivaroxaban	20mg once daily	Lifetime
Warfarin	INR 2-3	Lifetime
No long-term pharmacotherapy	-	-

Source BNF[71]

Table 6 Acute treatment comparators

Intervention	Dose	Time on treatment
Apixaban	10mg twice daily for 7 days, then 5mg twice daily	Six months
Dabigatran	150mg twice daily	Six months
Rivaroxaban	15mg twice daily for 21 days, then 20mg once daily	Six months
Warfarin	INR range 2-3 plus LMWH* for initial five days	Six months

Source BNF[71]

* Low molecular weight heparins (Enoxaparin 1mg per kg BD, Enoxaparin 1.5mg per kg OD and Tinzaparin 175IU per kg)

Table 7 THR and TKR Primary prevention comparators

Intervention	Dose	Time on treatment THR	Time on treatment TKR
Apixaban	2.5mg twice daily	28 to 35 days	10 to 14 days
Dabigatran	220mg once daily	28 to 35 days	10 to 14 days
LMWH	*	28 to 35 days	10 to 14 days
Rivaroxaban	10mg once daily	28 to 35 days	10 to 14 days

* Low molecular weight heparins (enoxaparin 40mg od, enoxaparin 30mg bd, enoxaparin 20mg bd , ardeparin 25 anti-X U/kg bd, ardeparin 35 anti-XU/kg bd, ardeparin 50 anti-XU/kg bd, nadroparin 3800IU anti-Xa od, certoparin 3000IU od, dalteparin 2.5mg od, dalteparin 5000IU od): Source BNF[71]

4.5.3 Outcomes of AF and VTE models

We present results on total costs and quality adjusted life years (QALYs), both discounted at 3.5%. We present a probabilistic analysis, where model parameters are given probability distributions to reflect uncertainty in their values[75]. We summarised the results with the expected costs, expected QALYs, expected net monetary benefit (NMB) for a range of willingness to pay per additional QALY gained (where expected values are an average over the joint distribution of the model parameters). NICE has a stated willingness to pay threshold of £20,000 to £30,000 per QALY[76].

Uncertainty in the model input parameters is captured using simulation (Monte Carlo simulation for parameters with assumed distributions, and Markov chain Monte Carlo simulation for parameters estimated from the network meta-analysis). We represent decision uncertainty using the cost-effectiveness plane, cost-effectiveness acceptability curves (CEACs), and cost-effectiveness acceptability frontiers (CEAFs). The cost-effectiveness plane plots incremental effects (QALYs) against incremental costs for each simulation sample. The CEAC plots the proportion of the simulation samples where each strategy had the highest net benefit (ie was most cost-effective) against willingness-to-pay per QALY threshold. These proportions are estimates of the probability that the treatment is the most cost-effective. If this probability is close to one for a particular treatment, this suggests very little uncertainty as to the most cost-effective treatment, whereas if it is low the choice of most cost-effective treatment is uncertain. This allows decision makers to identify interventions that are unlikely to be cost-effective at any plausible threshold and to judge how sensitive treatment choice is to the amount that the NHS is willing to pay for a QALY. The CEAC is not robust when there is a treatment with a high degree of uncertainty in net benefit, giving high probabilities of being both most cost-effective and least cost-effective. For this reason the CEAF has been proposed[77] . This plots, for each willingness to pay threshold, the probability of being most cost-effective only for the treatment with the highest expected net benefit at that willingness-to-pay threshold.

We use value of information methods to explore how sensitive the optimal treatment is to uncertainty in the model inputs, and guide research recommendations. We estimate the expected value of perfect information (EVPI) and the expected value of partial perfect information (EVPPI). EVPI and EVPPI measure the expected

improvement to our decision making (in monetary units) if we were to eliminate uncertainty in all (EVPI) or some (EVPPI) of the model input parameters. We present EVPI per-person per year and also per-population over 10 years discounted at 3.5%, for given annual incidence for each of our populations. EVPPI for subsets of parameters are computed using the Sheffield Accelerated Value of Information web-application[78,79]. This method only gives approximate results, which can be interpreted as indicative of the relative sensitivity of the decision to different groups of parameters.

4.6 Atrial fibrillation model structure

The discrete-time Markov multistate model structure (Figure 2) used a cycle length of 3 months, as in other recent models[37,46,80]. We ran the model for a cohort starting at age 70 and use a lifetime time horizon with a cut-off at 100 years, thus giving 120 cycles. Patients were initially assigned to first line treatment which may be warfarin or a NOAC. There is a probability of switching to another therapy or discontinuing treatment entirely (Figure 1).

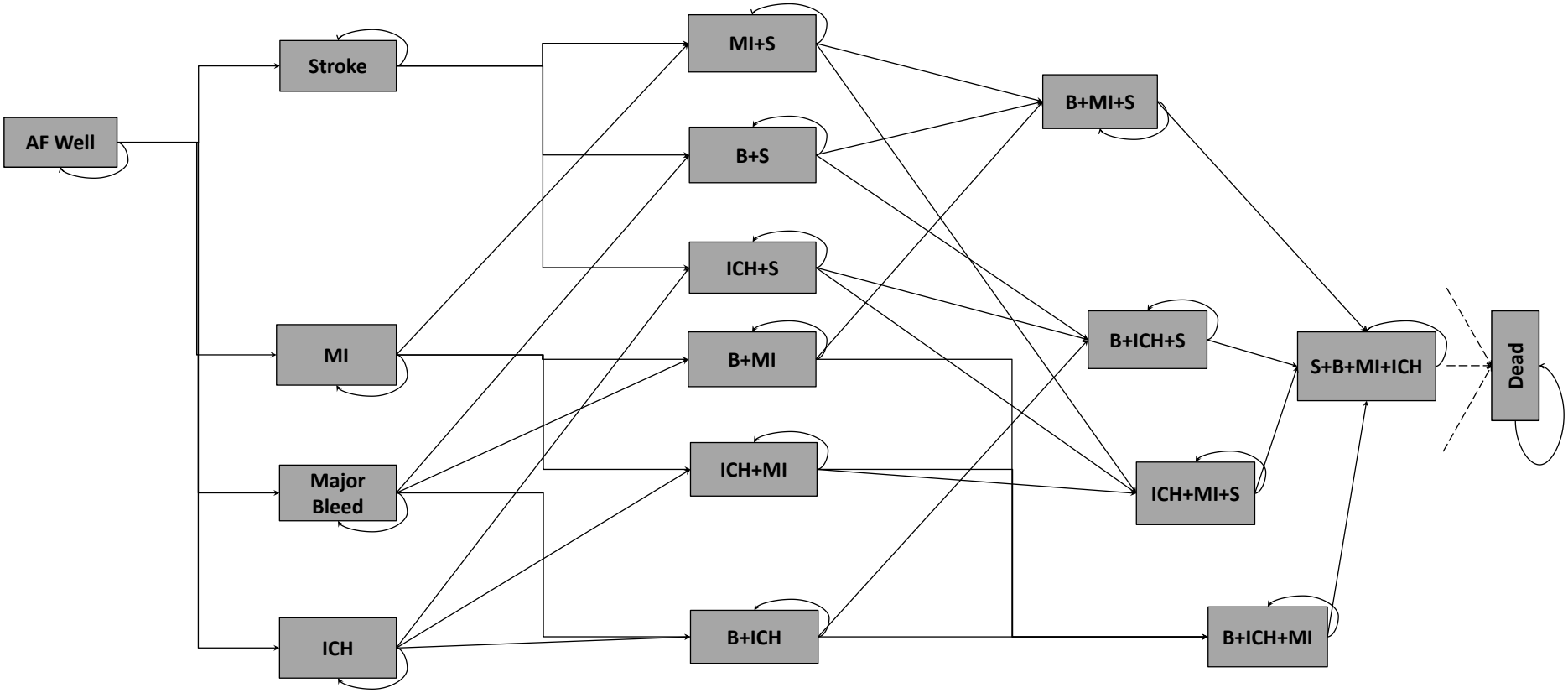
Each of the treatment strategies have the same model structure but with different costs, utilities, and event probabilities. From any state, a patient can have a clinically relevant (extracranial) bleed, an intracranial haemorrhage (ICH), an ischaemic stroke, a myocardial infarction (MI), a transient ischaemic attack (TIA), a systemic embolism (SE), can discontinue or switch treatment due to these events, or die. These events are similar to those used in earlier models[38,46]. The primary difference is that we do not distinguish between minor and major ischaemic stroke as there was limited evidence from the RCTs to estimate the relative rates of these events. We also do not include non-clinically relevant minor bleed events as it is assumed that they will not have a significant impact on costs, quality of life, or future risks. As in most previous models, memory states are used to record a history of the most important previous events. The model assumes that SE and TIA have only short term effects on future risks, costs and utilities, whilst ischaemic stroke, ICH, other CRB and MI have long term consequences that must be modelled. Up to four major events are therefore recorded and assumed to affect future risks, costs and utilities. For example, patients with MI+ICH will have different risks, costs and utilities to patients with MI or ICH alone. Unlike the Wisloff 2013 model[45], our model does not distinguish between bleed locations, such as gastro-intestinal and other types of bleed. Based on advice from clinical project team members we assumed that the greatest impact on risks, costs and effects is captured by the broad definition of “clinically relevant bleeds”, as reported in the RCTs. In total our model has 17 states, including a well state (“AF Well”) and death.

At any cycle, patients can switch treatments to second line or no treatment. All adverse health events increase the probability of treatment switching. An ICH is

assumed to always lead to treatment switching. Patients are assumed to always switch treatment from dabigatran to warfarin if they experience an MI due to recent findings suggesting a link between dabigatran and MI risk[81]. Whether or not patients switch treatment after an ischaemic stroke depends on whether it was due to treatment failure or non-compliance. We assume it is due to treatment failure, but that only a proportion of patients will switch treatment following an ischaemic stroke.

In the Markov model future state transitions depend only on the current state a patient is in (and not past history). We assume homogeneous transition probabilities that do not change with time. However, the age of the cohort will increase with each cycle and mortality risk increases accordingly, based on general population lifetables, as does and CHA_2DS_2-VASc when patients progress between <65, 65-74, and ≥75 year old categories. There is no available evidence to suggest treatment effects change with age or that they depend on event history. The model therefore makes the assumption that treatment effects are independent of age and event history.

Figure 2 Illustration of the Markov model for AF*



* Patients can experience transient events (TIA or SE) but stay in same health state, with possibly changed treatment, thereafter. (S = ischaemic stroke, B = other clinically relevant bleed, ICH = intra-cranial haemorrhage, MI = myocardial infarction)

4.7 VTE model structures: overview

There were three model structures for the primary prevention, acute treatment and secondary prevention decision problems. The structure of the primary prevention model was identical in the two subpopulations (THR & TKR) however the parameter values differ. Decision trees were used to model the initial costs and outcomes of primary prevention and acute treatment, where anticoagulation is used over short periods of time, and a Markov model evaluated secondary prevention, where anticoagulation may be prescribed over prolonged periods. The models are linked because most patients who have acute treatment for VTE will be considered for extended secondary prevention of recurrence and it is possible that a patient receiving anticoagulation for primary prevention will have a VTE requiring acute treatment and eventually secondary prevention (Figure 3). Therefore, we modelled the decision problems sequentially. We first estimated the most cost-effective method of secondary prevention. We then estimated the most cost-effective method of acute treatment, assuming that all patients who subsequently require secondary prevention are managed using the most cost-effective method from the secondary prevention model. Finally, we estimated the most cost-effective method of primary prevention, with the therapy used for acute treatment and secondary prevention determined based on the results of the first two models. For this reason, we begin our detailed discussion of the three models with the secondary prevention model.

4.7.1 VTE model structure: Secondary prevention

A Markov model with half cycle correction[82] was used to evaluate the cost effectiveness of prophylaxis in patients who have experienced a previous non-fatal VTE event (Figure 4). The model has a cycle length of one year and includes eight health states (Table 8). Subjects enter the model in post PE or post DVT. Subjects in the "post DVT" (or "post PE") state can have an additional non-fatal DVT (or PE) event with a transient utility decrement and cost, but remain in the same health state. Subjects in the "post DVT" state who experience a non-fatal PE and subjects in "post PE" who experience a non-fatal DVT transition to "post PE DVT". Subjects in the "post DVT" and "post PE DVT" states can develop post thrombotic syndrome (PTS) and transition to either "mild/moderate PTS" or "severe PTS". Subjects that have had a PE

may experience chronic thromboembolic pulmonary hypertension (CTPH). Subjects can transition to CTPH from “post PE” and “post PE DVT”.

All subjects that are receiving treatment can transition to the intracranial haemorrhage health state. After entering this state, we assumed anticoagulation therapy will be stopped and subjects will remain there until death as this is considered to be the state with the lowest quality of life.

Figure 3 Population pathway. THR primary prevention, TKR primary prevention, VTE with acute treatment and secondary prevention.

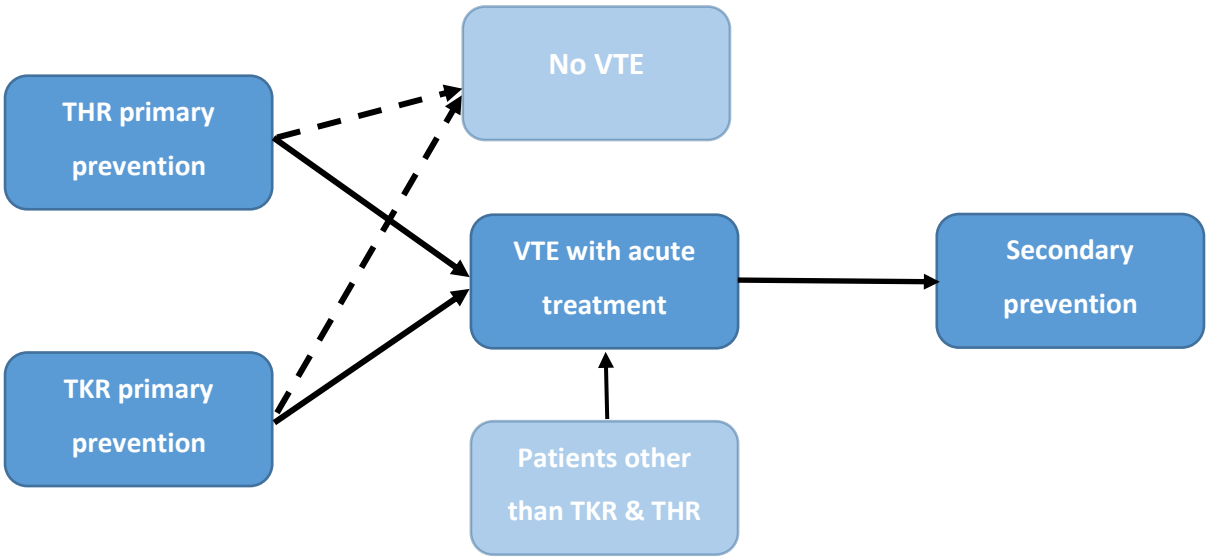
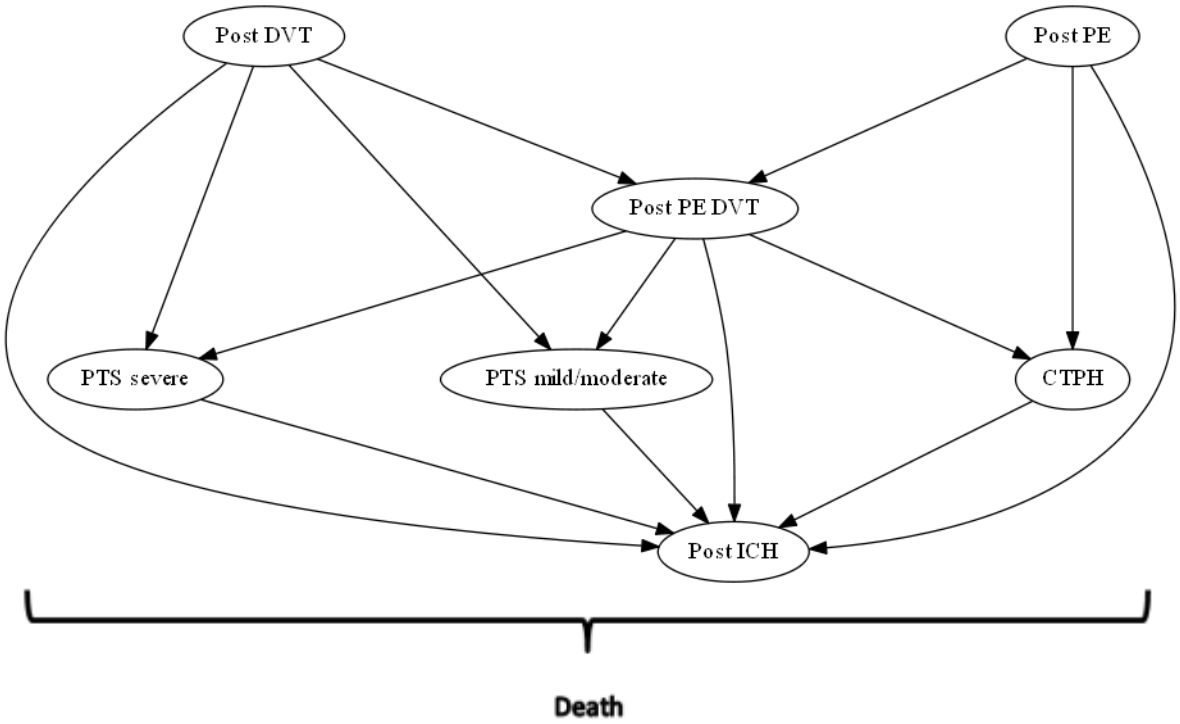


Figure 4 Illustration of the VTE secondary prevention Markov model*



* Nodes represent the health states, lines between nodes represent possible transitions, all health states can transition to death. ICH, other clinically relevant bleeds DVT and PE are acute events, which may lead to a change in chronic health state (e.g. post ICH).

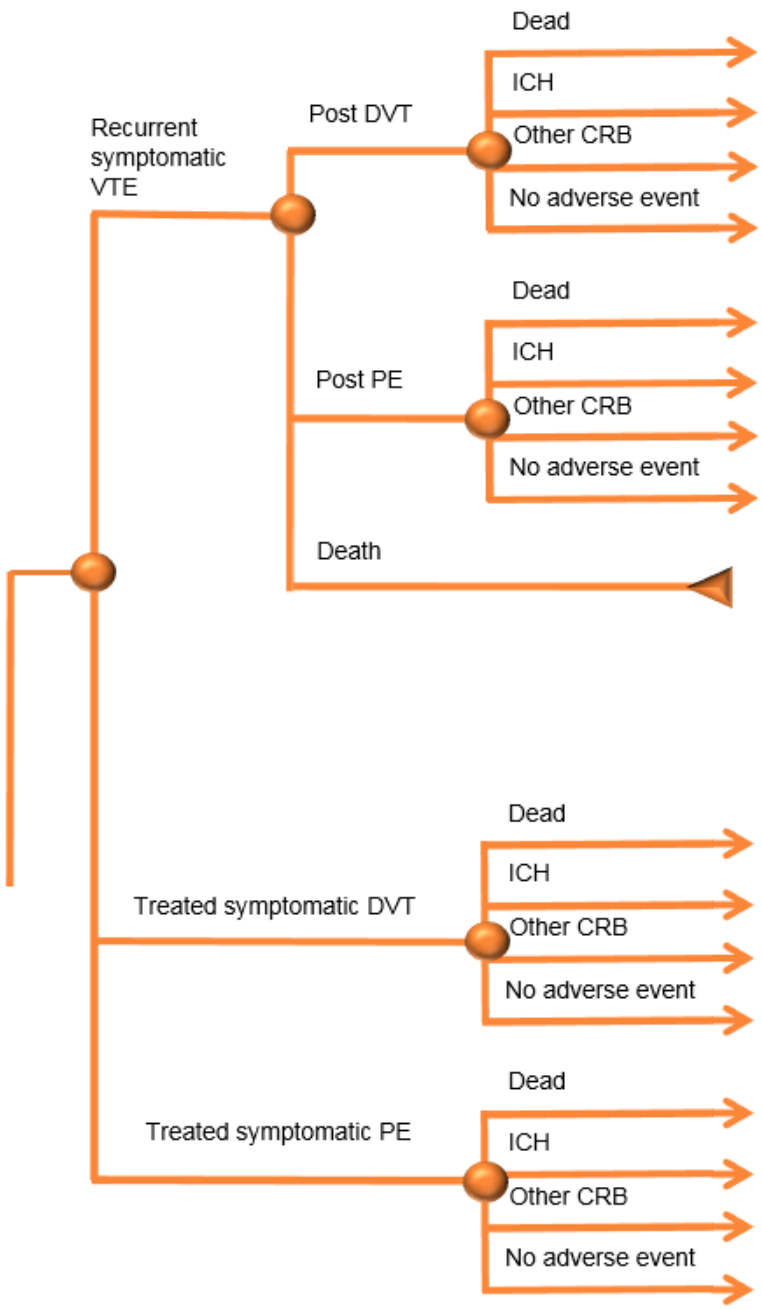
Table 8 Health states in the secondary prevention model

Health state	Description
Post DVT	Experienced at least one DVT event and no PE events
Post PE	Experienced at least one PE event and no DVT events
Post PE DVT	Experienced at least one DVT and at least one PE
PTS mild/moderate	Mild/moderate PTS after one or more DVT
PTS severe	Severe PTS after one or more DVT
CTPH	CTPH after PE
Post ICH	Post intracranial haemorrhage
Death	Dead (any cause)

4.7.2 VTE model structure: Acute treatment

The acute treatment of symptomatic VTE was modelled using a decision tree covering the first 6 months of therapy, in line with current guidelines for the duration of acute treatment (Figure 5). There is a probability that patients will experience recurrent symptomatic VTE during the acute treatment period and, regardless of VTE recurrence, all patients are at risk of other CRB or intracranial haemorrhage. Longer term costs and outcomes following acute treatment were estimated using the secondary prevention Markov model for patients who are alive at the end of acute treatment.

Figure 5 Illustration of VTE acute treatment decision tree*



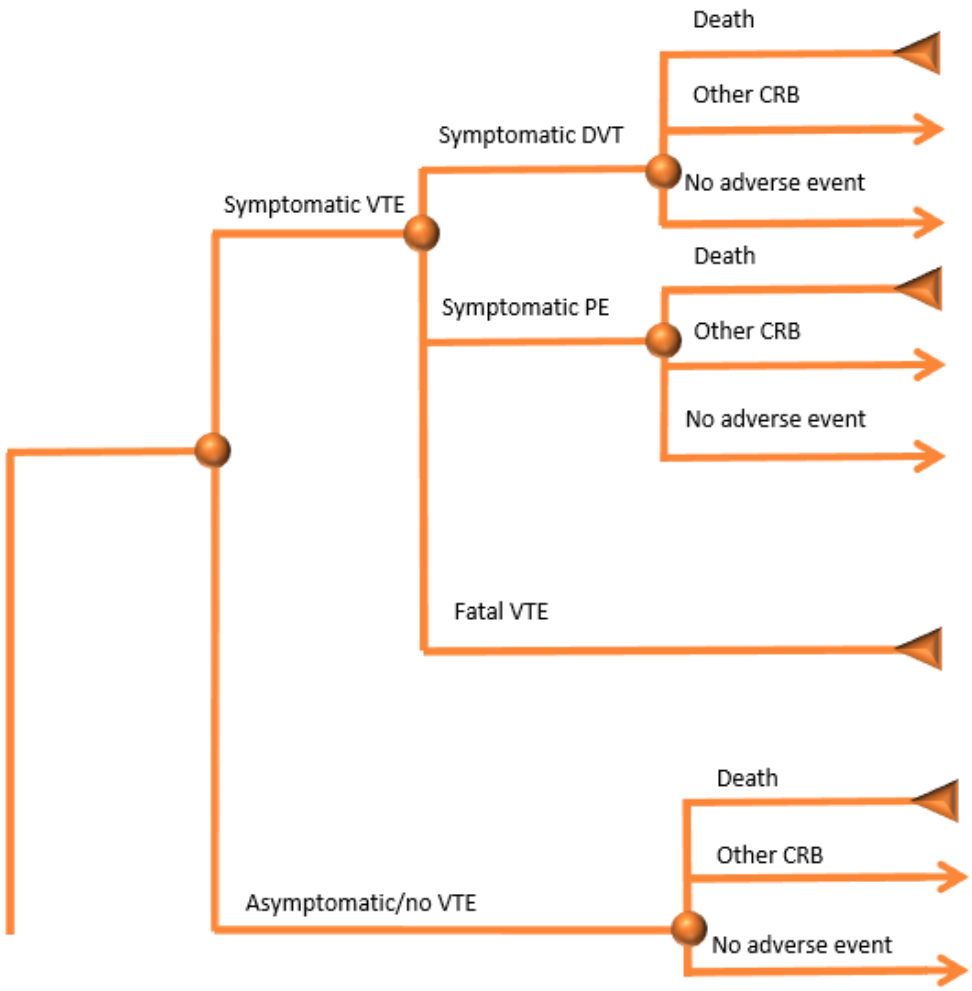
* At the end of each branch in the decision tree patients progress to the secondary prevention model. ICH branches enter in "post ICH" state, treated symptomatic DVT (with bleed or no adverse event) will enter the post DVT state, treated symptomatic PE (with bleed or no adverse event) will enter the post PE state, recurrent symptomatic VTE post DVT will enter the post DVT or post DVT PE state depending on the previous event and recurrent symptomatic VTE post PE will enter the post PE or post DVT PE state depending on the previous event.

4.7.3 VTE model structure: Primary prevention

The primary prevention model consists of a decision tree covering the first 180 days of prophylactic anticoagulation (Figure 6). After this initial period, the long term cost and outcomes of patients who do not have a symptomatic VTE are tracked using a two state Markov model (Figure 7). This Markov model has two health states; no VTE/asymptomatic VTE and dead. The Markov model has a lifetime time-horizon and yearly cycles. The longer term costs and outcomes of patients who have a symptomatic VTE are tracked in the acute treatment model (Figure 5) and the secondary prevention model (Figure 4).

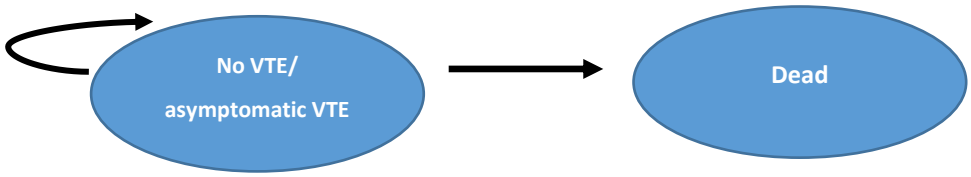
Patients enter the primary prevention model after having elective surgery (TKR or THR). They then either experience a symptomatic VTE event or no VTE/asymptomatic VTE. Patients that experience a symptomatic event either have a fatal PE, non-fatal PE or DVT and are treated. Regardless of VTE incidence, all patients are at risk of another CRB during the initial 90 day period of anticoagulation. Because treatment duration is short for primary prevention, the risk of ICH is very low and there is no evidence of a relative effect of NOACs compared with LMWH in this patient population. Therefore we have not incorporated ICH in the primary prevention model.

Figure 6 Illustration of the primary prevention decision tree*



* At the end of the decision tree subjects will have experienced a symptomatic VTE or not. If they have they will enter the acute treatment model. Those that did not experience a symptomatic VTE will enter the two stage Markov model

Figure 7 Primary prevention Markov model.



4.8 Inputs partially shared between AF and VTE models

4.8.1 Cost of pharmacotherapy

Average drug costs were based on the BNF March 2015 update[71] using the most economical pack size (Table 9, Table 10, Table 11). Edoxaban does not currently have a list price in the UK. For the base case we assume the six-monthly cost is equivalent to dabigatran. We tested this assumption in a sensitivity analysis. As all of the NOACs are taken orally it was assumed that there are no administration or monitoring costs, following the costing report in AF of Ali et al[83]. Average drug and monitoring cost of warfarin comes from a costing report by NICE [84] and cited in Kansal et al[46]. The cost of LMWH was an average over all of the LMWHs included in the meta-analyses and listed on the BNF.

The unit costs of drugs are assumed to be fixed and known, so that point estimates, rather than distributions, are entered into the models. However the administration and monitoring cost of warfarin is uncertain and in the absence of other information we assumed a Uniform distribution ranging from 50% to 150% of the estimated cost from the NICE costing report[84]. We performed a sensitivity analysis for the assumed cost of warfarin monitoring.

Table 9 Drug dose, duration and costs for the AF and VTE secondary prevention interventions

Intervention	Dose per day (mg)	mg per tablet	Number in pack	Cost per pack	Cost per day	Administration cost	Cost per 3 month cycle AF model	Cost per annual cycle VTE secondary prevention model
Apixaban	10	5	56	£53.20	£1.90	£0.00	£173.38	£802.25
Apixaban	5	2.5	60	£57.00	£1.90	£0.00	£173.38	£802.33
Dabigatran	300	150	60	£51.00	£1.70	£0.00	£155.13	£802.33
Dabigatran	220	110	60	£51.00	£1.70	£0.00	£155.13	n/a
Rivaroxaban	20mg	20	100	£180.00	£1.80	£0.00	£164.25	£767.03
Edoxaban	60mg	60	28	£49.00	£1.75	£0.00	£159.69	
Warfarin							£70.66[2]*	£420.52**

* We inflated from a 2014 annual cost of £241.54 to 2019 annual cost of £282.62 using the ONS Consumer Price Inflation index for medical services (DKC3)[85] We placed a Uniform distribution ~(35.33, 105.98) on the cost per 3 month cycle (50% and 150% of the mean cost).

** We inflated to 2013/14 values using the ONS Consumer Price Inflation index for medical services (DKC3)[85] and placed a Uniform distribution ~(52.57, 157.70) and (210.26, 630.79) (on the cost per three month and yearly cycles respectively.

Table 10 Drug dose, duration and costs for VTE acute treatment interventions

Intervention	Dose per day (mg)	mg per tablet	Number in pack	Cost per pack	Time (days)	Cost per treatment
Warfarin					182.5	£210.26*
Dabigatran	300	150	60	£65.90	182.5	£400.89
Edoxaban	60	-	-	-	-	£400.89**
Rivaroxaban	30	15	14	£29.40	21	£427.35
Rivaroxaban	20	20	100	£210	161.5	
Apixaban	10	5	56	£61.50	182.5	£400.85

*Total cost of warfarin includes five days of LMWH at £9.38 per day

**The six monthly cost of edoxaban is assumed to be equal to dabigatran

Table 11 Drug dose per day for VTE primary prevention comparators

Intervention	Dose per day (mg)	mg per tablet	Number in pack	Cost per pack	Cost per day
Apixaban (2.5mg bd)	5	2.5	60	£65.90	£2.20
Dabigatran (220mg od)	220	110	60	£65.90	£2.20
Rivaroxaban (10mg od)	10	10	100	£210.00	£2.10
LMWH (post-op, standard dose)	-	-	-	-	£4.17*

* Average daily cost of Enoxaparin 20mg bd, Enoxaparin 40mg od, Dalteparin 5000IU, Fondaparinux 2.5mg od

4.8.2 Cost of acute VTE, AF and anticoagulant related events

All costs of acute and chronic care used in the AF model were inflated to August 2019 values using the ONS Consumer Price Inflation index for medical services (DKC3), while costs used only in the VTE model were at 2013/14 levels [85,86]. Acute management costs for SE, MI, TIA, DVT, PE and clinically relevant bleeding come from the 2013/14 NHS reference costs and are inflated to 2019 values[87]. The reference costs for MI account for only direct hospitalization; we assumed total costs would be double this amount to account for follow-up costs[88]. The cost of a sudden fatal PE is assumed to be zero and the patients that have a non-fatal PE are assumed to accrue the full cost of a PE. Acute management costs for ischaemic stroke and ICH come from a study of AF patients on a UK stroke registry[3]. Normal distributions are assumed for the mean acute costs with standard deviations defined by the standard errors of the source data (Table 12).

Table 12 Acute event costs and their distributions

Event	Mean event cost £ (SD)	Distribution (mean, SE)	Source
Ischaemic stroke	13603.37 (SD=19736.94)	Normal (13603.37, 1550.68)	Ischaemic stroke, all strokes, based on 162 events [3]*** ******
ICH	13400 (SD=16164.68) (SD=13815)	Normal (13400, 3920.51)	ICH or haemorrhagic stroke, all haemorrhagic strokes, based on 17 patients [3] ******
SE (non-fatal)	2776.61	Uniform (1388.3, 4164.9)	NHS reference costs [87]******
TIA	1244.97	Uniform (622.5, 1867.5)	NHS reference costs [87]******
PE*	1596	Normal (1596, 159.6)****	NHS reference costs [87]
DVT**	712	Normal (712, 71.2)****	NHS reference costs [87]
Clinically relevant bleeding*****	2049.40	Uniform (1024.70, 3074.10)	NHS reference costs[87] ******
MI	5651.50	Uniform (2826.0, 8478.1)	Acute MI, NHS reference costs for hospitalization[87], doubled to include follow-up costs ******

* Weighted average of Healthcare Resource Group (HRG) codes DZ09D, DZ09E, DZ09F, DZ09G, DZ09H
** Weighted average of HRG codes YQ51A, YQ51B, YQ51C, YQ51D, YQ51E
*** We inflated to 2013/14 values using the ONS Consumer Price Inflation index for medical services (DKC3)[85].
**** We assumed a standard error of 10% of the mean event cost
***** Average of gastrointestinal and non-gastrointestinal bleed.
****** We inflated to August 2019 values using the ONS Consumer Price Inflation index for medical services (DKC3)[86].

4.8.3 Cost of chronic care for VTE, AF and anticoagulant related events

Long-term management costs of stroke (ischaemic stroke) also come from the UK stroke registry[3] (Table 13). This registry stratified the severity of ischaemic strokes by disability (non-disabling, moderately disabling, totally disabling) and we averaged their annual costs and standard deviations, weighted by the number of events. Management costs for ICH were derived from annual 1st and post 2nd year cost estimates in Wardlaw 2006[89]; this paper provided estimates for patients in dependent and independent states, which we averaged using a proportion reported in Rosand 2004[90]. Normal distributions are assumed, with standard deviations defined by the standard errors of the source data. For states with a history of multiple events, we assumed the additional post-event management costs were the maximum of the management costs for the constituent events. We divided sampled costs by four to obtain 3-monthly cycle costs.

Costs for mild to moderate and severe PTS have previously been estimated in a NICE technology appraisal[91] that looked at the clinical and cost effectiveness of dabigatran for the prevention of VTE after a TKR or TKR in adults. This study converted and inflated costs from a US economic burden study of long term complications of primary prevention of DVT following a THR[92]. This study estimated the cost of mild to moderate PTS to be £541 for the first year and £220 for subsequent years and severe PTS to be £2,461 for the first year and £602 for subsequent years. Inflating to 2013/14 values resulted in a cost of £689 for the first year and £280 for subsequent years for mild/moderate PTS and £3,136 for the first year and £767 for subsequent years of severe PTS. NICE guidance for the management of VTE[93] estimated a four weekly cost of CTPH to be £2,173, equivalent to an annual cost of £33,028 in 2013/14 prices.

Table 13 Annual post-ischaemic stroke and post-ICH management costs. These are divided by four to obtain 3-monthly cycle costs.

Event	Mean	Distribution	Source
Non-disabling	2135 (SD=3676, n=66)		Luengo et al.[3]
Moderately disabling	4165 (SD=7668, n=58)		Luengo et al.[3]
Totally disabling	6324 (SD=14898, n=6324)		Luengo et al.[3]

All (Ischaemic stroke)*	4227.51 (SD=4955.30, n=136)	Normal(4227.51, 424.91)	Weighted average of the mean and SD inflated to 2013/14 and then inflated to 2019 (for NICE AF guidelines) [85,86]
First year - dependent state	£30,307.36		Wardlaw 2006[89]
First year - independent state	£5,059.71		Wardlaw 2006 [89]
Second year onwards - dependent state	£15,377.60		Wardlaw 2006 [89]
Second year onwards - independent state	£1,192.91		Wardlaw 2006 [89]
Proportion of patients in independent state (GOS >3)*	0.405 (SE=0.024)	Beta(alpha=166.27, beta=249.4)	Rosand 2004 [90]
ICH management cost (year 1)	£20,082.06		Average of first year dependent and independent using proportion paitents independent (follows Beta distribution in model)
ICH management cost (after year 1)	£9,632.80		Average of first year dependent and independent using proportion paitents independent (follows Beta distribution in model)
Costs used in AF Ablation guidelines, explored as a sensitivity analysis			
ICH annual cost (year 1)	£29,641		Stroke cost in moderate symptoms from SSNAP audit, inflated to 2019 prices.
ICH annual cost (after year 1)	£13,994		
Ischemic stroke annual cost (year 1)	£22,132		Haemmorhage cost in moderate-severe symptoms from SSNAP audit, inflated to 2019 prices.
Ischemic stroke annual cost (after year 1)	£7,084		

* GOS = Glasgow Outcome Scale (1=death, 2=persistent vegetative, 3=severe disability, 4=moderate disability, 5=good recovery), SSNAP=**S**entinel Stroke National Audit Programme

4.8.4 Utilities

The AF and VTE models used utility weights combined with survival to estimate QALYs. Utility weights are anchored at 1 (best health) and zero (as bad as death) such that a year spent in an intermediate health state with a utility weight of 0.5 would be considered equivalent to 6 months in the best health state with a utility value of 1. The models have a number of acute health events which affect patients for a short period, followed by a partial or full recovery and a number of chronic health states from which patients do not recover. Several of these health events and health states are shared between the AF and VTE models.

Utilities were identified from a previous NICE technology appraisal submission on rivaroxaban[37] and from a rapid literature review to identify quality of life studies in VTE. The rivaroxaban technology appraisal submission conducted a systematic literature search for evidence on EQ-5D utility index in health states related to AF. For VTE events (DVT and PE), Locadia[94] estimated health utilities, using time trade off methods, from a cohort of 53 patients who had experienced a VTE event.

4.8.5 Utilities of VTE, AF and anticoagulant related acute health events

The acute health event disutilities for AF for other CRB, SE; and TIA are reported in Table 14. The remaining acute health event disutilities for AF (acute ICH and acute MI; Table 14) are obtained by subtracting "Stable AF" from the utility of the event. For example, the disutility for myocardial infarction would be

$$0.683 - 0.779 = -0.096$$

These disutilities are capped above at 0. When uncertainty estimates were reported, we assumed mean utilities would be Normally distributed, as indicated by the central limit theorem. When uncertainty estimates and sample sizes were not available (acute ischaemic stroke, TIA, SE), we assumed mean utilities to follow a Uniform distribution ranging from 50-150% of the reported mean. The duration of the decrements for DVT and PE was assumed to be six months[93] and three months for intracranial haemorrhage, before moving to the post-ICH health state[54]. Duration of decrements was generally not reported for the AF disutilities so they were assumed to last 1 cycle.

In both the AF and VTE model, to account for quality of life decreasing with age, all utility decrements were multiplied by the ratio of the utility for a given age range relative to a reference age (65-75), based on general population utilities estimated in Kind et al[95]
(Table 17). Utilities were also adjusted by sex in this way for the VTE models, whereas for the AF models all utilities were weighted averages across sex.

4.8.6 Utilities of VTE, AF and anticoagulant related chronic health states

In the AF model, where patients can have more than one chronic health condition, utilities for chronic health states are assumed to be multiplicative. For example, the utility of a patient who has experienced both an ischaemic stroke and a myocardial infarction will be the product of the two utility scores (Table 14),

$$0.690 \times 0.718 = 0.495$$

Utilities are multiplied by 0.25 to get a QALY for 3 month cycle.

For the VTE-related chronic health states, we used estimates from Lenert[96], who elicited preferences in 30 volunteers and 30 medicine physicians of mild/moderate PTS and severe PTS, and Meads[97] who used the Cambridge pulmonary hypertension outcome review (CAMPHOR) utility index[98] to estimate a utility value for CTPH from 308 patients (Table 14).

Table 14 Utilities

Health State	Utility score	Distribution*	Source
Reference group health state			
Stable AF quality of life (for AF model)	0.779 (SD=0.253, n=3045, SE=0.0045)	Normal(0.779, 0.0045)	Berg 2010 [99]
No VTE quality of life (for VTE model)	0.96 (SD=0.046)	Beta(16.52, 0.69)	Locadia[94]
Acute health events**			
TIA and SE disutility	-0.131	Uniform(-0.197, -0.066)	Robinson 2001 [100]
Acute Ischaemic stroke disutility	-0.59	Uniform(-0.885, -0.295)	Robinson 2001 [100]
DVT (1st and subsequent)	0.84 (SD=0.087)	Beta(14.17,2.70)	Locadia[94]
PE (1st and subsequent)	0.63 (SD=0.128)	Beta(8.40,4.93)	Locadia[94]
Acute ICH disutility	Median 0.60 (95% CI 0.02-1.00) (n=60)	Normal(0.60, 0.064) – AF well	Lenert 1997 [96]
Other CRB disutility	-0.03 (SE=0.001531)	Normal(-0.03, 0.001531)	Robinson 2001 [100]
Acute MI disutility	0.683 (SD=0.233, n=222, SE=0.0156)	Normal(0.683, 0.0156) – AF well	Lacey 2003 [101] *****
Chronic health states			
Post Ischaemic stroke quality of life	0.69 (SD=0.18, n=77, SE=0.0205)	Normal(0.69, 0.0205)	Haacke 2006 [102]***
Mild/moderate PTS	-0.02*****	Beta(97.98,4801.02)	Lenert 1997[96]
Severe PTS	-0.07*****	Beta(92.93,1234.64)	Lenert 1997[96]
CTPH	0.57 (SD 0.31)	Beta(1.20,0.94)	Meads 2008 [97]
Post ICH quality of life	0.74 (SD=0.39, n=5, SE=0.1744)	Beta(3.941, 1.385)	Haacke 2006 [102]****
Post Myocardial Infarction quality of life	0.718 (SD=0.243, n=222, SE=0.0163)	Normal(0.718, 0.0163)	Lacey 2003 [101]*****

* Capped above at 1 for quality of life and 0 for disutility
** Disutilities assumed to last for 3 months.
*** Table 2 in source article, weighted average EQ-5D score for ischaemic stroke
*** Table 3 in source article, EQ-5D for haemorrhagic stroke.
***** Table 3, year mean EQ-5D score
*****utility decrement with an assumed SE of 10% of the mean

Table 15 Transient event utility values for primary prevention, acute treatment and secondary prevention models

Transient event	Utility/Decrement	Duration of decrement	Source
DVT (1st and subsequent)	0.84 (0.64 to 0.98)	Six months	Locadia[94]
PE (1st and subsequent)	0.63 (0.36 to 0.86)	Six months	Locadia[94]
ICH	0.60 (0.02 to >0.99)	Three months	Lenert[96]
Other CR bleed	0.03 (SE 0.001531)*	Absolute decrement	Robinson[100]

*Decrement

Table 16 Health state utility values for primary prevention, acute treatment and secondary prevention models

Health state	Utility/Decrement	Source
Reference - No VTE	0.96 (0.82 to 1.00)	Locadia[94]
Mild/moderate PTS	0.02 (SD 0.04)*	Lenert[96]
Severe PTS	0.07 (SD 0.07)*	Lenert[96]
CTPH	0.57 (SD 0.31)	Meads[97]
Post ICH	0.74 (SE 0.1744)	Haacke[102]
Death	0.00 (0 to 0)	Definition

*Decrement

Table 17 General population utility values (mean and SD) by age and gender. Assumed Beta distribution parameters, alpha and Beta are given by age and gender.

	Males		Female		
Age	mean (SD)	Alpha, Beta	mean (SD)	Alpha, Beta	Source
Under 25	0.94 (0.12)		0.94 (0.12)		Kind et al[95]
25-34	0.93 (0.16)		0.93 (0.15)		Kind et al[95]
35-44	0.91 (0.17)	656.7, 65.0	0.91 (0.15)	1006.6, 99.5	Kind et al[95]
45-54	0.84 (0.27)	341.4, 65.0	0.85 (0.23)	544.1, 96.0	Kind et al[95]
55-64	0.78 (0.28)	330.4, 93.2	0.81 (0.26)	526.6, 123.5	Kind et al[95]
65-74	0.78 (0.28)	388.5, 109.6	0.78 (0.25)	551.7, 155.6	Kind et al[95]
75+	0.75 (0.28)	191.2, 63.7	0.71 (0.27)	406.4, 166.0	Kind et al[95]

4.9 Summary

This chapter summarises the decision problems addressed by the cost-effectiveness models, the structure, perspective, and target population of the models, and the interventions and outcomes represented by the models. We developed the structure of the model based on existing cost-effectiveness models identified in the literature and the structure evolved based on feedback from clinical experts in order to reflect current disease knowledge and clinical practice. We used decision trees to reflect the short term nature of the VTE primary prevention and acute treatment decision problems and Markov models to address the AF-related ischaemic stroke and VTE secondary prevention decision problems where longer periods of prophylaxis are required.

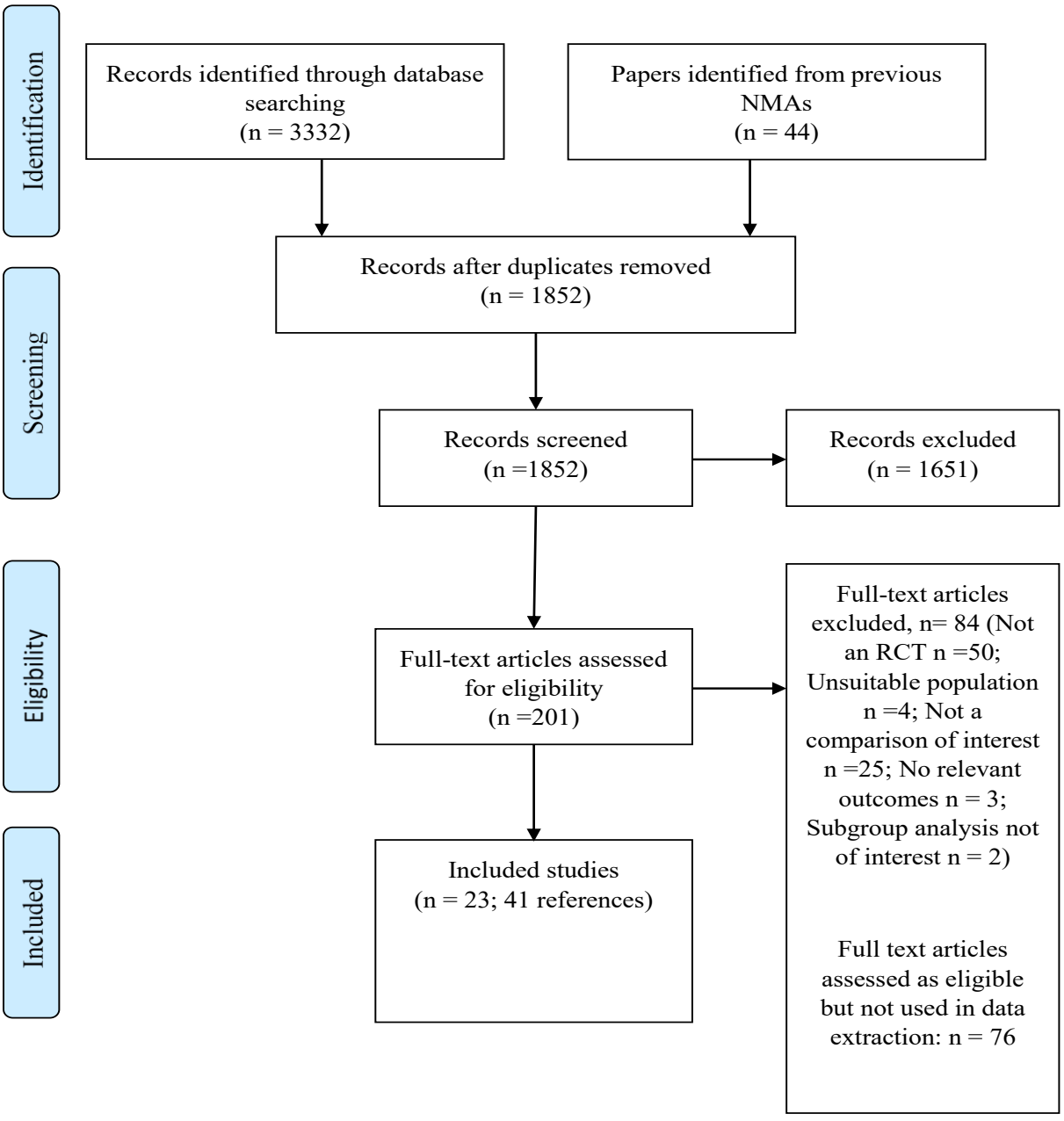
This chapter also summarises the cost and utility model inputs shared by the AF and VTE models. Model inputs on the relative treatment efficacy and safety of anticoagulants were derived from the results of meta-analyses of RCTs identified in our systematic review. We summarise these efficacy and safety model inputs in chapters 6 and 11 which also present the results of the cost-effectiveness models for AF and VTE.

5. Clinical results (1): Stroke prevention in atrial fibrillation

5.1 Included studies

A total of 1,852 unique records were identified from various data sources for the review of stroke prevention in AF (see Figure 8).

Figure 8 PRISMA flow chart for review of stroke prevention in AF



Twenty three completed eligible randomised controlled trials were identified for inclusion in the review, with a total of 41 associated references for these trials[103-143]. No ongoing trials were identified. A summary of the characteristics of the 23 trials is presented in Table 18. Twenty of the trials were multicentre, two trials were each conducted in two centres, and one trial was conducted in one centre. The majority of the multicentre trials were conducted across several countries in North and South America, Europe, Russia, Israel, Asia, Australia, and South Africa. The two-centre trials were conducted in one country; one in China and the other in Denmark. The single centre trial was conducted in Denmark. Sixteen of the trials were phase III studies and seven were phase II studies. The number of patients randomised across the 23 trials ranged from 75 to 21,105 patients, with a total of 94,656 patients of which 97% (91,333) were from the phase III studies. Thirteen studies; six phase III and seven phase II studies examined a NOAC. Four studies examined edoxaban, three each examined apixaban and dabigatran, two examined rivaroxaban and one study examined betrixaban.

Eligibility criteria for patient participation were similar across studies, all patients having non-valvular AF, whether new or existing, and including paroxysmal, persistent or permanent types. Diagnosis of AF was predominantly by electrocardiography. In a few cases, Holter recording, pacemaker or other intracardiac recording were used. The mean age of included patients was reported in only 61% of the studies and this ranged from 63.3 to 81.5 years. The percentage of male patients was reported in 78% of the studies, and this varied significantly across the studies, ranging from 44.9% to 82.9%. Mean body mass index was not often reported and ranged from 24.4 to 30.5. Percentage of patients with previous stroke, hypertension and chronic heart failure varied significantly across the studies, ranging from 5% to 63.8%, 38% to 93.7%, and 0% to 100% respectively. Bleeding risk among patients was assessed predominantly with the $CHADS_2$ scoring system.

Warfarin was examined in all but two of the 23 included studies; against a NOAC in 12 studies and against aspirin in nine studies. Standard intensity warfarin (INR 2-3) was examined by all the studies, although in a few studies the warfarin arm was a mixture of low intensity (INR <2) and standard intensity, in unknown proportions. Across all studies, mean time in therapeutic range for warfarin ranged from 45.1% to

83% of the treatment duration in the studies. One study[106] compared both low (INR <2) and standard intensity (INR 2.5-3.5) dicoumarol with aspirin, but the mean time in therapeutic range was not reported for the standard intensity dicoumarol arm. The doses of NOACs we examined were edoxaban 30mg, 45mg, and 60mg once daily and 30mg and 60mg twice daily, apixaban 2.5mg and 5mg twice daily, dabigatran 50mg, 110mg, 150mg and 300mg twice daily, rivaroxaban 15mg and 20mg once daily, and betrixaban 40mg, 60mg and 80mg once daily. Examined aspirin dosages ranged from 75mg to 325mg once daily.

Treatment duration in the edoxaban and dabigatran studies was predominantly three months, although one study reported mean treatment durations of 24 months and another reported a median treatment duration of 29.8 months. Mean treatment duration for apixaban studies ranged from 13.1 to 21.6 months and one study reported three months treatment duration. The two studies on rivaroxaban reported 30 months treatment duration and a mean treatment duration of 19.4 months respectively. Mean treatment duration 4.9 months was reported in the betrixaban study. Treatment duration was similar for each comparator in almost all the NOAC studies. Reported efficacy and safety outcome types were similar across studies and these were reported at the end of the treatment periods. All 23 studies reported data on stroke, 15 studies reported data on myocardial infarction, 18 studies reported data on major bleeding, 12 studies reported data on clinically relevant bleeding, and 18 studies reported data on all-cause mortality. Fifteen of the 23 studies, including all the NOAC studies, were sponsored by pharmaceutical companies. Six studies were funded by grants from medical research bodies although two of these grants contained contributions from a pharmaceutical company. Sponsor detail was not reported in two studies. In most of the pharmaceutical company sponsored studies, the sponsor(s) had influence on the study design, data management and analysis.

Table 18 Characteristics of 23 included randomised trials in stroke prevention in AF

Study (Centre type) [Countries]	Study type Sponsor (sponsor's role)	Age eligibility (Mean age) [% Male]	AF type	No. rand.	Interventions compared	Tmt duration (months)	Mean time in therapeutic range (INR)	Outcomes	Time of outcome assessment (months)
ACTIVE W[108] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Sanofi -Aventis and Bristol-Myers Squibb (The sponsor contributed to the study design "but had no role in data collection, data analysis, data Interpretation, or writing of the report")	≥18 yrs. (70.2 yrs.) [66.1%]	Non-valvular ECG diagnosed	6706	**Antiplatelet** 1. Clopidogrel 75mg + (aspirin 75-100mg) od **Warfarin** 2. INR 2-3 (some patients may have received other vitamin K antagonists in use in their country)	Not given	63.8%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, MI Safety-All bleeding, major bleeding, minor bleeding, fatal bleeding, death (all causes)	15.4
AFASAK[103] (Two centres) [Denmark]	Phase III NycoMed AS, Oslo, Norway; Henrik Henriksen's Foundation; Kathrine and Vigo Skovgaard's Foundation; and Danish Medical Research Foundation (Not stated)	≥18 yrs. (74.2 yrs.) [53.6%]	Chronic non-valvular ECG diagnosed	1007	**Warfarin** 1. INR 2-3 **Antiplatelet (aspirin)** 2. 75mg od 3. Placebo od	24	73%	Efficacy-All stroke, fatal stroke, minor ischemic stroke, TIA Safety-Bleeding, death (all causes)	24

AFASAK II[105] (Single centre) [Denmark]	Phase III The Danish Heart Foundation, Copenhagen; Nycomed DAK A/S Roskilde, Denmark; Du Pont Pharma, Wilmington, Del; The Danish Foundation for Medical Research for the Region of Copenhagen; and many other non-industry funders (Not stated)	≥18 yrs. (74.2 yrs.) [60%]	Chronic non-valvular ECG diagnosed	677	**Warfarin** 1. 1.25mg/day fixed dose 2. 1.25mg/day fixed dose plus aspirin 300mg/day od 3. INR 2-3 **Aspirin** 4. 300mg od	42	73%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, fatal stroke, stroke or systemic embolism, TIA, MI Safety-Major bleeding, minor bleeding, intracranial bleeding, death (all causes)	42
AF-ASA-VKA-CHINA[143] (Two centres) [China]	Phase III Grant from talent pool subject of Shanghai Shi Dong Hospital (Not applicable)	≥80 yrs. (NR) [NR]	Persistent & Permanent non-valvular Confirmed by the case history & ECG	110	**Warfarin** 1. INR 1.6-2.5 **Antiplatelet (aspirin)** 2. 100mg od	24	NR	Efficacy-Stroke or systemic embolism, ischemic stroke, MI Safety-All bleeding, major bleeding, minor bleeding, fatal bleeding, death (all causes)	1, 6, 12, 18, and 24

AF-DABIG-VKA-JAPAN[118] (Multicentre) [Japan]	Phase II Boehringer Ingelheim (The sponsor was involved in the trial)	≥20 yrs. (NR) [NR]	Paroxysmal, persistent or permanent non-valvular ECG diagnosed	174	**Dabigatran** 1. 110mg bd 2. 150mg bd **Warfarin** 3. INR 2-3 (INR ≥1.6 to ≤2.6 in ≥70 yrs.)	3	NR	Efficacy-Stroke or systemic embolism Safety-All bleeding, major bleeding, composite clinically relevant bleeding	3
AF-EDOX-VKA-ASIA[123] (Multicentre) [Taiwan, South Korea, Hong Kong & Singapore]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (The sponsor had influence on the study design, data management & analysis, and key decisions)	18-80 yrs. (65.1 yrs.) [65.4%]	Non-valvular ECG diagnosed $CHADS_2 \geq 1$	235	**Edoxaban** 1. 30mg od 2. 60mg od **Warfarin** 3. INR 2-3	3 (Edoxaban) 6 (Warfarin)	45.1%	Efficacy-Stroke or systemic embolism Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding	3
AF-EDOX-VKA-JAPAN[126] (Multicentre) [Japan]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (The funder "had input on the study design and data analysis & interpretation of results and wrote the clinical study report")	≥20 yrs. (NR) [NR]	Non-valvular ECG diagnosed $CHADS_2 \geq 1$	536	**Edoxaban** 1. 30mg od 2. 45mg od 3. 60mg od **Warfarin** 4. INR 2-3 (INR 1.6-2.6 in ≥70 yrs.)	3	83% (≥70 yrs.) 73% (<70 yrs.)	Efficacy-Stroke or systemic embolism Safety-All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	3

AF-EDOX-VKA-MULTI[116] (Multicentre) [North America, Chile, Europe & Russia]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (Not clear)	18-85 yrs. (65.1 yrs.) [62.1%]	Persistent non-valvular ECG diagnosed $CHADS_2$ ≤2	1146	**Edoxaban** 1. 30mg od 2. 60mg od 3. 30mg bd 4. 60mg bd **Warfarin** 5. INR 2-3	3	49.7%	Efficacy-Stroke or systemic embolism, MI, hospital admission Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major Bleed, composite clinically relevant bleeding, death (cardiovascular)	3
AF-VKA-ASA-CHINA[130] (Multicentre) [China]	Phase III 10th National Five-year Project of China (Not applicable)	50-80 yrs. (NR) [NR]	Non-valvular Diagnosis based on medical history, ECG and/or Holter recordings	690	**Warfarin** 1. INR 2.1-2.5 2. INR 1.6-2 **Antiplatelet (aspirin)** 3. 200mg od	24 (mean 15)	NR	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, TIA Safety-Major bleeding, minor bleeding, death (all causes)	24

ARISTOTLE[115,122,127,132-135,138,140-142] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Bristol-Myers Squibb and Pfizer (The trial was designed in conjunction with the sponsors & "The primary analyses were performed both at Bristol-Myers Squibb and at the Duke Clinical Research Institute")	≥18 yrs. (Median 70 yrs.) [64.7%]	Non-valvular or flutter ECG diagnosed	18201	**Apixaban** 1. 5mg bd (2.5mg bd in participants with more than one of: ≥80years, ≤60kg body weight, serum creatinine level of 1.5mg per decilitre or more **Warfarin** 2. INR 2-3	21.6 (median)	62.2%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, stroke or systemic embolism, MI Safety-All bleeding, major bleeding, composite clinically relevant bleeding, intracranial bleeding, death (all causes)	21.6 (median for Intracranial bleeding)
ARISTOTLE-J[121] (Multicentre) [Japan]	Phase II Pfizer Inc. and Bristol-Myers Squibb (Not clear)	≥20 yrs. (70.3 yrs.) [82.9%]	Non-valvular Diagnosis based on ECG, Holter recording or intracardiac electrogram	222	**Apixaban** 1. 2.5mg bd 2. 5mg bd **Warfarin** 3. INR 2-3 (INR 2-2.6 in ≥70 yrs.)	3	60%	Efficacy-Stroke or systemic embolism, ischaemic stroke, TIA Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	3

AVERROES[113,124,125,129] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Bristol-Myers Squibb and Pfizer (The sponsor was involved in the design, data collection and analysis)	≥50 yrs. (70 yrs.) [58.5%]	Non-valvular ECG diagnosed	5599	**Apixaban** 1. 5mg bd (2.5mg if >80 yrs./≤60 kg/renal status) **Antiplatelet (aspirin)** 2. 81-324mg od	13.1 (mean)		Efficacy-All stroke, stroke or systemic embolism, ischaemic stroke, haemorrhagic stroke, MI Safety-Major bleeding, minor bleeding, clinically relevant non-major bleeding, intracranial bleeding, fatal bleeding, death (cardiovascular), death (all causes)	13.1 (mean)
BAFTA[111] (Multicentre) [UK]	Phase III The Medical Research Council UK and supported by MidReC and the Primary Care Research trust (The sponsor had no direct role in study design, in data collection, analysis or interpretation, in writing the report, or in the decision to submit for publication)	≥75 yrs. (81.5 yrs.) [54.6%]	Non-valvular or atrial flutter ECG diagnosed	973	**Antiplatelet (aspirin)** 1. 75mg od **Warfarin** 2. INR 2-3	32.4 (mean)	67%	Efficacy-All stroke, MI Safety-Major bleeding, death (all causes)	32.4 (mean)

Chinese ATAFS[107] (Multicentre) [China]	Phase III Not disclosed	40-80 yrs. (63.3 yrs.) [59.7%]	Non-valvular	704	**Antiplatelet (aspirin)** 1. 150-160mg od **Warfarin** 2. INR 2-3 (INR 1.6-2.5 in >75 yrs.)	Not reported	NR	Efficacy-All stroke Safety-Death (all causes)	2-24 (median=19)
ENGAGE AF-TIMI 48[119,139] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Daiichi Sankyo Pharma Development (Not clear)	≥21 yrs. (NR) [61.9%]	Non-valvular ECG diagnosed $CHADS_2$ ≥2	21105	**Edoxaban** 1. 30mg od 2. 60mg od (half dose if creatinine clearance is 30-50ml/min, ≤60kg body weight, or concomitant use of verapamil or quinidine or dronedarone) **Warfarin** 3. INR 2-3	29.8 (median)	64.9%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, fatal stroke, stroke or systemic embolism, MI Safety-Major bleeding, minor bleeding, fatal bleeding, intracranial bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (cardiovascular), death (all causes)	29.8 (median)

EXPLORE-Xa[136] (Multicentre) [USA, Canada & Germany]	Phase II Portola Pharmaceuticals, South San Francisco, CA, USA (Not stated)	≥18 yrs. (73 yrs.) [66.5%]	New or existing non-valvular or atrial flutter Diagnosed by Holter, ECG, rhythm strip, pacemaker, or other intracardiac recording	508	**Betrixaban** 1. 40mg od 2. 60mg od 3. 80mg od **Warfarin** 4. INR 2-3	4.9 (mean)	 63.4%	Efficacy-All stroke Safety-All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	4.9 (mean)
J-ROCKET AF[128] (Multicentre) [Japan]	Phase III Bayer Yakuhin Ltd (The funder was "responsible for trial design and study data collection")	≥20 yrs. (71.1 yrs.) [80.6%]	Non-valvular ECG diagnosed	1280	**Rivaroxaban** 1. 15mg od (10mg od if creatinine clearance 30-49ml/min) **Warfarin** 2. INR 2-3 (INR 1.6-2.6 in ≥70 yrs.)	30	 65%	Efficacy-All stroke, ischemic stroke, haemorrhagic stroke, stroke or systemic embolism, MI Safety-Composite clinically relevant bleeding, death (cardiovascular), death (all causes)	30

PATAF[106] (Multicentre) [Netherlands]	Phase III Prevention fund (grant 002817010), Zorg Onder-zoek Nederland; Roche Nicholas BV, Bladel, Holland, donated aspirin (Not stated)	≥60 yrs. (74.8 yrs.) [44.9%]	Chronic or intermittent ECG diagnosed	729	**Warfarin** 1. INR <2 2. INR 2.5-3.5 (some patients received other coumarins – phenprocoumon or acenocoumarol) **Antiplatelet (aspirin)** 3. 150mg od	32.4 (mean)	NR	Efficacy-All stroke, ischaemic stroke, arterial event Safety-Death (cardiovascular), death (all causes)	32.4 (mean)
PETRO[110] (Multicentre) [USA, Denmark, Netherlands & Sweden]	Phase II Boehringer Ingelheim Pharmaceuticals, Biberach, Germany (The funder was responsible for the statistical analysis conducted according to a prospectively designed plan approved by the steering committee)	≥18 yrs. (69.5 yrs.) [81.9%]	Permanent, persistent, & paroxysmal non-valvular with coronary artery disease Diagnosis not explained	502*	**Dabigatran** 1. 50mg bd 2. 50mg + (aspirin 81mg) bd 3. 50mg + (aspirin 325mg) bd 4. 150mg bd 5. 150mg + (aspirin 81mg) bd 6. 150mg + (aspirin 325mg) bd 7. 300mg bd 8. 300mg + (aspirin 81mg) bd 9. 300mg + (aspirin 325mg) bd **Warfarin** 10. INR 2-3	3	57.2%	Efficacy-Stroke or Systemic embolism Safety-All bleeding, major bleeding, composite clinically relevant bleeding	3

RE-LY[112,117] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Phase III Boehringer Ingelheim (The sponsor contributed in the design, conduct, and reporting of the study)	≥18 yrs. (71 yrs.) [63.6%]	Non-valvular ECG diagnosed Mean $CHADS_2$ 2.1	18113	**Dabigatran** 1. 110mg bd 2. 150mg bd **Warfarin** 3. INR 2-3	24 (mean)	64%	Efficacy-Stroke or systemic embolism, ischaemic stroke, haemorrhagic stroke, MI, PE, Hospital admission Safety-Major bleeding, minor bleeding, intracranial bleeding, extra-cranial minor bleeding, death (cardiovascular), death (all causes)	24 (mean)
ROCKET AF[114,120,131,137] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, New Zealand, Asia, South Africa]	Phase III Johnson & Johnson and Bayer (The sponsor was not involved in the coordination of the trial, data management and analyses)	≥18 yrs. (Median 73 yrs.) [60.3%]	Non-valvular ECG diagnosed $CHADS_2$ ≥2	14264	**Rivaroxaban** 1. 20mg od (15mg in patients with creatinine clearance 30-49ml/min) **Warfarin** 2. INR 2-3	19.4 (median)	55%	Efficacy-All stroke, stroke or systemic embolism, MI Safety-Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, intracranial bleeding, death (all causes)	19.4 (median)

SPAF II[104] (Multicentre) [USA]	Phase III The Division of Stroke and Trauma, National Institute of Neurological Disorders and Stroke (Not clear)	Not clear (NR) [NR]	Non-valvular	1100	**Warfarin** 1. INR 2-4.5 in <75 yrs. 2. INR 2.0-4.5 in >75 yrs. **Antiplatelet (aspirin)** 3. 325mg (in <75 yrs.) od 4. 325mg (in >75 yrs.) od	37.2 (mean for age <75 years) 24 (mean for age >75 years)	NR	Efficacy-Stroke or systemic embolism, ischaemic stroke, MI, TIA Safety-Intracranial bleeding, death (all causes)	27.6 (mean)
WASPO[109] (Multicentre) [UK]	Phase III Not declared	>80 & <90 yrs. (Median 83 yrs.) [47%]	Permanent non-valvular ECG diagnosed	75	**Warfarin** 1. INR 2-3 **Antiplatelet (aspirin)** 2. 300mg od	12	69.2%	Efficacy-All stroke, TIA Safety-Death (all causes)	12

AF = atrial fibrillation; NVAF = non-valvular atrial fibrillation; MI = myocardial infarction; TIA = transient ischaemic attack; PE = pulmonary embolism; INR = international normalized ratio; ECG = electrocardiogram; rand = randomised; od = once daily; bd = twice daily; Tmt = treatment; NR = not reported.

*Our results are based on 515 patients as reported in the results tables; the trial report is inconsistent in this regard.

5.2 Time in therapeutic range for warfarin interventions

Table 19 shows the comparator interventions, target INR and (where reported) mean time in therapeutic range for the 22 studies that included a warfarin intervention arm. Sixteen (73%) of these studies reported mean time in therapeutic range, which varied substantially (from 45.1% to 83%) between studies.

Table 19 Mean time in therapeutic range for warfarin in stroke prevention in AF

Study	Interventions that were compared with warfarin	Warfarin INR	Mean time in therapeutic range (INR)
ACTIVE W[108]	Antiplatelet (Clopidogrel 75mg + (aspirin 75-100mg) od	2-3 (some patients may have received other vitamin K antagonists)	63.8%
AFASAK[103]	Aspirin 75mg od Placebo od	2-3	73%
AFASAK II[105]	Aspirin 300mg od	2-3	73%
AF-ASA-VKA-CHINA[143]	Aspirin 100mg od	1.6-2.5	NR
AF-DABIG-VKA-JAPAN[118]	Dabigatran110mg, 150mg bd	2-3 (≥1.6 to ≤2.6 in ≥70 yrs)	NR
AF-EDOX-VKA-ASIA[123]	Edoxaban 30mg, 60mg od	2-3	45.1%
AF-EDOX-VKA-JAPAN[126]	Edoxaban 30mg, 45mg, 60mg od	2-3 (1.6-2.6 in ≥70 yrs.)	83% (≥70 yrs.) 73% (<70 yrs.)
AF-EDOX-VKA-MULTI[116]	Edoxaban 30mg, 60mg od, 30mg, 60mg bd	2-3	49.7%
AF-VKA-ASA-CHINA[130]	Aspirin 200mg od	2.1-2.5	NR
ARISTOTLE[115,122,127,132-135,138,140-142]	Apixaban 5mg bd	2-3	62.2%
ARISTOTLE-J[121]	Apixaban 2.5mg, 5mg bd	2-3 (2-2.6 in ≥70 yrs.)	60%
BAFTA[111]	Aspirin 75mg od	2-3	67%
Chinese ATAFS[107]	Aspirin 150-160mg od	2-3 (1.6-2.5 in >75 yrs.)	NR
ENGAGE AF-TIMI 48[119,139]	Edoxaban 30mg, 60mg od	2-3	64.9%
EXPLORE-Xa[136]	Betrixaban 40mg, 60mg, 80mg od	2-3	63.4%
J-ROCKET AF[128]	Rivaroxaban 15mg od	2-3 (1.6-2.6 in ≥70 yrs.)	65%
PATAF[106]	Aspirin150mg od	2.5-3.5 (some patients received other coumarins – phenprocoumon or acenocoumarol)	NR

Study	Interventions that were compared with warfarin	Warfarin INR	Mean time in therapeutic range (INR)
PETRO[110]	Dabigatran 50mg, 50mg + (asp. 81mg), 50mg + (asp. 325mg),150mg, 150mg + (asp. 81mg), 150mg + (asp. 325mg), 300mg,300mg + (asp. 81mg), 300mg + (asp. 325mg) bd	2-3	57.2%
RE-LY[112,117]	Dabigatran 110mg, 150mg bd	2-3	64%
ROCKET AF[114,120,131,137]	Rivaroxaban 20mg od	2-3	55%
SPAF II[104]	Aspirin 325mg (in <75 yrs.), 325mg (in >75 yrs.) od	2-4.5 in <75 yrs. 2-4.5 in >75 yrs.	NR
WASPO[109]	Aspirin 300mg od	2-3	69.2%

AF = atrial fibrillation; INR = international normalized ratio; NR = not reported, od = once daily; bd = twice daily, asp = aspirin

5.3 Risk of bias in included studies

Detailed risk of bias assessments for each included study for each domain of the Cochrane assessment tool are provided in Table 20. The assessments ranged from low to high risk of bias, but it was difficult to judge some studies due to inaccessibility of study protocols. For most of the outcomes assessed in the studies, all randomised patients were either accounted for in the analysis, or in some cases a small number of patients were unaccounted for with reasons judged likely to be unrelated to the outcome. The majority of the studies were judged to be at low risk of bias for allocation concealment and incomplete outcome data. The majority of the studies were judged to be at a low or unclear risk of bias for sequence generation. Randomisation sequence across the low risk studies was predominantly computerised. Most studies were also judged to be of low risk of bias for blinding of outcome assessment, with three studies judged to be at high risk of bias in this domain. Fourteen studies were judged to be at high risk of bias for blinding of participants and personnel, mainly because they were open label. Where studies were blinded for different dose groups of a novel anticoagulant, but not in the comparison of these to warfarin, we assigned a high risk of bias because the principal contribution of the study to our analyses would be the comparison of warfarin with the licensed dose of the anticoagulant. Risk of bias judgments for studies contributing to analyses of each outcome are presented graphically in the sections that follow.

Table 20 Risk of bias assessment for 23 included randomised trials in stroke prevention in AF

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting
ACTIVE W[108]	L – "Patients were randomised by an automated central interactive voice response system, in a 1:1 ratio, to receive clopidogrel plus aspirin or oral anticoagulation therapy"	L – By means of a central, interactive, voice response system.	H – Treatment was open, with blinded adjudication of outcomes.	L – "All major outcomes were adjudicated by a blinded committee and all strokes were adjudicated by neurologists"	L – All patients were included in the analyses	U – Study protocol not found
AFASAK[103]	L – "The patients were randomised to receive warfarin, aspirin 75 mg once daily, or placebo. They received consecutive numbers, which corresponded to numbered packages containing the study medication, the order of which was determined by computer generated randomisation"	L – "They received consecutive numbers, which corresponded to numbered packages containing the study medication, the order of which was determined by computer generated randomisation"	H – "Warfarin was given openly, but the aspirin and placebo arms were double blind. The warfarin tablets looked different from the aspirin and placebo tablets, which were Indistinguishable."	U – No information on blinding of outcome assessors	L – All patients were included in the analyses	U – Study protocol not found

AFASAK II[105]	L – "According to a computer-generated sequence, eligible participants were assigned to daily treatment"	U – No information on whether and how treatment allocation was concealed	H – This was an open-label study	L – "All endpoints were evaluated by an end-point committee unaware of treatment status. The committee consisted of two neurologists and two cardiologists"	L – All patients were included in the analyses	U – Study protocol not found
AF-ASA-VKA-CHINA[143]	U – "A total of 110 patients met the inclusion criteria and were randomly divided into warfarin study and aspirin control groups".	H – No information and no indication of treatment allocation concealment	H – No details, but monitoring of INR implies the study was open label	H – No information, and no indication of blinding of outcomes assessors	L – Small numbers of missing data in the two randomised arms and the number missing in each arm seem to be balanced; also with comparable reasons for the missing data. It is unlikely that missing data is related to the outcome	U – Study protocol not found
AF-DABIG-VKA-JAPAN[118]	U – Available information is from a preliminary report and not a published article. Therefore, no information to enable judgment	U – Available information is from a preliminary report and not a published article. Therefore, no information to enable judgment	U – Available information is from a preliminary report and not a published article. Therefore, no information to enable judgment	U – Available information is from a preliminary report and not a published article. Therefore, no information to enable judgment	U – Available information is from a preliminary report and not a published article. Therefore, no information to enable judgment	U – Available information is from a preliminary report and not a published article. Therefore, no information to enable judgment

AF-EDOX-VKA-ASIA[123]	L – "Via Fisher Automated Clinical Trials System (FACTS)"	L – "Block randomisation was done by FACTS; Cenduit produced the randomisation schedule, which was kept confidential until the end of the study".	H – "The investigator, patients and sponsor were blinded to the dose of edoxaban, but not to the identity of edoxaban and warfarin"	L – "The independent CEC, which was blinded to study treatments, adjudicated all bleeding events and thromboembolic events (stroke, systemic embolic event, MI) during the study"	L – Only one person with missing outcome data	L – All outcomes are reported as per study protocol
AF-EDOX-VKA-JAPAN[126]	L – "Treatment was assigned using the biased coin method"	U – "Patients were randomized using the specifications of dynamic allocation procedures"	H – "This was a multicentre, randomized, dose-ranging study of edoxaban (double-blind to dose) and open-label warfarin"	U – "Secondary endpoints consisted of thromboembolic events including stroke assessed by an independent Event Assessment Committee"	L – Some missing data with reasons although the number of missing data is quite minimal and unlikely related to the outcome	L – All outcomes are reported as per study protocol
AF-EDOX-VKA-MULTI[116]	L – "The randomisation schedule was generated by an independent biostatistician who was not part of the study team. Using a central, interactive, automated telephone system"	L – "Using a central, interactive, automated telephone system, eligible patients who provided written informed consent were randomly allocated"	H – "The study was double-blind with respect to edoxaban dose, but open-label for randomisation between edoxaban and warfarin"	U – For efficacy outcomes: "Stroke confirmed by CT or autopsy; TIA confirmed by a neurologist" L – For safety outcomes: "Suspected bleeding events were assessed by an independent blinded adjudication committee"	L – Very minimal missing data in three arms (I patient); otherwise, all patients are accounted for in the analysis	L – All outcomes are reported as per protocol

AF-VKA-ASA-CHINA[130]	L – "Stratified block randomization"	U – Not enough information – "After giving a signed informed consent, patients who met the inclusion criteria were enrolled and randomly allocated to one of three study groups according to a stratified block randomization"	U – "In the warfarin groups, an initial dose of 1–3 mg/d of warfarin was prescribed after the baseline INR values were measured". "In the aspirin group, a fixed dose of 200 mg/d of aspirin was used".	U – Not clearly described "Medical records from all potential events were further reviewed by a 5-physician clinical outcomes committee"	U – A total of 96 patients withdrew from the study after randomisation but the remaining 690 patients were all included in the analysis	U – Study protocol not found
ARISTOTLE[11,5,122,127,132-135,138,140-142]	L – "Randomization was stratified according to whether patients had received warfarin previously and according to clinical site"	U – "An algorithm was provided to manage temporary discontinuations of the study drug around the time of interventional procedures while maintaining concealment of the group assignments"	L – "An algorithm was provided to manage temporary discontinuations of the study drug around the time of interventional procedures while maintaining concealment of the group assignments"	L – "The primary and secondary efficacy and safety outcomes were adjudicated on the basis of prespecified criteria by a clinical-events committee whose members were not aware of study-group assignments"	L – For efficacy outcomes: No missing outcome data U – For bleeding outcomes: Some missing outcome data with reason which appear to be similar in the groups. However, it is not clear whether the reasons for the missing outcome data is related to the outcome	L – All outcome are reported as per protocol

ARISTOTLE-J[121]	U – "Patients were randomized in a 1:1:1. The randomization assignment method (Pocock et al) incorporated trial site and warfarin status (experienced or naïve) as factors"	U – Not enough information. "On the first day of study drug dosing (week 0), patients were randomized in a 1:1:1 fashion"	H – "This was a randomized, partially blinded study comparing high double-blinded doses of apixaban with open-label warfarin"	L – "An independent blinded endpoint committee adjudicated all reported bleeding and efficacy events"	L – Few outcome missing data with reasons. Reasons almost balance out across groups and it is unlikely that the reasons are related to the outcome	L – All outcomes are reported as per protocol
AVERROES[11,3,124,125,129]	L – "Randomization was performed with the use of a twenty four hour central, computerized, automated voice-response system"	L – "Randomization was performed with the use of a twenty four hour central, computerized, automated voice-response system"	L – "In keeping with the double-dummy design, patients who were assigned to receive apixaban also received an aspirin placebo, and those assigned to receive aspirin also received an apixaban placebo"	L – "All outcomes were adjudicated by a committee whose members were unaware of the treatment assignments. Cases of stroke and intracranial hemorrhage were adjudicated by neurologists"	L – All participants included in the analyses	L – All outcomes are reported as per protocol
BAFTA[111]	L – "Within each stratum, randomly permuted blocks of eight were generated to produce allocation tables"	L – "Primary care physicians telephoned for the treatment allocation when they had an eligible patient"	H – "BAFTA was a prospective randomised open-label trial"	L – "Clinical details on possible primary events were sent to two independent neurologists who were blind to treatment allocation"	L – All patients were included in the analyses	L – All outcomes are reported as per protocol

Chinese ATAFS[107]	U – "The randomized study of efficacy and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin".	U – No information on whether and how treatment allocation was concealed	U – No information on whether participants and personnel were blinded to treatment	U – No information on blinding of outcome assessors	L – All patients were included in the analyses	U – Study protocol not found
ENGAGE AF-TIMI 48[119,139]	L – "Randomization was performed with the use of a central, twenty four hour, interactive, computerized response system"	L – "Randomization was performed with the use of a central, twenty four hour, interactive, computerized response system"	L – "Each patient received two sets of study drugs: either active edoxaban and a placebo matching warfarin, or a placebo matching edoxaban and active warfarin"	L – "An independent clinical end-point committee, whose members were unaware of the study assignment, adjudicated all deaths and suspected cerebrovascular events, systemic embolic events, myocardial infarctions, bleeding events, and hepatic events"	L – All patients were included in the analyses	L – All outcomes are reported as per study protocol
EXPLORE-Xa[136]	U – "Patients were randomly assigned (1:1:1:1 allocation) A dynamic randomization was used to assign and balance patients by country, concurrent aspirin use, and antecedent warfarin"	U – Not enough information. "Patients were randomly assigned (1:1:1:1 allocation)"	H – "Assignment to betrixaban or warfarin was not blinded, but the betrixaban dose was double-blinded"	L – "An independent adjudicator, blinded to treatment groups, adjudicated all major bleeds, CRNM bleeds, strokes, MI, other systemic embolism, and deaths"	L – All participants were included in analyses	L – All outcomes are reported as per study protocol

J-ROCKET AF[128]	L – No details provided but assumed to follow robust design of the ROCKET-AF study	L – No details provided but assumed to follow robust design of the ROCKET-AF study	L – "As part of the double-dummy design, patients in each group also received a tablet of either titrated warfarin placebo or rivaroxaban placebo, respectively, to preserve the treatment blind"	U – "An independent clinical endpoint committee adjudicated all suspected strokes, systemic embolisms, myocardial infarctions (MIs), deaths, and bleeding events contributing to the prespecified endpoints"	L – Very few missing data. Unlikely to influence the true outcome	L – All outcomes are reported as per study protocol
PATAF[106]	L – Randomisation was computer generated	L – "Patients eligible for standard anticoagulation were ran-domly assigned (centrally, by telephone)"	U – "Patients were single blinded for the two intensities of anticoagulant"	L – "Endpoint ascertainments were blinded for treatment. Events were independently reviewed by two members of the (neurological, cardiological, vascular, ophthalmological, and internal medicine) event com-mittees (or three, in case of disagreement"	U – Some missing data and although with similar reasons across groups, the missing numbers in the groups are not balanced.	L – Study protocol not found
PETRO[110]	U – "The PETRO study was a randomized trial of patients with AF at high risk for thromboembolic events"	U – Not enough information "Randomization was stratified in the ratio 6:9:9:4 (50-, 150-,and 300-mg dabigatran, and warfarin, respectively)"	H – "The trial was double-blind with respect to dabigatran dose but open-label for concomitant aspirin treatment"	U – For efficacy outcomes: No information but the outcomes may have been blinded. L – For bleeding outcomes: "An independent adjudication committee blinded to treatment evaluated all bleeding events"	L – All patients were included in the analyses	L – All outcomes are reported as per protocol

RE-LY[112,117]	L – "After providing written informed consent, all trial participants were randomly assigned to receive one of two doses of dabigatran, or to receive warfarin, by means of a central, interactive, automated telephone system"	L – By means of a central, interactive, automated telephone system.	H – "RE-LY was a randomized trial designed to compare two fixed doses of dabigatran, each administered in a blinded manner, with open-label use of warfarin"	L – "Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments"	L – All patients were included in the analyses	L – All outcomes are reported as per protocol
ROCKET AF[114,120,131,137]	L – "Randomization was performed with the use of a central twenty four hour, computerized, automated voice-response system"	L – "Randomization was performed with the use of a central twenty four hour, computerized, automated voice-response system"	L – "Patients were randomly assigned to receive fixed dose rivaroxaban or adjusted-dose warfarin. Patients in each group also received a placebo tablet in order to maintain blinding"	U – "An independent clinical end-point committee applied protocol definitions to adjudicate all suspected cases of stroke, systemic embolism, myocardial infarction, death, and bleeding events that contributed to the prespecified end points"	L – Very few missing outcome data but with reasons which appear to balance across groups. Unlikely that the missing data is related to the true outcome	L – All outcomes are reported as per protocol

SPAF II[104]	L – Randomisation was done separately at each clinical site by computer	U – Not enough information. "The randomisation sequence could not be pre-reviewed".	H – Both patient and investigator were aware of therapy assignment	L – For neurological efficacy outcomes: "All suspected neurological events were evaluated by an on-site study neurologist and verified by an events committee; evaluation was based on review of original medical records, from which information about therapy assignment had been removed" H – For safety outcomes: No details on blinding of outcome assessment	L – All patients were included in the analyses	U – Study protocol not found
WASPO[109]	L – "Randomisation was prepared from a computer-generated random numbers program"	L – "Randomisation was performed by opening sealed envelopes in numbered sequence"	H – This was an open label study	H – No information and no indication of blinding	L – All patients were included in the analyses	U – Study protocol not found

L = low risk; H = high risk; U = unclear risk; VTE = venous thromboembolism; DVT = deep vein thrombosis, PE = pulmonary embolism; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; Note: quotations are denoted by inverted commas

5.4 Results on clinical effectiveness and safety

The twenty-seven different interventions considered in the 23 trials are listed in Table 21. Table 22 and Table 23 show the number of patients analysed and the number of outcome events for each outcome reported in each trial. We performed network meta-analyses for seven outcomes: stroke or systemic embolism, ischaemic stroke, myocardial infarction, major bleeding, clinically relevant bleeding, intracranial bleeding and all cause mortality. Arms that were considered not to provide any evidence of interest to inform health decisions in the UK were excluded from the analyses. Specifically, we excluded the warfarin arm with INR range 1.6-2 from the AF-VKA-ASA-CHINA trial, the warfarin arm with INR range below 2 from PATAF, the placebo arm from AFASAK, and the two warfarin arms with a fixed daily dose from AFASAK II.

Table 21 List of distinct interventions examined by included randomised trials in stroke prevention in AF

1 Warfarin (INR 2-3)	15 Dabigatran (110mg bd)
2 Warfarin (INR 1.6-3)	16 Dabigatran (150mg bd)
3 Warfarin (INR 3-4 od)	17 Dabigatran (300mg bd)
4 Antiplatelet (<150mg od)	18 Betrixaban (40mg od)
5 Antiplatelet (≥150mg od)	19 Betrixaban (60mg od)
6 Dabigatran (50mg bd) + Aspirin (81mg bd)	20 Betrixaban (80mg od)
7 Dabigatran (50mg bd) + Aspirin (325mg bd)	21 Edoxaban (30mg od)
8 Dabigatran (150mg bd) + Aspirin (81mg bd)	22 Edoxaban (45mg od)
9 Dabigatran (150mg bd) + Aspirin (325mg bd)	23 Edoxaban (60mg od)
10 Dabigatran (300mg bd) + Aspirin (81mg bd)	24 Edoxaban (30mg bd)
11 Dabigatran (300mg bd) + Aspirin (325mg bd)	25 Edoxaban (60mg bd)
12 Apixaban (2.5mg bd)	26 Rivaroxaban (15mg od)
13 Apixaban (5mg bd)	27 Rivaroxaban (20mg od)
14 Dabigatran (50mg bd)	

We defined two independent nodes for warfarin interventions, labelled as “warfarin (INR 2-3)” and “warfarin (INR 3-4)” respectively. The first of these formed the reference treatment across all networks in the AF review. We included in “warfarin (INR 2-3)” trials with a therapeutic INR range of 2-3 (e.g., ACTIVE W, AFASAK), as well as some interventions with an INR range of 2.5-3.5 (AF-EDOX-VKA-ASIA and PATAF) or 2.0-4.5 (SPAF II). In some trials the INR range for some of patients in the warfarin arm was subtherapeutic (below 2.0), so that the total INR range was 1.6-3.0. These interventions were excluded from the main analysis, but merged with the INR 2-3 node in a sensitivity analysis. As a consequence, there were three two-arm trials (J-

ROCKET AF, Chinese ATAFS and AF-ASA-VKA-CHINA) that were only included in sensitivity analyses.

We also defined two independent nodes for antiplatelet interventions ("aspirin" or "aspirin plus clopidogrel"), using the cut-off point of 150mg with the understanding that daily doses above that were appropriate for stroke prevention in AF, while lower doses are appropriate for secondary prevention of cardiovascular events. The dose range considered in the AVERROES trial (81-324mg od) was much wider than in any other trial, and we included this intervention in the lower dose node (<150mg od) because some patients from that study had received a low daily dose. As a sensitivity analysis, we excluded the AVERROES trial from the network. Finally, our main analysis used a binomial model, assuming equal follow-up times across arms within trials and ignoring some variations in how results were reported. We undertook a separate analysis for all outcomes taking into account the differences in duration of follow-up within and between trials and the differences in the definition of event used across trials (e.g., total number of events vs. first events only).

Results are presented as follows for each of the six outcomes. First, we provide network plots to illustrate the comparisons of interventions made in the different trials. Second, we illustrate the risk of bias assessments specific to the outcome for each trial included in the network. Third, we present results tables for each intervention compared with the reference treatment (warfarin with a target INR range of 2-3). Fourth, we present results tables for pairwise comparisons among licensed doses of the NOACs. For both sets of results tables, posterior median odds ratios and 95% credible intervals from Bayesian fixed-effect analyses are shown, although we refer to the latter as confidence intervals for convenience. In these tables we present results separately for any available direct evidence, for any indirect comparisons that can be made (excluding the direct evidence) and for the network meta-analysis (which combines the direct and the indirect evidence). Comparisons from the NMA with a ratio between interval limits exceeding nine were considered "imprecisely estimated" and are presented at the bottom of each table (note that calculation of indirect evidence was not undertaken for imprecisely estimated comparisons). A summary of results across outcomes is provided at the end, in the form of a 'rankogram', which illustrates the probability that each treatment is best, second best, and so on, for each

outcome. Last, forest plots of all contributing data, with odds ratios calculated using standard frequentist methods, are included in Appendix 2.

Table 22 Efficacy outcomes reported by 23 included randomised trials in stroke prevention in AF: number of events for each outcome in each trial

Study	Study size	TIA	All stroke	Stroke or systemic embolism	Ischemic stroke	Minor ischemic stroke	Major ischemic stroke	Haemorr-hagic stroke	Fatal stroke	PE	MI	Hospital admission
ACTIVE W[108]	6706		159		132			20			59	
AF-ASA-VKA-CHINA[143]	101			18	14						5	
AF-DABIG-VKA-JAPAN[118]	166			1								
AF-EDOX-VKA-ASIA[123]	234			0								
AF-EDOX-VKA-JAPAN[126]	519			1								
AF-EDOX-VKA-MULTI[116]	1143			11							5	12
AF-VKA-ASA-CHINA[130]	440	13	10		9			1				
AFASAK[103]	671	2	20			1			4			
AFASAK II[105]	339	3	19	22	8			2	2		8	
ARISTOTLE[115,122,127,132-135,138,140-142]	18140		449	477	337			118			192	
ARISTOTLE-J[121]	218	1		3	1						0	
AVERROES[113,124,125,129]	5599		154	164	128			15			52	
BAFTA[111]	973		94								30	
Chinese ATAFS[107]	704		23									
ENGAGE AF-TIMI 48[119,139]	21026		958	1016	804			169	239		443	
EXPLORE-Xa[136]	508		2		2						0	
J-ROCKET AF[128]	1278		31	33	24			7			4	
PATAF[106]	272		7		7	2	5				5	
PETRO[110]	515			2								
RE-LY[112,117]	18113			519	389			71		43	270	7199
ROCKET AF[114,120,131,137]	14236		405	575	310						227	
SPAF II[104]	1100	25		67	63						34	
WASPO[109]	75	1	0									

Table 23 Safety outcomes reported by 23 included randomised trials in stroke prevention in AF: number of events for each outcome in each trial

Study	Study size	All bleeding	Minor bleeding	Major bleeding	Fatal bleeding	Extra-cranial bleeding	Intracranial bleeding	Arterial event	Clinically non-relevant bleeding	Clinically relevant bleeding	Cardiovascular deaths	All-cause mortality
ACTIVE W[108]	6706	1199	1049	194	18							317
AF-ASA-VKA-CHINA[143]	101	14	9	3	2							4
AF-DABIG-VKA-JAPAN[118]	166	45		3						14		
AF-EDOX-VKA-ASIA[123]	234	57	48	2					9	11		
AF-EDOX-VKA-JAPAN[126]	519	115		5					15	20		
AF-EDOX-VKA-MULTI[116]	1143	114	52	13					49	62	8	
AF-VKA-ASA-CHINA[130]	440		25	8								11
AFASAK[103]	671	23										15
AFASAK II[105]	339		68	9			3					31
ARISTOTLE[115,122,127,132-135,138,140-142]	18140	5416		789			174			1490		1272
ARISTOTLE-J[121]	218	41	36	1					5	6		0
AVERROES[113,124,125,129]	5599		341	83	10		24		180	263	180	251
BAFTA[111]	973			50								215
Chinese ATAFS[107]	704											12
ENGAGE AF-TIMI 48[119,139]	21026		1851	1196	112		234		3579	4450	1668	2349
EXPLORE-Xa[136]	508	118	109	8					12	18		2
J-ROCKET AF[128]	1278						15			262	8	12
PATAF[106]	272							8			18	29
PETRO[110]	515	88		4						36		
RE-LY[112,117]	18113		5284	1162		956	150				880	1371
ROCKET AF[114,120,131,137]	14236			781	82		139		2336	2924		458
SPAF II[104]	1100						18					127
WASPO[109]	75		10	3								3

5.4.1 Stroke or systemic embolism

Sixteen studies reported the number of stroke or systemic embolism events, and the other seven trials reported the number of stroke events, so that the resulting network was based on data from all 23 trials, comparing a total of 26 interventions (Figure 9). There were 3217 stroke or systemic embolism events. Twenty studies were included in the main analysis, with the remaining three included only in sensitivity analyses. The thicker lines joining interventions, which mainly correspond to comparisons between licensed doses of NOACs and warfarin (INR 2-3) represent the larger (mainly phase III) trials. Similarly, the larger red circles represent the interventions to which the largest number of patients were randomised. Importantly, there were no direct comparisons between different NOACs, although there were numerous comparisons between different doses of the same NOAC in mainly Phase II trials, and some such comparisons in larger trials. Therefore comparisons between the effects of different NOACs need to be inferred from the network (indirect evidence).

Figure 9 Network plot for stroke or systemic embolism (stroke prevention in AF)

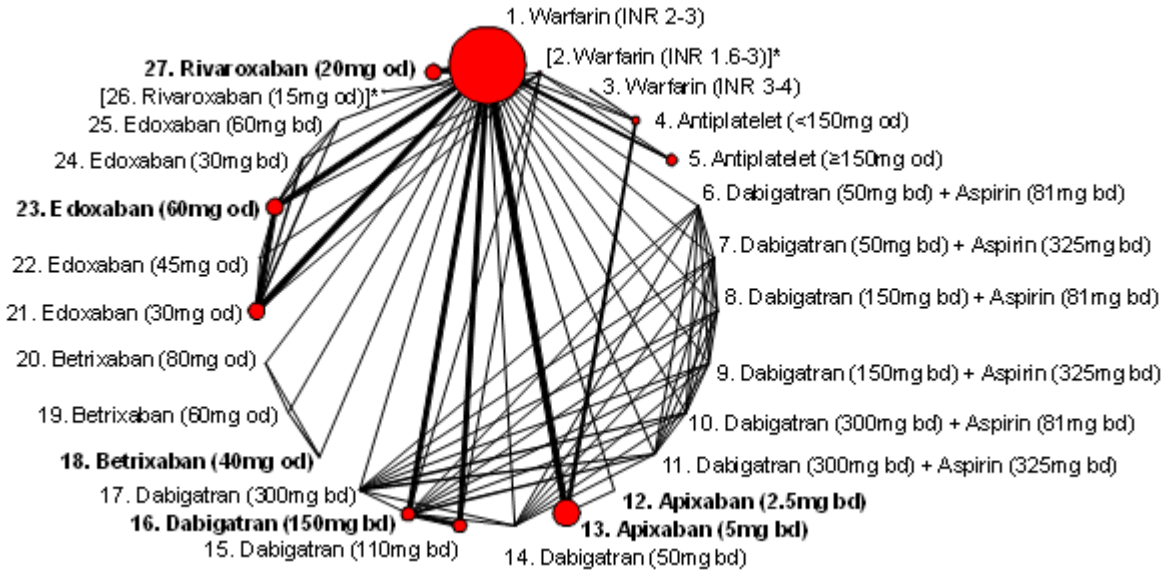


Figure 10 shows risk of bias judgments for studies reporting stroke or systemic embolism. The studies were at mixed risks of bias: there were concerns about lack of blinding of participants for most trials, and about lack of allocation concealment and blinding of outcome assessment in some.

Figure 10 Included trials and risk of bias assessment for stroke or systemic embolism (stroke prevention in AF)

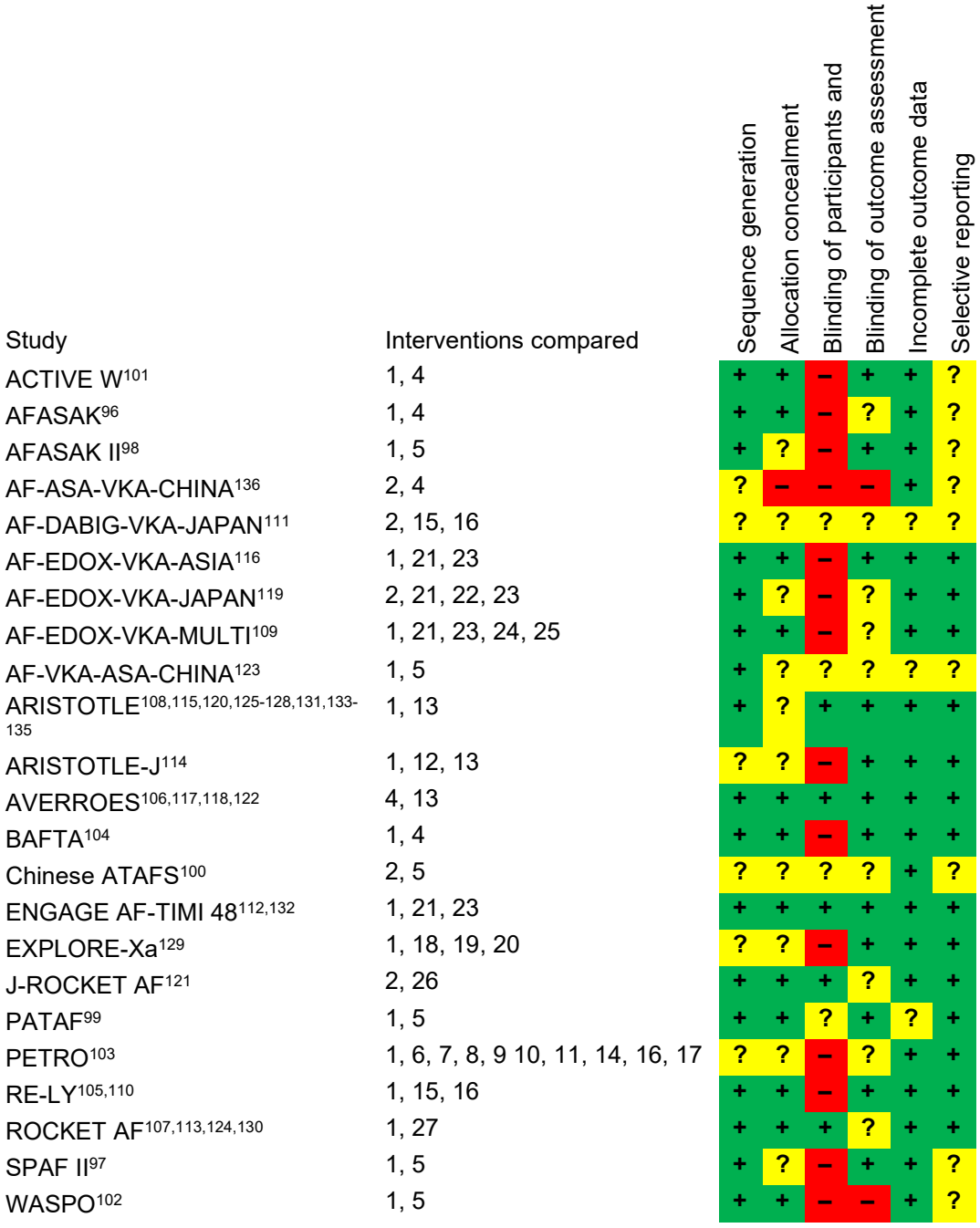


Table 24, which shows comparisons of licenced doses with warfarin (INR 2-3), suggests that both low and high dose antiplatelets increase the risk of stroke or systemic embolism compared with warfarin (INR 2-3). Among NOACs, there was some evidence that apixaban (5mg bd), dabigatran (150mg bd), edoxaban (60mg od) and rivaroxaban (20mg od) reduce the risk of stroke or systemic embolism compared with warfarin (INR 2-3). Most other comparisons were imprecisely estimated.

Comparisons among licensed doses of NOACs were almost all based on indirect evidence (Table 25). Among the comparisons that were not classified as imprecisely estimated, there was some evidence that edoxaban (60mg od) and rivaroxaban (20mg od) increase the risk of stroke or systemic embolism compared with dabigatran (150mg bd).

Table 24 Results for stroke or systemic embolism (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg od)	1.99 (1.28 , 3.15)	1.80 (1.22 , 2.65)	1.88 (1.40 , 2.51)
Antiplatelet (≥150mg od)	1.61 (1.25 , 2.07)	-	1.61 (1.25 , 2.07)
Apixaban (5mg bd)	0.79 (0.66 , 0.94)	-	0.79 (0.66 , 0.94)
Dabigatran (110mg bd)	0.90 (0.74 , 1.10)	-	0.90 (0.74 , 1.10)
Dabigatran (150mg bd)	0.65 (0.52 , 0.81)	-	0.65 (0.52 , 0.81)
Edoxaban (30mg od)	1.13 (0.97 , 1.32)	-	1.13 (0.97 , 1.32)
Edoxaban (60mg od)	0.86 (0.74 , 1.01)	-	0.86 (0.74 , 1.01)
Rivaroxaban (20mg od)	0.88 (0.74 , 1.03)	-	0.88 (0.74 , 1.03)
Imprecisely estimated comparisons			
Warfarin (INR 3-4)	-	*0.58 (0.17 , 1.62)*	*0.58 (0.17 , 1.62)*
Dabigatran (50mg bd) + Aspirin (81mg bd)	*11.4 (0.63 , 402)*	-	*11.4 (0.63 , 402)*
Dabigatran (50mg bd) + Aspirin (325mg bd)	*1.62 (0 , 94.3)*	-	*1.62 (0 , 94.3)*
Dabigatran (150mg bd) + Aspirin (81mg bd)	*1.23 (0 , 75.3)*	-	*1.23 (0 , 75.3)*
Dabigatran (150mg bd) + Aspirin (325mg bd)	*1.35 (0 , 81.1)*	-	*1.35 (0 , 81.1)*
Dabigatran (300mg bd) + Aspirin (81mg bd)	*1.32 (0 , 77.1)*	-	*1.32 (0 , 77.1)*
Dabigatran (300mg bd) + Aspirin (325mg bd)	*1.50 (0 , 89.1)*	-	*1.50 (0 , 89.1)*
Apixaban (2.5mg bd)	*0.11 (0 , 1.69)*	-	*0.11 (0 , 1.69)*
Dabigatran (50mg bd)	*3.90 (0.21 , 137)*	-	*3.90 (0.21 , 137)*
Dabigatran (300mg bd)	*0.42 (0 , 24)*	-	*0.42 (0 , 24)*
Betrixaban (40mg od)	*1.01 (0 , 977)*	-	*1.01 (0 , 977)*
Betrixaban (60mg od)	*5.14 (0.17 , 3780)*	-	*5.14 (0.17 , 3780)*
Betrixaban (80mg od)	*5.18 (0.17 , 3920)*	-	*5.18 (0.17 , 3920)*
Edoxaban (45mg od)	*3.36 (0.18 , 121)*	-	*3.36 (0.18 , 121)*
Edoxaban (30mg bd)	*1.39 (0.27 , 5.61)*	-	*1.39 (0.27 , 5.61)*
Edoxaban (60mg bd)	*1.19 (0.15 , 5.56)*	-	*1.19 (0.15 , 5.56)*

Table 25 Results for stroke or systemic embolism (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	0.82 (0.62 , 1.08)	0.82 (0.62 , 1.08)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.09 (0.87 , 1.39)	1.09 (0.87 , 1.39)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	1.11 (0.87 , 1.41)	1.11 (0.87 , 1.41)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	-	1.33 (1.02 , 1.75)	1.33 (1.02 , 1.75)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	1.35 (1.03 , 1.78)	1.35 (1.03 , 1.78)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	1.01 (0.80 , 1.27)	1.01 (0.80 , 1.27)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*7.01 (0.50 ,3450)*	-	*7.01 (0.47 , 3450)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*5.77 (0.38 , 2850)*	*5.77 (0.38 , 2850)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	-	*12.1 (0.01 , 70300)*	*12.1 (0.01 , 70300)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	-	*7.67 (0.51 , 3730)*	*7.67 (0.51 , 3730)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*7.78 (0.52 , 3820)*	*7.78 (0.52 , 3820)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	-	*1.28 (0 , 1210)*	*1.28 (0 , 1210)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	-	*1.56 (0 , 1490)*	*1.56 (0 , 1490)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	-	*0.85 (0 , 566)*	*0.85 (0 , 566)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	-	*0.86 (0 , 575)*	*0.86 (0 , 575)*

Results from a supplementary analysis taking into account the differences in duration of follow-up within and between trials and the differences in the definition of event used across trials (e.g., total number of events versus first events only) are presented in Table 26 and Table 27. They are very similar to those for odds ratios.

Table 26 Results for stroke or systemic embolism (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Warfarin (INR 3-4)	0.58 (0.18 , 1.58)
Antiplatelet (<150mg od)	1.82 (1.39 , 2.41)
Antiplatelet (≥150mg od)	1.58 (1.23 , 2.02)
Apixaban (5mg bd)	0.79 (0.67 , 0.94)
Dabigatran (110mg bd)	0.91 (0.75 , 1.11)
Dabigatran (150mg bd)	0.66 (0.53 , 0.82)
Edoxaban (30mg od)	1.13 (0.98 , 1.31)
Edoxaban (60mg od)	0.87 (0.74 , 1.01)
Rivaroxaban (20mg od)	0.88 (0.75 , 1.03)
Imprecisely estimated comparisons	
Dabigatran (50mg bd) + Aspirin (81mg bd)	*11.0 (0.66 , 366)*
Dabigatran (50mg bd) + Aspirin (325mg bd)	*1.73 (0 , 94.9)*
Dabigatran (150mg bd) + Aspirin (81mg bd)	*1.33 (0 , 63.4)*
Dabigatran (150mg bd) + Aspirin (325mg bd)	*1.41 (0 , 72.6)*
Dabigatran (300mg bd) + Aspirin (81mg bd)	*1.33 (0 , 75.9)*
Dabigatran (300mg bd) + Aspirin (325mg bd)	*1.48 (0 , 86.3)*
Apixaban (2.5mg bd)	*0.11 (0 , 1.66)*
Dabigatran (50mg bd)	*3.96 (0.18 , 121)*
Dabigatran (300mg bd)	*0.44 (0 , 23.9)*
Betrixaban (40mg od)	*0.82 (0 , 313)*
Betrixaban (60mg od)	*4.98 (0.17 , 1420)*
Betrixaban (80mg od)	*4.87 (0.16 , 1340)*
Edoxaban (45mg od)	*3.54 (0.19 , 159)*
Edoxaban (30mg bd)	*1.40 (0.28 , 5.57)*
Edoxaban (60mg bd)	*1.20 (0.15 , 5.39)*

Table 27 Results for stroke or systemic embolism (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

Licensed NOACs only	HR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	0.83 (0.63 , 1.10)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.10 (0.87 , 1.38)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	1.11 (0.88 , 1.40)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	1.32 (1.01 , 1.73)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	1.34 (1.02 , 1.76)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	1.01 (0.81 , 1.27)
Imprecisely estimated comparisons	
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*7.39 (0.48 , 1990)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*6.16 (0.38 , 1650)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	*10.1 (0 , 22900)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	*8.11 (0.51 , 2190)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*8.29 (0.53 , 2230)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	*1.05 (0 , 401)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*1.26 (0 , 466)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	*1.05 (0 , 2320)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*1.07 (0 , 2270)*

As a *post-hoc* sensitivity analysis, we fitted a fixed-effect meta-regression model using the mean time in therapeutic range for warfarin patients (see Table 19) as a covariate and the mean log odds ratio from each pairwise comparison (with warfarin as the reference category) as the response variable. There was little evidence of effect modification due to mean time in therapeutic range (estimated coefficient 0.0021 with 95% CI −0.07 to 0.08 per 1% increase). The model fit indices were very similar with and without the covariate.

5.4.2 Ischaemic stroke

Fourteen studies reported on 2228 ischaemic stroke events, leading to a connected network comparing a total of 15 interventions (Figure 11). Twelve studies were included in the main analysis, with the remaining two included only in sensitivity analyses. The studies were at mixed risks of bias (Figure 12). There were concerns about lack of blinding of participants for most trials, and about lack of allocation concealment and blinding of outcome assessment in one trial (AF-ASA-VKA-CHINA, only included in sensitivity analyses due to implementation of warfarin within non-standard INR range).

Figure 11 Network plot for ischaemic stroke (stroke prevention in AF)

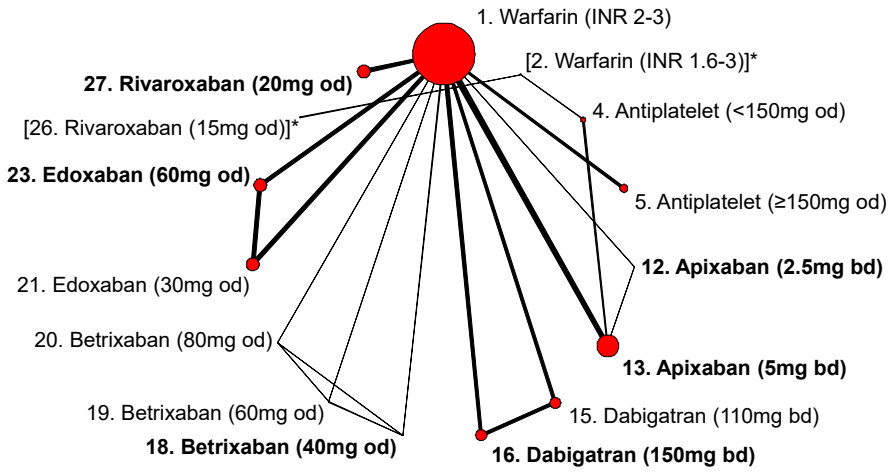


Figure 12 Included trials and risk of bias assessment for ischaemic stroke (stroke prevention in AF)

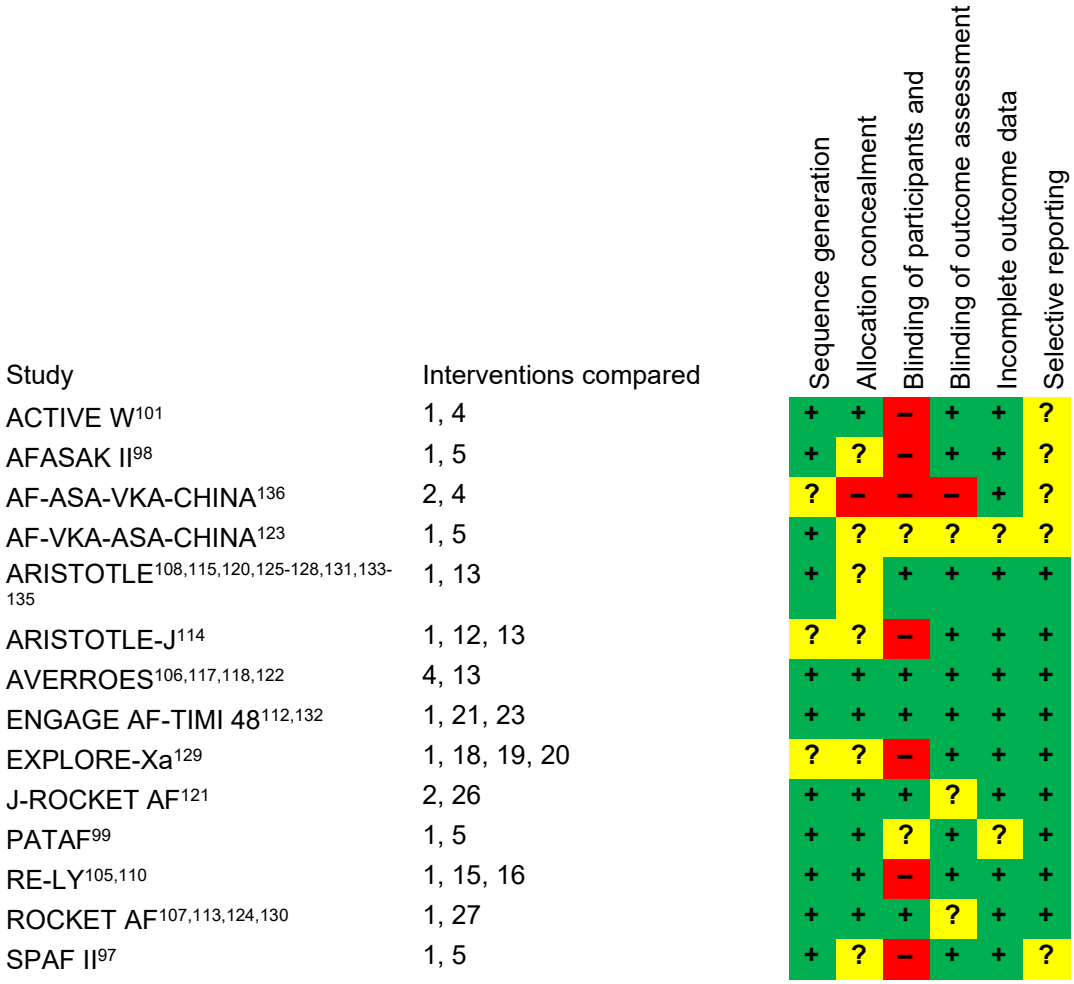


Table 28, which shows comparisons of all interventions with warfarin (INR 2-3), suggests that both low and high dose of antiplatelets increase the risk of ischaemic stroke compared with warfarin (INR 2-3). Among NOACs, there was some evidence that dabigatran (150mg bd) reduces the risk of ischaemic stroke compared with warfarin, whereas edoxaban (30mg od) increases that risk. There was little evidence that the risk of ischaemic stroke differed between licensed doses of NOACs (Table 29).

Table 28 Results for ischaemic stroke (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg od)	-	2.52 (1.62 , 3.99)	2.52 (1.62 , 3.99)
Antiplatelet (≥150mg od)	2.00 (1.51 , 2.67)	-	2.00 (1.51 , 2.67)
Apixaban (5mg bd)	0.92 (0.74 , 1.14)	-	0.92 (0.74 , 1.14)
Dabigatran (110mg bd)	1.14 (0.90 , 1.44)	-	1.14 (0.90 , 1.44)
Dabigatran (150mg bd)	0.76 (0.58 , 0.98)	-	0.76 (0.58 , 0.98)
Edoxaban (30mg od)	1.44 (1.21 , 1.71)	-	1.44 (1.21 , 1.71)
Edoxaban (60mg od)	1.01 (0.84 , 1.21)	-	1.01 (0.84 , 1.21)
Rivaroxaban (20mg od)	0.93 (0.74 , 1.16)	-	0.93 (0.74 , 1.16)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	*0.26 (0 , 5.89)*	-	*0.26 (0 , 5.89)*
Betrixaban (40mg od)	*1.05 (0 , 751)*	-	*1.05 (0 , 751)*
Betrixaban (60mg od)	*5.41 (0.18 , 3290)*	-	*5.41 (0.18 , 3290)*
Betrixaban (80mg od)	*5.43 (0.17 , 3230)*	-	*5.43 (0.17 , 3230)*

Table 29 Results for ischaemic stroke (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	0.83 (0.59 , 1.16)	0.83 (0.59 , 1.16)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.10 (0.83 , 1.46)	1.10 (0.83 , 1.46)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	1.01 (0.74 , 1.38)	1.01 (0.74 , 1.38)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	-	1.33 (0.97 , 1.83)	1.33 (0.97 , 1.83)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	1.22 (0.87 , 1.73)	1.22 (0.87 , 1.73)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	0.92 (0.69 , 1.23)	0.92 (0.69 , 1.23)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*3.47 (0.16 , 1730)*	-	*3.47 (0.16 , 1730)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*2.88 (0.13 , 1430)*	*2.88 (0.13 , 1430)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	-	*5.02 (0 , 25800)*	*5.02 (0 , 25800)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	-	*3.82 (0.17 , 1920)*	*3.82 (0.17 , 1920)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*3.52 (0.16 , 1740)*	*3.52 (0.16 , 1740)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	-	*1.15 (0 , 847)*	*1.15 (0 , 847)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	-	*1.39 (0 , 1010)*	*1.39 (0 , 1010)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	-	*0.96 (0 , 633)*	*0.96 (0 , 633)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	-	*0.88 (0 , 578)*	*0.88 (0 , 578)*

In a sensitivity analysis to take into account the differences in duration of follow-up, network meta-analysis results were as presented in Table 30 and Table 31, and show very similar results.

Table 30 Results for ischaemic stroke (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Antiplatelet (<150mg od)	2.46 (1.59 , 3.92)
Antiplatelet (≥150mg od)	1.94 (1.47 , 2.59)
Apixaban (5mg bd)	0.92 (0.75 , 1.15)
Dabigatran (110mg bd)	1.12 (0.89 , 1.42)
Dabigatran (150mg bd)	0.76 (0.59 , 0.99)
Edoxaban (30mg od)	1.43 (1.22 , 1.69)
Edoxaban (60mg od)	1.01 (0.84 , 1.20)
Rivaroxaban (20mg od)	0.92 (0.74 , 1.15)
Imprecisely estimated comparisons	
Apixaban (2.5mg bd)	*0.26 (0 , 5.77)*
Betrixaban (40mg od)	*0.90 (0 , 233)*
Betrixaban (60mg od)	*4.72 (0.18 , 787)*
Betrixaban (80mg od)	*4.67 (0.18 , 838)*

Table 31 Results for ischaemic stroke (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

Licensed NOACs only	HR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	0.83 (0.59 , 1.15)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.09 (0.83 , 1.44)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	1.00 (0.73 , 1.35)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	1.32 (0.96 , 1.80)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	1.21 (0.86 , 1.70)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	0.92 (0.69 , 1.22)
Imprecisely estimated comparisons	
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*3.54 (0.16 , 1750)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*2.90 (0.13 , 1480)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	*4.05 (0 , 9940)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	*3.81 (0.18 , 1960)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*3.50 (0.16 , 1780)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	*0.96 (0 , 241)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*1.18 (0 , 307)*

Edoxaban (60mg od) vs Betrixaban (40mg od)	*1.11 (0 , 723)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*1.03 (0 , 660)*

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5.4.3 Myocardial infarction

A total of fifteen studies reported 1334 myocardial infarction events, leading to a network of sixteen interventions (Figure 13). Thirteen studies were included in the main analysis, with the other two included only in sensitivity analyses. The studies were at mixed risks of bias (Figure 14). There were concerns about lack of blinding of participants for most trials, and about lack of allocation concealment and blinding of outcome assessment in some.

Figure 13 Network plot for myocardial infarction (stroke prevention in AF)

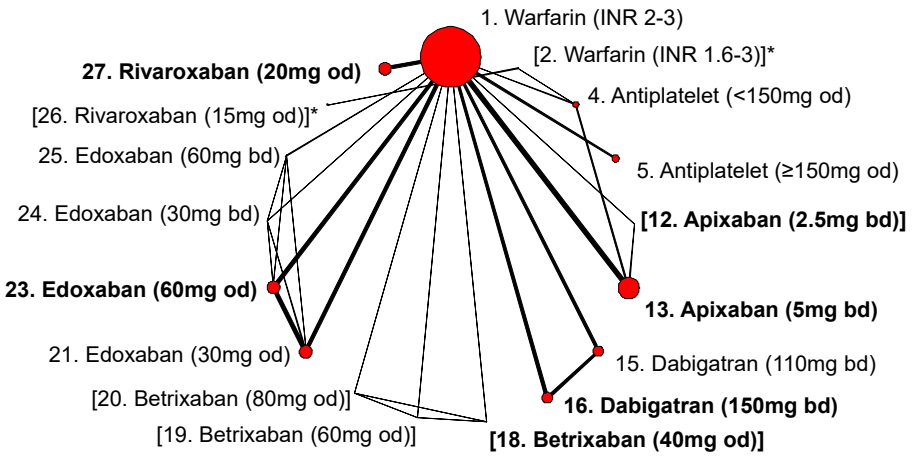


Table 32 shows weak evidence that dabigatran (110mg bd), dabigatran (150mg bd) and edoxaban (30mg od) increase the risk of MI compared with warfarin (INR 2-3), and weak evidence that rivaroxaban (20mg od) decreases risk of MI compared with warfarin (INR 2-3). none of the interventions were superior or inferior to warfarin (INR 2-3). The pairwise comparisons of licensed NOACs, presented in Table 33, show weak evidence that dabigatran (150mg bd) increases risk of MI compared with apixaban (5mg bd), and evidence that rivaroxaban (20mg od) reduces risk of MI compared with dabigatran (150mg bd). Results were similar in a sensitivity analysis taking into account the differences in duration of follow-up within and between trials and the differences in the definition of event used across trials (e.g., total number of events vs. first events only) (Table 34 and Table 35).

Figure 14 Included trials and risk of bias assessment for myocardial infarction (stroke prevention in AF)

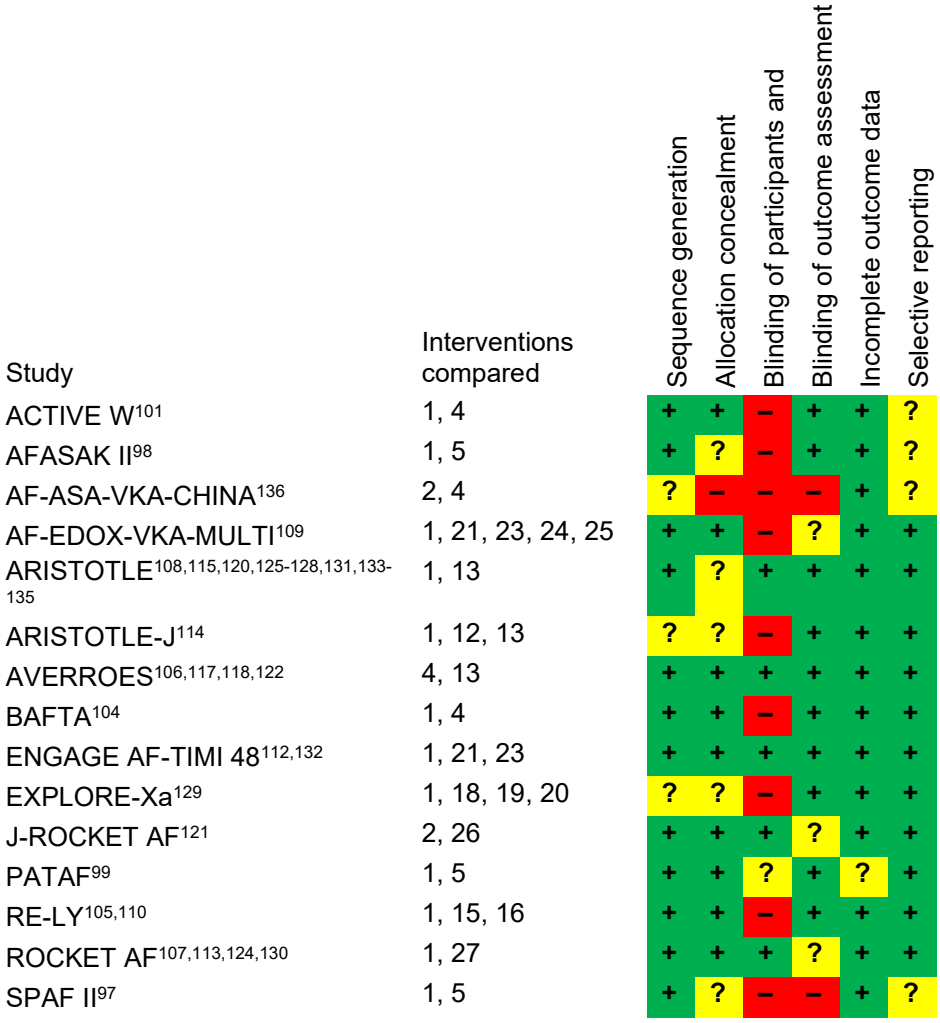


Table 32 Results for myocardial infarction (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg od)	1.00 (0.47 , 2.10)	1.02 (0.55 , 1.87)	1.01 (0.64 , 1.61)
Antiplatelet (≥150mg od)	1.38 (0.94 , 2.03)	-	1.38 (0.94 , 2.03)
Apixaban (5mg bd)	0.87 (0.66 , 1.15)	-	0.87 (0.66 , 1.15)
Dabigatran (110mg bd)	1.32 (0.97 , 1.79)	-	1.32 (0.97 , 1.79)
Dabigatran (150mg bd)	1.29 (0.96 , 1.75)	-	1.29 (0.96 , 1.75)
Edoxaban (30mg od)	1.22 (0.97 , 1.53)	-	1.22 (0.97 , 1.53)
Edoxaban (60mg od)	0.96 (0.75 , 1.22)	-	0.96 (0.75 , 1.22)
Rivaroxaban (20mg od)	0.80 (0.61 , 1.04)	-	0.80 (0.61 , 1.04)
Imprecisely estimated comparisons			
Edoxaban (30mg bd)	*0.71 (0.06 , 3.97)*	-	*0.71 (0.06 , 3.97)*
Edoxaban (60mg bd)	*0.19 (0 , 2.60)*	-	*0.19 (0 , 2.60)*

Table 33 Results for myocardial infarction (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	1.48 (0.98 , 2.22)	1.48 (0.98 , 2.22)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.10 (0.76 , 1.58)	1.10 (0.76 , 1.58)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	0.92 (0.63 , 1.34)	0.92 (0.63 , 1.34)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	-	0.74 (0.50 , 1.09)	0.74 (0.50 , 1.09)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	0.62 (0.41 , 0.93)	0.62 (0.41 , 0.93)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	0.84 (0.59 , 1.20)	0.84 (0.59 , 1.20)

Table 34 Results for myocardial infarction (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Antiplatelet (<150mg od)	1.01 (0.64 , 1.61)
Antiplatelet (≥150mg od)	1.36 (0.93 , 2.01)
Apixaban (5mg bd)	0.88 (0.67 , 1.16)
Dabigatran (110mg bd)	1.31 (0.96 , 1.77)
Dabigatran (150mg bd)	1.30 (0.96 , 1.77)
Edoxaban (30mg od)	1.22 (0.97 , 1.52)
Edoxaban (60mg od)	0.96 (0.76 , 1.22)
Rivaroxaban (20mg od)	0.80 (0.62 , 1.04)
Imprecisely estimated comparisons	
Edoxaban (30mg bd)	*0.97 (0.09 , 5.40)*
Edoxaban (60mg bd)	*0.13 (0 , 1.81)*

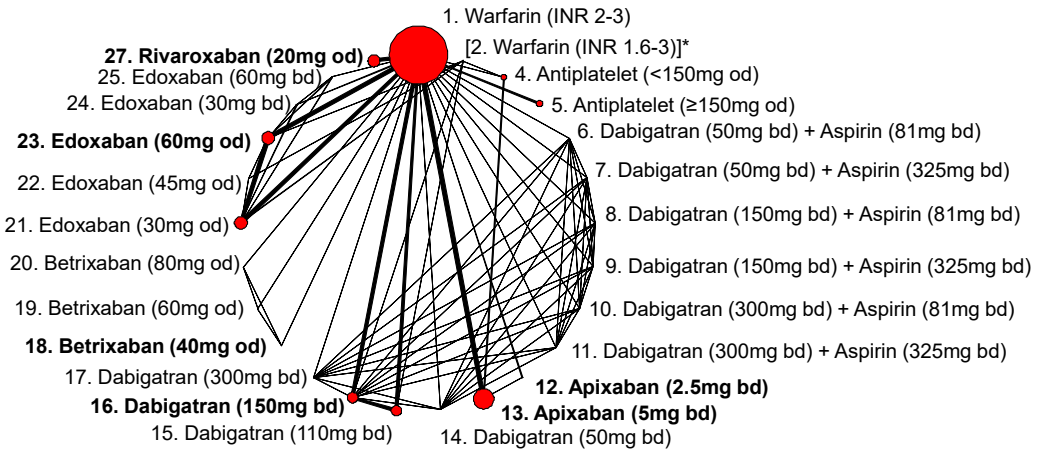
Table 35 Results for myocardial infarction (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

Licensed NOACs only	HR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	1.48 (0.98 , 2.23)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.09 (0.76 , 1.57)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	0.91 (0.62 , 1.33)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	0.74 (0.49 , 1.08)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	0.62 (0.41 , 0.92)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	0.84 (0.59 , 1.19)

5.4.4 Major bleeding

Eighteen studies reported 4314 major bleeding events, leading to a network of 24 interventions (Figure 15). Seventeen studies were included in the main analysis, with the remaining study included only in sensitivity analyses. These studies were at mixed risks of bias (Figure 16). There were concerns about lack of blinding of participants for most trials, and about lack of allocation concealment and blinding of outcome assessment in some.

Figure 15 Network plot for major bleeding (stroke prevention in AF)



There was weak evidence that that antiplatelet therapy (<150mg od) reduced major bleeding compared with warfarin (INR 2-3). There was evidence that apixaban (5mg bd), dabigatran (110mg bd), edoxaban (30mg od) and edoxaban (60mg od) reduced major bleeding risk compared with warfarin (INR 2-3) (Table 36). Comparisons among licensed doses of NOACs, presented in Table 37, suggest that dabigatran (150mg bd) increases risk of major bleeding compared with apixaban (5mg bd), while rivaroxaban (20mg od) increases risk of major bleeding compared with apixaban (5mg bd) and edoxaban (60mg od).

In a sensitivity analysis to take into account the differences in duration of follow-up, network meta-analysis results were as presented in Table 38 and Table 39, and show very similar results. Another sensitivity analysis involved fitting a fixed-effect meta-regression model using the mean time in therapeutic range for warfarin patients (see Table 19) as a covariate and the mean log odds ratio from each pairwise comparison (with warfarin as the reference category) as the response variable. We found no evidence of an effect modification according to mean time in therapeutic range (estimated coefficient 0.04 with 95% CI −0.03 to 0.12 per 1% increase). The model fit indices yielded almost identical values for the models with and without the covariate.

Figure 16 Included trials and risk of bias assessment for major bleeding (stroke prevention in AF)

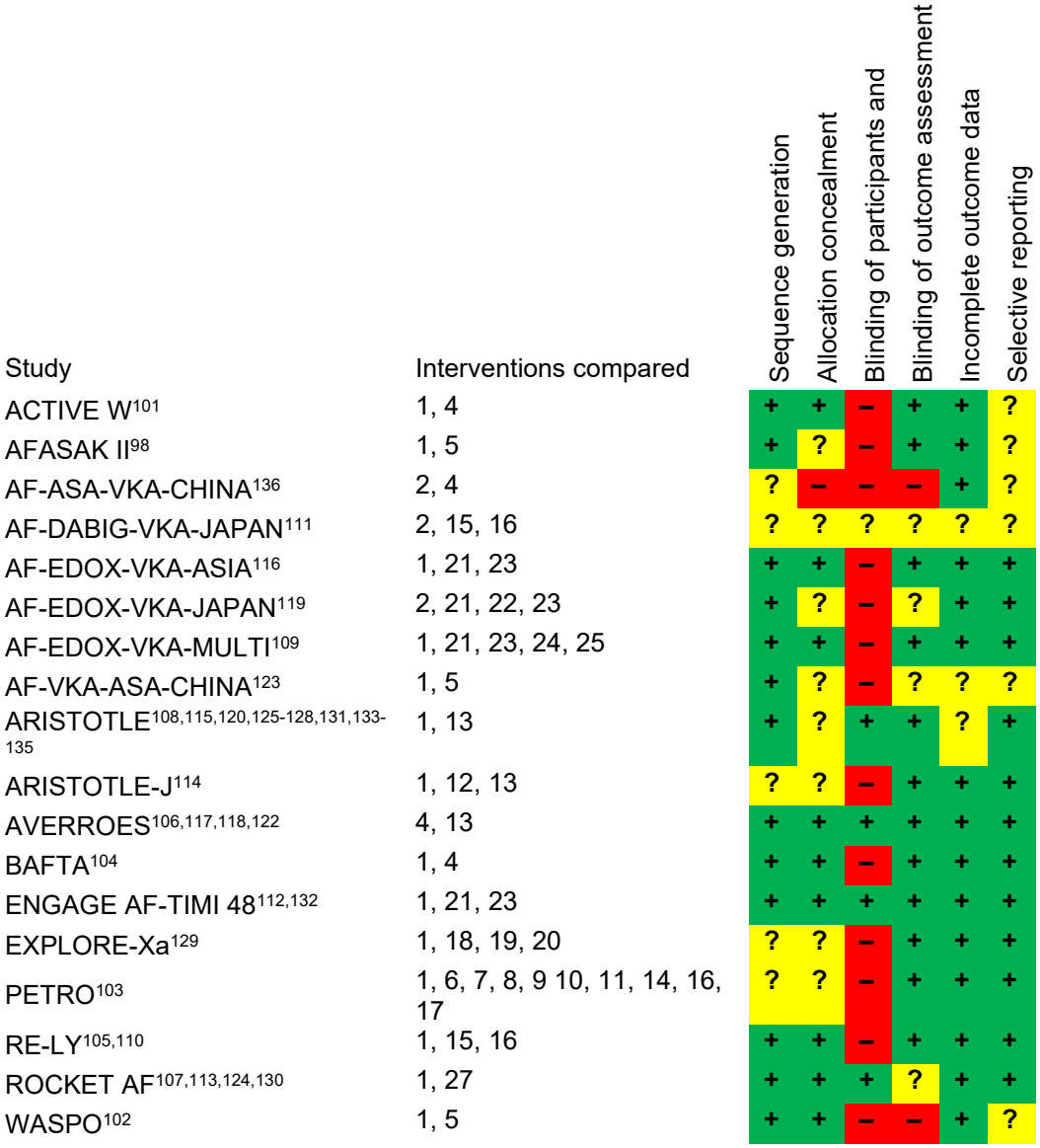


Table 36 Results for major bleeding (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg od)	1.00 (0.56 , 1.77)	0.63 (0.40 , 0.98)	0.75 (0.52 , 1.06)
Antiplatelet (≥150mg od)	1.07 (0.82 , 1.42)	-	1.07 (0.82 , 1.42)
Apixaban (5mg bd)	0.71 (0.61 , 0.81)	-	0.71 (0.61 , 0.81)
Dabigatran (110mg bd)	0.80 (0.69 , 0.93)	-	0.80 (0.69 , 0.93)
Dabigatran (150mg bd)	0.94 (0.81 , 1.08)	-	0.94 (0.81 , 1.08)
Edoxaban (30mg od)	0.46 (0.40 , 0.54)	-	0.46 (0.40 , 0.54)
Edoxaban (60mg od)	0.78 (0.69 , 0.90)	-	0.78 (0.69 , 0.90)
Rivaroxaban (20mg od)	1.03 (0.89 , 1.18)	-	1.03 (0.89 , 1.18)
Imprecisely estimated comparisons			
Dabigatran (50mg bd) + Aspirin (81mg bd)	*2.54 (0 , 146)*	-	*2.54 (0 , 146)*
Dabigatran (50mg bd) + Aspirin (325mg bd)	*1.99 (0 , 112)*	-	*1.99 (0 , 112)*
Dabigatran (150mg bd) + Aspirin (81mg bd)	*1.52 (0 , 82.0)*	-	*1.52 (0 , 82.0)*
Dabigatran (150mg bd) + Aspirin (325mg bd)	*1.63 (0 , 90.4)*	-	*1.63 (0 , 90.4)*
Dabigatran (300mg bd) + Aspirin (81mg bd)	*8.38 (0.45 , 266)*	-	*8.38 (0.45 , 266)*
Dabigatran (300mg bd) + Aspirin (325mg bd)	*27.6 (3.05 , 749)*	-	*27.6 (3.05 , 749)*
Apixaban (2.5mg bd)	*0.24 (0 , 5.48)*	-	*0.24 (0 , 5.48)*
Dabigatran (50mg bd)	*0.89 (0 , 52.4)*	-	*0.89 (0 , 52.4)*
Dabigatran (300mg bd)	*0.50 (0 , 28.6)*	-	*0.50 (0 , 28.6)*
Betrixaban (40mg od)	*0.04 (0 , 0.58)*	-	*0.04 (0 , 0.58)*
Betrixaban (60mg od)	*0.04 (0 , 0.59)*	-	*0.04 (0 , 0.59)*
Betrixaban (80mg od)	*0.60 (0.13 , 2.40)*	-	*0.60 (0.13 , 2.40)*
Edoxaban (45mg od)	*1.45 (0.27 , 8.29)*	-	*1.45 (0.27 , 8.29)*
Edoxaban (30mg bd)	*3.68 (0.94 , 16.9)*	-	*3.68 (0.94 , 16.9)*
Edoxaban (60mg bd)	*6.01 (1.64 , 27.0)*	-	*6.01 (1.64 , 27.0)*

Table 37 Results for major bleeding (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	1.33 (1.09 , 1.62)	1.33 (1.09 , 1.62)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.11 (0.92 , 1.35)	1.11 (0.92 , 1.35)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	1.45 (1.19 , 1.78)	1.45 (1.19 , 1.78)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	-	0.84 (0.69 , 1.02)	0.84 (0.69 , 1.02)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	1.10 (0.90 , 1.34)	1.10 (0.90 , 1.34)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	1.31 (1.07 , 1.59)	1.31 (1.07 , 1.59)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*2.93 (0.13 , 1320)*	*-*	*2.93 (0.13 , 1320)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*-*	*3.88 (0.17 , 1740)*	*3.88 (0.17 , 1740)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	*-*	*0.17 (0 , 124)*	*0.17 (0 , 124)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	*-*	*3.25 (0.14 , 1460)*	*3.25 (0.14 , 1460)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*-*	*4.27 (0.19 , 1910)*	*4.27 (0.19 , 1910)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	*-*	*0.06 (0 , 0.84)*	*0.06 (0 , 0.84)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*-*	*0.04 (0 , 0.63)*	*0.04 (0 , 0.63)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	*-*	*18.7 (1.34 , 9160)*	*18.7 (1.34 , 9160)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*-*	*24.5 (1.76 , 12000)*	*24.5 (1.76 , 12000)*

Table 38 Results for major bleeding (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Antiplatelet (<150mg od)	0.76 (0.53 , 1.08)
Antiplatelet (≥150mg od)	1.07 (0.82 , 1.41)
Apixaban (5mg bd)	0.72 (0.62 , 0.82)
Dabigatran (110mg bd)	0.81 (0.70 , 0.93)
Dabigatran (150mg bd)	0.94 (0.82 , 1.07)
Edoxaban (30mg od)	0.47 (0.41 , 0.55)
Edoxaban (60mg od)	0.79 (0.70 , 0.90)
Rivaroxaban (20mg od)	1.02 (0.89 , 1.18)
Imprecisely estimated comparisons	
Dabigatran (50mg bd) + Aspirin (81mg bd)	*2.58 (0 , 151)*
Dabigatran (50mg bd) + Aspirin (325mg bd)	*2.07 (0 , 114)*
Dabigatran (150mg bd) + Aspirin (81mg bd)	*1.51 (0 , 78.3)*
Dabigatran (150mg bd) + Aspirin (325mg bd)	*1.62 (0 , 94.8)*
Dabigatran (300mg bd) + Aspirin (81mg bd)	*8.36 (0.50 , 281)*
Dabigatran (300mg bd) + Aspirin (325mg bd)	*26.3 (3.08 , 697)*
Apixaban (2.5mg bd)	*0.25 (0 , 5.49)*
Dabigatran (50mg bd)	*0.93 (0 , 53.2)*
Dabigatran (300mg bd)	*0.52 (0 , 29.7)*
Betrixaban (40mg od)	*0.05 (0 , 0.55)*
Betrixaban (60mg od)	*0.04 (0 , 0.60)*
Betrixaban (80mg od)	*0.60 (0.13 , 2.38)*
Edoxaban (45mg od)	*1.49 (0.28 , 8.31)*
Edoxaban (30mg bd)	*3.64 (0.95 , 17.1)*
Edoxaban (60mg bd)	*6.00 (1.66 , 27.5)*

Table 39 Results for major bleeding (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

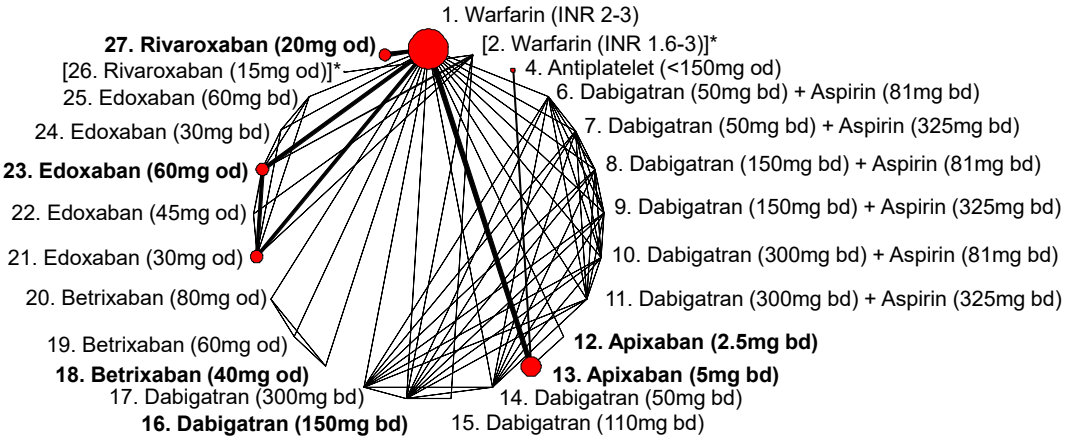
Licensed NOACs only	HR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	1.31 (1.08 , 1.59)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.10 (0.91 , 1.33)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	1.43 (1.17 , 1.75)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	0.84 (0.70 , 1.02)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	1.09 (0.90 , 1.33)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	1.30 (1.07 , 1.57)
Imprecisely estimated comparisons	
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*2.89 (0.13 , 519)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*3.80 (0.17 , 683)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	*0.18 (0 , 61.9)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	*3.19 (0.14 , 579)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*4.13 (0.19 , 751)*

Betrixaban (40mg od) vs Apixaban (5mg bd)	*0.06 (0 , 0.77)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*0.05 (0 , 0.58)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	*17.1 (1.44 , 2160)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*22.1 (1.89 , 2770)*

5.4.5 Clinically relevant bleeding

Twelve studies reported 9556 clinically relevant bleeding events, leading to a network of 23 interventions (Figure 17). Eleven studies were included in the main analyisis, with the remaining studiy included only in sensitivity analyses. These studies were at mixed risks of bias (Figure 18), the concerns being due to lack of blinding of participants for most trials.

Figure 17 Network plot for clinically relevant bleeding (stroke prevention in AF)



Results presented in Table 40 suggest that antiplatelet therapy (<150mg od) reduces clinically relevant bleeding compared with warfarin (INR 2-3). Note that the licenced dose for of antiplatelet therapy for AF is ≥150mg od: no studies provided data for that dose for clinically relevant bleeding. Among NOACs, there was evidence that apixaban (5mg bd), edoxaban (30mg od) and edoxaban (60mg od) reduce clinically relevant bleeding compared with warfarin (INR 2-3). However, edoxaban (30mg bd) and edoxaban (60mg bd) increased clinically relevant bleeding compared with warfarin (INR 2-3). Among licensed NOACs (Table 41), there was evidence that edoxaban (60mg od) and rivaroxaban (20mg od) increase clinically relevant bleeding compared with apixaban (5mg bd) and that rivaroxaban (20mg od) increased clinically relevant bleeding compared with edoxaban (60mg od).

Supplementary network meta-analyses of hazard ratios rather than odds ratios show very similar results (Table 42 and Table 43).

Figure 18 Included trials and risk of bias assessment for clinically relevant bleeding (stroke prevention in AF)

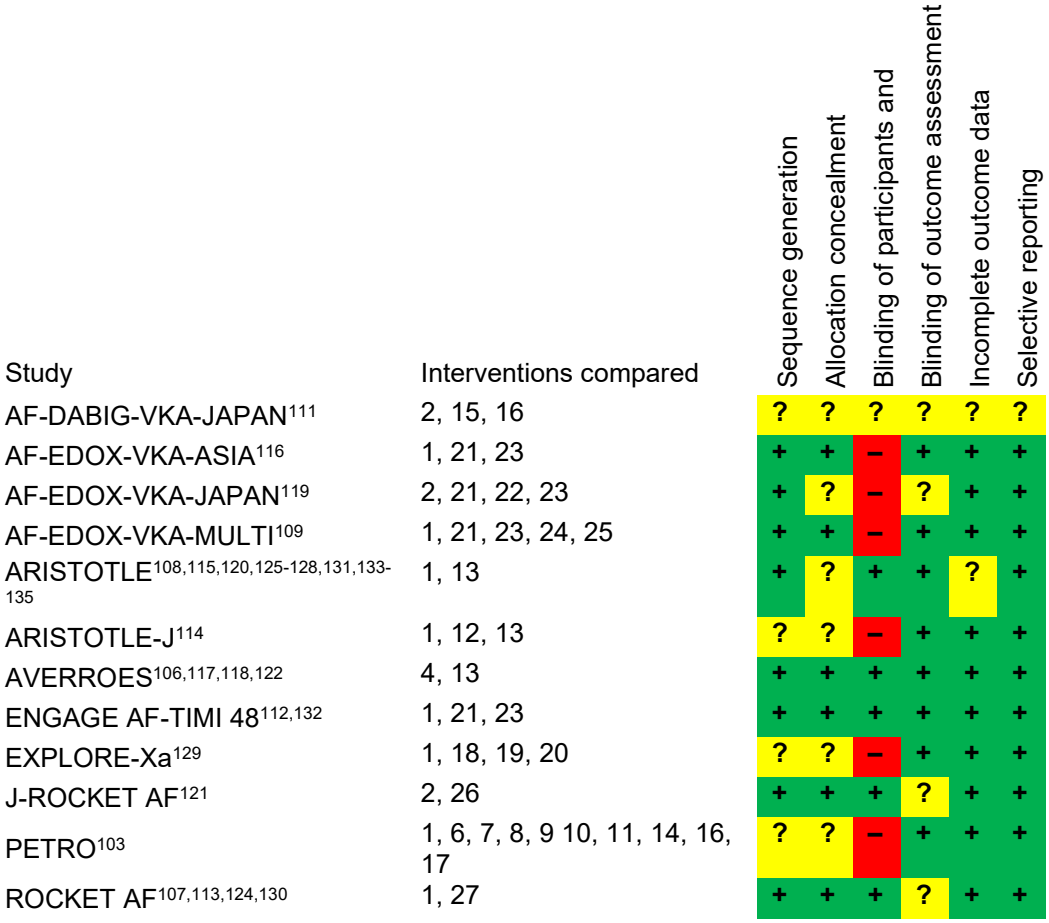


Table 40 Results for clinically relevant bleeding (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence	Indirect evidence	Network meta-analysis
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Antiplatelet (<150mg od)	-	0.59 (0.45 , 0.77)	0.59 (0.45 , 0.77)
Apixaban (5mg bd)	0.67 (0.60 , 0.75)	-	0.67 (0.60 , 0.75)
Edoxaban (30mg od)	0.59 (0.54 , 0.64)	-	0.59 (0.54 , 0.64)
Edoxaban (45mg od)	1.09 (0.37 , 3.04)	-	1.09 (0.37 , 3.04)
Edoxaban (60mg od)	0.84 (0.77 , 0.90)	-	0.84 (0.77 , 0.90)
Edoxaban (30mg bd)	1.97 (1.04 , 3.67)	-	1.97 (1.04 , 3.67)
Edoxaban (60mg bd)	2.76 (1.46 , 5.17)	-	2.76 (1.46 , 5.17)
Rivaroxaban (20mg od)	1.03 (0.95 , 1.11)	-	1.03 (0.95 , 1.11)
Imprecisely estimated comparisons			
Dabigatran (50mg bd) + Aspirin (81mg bd)	*0.91 (0.07 , 5.87)*	-	*0.91 (0.07 , 5.87)*
Dabigatran (50mg bd) + Aspirin (325mg bd)	*0.70 (0.06 , 4.50)*	-	*0.70 (0.06 , 4.50)*
Dabigatran (150mg bd) + Aspirin (81mg bd)	*0.99 (0.15 , 4.99)*	-	*0.99 (0.15 , 4.99)*
Dabigatran (150mg bd) + Aspirin (325mg bd)	*1.08 (0.17 , 5.58)*	-	*1.08 (0.17 , 5.58)*
Dabigatran (300mg bd) + Aspirin (81mg bd)	*2.76 (0.71 , 11.7)*	-	*2.76 (0.71 , 11.7)*
Dabigatran (300mg bd) + Aspirin (325mg bd)	*3.98 (1.10 , 16.3)*	-	*3.98 (1.10 , 16.3)*
Apixaban (2.5mg bd)	*0.25 (0.01 , 1.88)*	-	*0.25 (0.01 , 1.88)*
Dabigatran (50mg bd)	*0.06 (0 , 0.91)*	-	*0.06 (0 , 0.91)*
Dabigatran (110mg bd)	*0.67 (0.06 , 5.47)*	-	*0.67 (0.06 , 5.47)*
Dabigatran (150mg bd)	*1.56 (0.50 , 5.74)*	-	*1.56 (0.50 , 5.74)*
Dabigatran (300mg bd)	*0.96 (0.27 , 3.78)*	-	*0.96 (0.27 , 3.78)*
Betrixaban (40mg od)	*0.10 (0 , 0.67)*	-	*0.10 (0 , 0.67)*
Betrixaban (60mg od)	*0.69 (0.19 , 2.27)*	-	*0.69 (0.19 , 2.27)*
Betrixaban (80mg od)	*0.69 (0.19 , 2.22)*	-	*0.69 (0.19 , 2.22)*

Table 41 Results for clinically relevant bleeding (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence	Indirect evidence	Network meta-analysis
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.24 (1.09 , 1.42)	1.24 (1.09 , 1.42)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	1.53 (1.33 , 1.75)	1.53 (1.33 , 1.75)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	1.23 (1.10 , 1.37)	1.23 (1.10 , 1.37)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*2.69 (0.35 , 79.9)*	*-*	*2.69 (0.35 , 79.9)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*-*	*6.59 (0.60 , 220)*	*6.59 (0.60 , 220)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	*-*	*0.39 (0.01 , 18.7)*	*0.39 (0.01 , 18.7)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	*-*	*3.35 (0.44 , 99.4)*	*3.35 (0.44 , 99.4)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*-*	*4.12 (0.54 , 123)*	*4.12 (0.54 , 123)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	*-*	*2.32 (0.74 , 8.63)*	*2.32 (0.74 , 8.63)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	*-*	*0.15 (0 , 1.00)*	*0.15 (0 , 1.00)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*-*	*0.06 (0 , 0.60)*	*0.06 (0 , 0.60)*
Edoxaban (60mg od) vs Dabigatran (150mg bd)	*-*	*0.54 (0.14 , 1.68)*	*0.54 (0.14 , 1.68)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	*-*	*0.66 (0.18 , 2.07)*	*0.66 (0.18 , 2.07)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	*-*	*8.50 (1.25 , 251)*	*8.50 (1.25 , 251)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*-*	*10.4 (1.53 , 309)*	*10.4 (1.53 , 309)*

Table 42 Results for clinically relevant bleeding (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Antiplatelet (<150mg od)	0.59 (0.46 , 0.76)
Apixaban (5mg bd)	0.67 (0.60 , 0.75)
Edoxaban (30mg od)	0.59 (0.55 , 0.64)
Edoxaban (45mg od)	1.09 (0.37 , 3.01)
Edoxaban (60mg od)	0.83 (0.77 , 0.90)
Edoxaban (30mg bd)	1.98 (1.05 , 3.71)
Edoxaban (60mg bd)	2.78 (1.46 , 5.20)
Rivaroxaban (20mg od)	1.03 (0.95 , 1.11)
Imprecisely estimated comparisons	
Dabigatran (50mg bd) + Aspirin (81mg bd)	*0.93 (0.07 , 5.79)*
Dabigatran (50mg bd) + Aspirin (325mg bd)	*0.72 (0.06 , 4.54)*
Dabigatran (150mg bd) + Aspirin (81mg bd)	*1.01 (0.15 , 4.99)*
Dabigatran (150mg bd) + Aspirin (325mg bd)	*1.10 (0.17 , 5.53)*
Dabigatran (300mg bd) + Aspirin (81mg bd)	*2.84 (0.72 , 11.4)*
Dabigatran (300mg bd) + Aspirin (325mg bd)	*4.06 (1.10 , 16.1)*
Apixaban (2.5mg bd)	*0.25 (0.01 , 1.87)*
Dabigatran (50mg bd)	*0.06 (0 , 0.89)*
Dabigatran (110mg bd)	*0.68 (0.06 , 5.65)*
Dabigatran (150mg bd)	*1.60 (0.51 , 5.72)*
Dabigatran (300mg bd)	*0.99 (0.28 , 3.71)*
Betrixaban (40mg od)	*0.10 (0 , 0.66)*
Betrixaban (60mg od)	*0.69 (0.19 , 2.26)*
Betrixaban (80mg od)	*0.69 (0.19 , 2.30)*

Table 43 Results for clinically relevant bleeding (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

Licensed NOACs only	HR (95% CI)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.24 (1.09 , 1.42)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	1.53 (1.33 , 1.74)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	1.23 (1.10 , 1.37)
Imprecisely estimated comparisons	
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*2.67 (0.36 , 81.0)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*6.69 (0.61 , 235)*
Betrixaban (40mg od) vs Apixaban (2.5mg bd)	*0.39 (0.01 , 19.0)*
Edoxaban (60mg od) vs Apixaban (2.5mg bd)	*3.32 (0.44 , 100)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*4.08 (0.55 , 124)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	*2.38 (0.75 , 8.56)*
Betrixaban (40mg od) vs Apixaban (5mg bd)	*0.15 (0.01 , 0.99)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*0.06 (0 , 0.58)*
Edoxaban (60mg od) vs Dabigatran (150mg bd)	*0.52 (0.15 , 1.64)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	*0.64 (0.18 , 2.03)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	*8.45 (1.25 , 247)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*10.4 (1.55 , 305)*

5.4.6 Intracranial bleeding

Eight studies reported a total of 757 intracranial bleeds, leading to a network of ten interventions (Figure 19). Seven trials were included in the primary analysis, with the remaining study included only in sensitivity analyses. These studies were at mixed risks of bias (Figure 20), the concerns being due to lack of blinding of participants and, in one study, lack of blinding of outcome assessment.

Figure 19 Network plot for intracranial bleeding (stroke prevention in AF)

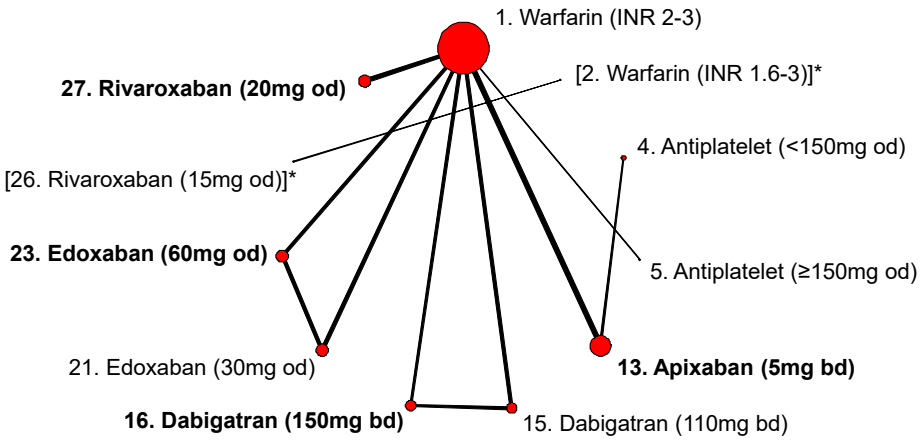
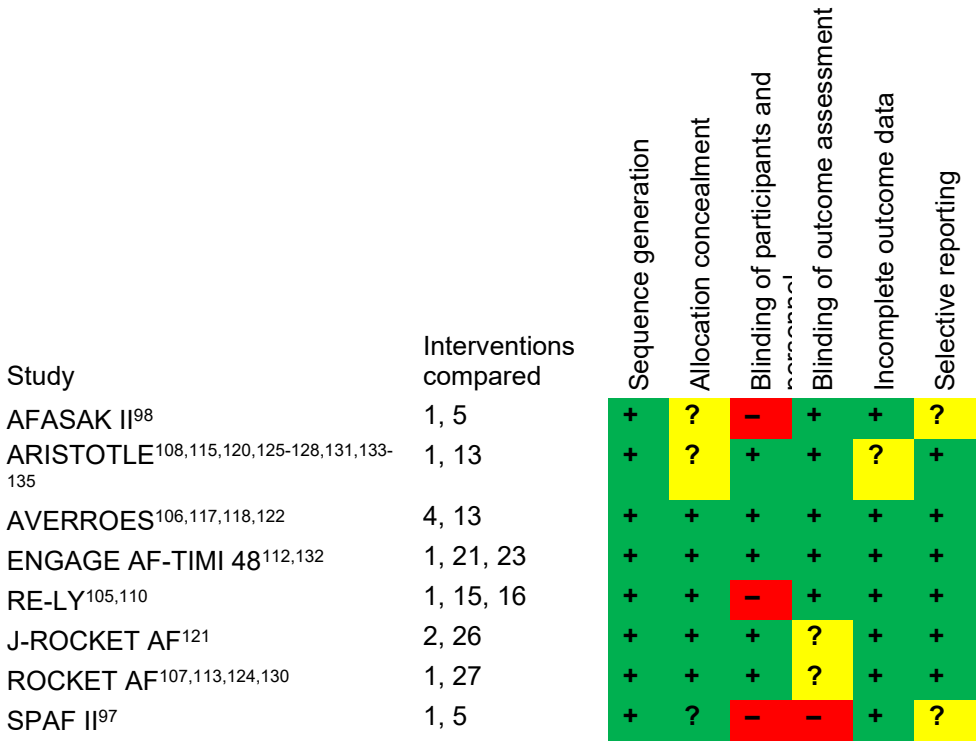


Figure 20 Included trials and risk of bias assessment for intracranial bleeding (stroke prevention in AF)



There was strong evidence that apixaban (5mg bd), dabigatran (110mg bd), dabigatran (150mg bd), edoxaban (30mg od), edoxaban (60mg od) and rivaroxaban (20mg od) reduced risk of intracranial bleeding compared with warfarin (INR 2-3) (Table 44). For each of these NOAC doses except rivaroxaban (20mg od) the estimated reduction in risk was more than 50%. There was weak evidence that risk of intracranial bleeding was increased for rivaroxaban (20mg od) compared with apixaban (5mg bd), dabigatran (150mg bd) and edoxaban (60mg od) (Table 45). Analysing hazard ratios rather than odds ratios led to similar results (Table 46 and Table 47).

Table 44 Results for intracranial bleeding (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg od)	-	0.50 (0.21 , 1.23)	0.50 (0.21 , 1.23)
Antiplatelet (≥150mg od)	0.39 (0.13 , 0.98)	-	0.39 (0.13 , 0.98)
Apixaban (5mg bd)	0.42 (0.30 , 0.58)	-	0.42 (0.30 , 0.58)
Dabigatran (110mg bd)	0.31 (0.19 , 0.47)	-	0.31 (0.19 , 0.47)
Dabigatran (150mg bd)	0.40 (0.27 , 0.59)	-	0.40 (0.27 , 0.59)
Edoxaban (30mg od)	0.31 (0.21 , 0.43)	-	0.31 (0.21 , 0.43)
Edoxaban (60mg od)	0.46 (0.33 , 0.62)	-	0.46 (0.33 , 0.62)
Rivaroxaban (20mg od)	0.65 (0.46 , 0.91)	-	0.65 (0.46 , 0.91)

Table 45 Results for intracranial bleeding (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	0.96 (0.58 , 1.60)	0.96 (0.58 , 1.60)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.09 (0.69 , 1.70)	1.09 (0.69 , 1.70)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	1.55 (0.97 , 2.49)	1.55 (0.97 , 2.49)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	-	1.13 (0.69 , 1.87)	1.13 (0.69 , 1.87)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	1.61 (0.96 , 2.72)	1.61 (0.96 , 2.72)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	1.43 (0.90 , 2.26)	1.43 (0.90 , 2.26)

Table 46 Results for intracranial bleeding (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Antiplatelet (<150mg od)	0.50 (0.21 , 1.20)
Antiplatelet (≥150mg od)	0.39 (0.14 , 0.97)
Apixaban (5mg bd)	0.42 (0.30 , 0.58)
Dabigatran (110mg bd)	0.31 (0.19 , 0.46)
Dabigatran (150mg bd)	0.41 (0.27 , 0.59)
Edoxaban (30mg od)	0.31 (0.21 , 0.43)
Edoxaban (60mg od)	0.46 (0.34 , 0.62)
Rivaroxaban (20mg od)	0.66 (0.47 , 0.91)

Table 47 Results for intracranial bleeding (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

Licensed NOACs only	HR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	0.97 (0.57 , 1.58)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.09 (0.70 , 1.71)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	1.55 (0.97 , 2.48)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	1.13 (0.70 , 1.87)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	1.62 (0.96 , 2.74)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	1.43 (0.91 , 2.25)

5.4.7 All-cause mortality

Eighteen studies reported 6479 all-cause mortality events, leading to a network of fifteen interventions (Figure 21). Fifteen studies were included in the primary analysis, with the remaining three studies included in sensitivity analyses. These studies were at mixed risks of bias (Figure 22). There were concerns about lack of blinding of participants for most trials, and about lack of allocation concealment and blinding of outcome assessment in some studies.

Figure 21 Network plot for all-cause mortality (stroke prevention in AF)

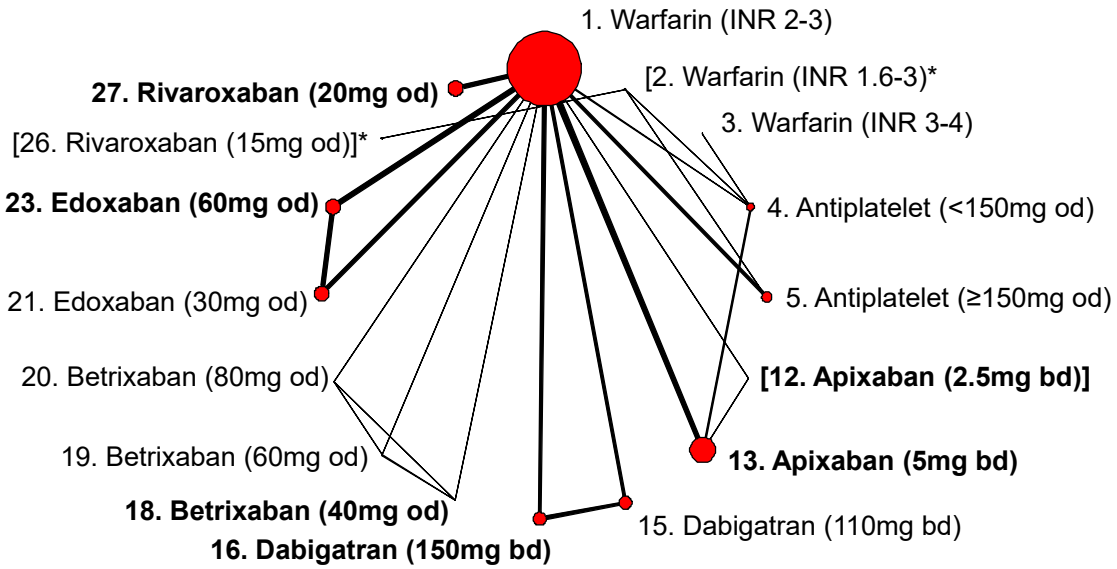


Table 48 suggests that all NOAC doses with comparisons that were not imprecisely estimated (apixaban (5mg bd), dabigatran (110mg bd), dabigatran (150mg bd), edoxaban (30mg od), edoxaban (60mg od) and rivaroxaban (20mg od)) were associated with a reduced risk of all-cause mortality compared with warfarin (INR 2-3). There was little evidence that the risk of all-cause mortality differed between licensed doses of NOACs (Table 49). Analysing hazard ratios rather than odds ratios produced similar results (Table 50 and Table 51).

Figure 22 Included trials and risk of bias assessment for all-cause mortality (stroke prevention in AF)

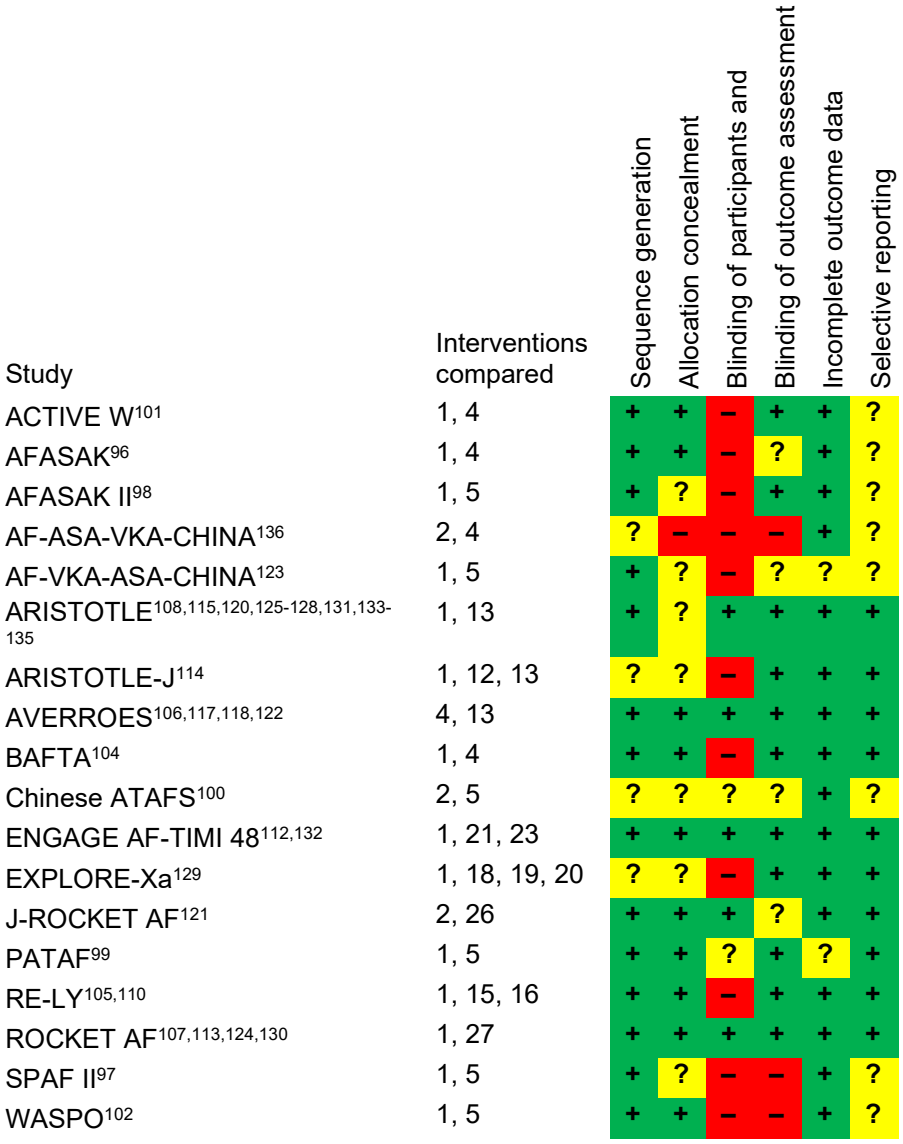


Table 48 Results for all-cause mortality (stroke prevention in AF): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg od)	1.02 (0.75 , 1.38)	1.13 (0.87 , 1.47)	1.08 (0.88 , 1.33)
Antiplatelet (≥150mg od)	1.04 (0.87 , 1.25)	-	1.04 (0.87 , 1.25)
Apixaban (5mg bd)	0.88 (0.79 , 0.98)	-	0.88 (0.79 , 0.98)
Dabigatran (110mg bd)	0.91 (0.80 , 1.04)	-	0.91 (0.80 , 1.04)
Dabigatran (150mg bd)	0.88 (0.77 , 1.01)	-	0.88 (0.77 , 1.01)
Edoxaban (30mg od)	0.86 (0.78 , 0.96)	-	0.86 (0.78 , 0.96)
Edoxaban (60mg od)	0.91 (0.82 , 1.01)	-	0.91 (0.82 , 1.01)
Rivaroxaban (20mg od)	0.83 (0.69 , 1.00)	-	0.83 (0.69 , 1.00)
Imprecisely estimated comparisons			
Warfarin (INR 3-4)	-	*0.24 (0.05 , 0.81)*	*0.24 (0.05 , 0.81)*
Betrixaban (40mg od)	*0.99 (0.06 , 15.5)*	-	*0.99 (0.06 , 15.5)*
Betrixaban (60mg od)	*0.19 (0 , 5.70)*	-	*0.19 (0 , 5.70)*
Betrixaban (80mg od)	*0.19 (0 , 5.88)*	-	*0.19 (0 , 5.88)*

Table 49 Results for all-cause mortality (stroke prevention in AF): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	1.00 (0.84 , 1.19)	1.00 (0.84 , 1.19)
Edoxaban (60mg od) vs Apixaban (5mg bd)	-	1.03 (0.89 , 1.20)	1.03 (0.89 , 1.20)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	0.94 (0.76 , 1.17)	0.94 (0.76 , 1.17)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	-	1.03 (0.87 , 1.22)	1.03 (0.87 , 1.22)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	0.94 (0.74 , 1.18)	0.94 (0.74 , 1.18)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	-	0.91 (0.73 , 1.13)	0.91 (0.73 , 1.13)
Imprecisely estimated comparisons			
Betrixaban (40mg od) vs Apixaban (5mg bd)	-	*1.13 (0.07 , 17.7)*	*1.13 (0.07 , 17.7)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	-	*1.12 (0.07 , 17.6)*	*1.12 (0.07 , 17.6)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	-	*0.92 (0.06 , 14.1)*	*0.92 (0.06 , 14.1)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	-	*0.83 (0.05 , 13.0)*	*0.83 (0.05 , 13.0)*

Table 50 Results for all-cause mortality (stroke prevention in AF): comparisons with warfarin (INR 2-3): sensitivity analysis using hazard ratios instead of odds ratios

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Antiplatelet (<150mg od)	1.07 (0.88 , 1.30)
Antiplatelet (≥150mg od)	1.04 (0.87 , 1.24)
Apixaban (5mg bd)	0.89 (0.80 , 0.99)
Dabigatran (110mg bd)	0.91 (0.80 , 1.04)
Dabigatran (150mg bd)	0.89 (0.78 , 1.01)
Edoxaban (30mg od)	0.88 (0.80 , 0.97)
Edoxaban (60mg od)	0.92 (0.83 , 1.02)
Rivaroxaban (20mg od)	0.83 (0.69 , 1.00)
Imprecisely estimated comparisons	
Warfarin (INR 3-4)	*0.24 (0.05 , 0.81)*
Betrixaban (40mg od)	*1.01 (0.06 , 15.7)*
Betrixaban (60mg od)	*
Betrixaban (80mg od)	*

*: not enough information to compute this pairwise comparison.

Table 51 Results for all-cause mortality (stroke prevention in AF): NOACs (licensed doses only): sensitivity analysis using hazard ratios instead of odds ratios

Licensed NOACs only	HR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	1.00 (0.85 , 1.18)
Edoxaban (60mg od) vs Apixaban (5mg bd)	1.03 (0.90 , 1.20)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	0.94 (0.76 , 1.15)
Edoxaban (60mg od) vs Dabigatran (150mg bd)	1.03 (0.88 , 1.22)
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	0.93 (0.75 , 1.17)
Rivaroxaban (20mg od) vs Edoxaban (60mg od)	0.90 (0.73 , 1.11)
Imprecisely estimated comparisons	
Betrixaban (40mg od) vs Apixaban (5mg bd)	*1.13 (0.07 , 17.6)*
Betrixaban (40mg od) vs Dabigatran (150mg bd)	*1.14 (0.07 , 17.6)*
Edoxaban (60mg od) vs Betrixaban (40mg od)	*0.91 (0.06 , 14.7)*
Rivaroxaban (20mg od) vs Betrixaban (40mg od)	*0.82 (0.05 , 13.2)*

5.4.8 Summary of results and ranking of interventions

Results from network meta-analyses suggest that a number of the licensed doses of NOACs reduce the risk of the outcomes stroke or systemic embolism, major bleeding, clinically relevant bleeding, intracranial bleeding and all-cause mortality compared to the reference treatment, warfarin (INR 2-3). There was evidence that edoxaban increased clinically relevant bleeding compared with warfarin (INR 2-3). Risk of MI

appeared higher for some NOACs than for warfarin (INR 2-3). Comparisons for some licensed NOAC doses, such as apixaban (2.5mg bd) and betrixaban (40mg od), could not be estimated precisely.

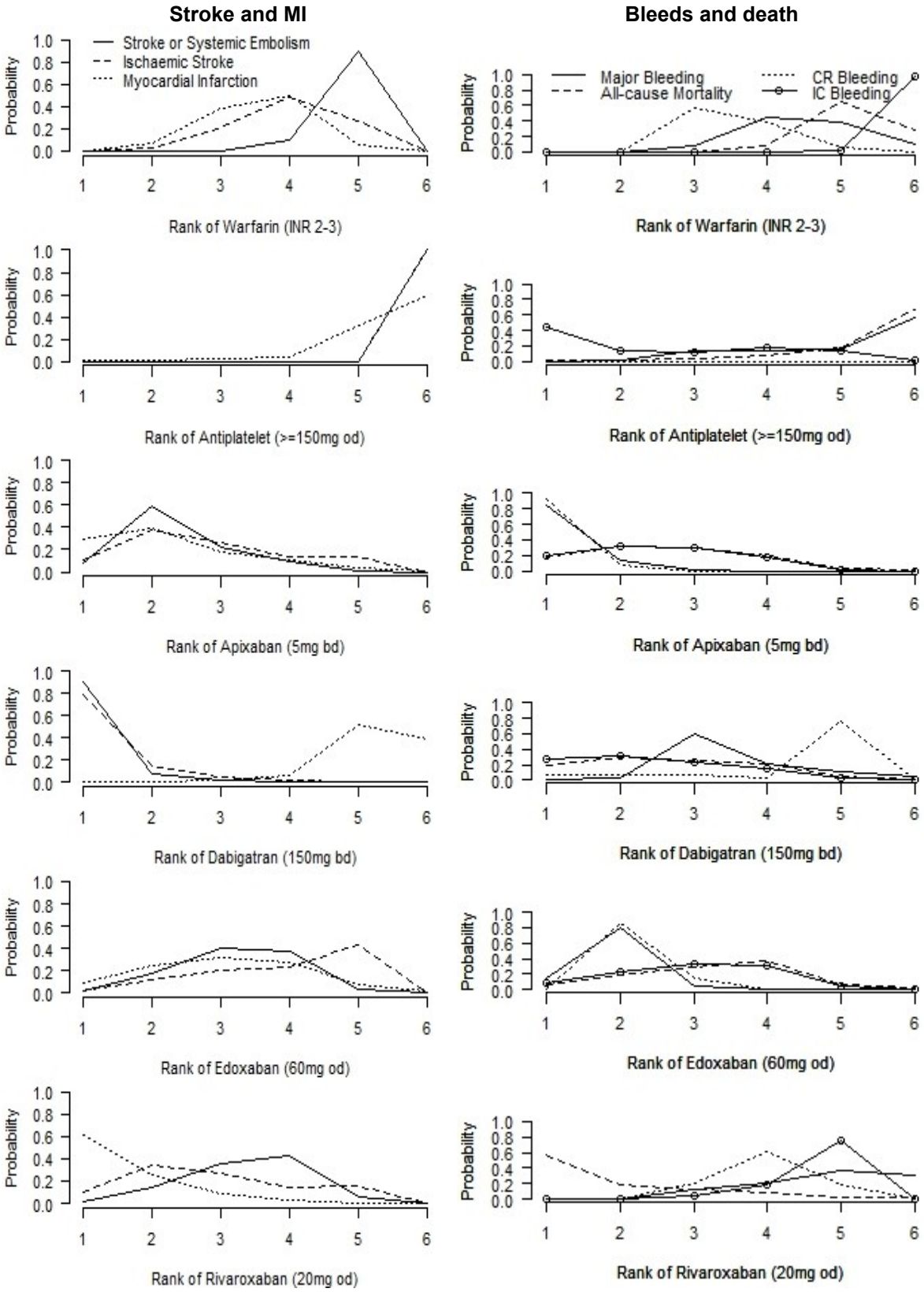
Several studies conducted in Asian countries considered a lower INR range for warfarin interventions in elderly patients. We excluded these from the main analysis, but included them (merged with the reference treatment, warfarin INR 2-3) as a second sensitivity analysis for each outcome. This allowed us to incorporate a non-licensed dose of rivaroxaban (15mg od) that was included in the J-ROCKET-AF trial, showing a reduced risk of stroke compared with warfarin (INR 1.6-3), with a median OR of 0.49 (0.24 to 0.99). Apart from this, results (available upon request) showed the same trends as described above.

The dose range for the antiplatelet arm in the AVERROES trial was unusually wide (81-324mg od). Because some of the patients had received a dose below standard, it was decided to merge it with the antiplatelets (<150mg od) node for the primary analysis. In a further sensitivity analysis for each outcome, this trial was excluded. Again, the results (available from the authors) were not substantially different from those presented above. With regards to model appraisal, we did not identify any instance of lack of convergence among the Markov chains, poor model fit or inconsistency. Few of the comparisons were replicated across studies; where there were multiple estimates we did not find evidence of statistical heterogeneity.

Rankograms plotting the probability that each of the licensed interventions for AF is ranked best, second best and so on for preventing each outcome are displayed in Figure 23. The non-NOAC interventions (warfarin (INR 2-3) and antiplatelet therapy (aspirin/clopidogrel≥150mg od)) were ranked worst for stroke or systemic embolism and ischaemic stroke and were not among the best three interventions for any of the outcomes. Warfarin (INR 2-3) was also ranked as the worst intervention to reduce the risk of intracranial bleeding. Among the licensed NOACs, apixaban (5mg bd) was ranked as among the best interventions for major bleeding, intracranial bleeding, all-cause mortality, stroke or systemic embolism, ischaemic stroke, and MI. Edoxaban (60mg od) was ranked second for major bleeding and all cause mortality. Except for all-cause mortality and MI, outcomes for rivaroxaban (20mg od) were ranked less

highly than those for apixaban (5mg bd), dabigatran (150mg bd) and edoxaban (60mg od).

Figure 23 Rankogram for licensed interventions examined in stroke prevention in AF



CR: Clinically relevant; IC: Intracranial.

6. Cost-effectiveness results (1) Stroke prevention in atrial fibrillation

6.1 Introduction

In this chapter we present the results of the cost-effectiveness analysis for first line treatments for atrial fibrillation patients. The decision question, population, interventions, outcomes, model structure, cost and utility inputs have been previously described in chapter 4. In this chapter we begin by describing clinical effectiveness inputs to the model, including relative treatment effects based on the evidence identified in the systematic review (chapter 5), other state transition probabilities based on evidence from longitudinal studies, transition probabilities on the reference treatment (warfarin) on which relative effects are applied, mortality, and treatment switching parameters. We then present the results from our cost-effectiveness model, together with sensitivity analyses to key assumptions made.

6.2 Model inputs

6.2.1 Relative treatment efficacy

The network meta-analysis results presented in chapter 5 consider each outcome separately and independently. However for our economic model we need to consider the different outcomes jointly. We use a competing risks network meta-analysis model to jointly estimate the log hazard ratios for the different possible events needed in the economic model. The analysis uses data from the RCTs identified in our systematic review, however results were reported in three different ways in the RCTs: number of first events, number of patients experiencing at least one event, and total number of events. The analysis needs to account for the way the results are reported. For example, if a patient's first event was clinically relevant bleeding, they cannot also have ischaemic stroke as their first event. Joint estimation leads to correlated estimates that need to be reflected in the economic model. In Appendix 7 we provide details on the competing risks network meta-analysis, and hazard ratios relative to warfarin (INR 2-3) are given in Table 52. Note that it was possible to include studies with zero events in this analysis. Lower doses for Apixaban and Dabigatran are included as they were evaluated in a sensitivity analysis. Myocardial infarction and all cause mortality are common to both the network meta-analysis of chapter 5 and the

competing risks analysis and their estimated hazard ratios are similar. The competing risks model is restricted to ischaemic stroke and excludes both haemorrhagic stroke and systemic embolism, and so is not precisely comparable to the stroke outcome of chapter 5.

Patients may discontinue NOACs and warfarin and so we also need estimates of the relative efficacy of warfarin compared to no treatment. Warfarin has been the established standard of care for AF patients for at least 20 years and we therefore relied on previous meta-analyses to estimate the relative effect of warfarin compared to no treatment. We chose the meta-analysis by Hart et al[144], as it is the most recent and comprehensive. Hart et al[144] identified six studies comparing warfarin to either 'control' or placebo[145-150], from which we extracted evidence on stroke, bleeds, ICH, death, SE and TIA, summarised in Table 53. The BAATAF study[147] used patients on no treatment but with the option of Aspirin as the control; this study was omitted in a sensitivity analysis. The INR ranges for warfarin were frequently outside of the 2-3 range chosen for our NMA. Under clinical advice, we did not exclude on the basis of INR range, however we note that the results from the only study with INR 2-3 (the CAFA study) were in line with the results from the other studies, providing support for the inclusion of all 6 studies. For each outcome, we separately conducted a random effects meta-analysis using a Poisson likelihood, as described in Appendix 7 but without accounting for competing risks due to insufficient detail available from the trials. Random effects models were used as we expected some heterogeneity due to differences in INR range, however, on the basis of the Deviance Information Criteria[26] there wasn't any evidence in favour or against a fixed effect model, and results were similar. We excluded studies with no events in any arm and added a continuity correction of 0.5 to arms with zero events if other arms in the trial had an event. The results of this analysis are presented in Table 53. Due to insufficient evidence for ICH, we assumed the treatment effect was the same as that for bleeds, as these are clinically similar adverse events. However, the estimated hazard ratios for NOACs presented in Table 52 does not support this assumption of similarity. We therefore conducted a sensitivity analysis that sets the hazard ratio of "no treatment" versus warfarin for ICH to 1.

Table 52 Mean and 95% CI for hazard ratios relative to warfarin from the competing risks NMA for each event and treatment included in the economic model.

	Ischaemic stroke	TIA	Systemic Embolism*	Intracranial Haemorrhage	Other clinically relevant bleeding	MI	Death (all causes)
Apixaban (5mg bd)	0.90 (0.72, 1.11)	0.74 (0.041, 3.26)	0.65 (0.33, 1.18)	0.46 (0.36, 0.58)	0.82 (0.70, 0.94)	0.86 (0.65, 1.1)	0.89 (0.8, 0.99)
Dabigatran (150mg bd)	0.75 (0.58, 0.97)	2.68 (0.062, 16.1)	0.65 (0.52, 0.80)	0.36 (0.26, 0.49)	1.07 (0.92, 1.24)	1.27 (0.93, 1.68)	0.88 (0.77, 1)
Edoxaban (60mg od)	1.00 (0.83, 1.2)	2.76 (0.06, 15.8)	0.58 (0.30, 0.97)	0.49 (0.39, 0.61)	0.88 (0.82, 0.94)	0.95 (0.74, 1.19)	0.92 (0.83, 1.01)
Rivaroxaban (20mg od)	0.92 (0.73, 1.13)	2.68 (0.063, 15.9)	0.95 (0.79, 1.13)	0.65 (0.46, 0.89)	1.05 (0.98, 1.13)	0.79 (0.61, 1.01)	0.83 (0.69, 0.99)
Apixaban (2.5mg bd)	0.74 (0.042, 3.37)	0.76 (0.041, 3.51)	0.48 (0.031, 1.97)	2.78 (0.06, 16.2)	0.63 (0.080, 2.06)	1.01 (0.049, 4.67)	1.03 (0.050, 5.03)
Dabigatran (110mg bd)	1.13 (0.89, 1.42)	2.82 (0.062, 16.4)	0.90 (0.73, 1.1)	0.31 (0.22, 0.43)	0.94 (0.81, 1.09)	1.29 (0.94, 1.71)	0.91 (0.80, 1.03)

*Systemic embolism excludes stroke events

Table 53 Data and hazard ratio (HR) from meta-analysis of no treatment/Placebo vs warfarin

	AFASAK I		SPAF I		BAATAF		CAFA		SPINAF		EAFT		HR Mean (SD)
Treatment	**Placebo**	**Warfarin**	**Placebo**	**Warfarin**	**Control***	**Warfarin**	**Placebo**	**Warfarin**	**Placebo**	**Warfarin**	**Placebo**	**Warfarin**	**-**
Patients	336	335	211	210	208	212	191	187	290	281	214	225	-
Patient years at risk	398	413	245	263	435	487	241	237	483	489	405	507	-
Warfarin INR	2.8-4.2		2.0-4.5		1.5-2.7		2.0-3.0		1.4-2.8		2.5-4.0		-
Strokes	19	9	19	8	13	2	9	6	23	7	50	20	0.359 (0.213)
Bleeds	NR	NR	1	5	21	38	18	35	50	72	14	60	2.3 (3.53)
Deaths	NR	NR	NR	NR	25	11	8	10	26	20	44	41	0.849 (3)
TIA	3	1	NR	NR	NR	NR	2	2	7	4	0	1	4.86 (369)
SE**	NR	NR	NR	NR	NR	NR	2	1	1	2	4	1	3.18 (63)
ICH	NR	NR	NR	NR	0	1	0	1	0	1	0	0	NA

* BAATAF control patients not given warfarin but could choose to take Aspirin.
** SE excludes stroke events

6.2.2 Baseline risk of stroke using CHA_2DS_2-VASc

We used Aspberg 2016 (from Table 4 in relevant publication) to estimate mean and SEs for rates of stroke by CHA_2DS_2-VASc category for patients not on treatment [1]. These estimates were based on follow-up of 152,153 AF patients not on treatment in Aspberg 2016. Mean and SE rates were calculated assuming the stroke event follows a Poisson distribution. The rate of stroke is assumed to follow a Normal distribution in the economic model with mean and SE of Table 54. Rates on warfarin and DOACs were estimated using the hazard ratios in Table 52 and Table 53.

States in the economic model (Figure 2) adjust stroke only through their impact on the CHA_2DS_2-VASc score. Stroke increases score by 2 (assuming this indicates Stroke/TIA/thromboembolism history), MI increases by 1 (assuming this indicates vascular disease history), age between 65 and 74 adds 1 while age 74 years or higher adds 2, and female gender increases by 1. In our implementation, the stroke risk in each state is averaged over that of the CHA_2DS_2-VASc distribution of the cohort. Note that we assume no impact of bleed or ICH on future stroke risk as they are not included in CHA_2DS_2-VASc. As the systemic embolism and TIA events are transient, they also have no impact on the stroke risk; this is a limitation of the modelling approach and is explored in a sensitivity analysis.

Certain aspects of the score are not modelled and therefore do not update the CHA2DS2-VASc score, these are: CHF history, (+1 point), hypertension history (+1 point), TIA/thromboembolism history (+1 point), other vascular disease history (peripheral artery disease or aortic plaque) (+1 point) and diabetes history (+1 point). They are accounted for in the baseline CHA2DS2-VASc score distribution applied in the model (see section 6.3) which represents an AF population, but if these events develop in the period modelled then they will not be accounted for. The one aspect that was explored in a sensitivity analysis was trying to account for systemic embolism and TIA history as detailed in section 6.4.

Table 54 Rates of stroke by CHA_2DS_2-VASc category for patients not on treatment (Aspberg 2016[1]).

CHA_2DS_2-VASc	Number of events	Person years	Mean rate (per 100 person years)*	SE Rate (per 100 person years)*
0	142	37839.13	0.375273	0.000162

1	337	45581.64	0.739333	0.000189
2	1028	54540.93	1.884823	0.000252
3	1927	65875.49	2.925215	0.00026
4	2499	59936.04	4.169445	0.000341
5	2198	39387.13	5.580503	0.0006
6	1768	23375.56	7.563455	0.001177
7	840	9974.05	8.421855	0.00291
8	270	3205.68	8.42255	0.009053
9	44	507.72	8.666194	0.057982

*In economic model rates assumed to follow a Normal distribution with mean and SE as above.

6.2.3 The effect of past health events and states on future event rates

The primary source of evidence for the effect of prior events on SE, TIA and bleed risk is a study in 182678 Swedish patients by Friberg[151]. Reported hazard ratios (Table 55) are for male patients under 65 years old. We make the assumption that these hazard ratios can be generalised to a population of 70 year olds with 60/40 split of males/females.

We also estimated the effect of previous events on mortality. Andersen[152] provided estimates of the hazard ratios for the effect of prior stroke or MI in patients with AF. These are reproduced in Table 56 and normal distributions representing uncertainty in the estimated log hazard ratios are summarised in Table 57. No evidence was available for the effect of prior bleeds or ICH on mortality. We made the assumption that bleeds and ICH would have the same effect on future risk of death as stroke. We conducted a sensitivity analysis in which we assumed bleeds and ICH to have no effect on future risk of death. The effects of prior events on future risks are assumed to be multiplicative, so a history of both stroke and MI will give a hazard ratio for mortality of

$$\frac{1}{0.758} \times \frac{1}{0.972} = 1.03 \times 1.32 = 1.36$$

We reflect uncertainty in the mean estimates by assuming Normal distributions for the logs of these hazard ratios (Table 57).

Table 55 Hazard ratios of effect of history of previous events on future non-stroke events (Friberg[151]).

Risk factor	Future TIA/SE	Future Intracranial Bleeding (ICH)	Future bleed
Ischaemic stroke	3.61 (3.44-3.78)	1.64 (1.39-1.94)	1.39 (1.27-1.52)
ICH	1.82 (1.62-2.04)	10.2 (8.59-12.2)	2.95 (2.57-3.39)
Any significant bleeding (major bleed)	1.36 (1.26-1.46)	3.54 (3.02-4.17)	3.32 (3.06-3.60)
MI	1.29 (1.22-1.36)	0.94 (0.78-1.12)	1.24 (1.15-1.35)

Table 56 Reported hazard ratios for effect of no previous events on mortality in patients with AF (Andersen[152]).

Event history	Effect on Mortality (Hazard ratio with 95% CI)
No MI	0.972 (0.687-1.378)
No Stroke	0.758 (0.565-1.017)

Table 57 Estimated log-hazard ratio (standard error) for the effect of previous events on future non-stroke events.

Risk factor	Future TIA/SE	Future ICH	Future Bleed	Future Death
Stroke	1.28 (0.02)	0.49 (0.09)	0.33 (0.05)	0.28 (0.15)
ICH	0.60 (0.06)	2.32 (0.09)	1.08 (0.07)	0.28 (0.15)
Bleed	0.31 (0.04)	1.26 (0.08)	1.20 (0.04)	0.28 (0.15)
MI	0.25 (0.03)	-0.06 (0.09)	0.22 (0.04)	0.03 (0.18)

Normal distributions are used to reflect uncertainty in the estimated log-hazard ratios.

6.2.4 Transition probabilities with usual care (warfarin)

We estimated transition probabilities for the usual care (first line warfarin) treatment strategy, using the trials identified in our systematic review that included a warfarin arm. The model includes the following correlated outcomes: 1) Ischaemic stroke; 2) ICH; 3) Other clinically relevant bleed; 4) TIA; 5) SE; 6) MI and 7) Death. However, the ischaemic stroke estimates were not used as these came from the Aspberg 2016 cohort study [1], described in Section 6.2.2.

Previous economic models have used evidence from single trials, such as RE-LY in Kansal et al[46], to estimate the risk of events with warfarin treatment. However, this disregards the evidence available from other published trials. QRISK2[153] provides long-term information on MI in AF patients. However, this only estimates a joint risk of stroke and MI, rather than for each event individually. Another possible source of evidence for the rate of MI in AF is Soliman et al[154], but this only provides a hazard ratio for MI in AF relative to the non-AF population, which is not what is needed for our model. Therefore, we used evidence from the warfarin arms in the trials identified in our systematic review because it is based on patients with AF, similar demographics to our target population, and represented the risk for patients specifically on warfarin treatment.

We estimated the hazard of events on warfarin, taking into account the competing risks nature of the outcomes and the format in which results are reported, in the same way as we did for the relative effects (Appendix 7). Details of the model are given in Appendix 8 and estimated hazards are shown in Table 58.

Table 58 Mean and 95% CI for hazard of events, estimated from warfarin arms of RCTs identified in our systematic review

Event	Mean hazard (95% CI)
MI	0.0079 (0.0064, 0.01)
Ischaemic stroke*	0.012 (0.01, 0.013)
Death (all causes)	0.038 (0.028, 0.052)
Transient ischaemic attack (TIA)	0.025 (0.006, 0.089)
Clinically relevant bleeding	0.066 (0.031, 0.13)
SE	0.017 (0.0059, 0.041)
ICH	0.0094 (0.0057, 0.017)

*Not used in economic model. Rates by CHA_2DS_2-VASc category were estimated using Aspberg 2016 [1]

6.2.5 Mortality

The risk of death in a 70 year old AF population on warfarin with a 60/40 male/female split is obtained from the usual care hazard described above. This is adjusted for each age group above 70 using the 2011-13 life tables for England and Wales[155], which provide the probability that an individual from the general population and at a specific age will die within one year. The hazard of death (λ) in each age group is

$$\lambda = -\log\left(1 - (0.6 * PD_{male} + 0.4 * PD_{female})\right)$$

where PD_{male} and PD_{female} are the annual probability of death for males and females, respectively. We use the ratio of this hazard for each age group to the hazard for 70 year olds to adjust the usual care (warfarin) hazard of death for each age group in the model.

6.2.6 Treatment switching probabilities

Post event treatment switching rules and probabilities were based on clinical opinion. Clinicians advised 'definite' switching in the event of ICH for all treatments and also in the event of MI for dabigatran; a "chance" of switching in the case of clinically relevant bleeding and ischaemic stroke; and a "slight chance" of switching following SE or TIA, due to concern about treatment failure. We assume a probability of switching of 0.3 for "chance" and 0.1 for "slight chance", but reflect our high degree of uncertainty in these switching probabilities with beta distributions, summarised in Table 59. We subject these assumed switching probabilities to sensitivity analysis.

Table 59 Treatment switching rules and assumed probabilities

Event leading to switching	Probability of switching Mean (95% CI)	Distribution for probability of switching	Rule for switching
Intra-cranial haemorrhage	1.00	-	Always switch to no treatment
Myocardial infarction	1.00	-	If on dabigatran, switch to warfarin. No switching otherwise
Clinically relevant bleeding	0.30 (0.00, 1.00)	Beta(0.3, 0.7)	Switch to next line treatment
Ischaemic stroke	0.30 (0.00, 1.00)	Beta(0.3, 0.7)	Switch to next line treatment
Transient ischaemic attack	0.10 (0.00, 1.00)	Beta(0.1,0.9)	Switch to next line treatment
Systemic embolism	0.10 (0.00, 1.00)	Beta(0.1,0.9)	Switch to next line treatment

6.3 Base case distribution of CHA_2DS_2-VASc

The base case of the AF economic model model assumes a proportion of patients in the AF well state (with no history of stroke, MI, bleed, or ICH) begin in each of the CHA_2DS_2-VASc categories. Aspberg 2016 report proportions of patients in each category but their sample consisted of Swedish patients hospitalized, or visiting a hospital-based outpatient clinic, with a diagnosis of AF[1]. Additionaly CHA_2DS_2-VASc is reported for patients not receiving anticoagulation. Our target are patients with newly diagnosed AF which likely have lower CHA_2DS_2-VASc than the population of Aspberg 2016. We therefore used a meta-analysis of studies, identified by a literature review in Welton 2017 economic evaluation of AF screening, that estimate the proportion of screen-detected AF with CHA_2DS_2-VASc ≥2 [156]. Estimated proportions are presented in Table 60; we use the fixed effects meta-analysis estimate that 25% of patients are below CHA_2DS_2-VASc 2 and 75% are above. Within this dichotomy, we assume the proportions are the same as in Aspberg 2016. Final proportions in each category are presented in Table 61.

These proportions are assumed for patients with age 70 years old and a split of 60% male and 40% female; these choices were made to match our base case to the populations of the trials included in the network meta-analysis. Note that as the initial age is greater than 65, all CHA_2DS_2-VASc scores are increased by 1 while the score for 70 year old females is increased by a total of 3. The CHA_2DS_2-VASc of patients in the highest category (i.e. score 9) does not increase while proportions in the highest categories are combined (i.e. the proportions of male 70 year old cohorts with score 8 and 9 are combined into score 9, and the proportions of female 70 year old cohorts with scores 7, 8, and 9 into score 9).

We explore younger ages, entirely male/female cohorts, and specific CHA_2DS_2-VASc starting values in scenario analyses described in Section 6.3.1.

Table 60 Meta-analysis of proportion Screen-detected AF with CHA2DS2-VASc ≥2 estimaed by studies identified by Welton 2017[156]

1st Author	Population	P(CHA_2DS_2-VASc ≥2), screen-detected AF
Claes 2012[157]	40y+ Belgium. Nationwide volunteers	164/228=72%

Kaasenbrood 2016[158]	10GPs in Netherlands, 60y+ invited to screening during flu vaccination.	29/37=78.4%
Lowres 2014[159]	Australia, 65y+ attending 10 community pharmacies, and invited to screening Australia	15/15=100%
Deif 2013[160]	Australia hospital. 65y+ attending for minor surgery invited for screening	11/12=91.7%
Pooled Fixed Effect Estimate		0.750 (0.699, 0.797)

Table 61 Proportion in each CHA2DS2-VASc category used in AF economic model

CHA_2DS_2-VASc	Number of patients in category based on Aspberg 2016	Proportion in category based on Aspberg 2016	Proportions adjusted by meta-analysis of screen detected AF
0	12266	0.08	0.110
1	15694	0.10	0.140
2	21463	0.14	0.130
3	29199	0.19	0.176
4	29479	0.19	0.178
5	21367	0.14	0.129
6	13755	0.09	0.083
7	6398	0.04	0.039
8	2166	0.01	0.013
9	366	0.00	0.002

6.3.1 Scenario analyses on starting age, gender, and CHA_2DS_2-VASc score

The base case analysis assumed a starting age of 70, a proportion male of 60%, and CHA_2DS_2-VASc distribution of Table 61. We explored in scenario analyses the consequences of changing these starting conditions. The full list is given in Table 62. Our selection of starting ages 60 and 80 are roughly one standard deviation from the mean age of patients included in the trials. The CHA_2DS_2-VASc scores explored correspond to the lowest three categories possible for the age and gender group under consideration; for male cohort aged 70, the lowest CHA_2DS_2-VASc possible is 1 due

to the high age, while for a female cohort aged 70, the lowest CHA_2DS_2-VASc possible is 2. We explored male/female and specific CHA_2DS_2-VASc scores for age 60 to include a cohort with starting CHA_2DS_2-VASc 0 (the cohorts with starting age 70 all have a CHA_2DS_2-VASc of at least 1 if male and 3 if female).

Table 62 Gender, age, and CHA_2DS_2-VASc scenarios explored. First row is base case.

Gender	Age (years)	CHA_2DS_2-VASc
Male 60%, Female 40%	70	Distribution as in Table 61
Male	70	1
Male	70	2
Male	70	3
Male	70	≥4 with distribution as in Table 61
Female	70	2
Female	70	3
Female	70	4
Female	70	≥5 with distribution as in Table 61
Male	60	0
Male	60	1
Male	60	2
Male	60	≥3 with distribution as in Table 61
Female	60	1
Female	60	2
Female	60	3
Female	60	≥4 with distribution as in Table 61
Male 60%, Female 40%	80	Distribution as in Table 61

6.4 Sensitivity analyses

We explored the robustness of our results to various assumptions through sensitivity analyses. Unless otherwise stated, these assume the age, gender split, and proportion CHA_2DS_2-VASc of the base case described in Section 6.3.

Warfarin monitoring costs: In this sensitivity analysis, we assumed that there is no drug or monitoring cost associated with warfarin. This explores whether warfarin is cost-effective even in the absence of monitoring costs. We also considered running sensitivity analyses to fixed warfarin monitoring costs at £70.75 and £106.13 per 3-month cycle (mean and upper limit of assumed distribution for warfarin monitoring costs). Note however, it is only worth doing these sensitivity analyses if warfarin is found to be cost-effective with no monitoring costs (otherwise clearly won't be cost-effective for positive monitoring costs).

Mortality risk following bleeds / ICH: In this sensitivity analysis we assumed that there is no effect of previous bleeds and ICH on future risk of death. This was motivated by the lack of evidence on this effect and the assumption of the base case that the effect of previous bleeds and ICH on mortality risk was the same as that of stroke.

Probabilities of treatment switching: We ran three sensitivity analyses to the assumptions around treatment switching. In the first, we assumed that no patients switch treatment following ischaemic stroke, bleed, SE or TIA, in the second we assumed all patients switch after a ischaemic stroke or bleed, but none switch after a SE or TIA, and in the third we assumed that all patients switch treatments following these four events. In all sensitivity analyses, all patients are assumed to discontinue treatment following an ICH and that patients on dabigatran switch to warfarin following an MI, as in the base case.

Excluding "no treatment control" study from meta-analysis of warfarin vs placebo trials: The meta-analysis estimating the effect of warfarin compared to "no treatment" included 5 studies comparing warfarin in placebo and one, BAATAF [147], comparing warfarin to "control". This control arm consisted of patients on no treatment

who had the option of starting aspirin. When the BAATAF study is removed from the meta-analysis comparing warfarin to no treatment (Table 63), the effect of no treatment compared to warfarin on bleeds and deaths is decreased, although the uncertainty is greatly increased. This sensitivity analysis uses a meta-analysis that excludes the BAATAF study.

Apixaban 2.5mg bd and dabigatran 110mg bd: This sensitivity analysis uses different doses (apixaban 2.5mg bd and dabigatran 110mg bd) than those used in the base case analysis (5mg and 150mg, respectively). This is motivated by the licensing of these drugs by the EMA which specifies the lower dose should be prescribed for older (>75 years old) patients.

No difference in hazard of ICH between "no treatment" and warfarin: As our meta-analysis comparing warfarin and "no treatment" had insufficient evidence to estimate the hazard ratio for ICH, we assumed it to be same as for bleeds. In this sensitivity analysis we assumed that the hazard of ICH is the same in warfarin and "no treatment" patients.

TIA and SE CHA_2DS_2-VASc by moving patients to post-stroke states: As our model structure only allowed history of stroke to be recorded, the transient events TIA and SE were assumed not to impact CHA_2DS_2-VASc score. In this sensitivity analysis we assumed that TIA and SE would move a patient to the post-stroke states. Although this correctly increases the CHA_2DS_2-VASc score, it is an unrealistic assumption as it incurs the management costs of stroke, which are likely not incurred by patients who have experienced TIA or SE. It also increases the risk of further TIA/SE, ICH, bleed, and death to the same extent as stroke (reported in Table 57), which is again unrealistic. This sensitivity analysis should therefore be viewed as an extreme analysis.

Costs for stroke and ICH following AF Ablation NICE guidelines: This sensitivity replaced the acute and annual management costs to match the 1st year and after 1st year costs used for stroke and ICH in the AF ablation NICE guidelines. These costs are summarised in Table 13 and were derived from the SSNAP audit [161].

Table 63 Hazard ratio (HR) from meta-analysis of no treatment/placebo vs warfarin including and excluding BAATAF study

Event	Mean HR including BAATAF (SD)	Mean HR excluding BAATAF (SD)
Strokes	0.359 (0.213)	0.391 (0.246)
Bleeds	2.3 (3.53)	3.23 (18.9)
Deaths	0.849 (3)	1.37 (13.6)
TIA	4.86 (369)	4.86 (369)
SE	3.18 (63)	3.18 (63)
ICH	NA	NA

DOAC costs: These sensitivity analyses were run to estimate the threshold price reductions in the cost of each DOAC at which they would become more cost-effective than the alternatives, assuming no changes in the costs of the other treatments or any other parameters in the model.

6.5 Sensitivity analysis on reversal agents following bleeds

A sensitivity analysis was explored where the use of reversal agents is modelled following both clinically relevant bleeds and ICH in the atrial fibrillation cost-effectiveness model. Parameter values used to calculate the cost associated with reversal agents are provided in Table 64. Clinical advice was that few patients need reversal on DOACs due to a short half-life; by the time reversal agents are needed patients are often beyond therapeutic effect. This has been well demonstrated in the ANNEXA-4 study which showed that 28% of patients with major bleeding had low anti-Xa levels at a mean of 12 hours after the last dose, while for most patients the question of reversal arises after 12 hours [162].

A key assumption is that the percentage of patients receiving bleeds is the same across extracranial and intracranial bleeds. Our model also assumes that no reversal agents are used for for non-clinically relevant extracranial bleeds, although there are likely few patients receiving agents for such minor bleeds. We further assume the same percentage of bleeds receiving reversal agents across all DOACs, despite the use of idaracizumab for dabigatran and prothrombin complex concentrate (PCC) (i.e. octaplex/beriplex) for all other DOACs. The average weight is calculated from the average male and female weights, as reported by Health Survey England 2014 average weight for 65-74 year olds[163], and is thus dependent on the proportion of the cohort assumed to be male.

The formula for costing a bleed on coumarin is as follows. Note that we are calculating the average cost of a bleed, and thus assume the same proportion of patients receiven vitamin K reversal agents (Phytomenadione) as receive PCC (octaplex/beriplex).

$$(coumarin\ proportion\ reversal\ agent) \times ($$

Cost from vitamin K

$$(vitamin\ K\ ampoules\ used) \times (unit\ cost\ of\ vitamin\ K\ injection) +$$
$$(PCC\ proportion\ octaplex) \times ($$
$$(proportion\ octaplex\ low\ dose) \times$$
$$\left(\frac{(octaplex\ low\ dose\ ml\ per\ kg) \times (average\ weight)}{octaplex\ ml\ per\ vial}\right) \times (octaplex\ cost\ per\ vial)$$
$$+(1 - proportion\ octaplex\ low\ dose) \times$$
$$\left(\frac{(octaplex\ high\ dose\ ml\ per\ kg) \times (average\ weight)}{octaplex\ ml\ per\ vial}\right) \times (octaplex\ cost\ per\ vial)$$
$$) +$$
$$(1 - PCC\ proportion\ octaplex) \times ($$
$$\left(\frac{(beriplex\ ml\ per\ kg) \times (average\ weight)}{1000}\right) \times (beriplex\ cost\ per\ vial))$$
$$\times (PCC\ number\ of\ doses)$$

The formula for costing a bleed on a non-dabigatran DOAC is the same as for coumarin except that no vitamin K is used and the percentages receiving reversal agents are different.

$$(non\ dabigatran\ DOAC\ proportion\ reversal\ agent) \times ($$
$$(PCC\ proportion\ octaplex) \times ($$
$$(proportion\ octaplex\ low\ dose) \times$$
$$\left(\frac{(octaplex\ low\ dose\ ml\ per\ kg) \times (average\ weight)}{octaplex\ ml\ per\ vial}\right) \times (octaplex\ cost\ per\ vial)$$
$$+(1 - proportion\ octaplex\ low\ dose) \times$$
$$\left(\frac{(octaplex\ high\ dose\ ml\ per\ kg) \times (average\ weight)}{octaplex\ ml\ per\ vial}\right) \times (octaplex\ cost\ per\ vial)$$
$$) +$$
$$(1 - PCC\ proportion\ octaplex) \times ($$
$$\left(\frac{(beriplex\ ml\ per\ kg) \times (average\ weight)}{1000}\right) \times (beriplex\ cost\ per\ vial))$$
$$\times (PCC\ number\ of\ doses)$$

The formula for costing a bleed on dabigatran is simpler than for non-dabigatran DOACs or coumarin. It is as follows

$$(dabigatran\ proportion\ reversal\ agent) \times (idarucizumab\ doses) \times (idarucizumab\ cost\ for\ 2.5\ mg\ per\ ml\ dose\ )$$

The above sensitivity analysis is referred to as the standard-of-care reversal agent sensitivity analysis. A further sensitivity was conducted assuming all apixaban and rivaroxaban reversal agents use adexanet alfa, with a cost provided in Table 64. Sensitivity analyses reducing the percentage receiving PCC following bleed on coumarin from 87.5% to 50% and 10% were also conducted.

A disadvantage of our approach is that some reversal agent use may have been counted in the NHS reference costs used for extracranial bleeds (i.e. Clinically relevant bleeding) and Luengo-Fernandez 2012 cost used for ICH, although the latter does not list this as a cost[3] (Table 12).

Table 64 Parameters used for costing reversal agent use in atrial fibrillation cost-effectiveness model

	Mean	Distribution in model (if not fixed)	Source
Bleeding event reversal unit costs			
Vitamin K - Phytomenadione 10mg/1ml solution for injection (£)	0.378	NA	NHS Drug Tariff 2018
Octaplex - 1,000 IU vial (£)	416.5	NA	Octaplex prescribing information
Octaplex - ml per 1,000 IU vial (£)	40	NA	Octaplex prescribing information
Beriplex - 1,000 IU vial (£)	600	NA	Beriplex prescribing information
Idarucizumab (Praxbind) - 2.5 g/50 ml (£)	1200	NA	NICE evidence summary [164]
Andexanet alfa per dose (£)	11000	NA	4 x 200mg powder for solution vials = £11,100 using NICE indicative price [165]
Bleeding events resource use			
Percentage reversal agents on coumarin	87.5%	Normal(mean=87.5%, sd=6.38%) truncated between 0% and 100%	Clinical advice range is 75% to 100% Considered 50% and 10% (with no uncertainty distribution) as sensitivity analyses.
Percentage reversal agents (non-dabigatran DOACs)	3%	Normal(mean=3.0%, sd=1.02%) truncated between 0% and 100%	Clinical advice range is 1% to 5%
Percentage reversal agents (dabigatran)	3%	Normal(mean=3.0%, sd=1.02%) truncated between 0% and 100%	Clinical advice range is 1% to 5%

Percentage of PCC usage which is Octaplex	50%	Normal(mean=50%, sd=5.1%)	Clincal advice range is 40% to 60%
Percentage of low-dose Octaplex use	50%	Normal(mean=50%, sd=5.1%)	Clincal advice range is 40% to 60%
Reversal agent dose			
Vitamin K - ampoules used	1.5	NA	Assumption
Octaplex - INR 2-2.5 - 0.9-1.3 ml/kg body weight	1.1	NA	Octaplex prescribing information
Octaplex - INR 2.5-3 - 1.3-1.6 ml/kg body weight	1.45	NA	Octaplex prescribing information
Beriplex - INR 2.0-3.9 - 25 IU/kg body weight	25	NA	Beriplex prescribing information
PCC - number of doses	1.25	NA	Assumption
Idarucizumab	2	NA	Assumption
Patient weights			
Average weight males (kg)	83.5	NA	Health Survey England 2014 average weight for 65-74 year olds[163]
Average weight females (kg)	72.1	NA	Health Survey England 2014 average weight for 65-74 year olds[163]

* PCC=prothrombin complex concentrate, which are octaplex and beriplex

6.6 Results of the cost effectiveness model: Atrial fibrillation

6.7 Results of base case analyses

We ran 10,000 iterations of our model for 120 cycles (each iteration representing a simulation from the joint distribution of our model parameters). We set the random number seed within R to 144108435. We estimated expected total costs and QALYs for each first line anticoagulation strategy (Table 65). Expected incremental costs and QALYs for each first line strategy compared to warfarin (INR 2-3) are also given. The treatment with greatest expected net benefit at £20,000 and £30,000 willingness-to-pay thresholds, along with the probability that this treatment has greatest net benefit, is provided for the base case and all scenario and sensitivity analyses in Table 66.

Dabigatran (150mg bd) has the lowest expected total cost (£25,922), followed by apixaban (5mg bd), edoxaban (60mg od), warfarin (INR 2-3), and rivaroxaban (20mg od) which had the highest expected total cost of all treatments (£30,427). No treatment had highest expected total costs (£39,345). Expected costs are similar across all treatments, and there is a high degree of uncertainty around the costs for all treatments.

Apixaban (5mg bd) has the highest expected QALYs (5.76), followed by rivaroxaban (20mg od) (5.69), dabigatran (150mg bd) (5.64) and edoxaban (60mg od) (5.62), warfarin (INR 2-3) (5.29), and no treatment (4.58). The NOACs have similar expected QALYs, all of which are higher than for Warfarin (INR 2-3). There is a high degree of uncertainty around the QALY estimates.

At a willingness to pay threshold of £20,000 per QALY, all NOACs have positive expected incremental net benefit compared to warfarin (INR 2-3), suggesting they may be a cost effective use of NHS resources. Apixaban (5mg bd) has the highest expected incremental net benefit (£10,528), followed by dabigatran (150mg bd) (£9,952), edoxaban (60mg od) (£6,777), and rivaroxaban (20mg od) (£6,555). Dabigatran (150mg bd) and apixaban (5mg bd) are the only NOACs for which the 95% confidence interval around incremental net benefit is positive, suggesting that dabigatran and apixaban are cost-effective compared with warfarin. These conclusions also hold at the higher threshold of £30,000, with apixaban (5mg bd) again having the highest

expected incremental net benefit (£15,264) and dabigtran (150mg bd) having the second highest (£13,450).

The key drivers of the results are the lower rates of MI, ICH and other CRB for apixaban (Table 52), as found in the NMA of chapter 5. Dabigatran has a much greater reduction in stroke risk than apixaban, and this has a greater impact on expected costs and QALYs as the stroke risk (represented by CHA_2DS_2-VASc) increases; this is confirmed in scenario analyses. The high cost and disutility of ICH has a great influence on total costs, total QALYs, and net benefits. Apixaban also has a low rate of TIA but the uncertainty surrounding the other treatment effects, and the minimal impact of this event means it is not a driving factor in the results. Dabigatran also has a low rate of ICH but the higher rate of MI offsets this benefit.

The uncertainty in the estimated total costs and QALYs is illustrated in the cost-effectiveness plane (Figure 24). The cost-effectiveness acceptability curve (CEAC; Figure 25) plots the probability of each intervention having the highest net benefit against a willingness to pay per QALY. The probabilities for the treatment with highest incremental net benefit are also provided in Table 66. It indicates that apixaban (5mg bd) has the highest probability of being the most cost-effective first line therapy for AF, 46.1% at the £20,000 willingness-to-pay and 47.2% at £30,000. Warfarin (INR 2-3) and edoxaban (60mg od) are unlikely to be cost-effective. These results are further highlighted by the cost-effectiveness acceptability frontier (CEAF; Figure 26), which plots the probability of having the highest net benefit against a willingness to pay per QALY for the intervention with the highest expected net benefit. Dabigatran (150mg bd) or Apixaban (5mg bd) are likely to be the most cost-effective first line therapy for AF, under the assumptions of our model.

Table 65 Cost-effectiveness of first line treatment strategies for AF patients.

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	28796 (17449, 49629)	27741 (18728, 42765)	25922 (16724, 40908)	28640 (18927, 43436)	30427 (20271, 49685)	39345 (13025, 86268)
Expected QALYs	5.285 (4.414, 6.113)	5.759 (4.931, 6.527)	5.638 (4.747, 6.519)	5.616 (4.778, 6.426)	5.694 (4.81, 6.57)	4.583 (2.488, 6.667)
Expected Incremental Total Costs	- (-, -)	-1055 (-10570, 4763)	-2874 (-12849, 2506)	-156.4 (-9423, 6459)	1631 (-6621, 7887)	10549 (-8736, 40666)
Incremental Expected QALYs	- (-, -)	0.4736 (0.1215, 0.7877)	0.3526 (-0.05732, 0.7083)	0.3311 (-0.04289, 0.6074)	0.4093 (-0.04162, 0.7922)	-0.7016 (-2.358, 1.035)
Expected Net Benefit (£20,000)	- (-, -)	10528 (3946, 20256)	9925 (1773, 19793)	6777 (-129.8, 14872)	6555 (-1438, 16191)	-24581 (-56532, -5074)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15264 (6595, 26793)	13450 (2433, 25919)	10088 (273.3, 19830)	10647 (-900.1, 23224)	-31597 (-77519, 1964)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Figure 24 Incremental cost-effectiveness plane, warfarin (INR 2-3) is reference.

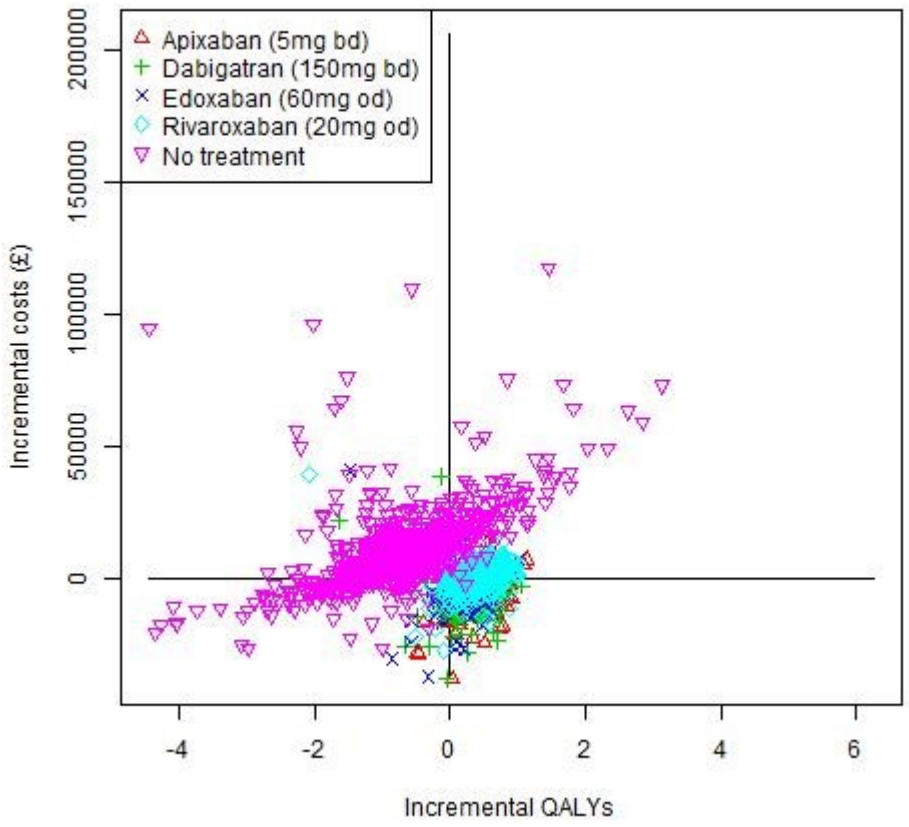


Figure 25 Cost-effectiveness acceptability curves. The probability each first line treatment is most cost-effective against willingness to pay per QALY threshold.

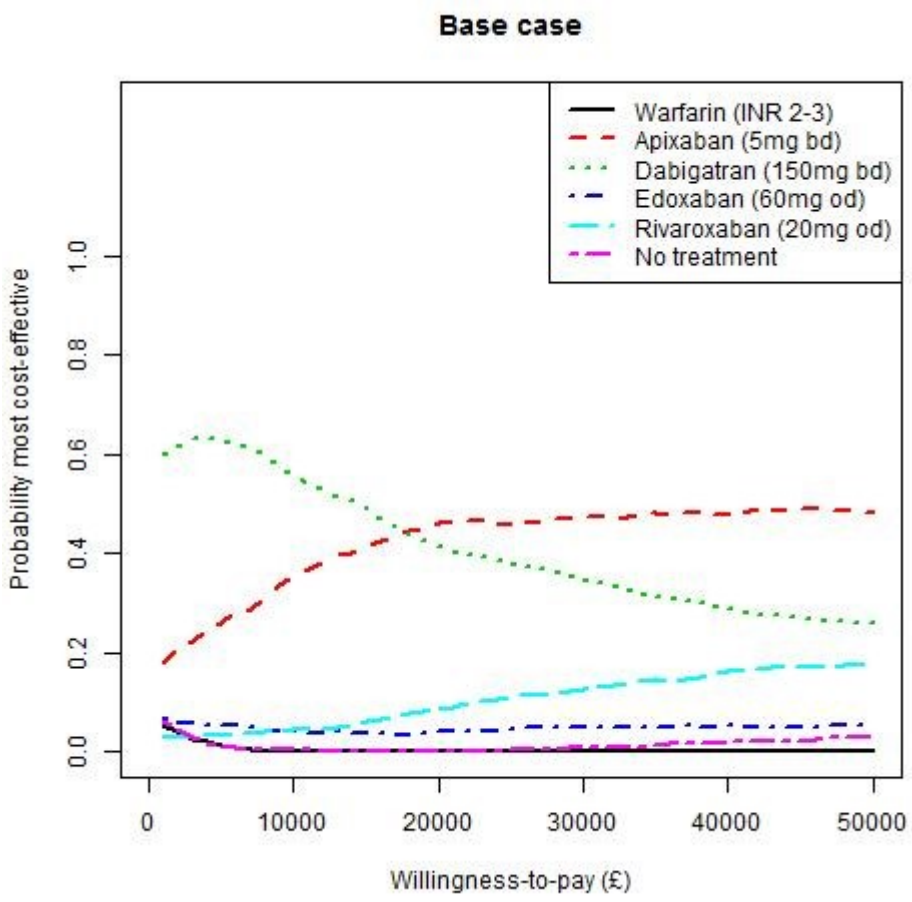


Figure 26 Cost-effectiveness acceptability frontier. For each willingness to pay per QALY threshold, the probability of being most cost-effective is plotted for

the treatment that has the highest expected net benefit at that willingness to pay threshold.

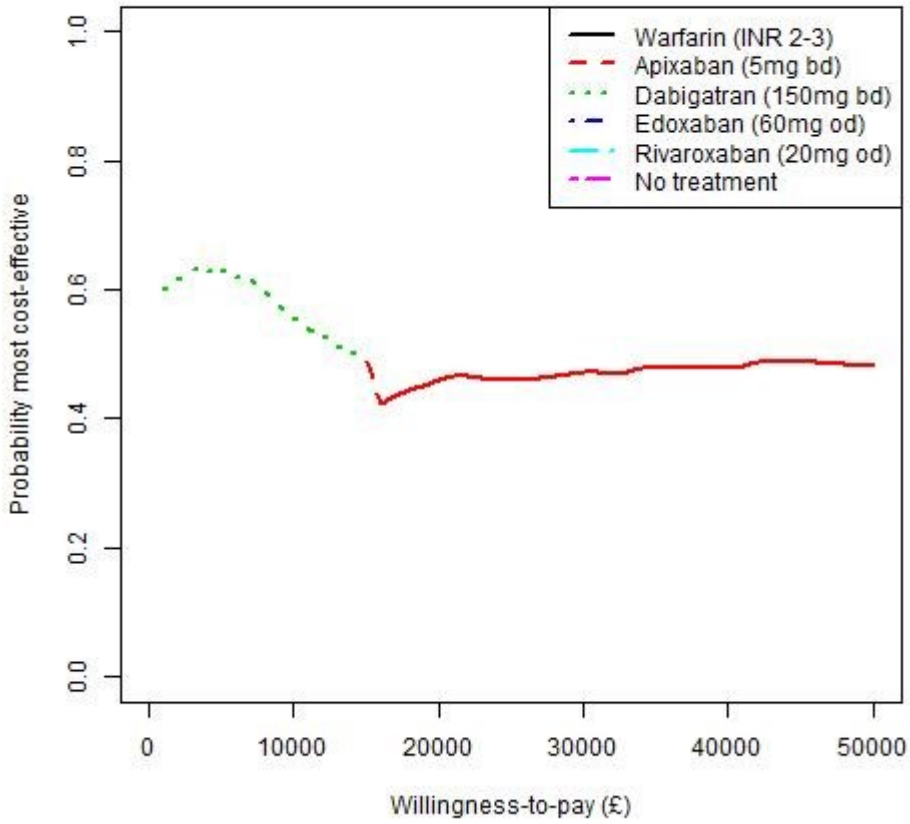


Table 66 First line treatment for AF with highest incremental net benefit for the base case, scenario analyses, and sensitivity analyses

	Scenario	Tretment with highest incremental net benefit at £20,000 (probability highest net benefit)	Tretment with highest incremental net benefit at £30,000 (probability highest net benefit)
Base case	Base case	Apixaban (5mg bd) (0.461)	Apixaban (5mg bd) (0.472)
Gender, age, CHA_2DS_2-VASc	Male Age 70 CHA_2DS_2-VASc 1	Apixaban (5mg bd) (0.518)	Apixaban (5mg bd) (0.5)
	Male Age 70 CHA_2DS_2-VASc 2	Apixaban (5mg bd) (0.523)	Apixaban (5mg bd) (0.523)
	Male Age 70 CHA_2DS_2-VASc 3	Apixaban (5mg bd) (0.514)	Apixaban (5mg bd) (0.521)

	Male Age 70 CHA_2DS_2-VASc >=4	Apixaban (5mg bd) (0.42)	Apixaban (5mg bd) (0.466)
	Female Age 70 CHA_2DS_2-VASc 2	Apixaban (5mg bd) (0.524)	Apixaban (5mg bd) (0.51)
	Female Age 70 CHA_2DS_2-VASc 3	Apixaban (5mg bd) (0.495)	Apixaban (5mg bd) (0.505)
	Female Age 70 CHA_2DS_2-VASc 4	Apixaban (5mg bd) (0.469)	Apixaban (5mg bd) (0.491)
	Female Age 70 CHA_2DS_2-VASc >=5	Dabigatran (150mg bd) (0.505)	Apixaban (5mg bd) (0.434)
	Male Age 60 CHA_2DS_2-VASc 0	Apixaban (5mg bd) (0.479)	Apixaban (5mg bd) (0.465)
	Male Age 60 CHA_2DS_2-VASc 1	Apixaban (5mg bd) (0.504)	Apixaban (5mg bd) (0.483)
	Male Age 60 CHA_2DS_2-VASc 2	Apixaban (5mg bd) (0.526)	Apixaban (5mg bd) (0.504)
	Male Age 60 CHA_2DS_2-VASc >=3	Apixaban (5mg bd) (0.46)	Apixaban (5mg bd) (0.485)
	Female Age 60 CHA_2DS_2-VASc 1	Apixaban (5mg bd) (0.519)	Apixaban (5mg bd) (0.504)
	Female Age 60 CHA_2DS_2-VASc 2	Apixaban (5mg bd) (0.512)	Apixaban (5mg bd) (0.511)
	Female Age 60 CHA_2DS_2-VASc 3	Apixaban (5mg bd) (0.518)	Apixaban (5mg bd) (0.503)
	Female Age 60 CHA_2DS_2-VASc >=4	Apixaban (5mg bd) (0.416)	Apixaban (5mg bd) (0.463)
	Age 80 (Gender and CHA_2DS_2-VASc distribution as in base case)	Apixaban (5mg bd) (0.428)	Apixaban (5mg bd) (0.467)
Sensitivty analyses	No switching after MI on dabigatran	Apixaban (5mg bd) (0.414)	Apixaban (5mg bd) (0.437)
	no patients switch treatment following ischaemic stroke, bleed, SE or TIA	Apixaban (5mg bd) (0.461)	Apixaban (5mg bd) (0.492)
	All patients switch treatments following stroke, bleed, SE, or TIA.	Apixaban (5mg bd) (0.621)	Apixaban (5mg bd) (0.634)

	All patients switch after a ischaemic stroke or bleed, but none switch after a SE or TIA	Apixaban (5mg bd) (0.573)	Apixaban (5mg bd) (0.599)
	No cost for warfarin	Apixaban (5mg bd) (0.451)	Apixaban (5mg bd) (0.471)
	No impact on mortality risk of bleeds or ICH	Apixaban (5mg bd) (0.418)	Apixaban (5mg bd) (0.44)
	Excluding Baataf study from warfarin vs no treatment meta-analysis	Apixaban (5mg bd) (0.458)	Apixaban (5mg bd) (0.473)
	Low dose apixaban and dabigatran	Apixaban (5mg bd) (0.507)	Apixaban (5mg bd) (0.516)
	No impact of warfarin on ICH	Apixaban (5mg bd) (0.473)	Apixaban (5mg bd) (0.509)
	TIA and SE move patients to post-stroke states (thus increasing CHA_2DS_2-VASc)	Apixaban (5mg bd) (0.478)	Apixaban (5mg bd) (0.502)
	Stroke and ICH costs ablation guidelines	Apixaban (5mg bd) (0.462)	Apixaban (5mg bd) (0.513)
Reversal agents sensitivity analyses	Standard-of-care reversal agents	Apixaban (5mg bd) (0.472)	Apixaban (5mg bd) (0.482)
	Reversal agenets with andexanet alfa for apixaban and rivaroxaban	Apixaban (5mg bd) (0.448)	Apixaban (5mg bd) (0.476)
	Standard-of-care reversal agents with 50% receiving PCC following bleed on coumarin	Apixaban (5mg bd) (0.456)	Apixaban (5mg bd) (0.481)
	Standard-of-care reversal agents with 10% receiving PCC following bleed on coumarin	Apixaban (5mg bd) (0.469)	Apixaban (5mg bd) (0.489)

6.8 Results of age, gender, and CHA_2DS_2-VASc scenario analyses

We used 10,000 simulations of the model for each scenario analysis. A summary of the results is provided in Table 66. Full cost-effectiveness acceptability curves and results matrices for each scenario are below. These scenario analyses indicate that for all men and for all women except those aged 70 with high stroke risk (i.e. CHA_2DS_2-VASc>=5) apixaban (5mg bd) has highest incremental net benefit at the £20,000-

30,000 range of willingness-to-pay thresholds. However, for women aged 70 with CHA_2DS_2-VASc≥5 dabigatran (150mg bd) has the highest incremental net benefit at the £20,000 willingness-to-pay threshold while apixaban (5mg bd) has the highest increment net benefit at the £30,000 willingness-to-pay threshold. This pattern is explained by the greater reduction in stroke risk conferred by dabigatran (as indicted by the NMA in Table 52) compared to apixaban; this reduction outweighs the higher risk of MI and bleed on dabigatran, relative to apixaban, when the stroke risk is higher. The scenario for a cohort aged 80 with 60% male and the distribution of CHA_2DS_2-VASc as in Table 61, apixaban (5mg bd) has highest incremental net benefit at £20,000-30,000 willingness-to-pay.

Note that there are two issues with face validity of these results. The first is that expected QALYs, which should be related to life expectancy, are not substantially lower going from age 60 to age 70 or from age 70 to age 80. The reason for this is that baseline mortality (i.e. mortality on warfarin (INR 2-3)) was based on a meta-analysis of mortality in the warfarin (INR 2-3) arms of RCTs included in the NMA (Section 6.2.4). These RCTs generally recruited from a sicker than the general population, with patients having at least one risk factor for stroke such as prior stroke or prior heart failure, and mean CHA_2DS_2-VASc was often around 2 for RCTs. Lifetables were only used to increment mortality with age, not estimate absolute mortality (Section 6.2.5). For this reason, life expectancy in the economic model is shorter than would be expected for an AF patient who is otherwise healthy.

The second issue is that expected QALYs are not decreasing uniformly with CHA_2DS_2-VASc score, as would be expected. For example, expected QALYs for all treatments for males aged 60 with CHA_2DS_2-VASc=0 (Table 75) are lower than for the same group with CHA_2DS_2-VASc=1 (Table 76). This could not be explained by reference to model inputs or structure and is likely due to simulation error; note the very wide credible intervals.

Neither of these issues greatly impact incremental QALYs and are not expected to have an impact on the conclusions that apixaban (5mg bd) and dabigatran (150mg bd) are the most cost-effective therapies for the cohorts under consideration.

Figure 27 Cost-effectiveness acceptability curves for scenario analysis of females, aged 60, with CHA_2DS_2-VASc 1

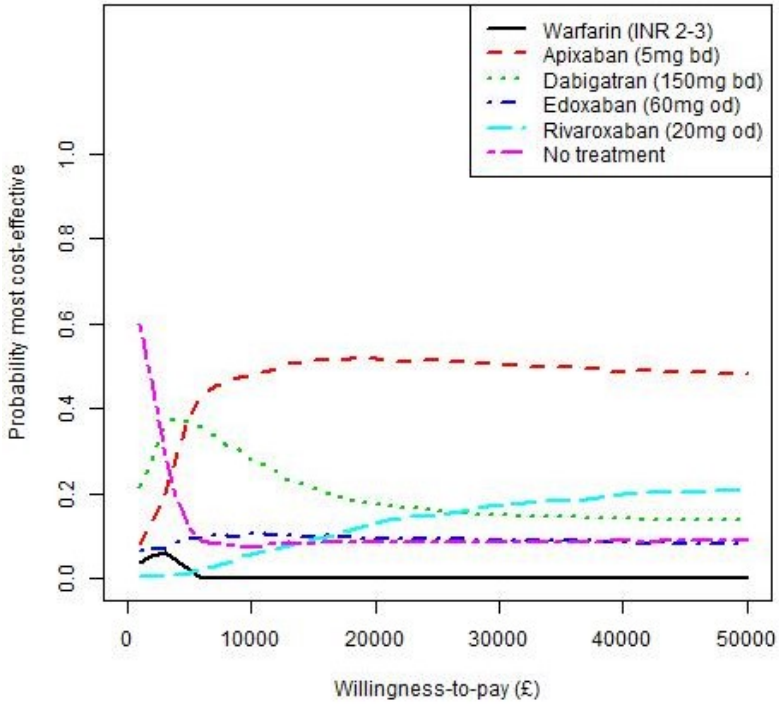


Figure 28 Cost-effectiveness acceptability curves for scenario analysis of females, aged 60, with CHA_2DS_2-VASc 2

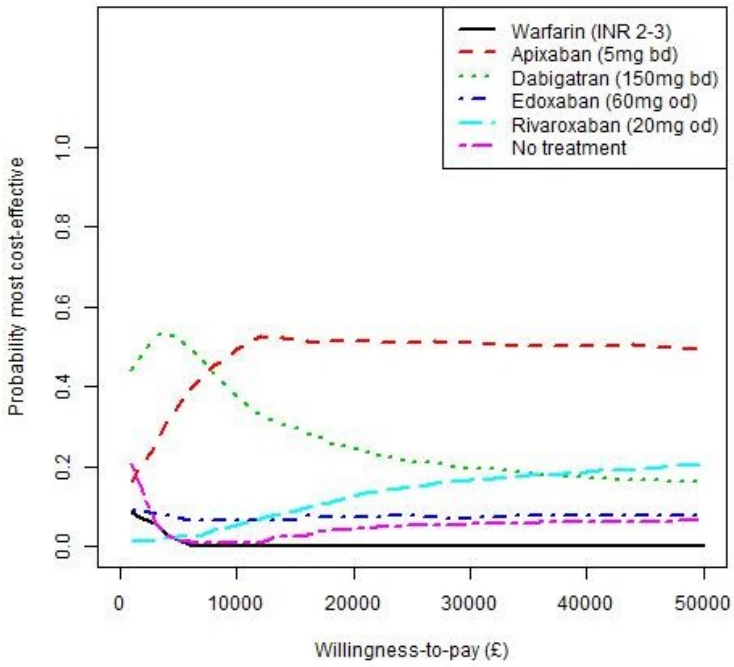


Figure 29 Cost-effectiveness acceptability curves for scenario analysis of females, aged 60, with CHA_2DS_2-VASc 3

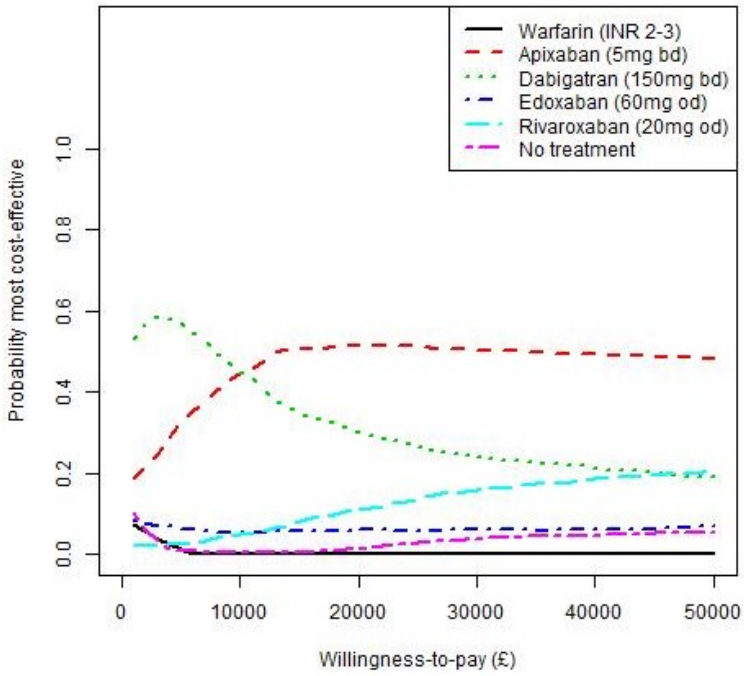


Figure 30 Cost-effectiveness acceptability curves for scenario analysis of females, aged 60, with CHA_2DS_2-VASc ≥4

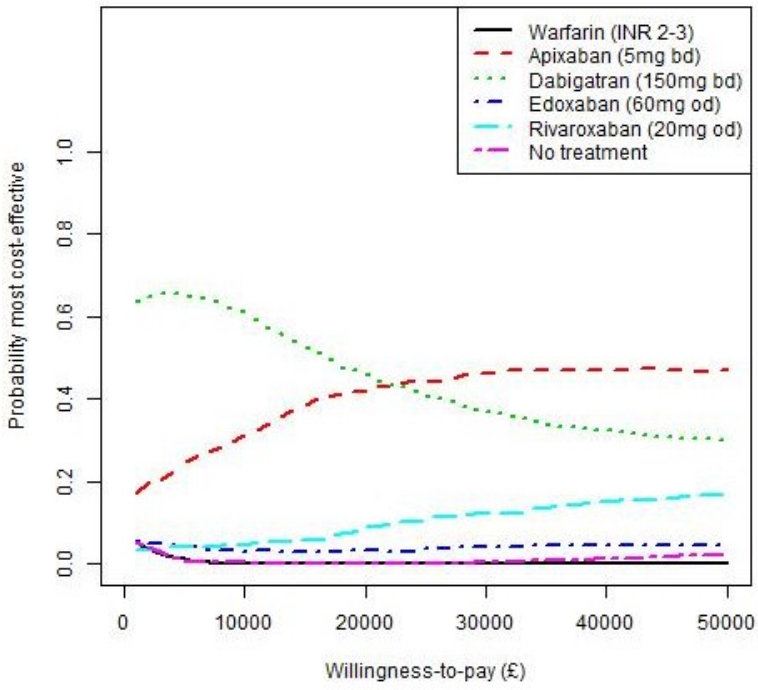


Figure 31 Cost-effectiveness acceptability curves for scenario analysis of females, aged 70, with CHA_2DS_2-VASc 2

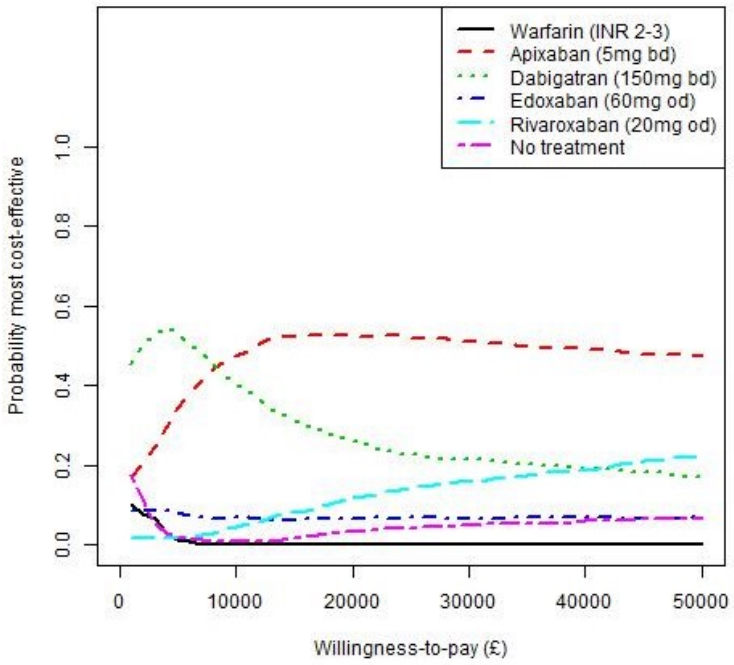


Figure 32 Cost-effectiveness acceptability curves for scenario analysis of females, aged 70, with CHA_2DS_2-VASc 3

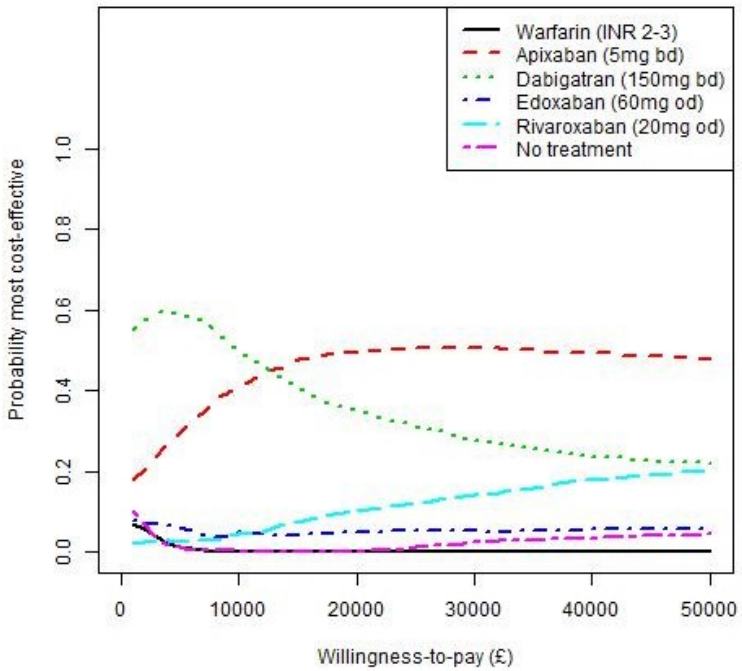


Figure 33 Cost-effectiveness acceptability curves for scenario analysis of females, aged 70, with CHA_2DS_2-VASc 4

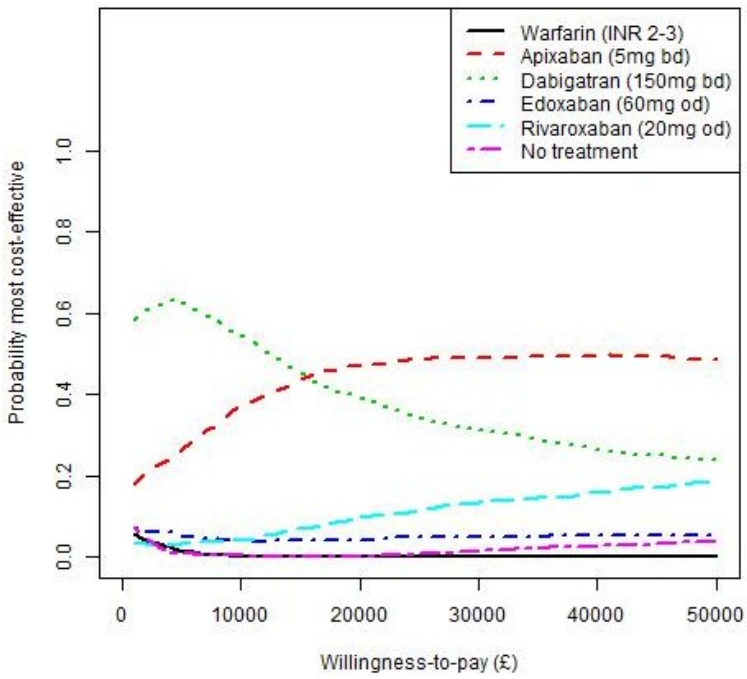


Figure 34 Cost-effectiveness acceptability curves for scenario analysis of females, aged 70, with CHA_2DS_2-VASc ≥5

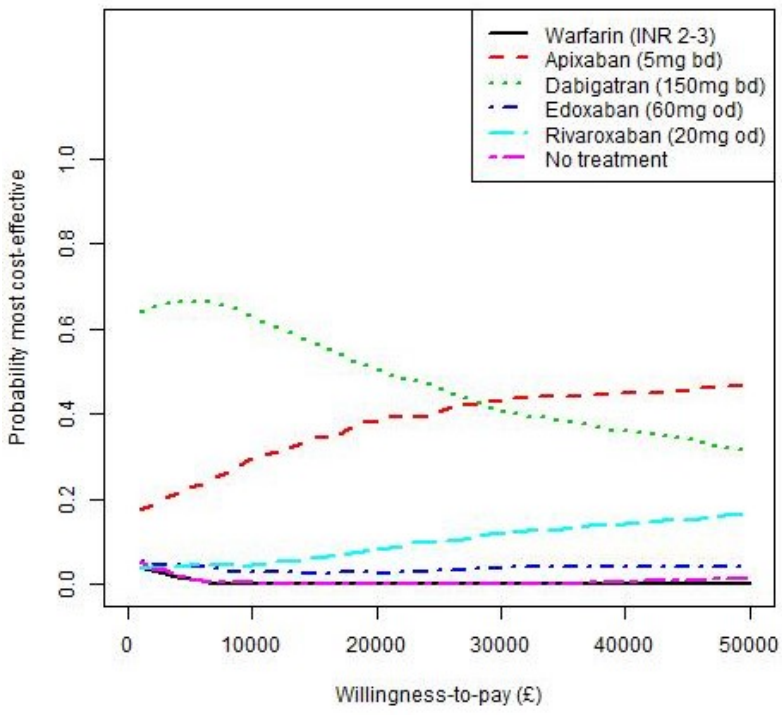


Figure 35 Cost-effectiveness acceptability curves for scenario analysis of males, aged 60, with CHA_2DS_2-VASc 0

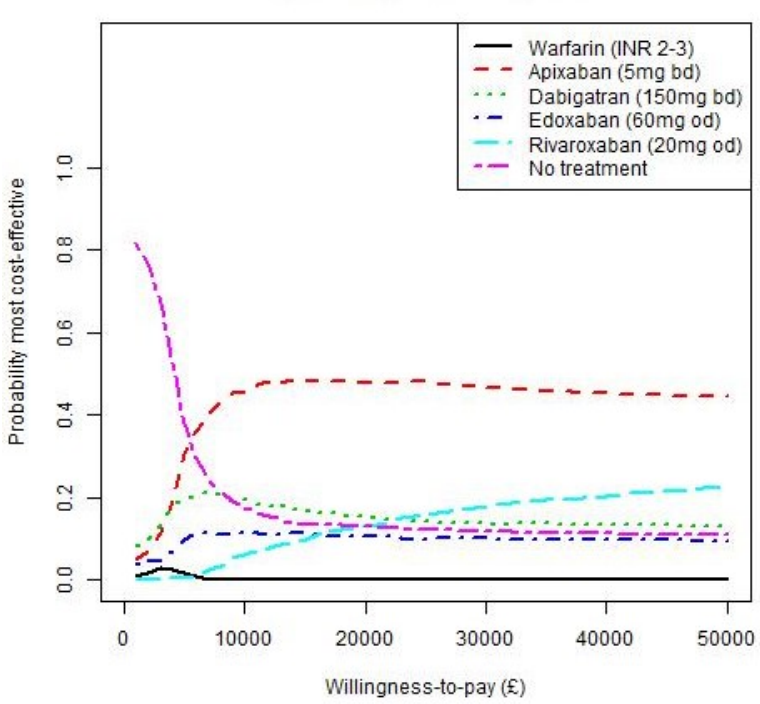


Figure 36 Cost-effectiveness acceptability curves for scenario analysis of males, aged 60, with CHA_2DS_2-VASc 1

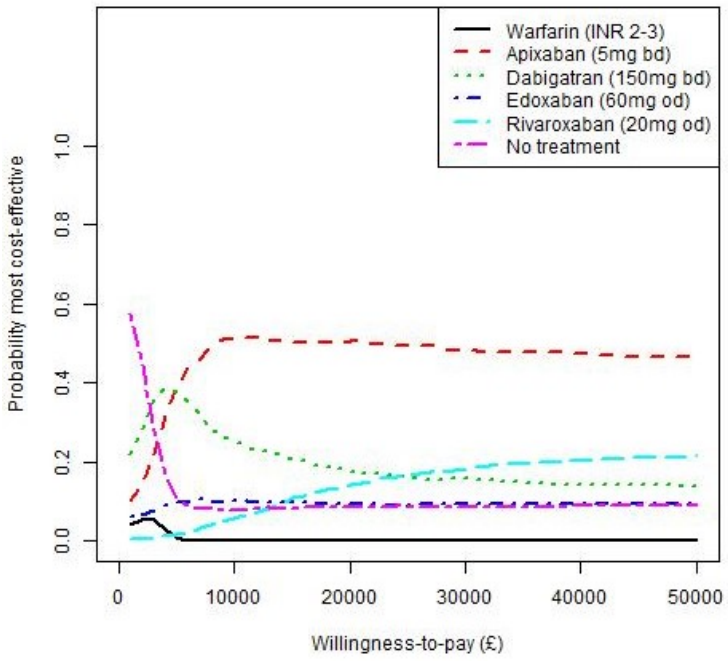


Figure 37 Cost-effectiveness acceptability curves for scenario analysis of males, aged 60, with CHA_2DS_2-VASc 2

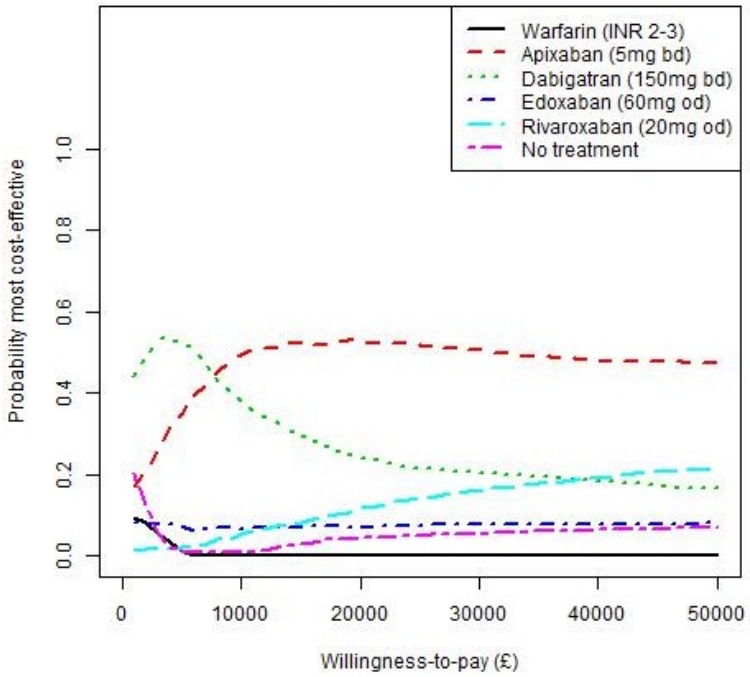


Figure 38 Cost-effectiveness acceptability curves for scenario analysis of males, aged 60, with CHA_2DS_2-VASc ≥3

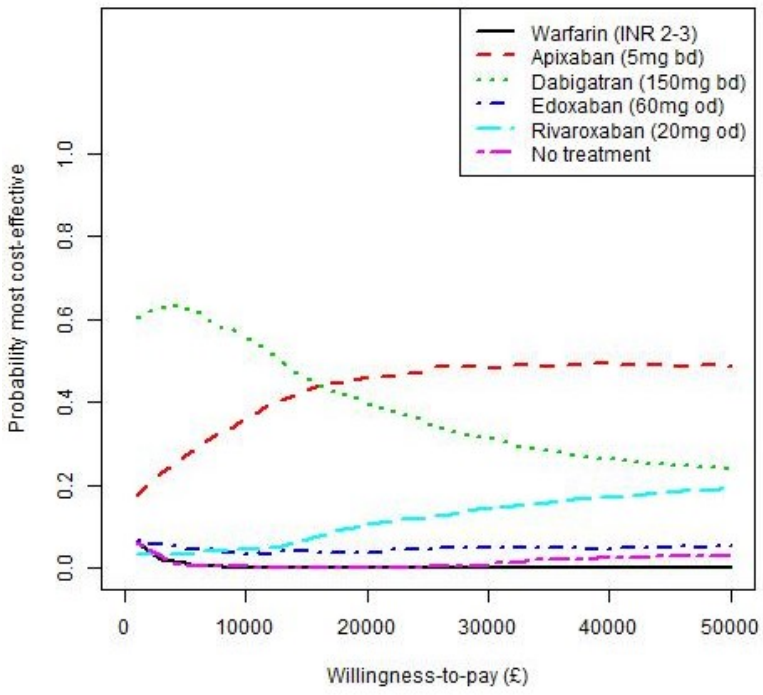


Figure 39 Cost-effectiveness acceptability curves for scenario analysis of males, aged 70, with CHA_2DS_2-VASc 1

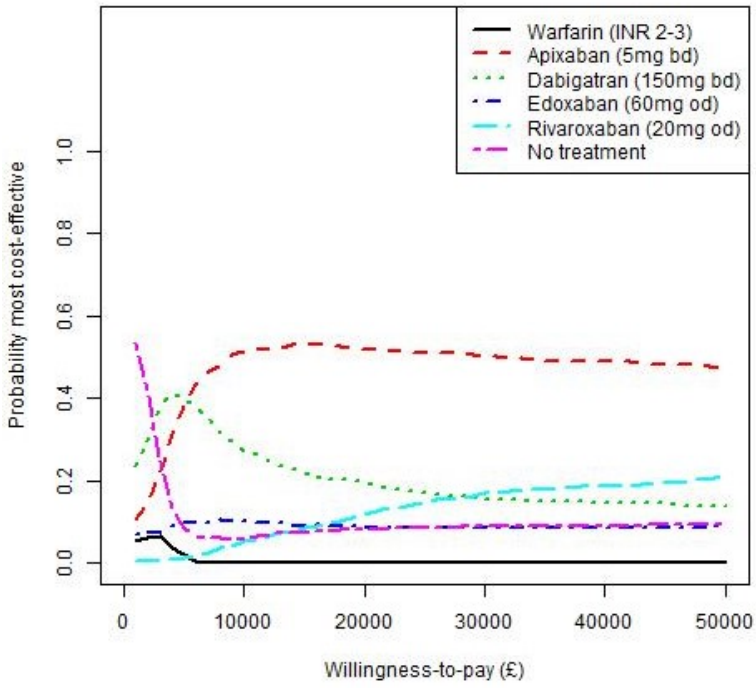


Figure 40 Cost-effectiveness acceptability curves for scenario analysis of males, aged 70, with CHA_2DS_2-VASc 2

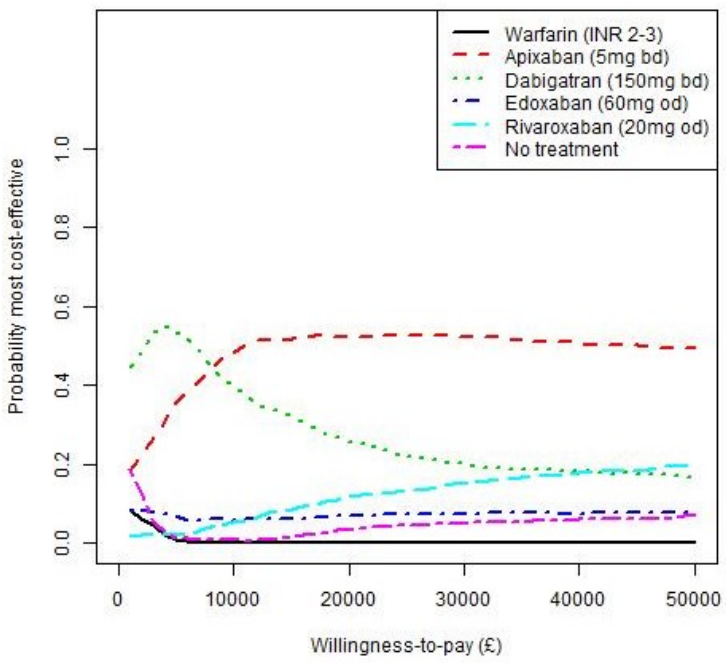


Figure 41 Cost-effectiveness acceptability curves for scenario analysis of males, aged 70, with CHA_2DS_2-VASc 3

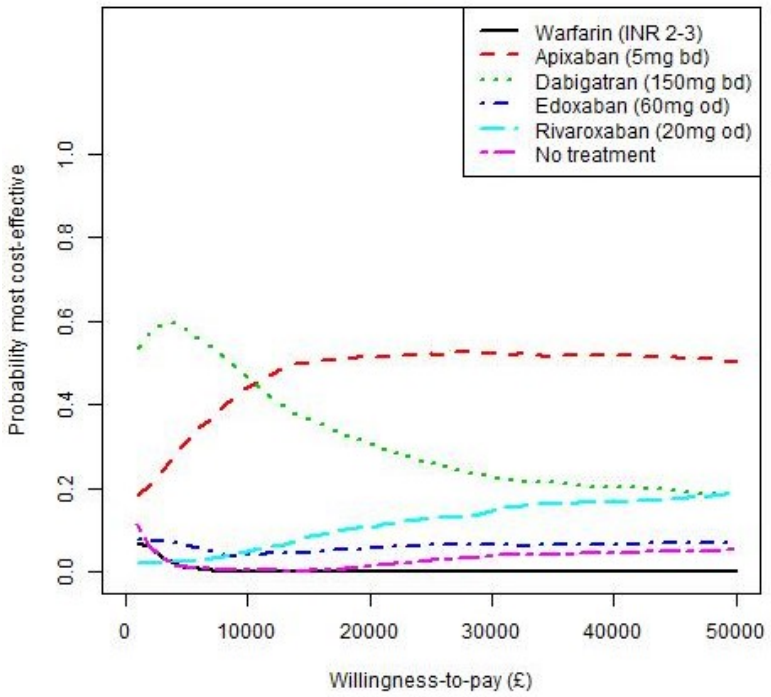


Figure 42 Cost-effectiveness acceptability curves for scenario analysis of males, aged 70, with CHA_2DS_2-VASc ≥4

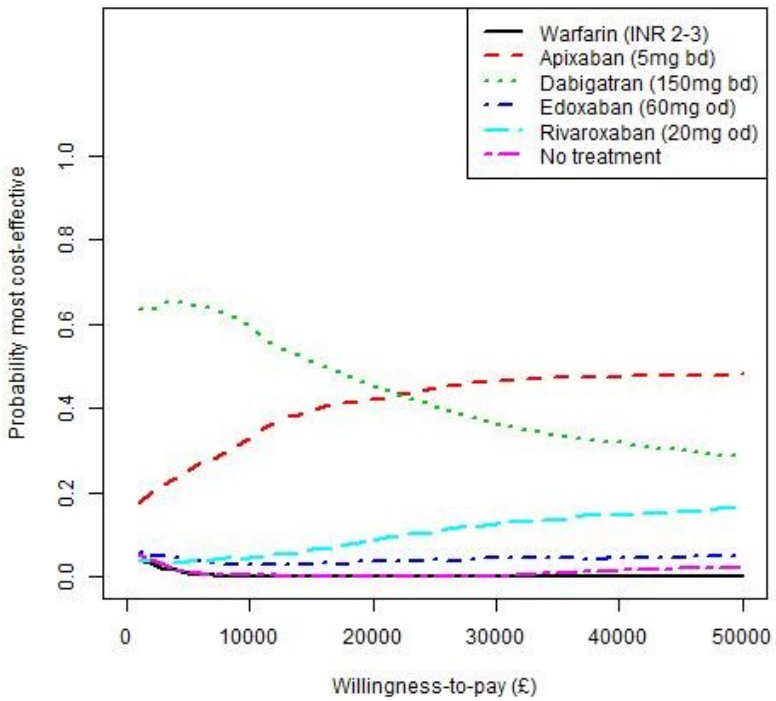


Figure 43 Cost-effectiveness acceptability curves for scenario analysis of a cohort starting at age 80 and gender split and CHA_2DS_2-VASc as in base case.

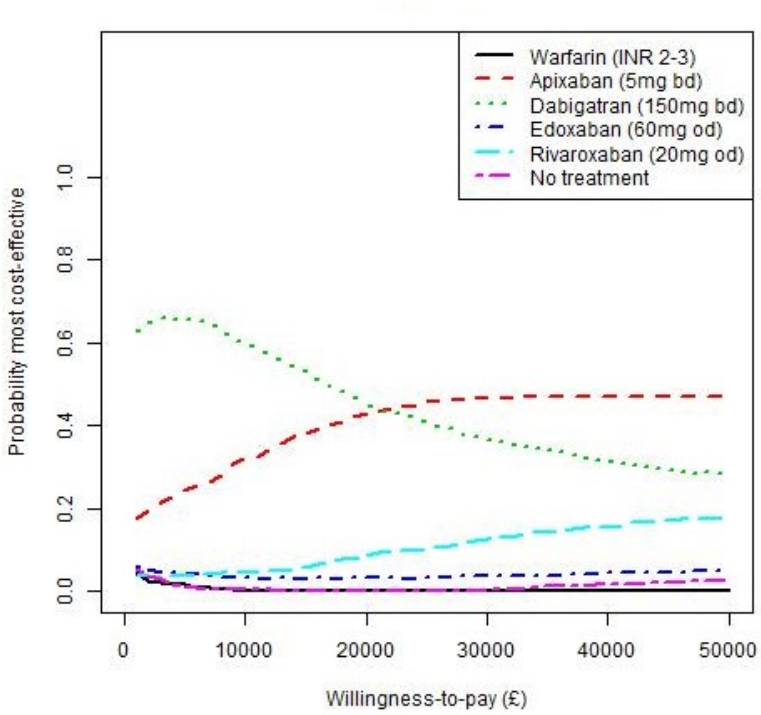


Table 67 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 70 with CHA_2DS_2-VASc 1

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	17263 (10161, 31553)	16962 (12085, 26124)	16553 (10933, 26890)	17268 (11863, 27263)	19355 (12720, 32781)	16459 (4543, 43771)
Expected QALYs	5.678 (4.755, 6.627)	6.162 (5.257, 7.083)	6.009 (5.089, 6.9)	6.016 (5.095, 6.913)	6.101 (5.108, 7.083)	5.112 (2.752, 7.672)
Expected Incremental Total Costs	- (-, -)	-301.1 (-6916, 3087)	-709.9 (-8199, 3075)	4.492 (-6241, 4245)	2092 (-3578, 5845)	-804.4 (-9656, 16852)
Incremental Expected QALYs	- (-, -)	0.4841 (0.07249, 0.8214)	0.3303 (-0.1114, 0.704)	0.338 (-0.09311, 0.67)	0.423 (-0.06352, 0.8284)	-0.5661 (-2.477, 1.452)
Incremental Expected Net Benefit (£20,000)	- (-, -)	9983 (3458, 17937)	7317 (-1595, 16087)	6755 (-1257, 14598)	6369 (-2576, 15057)	-10518 (-50213, 20710)
Incremental Expected Net Benefit (£30,000)	- (-, -)	14824 (4559, 25730)	10620 (-2188, 22378)	10135 (-886.9, 21089)	10599 (-3179, 23043)	-16178 (-74222, 35055)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 68 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 70 with CHA_2DS_2-VASc 2

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	21040 (12170, 37931)	20456 (13926, 31612)	19615 (12834, 33016)	20969 (14007, 33042)	22969 (15134, 39205)	24122 (7200, 58375)
Expected QALYs	5.686 (4.676, 6.585)	6.197 (5.236, 7.112)	6.051 (5.097, 6.996)	6.043 (5.037, 6.92)	6.128 (5.097, 7.059)	5.055 (2.65, 7.616)
Expected Incremental Total Costs	- (-, -)	-583.5 (-9156, 3530)	-1424 (-9522, 3001)	-70.61 (-7552, 4566)	1929 (-4249, 6045)	3082 (-9071, 25979)
Incremental Expected QALYs	- (-, -)	0.5118 (0.09304, 0.8391)	0.3653 (-0.07122, 0.739)	0.3571 (-0.02738, 0.708)	0.442 (-0.0407, 0.8664)	-0.6302 (-2.566, 1.231)

Incremental Expected Net Benefit (£20,000)	- (-, -)	10820 (4388, 18923)	8729 (-342.7, 17331)	7212 (3.374, 15210)	6911 (-1463, 16031)	-15685 (-51778, 11426)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15938 (6181, 26638)	12382 (-537.5, 23766)	10783 (106.8, 21036)	11331 (-1460, 23732)	-21987 (-75857, 23988)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 69 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 70 with CHA_2DS_2-VASc 3

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	23342 (13898, 41202)	22615 (15462, 34641)	21438 (14090, 34518)	23246 (15702, 35375)	25212 (16809, 41289)	29149 (9101, 65609)
Expected QALYs	5.592 (4.668, 6.467)	6.101 (5.241, 6.981)	5.954 (5.054, 6.844)	5.944 (5.069, 6.846)	6.03 (5.103, 6.993)	4.932 (2.693, 7.343)
Expected Incremental Total Costs	- (-, -)	-727.2 (-8524, 3912)	-1904 (-9563, 2827)	-95.78 (-7842, 5574)	1870 (-4328, 6314)	5807 (-9259, 28547)
Incremental Expected QALYs	- (-, -)	0.5088 (0.1102, 0.8332)	0.3616 (-0.07855, 0.7492)	0.3519 (-0.03564, 0.705)	0.4379 (-0.02873, 0.8399)	-0.6601 (-2.415, 1.216)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10904 (4326, 19678)	9136 (726.7, 18334)	7135 (-801.2, 15255)	6887 (-1083, 16494)	-19009 (-53989, 5102)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15992 (6404, 26924)	12753 (695.9, 24963)	10654 (-132.3, 20759)	11265 (-1119, 24822)	-25611 (-74130, 15586)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 70 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 70 with CHA_2DS_2-VASc ≥4

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	31815 (19552, 56467)	30690 (20915, 47194)	28498 (18616, 44529)	31633 (21061, 48843)	33399 (22314, 53123)	44759 (15621, 94984)
Expected QALYs	5.512 (4.609, 6.434)	6.043 (5.115, 6.957)	5.917 (4.985, 6.82)	5.885 (4.986, 6.797)	5.97 (4.944, 6.946)	4.731 (2.52, 7.13)
Expected Incremental Total Costs	- (-, -)	-1124 (-11307, 5143)	-3317 (-13065, 3117)	-182 (-10533, 6493)	1584 (-6765, 8720)	12944 (-10343, 49384)
Incremental Expected QALYs	- (-, -)	0.5315 (0.09711, 0.8816)	0.4053 (-0.06243, 0.8019)	0.3734 (-0.02613, 0.716)	0.4582 (-0.01991, 0.8761)	-0.7813 (-2.52, 1.076)
Incremental Expected Net Benefit (£20,000)	- (-, -)	11753 (4531, 21581)	11424 (1898, 22031)	7649 (480.4, 15924)	7580 (-688, 18125)	-28571 (-62304, -8930)
Incremental Expected Net Benefit (£30,000)	- (-, -)	17068 (7601, 29658)	15477 (2150, 28686)	11383 (1767, 21796)	12162 (51.23, 26294)	-36384 (-85940, -2163)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 71 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 70 with CHA_2DS_2-VASc 2

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	19989 (11503, 37346)	19475 (13501, 31271)	18669 (12285, 31190)	19936 (13438, 31112)	21865 (14529, 37213)	23091 (7299, 59141)
Expected QALYs	5.415 (4.582, 6.284)	5.88 (5.03, 6.717)	5.744 (4.889, 6.625)	5.742 (4.899, 6.54)	5.817 (4.901, 6.714)	4.822 (2.575, 7.125)
Expected Incremental Total Costs	- (-, -)	-514.9 (-8365, 3559)	-1320 (-9211, 2748)	-53.38 (-7542, 4518)	1875 (-4811, 5998)	3101 (-8987, 27796)
Incremental Expected QALYs	- (-, -)	0.4652 (0.06966, 0.7814)	0.3286 (-0.1092, 0.6764)	0.3269 (-0.04868, 0.6355)	0.4023 (-0.04361, 0.7916)	-0.5929 (-2.344, 1.176)

Incremental Expected Net Benefit (£20,000)	- (-, -)	9818 (3695, 18357)	7892 (-381.9, 16460)	6592 (-440.6, 13820)	6172 (-1679, 14603)	-14960 (-53885, 9957)
Incremental Expected Net Benefit (£30,000)	- (-, -)	14470 (5279, 24971)	11178 (-682.3, 22368)	9862 (-144.6, 19938)	10195 (-1534, 21587)	-20889 (-74103, 21002)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 72 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 70 with CHA_2DS_2-VASc 3

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	24300 (14928, 43727)	23555 (16428, 35963)	22224 (14893, 34988)	24229 (16404, 37962)	26047 (17437, 41101)	31167 (9503, 73675)
Expected QALYs	5.438 (4.547, 6.307)	5.927 (5.001, 6.763)	5.792 (4.856, 6.704)	5.778 (4.885, 6.671)	5.861 (4.873, 6.815)	4.762 (2.522, 6.913)
Expected Incremental Total Costs	- (-, -)	-744.8 (-9956, 4314)	-2075 (-10677, 2793)	-70.3 (-8801, 5985)	1747 (-5454, 7374)	6867 (-9630, 34642)
Incremental Expected QALYs	- (-, -)	0.4884 (0.09985, 0.822)	0.3536 (-0.05473, 0.7056)	0.3398 (-0.05437, 0.645)	0.4231 (-0.0183, 0.8195)	-0.6759 (-2.429, 1.007)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10512 (4122, 19129)	9147 (604.3, 17949)	6867 (-1020, 14438)	6715 (-920.5, 16003)	-20385 (-56785, 1020)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15396 (6252, 25620)	12683 (563.9, 23826)	10265 (-693.9, 20352)	10947 (-850.6, 22833)	-27143 (-77839, 9960)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 73 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 70 with CHA_2DS_2-VASc 4

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	25913 (14990, 45765)	24995 (16808, 40589)	23458 (15224, 39042)	25723 (16977, 42395)	27550 (17909, 45165)	34597 (10819, 74386)
Expected QALYs	5.331 (4.403, 6.192)	5.805 (4.983, 6.672)	5.682 (4.826, 6.525)	5.663 (4.775, 6.486)	5.741 (4.811, 6.654)	4.66 (2.611, 6.941)
Expected Incremental Total Costs	- (-, -)	-917.8 (-9157, 4338)	-2455 (-11225, 3041)	-190 (-8726, 6382)	1637 (-5978, 7379)	8684 (-7540, 35753)
Incremental Expected QALYs	- (-, -)	0.474 (0.1, 0.7977)	0.3505 (-0.04628, 0.716)	0.3314 (-0.02378, 0.6385)	0.4093 (-0.009175, 0.8304)	-0.671 (-2.267, 1.021)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10398 (4222, 18407)	9466 (1595, 18854)	6818 (-122.5, 14087)	6549 (-893.2, 15770)	-22105 (-51391, -1238)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15138 (6411, 24736)	12971 (2292, 25727)	10132 (642.8, 19237)	10643 (-393.1, 23894)	-28816 (-77505, 6972)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 74 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 70 with CHA_2DS_2-VASc ≥5

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	33155 (20050, 59446)	31843 (21333, 48218)	29474 (18730, 47327)	32915 (21552, 50516)	34517 (22212, 52888)	47681 (16698, 97282)
Expected QALYs	5.128 (4.272, 5.916)	5.597 (4.733, 6.335)	5.491 (4.62, 6.283)	5.456 (4.612, 6.21)	5.529 (4.61, 6.353)	4.39 (2.364, 6.498)
Expected Incremental Total Costs	- (-, -)	-1311 (-12349, 5149)	-3680 (-14669, 2702)	-240 (-11316, 6930)	1363 (-8534, 8929)	14526 (-9097, 47546)
Incremental Expected QALYs	- (-, -)	0.4695 (0.07851, 0.782)	0.3636 (-0.0449, 0.7234)	0.3284 (-0.06663, 0.642)	0.4015 (-0.02382, 0.7569)	-0.7381 (-2.352, 0.8133)

Incremental Expected Net Benefit (£20,000)	- (-, -)	10700 (3366, 21831)	10952 (2716, 21664)	6809 (-538.1, 16092)	6667 (-877.8, 16871)	-29288 (-57180, -10719)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15395 (6289, 28869)	14588 (3675, 27148)	10093 (112.4, 21229)	10681 (-8.924, 22587)	-36670 (-79073, -5423)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 75 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 60 with CHA_2DS_2-VASc 0

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	14747 (8338, 28363)	14610 (10328, 22635)	14402 (9594, 23997)	14852 (9953, 24447)	16925 (11011, 28570)	11323 (3173, 32485)
Expected QALYs	5.717 (4.813, 6.67)	6.207 (5.34, 7.126)	6.045 (5.144, 6.988)	6.058 (5.131, 6.973)	6.147 (5.185, 7.175)	5.179 (2.712, 7.835)
Expected Incremental Total Costs	- (-, -)	-137.1 (-6618, 3061)	-345 (-7090, 3358)	105.3 (-6202, 3757)	2178 (-3207, 5402)	-3424 (-11266, 10142)
Incremental Expected QALYs	- (-, -)	0.4906 (0.08757, 0.8223)	0.3278 (-0.1255, 0.7077)	0.3416 (-0.053, 0.658)	0.4303 (-0.03827, 0.8414)	-0.538 (-2.727, 1.541)
Incremental Expected Net Benefit (£20,000)	- (-, -)	9949 (2569, 18862)	6902 (-2791, 16147)	6726 (-2127, 15076)	6427 (-2909, 15815)	-7335 (-50007, 32760)
Incremental Expected Net Benefit (£30,000)	- (-, -)	14855 (3884, 25984)	10180 (-3827, 22982)	10142 (-2376, 21389)	10730 (-3406, 23696)	-12715 (-77670, 49444)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 76 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 60 with CHA_2DS_2-VASc 1

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	16913 (9745, 31307)	16634 (11666, 25954)	16172 (10909, 27311)	16952 (11628, 27076)	18997 (12602, 32095)	15867 (4239, 42273)
Expected QALYs	5.875 (4.942, 6.888)	6.387 (5.425, 7.356)	6.224 (5.294, 7.239)	6.234 (5.326, 7.199)	6.323 (5.346, 7.345)	5.295 (2.737, 8.101)
Expected Incremental Total Costs	- (-, -)	-279 (-7363, 3208)	-741.3 (-7144, 2859)	38.71 (-6613, 3829)	2084 (-3087, 5390)	-1046 (-9613, 14602)
Incremental Expected QALYs	- (-, -)	0.5114 (0.08062, 0.857)	0.3489 (-0.09347, 0.7389)	0.3587 (-0.03753, 0.7104)	0.4479 (-0.04282, 0.9144)	-0.5801 (-2.694, 1.635)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10507 (3605, 18969)	7720 (-1867, 17365)	7135 (-1104, 14575)	6874 (-2296, 16655)	-10557 (-49744, 23873)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15621 (5029, 26314)	11209 (-2653, 24127)	10722 (-1249, 21191)	11352 (-2607, 25953)	-16358 (-75653, 37989)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 77 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 60 with CHA_2DS_2-VASc 2

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	20209 (11791, 36291)	19666 (13770, 30998)	18870 (12539, 31973)	20125 (13810, 32907)	22164 (14709, 37913)	22649 (7196, 60183)
Expected QALYs	5.705 (4.751, 6.67)	6.21 (5.269, 7.114)	6.051 (5.115, 7.015)	6.059 (5.167, 6.959)	6.141 (5.101, 7.116)	5.069 (2.527, 7.69)
Expected Incremental Total Costs	- (-, -)	-543.1 (-7619, 3591)	-1340 (-8383, 3216)	-83.84 (-6930, 4304)	1955 (-3659, 6226)	2440 (-8906, 23509)

Incremental Expected QALYs	- (-, -)	0.5044 (0.05009, 0.8545)	0.3462 (-0.1237, 0.727)	0.3542 (-0.06317, 0.7152)	0.4356 (-0.07814, 0.8728)	-0.6356 (-2.792, 1.472)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10632 (3765, 19519)	8263 (-302.1, 17030)	7167 (-642.2, 15232)	6757 (-1850, 15529)	-15151 (-55299, 14609)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15677 (4989, 27081)	11725 (-1461, 23739)	10709 (-1950, 21528)	11113 (-2302, 23771)	-21507 (-86185, 29039)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 78 Cost-effectiveness of first line treatment strategies for AF patients for males, aged 60 with CHA_2DS_2-VASc ≥3

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	28638 (17306, 49752)	27618 (18882, 42286)	25861 (16629, 40710)	28454 (18949, 43611)	30286 (19863, 48396)	39128 (12712, 86613)
Expected QALYs	5.426 (4.476, 6.322)	5.953 (5.022, 6.823)	5.819 (4.832, 6.782)	5.797 (4.878, 6.655)	5.881 (4.891, 6.865)	4.696 (2.364, 7.128)
Expected Incremental Total Costs	- (-, -)	-1020 (-10787, 4785)	-2778 (-12001, 3243)	-183.9 (-9332, 6189)	1648 (-6282, 8027)	10490 (-8551, 40088)
Incremental Expected QALYs	- (-, -)	0.5276 (0.08924, 0.869)	0.3934 (-0.03382, 0.8072)	0.3709 (-0.07925, 0.7702)	0.4551 (-0.004683, 0.9044)	-0.7301 (-2.521, 1.106)
Incremental Expected Net Benefit (£20,000)	- (-, -)	11573 (4737, 21741)	10645 (1323, 20492)	7602 (-456, 17242)	7455 (-567.5, 17434)	-25093 (-58751, -4065)
Incremental Expected Net Benefit (£30,000)	- (-, -)	16849 (7629, 28301)	14579 (2383, 27518)	11310 (257.8, 22247)	12006 (79.17, 25453)	-32394 (-79761, 3420)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 79 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 60 with CHA_2DS_2-VASc 1

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	16080 (9208, 28460)	15890 (11222, 24314)	15431 (10425, 24966)	16118 (11096, 25139)	18161 (12110, 29480)	15087 (4298, 42900)
Expected QALYs	5.837 (4.878, 6.758)	6.323 (5.394, 7.209)	6.167 (5.241, 7.052)	6.179 (5.287, 7.058)	6.256 (5.293, 7.226)	5.277 (2.918, 7.909)
Expected Incremental Total Costs	- (-, -)	-189.7 (-6609, 3146)	-649.4 (-7273, 3010)	37.76 (-6041, 3927)	2081 (-3037, 5438)	-992.8 (-9530, 16031)
Incremental Expected QALYs	- (-, -)	0.4864 (0.08677, 0.8496)	0.3305 (-0.09979, 0.7129)	0.3421 (-0.03996, 0.6924)	0.4198 (-0.06049, 0.8298)	-0.5594 (-2.52, 1.412)
Incremental Expected Net Benefit (£20,000)	- (-, -)	9917 (3228, 18030)	7260 (-1998, 16278)	6805 (-1108, 14423)	6316 (-2733, 15089)	-10196 (-50912, 22660)
Incremental Expected Net Benefit (£30,000)	- (-, -)	14781 (4255, 25665)	10566 (-2829, 22985)	10226 (-1250, 21155)	10514 (-2896, 23302)	-15790 (-79331, 36758)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 80 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 60 with CHA_2DS_2-VASc 2

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	19443 (11450, 34903)	18960 (13359, 29532)	18137 (12207, 29761)	19449 (13250, 30277)	21373 (14390, 34982)	21891 (6682, 54609)
Expected QALYs	5.863 (4.87, 6.735)	6.352 (5.417, 7.265)	6.204 (5.243, 7.138)	6.203 (5.293, 7.087)	6.285 (5.28, 7.228)	5.226 (2.703, 7.734)
Expected Incremental Total Costs	- (-, -)	-482.3 (-7311, 3442)	-1306 (-8261, 2762)	6.618 (-6303, 4380)	1931 (-3784, 5744)	2448 (-9168, 22764)
Incremental Expected QALYs	- (-, -)	0.4888 (0.08814, 0.8392)	0.3409 (-0.0753, 0.716)	0.3397 (-0.05144, 0.6645)	0.4221 (-0.05272, 0.8414)	-0.6367 (-2.574, 1.342)

Incremental Expected Net Benefit (£20,000)	- (-, -)	10258 (3677, 19004)	8123 (-597.6, 16563)	6788 (-932.6, 14636)	6511 (-2098, 15233)	-15182 (-52667, 13326)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15145 (5366, 26377)	11532 (-951.7, 23408)	10186 (-721.9, 20297)	10732 (-1653, 22805)	-21548 (-75849, 24906)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 81 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 60 with CHA_2DS_2-VASc 3

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	22258 (13426, 39990)	21654 (15336, 33385)	20556 (13704, 32578)	22229 (15009, 34064)	24084 (16041, 39538)	27734 (8780, 63542)
Expected QALYs	5.794 (4.83, 6.677)	6.295 (5.342, 7.18)	6.151 (5.183, 7.083)	6.141 (5.199, 6.972)	6.228 (5.232, 7.144)	5.118 (2.751, 7.545)
Expected Incremental Total Costs	- (-, -)	-603.6 (-8576, 3740)	-1702 (-9179, 2921)	-28.67 (-7489, 4902)	1826 (-4621, 6726)	5476 (-8454, 31417)
Incremental Expected QALYs	- (-, -)	0.5009 (0.1039, 0.8222)	0.3561 (-0.0641, 0.7237)	0.3469 (-0.04158, 0.6803)	0.4337 (-0.05349, 0.83)	-0.676 (-2.584, 1.243)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10621 (4363, 20063)	8824 (-267.8, 18781)	6967 (233.3, 15890)	6848 (-1503, 15256)	-18995 (-56830, 5948)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15630 (6043, 28161)	12385 (474, 24730)	10437 (437, 22224)	11185 (-1292, 23193)	-25755 (-81732, 16534)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 82 Cost-effectiveness of first line treatment strategies for AF patients for females, aged 60 with CHA_2DS_2-VASc ≥4

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	30393 (18233, 53120)	29273 (19961, 45513)	27153 (17701, 42510)	30249 (19995, 46417)	31860 (21100, 50653)	43151 (15569, 91460)
Expected QALYs	5.378 (4.443, 6.242)	5.883 (4.945, 6.696)	5.762 (4.895, 6.589)	5.728 (4.805, 6.555)	5.812 (4.856, 6.709)	4.628 (2.474, 6.81)
Expected Incremental Total Costs	- (-, -)	-1120 (-12190, 5173)	-3241 (-13007, 2768)	-144.2 (-9980, 7334)	1467 (-6878, 8542)	12758 (-7613, 47098)
Incremental Expected QALYs	- (-, -)	0.5044 (0.115, 0.8332)	0.3836 (-0.03772, 0.7441)	0.3495 (-0.07428, 0.6685)	0.4333 (-0.01674, 0.8247)	-0.7502 (-2.467, 0.9582)
Incremental Expected Net Benefit (£20,000)	- (-, -)	11207 (4167, 20944)	10913 (1753, 20362)	7135 (-190, 16671)	7199 (-883.8, 17675)	-27762 (-60997, -8373)
Incremental Expected Net Benefit (£30,000)	- (-, -)	16251 (7051, 28646)	14749 (2062, 26046)	10631 (262.8, 21009)	11533 (-571.3, 24041)	-35264 (-82040, -1774)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 83 Cost-effectiveness of first line treatment strategies for AF patients for a cohort aged 80 with gender and CHA_2DS_2-VASc distribution as in the base case

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	30639 (18628, 53568)	29502 (19619, 44839)	27412 (17956, 43865)	30450 (20534, 46678)	32223 (21026, 51879)	43266 (15046, 92801)
Expected QALYs	5.178 (4.315, 6.031)	5.672 (4.837, 6.473)	5.553 (4.745, 6.454)	5.528 (4.744, 6.352)	5.602 (4.718, 6.502)	4.439 (2.431, 6.659)
Expected Incremental Total Costs	- (-, -)	-1138 (-10788, 4748)	-3227 (-12968, 2994)	-189.7 (-10692, 6774)	1584 (-6721, 8576)	12626 (-10188, 47921)
Incremental Expected QALYs	- (-, -)	0.4938 (0.1074, 0.8149)	0.375 (-0.03421, 0.7328)	0.3498 (-0.00241, 0.6549)	0.4239 (-0.03613, 0.8102)	-0.7387 (-2.38, 0.9924)
Incremental Expected Net Benefit (£20,000)	- (-, -)	11015 (4230, 20621)	10728 (2753, 20229)	7187 (-171.4, 15645)	6894 (-445.3, 16924)	-27401 (-62847, -7240)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15953 (7204, 27029)	14478 (3428, 27196)	10685 (1124, 20708)	11133 (-6.71, 23310)	-34788 (-82110, -160.2)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

6.9 Results of sensitivity analyses

We used 10,000 simulations of the model for each sensitivity analysis. A general overview of impact on conclusions is provided in Table 66. Our conclusion that apixaban (5mg bd) and dabigatran (150mg bd) have the highest incremental net benefits at willingness-to-pay thresholds in the range £20,000-30,000 was unchanged by any sensitivity.

To explore whether results were sensitive to the assumed costs of warfarin, we began with the extreme case where there is no administration or monitoring costs for warfarin. We found this had little effect on the conclusion that apixaban (5mg bd) is most cost-effective at £20,000-30,000 (Figure 44). Clearly if warfarin is not cost-effective with zero monitoring costs, then it will not be cost-effective with monitoring costs greater than this. We therefore omit the sensitivity analyses with higher monitoring costs. Similarly, the assumption that ICH and other CRBs have no effect on future mortality risk did not alter the conclusions (Figure 45).

Different treatment switching strategies were also explored. If patients only switch to no treatment when they experience an ICH or an MI (if on dabigatran), apixaban (5mg bd) remains most cost-effective in the range £20,000-30,000 (Figure 46). If all patients switch treatments after ischaemic stroke, bleed, SE and TIA, in addition to the switching after ICH and MI (for dabigatran), then patients only spend a short time on a NOAC before switching to warfarin. In this scenario, apixaban (5mg bd) remains most cost-effective in the range £20,000-30,000 (Figure 47). We also considered a switching strategy where all patients switch after an ischaemic stroke or clinically relevant bleed, and none switch after a TIA or SE, and again found apixaban (5mg bd) remains most cost-effective in the range £20,000-30,000 (Figure 48). Excluding the BAATAF also did not change apixaban (5mg bd) being most cost-effective in the range £20,000-30,000 (Figure 49).

Lower doses of apixaban (2.5mg bd) and dabigatran (110mg bd) are recommended for elderly patients and were compared in a sensitivity analysis (Figure 50). In this

sensitivity apixaban (2.5mg bd) is most likely to be the most cost-effective first line therapy for the prevention of stroke in AF. If assuming that the hazard of ICH is the same for no treatment as for warfarin apixaban (5mg bd) remains most cost-effective in the range £20,000-30,000 (Figure 51). In the sensitivity analysis where TIA and SE move patients into the post-stroke states, apixaban (5mg bd) remains most cost-effective in the range £20,000-30,000 (Figure 52).

Using the costs of stroke and ICH from the NICE AF ablation guidelines gives apixaban (5mg bd) as most cost-effective at £20,000 (probability 0.462) and £30,000 (probability 0.513) (Figure 53).

Figure 44 Cost-effectiveness acceptability curves for sensitivity analysis assuming cost of warfarin treatment is zero.

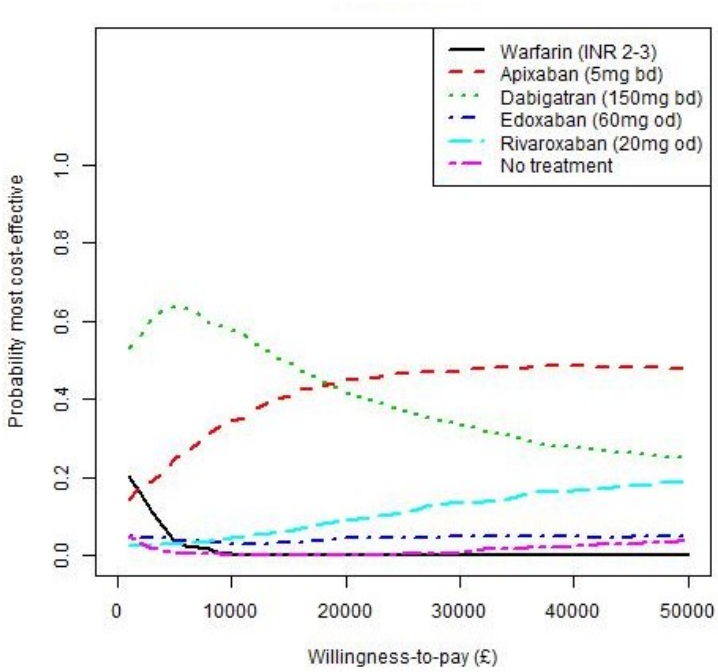


Figure 45 Cost-effectiveness acceptability curves for sensitivity analysis assuming no effect of bleed or ICH on mortality risk.

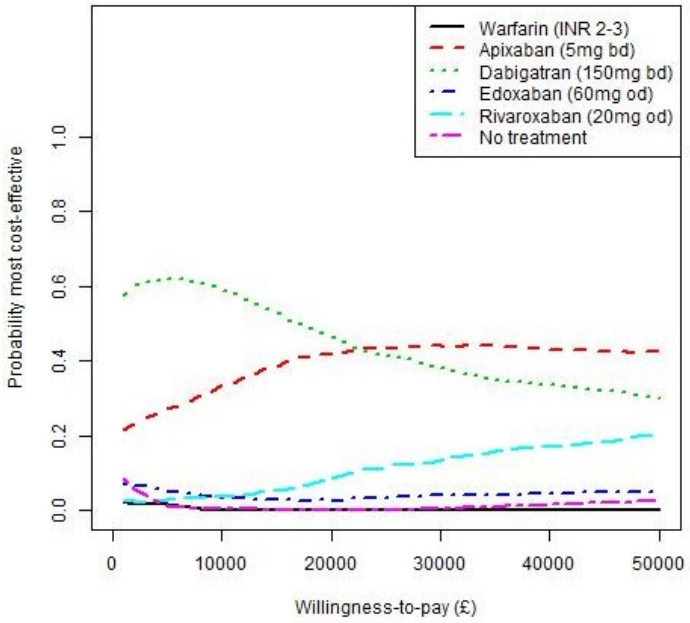


Figure 46 Cost-effectiveness acceptability curves for sensitivity analysis assuming no patients switch treatment following stroke, bleed, SE or TIA.

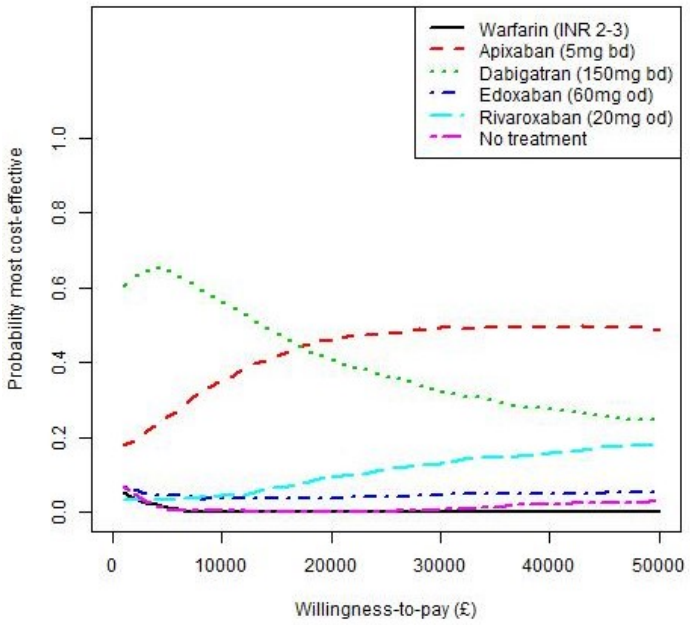


Figure 47 Cost-effectiveness acceptability curves for sensitivity analysis assuming all patients switch treatment following stroke, bleed, SE or TIA.

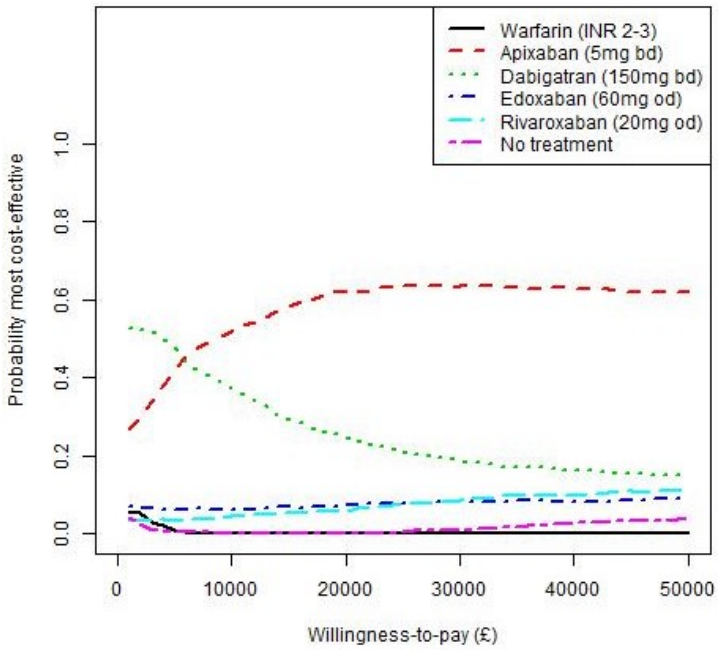


Figure 48 Cost-effectiveness acceptability curves for sensitivity analysis assuming all patients switch treatment following stroke or bleed, and none switch following SE or TIA.

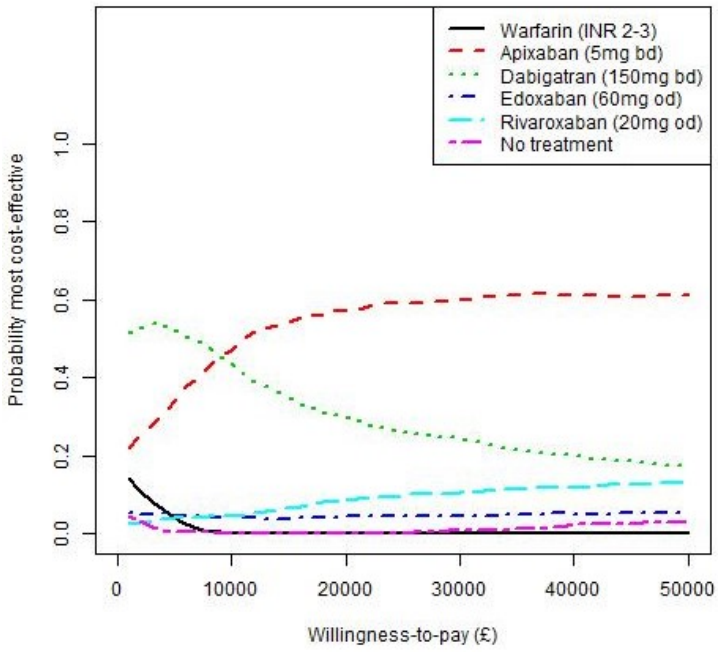


Figure 49 Cost-effectiveness acceptability curves for sensitivity analysis excluding BAATAF study from meta-analysis of treatment effect of warfarin compared to no treatment.

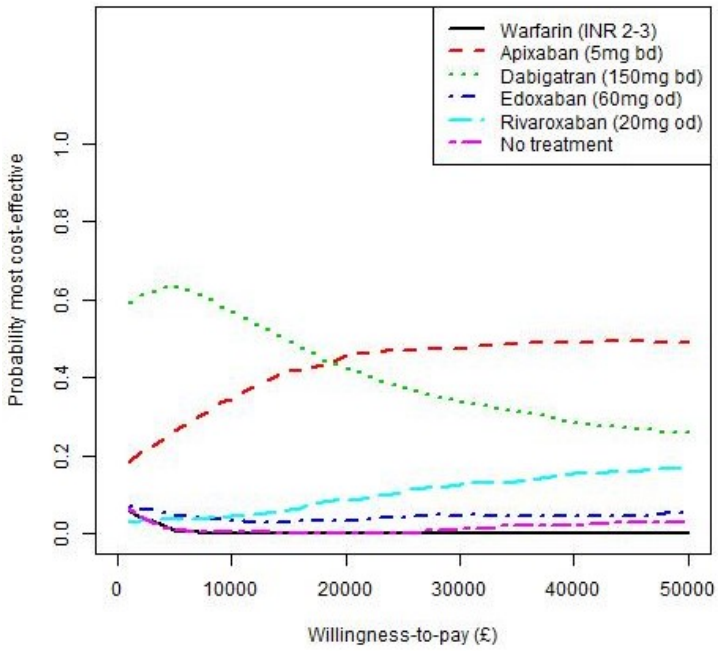


Figure 50 Cost-effectiveness acceptability curves for sensitivity analysis comparing lower doses of apixaban and dabigatran, as would be administered in older AF patients.

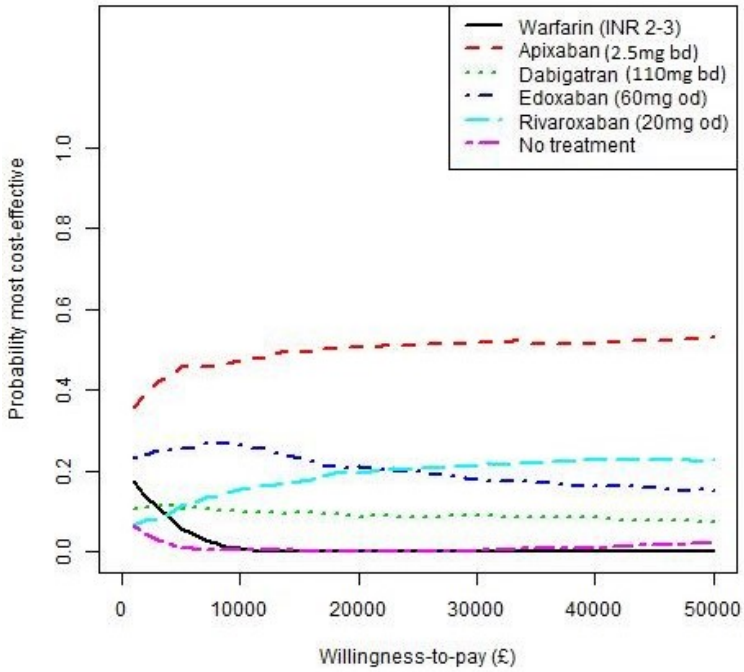


Figure 51 Cost-effectiveness acceptability curves for sensitivity analysis assuming hazard of ICH is the same on warfarin and no treatment.

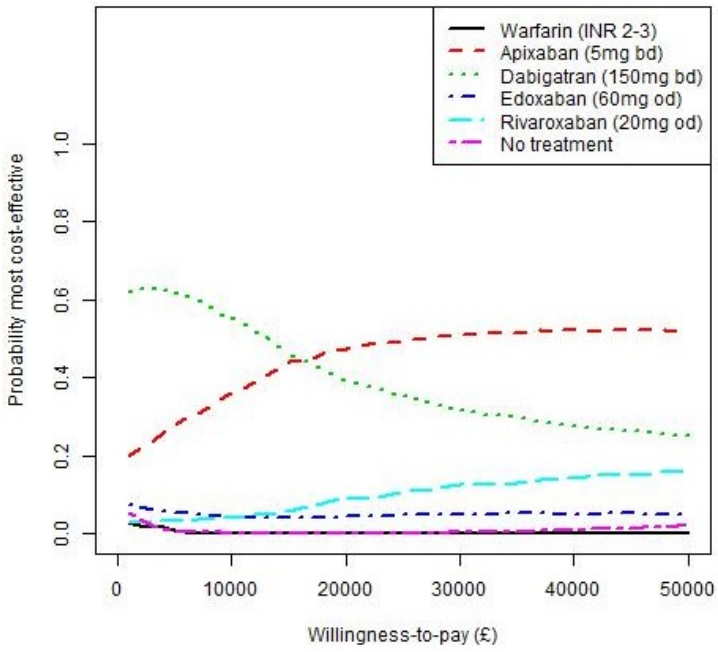


Figure 52 Cost-effectiveness acceptability curves for sensitivity analysis assuming TIA and SE move patients to the history of stroke state.

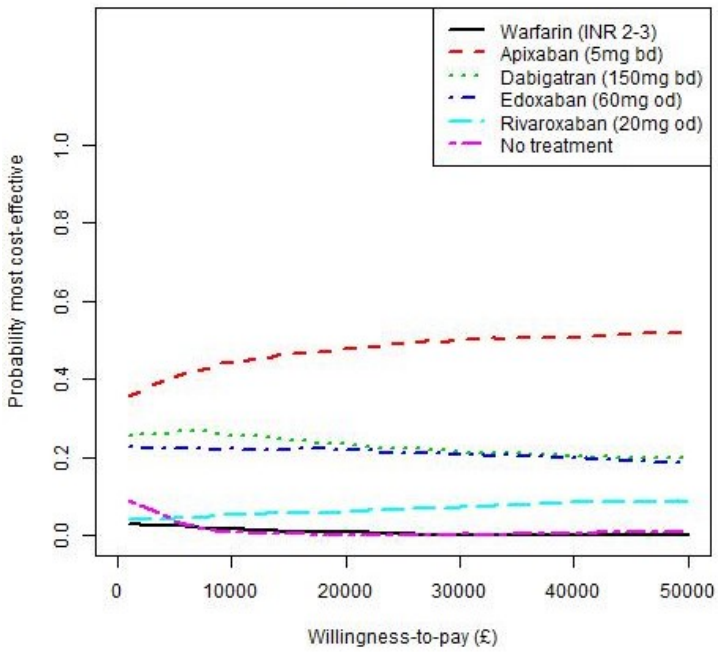
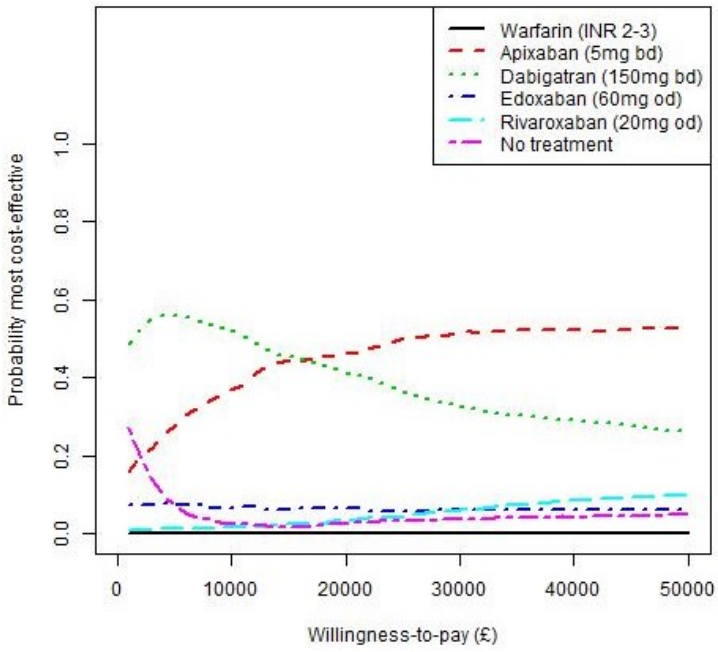


Figure 53 Cost-effectiveness acceptability curves for sensitivity analysis using stroke and ICH costs from AF ablation NICE guidelines



6.10 Results of DOAC costs sensitivity analyses

Using a willingness to pay of £20,000/QALY, in the base case analysis, dabigatran would need a price discount of 14.7% from the list price to overtake apixaban and become the treatment with the highest expected net monetary benefit, assuming all other prices remained constant. Similarly, edoxaban would need price discounts of 70.2% and 83.7% from the list price to overtake dabigatran and apixaban and become the treatment with the second highest and highest expected net monetary benefit, respectively, assuming all other prices remained constant. Finally, rivaroxaban would need price discounts of 4.9%, 73.7% and 86.8% from the list price to overtake edoxaban, dabigatran and apixaban and become the treatment with the third highest, second highest and highest expected net monetary benefit, respectively, assuming all other prices remained constant.

Using a willingness to pay of £30,000/QALY, in the base case analysis, dabigatran would need a price discount of 44.0% from the list price to overtake apixaban and become the treatment with the highest expected net monetary benefit, assuming all other prices remained constant. Similarly, rivaroxaban would need a price discounts of 61.3% to overtake dabigatran and become the treatment with the second highest expected net monetary benefit, assuming all other prices remained constant (there was no price at which rivaroxaban had a higher expected net monetary benefit than apixaban). Finally, edoxaban would need price discounts of 12.5% and 75.0% from the list price to overtake rivaroxaban and dabigatran become the treatment with the third highest and second highest expected net monetary benefit, respectively, assuming all other prices remained constant (there was no price at which edoxaban had a higher expected net monetary benefit than apixaban).

6.11 Results of reversal agent sensitivity analyses

We used 10,000 simulations of the model for each sensitivity analysis. The cost-effectiveness acceptability curves for the standard-of-care reversal agent sensitivity analysis and the andexanet alfa sensitivity analysis and are presented in Figure 54 and Figure 55 and results matrices in Table 84 and Table 85, respectively. In the standard-of-care reversal agent sensitivity apixaban (150mg bd) is the most cost-

effective at the £20,000 threshold. In the andexanet alfa reversal agent sensitivity analysis, apixaban (5mg bd) is most cost-effective at the £20,000, but with a low probability (0.448). In both sensitivity analyses exploring alternative percentages of bleeds on coumarin receiving reversal agents, apixaban (5mg bd) remained most cost-effective (Figure 56 and Figure 57). In all reversal agent sensitivity analyses, apixaban (5mg bd) has highest probability of being cost-effective and has greatest incremental net benefit at the £30,000 threshold, in line with the base case.

Figure 54 Cost-effectiveness acceptability curves for sensitivity analysis assuming reversal agents are employed following extracranial or intracranial bleeds

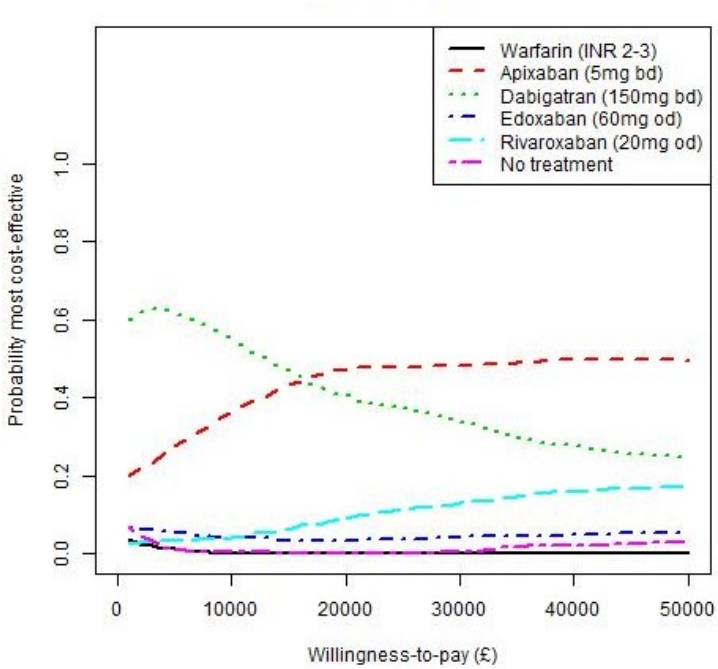


Figure 55 Cost-effectiveness acceptability curves for sensitivity analysis assuming reversal agents are used following extracranial and intracranial

bleeds, with Andexanet alfa used for bleeds in apixaban and rivaroxaban patients.

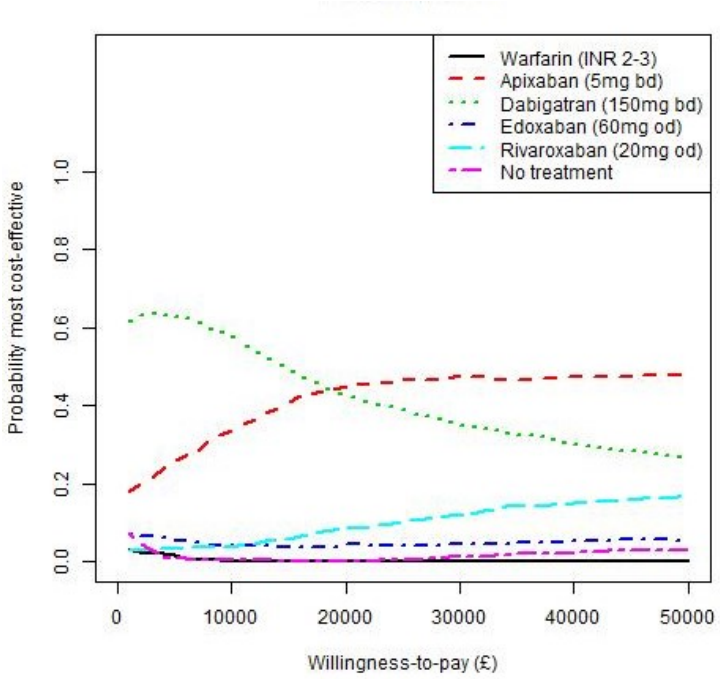


Figure 56 Cost-effectiveness acceptability curves for sensitivity analysis assuming reversal agents are employed following extracranial or intracranial bleeds but with only 50% of bleeds on coumarin receiving reversal agent

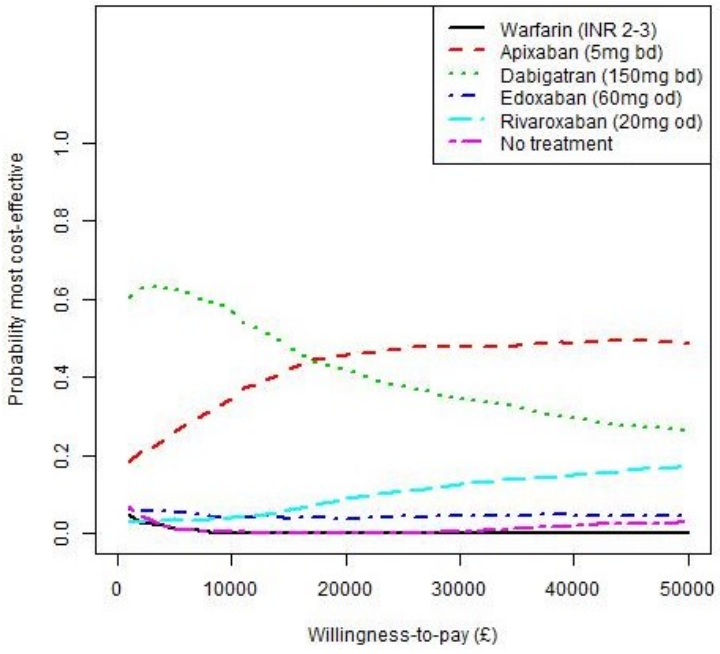


Figure 57 Cost-effectiveness acceptability curves for sensitivity analysis assuming reve rsal agents are employed following extracranial or intracranial bleeds but with only 10% of bleeds on coumarin receiving reversal agent

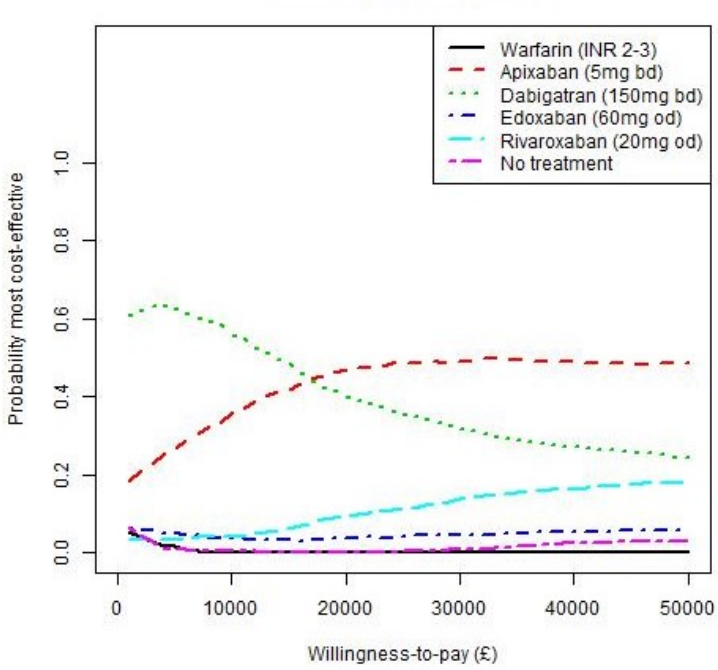


Table 84 Cost-effectiveness of first line treatment strategies for AF patients for sensitivity analysis assuming standard-of-care reversal agents are employed following extracranial or intracranial bleeds

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	29483 (17032, 49951)	27855 (19053, 43104)	26184 (17106, 43096)	28741 (19313, 43951)	30574 (19787, 48474)	39518 (13402, 84078)
Expected QALYs	5.4 (4.48, 6.259)	5.899 (5.02, 6.763)	5.775 (4.912, 6.655)	5.746 (4.894, 6.611)	5.827 (4.9, 6.791)	4.683 (2.581, 6.889)
Expected Incremental Total Costs	- (-, -)	-1628 (-11512, 4534)	-3299 (-13433, 3204)	-742.2 (-9438, 6367)	1091 (-7282, 7938)	10035 (-8963, 40899)
Incremental Expected QALYs	- (-, -)	0.4991 (0.1335, 0.8219)	0.3751 (-0.02145, 0.7275)	0.3467 (-0.01628, 0.6896)	0.4275 (-0.01519, 0.8218)	-0.7169 (-2.491, 0.9688)
Expected Net Benefit (£20,000)	- (-, -)	11610 (4853, 20319)	10801 (2046, 21694)	7676 (-896.8, 17162)	7459 (-829.3, 17586)	-24373 (-57840, -4655)
Incremental Expected Net Benefit (£30,000)	- (-, -)	16602 (7267, 28035)	14552 (2823, 26909)	11142 (998.1, 22088)	11735 (649.4, 24737)	-31543 (-80345, 3316)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 85 Cost-effectiveness of first line treatment strategies for AF patients for sensitivity analysis assuming reversal agents are used following extracranial and intracranial bleeds, with Andexanet alfa used for bleeds in apixaban and rivaroxaban patients.

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	29447 (18215, 51182)	28022 (18778, 43704)	26114 (16983, 41909)	28763 (19046, 45088)	30732 (20323, 49141)	39361 (13478, 85357)
Expected QALYs	5.42 (4.514, 6.257)	5.922 (5.039, 6.732)	5.796 (4.907, 6.673)	5.772 (4.882, 6.565)	5.851 (4.931, 6.769)	4.703 (2.644, 7.057)
Expected Incremental Total Costs	- (-, -)	-1425 (-10703, 4596)	-3333 (-12461, 2700)	-684.1 (-9860, 5735)	1284 (-7569, 7448)	9914 (-8773, 41164)
Incremental Expected QALYs	- (-, -)	0.5016 (0.09689, 0.8461)	0.3758 (-0.05096, 0.7326)	0.3512 (-0.03047, 0.6838)	0.4304 (-0.0117, 0.8387)	-0.7174 (-2.509, 1.053)
Incremental Expected Net Benefit (£20,000)	- (-, -)	11456 (4618, 20509)	10848 (2257, 20432)	7709 (558.6, 16066)	7325 (-505.5, 17295)	-24262 (-55889, -3443)
Incremental Expected Net Benefit (£30,000)	- (-, -)	16472 (7120, 28430)	14606 (3513, 26867)	11221 (1260, 21871)	11629 (385.1, 25052)	-31436 (-76484, 4555)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 86 Cost-effectiveness of first line treatment strategies for AF patients for sensitivity analysis assuming standard-of-care reversal agents are employed following extracranial or intracranial bleeds but with only 50% of bleeds on coumarin receiving reversal agent

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	29180 (17161, 51206)	27777 (18896, 44724)	25991 (17299, 42554)	28679 (18994, 46104)	30474 (19904, 49749)	39350 (13016, 87236)
Expected QALYs	5.265 (4.378, 6.052)	5.742 (4.855, 6.5)	5.619 (4.737, 6.43)	5.594 (4.719, 6.355)	5.671 (4.742, 6.514)	4.57 (2.476, 6.671)
Expected Incremental Total Costs	- (-, -)	-1404 (-11722, 4670)	-3189 (-13296, 2468)	-500.9 (-10386, 6426)	1294 (-7079, 7515)	10170 (-9046, 41413)
Incremental Expected QALYs	- (-, -)	0.4767 (0.1133, 0.781)	0.3539 (-0.05412, 0.707)	0.3288 (-0.02409, 0.6599)	0.4062 (-0.0357, 0.7745)	-0.695 (-2.469, 0.9501)
Incremental Expected Net Benefit (£20,000)	- (-, -)	10938 (4315, 21245)	10266 (2005, 20491)	7078 (-361.4, 16228)	6830 (-910, 16615)	-24070 (-57441, -5632)
Incremental Expected Net Benefit (£30,000)	- (-, -)	15706 (6952, 26833)	13805 (2873, 25639)	10366 (989.6, 20918)	10892 (-413.3, 23047)	-31021 (-76816, 1889)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

Table 87 Cost-effectiveness of first line treatment strategies for AF patients for sensitivity analysis assuming standard-of-care reversal agents are employed following extracranial or intracranial bleeds but with only 10% of bleeds on coumarin receiving reversal agent

	Warfarin (INR 2-3)	Apixaban (5mg bd)	Dabigatran (150mg bd)	Edoxaban (60mg od)	Rivaroxaban (20mg od)	No treatment
Expected Total Costs (£)	28715 (17020, 50406)	27566 (18618, 43145)	25768 (16830, 42499)	28445 (19051, 44227)	30187 (19673, 48715)	39329 (13526, 86863)
Expected QALYs	5.414 (4.512, 6.291)	5.92 (5.034, 6.735)	5.79 (4.891, 6.705)	5.765 (4.899, 6.611)	5.852 (4.892, 6.78)	4.7 (2.458, 6.982)

Expected Incremental Total Costs	- (-, -)	-1148 (-12180, 5044)	-2947 (-13143, 2847)	-270.1 (-9747, 6723)	1472 (-6447, 8189)	10614 (-9070, 41464)
Incremental Expected QALYs	- (-, -)	0.5064 (0.12, 0.8202)	0.3764 (-0.04657, 0.7398)	0.3516 (-0.02604, 0.7123)	0.4379 (-0.02716, 0.8355)	-0.714 (-2.475, 1.163)
Incremental Expected Net Benefit (£20,000)	- (-, -)	11277 (4652, 21337)	10475 (2260, 20839)	7302 (-148, 17725)	7286 (-377.6, 16488)	-24894 (-61832, -4833)
Incremental Expected Net Benefit (£30,000)	- (-, -)	16341 (7011, 28809)	14239 (2407, 26751)	10819 (409.9, 22781)	11666 (-218.5, 24120)	-32034 (-81567, 3753)

Expected (mean) values are reported with 95% confidence intervals. Incremental values are relative to warfarin (INR 2-3). Incremental net benefit is the difference in QALYs and costs for willingness to pay per QALY thresholds of £20,000 and £30,000.

6.12 Summary of cost-effectiveness findings

We found that although there was a high degree of uncertainty in the inputs to our model, apixaban (5mg bd) and dabigatran (150mg bd) were identified with the highest probability of being the most cost-effective first line treatment over a range of willingness to pay per QALY thresholds. The driver of this result is the generally lower rates of stroke and ICH on dabigatran (150mg bd), and of MI, ICH, and other CRB on apixaban (5mg bd). Only at higher stroke risk is dabigatran (150mg bd) most cost-effective, and this is due to its greater reduction of stroke. We did not find that age or gender had an impact on our conclusions.

Our model makes several assumptions (summarised in Table 88). However, the conclusions were robust to a wide range of sensitivity analyses, with only the probability that apixaban (5mg bd) is most cost-effective changing. We have taken the costs of warfarin from NICE assessments[2], but there is uncertainty in this estimate, which is difficult to quantify. We therefore conducted an extreme case scenario analysis in which we assumed zero cost for warfarin treatment and monitoring. Apixaban 5mg bd was the most cost-effective treatment under this assumption. Apixaban and dabigatran may be given in lower doses to the elderly. We assumed that all patients would receive the higher dose, and remain on it, even as they age. However, results were robust to a sensitivity analysis assuming only the lower doses of apixaban (2.5mg bd) and dabigatran (110mg bd) were administered.

We were unable to include betrixaban due to lack of evidence, and are therefore unable to draw any conclusions about the relative cost-effectiveness of betrixaban, or other unlicensed treatments. We have assumed that age determines mortality rate, but that other event rates and relative treatment effects do not depend on age. We have not distinguished between minor and major stroke in our model. Some previous models have done so[38,41,166], but we found that there was insufficient evidence to be able to estimate rates differently. We have assumed that systemic embolism is a transient event with no long-term consequences. Although there can be long-term consequences, such as limb loss, these are very rare, and we would not expect inclusion of these to affect the results. We assumed systemic embolism and TIA had no impact on CHA_2DS_2-VASc, although a sensitivity assuming their equivalence in

impact on risks, costs, and quality of life to stroke shifted results in favour of apixaban (5mg bd).

One notable limitation of our model is that we have not distinguished between different types of AF. There is emerging evidence that there may be a "dose-response" relationship in stroke risk with increasing "persistence" of AF[167], although others have suggested that risk of stroke is as high in paroxysmal AF patients as with persistent or permanent AF [168]. The RCTs included in our review are likely to have recruited mostly persistent or permanent AF patients, and so our conclusions may not extend to patients with paroxysmal AF.

There have been few cost-effectiveness analyses of NOACs for the prevention of stroke in AF in the UK population. Kansal et al[46] found dabigatran to be cost-effective compared with warfarin and aspirin in the UK setting, as in our model. However, they did not include any other NOACs. The Bayer submission to NICE on rivaroxaban[37] found it be cost-effective compared with warfarin. This submission also found rivaroxaban and dabigatran to have equivalent effects but dabigatran to have higher costs, thus concluding that rivaroxaban is the most cost-effective. Their CEACs compared only rivaroxaban with warfarin but found close to a 60% probability that rivaroxaban was cost-effective in the £20,000 to £30,000 threshold range, similar to our probability that a NOAC (apixaban) was most cost-effective. The Harrington et al[42] model in the US setting compared apixaban (5mg bd), dabigatran (110mg bd), rivaroxaban (20mg od), and warfarin and found that apixaban had the highest expected QALYs, followed by dabigatran, rivaroxaban and warfarin. Our model also found apixaban to have the highest expected QALYs and that dabigatran and rivaroxaban would have higher expected QALYs than warfarin, although the high degree of uncertainty in our results renders them compatible with the order found by Harrington. Harrington also found apixaban and dabigatran to be cost-effective compared with warfarin, and other US studies found apixaban[40], rivaroxaban[41], and dabigatran[38] to be cost-effective compared with warfarin. While costs in the US are not strictly comparable with those in the UK setting, our results are in line with these earlier findings.

Table 88 Main assumptions in the AF model

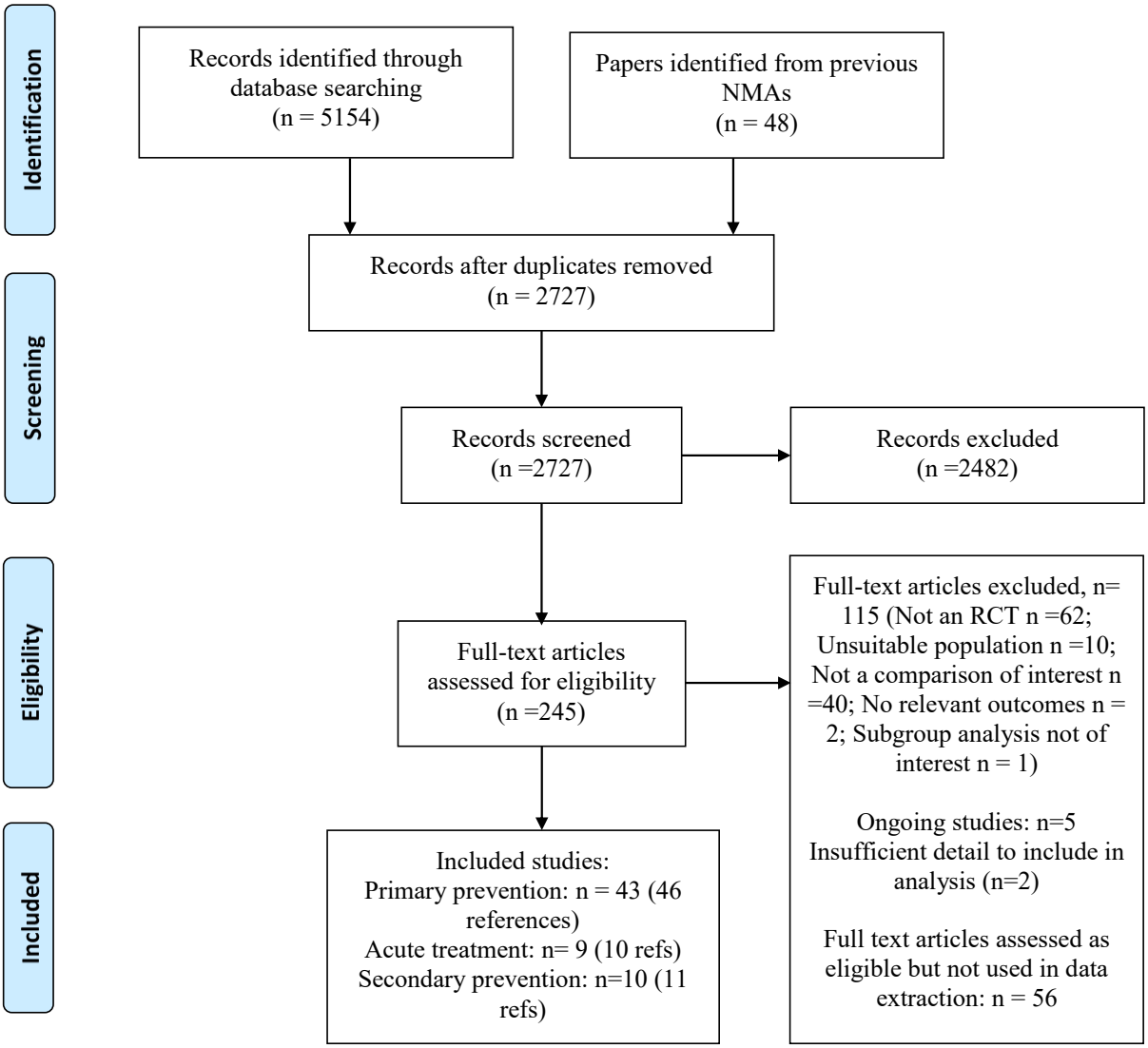
Does not include minor non-clinically relevant bleeds as transient events.
No distinction between severity of ischaemic strokes.
SE assumed to be a transient event without long-term consequences
Dose of apixaban and dabigatran given does not reduce as patients age.
Bleeds and ICH (and with it, haemorrhagic stroke) have same effect on future risk of death as stroke
Patients on dabigatran who experience an MI will always switch to warfarin.
Patients switch to no treatment after ICH/haemorrhagic stroke.
Patients may switch (with an assumed probability) from NOAC to warfarin or warfarin to no treatment after ischaemic stroke, bleed, SE or TIA.
Patients may (with an assumed probability) discontinue warfarin treatment or switch from a NOAC to warfarin, even if they do not experience an event (due to lack of compliance).
Warfarin arms from the RCTs identified in our systematic review are representative of the AF population in England and Wales for the bleed, ICH, and MI outcomes
Stroke risk for populations with CHA_2DS_2-VASc scores from Aspberg 2016 Swedish cohort representative of risk in corresponding populations in UK
Treatment effects, in particular the hazard ratio for stroke, don't vary with CHA_2DS_2-VASc score.
TIA and SE do not increase CHA_2DS_2-VASc score
Events rate and relative treatment effects are assumed not to vary with age, beyond variation in stroke through CHA_2DS_2-VASc
Relative mortality rate in AF patients relative to the general population does not vary with age.
Warfarin treatment costs over 3 months are taken from the NICE costing report. Uncertainty in this is represented using a uniformly distribution from 50% to 150% of the NICE costing report estimate.
Assumes no monitoring or administration costs for NOACs
Combined management costs for post-multiple event states (eg. MI+Stroke) to be the maximum of management costs for constituent events.
Assumed quality of life for patients with a history of multiple events to be multiplicative combination of quality of life for constituent events.

7. Clinical results (2): Primary prevention of venous thromboembolism

7.1 Included studies

A total of 2727 unique records were identified from various data sources for the three VTE reviews: see Figure 58.

Figure 58 PRISMA flow chart for reviews of primary prevention, acute treatment and secondary prevention of VTE



Forty three completed eligible randomised controlled trials were identified for inclusion in the review of primary prevention of VTE, with a total of 46 associated references[169-214]. One further trial contained insufficient detail to include in the quantitative

synthesis[215]. Three additional ongoing trials were also identified; two trials in knee surgery patient population and one trial in medical patient population.[216-218] A summary of the characteristics of the completed trials included in the analyses is presented in Table 89. There were 18 trials in hip surgery patient population (with 20 associated references)[170-172,175-177,181-183,191,193,194,196,198,200,203,206,209-211], 17 trials in knee surgery patient population (with 18 associated references)[169,173,174,178-180,184-186,188-190,192,195,197,199,204,213], seven trials in medical patient population (with seven associated references)[187,201,202,205,207,208,214], and one trial (with one associated reference)[212] involving both hip and knee surgery patients. Thirty nine of the trials were multicentre and four were single centre trials. Most of the multicentre trials were conducted across several countries mainly in North and South America, Europe, Russia and Israel, Asia, Australia and South Africa. Three of the single centre studies were conducted in Japan, Brazil, and China, and one study did not report the country where it was conducted. Thirty one of the trials were phase III studies and 12 were phase II studies. The number of patients randomised ranged from 67 to 5,407 patients across the 18 trials on hip surgery, 160 to 3,195 patients across the 17 trials on knee surgery (one trial was below knee fracture patient population), 125 to 8,823 patients across the seven trials on medical cases, 1973 patients in the trial involving both hip and knee surgery patients, and 67 to 8,323 patients across the whole trials, with a total of 77563 patients of which 88.9% (68,953 patients) were from phase III studies. Thirty one studies (19 phase III and 12 phase II) examined a NOAC. Overall, 11 studies examined rivaroxaban, seven studies examined dabigatran, six studies each examined apixaban and edoxaban, and one study examined betrixaban. Apart from two studies without sponsor information, all studies on NOACs were sponsored by one or more pharmaceutical companies. The role of sponsor was not declared in some of the studies, but where the sponsor role was declared the sponsor was commonly involved in the study design, data management and analysis.

Eligibility criteria for patient participation were similar across surgical studies of the same type, all patients in hip surgery studies having elective unilateral hip arthroplasty, and all patients in knee surgery studies having elective unilateral knee arthroplasty. Patients in medical studies were selected based on specific clinical conditions, either having a metastatic cancer or one or more acute medical conditions, so the criteria varied slightly across the medical studies. The minimum age for inclusion in a majority

of the studies was 18 years, the mean age across studies (where reported) ranging from 41 years to 76 years. The percentage of male patients, reported in 88% of the studies, ranged from 13.1% to 62.7%. Mean body mass index and mean weight ranged from 23 to 32.4 kg/m^2 and from 52.3 to 90.9 kg respectively across studies where reported. Proportions of cormobidities were poorly reported across studies. Where reported, the proportion of patients with a previous thromboembolic event, chronic heart failure and cancer ranged from 0.1% to 10.2%, 0.6% to 34.8% (higher of the range from medical patient population studies), and 6% to 100% (100% in cancer patient studies), respectively.

Of the 31 studies that examined NOACs, a NOAC was compared with a LMWH in 27 studies, with placebo in three studies, and with both a LMWH and warfarin in one study. Fourteen of the 31 studies were on hip surgery patients, 12 on knee surgery patients, one on below knee fracture patients, one on both hip and knee surgery patients, and three on medical patients. The doses of NOACs examined were apixaban 5mg, 10mg and 20mg once daily, and 2.5mg, 5mg and 10mg twice daily; edoxaban 5mg, 15mg, 30mg, 60mg and 90mg once daily, rivaroxaban 5mg, 10mg, 20mg, 30mg and 40mg once daily, and 2.5mg, 5mg, 10mg, 20mg and 30mg twice daily; betrixaban 15mg and 40mg twice daily; dabigatran 110mg, 150mg, 220mg, and 300mg once daily, and 50mg, 150mg, and 225mg twice daily. Among the studies that did not examine a NOAC, six studies each compared LMWH with warfarin, and with placebo. Standard intensity warfarin (INR 2-3) was examined in all studies involving a warfarin arm although in one study the lower end of the INR range was 1.8. None of these studies that examined warfarin reported mean time in therapeutic range. LMWHs varied in type and dose across studies. Start of treatment with LMWH varied across surgical patient studies with pre-operative treatment start in 11 studies in hip surgery, four studies in knee surgery, and one study involving both hip and knee surgery patients, and post-operative treatment start in eight studies in hip surgery and 11 studies in knee surgery. In one (hip surgery) study, pre- and post-operative LMWH treatment start were compared.

Treatment duration varied greatly across hip surgery, knee surgery and medical patient studies, from four to 130 days. There is less variation in treatment duration within the knee and hip surgery studies, with treatment duration ranging from ten to 14

days in most of the knee surgery studies, and from five to 14 days and 28 to 35 days in most of the hip surgery studies. Treatment duration was the same for the interventions compared with studies, except in three studies where the LMWH comparator was given for a shorter duration than the NOAC (rivaroxaban in two studies and apixaban in one study). However, time to outcome assessment was the same in all studies including those with different treatment durations for the interventions compared.

Reported efficacy and safety outcome types were similar across studies irrespective of the patient group, and were reported at the end of the treatment periods. Two rivaroxaban studies reported only efficacy outcomes: in both cases few outcomes were reported. One study reported only safety outcomes. Overall, 29 studies reported data on symptomatic VTE; 25 on symptomatic DVT, 35 on symptomatic PE, nine on myocardial infarction, 39 on major bleeding, 27 on clinically relevant bleeding, and 28 on all-cause mortality. Diagnosis of VTE was predominantly by compression ultrasonography or venography for DVT, and by spiral computerised tomography scan or ventilation/perfusion lung scan for PE.

Table 89 Characteristics of 43 included randomised trials in primary prevention of VTE

Study (Centre type) [Countries]	Study type Sponsor (sponsor's role)	Age eligibility (Mean age) [%Male]	Clinical condition	No. rand.	Interventions compared	Tmt duration (days)	Outcomes	Time of outcome assessment (days)
ADOPT[205] (Multicentre) [North & South America, Europe, Russia, Ukraine, Israel, Australia, Asia, South Africa]	Phase III Bristol-Myers Squibb and Pfizer (NR)	≥40 yrs. (66.8 yrs.) [49.1%]	Acute medical conditions	6528	**Apixaban** 1. 2.5mg bd **LMWH** 2. Enoxaparin 40mg od	14.9-34.9 Apixaban 3.3-11.3 LMWH	Efficacy: Major VTE, symptomatic DVT, proximal DVT, symptomatic proximal DVT, symptomatic distal DVT, symptomatic non-fatal PE Safety: All bleeding, major bleeding, composite clinically relevant bleeding, intracranial bleeding	30 (for efficacy outcomes) 2-30 (for safety outcomes)

ADVANCE-1[188] (Multicentre) [North & South America, Europe, Russia, Israel, Australia]	Phase III Bristol-Myers Squibb and Pfizer (Data were collected and analysed by the study sponsors)	≥18 yrs. (65.8 yrs.) [37.9%]	Total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint.	3195	**Apixaban** 1. 2.5mg bd **LMWH** 2. Enoxaparin 30mg bd	10-14	Efficacy: DVT, Symptomatic DVT, proximal DVT, symptomatic PE, fatal PE, all stroke Safety: All bleeding, major bleeding, minor bleeding, fatal bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, thrombocytopenia, MI, death (all causes)	10-14 (for the efficacy outcomes) 16 for the safety outcomes
ADVANCE-2[195] (Multicentre) [South America, Europe, Russia, Ukraine, Israel, Australia, Asia, South Africa]	Phase III Bristol-Myers Squibb and Pfizer (NR)	≥18 yrs. (67 yrs.) [27.5%]	Either elective unilateral or same-day bilateral total knee replacement surgery (TKR) or a revision of at least 1 component of a TKR	3057	**Apixaban** 1. 2.5mg bd **LMWH** 2. Enoxaparin 40mg od	10-14	Efficacy: Major VTE, DVT, symptomatic proximal DVT, Symptomatic PE, Fatal PE, all stroke Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, bleeding from surgical site, thrombocytopenia, MI, death (all causes)	2-14

ADVANCE-3[193] (Multicentre) [North & South America, Europe, Russia, Ukraine, Israel, Australia, Asia]	Phase III Bristol-Myers Squibb and Pfizer (The sponsor was involved in data collection and analyse)	≥18 yrs. (6O.8 yrs.) [46.7%]	Elective unilateral total hip replacement or a revision of at least 1 component of a total hip replacement	5407	**Apixaban** 1. 2.5mg bd **LMWH** 2. Enoxaparin 40mg od	32-38	Efficacy: Major VTE, DVT, proximal DVT, symptomatic DVT, fatal PE, symptomatic PE, symptomatic non-fatal PE, all stroke Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, bleeding from surgical site, thrombocytopenia, MI, death (all causes)	32-38 (for efficacy outcomes and thrombocytopenia) 38 (for other safety outcomes and all stroke)
APROPOS[179] (Multicentre) [North America, Argentina, Denmark, Poland, Israel, Australia]	Phase II Bristol-Myers Squibb (NR)	18-90 yrs. (66.7 yrs.) [36.7%]	Elective unilateral total knee replacement surgery and who are willing and able to undergo bilateral ascending contrast venography	1238	**Apixaban** 1. 5mg od 2. 10mg od 3. 20mg od 4. 2.5mg bd 5. 5mg bd 6. 10mg bd **LMWH** 7. Enoxaparin 30mg bd **Warfarin** 8. INR 1.8-3	10-14	Efficacy: VTE, symptomatic DVT, symptomatic proximal DVT, symptomatic PE, fatal PE Safety: All bleeding, major bleeding, minor bleeding, fatal bleeding, MI, all stroke, death (all causes)	10-14 (42 for major bleeding and death (all cause))

ARDEPARIN ATHROPLASTY STUDY[213] (Multicentre) [USA]	Phase II Supported by a grant from Wyeth-Ayerst Research, Philadelphia, Pennsylvania (NR)	≥18 yrs. (68.6 yrs.) [42.1%]	Primary unilateral, simultaneous bilateral or unilateral revision total knee replacement surgery	860	**LMWH** 1. Ardeparin 25 anti-X U/kg bd 2. Ardeparin 35 anti-XU/kg bd 3. Ardeparin 50 anti-XU/kg bd **Warfarin** 4. INR 2-3	14 Or at discharge post-op	Efficacy: VTE, DVT, proximal DVT, symptomatic PE Safety: Major bleeding, bleeding from surgical site, thrombocytopenia, death (all causes)	5-14 (for efficacy outcomes except symptomatic PE which was prior to discharge) Unclear for safety outcomes
BISTRO II[212] (Multicentre) [Europe & South Africa]	Phase II Boehringer Ingelheim (The sponsor was responsible for the overall planning and conduct of the study, and statistical analyses)	≥18 yrs. (66 yrs.) [39%]	Total hip or knee replacement surgery	1973	**Dabigatran** 1. 50mg bd 2. 150mg bd 3. 300mg od 4. 225mg bd **LMWH** 5. Enoxaparin 40mg od	6-10	Efficacy: VTE, symptomatic VTE, DVT, Symptomatic DVT, proximal DVT, distal DVT, symptomatic PE Safety: Major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	6-10

EXPERT[185] (Multicentre) [USA & Canada]	Phase II Portola Pharmaceuticals Inc., South San Francisco, CA, USA (NR)	18-75 yrs. (63.3 yrs.) [39.7%]	Elective primary unilateral total knee arthroplasty	215	**Betrixaban** 1. 15mg bd 2. 40mg bd **LMWH** 3. Enoxaparin 30mg bd	10-14	Efficacy: VTE, symptomatic VTE, symptomatic distal DVT, symptomatic proximal DVT, symptomatic DVT, non-symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	10-14
LIFENOX[202] (Multicentre) [Asia, Mexico, Tunisia]	Phase III Sanofi (The data were gathered by the sponsor)	≥40 yrs. (65.5 yrs.) [62.7%]	Acute medical conditions	8323	**LMWH** 1. Enoxaparin 40mg od 2. **Placebo** od	6 –14	Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, death (cardiovascular), death (all causes)	14 (for bleeding outcomes) 14, 30, 90 (for death outcomes)
MAGELLAN[201,208] (Multicentre) [North & South America, Europe, Israel, Australia, New Zealand, Asia]	Phase III Bayer HealthCare Pharmaceuticals and Janssen Research and Development (The data were collected and analysed by the sponsors)	≥40 yrs. (71.1 yrs.) [54.2%]	Acute medical conditions	8101	**Rivaroxaban** 1. 10mg od **LMWH** 2. Enoxaparin 40mg od	31-39 Rivaroxaban 6-14 LMWH	Efficacy: Major VTE, symptomatic DVT, symptomatic non-fatal PE Safety: Major bleeding, composite clinically relevant bleeding, fatal bleeding, death (all causes)	10 & 35

ODiXa-HIP[211] (Multicentre) [Europe & Israel]	Phase II Bayer (The sponsor was involved in the study but the exact contributions are not reported)	≥18 yrs. (65.1 yrs.) [40.9%]	Total hip replacement surgery	641	**Rivaroxaban** 1. 2.5mg bd 2. 5mg bd 3. 10mg bd 4. 30mg od 5. 20mg bd 6. 30mg bd **LMWH** 7. Enoxaparin 40mg od	5-9 Mean – rivaroxaban 7.5±1.0 LMWH 7.6±1.5	Efficacy: Major VTE, DVT, symptomatic DVT, proximal DVT, symptomatic PE, symptomatic non-fatal PE, fatal PE Safety: Major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, death (all causes)	5-9
ODiXa-HIP2[176] (Multicentre) [Europe & Israel]	Phase II Bayer HealthCare AG (NR)	≥18 yrs. (65.3 yrs.) [40.3%]	Elective primary total hip replacement	722	**Rivaroxaban** 1. 2.5mg bd 2. 5mg bd 3. 10mg bd 4. 20mg bd 5. 30mg bd **LMWH** 6. Enoxaparin 40mg od	5-9	Efficacy: Major VTE, DVT, proximal DVT, symptomatic PE Safety: Major bleeding, minor bleeding, clinically relevant non-major bleeding, bleeding from surgical site	5-9
ODIXa-KNEE[174] (Multicentre) [USA & Canada]	Phase II Bayer HealthCare AG, Germany (NR)	≥18 yrs. (66.5 yrs.) [38.5%]	Elective total knee replacement	621	**Rivaroxaban** 1. 2.5mg bd 2. 5mg bd 3. 10mg bd 4. 20mg bd 5. 30mg bd **LMWH** 6. Enoxaparin 30mg bd	5-9	Efficacy: Major VTE, DVT, distal DVT, proximal DVT, symptomatic DVT, symptomatic PE Safety: Major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	5-9 (for efficacy outcomes) 11 (for safety outcomes)

ODIXa-OD.HIP[175] (Multicentre) [Europe and Israel according to study report but protocol says Japan]	Phase II Bayer HealthCare (NR)	≥18 yrs. (64.9 yrs.) [41.1%]	Primary total hip replacement surgery	873	**Rivaroxaban** 1. 5mg od 2. 10mg od 3. 20mg od 4. 30mg od 5. 40mg od **LMWH** 6. Enoxaparin 40mg od	5-9	Efficacy: Major VTE, DVT, distal DVT, proximal DVT, symptomatic distal DVT, symptomatic PE Safety: Major bleeding, minor bleeding, clinically relevant non-major bleeding, death (all causes)	10
PROTECHT[187] (Multicentre) [Japan]	Phase III Italfarmaco SpA, Milan, Italy (NR)	≥18 yrs. (62.9 yrs.) [51.7%]	Metastatic or locally advanced cancer	1166	**LMWH** 1. Nadroparin 3800IU anti-Xa od 2. **Placebo** od	110-130	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, death (all causes)	111-113 (median)
RECORD 1[182] (Multicentre) [North & South America, Europe, Israel, Australia, South Africa]	Phase III Bayer HealthCare and Johnson & Johnson (The data were collected and analysed by the sponsors)	≥18 yrs. (63.2 yrs.) [44.5%]	Elective total hip arthroplasty	4541	**Rivaroxaban** 1. 10mg od **LMWH** 2. Enoxaparin 40mg od	35 (31-39)	Efficacy: Major VTE, symptomatic VTE, DVT, distal DVT, proximal DVT, Symptomatic non-fatal PE, ischemic stroke Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, MI, death (cardiovascular), death (all causes)	36 (30-42) for all efficacy outcomes 37 (for all safety outcomes)

RECORD 2[183] (Multicentre) [North & South America, Europe, Australia, New Zealand, Asia, South Africa]	Phase III Bayer HealthCare AG, Johnson & Johnson Pharmaceutical Research and Development LLC (The study sponsors were involved in the study design, data collection and analysed)	≥18 yrs. (61.5 yrs.) [46.4%]	Elective total hip arthroplasty	2509	**Rivaroxaban** 1. 10mg od **LMWH** 2. Enoxaparin 40mg od	31-39 Rivaroxaban 10-14 LMWH	Efficacy: Symptomatic VTE, major VTE, DVT, distal DVT, proximal DVT, symptomatic non-fatal PE, fatal PE, ischemic stroke Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, MI, death (cardiovascular), death (all causes)	30 - 42 (32-42 for major VTE, DVT, symptomatic non-fatal PE and composite clinically relevant bleeding)
RECORD 3[180] (Multicentre) [North & South America, Europe, Israel, China, South Africa]	Phase III Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development (Data were collected and analysed by the study sponsors)	≥18 yrs. (67.6 yrs.) [31.8%]	Total knee arthroplasty	2531	**Rivaroxaban** 1. 10mg od **LMWH** 2. Enoxaparin 40mg od	10-14	Efficacy: Major VTE, symptomatic VTE, DVT, distal DVT, proximal DVT, symptomatic non-fatal PE, ischemic stroke Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, fatal bleeding, MI, death (cardiovascular), death (all causes)	17 (for all efficacy outcomes excluding ischaemic stroke) 16 (for bleeding outcomes) 15 (for MI, ischaemic stroke and death outcomes)

RECORD 4[190] (Multicentre) [North America, Europe, Israel, India, Sri Lanka]	Phase III Bayer Schering Pharma AG, Johnson & Johnson Pharmaceutical Research & Development (The study sponsors were involved in the design of the trial and collected and analysed the data)	≥18 yrs. (64.6 yrs.) [34.9%]	Total knee arthroplasty	3148	**Rivaroxaban** 1. 10mg od **LMWH** 2. Enoxaparin 30mg bd	10-14	Efficacy: Major VTE, symptomatic VTE, DVT, symptomatic DVT, non-symptomatic DVT, symptomatic PE, symptomatic non-fatal PE, fatal PE, ischemic stroke Safety: Major bleeding, fatal bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, MI, death (cardiovascular), death (all causes)	17 (for all efficacy outcomes excluding ischaemic stroke) 16 (for all safety outcomes and ischaemic stroke)
RE-MOBILISE[184] (Multicentre) [North America & UK]	Phase III Boehringer Ingelheim (The sponsor was responsible for data collection and statistical analysis)	≥18 yrs. (66.1 yrs.) [42.3%]	Primary elective unilateral total knee arthroplasty	2615	**Dabigatran** 1. 150mg od 2. 220mg od **LMWH** 3. Enoxaparin 30mg bd	12-15 median-14	Efficacy: VTE, major VTE, distal DVT, proximal DVT, symptomatic DVT, symptomatic PE, symptomatic non-fatal PE Safety: All bleeding, major bleeding, death (all causes)	12-15

RE-MODEL[178] (Multicentre) [Europe, Australia, South Africa]	Phase III Boehringer Ingelheim, Copenhagen, Denmark (The sponsor was responsible for data collection and statistical analysis)	≥18 yrs. (67.7 yrs.) [34%]	Primary elective unilateral total knee replacement	2101	**Dabigatran** 1. 150mg od 2. 220mg od **LMWH** 3. Enoxaparin 40mg od	6-10	Efficacy: VTE, symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	6-10
RE-NOVATE[177] (Multicentre) [Europe, Australia, South Africa]	Phase III Boehringer Ingelheim Alkmaar, Netherlands (Data collection and analysis were done by the sponsor)	≥18 yrs. (64 yrs.) [43.5%]	Primary elective unilateral total hip replacement	3494	**Dabigatran** 1. 150mg od 2. 220mg od **LMWH** 3. Enoxaparin 40mg od	28-35	Efficacy: Symptomatic DVT, symptomatic PE, fatal PE Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	31-38
RE-NOVATE II[200,206] (Multicentre) [North America, Europe, Australia, New Zealand, India, South Africa]	Phase III Boehringer Ingelheim, Sweden (NR)	≥18 yrs. (62 yrs.) [48.2%]	Unilateral, elective total hip arthroplasty	2055	**Dabigatran** 1. 220mg od **LMWH** 2. Enoxaparin 40mg - od	28-35	Efficacy: Major VTE, symptomatic VTE, DVT, distal DVT, proximal DVT, symptomatic DVT, symptomatic non-fatal PE, ischemic stroke Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, MI, death (all causes)	28-35

STARS E-3[199] (Multicentre) [Japan, Taiwan]	Phase III Daiichi Sankyo Inc. (NR)	20-84 yrs. (NR) [NR]	Unilateral total knee arthroplasty	716	**Edoxaban** 1. 30mg od **LMWH** 2. Enoxaparin 2000IU (20mg)) bd	11-14	Efficacy: VTE, DVT, symptomatic PE Safety: Major bleeding, composite clinically relevant bleeding	14
STARS J-1[189,197] (Multicentre) [Japan]	Phase II Daiichi Sankyo Co., Ltd., Tokyo, Japan (NR)	20-84 yrs. (71.1 yrs.) [21.2%]	Unilateral total knee arthroplasty	523	**Edoxaban** 1. 5mg od 2. 15mg od 3. 30mg od 4. 60mg od 5. **Placebo** od	11-14	Efficacy: VTE, DVT, distal DVT, proximal DVT, symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	14
STARS J-2[191] (Multicentre) [Japan & Taiwan]	Phase II Daiichi Sankyo Inc. (NR)	20-84 yrs. (NR) [NR]	Unilateral total hip arthroplasty	264	**Edoxaban** 1. 15mg od 2. 30mg od **LMWH** 3. Enoxaparin 20mg bd	11-14	Efficacy: VTE, Distal DVT Safety: Composite Clinically relevant bleeding	14
STARS J-4[198,210] (Multicentre) [Japan]	Phase III Daiichi Sankyo Co., Ltd. Tokyo, Japan (NR)	≥20 yrs. (76 yrs.) [20.5%]	Hip surgery-for inner or outer femoral neck (trochanteric or subtrochanteric) fracture	92	**Edoxaban** 1. 30mg od **LMWH** 2. Enoxaparin 2000IU (20mg)) bd	11-14	Efficacy: VTE, Major VTE, symptomatic DVT, non-symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	14

STARS J-V[196] (Multicentre) [Japan]	Phase III Daiichi Sankyo (NR)	20-84 yrs. (62.8 yrs.) [NR]	Unilateral total hip arthroplasty	610	**Edoxaban** 1. 30mg od **LMWH** 2. Enoxaparin 20mg bd	11-14	Efficacy: VTE, Symptomatic DVT, non-symptomatic DVT, symptomatic PE Safety: Major bleeding, composite clinically relevant bleeding	14
TOPIC-1[214] (Multicentre) [Germany, Czech Republic, Ukraine, Romania, Belarus]	Phase III ovartis Pharma GmbH Germany (NR)	Adults (55.6 yrs.) [NR]	Metastatic breast cancer	353	**LMWH** 1. Certoparin 3000IU od 2. **Placebo** od	182.6	Efficacy: VTE, DVT, symptomatic VTE, symptomatic DVT, non-symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, thrombocytopenia, death (all causes)	182.6
TOPIC-2[214] (Multicentre) [Germany, Czech Republic, Ukraine, Romania, Belarus]	Phase III Novartis Pharma GmbH Germany (NR)	Adults (60.6 yrs.) [NR]	Inoperable disseminated primary non–small cell lung carcinoma	547	**LMWH** 1. Certoparin 3000IU od 2. **Placebo** od	182.6	Efficacy: VTE, DVT, symptomatic VTE, symptomatic DVT, non-symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, thrombocytopenia, death (all causes)	182.6
VTE-APIX-PLACEBO-USACAN[207] (Multicentre) [USA & Canada]	Phase II Bristol-Myers Squibb and Pfizer Inc. (NR)	≥18 yrs. (60 yrs.) [50.4%]	Receiving either first-line or second-line chemotherapy for advanced or metastatic cancer	125	**Apixaban** 1. 5mg od 2. 10mg od 3. 20mg od 4. **Placebo** od	84 (16-90)	Efficacy: Symptomatic VTE Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding	114-121

VTE-DABIG-LMWH-GREECE[204] (Single centre) [NR]	Phase III Not declared (NR)	Adults (NR) [13.1%]	total knee arthroplasty	160	**LMWH** 1. Dalteparin 2.5mg od 2. Enoxaparin 40mg od 3. Tinzaparin 0.45 ml od **Dabigatran** 4. 110mg od	Not given	Efficacy: VTE, DVT, PE, ischemic stroke Safety: All bleeding	Not given
VTE-DABIG-PLAC-JAPAN[192] (Multicentre) [Japan]	Phase III Boehringer Ingelheim Co, Ltd Kawanishi, Japan (NR)	≥20 yrs. (71.6 yrs.) [17%]	Primary, unilateral, elective total knee arthroplasty	512	**Dabigatran** 1. 110mg od 2. 150mg od 3. 220mg od 4. **Placebo** od	11-14	Efficacy: Major VTE, DVT, proximal DVT, symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, bleeding from surgical site, death (all causes)	14
VTE-EDOX-LMWH-MULTI[194] (Multicentre) [North & South America, Europe, Russian, Ukraine]	Phase II Daiichi Sankyo Pharma Development (NR)	≥18 yrs. (57.8 yrs.) [39.9%]	Primary, unilateral total hip replacement surgery	903	**Edoxaban** 1. 15mg od 2. 30mg od 3. 60mg od 4. 90mg od **LMWH** 5. Dalteparin 5000IU od	7-10	Efficacy: VTE, major VTE, proximal DVT Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	7-10 (for efficacy outcomes) 10 (for safety outcomes)

VTE-LMWH-PLAC-CAN[186] (Multicentre) [Canada]	Phase III Fragmin, Pharmacia, Pfizer Global Pharmaceuticals, Kirkland, Quebec (NR)	18-75 yrs. (41 yrs.) [62%]	Unilateral isolated fractures below the knee which required operative fixation. (Patients with minor simultaneous injuries were also included if they were able to mobilise)	305	**LMWH** 1. Dalteparin 5000IU od 2. **Placebo** od	14	Efficacy: Non-symptomatic DVT Safety: All bleeding, major bleeding, minor bleeding, thrombocytopenia, death (all causes)	14
VTE-LMWH-PLAC-JAPAN[203] (Single centre) [Japan]	Phase III None declared (NR)	≥20 yrs. (NR) [18.4%]	Unilateral total hip replacement surgery	255	**LMWH** 1. Fondaparinux 2.5mg od 2. Enoxaparin 20mg bd 3. **Placebo** od	10	Efficacy: VTE, symptomatic VTE, DVT, distal DVT, proximal DVT, symptomatic DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding	11
VTE-RIVAROX-LMWH-BRAZIL[181] (Single centre) [Brazil]	Phase III Bayer Healthcare (NR)	≥18 yrs. (57.9 yrs.) [55.4%]	Elective total hip arthroplasty	67	**Rivaroxaban** 1. 10mg od **LMWH** 2. Enoxaparin 40mg od	32-36	Efficacy: DVT, symptomatic PE	32-36
VTE-RIVAROX-LMWH-CHINA[209] (Single centre) [China]	Phase III Not declared (NR)	>50 yrs. (64.6 yrs.) [56.6%]	Unilateral hip arthroplasty	106	**Rivaroxaban** 1. 10mg od **LMWH** 2. 4100IU od (type not reported)	35	Efficacy: DVT	182.6

VTE-VKA-LMWH-CANADA[169] (Multicentre) [NR]	Phase III Rhone-Poulenc Rorer Canada (NR)	Adults (68.8 yrs.) [36.9%]	Knee arthroplasty	670	**Warfarin** 1. INR 2-3 **LMWH** 2. Enoxaparin 30mg bd	5.9-11.5 (mean)	Efficacy: Symptomatic VTE, DVT, proximal DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, thrombocytopenia, death (all causes)	14
VTE-VKA-LMWH-US[170] (Multicentre) [USA]	Phase III National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, and a grant from Pharmacia-Upjohn, Kalamazoo, Michigan (NR)	≥18 yrs. (63 yrs.) [47.1%]	Unilateral primary or revision total hip arthroplasty	580	**Warfarin** 1. INR 2.0 - 3.0 **LMWH** 2. Dalteparin 5000IU od	5-9	Efficacy: DVT, distal DVT, proximal DVT Safety: Major bleeding	5-9 Unclear for major bleeding
VTE-VKA-LMWH-US-2[171] (Multicentre) [NR]	Phase III Rhône-Poulenc Rorer Pharmaceuticals (NR)	≥18 yrs. (64 yrs.) [44.4%]	Elective unilateral primary hip arthroplasty	3011	**Warfar**in 1. INR 2-3 **LMWH** 2. Enoxaparin 30mg bd	14	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic PE, fatal PE Safety: All bleeding, major bleeding, minor bleeding, bleeding from surgical site, thrombocytopenia, death (all causes)	14

VTE-VKA-LMWH-US-3[172] (Multicentre) [USA & Canada]	Phase III Grant-in-aid by Pharmacia and Upjohn to the University of Calgary (NR)	≥18 yrs. (63.3 yrs.) [48.2%]	Elective unilateral total hip arthroplasty (primary or revision)	1501	**Warfari**n 1. INR 2.0 - 3.0 **LMWH** 2. Dalteparin 5000IU- started pre operatively and then once daily 3. Dalteparin 5000IU-started post operatively and then once daily	4-8	Efficacy: DVT, symptomatic DVT, proximal DVT, symptomatic PE Safety: Major bleeding, minor bleeding, death (all causes)	5-9 8
VTE-VKA-LMWH-US-4[173] (Multicentre) [USA]	Phase III Aventis Pharmaceuticals, Incorporated, Bridgewater, New Jersey (NR)	≥38 yrs. (NR) [44%]	unilateral total knee arthroplasty	349	**Warfarin** 1. INR 2-3 **LMWH** 2. Enoxaparin 30mg bd	4-14	Efficacy: VTE, DVT, distal DVT, proximal DVT, symptomatic PE Safety: All bleeding, major bleeding, minor bleeding, death (all causes)	5-15

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; MI = myocardial infarction; INR = international normalized ratio; rand = randomised; od = once daily; bd = twice daily; Tmt = treatment; NR = not reported

7.2 Time in therapeutic range for warfarin interventions

Seven studies of primary prevention of VTE included a warfarin intervention arm, but none of these reported mean time in therapeutic range.

7.3 Risk of bias in included studies

Detailed risk of bias assessments for each included study for each domain of the Cochrane assessment tool are provided in Table 90. Overall, the studies were judged at low risk of bias. Assessment of a few studies was based on abstract information only, in which case risk of bias for most domains was judged to be unclear. The majority of the studies were judged to be at low risk of bias for blinding of outcome assessment and incomplete outcome data. The risk of bias in these two domains differed slightly in a few studies because of differences in blinding of outcome assessment and the number of patients included in analysis according to outcome type, mainly whether an outcome is for efficacy or for safety. Most studies were judged to be at low risk of bias for selective outcome reporting. Among those not judged to be at low risk, the main reason for the judgment was either unavailability of the study protocol or insufficient information to enable a judgment of low risk. Randomisation sequence generation and allocation concealment were predominantly by computer generation and central allocation respectively. In some studies, randomisation was used a standard permuted block and some of the studies were stratified according to study centre. A few studies[170,171,173,185,191,210,211], predominantly of open-label design, were judged to be at high risk of bias for blinding of participants. The risk of bias judgments for studies contributing to analyses of each outcome are presented graphically in the sections that follow.

Table 90 Risk of bias assessments for 43 included randomised trials in primary prevention of VTE

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
ADOPT[205]	L-"Randomization was performed through a central telephone system with the use of a computer-generated randomization list"	L-"Randomization was performed through a central telephone system with the use of a computer-generated randomization list"	L-"The study medications were packaged in identical-appearing dispensing kits. Patients who were randomly assigned to apixaban received daily injections of an enoxaparin placebo" "Patients who were randomly assigned to enoxaparin received tablets containing an apixaban placebo"	L-"All components of the primary efficacy outcome were adjudicated by the independent central adjudication committee. All compression ultrasound examinations were recorded for submission to an independent central adjudication committee whose members were unaware of the treatment assignments"	L-For efficacy outcomes: All patients were included in the analyses	L-All outcomes are reported as per protocol
				L-"Each of these events (bleeding) was reviewed and adjudicated by the independent central adjudication committee (whose members were unaware of the treatment assignments)"	L-For safety outcomes: Some missing data; reasons given; reasons for missing data unlikely related to true outcome	

ADVANCE-1[188]	U-"The randomization was stratified according to study site and whether a patient was undergoing replacement of one or both knees, with a block size of 4"	U-No information to enable judgment	L-One group of patients received 2.5 mg of apixaban orally twice daily as well as an injection of placebo that mimicked injection with enoxaparin. The other group received 30 mg of enoxaparin subcutaneously every 12 hours along with placebo tablets that were identical in appearance to apixaban tablets.	L-"All venograms and all episodes of suspected symptomatic venous thromboembolism, bleeding, myocardial infarction, stroke, thrombocytopenia, or death were adjudicated, without knowledge of the patient's assigned treatment, by an independent central adjudication committee"	L-No missing outcome data except for DVT outcomes U-For DVT outcomes: Some missing outcome data; not entirely balanced in numbers across intervention groups. Not clear if missing data is unlikely to be related to true outcome	L-All outcomes are reported as per protocol
ADVANCE-2[195]	L-"The randomisation schedule was generated by the Bristol-Myers Squibb randomisation centre with SAS and was stratified by study site and by unilateral or bilateral surgery with a block size of four"	L-"The randomisation schedule was generated by the Bristol-Myers Squibb randomisation centre with SAS and was stratified by study site and by unilateral or bilateral surgery with a block size of four"	L-"Investigators, patients, statisticians, adjudicators, and the steering committee were masked to treatment allocation"	L-"Investigators, patients, statisticians, adjudicators, and the steering committee were masked to treatment allocation"	U-For safety outcomes: High proportion of missing outcome data; reasons for missing data given and reasons are similar across intervention groups and appear to be balanced in number across intervention groups. However, it's not clear whether the reasons are related to true outcome or not	L-All outcomes are reported as per protocol

					L-For safety outcomes: Missing outcome data, however few; reasons for missing data given and reasons balance in number across intervention groups; it's unlikely that that reason for missing data is related to true outcome L-For death outcome: All patients were included in the analyses	
ADVANCE-3[193]	L-"The randomization schedule was generated at the randomisation centre of Bristol-Myers Squibb with the use of SAS software and was stratified according to study site, with a block size of four"	L-"Potentially eligible patients were identified during a screening period of up to 14 days before surgery and were randomly assigned, with the use of an interactive telephone system"	L-"The study was a randomized, double-blind, double-dummy clinical trial" Patients were assigned "to receive apixaban at a dose of 2.5 mg orally twice daily plus placebo injections once daily or enoxaparin at a dose of 40 mg subcutaneously once daily plus placebo tablets twice daily"	L-"All venograms and all episodes of suspected symptomatic venous thromboembolism, bleeding, myocardial infarction, stroke, thrombocytopenia, and death were adjudicated by an independent central adjudication committee whose members were unaware of the treatment assignments"	L-For symptomatic DVT and symptomatic PE: All patients were included in the analyses U-For other efficacy outcomes and safety outcomes: Some missing outcome data; similar reasons for missing data across groups but not balanced in numbers. Reasons for missing outcome data may be related to true outcome	L-All outcomes are reported as per protocol

APROPOS[179]	L-“Randomization was done by computer generated allocation”	U-Not enough information to enable judgment. “Patients were randomly assigned to one of the following eight treatment groups”	U-“The study was conducted in a blinded fashion with regards to apixaban dosing and enoxaparin; the warfarin arm was open-label. In order to maintain blinding, apixaban and enoxaparin were administered in a double-dummy fashion”	L-“Efficacy, bleeding events and cause of death were adjudicated by an independent central committee whose members were unaware of treatment assignments”	L-For efficacy outcomes: Some missing data but reasonable reasons for the missing data were provided and it is unlikely that missing data could influence the result L-For safety outcomes: Minimal missing data unlikely to affect result. Also, reasons were provided for the missing data	L-All outcomes are reported as per protocol
ARDEPARIN ATHROPLASTY STUDY[213]	U-“The study utilized a randomized, multicenter, stratified, parallel, double blind design' 'Eligible patients were randomly assigned to one of three ardeparin doses or oral warfarin prophylaxis in a 1:1:2:2 ratio.”	U-Not enough information to enable judgment. “'Eligible patients were randomly assigned to one of three ardeparin doses or oral warfarin prophylaxis in a 1:1:2:2 ratio.”	L-“To maintain blinding of prophylaxis assignment, all patients received twice daily injections (either ardeparin or placebo), daily tablets (either placebo or warfarin) and daily prothrombin time measurement”	L-“The efficacy endpoint measures (mandatory venography of the operated leg, or lung scan or pulmonary angiogram for clinically suspected PE) were determined by objective testing and were interpreted by experts blinded to treatment assignment” “All other members of the clinical team, the patient, the pharmacist, and the sponsor, were blinded to prophylaxis treatment”	L-For efficacy outcomes: “Twenty one percent of randomized patients failed to complete the study. The number of patients who did not completed the study was evenly distributed among the four prophylaxis groups in proportion to the randomization ratio” L-For safety outcomes: “All patients who received at least one dose of the study drug were included in the analysis”	L-All outcomes are reported as per protocol

BISTRO II[212]	L-"On the day before surgery, patients were assigned randomly to five treatment groups, stratified by the study center and surgical procedure (hip or knee replacement), using a computer-generated scheme."	U- "On the day before surgery, patients were assigned randomly to five treatment groups, stratified by the study center and surgical procedure (hip or knee replacement), using a computer-generated scheme. Separate medication kits for hip and knee replacement were provided to each site in blocks of 10"	L- "Patients were assigned to either oral dabigatran etexilate with doses of 50 and 150 mg twice daily, 300 mg once daily and 225 mg twice daily, or 40 mg of enoxaparin (Aventis Pharma, Bridgewater, NJ, USA) subcutaneously, once daily. Both study groups received active or matching placebo medications"	L- For efficacy outcomes: "All tests for VTE during the treatment period were first evaluated locally and subsequently by an independent central adjudication committee blinded to the treatment allocation. The results of the central adjudication were used in the primary analysis." L- For safety outcomes: "A centralized independent committee classified all bleeding events"	L- For efficacy outcomes: Of 1973 randomised patients, only 1464 were included in efficacy outcome analysis. However missing outcome data are balanced in numbers across the trial arms and the reasons for missing data in the dabigatran arms have a similar spread to those of the enoxaparin arm. L- For safety outcomes: "1973 were randomized to either dabigatran etexilate (1576) or enoxaparin (397). Of these, 24 were not treated. The safety population comprised 1949 patients who received at least one dose of study drug"	L-All outcomes are reported as per protocol

EXPERT[185]	L-"The computer-generated randomization code provided assignments in a 2:2:1 ratio to either betrixaban 15 mg, betrixaban 40 mg, or enoxaparin 30 mg, respectively"	U-Not enough information to judge allocation concealment. "The computer-generated randomization code provided assignments in a 2:2:1 ratio to either betrixaban 15 mg, betrixaban 40 mg, or enoxaparin 30 mg, respectively"	H-"Randomization was either to enoxaparin or one of two dose levels (15 or 40 mg bid) of betrixaban; patients and physicians were blinded to the betrixaban dose level, but unblinded to enoxaparin versus betrixaban"	L-"All primary efficacy data and suspected bleeding events were evaluated centrally by an Independent Central Adjudication Committee (ICAC) blinded to treatment allocation"	U-For efficacy outcomes: There are missing data and although reasons for the missing data are provided, they do not balance in numbers across intervention groups and may be related to true outcome L-For safety outcomes: All patients were included in the analyses	L-All outcomes are reported as per protocol
LIFENOX[202]	L-"The treatment-code list of random permuted blocks was generated by an independent contract research organization and was stratified according to center"	U-"The investigators assigned the patients to a group in the sequential order of the treatment numbers available at the site"	L-"The investigators, patients, and research personnel, as well as the members of the steering committee and of the data and safety monitoring committee, were unaware of the group assignments"	L-"The investigators, patients, and research personnel, as well as the members of the steering committee and of the data and safety monitoring committee, were unaware of the group assignments"	L-A negligible number of participants did not receive study drug and had no follow-up data. This reason is the same in both arms. All patients who received study drug were included in the analyses	L-All outcomes are reported as per protocol

MAGELLAN[201,208]	L-“Randomization was performed in permuted blocks with the use of an interactive voice response system, with stratification according to centre”	L-“Randomization was performed in permuted blocks with the use of an interactive voice response system, with stratification according to centre”	L-“Eligible patients were randomly assigned to receive subcutaneous enoxaparin, 40 mg once daily, for 10±4 days and oral placebo, once daily, for 35±4 days or to receive subcutaneous placebo, once daily, for 10±4 days and oral rivaroxaban, 10 mg once daily, for 35±4 days”	L-“All outcomes were assessed by an independent, central adjudication committee whose members were unaware of the study assignments”	L-Missing data; reasons provided with similarity between the treatment groups; reasons also balance in number in the treatment groups	L-All outcomes are reported as per protocol

ODiXa-HIP[211]	U-“In this dose-escalation study, patients were randomized to receive rivaroxaban (Bayer HealthCare AG) or enoxaparin (Clexane®/Lovenox®, sanofi-aventis), in a 3:1 ratio.”	U-“In this dose-escalation study, patients were randomized to receive rivaroxaban (Bayer HealthCare AG) or enoxaparin (Clexane®/Lovenox®, sanofi-aventis), in a 3:1 ratio.”	H-“This was a randomized, open-label, active-comparator-controlled, European, multinational, dose-escalation study.”	L-“All symptomatic events, including deaths, were assessed centrally by the VTE Adjudication Committee. Study drug allocation was not revealed to the adjudication committees, who performed their assessments in a blinded manner.”	H- For efficacy outcomes: Analysis was per-protocol n = 466. 14, 21, 13, 18, 20, 34, and 55 patients were excluded from the randomised numbers in arms 1 to 7 respectively, of which16 patients did not receive allocated drug treatment. “A patient was valid for the per-protocol (PP) analysis if they were valid for the ITT analysis, had no major protocol deviations and had adequate assessment of VTE no more than 1 day after stopping study medication” U-For safety outcomes: Analysis was based on n = 625. 1, 4, 3, 2, and 6 patients did not receive allocated drug treatment in arms 1, 2, 4, 5 and 6 respectively. “16 patients did not receive allocated drug treatment”	L-All outcomes are reported as per protocol

ODiXa-HIP2[176]	U-Not enough information to enable judgment. "In this double-blind, double-dummy, doseranging study, patients were randomized to oral BAY 59-7939 (2.5, 5, 10, 20, or 30 mg b.i.d.), starting 6–8 h after surgery, or s.c. enoxaparin 40 mg once daily, starting on the evening before surgery."	U-Not enough information to enable judgment. "This was a prospective, randomized, double-blind, double-dummy, active-comparator-controlled, multicentre, multinational study. All patients received matching placebo injections or tablets"	L-"This was a prospective, randomized, double-blind, double-dummy, active-comparator-controlled, multicentre, multinational study. All patients received matching placebo injections or tablets"	L-"All adjudication committees were independent and blinded to treatment allocation"	U-For efficacy outcomes: Large numbers of outcome missing data. The number of missing data seems to be balanced in the treatment groups, with similar reasons for missing data. However, it isn't clear whether missing data could be related to the true outcome L-For safety outcomes: Very little numbers of missing data; however number is balanced in the treatment groups. Reason for missing data is unlikely to be related to the true outcome.	L-All outcomes are reported as per protocol
ODIXa-KNEE[174]	L-"Patients were randomly assigned to six treatment groups, using a computer-generated randomization list"	L-"Patients were randomly assigned to six treatment groups, using a computer-generated randomization list and interactive voice response system"	L-"This was a randomized, double-blind, double-dummy, active comparator controlled, parallel-group, dose-ranging study. All patients received matching placebo injections or tablets"	L-For efficacy outcomes: "The assessment of the efficacy endpoints was based solely on the analysis made by two independent central adjudication committees (Venography and VTE) blinded to the treatment allocation"	U-For efficacy outcomes: Some missing outcome data and reasons for missing data are provided but missing outcome data does not balance in numbers across intervention groups. Not clear whether reason for missing data is unrelated to true outcome	L-All outcomes are reported as per protocol

				L-For safety outcomes: "All bleeding events were assessed centrally by a blinded independent bleeding event committee"	L-For safety outcomes: All patients were included in the analyses	
ODIXa-OD.HIP[175]	U-Not enough information to enable judgment. "The ODIXa-OD-HIP study was a randomized, double-blind, double-dummy, active-comparator–controlled, multinational, dose-ranging study.	U-Not enough information to enable judgment. "The ODIXa-OD-HIP study was a randomized, double-blind, double-dummy, active-comparator–controlled, multinational, dose-ranging study.	L-"The ODIXa-OD-HIP study was a randomized, double-blind, double-dummy, active-comparator–controlled, multinational, dose-ranging study. Patients received matching placebo tablets or injections, so that each patient received 2 tablets and an injection every evening"	L-"All venograms were assessed centrally by the Venography Adjudication Committee. All adjudication committees were independent and blinded to treatment allocation"	U-For efficacy outcomes: Fairly large proportions of missing data; reasons for missing data are given but the reasons and numbers do not balance across the groups. Reasons for missing outcome data may be related to the true outcome	U-Symptomatic VTE was not reported
				L-"All bleeding events were assessed centrally by the Bleeding Event Adjudication Committee. All adjudication committees were independent and blinded to treatment allocation"	L-For safety outcomes: Small number of missing data with similar reasons. Unlikely that reasons are related to the true outcome	

PROTECHT[187]	L-“The randomisation list was generated by an independent statistician who used a standard permuted block of six without stratification. The list was generated with SAS version 8.2”	L-“The allocation sequence was available online to the investigators using the Hypernet web-based system”	L-“Treatment assignments were masked from all study personnel and participants for the duration of the study”	L-“All study outcomes were assessed by a central independent adjudication committee whose members were unaware of patients’ study-group allocation”	L-Almost 99% of the randomised patients were included in the efficacy and safety analysis. Reason for the minimal loss unlikely related to the outcome	L-All outcomes are reported as per protocol
RECORD 1[182]	L-“Before surgery, patients were randomly assigned to a study group with the use of permuted blocks and stratification according to center by means of a central telephone system with a computer-generated randomization list”	L-“Before surgery, patients were randomly assigned to a study group with the use of permuted blocks and stratification according to center by means of a central telephone system with a computer-generated randomization list”	U-“In a double-blind fashion, patients were assigned to receive either once-daily oral rivaroxaban in 10-mg tablets (Xarelto, Bayer HealthCare) or 40 mg of enoxaparin sodium administered by subcutaneous injection (Clexane/Lovenox, Sanofi-Aventis)”	L-“All outcomes were assessed by central independent adjudication committees whose members were unaware of the patients’ study-group assignments”	L-There is a substantial amount of missing data with reasons. However, missing data appear to be balanced in numbers across intervention groups	L-All outcomes are reported as per protocol

RECORD 2[183]	L-“Patients were randomly assigned to study medication before surgery, using permutated blocks (size four) with stratification according to centre, via a central telephone system using a computer-generated randomisation code”	L-“Patients were randomly assigned to study medication before surgery, using permutated blocks (size four) with stratification according to centre, via a central telephone system using a computer-generated randomisation code”	U-“Patients were randomly assigned to receive double-blind, oral rivaroxaban 10 mg tablets once daily (Xarelto, Bayer HealthCare AG, Wuppertal, Germany) or subcutaneous injections of enoxaparin sodium 40 mg once daily (Clexane/Lovenox, Sanofi -Aventis, Frankfurt am Main, Germany)”	L-“All outcomes were assessed by independent, central adjudication committees blinded to treatment allocation”	U-For efficacy outcomes: Some missing data (about 31%); missing data seems balanced in number across intervention groups with similar reasons for missing data across groups but not sure if missing data is related to true outcome or not L-For safety outcomes: Few missing data; missing data seems balanced in number across intervention groups with similar reasons for missing data across groups and missing data is unlikely related to true outcome	L-All outcomes are reported as per protocol
RECORD 3[180]	U-“On a double-blind and double-dummy basis, before surgery, patients were randomly assigned through a central telephone system”	L-“On a double-blind and double-dummy basis, before surgery, patients were randomly assigned through a central telephone system”	U-“On a double-blind and double-dummy basis, before surgery, patients were randomly assigned through a central telephone system to receive once-daily oral rivaroxaban (Bayer HealthCare), in a 10-	L-“All outcomes were assessed by central, independent adjudication committees who were unaware of the treatment assignments”	U-For efficacy outcomes: Some missing outcome data; reasons for missing data provided. However, it is not clear whether missing data is unlikely to be related to true outcome	L-All outcomes are reported as per protocol

			mg tablet, or a once-daily injection of enoxaparin sodium (Clexane or Lovenox, Sanofi-Aventis), in a 40-mg dose”		L-For safety outcomes: Few missing outcomes data; reasons for missing data provided and appears to be the same in both intervention arms; it is unlikely that missing data is related to true outcome	
RECORD 4[190]	L-“Before surgery, participants were randomly assigned to study drug through a central telephone system, stratified by centre with permuted blocks of four patients, on a double-blind and double-dummy basis”	L-“Before surgery, participants were randomly assigned to study drug through a central telephone system, stratified by centre with permuted blocks of four patients, on a double-blind and double-dummy basis”	U-“Before surgery, participants were randomly assigned to study drug through a central telephone system, stratified by centre with permuted blocks of four patients, on a double-blind and double-dummy basis”	L-“Central independent adjudication committees masked to allocation assessed all outcomes”	L-For efficacy outcomes: “Proportions of patients with venograms adequate for assessment for the primary efficacy analysis were lower than anticipated but similar (including the underlying reasons) in the two treatment groups (965 [60•9%] of 1584 patients in the rivaroxaban group and 959 [61•3%] of 1564 patients in the enoxaparin group). The groups were well balanced in terms of baseline demographic and surgery characteristics” L-For safety outcomes: All patients were included in the analyses	L-All outcomes are reported as per protocol

RE-MOBILISE[184]	L-“An Interactive Voice Response System was used for randomization in blocks of 6 and was based on an independently generated scheme”	L-“This was a double-blind, centrally randomized trial” “An Interactive Voice Response System was used for randomization”	L-"This was a randomized, double-blind, active controlled, noninferiority study”. "All 3 groups received one active and one placebo treatment (i.e., double-dummy blinding)"	L-For efficacy outcomes: “Diagnostic tests for VTE events were initially evaluated locally and subsequently reviewed by an independent central adjudication committee blinded to treatment allocation” L-For safety outcomes: “An independent expert adjudication committee blinded to treatment allocation classified and reviewed all bleeding events”	L-Missing data were accounted for and similar across study groups. It is unlikely that missing data and reasons are related to the ouctomes	L-All outcomes are reported as per protocol
RE-MODEL[178]	L-“Patients were randomly assigned to one of three treatment groups, using a computer-generated central scheme stratified by study centre”	L-“Patients were randomly assigned to one of three treatment groups, using a computer-generated central scheme stratified by study centre”	U-“This was a randomized, double-blind, active controlled, noninferiority study conducted at 105 centers in Europe, Australia, and South Africa”	L-For efficacy outcomes: “Diagnostic tests for VTE events were initially evaluated locally, and subsequently reviewed by an independent central adjudication committee blinded to treatment allocation”	L-Missing data almost balanced across intervention groups and clear reasons given as to why data was missing	L-All outcomes are reported as per protocol

RE-NOVATE[177]	L-“Patients were randomly assigned to one of three treatment groups, stratified by study centre with a central computer generated scheme”	L-“Patients were randomly assigned to one of three treatment groups, stratified by study centre with a central computer generated scheme”	L-“All three groups received one active and one placebo medication identical in appearance to the other active treatment”	U-For safety outcomes: “An independent expert adjudication committee classified all bleeding events” L-For efficacy outcomes: “Diagnostic tests for venous thromboembolic events were initially assessed locally, then by an independent central adjudication committee blinded to treatment allocation. The results of the independent committee were used in the primary analysis”. Other outcomes were also reviewed by Independent committees, masked to treatment allocation	U-For efficacy outcomes: Data for a substantial number of participants in the three groups - missing! Reasons for the missing data were provided. Proportion of missing data is not the same for the groups. L-For safety outcomes: All patients were included in the analyses	L-All outcomes are reported as per protocol

RE-NOVATE II[200,206]	L-"Up to three days before surgery, eligible patients were randomised in accordance with a computer-generated scheme using a central telephone randomisation procedure"	L-"Up to three days before surgery, eligible patients were randomised in accordance with a computer-generated scheme using a central telephone randomisation procedure"	L-"Treatment-group assignment was concealed from the investigators and their staff and the clinical monitors." "Patients were assigned to either once-daily oral dabigatran 220 mg (2 x 110 mg capsules) or enoxaparin 40 mg subcutaneous injection, together with a placebo of the other study drug (double-dummy design). Active and placebo medications were identical in appearance"	L-For efficacy outcomes: "Diagnostic tests for thromboembolic events were initially evaluated locally, and subsequently by an independent central adjudication committee who were blinded to treatment allocation" U-For safety outcomes: Not clear: "Perioperative and post-operative blood loss that was considered normal by the investigator was not recorded as a bleeding event."	L-For symptomatic DVT, symptomatic non-fatal PE and all safety outcomes, no missing outcome data. However, missing data for other efficacy outcomes but with reasons. Reasons for missing data are balanced in number across intervention groups; unlikely that reasons are related to true outcome	L-All outcomes are reported as per protocol
STARS E-3[199]	U-Abstract; not enough information. "This was a double-blind, double-dummy, centrally randomized trial"	L-This was a double-blind, double-dummy, centrally randomized trial"	U-Abstract; not enough information. "This was a double-blind, double-dummy, centrally randomized trial"	U-Abstract; not enough information. "This was a double-blind, double-dummy, centrally randomized trial"	U-Abstract; not enough information. "This was a double-blind, double-dummy, centrally randomized trial"	U-Study protocol not found
STARS J-1[189,197]	L-"Patients were randomized via an allocation table containing random numbers according to the Excel Visual Basic program using the permuted block	U-Not enough information to enable judgment. "Patients were randomized via an allocation table containing random numbers according to the Excel Visual	U-"This was a multicenter, randomized, double-blind, placebo controlled, dose-ranging study"	L-"All venograms were assessed centrally by The Venous Thromboembolic Event Adjudication Committee under blinded conditions"	L-For efficacy outcomes: Some missing outcome data. Reasons for missing outcome was provided and it is unlikely that missing outcome is related to true outcome	L-All outcomes are reported as per protocol

	method, and a pre-treatment examination was then performed"	Basic program using the permuted block method, and a pre-treatment examination was then performed"			L-For safety outcomes: All patients were included in the analyses	
STARS J-2[191]	U-Abstract information; not enough information to enable judge. "This was a randomized, enoxaparin-controlled, multicenter, parallel group study."	U-Abstract information; not enough information to enable judge. "This was a randomized, enoxaparin-controlled, multicenter, parallel group study."	H-"Double-blind edoxaban 15 mg or 30 mg once daily or open-label, subcutaneous enoxaparin 20 mg BID was administered for 11 to 14 days."	U-"Outcome assessors were blinded to treatment allocation but not for enoxaparin allocation which was open-blinded"	U-Some missing outcome data (substantial proportion). Reasons for missing outcome data not available. Unclear if reasons for missing data is related to true outcome	L-All outcomes are reported as per protocol
STARS J-4[198,210]	U-Not enough information to enable judgment –"Japanese patients were randomized 2:1 to receive an oral dose of edoxaban 30 mg once daily or the active control, enoxaparin 2000	U-Not enough information to enable judgment –"Japanese patients were randomized 2:1 to receive an oral dose of edoxaban 30 mg once daily or the active control, enoxaparin 2000	H-"This was a multicenter, open-label, active-comparator, phase 3 trial"	L-"To ensure objectivity, independent committees assessed bleeding events and thromboembolic events under blinded conditions"	U-For efficacy outcomes: Some missing outcome data although with reasons; the number of missing data is not balanced between the arms. The reasons for missing data may be related to the true outcome	L-All outcomes are reported as per protocol

	IU sc every 12 hours (BID), which is the approved dosing regimen in Japan".	IU sc every 12 hours (BID), which is the approved dosing regimen in Japan".			L-For safety outcomes: Small amount of missing outcome data with reasons; the number of missing data is balanced between the arms. Unlikely that the reasons for missing data are related to the true outcome	
STARS J-V[196]	U-Abstract; not enough information to enable judgment. "This was a randomized, double-blind, double-dummy, enoxaparin-controlled, multicentre trial"	U-Abstract; not enough information to enable judgment. "This was a randomized, double-blind, double-dummy, enoxaparin-controlled, multicentre trial"	U-Abstract; not enough information to enable judgment. "This was a randomized, double-blind, double-dummy, enoxaparin-controlled, multicentre trial"	U-Abstract; not enough information to enable judgment. "This was a randomized, double-blind, double-dummy, enoxaparin-controlled, multicentre trial"	U-For efficacy outcomes: Some missing outcome data although with reasons; not enough information to judge whether the number of missing data is balanced between the arms. The reasons for missing data may be related to the true outcome. L-For safety outcomes: Minimal amount of missing outcome data and although not enough information to judge the balance between the groups, it is unlikely that the reasons for missing data are related to the true outcome	L-All outcomes are reported as per protocol

TOPIC-1[214]	L-“Patients were randomly assigned to placebo or certoparin sodium (Mono Embolex, Novartis GmbH, Nurnberg, Germany) using a computer-generated randomization list”	L-“Randomization numbers were allocated sequentially as patients were enrolled at each centre. Only the external statistician from the Safety Committee had access to the randomization codes”	U-“These were randomized, double-blind, adaptive group sequential, placebo controlled trials”	L-For efficacy outcomes: “Validated by a blinded, independent Central Thrombosis Evaluation Team” L-For safety outcomes: “Validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments”	L-Only one and two patients were not included in the efficacy and safety analyses respectively	U-Study protocol not found
TOPIC-2[214]	L-“Patients were randomly assigned to placebo or certoparin sodium (Mono Embolex, Novartis GmbH,	L-“Randomization numbers were allocated sequentially as patients were enrolled at each centre. Only the	U-“These were randomized, double-blind, adaptive group sequential, placebo controlled trials”	L-For efficacy outcomes: “Validated by a blinded, independent Central Thrombosis Evaluation Team”	L-Some missing outcome data; reasons not given and missing data isn’t exactly balanced in both arms. However, the numbers are quite small and	U-Study protocol not found

	Nurnberg, Germany) using a computer-generated randomization list”	external statistician from the Safety Committee had access to the randomization codes”		L-For safety outcomes: “Validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments”	reasons unlikely to be related to the outcome.	
VTE-APIX-PLACEBO-USACAN[207]	L-“Randomization was performed centrally by contacting a computerized telephone voice response system provided by Bristol Myers Squibb (BMS) (Lawrenceville, NJ, USA). Treatment assignments were implemented with a randomization schedule with blocks of size four; blocks were stratified by the presence (or not) of metastatic liver disease and clinical center”	L-“Randomization was performed centrally by contacting a computerized telephone voice response system provided by Bristol Myers Squibb (BMS) (Lawrenceville, NJ, USA). Treatment assignments were implemented with a randomization schedule with blocks of size four; blocks were stratified by the presence (or not) of metastatic liver disease and clinical center”	L-“All subjects took four tablets orally once daily; these consisted of a combination of apixaban and matching placebo tablets for the apixaban treatment groups, or all placebo tablets for the placebo treatment group, such that the study supplies for subjects in all treatment groups were identical in appearance.”	L-Outcome assessors were blinded to treatment allocation	L-Missing data is of the same quantity (minimal) in all groups and reasons unlikely to be related to the true outcome	L-All outcomes are reported as per protocol

VTE-DABIG-LMWH-GREECE[204]	U-Abstract; not enough information to enable judgment. "The patients were randomly assigned in the first group, that fondaparinux 2.5 mg were used for thomboprophylaxis, in the enoxaparine 40 mg group, in the Tinzaparin 0.45 group and in the forth Dabigatran 110 mg group (75 mg over 75 years old)."	U-Abstract; not enough information to enable judgment. "The patients were randomly assigned in the first group, that fondaparinux 2.5 mg were used for thomboprophylaxis, in the enoxaparine 40 mg group, in the Tinzaparin 0.45 group and in the forth Dabigatran 110 mg group (75 mg over 75 years old)."	U-Abstract; there is no information on blinding of participants and personnel	U-Abstract; there is no information on blinding of outcome assessment	U-Abstract; there is no information on the number of participants included in the analyses, for comparison with the number randomised to treatments.	U-Study protocol not found
VTE-DABIG-PLAC-JAPAN[192]	L-"Patients were randomly assigned to 1 of 4 treatment groups using a computer-generated scheme stratified by study center."	U-Not enough information to enable judgment. "Randomization was performed in blocks of 4"	U-"This was a double-blind, multicenter, randomized, parallel-group, placebo-controlled study conducted at 38 centers in Japan"	L-For efficacy outcomes: "Diagnostic tests for VTE were evaluated centrally by an independent adjudication committee blinded to treatment allocation" U-For safety outcomes: "Two medical experts reviewed all cases of bleeding."	L-There were missing data but missing data appear to balance in numbers across intervention groups, with similar reasons for missing data across groups.	L-All outcomes are reported as per protocol

VTE-EDOX-LMWH-MULTI[194]	L-“The study was a multicentre study that used a randomized, parallel- group, multi-dose, active-controlled, double-blind, and double-dummy design”	L-“randomly allocated, using an interactive voice recognition system”	L-“Eligible patients who provided written informed consent were randomly allocated, using an interactive voice recognition system to receive either oral edoxaban and subcutaneous injections of placebo, or subcutaneous dalteparin and oral placebo”	L-“All venograms were interpreted by a central independent adjudication committee blinded to treatment allocation and were categorised as proximal DVT (with or without associated distal thrombosis), distal DVT only, normal, or non-evaluable. All episodes of suspected bleeding, suspected symptomatic DVT or PE, and all deaths were reviewed by a blinded central independent clinical events committee and classified according to the definitions provided”	U-For efficacy outcomes: Some missing outcome data and reasons for missing data are provided but missing outcome data does not balance in numbers across intervention groups. Not clear whether reason for missing data is unrelated to true outcome L-For safety outcomes: Very few missing outcome data; reasons for missing outcome data are provided and it is likely that reasons are unrelated to true outcome	L-All outcomes are reported as per protocol
VTE-LMWH-PLAC-CAN[186]	L-“A statistician and pharmacist at the co-ordinating centre randomised a total of 305 patients via computer generation in a ratio of 1:1 to receive either LMWH or a	U-A statistician and pharmacist at the co-ordinating centre randomised a total of 305 patients via computer generation in a ratio of 1:1 to receive either LMWH or a	U-“Owing to the double-blind nature of the study, all patients received a general anaesthetic for surgical fixation to avoid any potential adverse reaction to spinal anaesthesia in those patients receiving Fragmin”	L-For efficacy outcomes: “Three senior interventional radiologists reviewed the venograms, with any difference of opinion resolved by consensus. All the radiologists were blinded to the study group”	L-The number randomised is not the number analysed. However, participants removed from the analyses are those that didn't meet baseline venography eligibility after randomisation even though they met the study inclusion criteria	U-Study protocol not found

	placebo for 14 days”	placebo for 14 days.		U-For safety outcomes: Not enough information to enable judgment; “All adverse events were monitored and recorded with clinical examination and regular haematological, biochemical and urinary investigations during the routine management of the patients while in hospital”.	prior to randomisation. All finally included participants were accounted for in the analysis	
VTE-LMWH-PLAC-JAPAN[203]	U-Not enough information to enable judgment. “A randomised controlled trial was performed to evaluate whether the incidence of post-operative venous thromboembolism was reduced by using pharmacological anticoagulation with either fondaparinux or enoxaparin in addition to our prophylactic mechanical regimen.”	U-Not enough information to enable judgment. “The 255 patients were randomly assigned into three Groups”.	U-Not enough information to enable judgment. “The 255 patients were randomly assigned into three groups (each of 85) to receive post-operative subcutaneous injections of fondaparinux (Arixtra; GlaxoSmithKline, London, United Kingdom: 2.5 mg once daily), enoxaparin (Clexane; Sanofi-Aventis, Paris, France: 40 mg, 20 mg twice daily) or placebo (0.5 ml of isotonic saline) for ten consecutive days.”	L-All the scans were performed by experienced vascular technicians and were read by experienced radiologists who were blinded to the patient’s randomisation	L-For efficacy outcomes: Very small missing data <1%; missing data unlikely to be related to the outcome L-For safety outcomes: All patients were included in the analyses	U-Study protocol not found

VTE-RIVAROX-LMWH-BRAZIL[181]	U-Not enough information to enable judgment. "From September 2006 to April 2007, at the Orthopedics and Traumatology Clinic of the Hospital Complex of the Santa Casa of Porto Alegre, State of Rio Grande do Sul, a randomized, double-blind clinical trial was carried out"	U-Not enough information to enable judgment. "From September 2006 to April 2007, at the Orthopedics and Traumatology Clinic of the Hospital Complex of the Santa Casa of Porto Alegre, State of Rio Grande do Sul, a randomized, double-blind clinical trial was carried out"	L-One of the groups was given subcutaneous 40 mg enoxaparin 6 hours to 8 hours before surgery, and after surgery a placebo pill was added, for once a day oral intake, during the first 32 to 36 days. The other group was given oral 10 mg rivaroxaban, once a day, during the first 32 to 36 post-operative days. In order to have the double-blind feature of the study, a subcutaneous placebo injection was given 6 hours to 8 hours before surgery and on the 32 to 36 days following surgery.	U-There is no specific information on blinding of outcome assessors. This may have been done but not stated.	L-All patients were included in the analyses	U-Study protocol not found

VTE-RIVAROX-LMWH-CHINA[209]	U-"The patients were randomly divided into rivaroxaban group and low-molecular-weight heparin group".	H-No information and no indication of concealment of treatment allocation	U-Not enough information-"The patients in two groups were given drugs at 6 hours after replacement, the patients in the rivaroxaban group were given rivaroxaban 10 mg/d with the course of 5 weeks; the patients in the low-molecular-weight heparin group were given low molecular weight heparin 4 100 U/d with the course of 2 weeks".	H-No information and no indication of blinding of outcome assessors	L-All patients were included in the analyses	U-Study protocol not found
VTE-VKA-LMWH-CANADA[169]	L-"The 670 eligible and consenting patients were randomly allocated after surgery to receive either warfarin sodium (334 patients) or enoxaparin (336 patients) in a 1:1 ratio in blocks of four. A computer generated the randomization schedule"	U-Not enough information to enable judgment. "We stratified randomization by study center, history of venous thromboembolism , and use of a cemented or uncemented prosthesis"	L-"Patients in the warfarin group also received subcutaneous saline placebo every 12 hours. Patients in the enoxaparin group received 30 mg of enoxaparin subcutaneously every 12 hours and warfarin placebo once daily"	L-"All diagnostic tests and bleeding episodes were adjudicated by a central committee that was unaware of treatment allocation or clinical findings"	L-Missing outcome data with reasons which are balance between the treatment arms. Unlikely to be related to the true outcome	U-Study protocol not found

VTE-VKA-LMWH-US[170]	U-Not enough information to enable judgment. "The effectiveness and safety of warfarin were compared with those of a low-molecularweight heparin (dalteparin) for the prevention of deep-vein thrombosis after total hip arthroplasty in a prospective, randomized, multi-institutional trial"	U-Not enough information to enable judgment. "The patients were randomly assigned to receive prophylaxis with either warfarin or low-molecular-weight heparin"	H-The study used an open-label design	L-For efficacy outcomes: "All venograms were evaluated by a radiologist who had no knowledge of the treatment-group assignment" U-For safety outcomes: No information is reported about who assessed major bleeding and if the assessor was blinded	L-"Thirty patients (seventeen who were randomized to treatment with dalteparin and thirteen who were randomized to treatment with warfarin) were excluded from the intent-to-treat population because they had never received the drug (twenty-seven patients) or they had received the drug but the operation had been cancelled (three patients). All patients in the intent-to-treat population were included in the per-protocol analysis if they had at least one evaluable venogram"	U-Study protocol not found

VTE-VKA-LMWH-US-2[171]	U-“The study was a randomized, open-label, parallel group clinical trial conducted in 156 centres and divided into two phases”	U-Not enough information to enable judgment. “The study was a randomized, open-label, parallel group clinical trial conducted in 156 centres and divided into two phases”	H-The study was a randomized, open-label, parallel group clinical trial conducted in 156 centres and divided into two phases	U-Not enough information to enable judgment. “each patient was examined for clinical signs and symptoms of deep vein thrombosis (pain, inflammation, swelling, and redness of the lower extremity) and pulmonary embolism (chest pain and difficulty breathing)”	L-“As already stated, the results and conclusions are based on the intent-to-treat analysis, including all patients who received at least one dose of a study medication”	U-Study protocol not found

VTE-VKA-LMWH-US-3[172]	L-“We used a randomized, computer-derived treatment schedule to assign treatment regimens. To obtain continuing balance of treatments, the randomization list was divided into consecutive blocks”	U-Not enough information to enable judgment. Allocation sequence was generated by computer but not clear if allocation was done centrally.	L-“Patients randomized to receive warfarin also received subcutaneous placebo injections. Patients randomized to receive dalteparin also received placebo capsules (warfarin and its placebo were encapsulated to maintain blinding)”	L-“Venograms were interpreted by the local radiologist and an independent, blinded central reader. Disagreements between the local radiologist and the central reader were resolved by a second blinded independent central interpretation; this second reading was decisive” “Thus the use of placebo capsules and injections and the assignment of an independent anticoagulant monitor to adjust INR values maintained double blinding throughout the study”	L-“Twenty nine patients were randomized but did not received study medication; this occurred because of traumatic spinal tap (1,3, and 3 patients per group respectively), cancelled operation (0,2 and 1 patients), presence of exclusion criteria (1,1, and 1 patient), withdrawn consent (2,1, and 3 patients), or miscellaneous reasons making the patient ineligible (4,2, and 4 patients)”	U-Study protocol not found

VTE-VKA-LMWH-US-4[173]	U-“Randomization numbers generated by the study sponsor were affixed to the exterior of each kit; randomization was performed by the investigator allocating the kits in ascending order”	L-“Each center was provided with sealed medication kits containing either syringes filled with enoxaparin or warfarin tablets.” “Randomization numbers generated by the study sponsor were affixed to the exterior of each kit; randomization was performed by the investigator allocating the kits in ascending order”	H-“We report the results of a prospective, randomized, multicenter, open-label, inpatient, parallel-group study”	L-“In addition to the assessment by the investigator, a blinded, independent review of all venograms and ultrasonograms was carried out by a panel of vascular imaging specialists”	L-All patients were included in the analyses	U-Study protocol not found

L = low risk; H = high risk; U = unclear risk; VTE = venous thromboembolism; DVT = deep vein thrombosis, PE = pulmonary embolism; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; Note: quotations are denoted by inverted commas

7.4 Results of clinical effectiveness and safety

Three trials (TOPIC-1, TOPIC-2 and ARDEPARIN ATHROPLASTY STUDY) were not included in any of the networks. They used non-standard variants of heparin that could not be assumed to be comparable to standard heparin, so these studies do not contribute information on the comparisons of interest.

The 38 trials included in these analyses implemented a total of 35 interventions, listed in Table 91. The interventions labelled as "standard dose" for LMWH included tinzaparin (0.45ml od), enoxaparin (40mg od or 30mg bd) and dalteparin (5000IU) The "warfarin variable" node included interventions in which a subtherapeutic INR range had been considered for some patients, and for that reason this node was only included in sensitivity analyses in which it was merged with the warfarin INR 2-3 node). Table 92 and Table 93 show the numbers of events for each outcome reported in each trial. We performed network meta-analyses for seven outcomes: symptomatic VTE, symptomatic DVT, symptomatic PE, myocardial infarction, major bleeding, clinically relevant bleeding and all cause mortality. For the first three outcomes, hip surgery, knee surgery and non-surgical patients were analysed separately, while for each of the four remaining outcomes all patients were combined in a single network.

Table 91 List of distinct interventions examined by included randomised trials of primary prevention of VTE

1 LMWH Post-op (standard dose)	19 Dabigatran (150mg od)
2 LMWH Pre-op (standard dose)	20 Dabigatran (220mg od)
3 LMWH (standard dose)	21 Edoxaban (5mg od)
4 LMWH (Enoxaparin 20mg bd)	22 Edoxaban (15mg od)
5 LMWH (4100 IU od)	23 Edoxaban (30mg od)
6 LMWH (Nadroparin 3800 IU anti-Xa od)	24 Edoxaban (60mg od)
7 Warfarin (INR 2-3)	25 Edoxaban (90mg od)
8 Warfarin variable	26 Rivaroxaban (2.5mg bd)
9 Placebo	27 Rivaroxaban (5mg od)
10 Apixaban (2.5mg bd)	28 Rivaroxaban (5mg bd)
11 Apixaban (5mg od)	29 Rivaroxaban (10mg od)
12 Apixaban (5mg bd)	30 Rivaroxaban (10mg bd)
13 Apixaban (10mg od)	31 Rivaroxaban (20mg od)
14 Apixaban (10mg bd)	32 Rivaroxaban (30mg od)
15 Apixaban (20mg od)	33 Rivaroxaban (20mg bd)
16 Betrixaban (15mg bd)	34 Rivaroxaban (40mg od)
17 Betrixaban (40mg bd)	35 Rivaroxaban (30mg bd)
18 Dabigatran (110mg od)	

Results are presented as follows for each of the seven outcomes. First, we provide network plots to illustrate the comparisons of interventions made in the different trials. Second, we illustrate the risk of bias assessments specific to the outcome for each trial included in the network. Third, we present results tables for each intervention compared with the reference treatment (standard dose of LMWH administered before surgery for hip surgery patients, after surgery for knee surgery patients, or at start of treatment for other patients). Fourth, we present results tables for pairwise comparisons among licensed doses of the NOACs. For both sets of results tables, posterior median odds ratios and 95% credible intervals from Bayesian fixed-effect analyses are shown, although we refer to the latter as confidence intervals for convenience. In these tables we present results separately for any available direct evidence, for any indirect comparisons that can be made (excluding the direct evidence) and for the network meta-analysis (which combines the direct and the indirect evidence). Comparisons from the NMA with a ratio between interval limits exceeding nine were considered “imprecisely estimated” and are presented at the bottom of each table (note that calculation of indirect evidence was not undertaken for imprecisely estimated comparisons). A summary of results across outcomes is provided at the end in the form of a ‘rankogram’, which illustrates the probability that each treatment is best, second best, and so on, for each outcome. Last, forest plots of all contributing data, with odds ratios calculated using standard frequentist methods, are included in Appendix 3.

Table 92 Efficacy outcomes reported by 38 included randomised trials in primary prevention of VTE: number of events for each outcome in each trial

Study	Study size	DVT	Symp. DVT	Non-symp. DVT	Proximal DVT	Distal DVT	Symp. Proxi-mal DVT	Symp. Distal DVT	PE	Symp. PE	Fatal PE	Symp. Non-fatal PE	VTE	Symp. VTE	Major VTE
ADOPT[205]	6401		21		110		17	5				15			130
ADVANCE-1[188]	3184	181	10		20					23	4				
ADVANCE-2[195]	3009	385			10		35			4	1				39
ADVANCE-3[193]	4394	90	6		27					8	1	7			35
APROPOS[179]	856		5				13			4	1		100		
EXPERT[185]	215		2	24			1	1		2			28	4	
LIFENOX[202]	8307														
MAGELLAN[201,208]	7998		28									24			160
ODiXa-HIP2[176]	548	81			14					0					14
ODIXa-KNEE[174]	613	121	4		12	109				2					14
ODIXa-OD.HIP[175]	618	82			18	64		1		0					18
PROTECHT[187]	1150		16							6				22	
RE-MOBILISE[184]	1896		26		44	513				15		11	569		56
RE-MODEL[178]	2076		12							2			587		
RE-NOVATE[177]	3463		16							9	1				
RE-NOVATE II[200,206]	2013	127	4		48	78						3		7	51
RECORD 1[182]	4433	65			32	33						5		22	37
RECORD 2[183]	2457	85									1	5		21	55
RECORD 3[180]	1833	239			29	210						4		40	33
RECORD 4[190]	3034	147	16	131						13	1	12		35	35
STARS E-3[199]	706	63								0			63		
STARS J-1[189,197]	520	111	1		6	110				0			112		
STARS J-2[191]	261					8							8		
STARS J-4[198,210]	88		0	4						0			4		0
STARS J-V[196]	604		0	23						0			23		
VTE-APIX-PLACEBO-USACAN[207]	122													3	
VTE-DABIG-LMWH-GREECE[204]	120	0							0				0		
VTE-DABIG-PLAC-JAPAN[192]	512	156	6		10					0					10
VTE-EDOX-LMWH-MULTI[194]	896				40								183		41
VTE-LMWH-PLAC-CAN[186]	237			25											

Study	Study size	DVT	Symp. DVT	Non-symp. DVT	Proximal DVT	Distal DVT	Symp. Proxi-mal DVT	Symp. Distal DVT	PE	Symp. PE	Fatal PE	Symp. Non-fatal PE	VTE	Symp. VTE	Major VTE
VTE-LMWH-PLAC-JAPAN[203]	170	11	0		0	11				0			11	0	
VTE-RIVAROX-LMWH-BRAZIL[181]	65	5								0					
VTE-RIVAROX-LMWH-CHINA[209]	106	7													
VTE-VKA-LMWH-CANADA[169]	670	185			46					4				4	
VTE-VKA-LMWH-US[170]	550	77			26	64									
VTE-VKA-LMWH-US-2[171]	3011		96							27	1			111	
VTE-VKA-LMWH-US-3[172]	1472	161	30		17					0					
VTE-VKA-LMWH-US-4[173]	349	123			23	100				1			124		

Table 93 Safety outcomes reported by 38 included randomised trials in primary prevention of VTE: number of events for each outcome in each trial

Study	Study size	MI	TCP	All bleeds	Minor bleeds	Major bleeds	Fatal bleeds	IC bleeds	Bleeds from surgical site	Clinically relevant non-major	Clinically relevant bleeding	CV death	All-cause mortality
ADOPT[71]	6401			465		21		2			152		
ADVANCE-1[188]	3184	5	2	193	79	33	1	1		82	115		9
ADVANCE-2[195]	3009	2	1	230	105	23		0	95	102	125		2
ADVANCE-3[193]	4394	8	5	647	384	40		0	201	229	269		4
APROPOS[179]	856	4		78	57	18	0						1
EXPERT[185]	215			5		1				4	5		
LIFENOX[202]	8307			151	120	27				32	59	425	703
MAGELLAN[201,208]	7998					58	8	2			231		312
ODiXa-HIP2[176]	548				42	17		0	15	20	37		
ODIXa-KNEE[174]	613				43	16		0		21	37		0
ODIXa-OD.HIP[175]	618				44	27		0		18	45		0
PROTECHT[187]	1150			92	87	5		1					49
RE-MOBILISE[184]	1896			88		22							7
RE-MODEL[178]	2076			341	188	28				125	153		3
RE-NOVATE[177]	3463			415	216	56				143	199		
RE-NOVATE II[200,206]	2013	2		181	115	23				43	66		1
RECORD 1[182]	4433	22		264	148	8				119	127	5	9
RECORD 2[183]	2457	7		149		2	0				72		10
RECORD 3[180]	1833	3		120		13	0			61	74	1	6
RECORD 4[190]	3034	10				14	1	2		69	83	8	12
STARS E-3[199]	706					5		0			35		
STARS J-1[189,197]	520			53		1				18	19		
STARS J-2[191]	261										5		
STARS J-4[198,210]	88			20	16	2		0		2	4		0
STARS J-V[196]	604					8					19		
VTE-APIX-PLACEBO-USACAN[207]	122					3				4	7		
VTE-DABIG-LMWH-GREECE[204]	120			0									
VTE-DABIG-PLAC-JAPAN[192]	512			50	39	5	0		3	6	11		0
VTE-EDOX-LMWH-MULTI[194]	896			24		5				10	14		4
VTE-LMWH-PLAC-CAN[186]	237		0	0	0	0							0
VTE-LMWH-PLAC-JAPAN[203]	170			8	8	0							

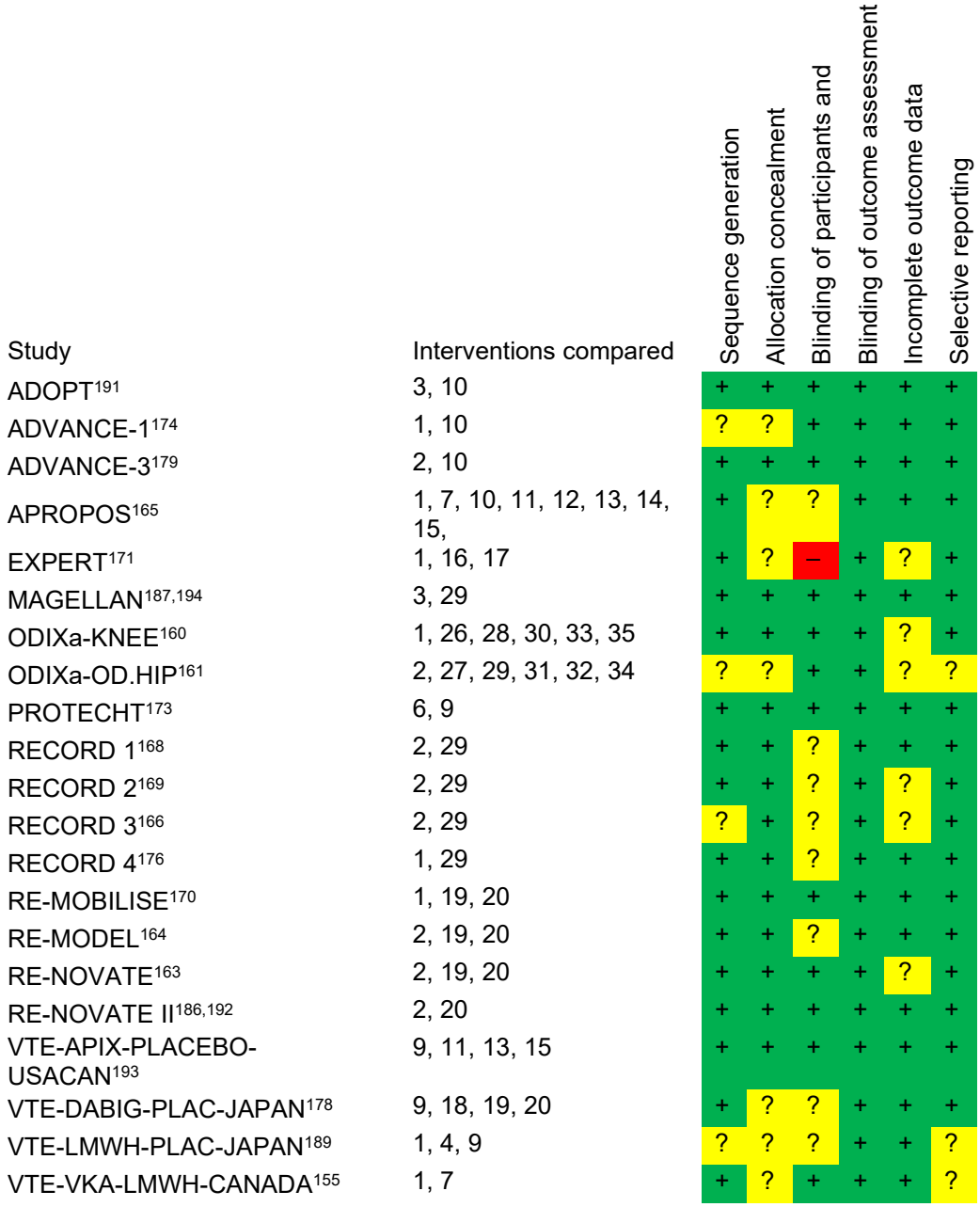
Study	Study size	MI	TCP	All bleeds	Minor bleeds	Major bleeds	Fatal bleeds	IC bleeds	Bleeds from surgical site	Clinically relevant non-major bleeding	Clinically relevant bleeding	CV death	All-cause mortality
VTE-RIVAROX-LMWH-BRAZIL[181]	65												
VTE-RIVAROX-LMWH-CHINA[209]	106												
VTE-VKA-LMWH-CANADA[169]	670		2	190	177	13							2
VTE-VKA-LMWH-US[170]	550					10							
VTE-VKA-LMWH-US-2[171]	3011		0	262	249	26		0	19				19
VTE-VKA-LMWH-US-3[172]	1472				60	98							4
VTE-VKA-LMWH-US-4[173]	349			99	86	13							4

TCP: thrombocytopaenia; IC: intracranial; CV: cardiovascular.

7.4.1 Symptomatic venous thromboembolism

Of 28 studies that contributed data to analyses of symptomatic VTE 11 reported direct data on symptomatic VTE events (Table 92). Figure 59 shows risk of bias judgments for these studies. They were generally judged to be at low risk of bias, though with some concerns about allocation concealment and blinding of participants and personnel.

Figure 59 Included trials and risk of bias assessment for symptomatic VTE (primary prevention of VTE)



VTE-VKA-LMWH-US-2[157]	1, 7	? ? – ? + ?
VTE-VKA-LMWH-US-3[158]	1, 2, 7	+ ? + + + ?

Nine studies of hip surgery patients reported 231 symptomatic VTE events, leading to a network of 13 interventions (Figure 60). This network was disconnected, so that two interventions could not be included in the analysis. Most comparisons were imprecisely estimated, but there was evidence that risk of symptomatic VTE is lower with rivaroxaban (10mg od) compared with LMWH (pre-op, standard dose) but higher with LMWH (post-op, standard dose) and warfarin (INR 2-3) compared with LMWH (pre-op, standard dose) (Table 94). Indirect evidence about warfarin (INR 2-3) versus LMWH (pre-op, standard dose) pointed in the opposite direction to the direct evidence, but was extremely imprecisely estimated.

Comparisons between licensed doses of NOACs were imprecisely estimated (Table 95). In addition, there was some heterogeneity in the direction of effects among studies of dabigatran (150 mg od) versus post-operative LMWH (standard dose) and of dabigatrain (220 mg od) versus post-operative LMWH (standard dose) (see Appendix 3).

Figure 60 Network plot for symptomatic VTE in hip surgery patients (primary prevention of VTE)

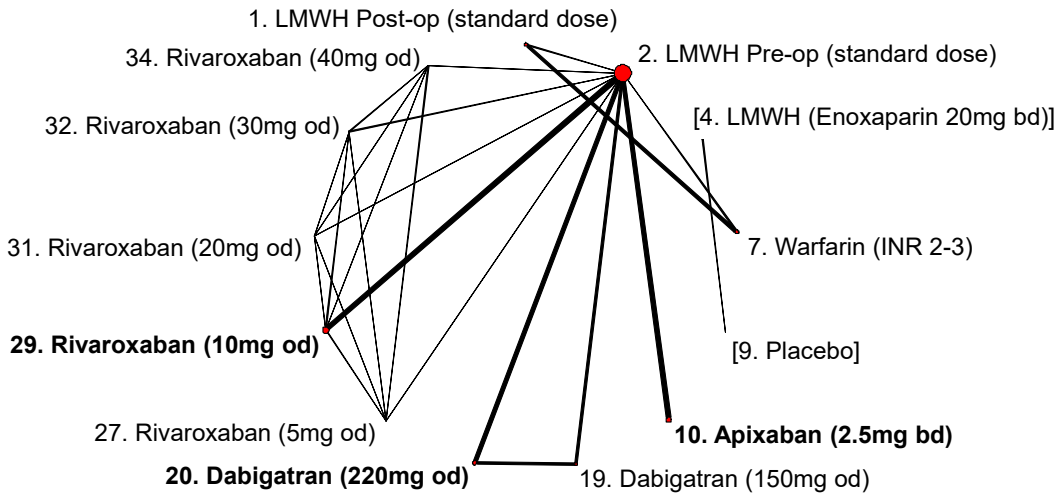


Table 94 Results for symptomatic VTE in hip surgery patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (pre-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Post-op (standard dose)	2.16 (0.73 , 7.03)	6.49 (0.50 , 83.8)	2.59 (1.03 , 8.36)
Warfarin (INR 2-3)	3.33 (1.21 , 10.4)	0.29 (0 , 19.5)	2.87 (1.14 , 9.25)
Dabigatran (150mg od)	1.46 (0.57 , 3.75)	-	1.46 (0.57 , 3.75)
Dabigatran (220mg od)	1.20 (0.51 , 2.86)	-	1.20 (0.51 , 2.86)
Rivaroxaban (10mg od)	0.33 (0.16 , 0.64)	-	0.33 (0.16 , 0.64)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	*0.38 (0.10 , 1.16)*	-	*0.38 (0.10 , 1.16)*
Rivaroxaban (5mg od)	*0.22 (0 , 4.76)*	-	*0.22 (0 , 4.76)*
Rivaroxaban (20mg od)	*0.19 (0 , 4.01)*	-	*0.19 (0 , 4.01)*
Rivaroxaban (30mg od)	*0.19 (0 , 4.19)*	-	*0.19 (0 , 4.19)*
Rivaroxaban (40mg od)	*0.21 (0 , 4.62)*	-	*0.21 (0 , 4.62)*

Table 95 Results for symptomatic VTE in hip surgery patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	0.28 (0.09 , 0.81)	0.28 (0.09 , 0.81)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*3.21 (0.77 , 15.5)*	*3.21 (0.77 , 15.5)*
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*0.89 (0.23 , 3.90)*	*0.89 (0.23 , 3.90)*

Ten trials including knee surgery patients reported 186 symptomatic VTE events, leading to a network of 21 interventions (Figure 61). There was little evidence that risk of symptomatic VTE differed between apixaban (2.5mg bd), dabigatran (220mg od), or rivaroxaban (10mg od) compared with LMWH (post-op, standard dose) (Table 96). Comparisons between licensed doses of NOACs were imprecisely estimated (Table 97).

Figure 61 Network plot for symptomatic VTE in knee surgery patients (primary prevention of VTE)

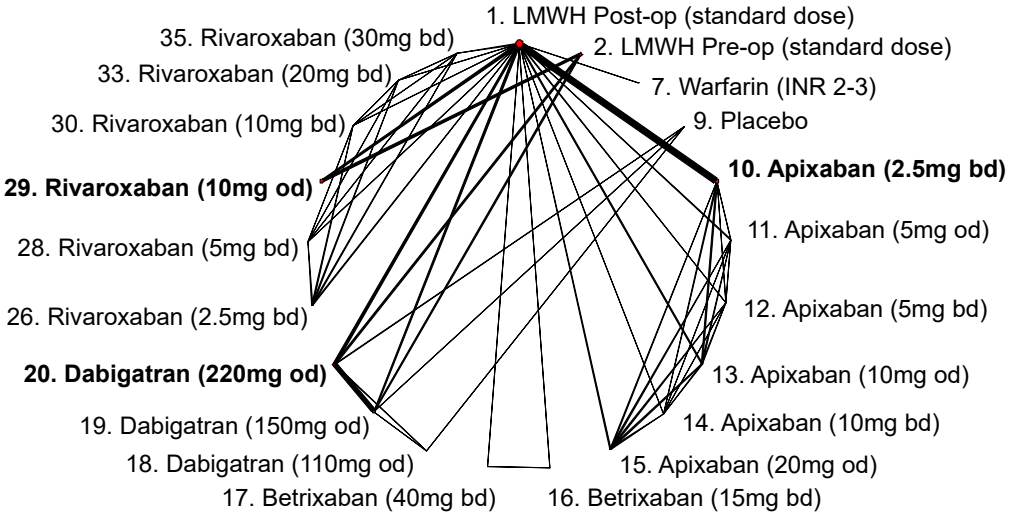


Table 96 Results for symptomatic VTE in knee surgery patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Pre-op (standard dose)	-	1.96 (0.91 , 4.27)	1.96 (0.91 , 4.27)
Apixaban (2.5mg bd)	1.24 (0.64 , 2.43)	-	1.24 (0.64 , 2.43)
Dabigatran (150mg od)	0.82 (0.40 , 1.67)	-	0.82 (0.40 , 1.67)
Dabigatran (220mg od)	0.92 (0.45 , 1.86)	-	0.92 (0.45 , 1.86)
Rivaroxaban (10mg od)	0.80 (0.43 , 1.46)	-	0.80 (0.43 , 1.46)
Imprecisely estimated comparisons			
Warfarin (INR 2-3)	*0.25 (0.01 , 2.34)*	-	*0.25 (0.01 , 2.34)*
Placebo	-	*1.14 (0.12 , 8.36)*	*1.14 (0.12 , 8.36)*
Apixaban (5mg od)	*0.12 (0 , 1.84)*	-	*0.12 (0 , 1.84)*
Apixaban (5mg bd)	*0.11 (0 , 1.66)*	-	*0.11 (0 , 1.66)*
Apixaban (10mg od)	*1.11 (0.17 , 5.41)*	-	*1.11 (0.17 , 5.41)*
Apixaban (10mg bd)	*0.57 (0.05 , 3.43)*	-	*0.57 (0.05 , 3.43)*
Apixaban (20mg od)	*0.57 (0.04 , 3.45)*	-	*0.57 (0.04 , 3.45)*
Betrixaban (15mg bd)	*1.34 (0.10 , 44.6)*	-	*1.34 (0.10 , 44.6)*
Betrixaban (40mg bd)	*0.59 (0.01 , 22.8)*	-	*0.59 (0.01 , 22.8)*
Dabigatran (110mg od)	-	*0.43 (0.01 , 4.41)*	*0.43 (0.01 , 4.41)*
Rivaroxaban (2.5mg bd)	*0.59 (0.04 , 5.21)*	-	*0.59 (0.04 , 5.21)*
Rivaroxaban (5mg bd)	*1.24 (0.17 , 9.07)*	-	*1.24 (0.17 , 9.07)*
Rivaroxaban (10mg bd)	*0.12 (0 , 2.36)*	-	*0.12 (0 , 2.36)*
Rivaroxaban (20mg bd)	*0.66 (0.05 , 5.93)*	-	*0.66 (0.05 , 5.93)*
Rivaroxaban (30mg bd)	*0.12 (0 , 2.3)*	-	*0.12 (0 , 2.33)*

Table 97 Results for symptomatic VTE in knee surgery patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence	Indirect evidence	Network meta-analysis
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	0.74 (0.28 , 1.95)	0.74 (0.28 , 1.95)
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	0.64 (0.26 , 1.56)	0.64 (0.26 , 1.56)
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	0.87 (0.37 , 2.01)	0.87 (0.37 , 2.01)

Four trials in non-surgical patients reported 45 symptomatic VTE events, leading to a network of 8 interventions (Figure 62). Because the network was disconnected we excluded two phase II trials (PROTECHT and VTE-APIX-PLACEBO-USACAN) so that analyses were of the connected network. This enabled us to compare two licensed doses of NOACs. There was weak evidence that risk of symptomatic VTE is lower with apixaban (2.5mg bd) compared with LMWH (standard dose) (Table 98), and also compared with rivaroxaban (10 mg od) (Table 99), although these comparisons were imprecisely estimated.

Figure 62 Network plot for symptomatic VTE in medical patients (primary prevention of VTE)

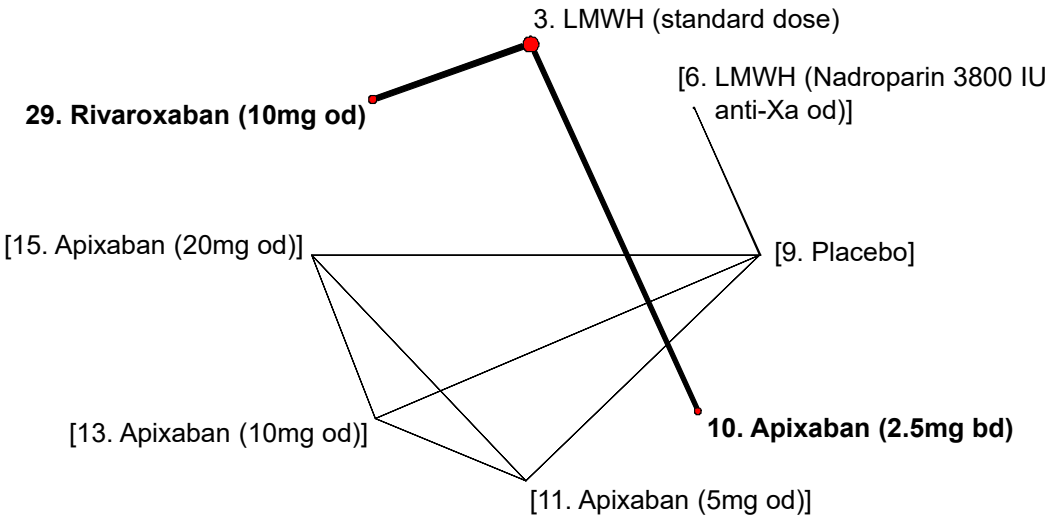


Table 98 Results for symptomatic VTE in medical patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	0.50 (0.24 , 0.97)	-	0.50 (0.24 , 0.97)
Rivaroxaban (10mg od)	1.53 (0.73 , 3.28)	-	1.53 (0.73 , 3.28)

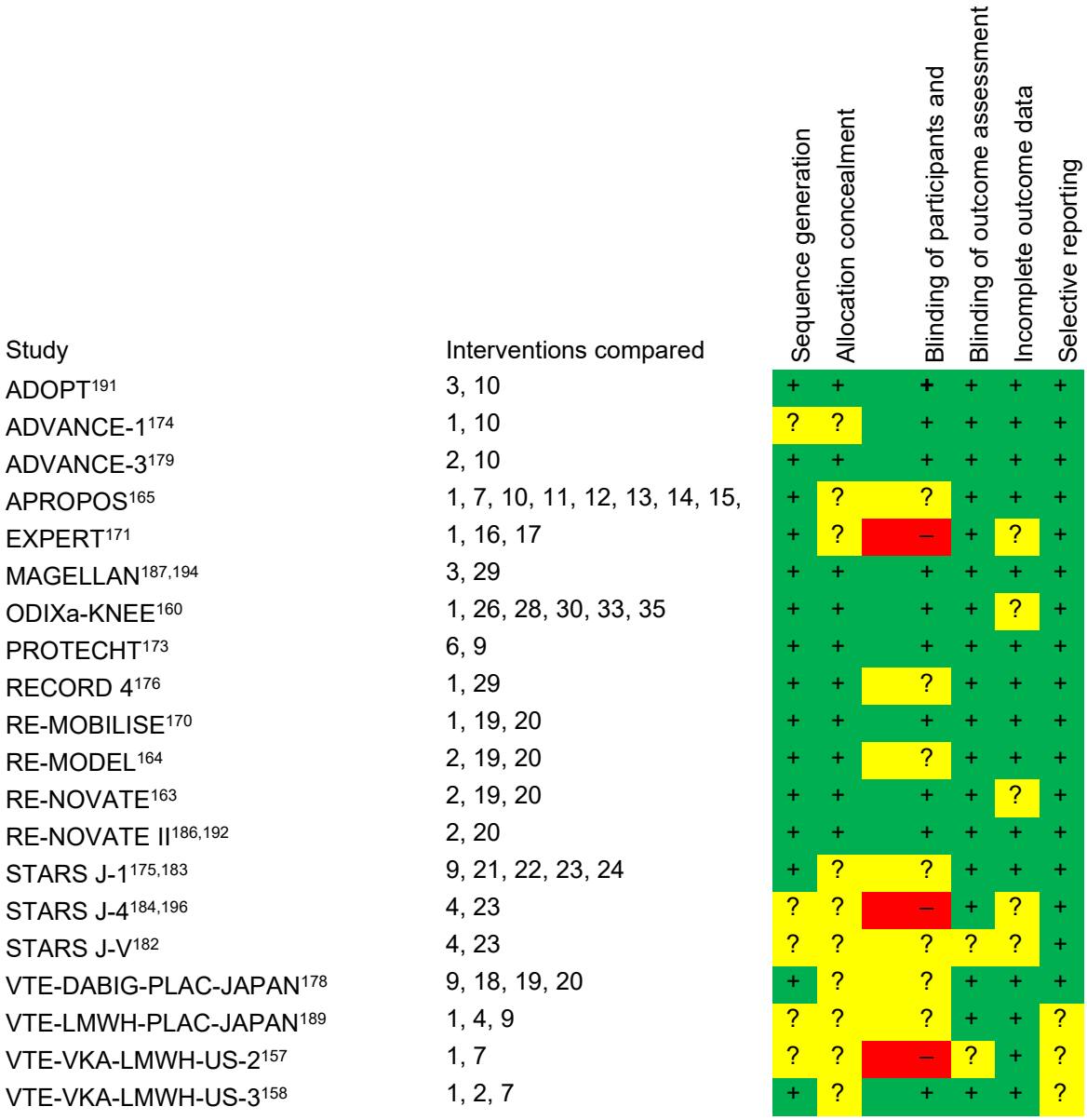
Table 99 Results for symptomatic VTE in medical patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	3.09 (1.13 , 8.87)	3.09 (1.13 , 8.87)

7.4.2 Symptomatic deep vein thrombosis

Twenty studies contributed data to analyses of symptomatic DVT. Figure 63 shows risk of bias judgments for these studies. Most were judged to be at low risk of bias, though with a few concerns about blinding of participants and personnel.

Figure 63 Included trials and risk of bias assessment for symptomatic DVT (primary prevention of VTE)



Eight studies of hip surgery patients provided data on 157 symptomatic DVT events, leading to a network of nine interventions (Figure 64). Because the resulting network was disconnected we excluded several interventions from the analysis. All comparisons were imprecisely estimated (Table 100 and Table 101), but there was evidence that risk of symptomatic DVT is higher for that LMWH (post-op, standard dose) and warfarin (INR 2-3) compared with LMWH (pre-op, standard dose).

Figure 64 Network plot for symptomatic DVT in hip surgery patients (primary prevention of VTE)

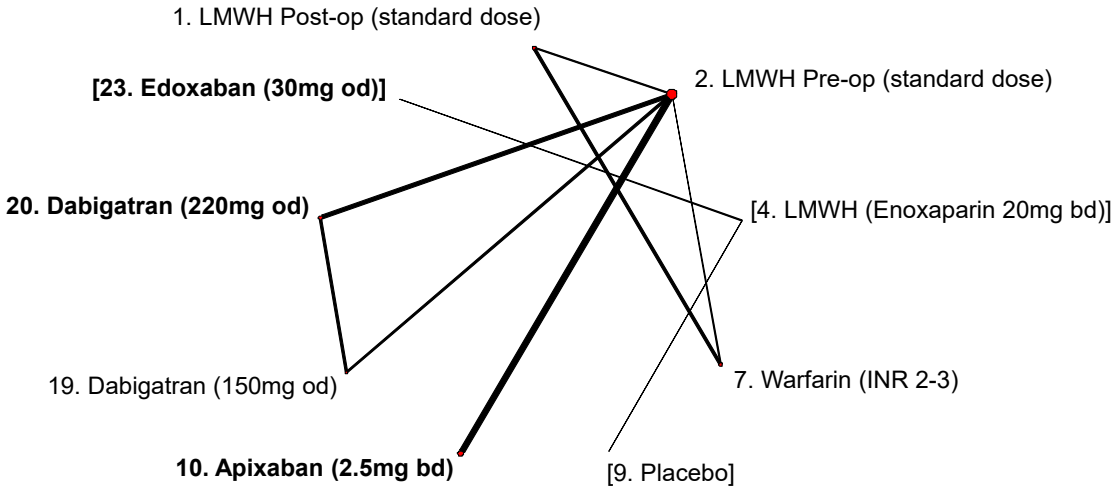


Table 100 Results for symptomatic DVT in hip surgery patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (pre-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Post-op (standard dose)	2.14 (0.72 , 7.34)	4.95 (0.57 , 42.8)	2.58 (1.03 , 7.94)
Warfarin (INR 2-3)	3.31 (1.21 , 10.8)	0.84 (0.05 , 13.1)	2.74 (1.10 , 8.39)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	*0.15 (0.01 , 1.09)*	-	*0.15 (0.01 , 1.09)*
Dabigatran (150mg od)	*2.90 (0.93 , 10.5)*	-	*2.90 (0.93 , 10.5)*
Dabigatran (220mg od)	*1.19 (0.37 , 4.05)*	-	*1.19 (0.37 , 4.05)*

Table 101 Results for symptomatic DVT in hip surgery patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*8.37 (0.79 , 286)*	*8.37 (0.79 , 286)*

Nine studies of knee surgery patients reported 81 symptomatic DVT events, leading to a network of 24 interventions (Figure 65). All comparisons were imprecisely estimated (Table 102 and Table 103). Indirect evidence about warfarin (INR 2-3) versus LMWH (pre-op, standard dose) pointed in the opposite direction to the direct evidence, but was very imprecisely estimated.

Figure 65 Network plot for symptomatic DVT in knee surgery patients (primary prevention of VTE)

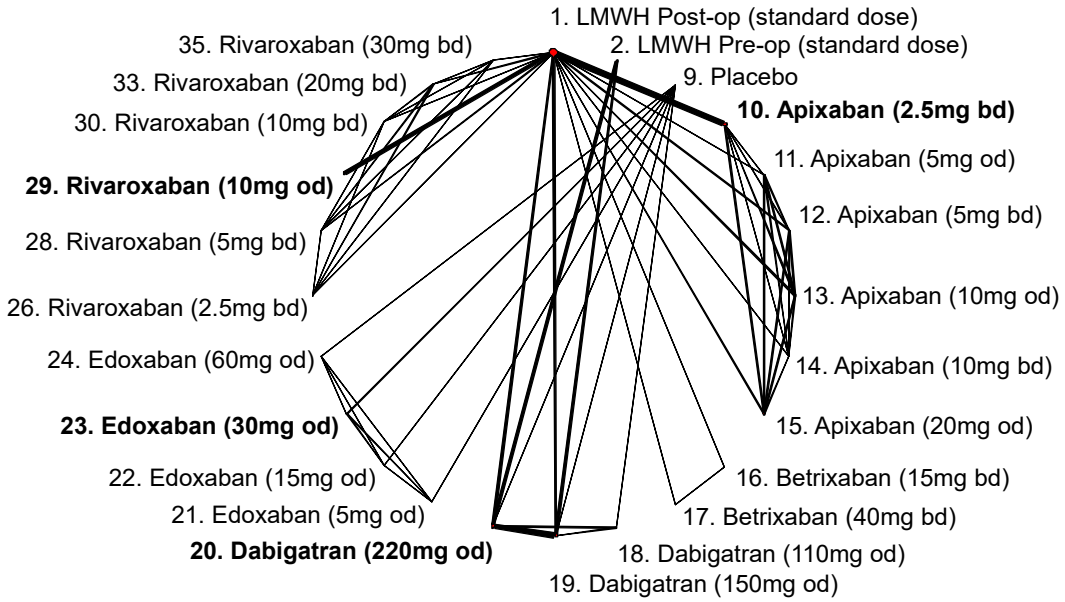


Table 102 Results for symptomatic DVT in knee surgery patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence	Indirect evidence	Network meta-analysis
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Dabigatran (150mg od)	1.58 (0.64 , 4.31)	-	1.58 (0.64 , 4.31)
Dabigatran (220mg od)	1.21 (0.46 , 3.43)	-	1.21 (0.46 , 3.43)
Rivaroxaban (10mg od)	0.58 (0.19 , 1.59)	-	0.58 (0.19 , 1.59)
Imprecisely estimated comparisons			
LMWH pre-op (standard dose)	-	*6.06 (1.38 , 31.0)*	*6.06 (1.38 , 31.0)*
Placebo	-	*1.82 (0.18 , 15.1)*	*1.82 (0.18 , 15.1)*
Apixaban (2.5mg bd)	*0.50 (0.14 , 1.55)*	-	*0.50 (0.14 , 1.55)*
Apixaban (5mg od)	*0.15 (0 , 2.64)*	-	*0.15 (0 , 2.64)*
Apixaban (5mg bd)	*0.13 (0 , 2.48)*	-	*0.13 (0 , 2.48)*
Apixaban (10mg od)	*1.32 (0.18 , 8.59)*	-	*1.32 (0.18 , 8.59)*
Apixaban (10mg bd)	*0.13 (0 , 2.37)*	-	*0.13 (0 , 2.37)*
Apixaban (20mg od)	*0.13 (0 , 2.37)*	-	*0.13 (0 , 2.37)*
Betrixaban (15mg bd)	*0.57 (0.04 , 8.47)*	-	*0.57 (0.04 , 8.47)*
Betrixaban (40mg bd)	*0.12 (0 , 3.43)*	-	*0.12 (0 , 3.43)*
Dabigatran (110mg od)	-	*0.69 (0.02 , 8.04)*	*0.69 (0.02 , 8.04)*
Edoxaban (5mg od)	*9.54 (0.15 , 3760)*	-	*9.54 (0.15 , 3760)*
Edoxaban (15mg od)	*1.60 (0 , 894)*	-	*1.60 (0 , 894)*
Edoxaban (30mg od)	*1.72 (0 , 978)*	-	*1.72 (0 , 978)*
Edoxaban (60mg od)	*1.69 (0 , 1010)*	-	*1.69 (0 , 1010)*
Rivaroxaban (2.5mg bd)	*0.60 (0.04 , 5.56)*	-	*0.60 (0.04 , 5.56)*
Rivaroxaban (5mg bd)	*0.12 (0 , 2.52)*	-	*0.12 (0 , 2.52)*
Rivaroxaban (10mg bd)	*0.12 (0 , 2.36)*	-	*0.12 (0 , 2.36)*
Rivaroxaban (20mg bd)	*0.66 (0.05 , 5.99)*	-	*0.66 (0.05 , 5.99)*
Rivaroxaban (30mg bd)	*0.12 (0 , 2.41)*	-	*0.12 (0 , 2.41)*

Table 103 Results for symptomatic DVT in knee surgery patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*2.43 (0.54 , 12.6)*	*2.43 (0.54 , 12.6)*
Edoxaban (30mg od) vs Apixaban (2.5mg bd)	-	*3.47 (0 , 2150)*	*3.47 (0 , 2150)*
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*1.16 (0.24 , 5.84)*	*1.16 (0.24 , 5.84)*
Edoxaban (30mg od) vs Dabigatran (220mg od)	-	*1.41 (0 , 779)*	*1.41 (0 , 779)*
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	*0.47 (0.11 , 1.97)*	*0.47 (0.11 , 1.97)*
Rivaroxaban (10mg od) vs Edoxaban (30mg od)	-	*0.33 (0 , 295)*	*0.33 (0 , 295)*

Three studies of medical patients provided data on 65 symptomatic DVT events, leading to a network of five interventions. Because the resulting network was disconnected (Figure 66) we excluded the PROTECHT trial, which allowed us to make an indirect comparison between two licensed NOAC doses. All comparisons were imprecisely estimated, although threre was evidence that risk of symptomatic DVT is lower for apixaban (2.5mg bd) compared with LMWH (standard dose) (Table 104). The comparison between apixaban (2.5mg bd) and rivaroxaban (10mg od) was imprecisely estimated (Table 105).

Figure 66 Network plot for symptomatic DVT in medical patients (primary prevention of VTE)

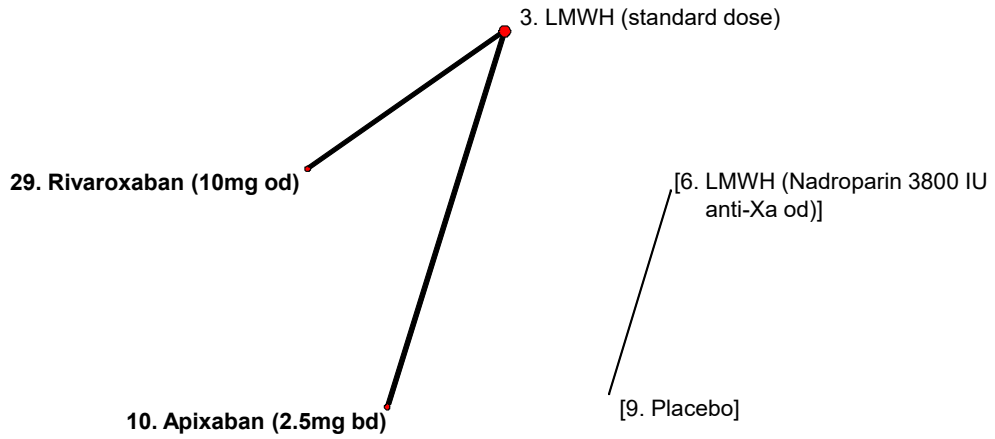


Table 104 Results for symptomatic DVT in medical patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	0.30 (0.10 , 0.78)	-	0.30 (0.10 , 0.78)
Rivaroxaban (10mg od)	0.89 (0.41 , 1.89)	-	0.89 (0.41 , 1.89)

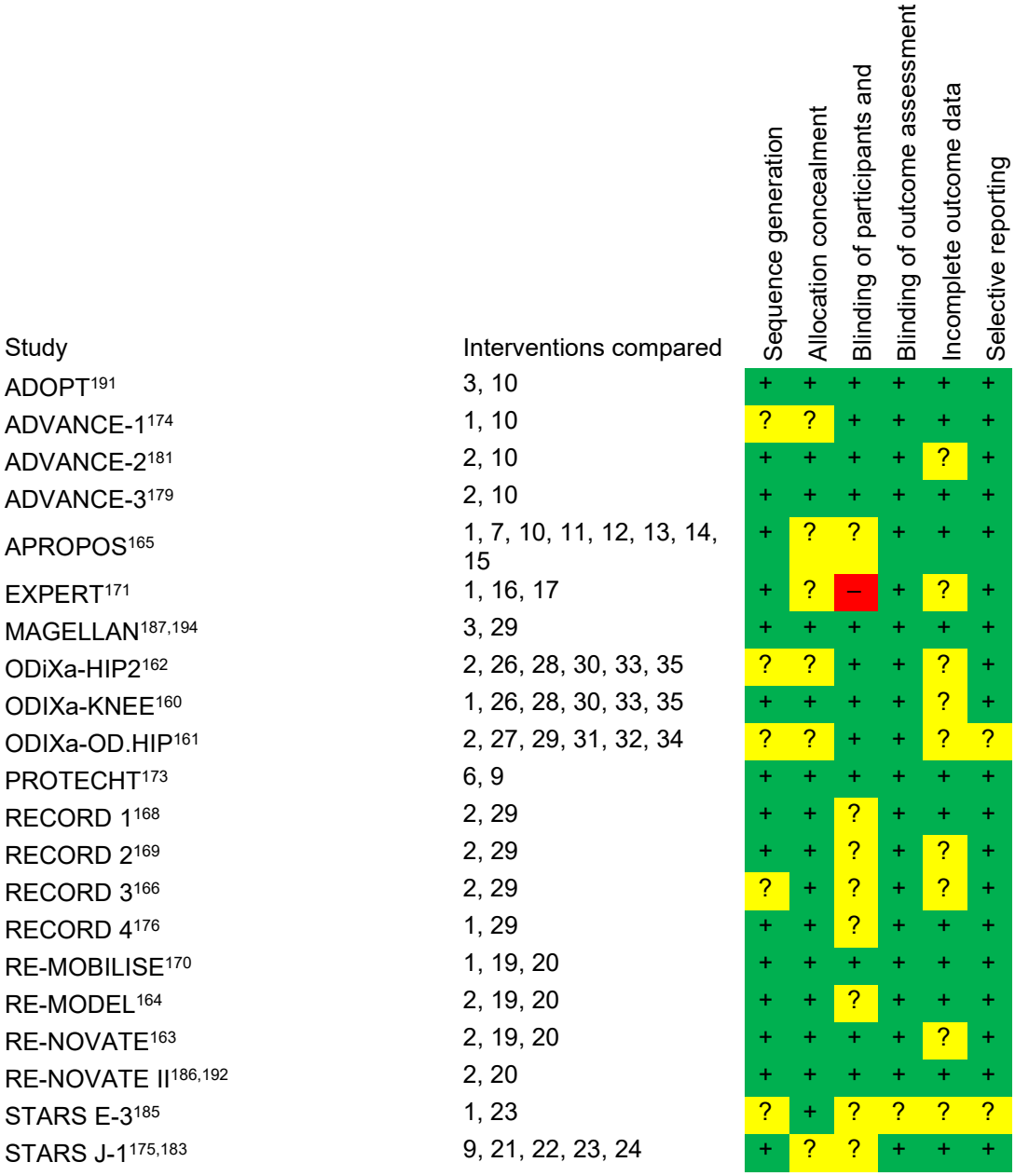
Table 105 Results for symptomatic DVT in medical patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*3.01 (0.87 , 11.6)*	*3.01 (0.87 , 11.6)*

7.4.3 Symptomatic pulmonary embolism

Thirty studies contributed data to analyses of symptomatic PE: few reported directly on symptomatic PE events (Table 92) so we inferred these by summing symptomatic non-fatal and fatal PE events if that information was available. Most studies were judged to be at low risk of bias (Figure 67), though there were some concerns about sequence generation, lack of allocation concealment, blinding of participants and personnel, and incomplete outcome data.

Figure 67 Included trials and risk of bias assessment for symptomatic PE (primary prevention of VTE)



STARS J-4[184,196]	4, 23	? ? – + ? +
STARS J-V[182]	4, 23	? ? ? ? ? +
VTE-DABIG-PLAC-JAPAN[178]	9, 18, 19, 20	+ ? ? + + +
VTE-LMWH-PLAC-JAPAN[189]	1, 4, 9	? ? ? + + ?
VTE-RIVAROX-LMWH-BRAZIL[167]	2, 29	? ? + ? + ?
VTE-VKA-LMWH-CANADA[155]	1, 7	+ ? + + + ?
VTE-VKA-LMWH-US-2[157]	1, 7	? ? – ? + ?
VTE-VKA-LMWH-US-3[158]	1, 2, 7	+ ? + + + ?
VTE-VKA-LMWH-US-4[159]	1, 7	? + – + + ?

Thirteen studies in hip surgery patients provided data on 58 symptomatic PE events, leading to a network of 19 interventions (Figure 68). However, most interventions were either disconnected from the network or considered only in trials where there were no events in any arm, so that only five interventions were included in the analysis. All comparisons were imprecisely estimated (Table 106 and Table 107).

Figure 68 Network plot for symptomatic PE in hip surgery patients (primary prevention of VTE)

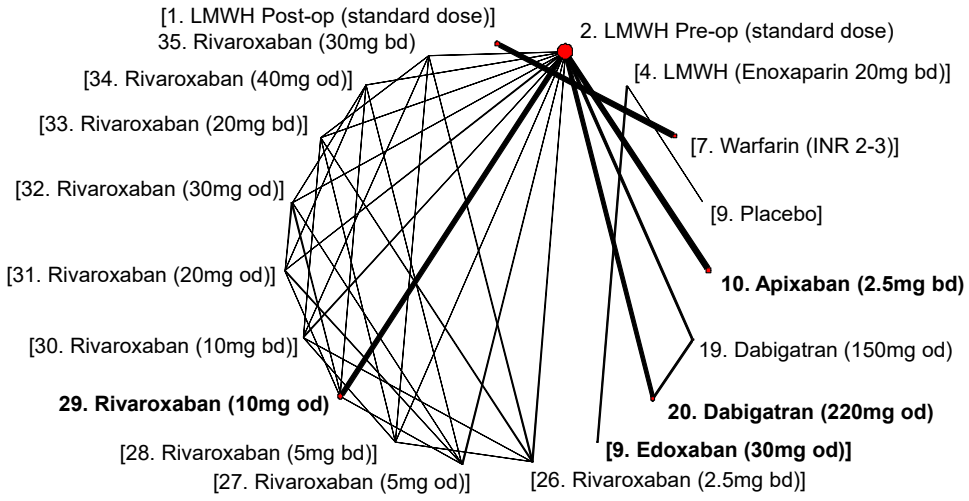


Table 106 Results for symptomatic PE in hip surgery patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (pre-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	*0.57 (0.11 , 2.40)*	-	*0.57 (0.11 , 2.40)*
Dabigatran (150mg od)	*0.20 (0.01 , 1.56)*	-	*0.20 (0.01 , 1.56)*
Dabigatran (220mg od)	*1.22 (0.35 , 4.31)*	-	*1.22 (0.35 , 4.31)*
Rivaroxaban (10mg od)	*0.82 (0.22 , 2.84)*	-	*0.82 (0.22 , 2.84)*

Table 107 Results for symptomatic PE in hip surgery patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*2.16 (0.32 , 16.7)*	*2.16 (0.32 , 16.7)*
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*1.46 (0.21 , 11.1)*	*1.46 (0.21 , 11.1)*
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	*0.67 (0.11 , 3.95)*	*0.67 (0.11 , 3.95)*

Fourteen studies in knee surgery patients reported 74 symptomatic PE events, leading to a network of 26 interventions (Figure 69). We excluded three trials with zero events in each arm, hence some interventions were not part of the analysis. All comparisons were imprecisely estimated (Table 108) but there was some evidence that risk of symptomatic PE is lower with dabigatran (150mg od) and higher with apixaban (2.5mg bd) compared with LMWH (post-op, standard dose). Among licensed doses of NOACs the risk of symptomatic PE may be lower for rivaroxaban (10mg od) compared with apixaban (2.5mg bd) (Table 109).

Figure 69 Network plot for symptomatic PE in knee surgery patients (primary prevention of VTE)

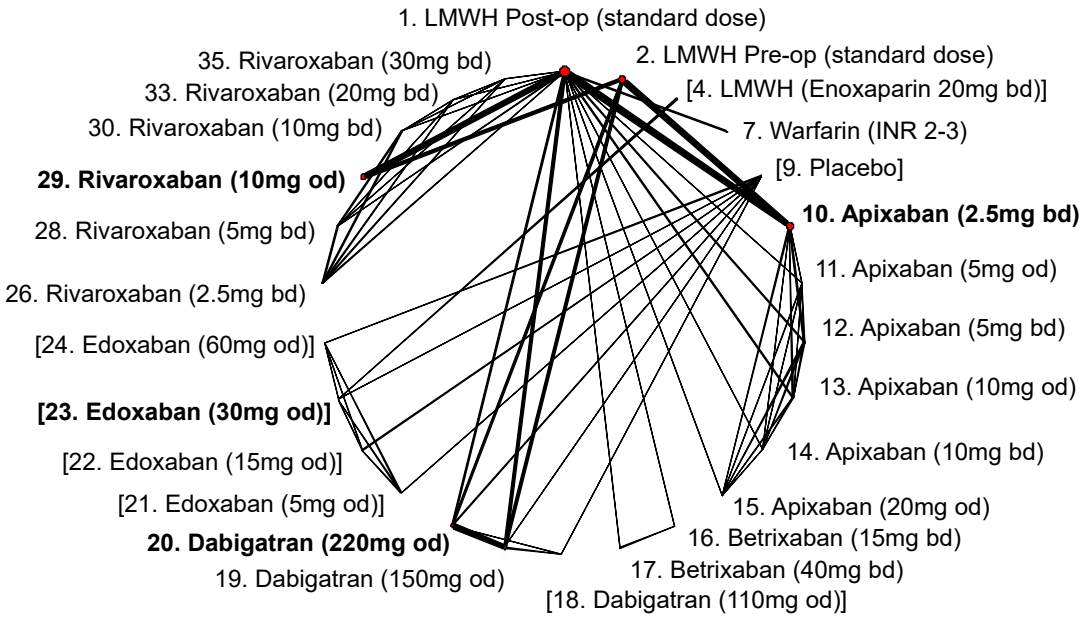


Table 108 Results for symptomatic PE in knee surgery patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence	Indirect evidence	Network meta-analysis
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Apixaban (2.5mg bd)	2.14 (1.00 , 4.94)	-	2.14 (1.00 , 4.94)
Dabigatran (220mg od)	1.05 (0.39 , 2.85)	-	1.05 (0.39 , 2.85)
Imprecisely estimated comparisons			
LMWH Pre-op (standard dose)	-	*0.90 (0.23 , 3.39)*	*0.90 (0.23 , 3.39)*
Warfarin (INR 2-3)	*3.44 (0.58 , 44.0)*	-	*3.44 (0.58 , 44.0)*
Apixaban (5mg od)	*0.31 (0 , 5.87)*	-	*0.31 (0 , 5.87)*
Apixaban (5mg bd)	*0.28 (0 , 5.31)*	-	*0.28 (0 , 5.31)*
Apixaban (10mg od)	*0.29 (0 , 5.32)*	-	*0.29 (0 , 5.32)*
Apixaban (10mg bd)	*1.43 (0.10 , 11.6)*	-	*1.43 (0.10 , 11.6)*
Apixaban (20mg od)	*1.42 (0.11 , 11.8)*	-	*1.42 (0.11 , 11.8)*
Betrixaban (15mg bd)	*2.99 (0.10 , 1930)*	-	*2.99 (0.10 , 1930)*
Betrixaban (40mg bd)	*3.23 (0.11 , 2070)*	-	*3.23 (0.11 , 2070)*
Dabigatran (150mg od)	*0.19 (0.02 , 0.80)*	-	*0.19 (0.02 , 0.80)*
Rivaroxaban (2.5mg bd)	*1.03 (0 , 759)*	-	*1.03 (0 , 759)*
Rivaroxaban (5mg bd)	*11.0 (0.61 , 6860)*	-	*11.0 (0.61 , 6860)*
Rivaroxaban (10mg od)	*0.41 (0.12 , 1.17)*	-	*0.41 (0.12 , 1.17)*
Rivaroxaban (10mg bd)	*1.08 (0 , 769)*	-	*1.08 (0 , 769)*
Rivaroxaban (20mg bd)	*1.13 (0 , 887)*	-	*1.13 (0 , 887)*
Rivaroxaban (30mg bd)	*1.10 (0 , 781)*	-	*1.10 (0 , 781)*

Table 109 Results for symptomatic PE in knee surgery patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*0.49 (0.14 , 1.66)*	*0.49 (0.14 , 1.66)*
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*0.19 (0.05 , 0.67)*	*0.19 (0.05 , 0.67)*
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	*0.39 (0.09 , 1.58)*	*0.39 (0.09 , 1.58)*

Three studies in medical patients reported 45 symptomatic PE events. Because the resulting network was disconnected (Figure 70), we excluded the PROTECHT trial. This led to a connected network that enabled an indirect comparison among two licensed NOACs. All comparisons were imprecisely estimated (Table 110 and Table 111).

Figure 70 Network plot for symptomatic PE in medical patients (primary prevention of VTE)

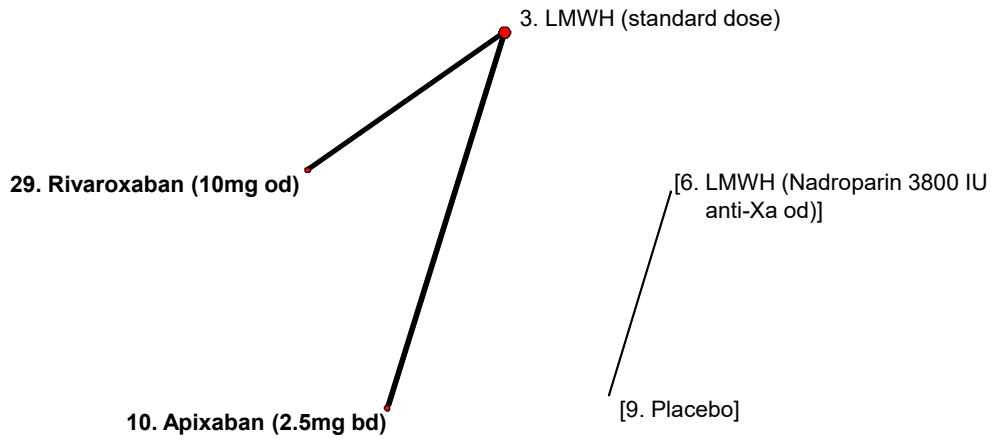


Table 110 Results for symptomatic PE in medical patients (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	0.88 (0.30 , 2.48)	-	0.88 (0.30 , 2.48)
Rivaroxaban (10mg od)	0.73 (0.31 , 1.64)	-	0.73 (0.31 , 1.64)

Table 111 Results for symptomatic PE in medical patients (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*0.83 (0.22 , 3.18)*	*0.83 (0.22 , 3.18)*

7.4.4 Myocardial infarction

Nine studies provided data on 63 myocardial infarction events, leading to a network of 11 interventions (Figure 71). The included studies were mainly judged to be at low risk of bias (

Figure 72), although there were some concerns about blinding of participants and personnel.

Figure 71 Network plot for myocardial infarction (primary prevention of VTE)

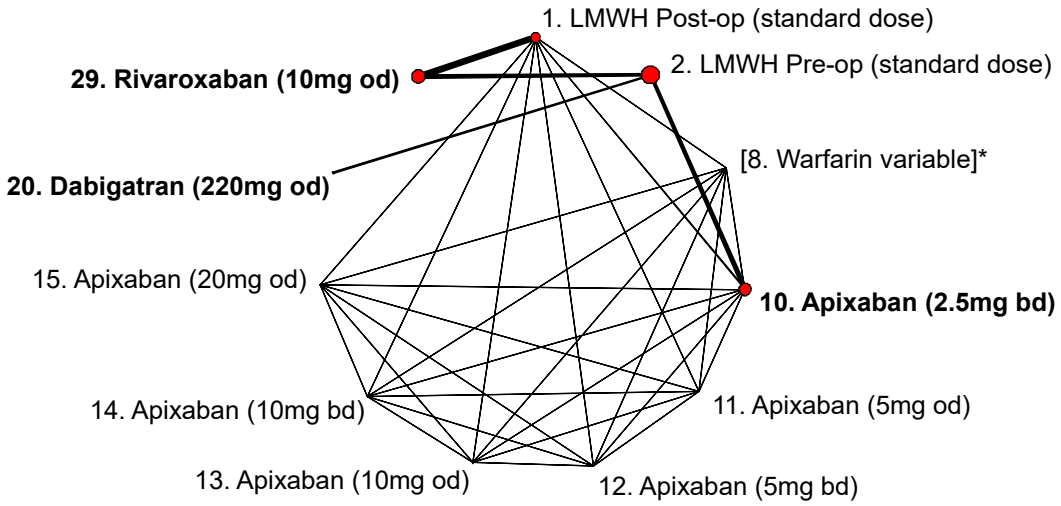
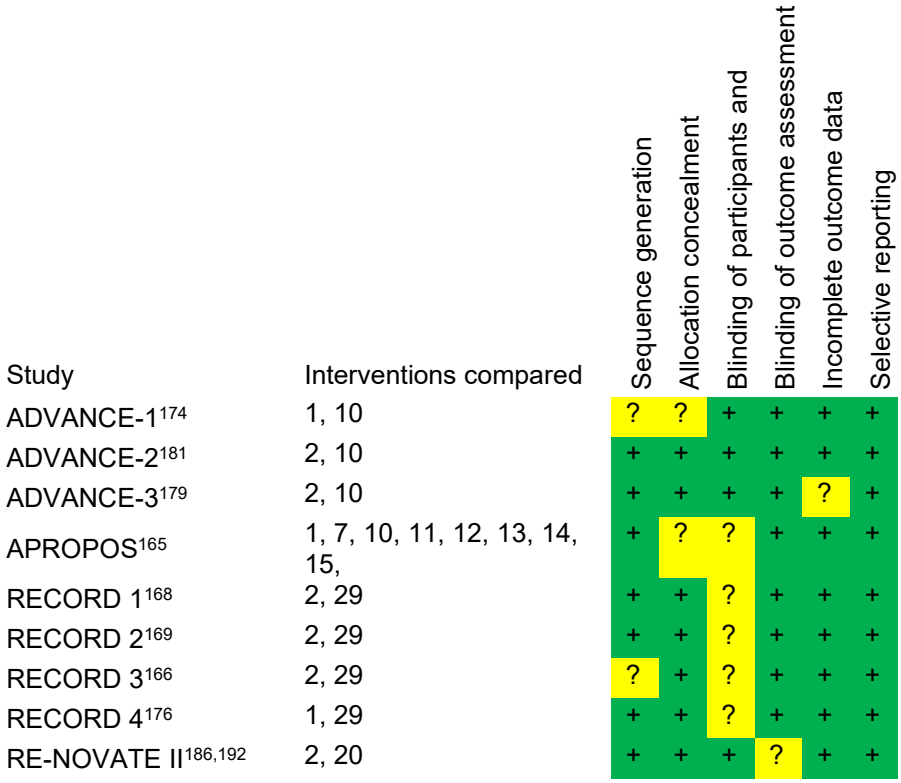


Figure 72 Included trials and risk of bias assessment for myocardial infarction (primary prevention of VTE)



All comparisons were imprecisely estimated (Table 114 and Table 115), although there was some evidence that rivaroxaban (10mg od) may reduce the risk of myocardial infarction compared with LMWH (post-op, standard dose).

Table 112 Results for myocardial infarction (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
LMWH Pre-op (standard dose)	-	*0.37 (0.09 , 1.25)*	*0.37 (0.09 , 1.25)*
Apixaban (2.5mg bd)	*0.65 (0.18 , 2.11)*	-	*0.65 (0.18 , 2.11)*
Apixaban (5mg od)	*0.75 (0.05 , 6.23)*	-	*0.75 (0.05 , 6.23)*
Apixaban (5mg bd)	*0.14 (0 , 2.63)*	-	*0.14 (0 , 2.63)*
Apixaban (10mg od)	*0.14 (0 , 2.61)*	-	*0.14 (0 , 2.61)*
Apixaban (10mg bd)	*0.14 (0 , 2.64)*	-	*0.14 (0 , 2.64)*
Apixaban (20mg od)	*0.14 (0 , 2.69)*	-	*0.14 (0 , 2.69)*
Dabigatran (220mg od)	*0.37 (0.01 , 17.5)*	-	*0.37 (0.01 , 17.5)*
Rivaroxaban (10mg od)	*0.27 (0.07 , 0.88)*	-	*0.27 (0.07 , 0.88)*

Table 113 Results for myocardial infarction (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*0.57 (0.01 , 26.4)*	*0.57 (0.01 , 26.4)*
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	*0.42 (0.12 , 1.44)*	*0.42 (0.12 , 1.44)*
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	*0.74 (0.02 , 31.0)*	*0.74 (0.02 , 31.0)*

7.4.5 Major bleeding

Thirty-four studies reported 706 major bleeding events, leading to a network of 32 interventions (Figure 74). The studies were mainly judged to be at low risk of bias (Figure 74), though there were some concerns about sequence generation and blinding of participants and personnel.

Figure 73 Network plot for major bleeding (primary prevention of VTE)

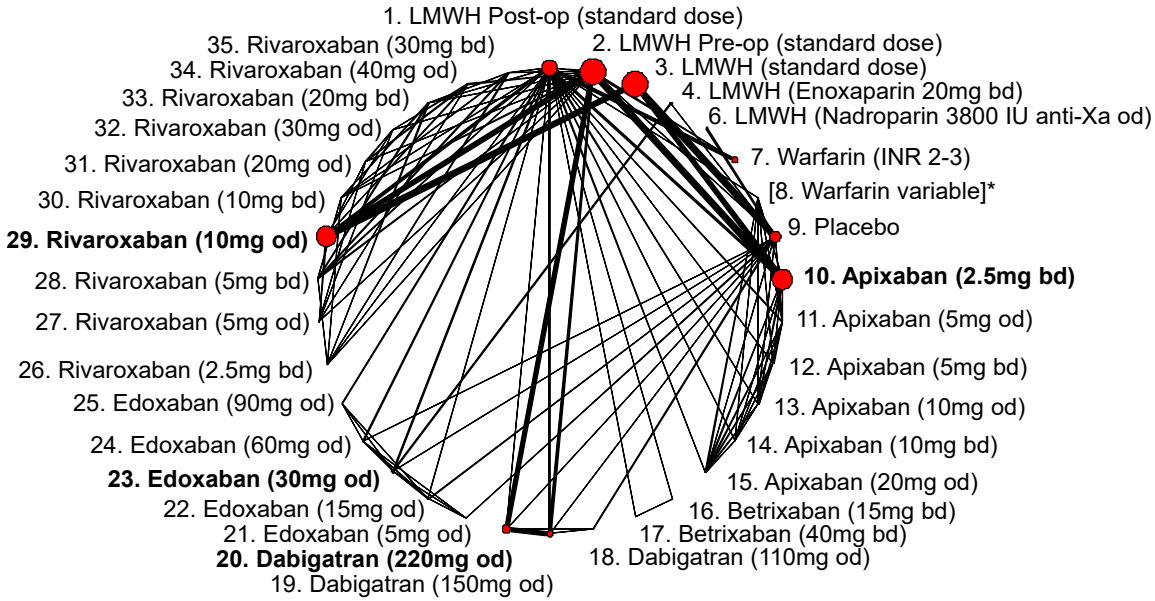


Figure 74 Included trials and risk of bias assessment for major bleeding (primary prevention of VTE)

Study	Interventions compared	Sequence generation	Allocation concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
ADOPT[191]	3, 10	+	+	+	+	+	+
ADVANCE-1[174]	1, 10	?	?	+	+	+	+
ADVANCE-2[181]	2, 10	+	+	+	+	+	+
ADVANCE-3[179]	2, 10	+	+	+	+	?	+
APROPOS[165]	1, 7, 10, 11, 12, 13, 14, 15,	+	?	?	+	+	+

EXPERT[171]	1, 16, 17	+	?	–	+	+	+
LIFENOX[188]	3, 9	+	?	+	+	+	+
MAGELLAN[187,194]	3, 29	+	+	+	+	+	+
ODiXa-HIP2[162]	2, 26, 28, 30, 33, 35	?	?	+	+	+	+
ODIXa-KNEE[160]	1, 26, 28, 30, 33, 35	+	+	+	+	+	+
ODIXa-OD.HIP[161]	2, 27, 29, 31, 32, 34	?	?	+	+	+	?
PROTECHT[173]	6, 9	+	+	+	+	+	+
RECORD 1[168]	2, 29	+	+	?	+	+	+
RECORD 2[169]	2, 29	+	+	?	+	+	+
RECORD 3[166]	2, 29	?	+	?	+	+	+
RECORD 4[176]	1, 29	+	+	?	+	+	+
RE-MOBILISE[170]	1, 19, 20	+	+	+	+	+	+
RE-MODEL[164]	2, 19, 20	+	+	?	?	+	+
RE-NOVATE[163]	2, 19, 20	+	+	+	+	+	+
RE-NOVATE II[186,192]	2, 20	+	+	+	?	+	+
STARS E-3[185]	4, 23	?	+	?	?	?	?
STARS J-1[175,183]	9, 21, 22, 23, 24	+	?	?	+	+	+
STARS J-4[184,196]	4, 23	?	?	–	+	+	+
STARS J-V[182]	4, 23	?	?	?	?	+	+
VTE-APIX-PLACEBO-USACAN[193]	9, 11, 13, 15	+	+	+	+	+	+
VTE-DABIG-PLAC-JAPAN[178]	9, 18, 19, 20	+	?	?	?	+	+
VTE-EDOX-LMWH-MULTI[180]	1, 22, 23, 24, 25	+	+	+	+	+	+
VTE-LMWH-PLAC-CAN[172]	2, 9	+	?	?	?	+	?
VTE-LMWH-PLAC-JAPAN[189]	1, 4, 9	?	?	?	+	+	?
VTE-VKA-LMWH-CANADA[155]	1, 7	+	?	+	+	+	?
VTE-VKA-LMWH-US[156]	2, 7	?	?	–	+	+	?
VTE-VKA-LMWH-US-2[157]	1, 7	?	?	–	?	+	?
VTE-VKA-LMWH-US-3[158]	1, 2, 7	+	?	+	+	+	?
VTE-VKA-LMWH-US-4[159]	1, 7	?	+	–	+	+	?

There was little evidence that risk of major bleeding differs between pre-operative and post-operative LMWH (standard dose). There was evidence that risk of major bleeding is lower with warfarin (INR 2-3) and higher with rivaroxaban (10mg od) compared with LMWH (post-op, standard dose) (Table 114). We observed statistical inconsistency between the direct and indirect estimates comparing dabigatran (220mg od) with post-operative LMWH (standard dose). The direct evidence indicated a reduction in bleeding with dabigatran and the indirect evidence indicated an increase. The estimated OR from the network meta-analysis was 1.20 (95% CI 0.75 to 1.92). All three of these results had confidence intervals compatible with increases and decreases in risk. There was evidence that risk of major bleeding is higher with rivaroxaban (10mg od) compared with with LMWH (post-op, standard dose) and compared with apixaban (2.5mg bd) and dabigatran (220mg od) (Table 115).

1

Table 114 Results for major bleeding (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Pre-op (standard dose)	1.32 (0.85 , 2.06)	0.90 (0.58 , 1.40)	1.09 (0.79 , 1.49)
Warfarin (INR 2-3)	0.59 (0.39 , 0.88)	0.47 (0.18 , 1.23)	0.57 (0.39 , 0.82)
Placebo	0.68 (0.31 , 1.50)	1.75 (0.36 , 8.54)	0.82 (0.41 , 1.64)
Apixaban (2.5mg bd)	0.93 (0.55 , 1.58)	1.02 (0.57 , 1.82)	0.97 (0.65 , 1.45)
Dabigatran (150mg od)	0.39 (0.13 , 1.16)	1.00 (0.53 , 1.89)	0.79 (0.46 , 1.35)
Dabigatran (220mg od)	0.39 (0.13 , 1.17)	1.55 (0.92 , 2.60)	1.20 (0.75 , 1.92)
Rivaroxaban (10mg od)	2.86 (1.67 , 4.88)	1.41 (0.61 , 3.26)	2.33 (1.51 , 3.68)
Imprecisely estimated comparisons			
LMWH (Enoxaparin 20mg bd)	-	*2.98 (0.18 , 93.9)*	*2.98 (0.18 , 93.9)*
LMWH (Nadroparin 3800 IU anti-Xa od)	-	*9.42 (0.61 , 4420)*	*9.42 (0.61 , 4420)*
Apixaban (5mg od)	*3.53 (0.75 , 23.1)*	-	*3.53 (0.75 , 23.1)*
Apixaban (5mg bd)	*4.66 (0.93 , 31.3)*	-	*4.66 (0.93 , 31.3)*
Apixaban (10mg od)	*1.25 (0.14 , 10.0)*	-	*1.25 (0.14 , 10.0)*
Apixaban (10mg bd)	*4.65 (0.95 , 30.9)*	-	*4.65 (0.95 , 30.9)*
Apixaban (20mg od)	*5.94 (1.49 , 37.4)*	-	*5.94 (1.49 , 37.4)*
Betrixaban (15mg bd)	*0.09 (0 , 2.90)*	-	*0.09 (0 , 2.90)*
Betrixaban (40mg bd)	*0.10 (0 , 3.02)*	-	*0.10 (0 , 3.02)*
Dabigatran (110mg od)	-	*0.63 (0.05 , 3.72)*	*0.63 (0.05 , 3.72)*
Edoxaban (5mg od)	-	*0.85 (0 , 51.4)*	*0.85 (0 , 51.4)*
Edoxaban (15mg od)		*2.03 (0.16 , 55.4)*	*2.03 (0.16 , 55.4)*
Edoxaban (30mg od)		*2.24 (0.17 , 61.1)*	*2.24 (0.17 , 61.1)*
Edoxaban (60mg od)		*3.32 (0.36 , 87.5)*	*3.32 (0.36 , 87.5)*
Edoxaban (90mg od)		*4.80 (0.42 , 135)*	*4.80 (0.42 , 135)*
Rivaroxaban (2.5mg bd)		*0.56 (0.09 , 2.78)*	*0.56 (0.09 , 2.78)*
Rivaroxaban (5mg od)	-	*2.90 (0.52 , 14.2)*	*2.90 (0.52 , 14.2)*
Rivaroxaban (5mg bd)	*0.79 (0.16 , 3.53)*	-	*0.79 (0.16 , 3.53)*

Rivaroxaban (10mg bd)	*1.31 (0.36 , 5.32)*	-	*1.31 (0.36 , 5.32)*
Rivaroxaban (20mg od)	-	*5.77 (1.53 , 24.4)*	*5.77 (1.53 , 24.4)*
Rivaroxaban (30mg od)	-	*6.69 (1.87 , 27.7)*	*6.69 (1.87 , 27.7)*
Rivaroxaban (20mg bd)	*2.41 (0.77 , 9.05)*	-	*2.41 (0.77 , 9.05)*
Rivaroxaban (40mg od)	-	*6.98 (1.92 , 28.6)*	*6.98 (1.92 , 28.6)*
Rivaroxaban (30mg bd)	*4.46 (1.43 , 16.9)*	-	*4.46 (1.43 , 16.9)*

Table 115 Results for major bleeding (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	**Direct evidence OR (95% CI)**	**Indirect evidence OR (95% CI)**	**Network meta-analysis OR (95% CI)**
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	1.23 (0.72 , 2.12)	1.23 (0.72 , 2.12)
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	2.40 (1.37 , 4.29)	2.40 (1.37 , 4.29)
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	1.95 (1.06 , 3.61)	1.95 (1.06 , 3.61)
Imprecisely estimated comparisons			
Edoxaban (30mg od) vs Apixaban (2.5mg bd)	-	*2.31 (0.16 , 64.3)*	*2.31 (0.16 , 64.3)*
Edoxaban (30mg od) vs Dabigatran (220mg od)	-	*1.87 (0.13 , 52.5)*	*1.87 (0.13 , 52.5)*
Rivaroxaban (10mg od) vs Edoxaban (30mg od)	-	*1.04 (0.04 , 14.5)*	*1.04 (0.04 , 14.5)*

7.4.6 Clinically relevant bleeding

Twenty-five studies reported 1973 clinically relevant bleeding events, leading to a network of 29 interventions. The studies were mostly judged to be at low risk of bias (Figure 76), although there were some concerns about lack of blinding of participants and personnel.

Figure 75 Network plot for clinically relevant bleeding (primary prevention of VTE)

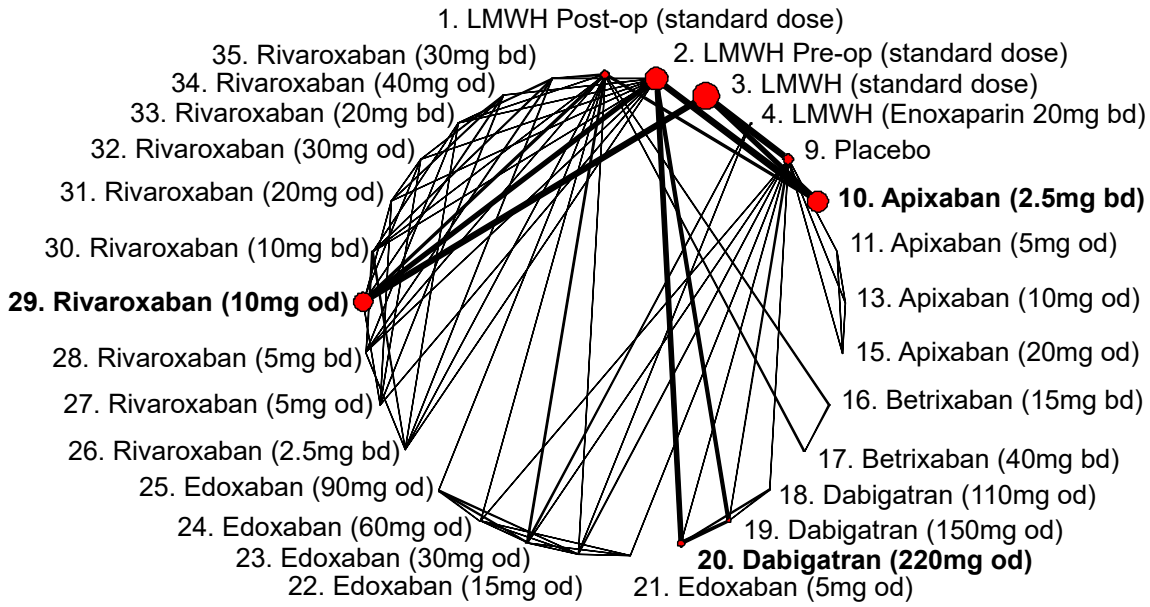
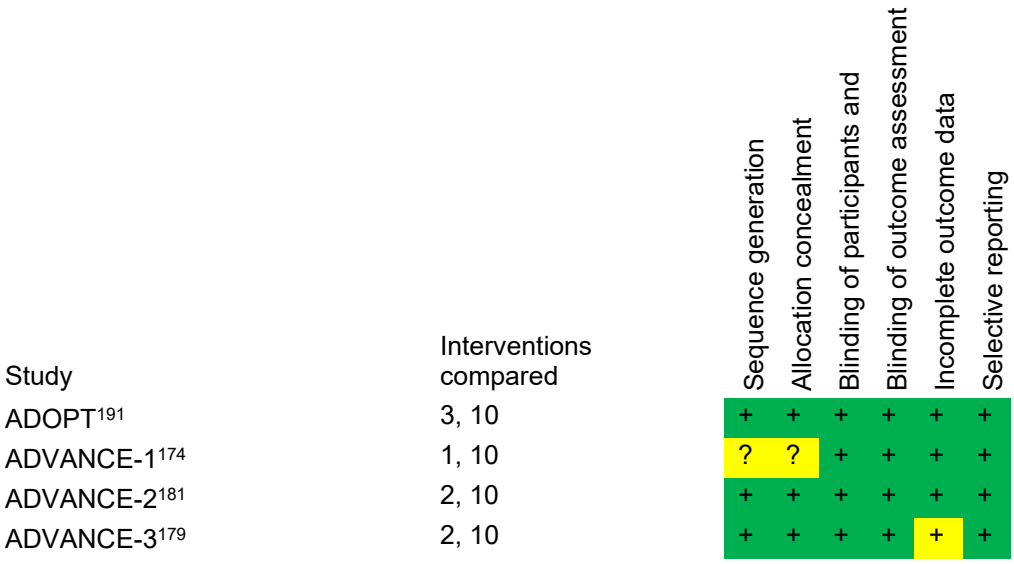


Figure 76 Included trials and risk of bias assessment for clinically relevant bleeding (primary prevention of VTE)



EXPERT[171]	1, 16, 17	+ ? – + + +
LIFENOX[188]	3, 9	+ ? + + + +
MAGELLAN[187,194]	3, 29	+ + + + + +
ODiXa-HIP2[162]	2, 26, 28, 30, 33, 35	? ? + + + +
ODIXa-KNEE[160]	1, 26, 28, 30, 33, 35	+ + + + + +
ODIXa-OD.HIP[161]	2, 27, 29, 31, 32, 34	? ? + + + ?
RECORD 1[168]	2, 29	+ + ? + + +
RECORD 2[169]	2, 29	+ + ? + + +
RECORD 3[166]	2, 29	? + ? + + +
RECORD 4[176]	1, 29	+ + ? + + +
RE-MODEL[164]	2, 19, 20	+ + ? ? + +
RE-NOVATE[163]	2, 19, 20	+ + + + + +
RE-NOVATE II[186,192]	2, 20	+ + + ? + +
STARS E-3[185]	4, 23	? + ? ? ? ?
STARS J-1[175,183]	9, 21, 22, 23, 24	+ ? ? + + +
STARS J-2[177]	4, 22, 23	? ? – + + +
STARS J-4[184,196]	4, 23	? ? – + + +
STARS J-V[182]	4, 23	? ? ? ? ? +
VTE-APIX-PLACEBO-USACAN[193]	9, 11, 13, 15	+ + + + + +
VTE-DABIG-PLAC-JAPAN[178]	9, 18, 19, 20	+ ? ? ? + +
VTE-EDOX-LMWH-MULTI[180]	1, 22, 23, 24, 25	+ + + + + +

There was evidence that risk of clinically relevant bleeding is higher for pre-operative LMWH (standard dose) compared with post-operative LMWH (standard dose), and higher for dabigatran (150mg or 220mg od) and rivaroxaban (10mg od) compared with LMWH (post-op, standard dose) (Table 116). We observed statistical inconsistency between direct and indirect estimates comparing rivaroxaban with post-operative LMWH (standard dose). In particular, the direct evidence for rivaroxaban (5mg bd) indicated a reduction in bleeding with rivaroxaban while the indirect evidence indicated an increase. The combined estimate for this comparison from the network meta-analysis suggested a small increase with OR = 1.53 (95% CI 0.54 to 4.47)); all three of these results had confidence intervals compatible with increases and decreases in risk. There was evidence that risk of clinically relevant bleeding is higher for dabigatran (220mg od) and rivaroxaban (10mg od) compared with apixaban (2.5mg bd) (Table 117).

Table 116 Results for clinically relevant bleeding (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Pre-op (standard dose)	-	1.30 (1.03 , 1.62)	1.30 (1.03 , 1.62)
Placebo	0.71 (0.45 , 1.12)	-	0.71 (0.45 , 1.12)
Apixaban (2.5mg bd)	0.97 (0.76 , 1.24)	1.16 (0.74 , 1.82)	1.06 (0.86 , 1.30)
Dabigatran (150mg od)	-	1.53 (1.09 , 2.15)	1.53 (1.09 , 2.15)
Dabigatran (220mg od)	-	1.55 (1.12 , 2.15)	1.55 (1.12 , 2.15)
Rivaroxaban (10mg od)	1.85 (1.52 , 2.26)	1.30 (0.91 , 1.85)	1.85 (1.52 , 2.26)
Rivaroxaban (5mg bd)	0.56 (0.11 , 2.54)	5.94 (1.76 , 20.0)	2.45 (0.97 , 6.73)
Rivaroxaban (10mg bd)	0.55 (0.11 , 2.49)	3.55 (0.85 , 14.9)	1.53 (0.54 , 4.47)
Rivaroxaban (20mg od)	1.93 (0.68 , 5.07)	-	1.93 (0.68 , 5.07)
Rivaroxaban (30mg od)	2.81 (1.13 , 6.88)	-	2.81 (1.13 , 6.88)
Rivaroxaban (20mg bd)	1.84 (0.57 , 6.44)	10.5 (2.47 , 44.4)	3.73 (1.57 , 9.98)
Rivaroxaban (40mg od)	3.26 (1.34 , 7.89)	-	3.26 (1.34 , 7.89)
Rivaroxaban (30mg bd)	3.53 (1.25 , 11.1)	32.5 (4.47 , 236)	5.94 (2.39 , 16.4)
Imprecisely estimated comparisons			
LMWH (Enoxaparin 20mg bd)	-	*1.25 (0.35 , 4.95)*	*1.25 (0.35 , 4.95)*
Apixaban (5mg od)	-	*0.64 (0.02 , 32.0)*	*0.64 (0.02 , 32.0)*
Apixaban (10mg od)	-	*0.71 (0.02 , 36.0)*	*0.71 (0.02 , 36.0)*
Apixaban (20mg od)	-	*3.78 (0.41 , 150)*	*3.78 (0.41 , 150)*
Betrixaban (15mg bd)	*0.03 (0 , 0.54)*		*0.03 (0 , 0.54)*
Betrixaban (40mg bd)	*0.33 (0.05 , 1.88)*		*0.33 (0.05 , 1.88)*
Dabigatran (110mg od)	-	*0.25 (0.01 , 1.63)*	*0.25 (0.01 , 1.63)*
Edoxaban (5mg od)	*0.54 (0.06 , 3.04)*	-	*0.54 (0.06 , 3.04)*
Edoxaban (15mg od)	*1.40 (0.43 , 5.03)*	-	*1.40 (0.43 , 5.03)*
Edoxaban (30mg od)	*1.42 (0.44 , 5.17)*	-	*1.42 (0.44 , 5.17)*
Edoxaban (60mg od)	*1.77 (0.56 , 6.33)*	-	*1.77 (0.56 , 6.33)*

Edoxaban (90mg od)	*2.13 (0.49 , 9.24)*	-	*2.13 (0.49 , 9.24)*
Rivaroxaban (2.5mg bd)	*1.01 (0.31 , 3.18)*	-	*1.01 (0.31 , 3.18)*
Rivaroxaban (5mg od)	*1.46 (0.43 , 4.16)*	-	*1.46 (0.43 , 4.16)*

Table 117 Results for clinically relevant bleeding (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	**Direct evidence** **OR (95% CI)**	**Indirect evidence** **OR (95% CI)**	**Network meta-analysis** **OR (95% CI)**
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	1.47 (1.09 , 1.98)	1.47 (1.09 , 1.98)
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	1.75 (1.40 , 2.20)	1.75 (1.40 , 2.20)
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	1.19 (0.88 , 1.63)	1.19 (0.88 , 1.63)
Imprecisely estimated comparisons			
Edoxaban (30mg od) vs Apixaban (2.5mg bd)	-	*1.34 (0.41 , 5.00)*	*1.34 (0.41 , 5.00)*
Edoxaban (30mg od) vs Dabigatran (220mg od)	-	*0.92 (0.27 , 3.44)*	*0.92 (0.27 , 3.44)*
Rivaroxaban (10mg od) vs Edoxaban (30mg od)	-	*1.30 (0.35 , 4.32)*	*1.30 (0.35 , 4.32)*

7.4.7 All-cause mortality

Twenty-four studies reported 1161 all-cause mortality events, leading to a network of 29 interventions (Figure 77). The studies were mostly judged to be at low risk of bias (Figure 78), with some concerns about lack of blinding of participants and personnel.

Figure 77 Network plot for all-cause mortality (primary prevention of VTE)

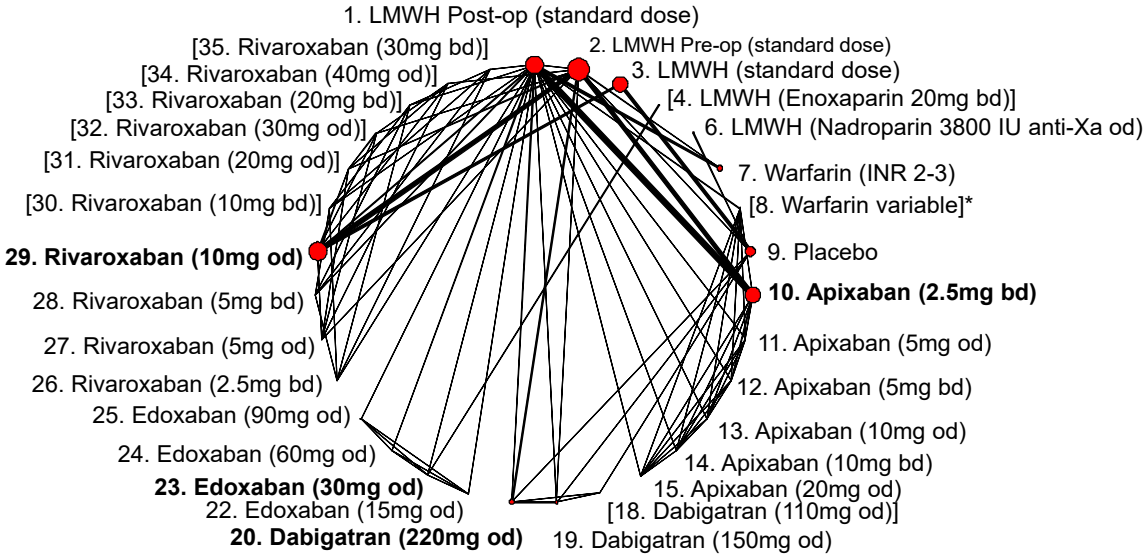
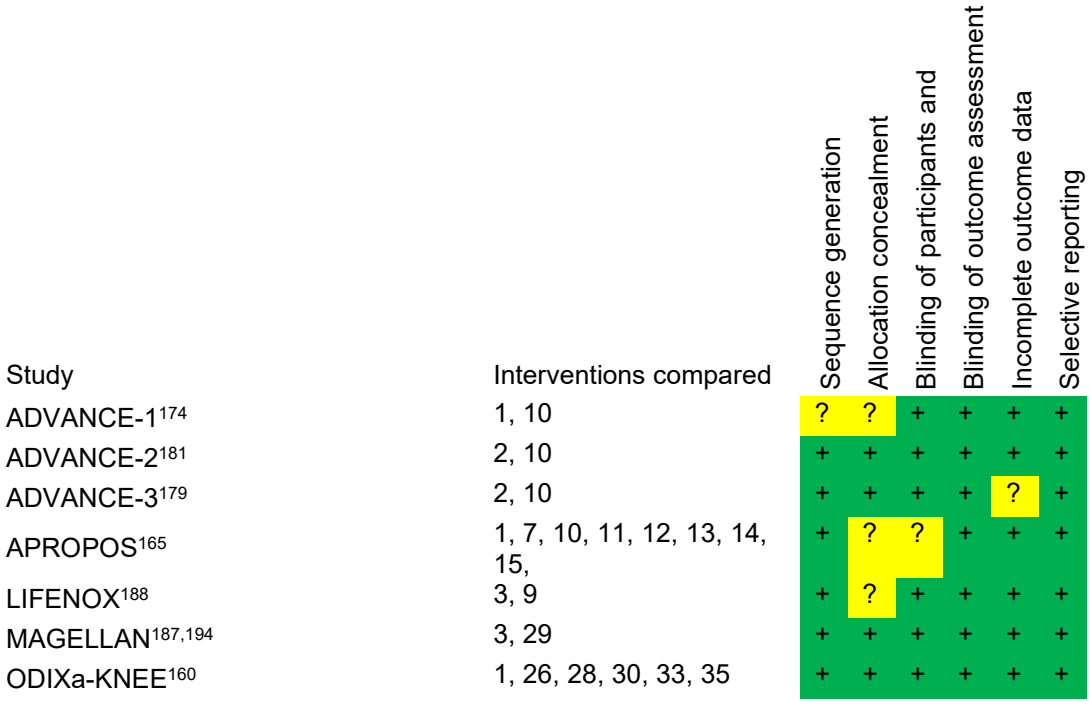


Figure 78 Included trials and risk of bias assessment for all-cause mortality (primary prevention of VTE)



ODIXa-OD.HIP[161]	2, 27, 29, 31, 32, 34	? ? + + + ?
PROTECHT[173]	6, 9	+ + + + + +
RECORD 1[168]	2, 29	+ + ? + + +
RECORD 2[169]	2, 29	+ + ? + + +
RECORD 3[166]	2, 29	? + ? + + +
RECORD 4[176]	1, 29	+ + ? + + +
RE-MOBILISE[170]	1, 19, 20	+ + + + + +
RE-MODEL[164]	2, 19, 20	+ + ? ? + +
RE-NOVATE II[186,192]	2, 20	+ + + ? + +
STARS J-4[184,196]	4, 23	? ? – + + +
VTE-DABIG-PLAC-JAPAN[178]	9, 18, 19, 20	+ ? ? ? + +
VTE-EDOX-LMWH-MULTI[180]	1, 22, 23, 24, 25	+ + + + + +
VTE-LMWH-PLAC-CAN[172]	2, 9	+ ? ? ? + ?
VTE-VKA-LMWH-CANADA[155]	1, 7	+ ? + + + ?
VTE-VKA-LMWH-US-2[157]	1, 7	? ? – ? + ?
VTE-VKA-LMWH-US-3[158]	1, 2, 7	+ ? + + + ?
VTE-VKA-LMWH-US-4[159]	1, 7	? + – + + ?

Rates of all-cause mortality were substantially higher in studies of cancer patients than in studies of surgical patients (Table 93). There was little evidence that risk of all-cause mortality differed for any intervention compared with LMWH (post-op, standard dose) (Table 118). We observed statistical inconsistency between the direct and indirect estimates comparing apixaban (2.5mg bd) with post-operative LMWH (standard dose). The direct evidence indicated a reduction in bleeding with apixaban and the indirect evidence showed an increase. The combined estimate from the network meta-analysis suggested a small increase with OR = 1.57 (95% 0.6 to 4.37). Comparisons between licensed doses of NOACs were imprecisely estimated (Table 119).

Table 118 Results for all-cause mortality (primary prevention of VTE): comparisons with LMWH

Comparisons with LMWH (post-op, standard dose)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Pre-op (standard dose)	2.00 (0.30 , 13.47)	1.79 (0.86 , 3.74)	1.82 (0.93 , 3.62)
LMWH (Nadroparin 3800 IU anti-Xa od)	-	1.06 (0.57 , 2.05)	1.06 (0.57 , 2.05)
Warfarin (INR 2-3)	1.44 (0.69 , 3.06)	-	1.44 (0.69 , 3.06)
Placebo	1.03 (0.88 , 1.20)	-	1.03 (0.88 , 1.20)
Apixaban (2.5mg bd)	0.66 (0.18 , 2.29)	6.29 (1.25, 31.5)	1.57 (0.6 , 4.37)
Rivaroxaban (10mg od)	1.06 (0.85 , 1.33)	0.80 (0.35 , 1.83)	1.04 (0.83 , 1.29)
Imprecisely estimated comparisons			
Apixaban (5mg od)	*0.41 (0 , 9.80)*	-	*0.41 (0 , 9.80)*
Apixaban (5mg bd)	*0.37 (0 , 9.27)*	-	*0.37 (0 , 9.27)*
Apixaban (10mg od)	*0.38 (0 , 9.42)*	-	*0.38 (0 , 9.42)*
Apixaban (10mg bd)	*0.36 (0 , 8.91)*	-	*0.36 (0 , 8.91)*
Apixaban (20mg od)	*0.36 (0 , 8.71)*	-	*0.36 (0 , 8.71)*
Dabigatran (150mg od)	*1.49 (0.31 , 7.13)*	-	*1.49 (0.31 , 7.13)*
Dabigatran (220mg od)	*1.04 (0.21 , 4.86)*	-	*1.04 (0.21 , 4.86)*
Edoxaban (15mg od)	*4.37 (0.15 , 1610)*	-	*4.37 (0.15 , 1610)*
Edoxaban (30mg od)	*13.6 (0.87 , 4510)*	-	*13.6 (0.87 , 4510)*
Edoxaban (60mg od)	*0.88 (0 , 421)*	-	*0.88 (0 , 421)*
Edoxaban (90mg od)	*0.93 (0 , 423)*	-	*0.93 (0 , 423)*

Table 119 Results for all-cause mortality (primary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Rivaroxaban (10mg od) vs Apixaban (2.5mg bd)	-	0.66 (0.23 , 1.76)	0.66 (0.23 , 1.76)
Imprecisely estimated comparisons			
Dabigatran (220mg od) vs Apixaban (2.5mg bd)	-	*0.66 (0.10 , 3.85)*	*0.66 (0.10 , 3.85)*
Edoxaban (30mg od) vs Apixaban (2.5mg bd)	-	*8.79 (0.44 , 3220)*	*8.79 (0.44 , 3220)*
Edoxaban (30mg od) vs Dabigatran (220mg od)	-	*13.8 (0.53 , 5360)*	*13.8 (0.53 , 5360)*
Rivaroxaban (10mg od) vs Dabigatran (220mg od)	-	*0.99 (0.21 , 4.95)*	*0.99 (0.21 , 4.95)*
Rivaroxaban (10mg od) vs Edoxaban (30mg od)	-	*0.08 (0 , 1.22)*	*0.08 (0 , 1.22)*

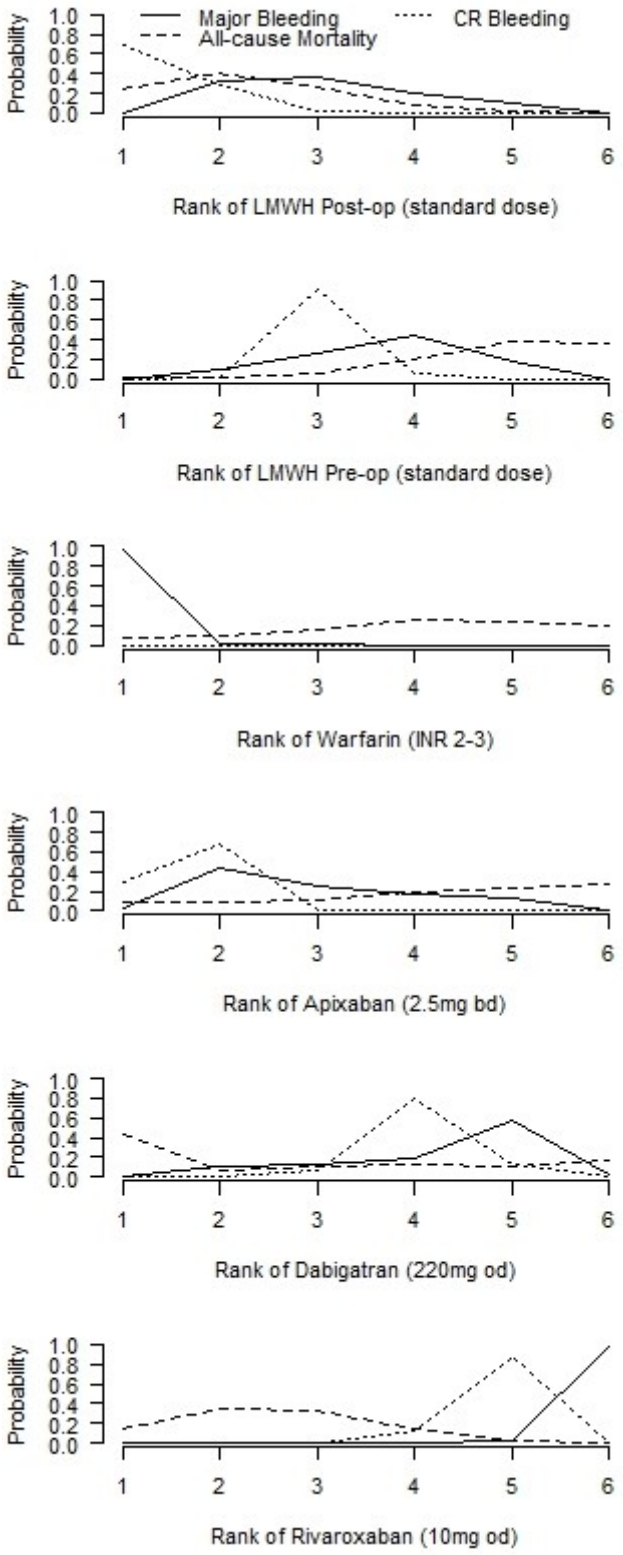
7.4.8 Summary of results and ranking of interventions

Despite the substantial number of patients randomised to trials of primary prevention of VTE, low numbers of clinically relevant outcome events meant that most comparisons were imprecisely estimated. Conclusions can mainly be drawn from analyses of symptomatic VTE, major bleeding and clinically relevant bleeding. There was evidence that risk of symptomatic VTE is lower with rivaroxaban (10mg od) compared with LMWH (pre-op, standard dose) in hip surgery patients, but that risk of major bleeding and clinically relevant bleeding is higher with rivaroxaban (10mg od) compared with LMWH (post-op, standard dose).

We conducted sensitivity analyses merging warfarin interventions with variable INR range with those with INR range 2-3. Results, which are available from the authors upon request, were similar to those presented above. With regards to model appraisal, we did not identify any instance of lack of convergence among the Markov chains or poor model fit. There were some instances of inconsistency between direct and indirect estimates of the same effect, although in most instances these results were accompanied by wide confidence intervals. Few of the comparisons were replicated across studies; where there were multiple estimates we did not find evidence of statistical heterogeneity.

Because of the substantial imprecision in comparisons of efficacy outcomes, we present only one rankogram containing the bleeding and death outcomes for which all patients were jointly analysed (Figure 79). Warfarin was ranked with high probability as the best intervention for major bleeding events and LMWH (post-op, standard dose) was ranked with high probability as best or second-best intervention for clinically relevant bleeding. Rivaroxaban (10mg od) was ranked among the worst interventions for bleeding outcomes.

Figure 79 Rankogram for licensed interventions examined in primary prevention of VTE



CR: Clinically relevant.

8. Clinical results (3): Acute treatment of venous thromboembolism

8.1 Included studies

Nine completed randomised controlled trials with ten references[219-228] were identified for inclusion in the review of acute treatment of VTE (see Figure 58) as well as one ongoing trial[229]. A summary of the characteristics of the nine included studies is presented in Table 120. All studies were multicentre and many were conducted across countries in North and South America, Europe, Asia, Australia, New Zealand, South Africa, and Russia and Israel. Six were phase III studies and three were phase II studies. The number of patients randomised ranged from 520 to 8,292, with a total of 28,803 patients across the nine studies. The phase III studies examined edoxaban, apixaban, dabigatran, and rivaroxaban, and these studies randomised 27,127 patients (94% of the total). The phase II studies, which examined apixaban and rivaroxaban, contributed 1,676 patients (6%).

Eligibility criteria were similar across studies: all patients had acute symptomatic and objectively confirmed DVT and/or PE. The mean ages of included patients were similar, ranging from 54.7 to 59.1 years. The percentage of males across studies ranged from 51% to 62%. Mean body mass index (BMI) was reported by four studies, ranged from 27kg/m^2 to 28.9kg/m^2, and was comparable between study arms.[219,220,222,228] Five studies reported percentages of cancer cases[220,221,226-228], which were comparable between study arms and ranged from 2% to 12%.

All studies compared a NOAC with standard intensity warfarin (INR 2-3): mean time in therapeutic range ranged from 50.3% to 62.7%. Of the studies that examined rivaroxaban two phase III studies administered 15mg twice daily and two phase II studies examined six dosing strategies. Two studies examined apixaban: one phase III study administered 5mg twice daily and one phase II study compared this with two alternative dosing strategies. Two phase III studies examined dabigatran 150mg twice daily; and one phase III study examined edoxaban 60mg once daily.

Treatment duration ranged from 12 to 48 weeks in the rivaroxaban studies, 12 to 24 weeks in the apixaban studies, 24 weeks in the dabigatran studies, and 12 to 48 weeks

in the edoxaban study. Reported efficacy and safety outcome types were similar across studies and reported at the end of the treatment periods. All nine studies reported symptomatic DVT, symptomatic PE, and major bleeding. Eight studies reported all-cause mortality and clinically relevant bleeding, seven reported symptomatic VTE and five reported myocardial infarction. Each of the studies was sponsored by one or more pharmaceutical companies. In almost all studies the sponsor(s) was responsible for the study design and data collection, and in some cases data analysis.

Table 120 Characteristics of nine included randomised trials in acute treatment of VTE

Study (Centre type) [Countries]	Study type Sponsor (sponsor's role)	Age eligibility (Mean age) [% Male]	Clinical condition	No. rand	Interventions compared	Tmt duration (weeks)	Outcomes	Time of outcome assessment (weeks)
AMPLIFY[227] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia & South Africa]	Phase III Pfizer and Bristol-Myers Squibb ("The sponsors collected and maintained the data; the academic authors had full access to the data through the sponsors")	≥18 yrs. (57 yrs.) [58.7%]	Acute objectively confirmed, symptomatic proximal DVT or PE (with or without deep-vein thrombosis)	5400	**Apixaban** 1. 5mg bd **Warfarin** 2. INR 2-3 (Mean ttr: 61%)	24	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE, fatal PE Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, MI, death (all causes)	24
BOTTICELLI DVT[221] (Multicentre) [USA, European, Israel, Australia, & South Africa]	Phasse II Bristol-Myers Squibb (Not declared)	≥18 yrs. (58.5 yrs.) [62.1%]	Acute symptomatic and objectively confirmed proximal DVT or extensive calf vein thrombosis involving at least the upper third of the deep calf veins	520	**Apixaban** 1. 5mg bd 2. 10mg bd 3. 20mg bd **Warfarin** 4. INR 2-3 (Mean ttr: 57%)	12-13	Efficacy: Symptomatic DVT, symptomatic PE Safety: Major bleeding, minor bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	12-13

EINSTEIN DVT[223] (Multicentre) [North & South America, Europe, Israel, Australia, New Zealand, Asia & South Africa]	Phase III Bayer Schering Pharma and Ortho-McNeil ("The data were collected and maintained by the Sponsor)	≥18 yrs. (56.1 yrs.) [56.8%]	Acute, objectively confirmed proximal DVT without symptomatic PE	3449	**Rivaroxaban** 1. 15mg bd (then 20mg od) **Warfarin** 2. INR 2-3 (Mean ttr: 57.7%)	12-48	Efficacy: Symptomatic VTE, symptomatic DVT, fatal PE, symptomatic non-fatal PE Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, MI, death (cardiovascular), death (all causes)	12-48
EINSTEIN DVT dose ranging study[220] (Multicentre) [North & South America, Europe, Israel, Australia & South Africa]	Phase II Bayer HealthCare ("The data were gathered and maintained by the sponsor")	≥18 yrs. (58 yrs.) [51.1%]	Acute symptomatic and objectively confirmed DVT (proximal or isolated extensive calf vein thrombosis involving at least the upper one-third of the calf veins)	543	**Rivaroxaban** 1. 20mg od 2. 30mg od 3. 40mg od **Warfarin** 4. INR 2-3 (Mean ttr: NR)	12	Efficacy: Symptomatic DVT, symptomatic non-fatal PE, symptomatic VTE Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, clinically relevant bleeding, death (all causes)	12
EINSTEIN PE[224] (Multicentre) [North & South America, Europe, Israel, Australia, New Zealand, Asia & South Africa]	Phase III Bayer Health-Care and Janssen Pharmaceuticals ("The data were collected and maintained by the Sponsor")	≥18 yrs. (57.7 yrs.) [52.9%]	Acute symptomatic PE, objectively confirmed, with or without DVT	4833	**Rivaroxaban** 1. 15mg bd (then 20mg od) **Warfarin** 2. INR 2-3 (Mean ttr: 62.7%)	31 (mean)	Efficacy: Symptomatic VTE, Symptomatic DVT, fatal PE, symptomatic non-fatal PE Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	12-48

HOKUSAI-VTE[225,226] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, Asia & South Africa]	Phase III Daiichi Sankyo (The sponsor was responsible for the collection and maintenance of the data)	≥18 yrs. (55.8 yrs.) [57.2%]	Acute objectively confirmed, symptomatic DVT involving the popliteal, femoral, or iliac veins, or acute, symptomatic PE (with or without DVT)	8292	**Edoxaban** 1. 60mg od* **Warfarin** 2. INR 2-3 (Mean ttr: 63.5%)	12-48	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE, fatal PE Safety: All bleeding, major bleeding, fatal bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, MI, death (all causes)	48
ODiXa-DVT[219] (Multicentre) [Canada, South America, Europe, Israel, Australia, New Zealand & South Africa]	Phase II Bayer HealthCare AG (The statistical analysis was performed by the Sponsor)	≥18 yrs. (59.1 yrs.) [60.9%]	Acute symptomatic and objectively confirmed thrombosis of the popliteal or more proximal veins, who have no symptoms of PE	613	**Rivaroxaban** 1. 10mg bd 2. 20mg bd 3. 30mg bd 4. 40mg od **Warfarin** 5. INR 2-3 (Mean ttr: 60%)	12	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE Safety: All bleeding, major bleeding, minor bleeding	12
RE-COVER[222] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, New Zealand, India & South Africa]	Phase III Boehringer Ingelheim (The study was funded, designed, conducted, and the data analysed by the sponsor in conjunction with the steering committee)	≥18 yrs. (54.7 yrs.) [58.4%]	Acute, symptomatic, objectively confirmed proximal DVT of the legs or PE and for whom six months of anticoagulant therapy was considered to be an appropriate treatment	2564	**Dabigatran** 1. 150mg bd **Warfarin** 2. INR 2-3 (Mean ttr: 59.9%)	24	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE Safety: All bleeding, major bleeding, composite clinically relevant bleeding, MI, death (all causes)	24

RE-COVER II[228] (Multicentre) [North & South America, Europe, Russia, Israel, Australia, New Zealand, Asia & South Africa]	Phase III Boehringer Ingelheim (The study was funded, designed, conducted, and the data analysed, by the sponsor in conjunction with the steering committee)	≥18 yrs. (54.9 yrs.) [60.6%]	Acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins, and/or PE	2589	**Dabigatran** 1. 150mg bd **Warfarin** 2. INR 2-3 (Mean ttr: 56.9%)	24	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, MI, Death (all causes)	24

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; MI = myocardial infarction; INR = international normalised ratio, rand = randomised; od = once daily; bd = twice daily; Tmt = treatment; ttr = time in therapeutic range); NR = not reported
Note: In warfarin arms, participants also received LMWH (treatment duration 5 days; except in BOTTICELLI DVT study where treatment was continued until a stable INR >2 was observed on two measurements at least 24 hours apart-and minimum duration of treatment was 5 days
* Note that 17.6% of the patients in the edoxaban 60mg od arm received a lower dose of 30mg od

8.2 Time in therapeutic range for warfarin interventions

Table 121 shows the comparator interventions, target INR and (where reported) mean time in therapeutic range for the nine studies that included a warfarin intervention arm. Eight (89%) of these studies reported mean time in therapeutic range, which varied between 56.9% and 63.5%.

Table 121 Mean time in therapeutic range for warfarin in acute treatment of VTE

Study	Interventions that were compared with warfarin	Warfarin INR	Mean time in therapeutic range (INR)
AMPLIFY[227]	Apixaban 5mg bd	2-3	61%
BOTTICELLI DVT[221]	Apixaban 5mg,10mg, 20mg bd	2-3	57%
EINSTEIN DVT[223]	Rivaroxaban 15mg bd (then 20mg od)	2-3	57.7%
EINSTEIN DVT dose ranging study[220]	Rivaroxaban 20mg, 30mg, 40mg od	2-3	NR
EINSTEIN PE[224]	Rivaroxaban 15mg bd (then 20mg od)	2-3	62.7%
HOKUSAI-VTE[225,226]	Edoxaban 60mg od	2-3	63.5%
ODiXa-DVT[219]	Rivaroxaban 10mg, 20mg, 30mg bd, 40mg od	2-3	60%
RE-COVER[222]	Dabigatran 150mg bd	2-3	59.9%
RE-COVER II[228]	Dabigatran 150mg bd	2-3	56.9%

VTE = venous thromboembolism; INR = international normalized ratio; NR = not reported, od = once daily; bd = twice daily

8.3 Risk of bias in included studies

Table 122 shows the detailed risk of bias assessments for each included study for each domain. Generally, the studies were judged to be at low risk of bias. The randomisation sequence was predominantly computer generated. The studies were judged to be at low risk of bias for sequence generation, blinding of outcome assessment and selective reporting although one study did not explain how randomisation was performed, stating only that a veiled randomisation process was carried out. In all studies concealed allocation to intervention arms was achieved through central allocation, either an interactive voice or web-based system. Five studies were of open-label design and as such were judged to be of high risk of bias for blinding of participants and personnel. Completeness of the data analysed depended in a few studies on whether the outcome was for efficacy or safety. For the majority of outcomes all patients were accounted for in the analysis or, in some situations, a small number of patients were not included in the analysis but reasons

were provided and judged to be similar across intervention arms and unlikely to be related to the outcome. These studies were therefore judged to be at low risk of bias due to incomplete outcome data. In one study the reasons for not including some patients in the efficacy analyses were judged to be similar across study arms butwere judged to be potentially related to the outcome, and the study was therefore considered at high risk of bias for the domain. Outcomes were reported as stated in the protocols in all studies, which were therefore judged to be at low risk of bias due to selective reporting. Risk of bias judgements for studies contributing to analyses of each outcome are presented graphically in the sections that follow.

Table 122 Risk of bias assessments for nine included randomised trials in acute treatment of VTE

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AMPLIFY[227]	L-"Randomisation was performed with the use of an interactive voice-response system"	L-"Randomisation was performed with the use of an interactive voice-response system"	L-"Patients were assigned to receive apixaban tablets plus placebo enoxaparin injections and placebo warfarin tablets or conventional therapy with enoxaparin injections and warfarin tablets plus placebo apixaban tablets"	L-"An independent committee, whose members were unaware of the study-group assignments, adjudicated the qualifying diagnosis, the anatomical extent of the initial deep-vein thrombosis or pulmonary embolism, and all suspected outcomes"	U-For efficacy and safety outcomes except symptomatic DVT: There are missing outcome data with reasons. Although missing outcome data seem to be balanced in numbers across intervention groups, it isn't quite clear whether the reasons could be related to true outcome L-For symptomatic DVT: All patients were included in the analyses	L-Outcomes reported as stated in the study protocol
BOTTICELLI DVT[221]	U-"The Botticelli study was a veiled randomised, parallel group dose-ranging study"	L-"An interactive voice response system was used for randomisation. The study was conducted according to current methodological standards; that is, consecutive patients were centrally randomised"	H-"The Botticelli study was a veiled randomised, parallel group dose-ranging study that was double-blind for the different doses of apixaban and open-label for the LMWH/VKA comparator"	L-"All potential study outcomes were assessed by an independent committee, whose members were unaware of treatment assignment"	L-There are missing data; however numbers missing in each arm are almost the same; also reasons for missing data unlikely to be related to the outcome.	L-Outcomes reported according to study protocol

EINSTEIN DVT[223]	L-“Patients were randomly assigned to a study group with the use of a computerised voice–response system, with stratification by country”	L-“Patients were randomly assigned to a study group with the use of a computerised voice–response system”	H-“The Acute DVT Study was a randomised, open-label study”	L-“All suspected outcome events were classified by a central adjudication committee whose members were unaware of the treatment assignments”	L-Few missing data with reasons and number of missing data similar in the two groups; reasons for missing data unlikely to be related to true outcome. Analysis by intension to treat	L-Outcomes reported according to study protocol
EINSTEIN DVT dose ranging study[220]	L-“Patients were randomised, via an interactive voice response system”	L-“Patients were randomised, via an interactive voice response system”-A central allocation system	H-“The Einstein–DVT study was a randomised, dose-ranging study that was double-blind for rivaroxaban doses and open-label for the LMWH/VKA”	L-“An independent adjudication committee, unaware of treatment allocation, evaluated all suspected thromboembolic complications, deaths, baseline and repeat ultrasound and perfusion lung scans, as well as all episodes of suspected bleeding”	H-For efficacy outcomes: Missing data but with reasons. Reasons are similar across all rivaroxaban arms. Numbers are similar across rivaroxaban arm but differ significantly when each is compared with the comparator arm. Reasons for missing data may be related to the outcome L-For safety outcomes: All patients were included in the analyses	L-Outcomes reported according to study protocol

EINSTEIN PE[224]	L-“Randomisation was performed with the use of a computerised voice-response system”	L-“Randomisation was performed with the use of a computerised voice-response system”	H-“The EINSTEIN–PE study was a randomised, open-label trial”	L-“All events were adjudicated and confirmed by a central independent adjudication committee blinded to treatment”	L-Few missing data; missing data is balanced in numbers across groups. Reasons for missing data given, unlikely to be related to true outcome	L-Outcomes reported according to study protocol
HOKUSAI-VTE[225,226]	L-“Randomisation was performed with the use of an interactive Web-based system”	L-“Randomisation was performed with the use of an interactive Web-based system”-central allocation	L-“Edoxaban or warfarin was administered in a double-blind, double-dummy fashion”	L-“An independent committee, whose members were unaware of the study-group assignments, adjudicated all suspected outcomes”	L-Small numbers of missing data; however balanced in the treatment groups. Reason for missing data is unlikely to be related to the true outcome. Data analysis was by intention-to-treat	L-Outcomes reported as stated in the study protocol

ODiXa-DVT[219]	L-“The ODIXa-DVT study was a multinational, multicentre, partially blinded, parallel-group study in which patients were randomised by central computer”	L-“The ODIXa-DVT study was a multinational, multicentre, partially blinded, parallel-group study in which patients were randomised by central computer”-Central allocation system	H-“The ODIXa-DVT study was a multinational, multicentre, partially blinded, parallel-group study” “Patients in the oral rivaroxaban treatment groups received double blinded doses of 10, 20, or 30 mg twice daily (BID) or 40 mg once daily, with food, for 12 weeks. Patients in the open-label, standard-anticoagulant group received enoxaparin 1 mg/kg BID by subcutaneous injection and a VKA”	L-“All clinically suspected VTE, bleeding events, deaths, and paired perfusion lung scans (see be1) were adjudicated, without knowledge of the treatment group, by an independent central adjudication committee”	L-All patients were included in the analyses	L-Outcomes reported according to study protocol
RE-COVER[222]	L-“We used a computer generated randomisation scheme with variable block sizes, stratified according to presentation”	L-“Staff members at the clinical centres called an interactive voice-response system that randomly assigned subjects to one of the supplied medication kits”-A central allocation system	L-“Active dabigatran and warfarin- like placebo or active warfarin and dabigatran- like placebo were then given for 6 months (“double-dummy phase”)”	L-“All suspected outcome events and deaths were classified by central adjudication committees, whose members were unaware of the treatment assignments”	L-All patients were included in the analyses	L-Outcomes reported according to study protocol

RE-COVER II[228]	L-“Patients were randomised using an interactive voice response system and a computer generated randomisation scheme in blocks of 4”	L-“Patients were randomised using an interactive voice response system”	L-“Patients were assigned in a 1:1 ratio to receive active fixed dose dabigatran 150 mg twice daily and warfarin-like placebo, or active warfarin and dabigatran-like placebo”	L-“All suspected outcome events and deaths were classified by central adjudication committees, whose members were unaware of the treatment assignments”	L-All patients were included in the analyses	L-Outcomes reported as stated in the study protocol

L = low risk; H = high risk; U = unclear risk; VTE = venous thromboembolism; DVT = deep vein thrombosis, PE = pulmonary embolism; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; Note: quotations are denoted by inverted commas

8.4 Results of clinical effectiveness and safety

The nine trials of acute treatment for VTE examined thirteen distinct interventions (Table 123). Table 124 and Table 125 show the number of outcome events for each outcome as reported in each trial. We performed network meta-analyses for seven outcomes: symptomatic DVT, symptomatic PE, symptomatic VTE, myocardial infarction, major bleeding, clinically relevant bleeding and all-cause mortality.

Table 123 List of distinct interventions examined by included randomised trials in acute treatment of VTE

Warfarin (INR 2-3)	Rivaroxaban (10mg bd)
Apixaban (5mg bd)	Rivaroxaban (20mg od)
Apixaban (10mg bd)	Rivaroxaban (15mg bd then 20mg od)
Apixaban (20mg od)	Rivaroxaban (30mg od)
Dabigatran (150mg bd)	Rivaroxaban (20mg bd)
Edoxaban (60 or 30 (17.6%) mg od)*	Rivaroxaban (40mg od)
	Rivaroxaban (30mg bd)

* The planned edoxaban dose in the HOKUSAI-VTE study was 60mg od, but 17.6% of the patients in that intervention arm received a lower dose of 30mg od). This intervention is denoted "Edoxaban (60 or 30 (17.6%) mg od)"

Results are presented as follows for each of the seven outcomes. First, we provide network plots to illustrate the comparisons of interventions made in the different trials. Second, we illustrate the risk of bias assessments specific to the outcome for each trial included in the network. Third, we present results tables for each intervention compared with the reference treatment (warfarin with a target INR range of 2-3). Fourth, we present results tables for pairwise comparisons among licensed doses of the NOACs. For both sets of results tables, posterior median odds ratios and 95% credible intervals from Bayesian fixed-effect analyses are shown, although we refer to the latter as confidence intervals for convenience. In these tables we present results separately for any available direct evidence, for any indirect comparisons that can be made (excluding the direct evidence) and for the network meta-analysis (which combines the direct and the indirect evidence). Comparisons from the NMA with a ratio between interval limits exceeding nine were considered "imprecisely estimated" and are presented at the bottom of each table (note that calculation of indirect evidence was not undertaken for imprecisely estimated comparisons). A summary of results across outcomes is provided at the end in the form of a 'rankogram', which illustrates the probability that each treatment is best, second best, and so on, for each

outcome. Last, forest plots of all contributing data, with odds ratios calculated using standard frequentist methods, are included in Appendix 4.

Table 124 Efficacy outcomes reported by nine included randomised trials in acute treatment of VTE: number of events for each outcome in each trial

Study	Study size	Symptomatic DVT	Symptomatic proximal DVT	Symptomatic PE	Fatal PE	Symptomatic non-fatal PE	Symptomatic VTE	Cardiovascular deaths	All-cause mortality
AMPLIFY[227]	5365	53			3	50	130	10	93
BOTTICELLI DVT[221]	511	10		1					5
EINSTEIN DVT[223]	3429	42			1	38	87	6	87
EINSTEIN DVT dose ranging study[220]	542	10			0	3	16		19
EINSTEIN PE[224]	4817	35			3	41	94		108
HOKUSAI-VTE[225,226]	8240	120			7	108	276	27	258
ODiXa-DVT[219]	543	5	6		2	3	10		
RE-COVER[222]	2539	34				20	57		42
RE-COVER II[228]	2568	42				20	58		50

Table 125 Safety outcomes reported for nine included randomised trials in acute treatment of VTE: number of events for each outcome in each trial

Study	Study size	MI	All bleeding	Minor bleeding	Major bleeding	Fatal bleeding	Intracranial bleeding	Clinically relevant non-major bleeding	Clinically relevant bleeding
AMPLIFY[227]	5365	6	1110		64	3	9	318	376
BOTTICELLI DVT[221]	511			29	3	0		35	38
EINSTEIN DVT[223]	3429	6			34		4	245	277
EINSTEIN DVT dose ranging study[220]	542		127		5	1		26	31
EINSTEIN PE[224]	4817				78		14	463	523
HOKUSAI-VTE[225,226]	8240	33					23		
ODiXa-DVT[219]	543		52	44	10	0			
RE-COVER[222]	2539	6	482		44	2	3		182
RE-COVER II[228]	2568	6	485		37	1	4	129	166

8.4.1 Symptomatic venous thromboembolism

Eight studies reported 728 symptomatic VTE events, leading to a network of 11 interventions (Figure 80). Figure 81 shows risk of bias judgments for these studies. They were mostly judged to be at low risk of bias, although there were some concerns about lack of blinding of participants and personnel. There was little evidence that risk of symptomatic VTE differed for any of the NOAC interventions compared with warfarin (INR 2-3) (Table 126). Neither was there evidence that risk of symptomatic VTE differed between licensed doses of NOACs (Table 127).

Figure 80 Network plot for symptomatic VTE (acute treatment of VTE)

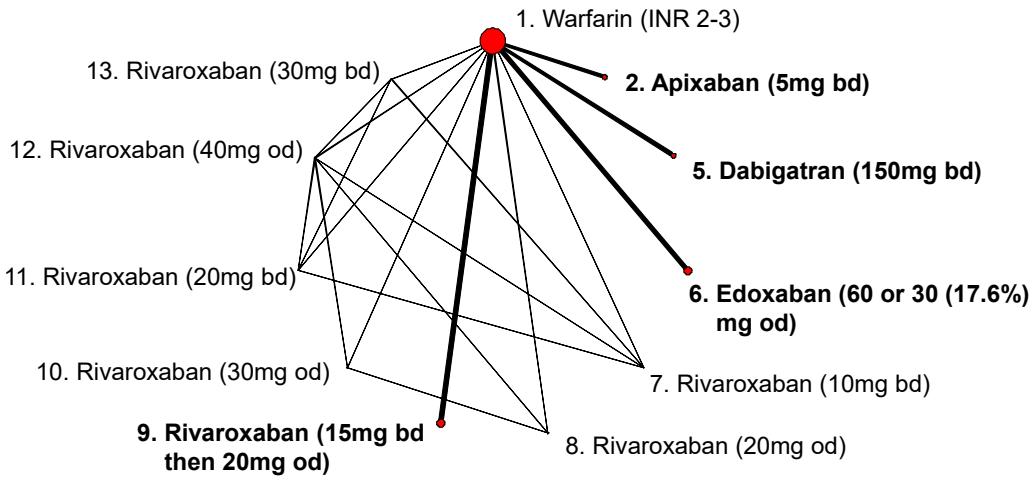


Figure 81 Included trials and risk of bias assessment for symptomatic VTE (acute treatment of VTE)

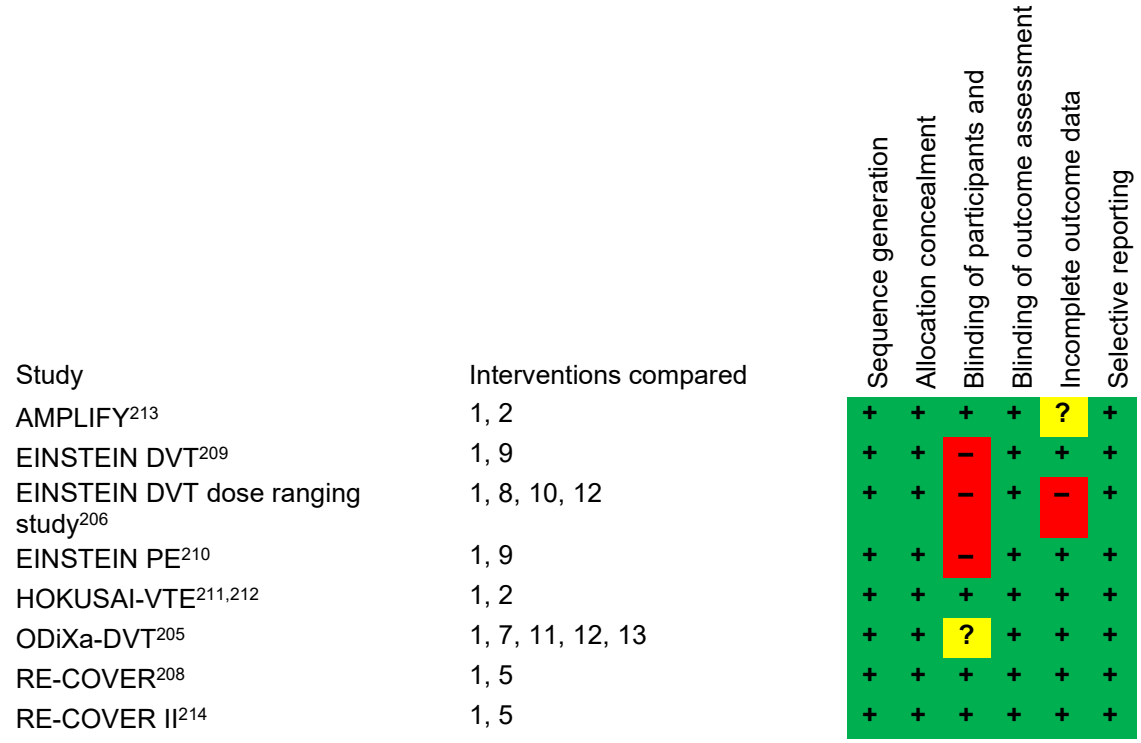


Table 126 Results for symptomatic VTE (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd)	0.83 (0.58 , 1.18)	-	0.83 (0.58 , 1.18)
Dabigatran (150mg bd)	1.09 (0.75 , 1.58)	-	1.09 (0.75 , 1.58)
Edoxaban (60 or 30 (17.6%) mg od)	0.89 (0.70 , 1.13)	-	0.89 (0.70 , 1.13)
Rivaroxaban (15mg bd then 20mg od)	0.90 (0.67 , 1.20)	-	0.90 (0.67 , 1.20)
Imprecisely estimated comparisons			
Rivaroxaban (10mg bd)	*0.77 (0.09 , 4.53)*	-	*0.77 (0.09 , 4.53)*
Rivaroxaban (20mg od)	*0.44 (0.09 , 1.76)*	-	*0.44 (0.09 , 1.76)*
Rivaroxaban (30mg od)	*0.63 (0.15 , 2.29)*	-	*0.63 (0.15 , 2.29)*
Rivaroxaban (20mg bd)	*0.81 (0.09 , 4.81)*	-	*0.81 (0.09 , 4.81)*
Rivaroxaban (40mg od)	*0.52 (0.15 , 1.65)*	-	*0.52 (0.15 , 1.65)*
Rivaroxaban (30mg bd)	*0.73 (0.09 , 4.42)*	-	*0.73 (0.09 , 4.42)*

Table 127 Results for symptomatic VTE (acute treatment of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)		1.31 (0.79 , 2.19)	1.31 (0.79 , 2.19)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	1.06 (0.70 , 1.63)	1.06 (0.70 , 1.63)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	1.08 (0.68 , 1.71)	1.08 (0.68 , 1.71)
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)	-	0.81 (0.52 , 1.27)	0.81 (0.52 , 1.27)
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	0.82 (0.51 , 1.33)	0.82 (0.51 , 1.33)
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	1.01 (0.69 , 1.48)	1.01 (0.69 , 1.48)

8.4.2 Symptomatic deep vein thrombosis

Nine studies reported 351 symptomatic DVT events, leading to a network of 13 interventions (Figure 82). The studies were mostly judged to be at low risk of bias (Figure 83), with some concerns about lack of blinding of participants and personnel. There was little evidence that risk of symptomatic DVT differed for any of the NOAC interventions compared with warfarin (INR 2-3) (Table 128). Neither was there evidence that risk of symptomatic VTE differed between licensed doses of NOACs (Table 129).

Figure 82 Network plot for symptomatic DVT (acute treatment of VTE)

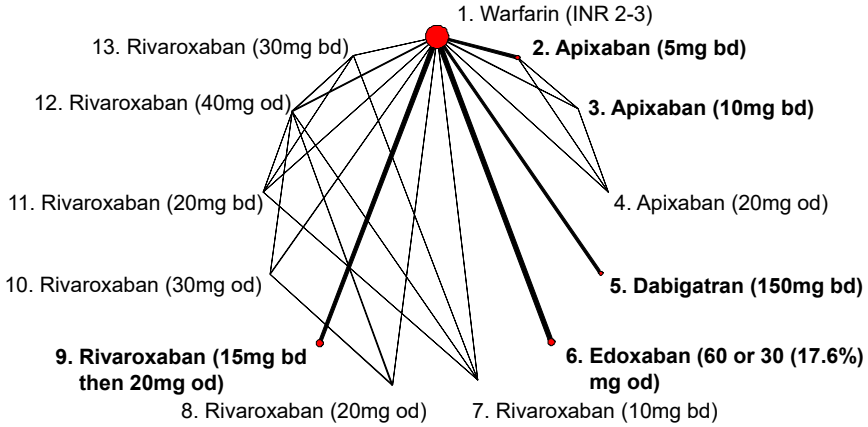


Figure 83 Included trials and risk of bias assessment for symptomatic DVT (acute treatment of VTE)

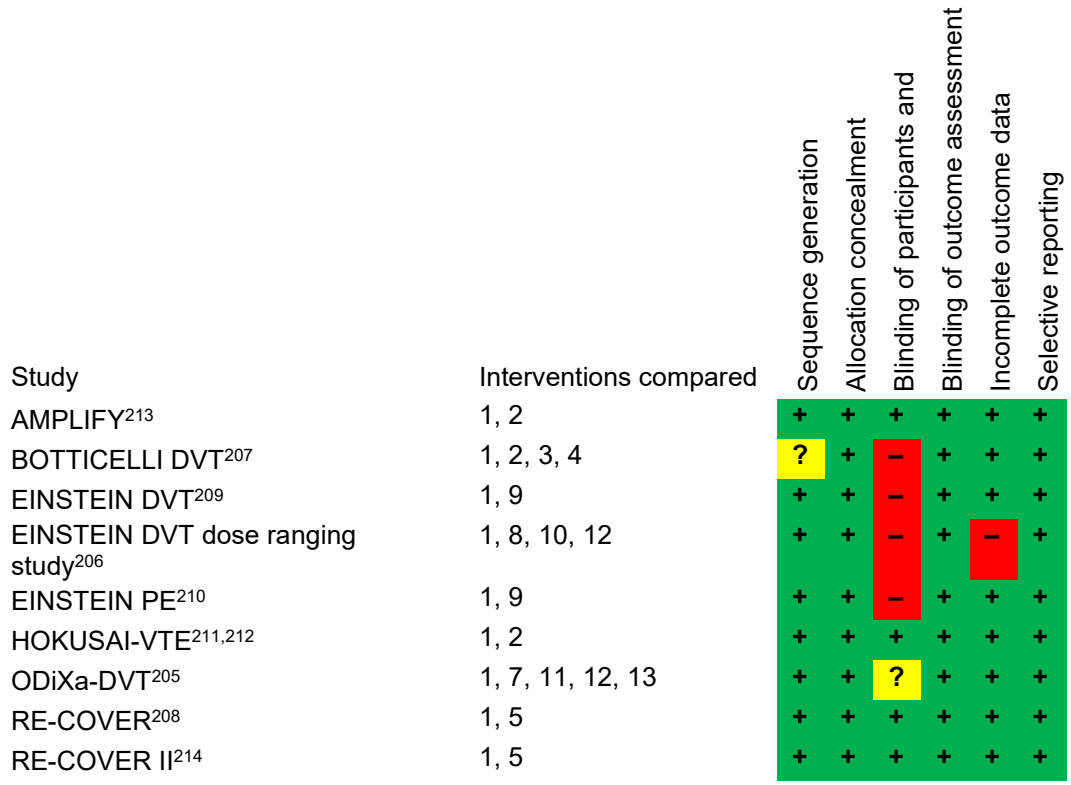


Table 128 Results for symptomatic DVT (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd)	0.66 (0.38 , 1.11)	-	0.66 (0.38 , 1.11)
Dabigatran (150mg bd)	1.18 (0.75 , 1.86)	-	1.18 (0.75 , 1.86)
Edoxaban (60 or 30 (17.6%) mg od)	0.91 (0.63 , 1.30)	-	0.91 (0.63 , 1.30)
Rivaroxaban (15mg bd then 20mg od)	0.70 (0.44 , 1.10)	-	0.70 (0.44 , 1.10)
Imprecisely estimated comparisons			
Apixaban (10mg bd)	*1.27 (0.29 , 5.11)*	-	*1.27 (0.29 , 5.11)*
Apixaban (20mg od)	*0.25 (0.01 , 1.87)*	-	*0.25 (0.01 , 1.87)*
Rivaroxaban (10mg bd)	*0.56 (0.02 , 7.51)*	-	*0.56 (0.02 , 7.51)*
Rivaroxaban (20mg od)	*0.28 (0.03 , 1.33)*	-	*0.28 (0.03 , 1.33)*
Rivaroxaban (30mg od)	*0.12 (0 , 0.86)*	-	*0.12 (0 , 0.86)*
Rivaroxaban (20mg bd)	*0.59 (0.02 , 8.08)*	-	*0.59 (0.02 , 8.08)*
Rivaroxaban (40mg od)	*0.21 (0.03 , 0.94)*	-	*0.21 (0.03 , 0.94)*
Rivaroxaban (30mg bd)	*0.53 (0.02 , 7.27)*	-	*0.53 (0.02 , 7.27)*

Table 129 Results for symptomatic DVT (acute treatment of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	1.80 (0.90 , 3.64)	1.80 (0.90 , 3.64)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	1.38 (0.73 , 2.65)	1.38 (0.73 , 2.65)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	1.07 (0.53 , 2.18)	1.07 (0.53 , 2.18)
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)	-	0.77 (0.43 , 1.38)	0.77 (0.43 , 1.38)
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	0.60 (0.31 , 1.13)	0.60 (0.31 , 1.13)
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	0.77 (0.43 , 1.39)	0.77 (0.43 , 1.39)
Imprecisely estimated comparisons			
Apixaban (10mg bd) vs Apixaban (5mg bd)	*1.94 (0.44 , 7.95)*	-	*1.94 (0.44 , 7.95)*
Dabigatran (150mg bd) vs Apixaban (10mg bd)	-	*0.93 (0.21 , 4.36)*	*0.93 (0.21 , 4.36)*
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (10mg bd)	-	*0.71 (0.17 , 3.27)*	*0.71 (0.17 , 3.27)*
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (10mg bd)	-	*0.55 (0.13 , 2.60)*	*0.55 (0.13 , 2.60)*

8.4.3 Symptomatic pulmonary embolism

One study reported direct data on symptomatic PE events (Table 124) while for the remaining eight studies, we derived symptomatic PE events by adding fatal PE and symptomatic non-fatal PE events leading to a total of 300 symptomatic PE events across network, which is displayed in Figure 84. The studies were mostly judged to be at low risk of bias (Figure 85), with some concerns about lack of blinding of participants and personnel. There was little evidence that risk of symptomatic PE differed for any of the NOAC interventions compared with warfarin (INR 2-3) (Table 130). Neither was there evidence that risk of symptomatic PE differed between licensed doses of NOACs (Table 131).

Figure 84 Network plot for symptomatic PE (acute treatment of VTE)

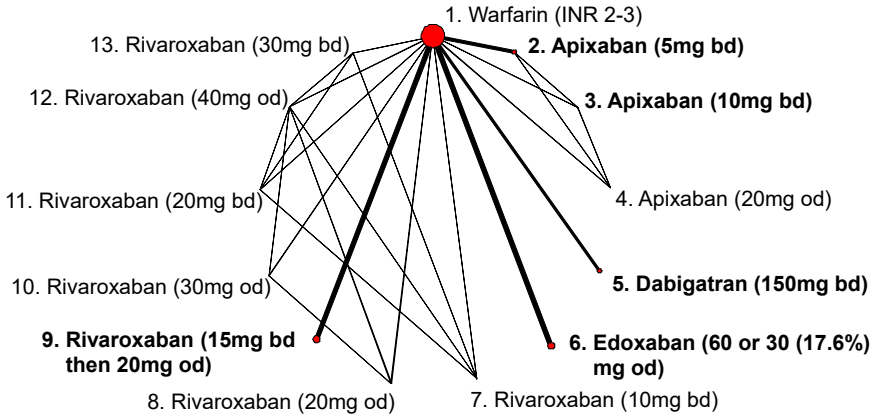


Figure 85 Included trials and risk of bias assessment for symptomatic PE (acute treatment of VTE)

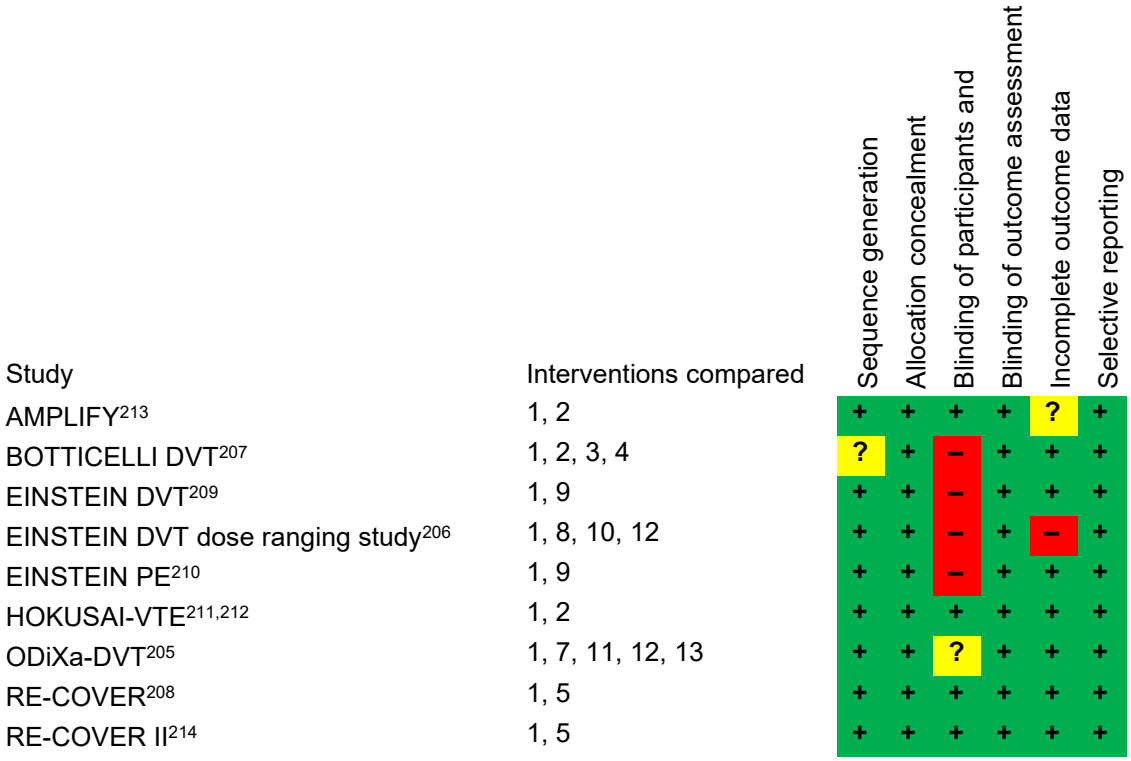


Table 130 Results for symptomatic PE (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd)	1.09 (0.64 , 1.87)	-	1.09 (0.64 , 1.87)
Dabigatran (150mg bd)	1.00 (0.53 , 1.89)	-	1.00 (0.53 , 1.89)
Edoxaban (60 or 30 (17.6%) mg od)	0.85 (0.59 , 1.23)	-	0.85 (0.59 , 1.23)
Rivaroxaban (15mg bd then 20mg od)	1.18 (0.77 , 1.83)	-	1.18 (0.77 , 1.83)
Imprecisely estimated comparisons			
Apixaban (10mg bd)	*0.28 (0 , 6.40)*	-	*0.28 (0 , 6.40)*
Apixaban (20mg od)	*0.29 (0 , 6.53)*	-	*0.29 (0 , 6.53)*
Rivaroxaban (10mg bd)	*0.73 (0.02 , 11.6)*	-	*0.73 (0.02 , 11.6)*
Rivaroxaban (20mg od)	*1.10 (0.07 , 14.9)*	-	*1.10 (0.07 , 14.9)*
Rivaroxaban (30mg od)	*1.12 (0.07 , 15.6)*	-	*1.12 (0.07 , 15.6)*
Rivaroxaban (20mg bd)	*0.78 (0.02 , 12.2)*	-	*0.78 (0.02 , 12.2)*
Rivaroxaban (40mg od)	*0.49 (0.04 , 4.19)*	-	*0.49 (0.04 , 4.19)*
Rivaroxaban (30mg bd)	*0.69 (0.02 , 11.3)*	-	*0.69 (0.02 , 11.3)*

Table 131 Results for symptomatic PE (acute treatment of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	0.92 (0.40 , 2.09)	0.92 (0.40 , 2.09)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	0.78 (0.41 , 1.49)	0.78 (0.41 , 1.49)
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)		0.85 (0.41 , 1.77)	0.85 (0.41 , 1.77)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	1.09 (0.54 , 2.16)	1.09 (0.54 , 2.16)
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	1.18 (0.55 , 2.54)	1.18 (0.55 , 2.54)
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	1.39 (0.79 , 2.46)	1.39 (0.79 , 2.46)
Imprecisely estimated comparisons			
Apixaban (10mg bd) vs Apixaban (5mg bd)	*0.25 (0 , 5.86)*	-	*0.25 (0 , 5.86)*
Dabigatran (150mg bd) vs Apixaban (10mg bd)	-	*3.66 (0.15 , 1860)*	*3.66 (0.15 , 1860)*
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (10mg bd)	-	*3.10 (0.13 , 1530)*	*3.10 (0.13 , 1530)*
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (10mg bd)	-	*4.32 (0.18 , 2160)*	*4.32 (0.18 , 2160)*

8.4.4 Myocardial infarction

Five studies reported 57 myocardial infarction events, leading to a network of five interventions (Figure 86). These studies were judged to be at low risk of bias (Figure 87). All comparisons were imprecisely estimated (Table 132 and Table 133).

Figure 86 Network plot for myocardial infarction (acute treatment of VTE)

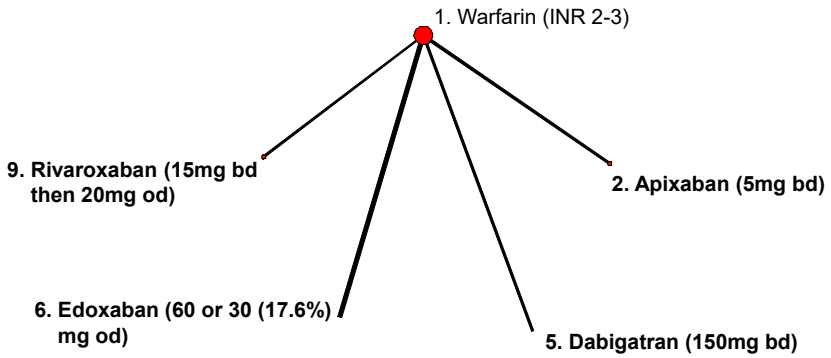


Figure 87 Included trials and risk of bias assessment for myocardial infarction (acute treatment of VTE)

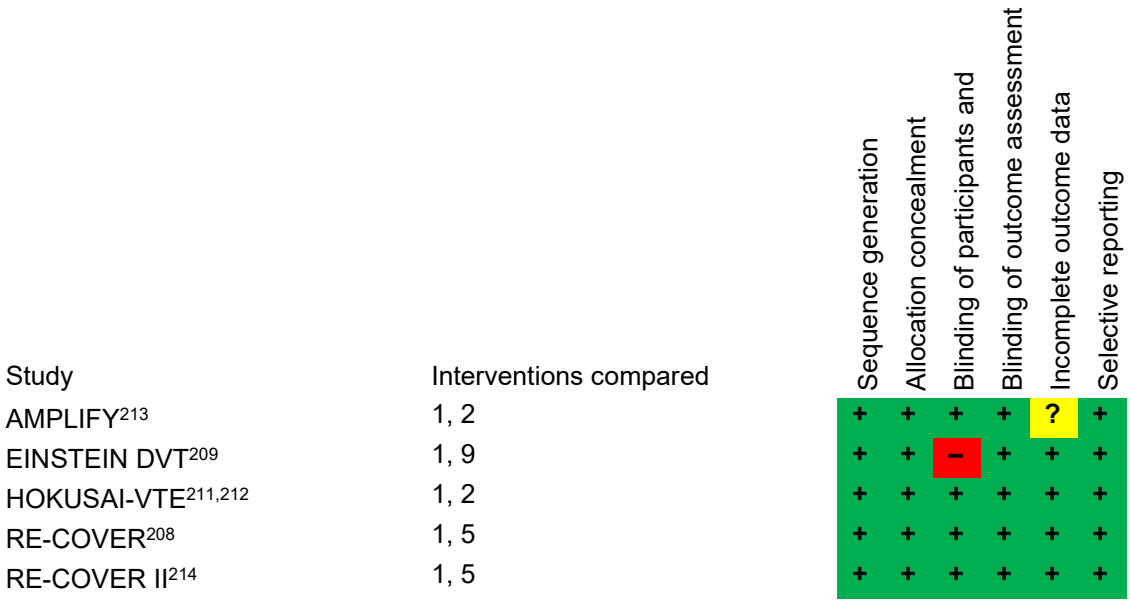


Table 132 Results for myocardial infarction (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Edoxaban (60 or 30 (17.6%) mg od)	1.56 (0.78 , 3.24)	-	1.56 (0.78 , 3.24)
Imprecisely estimated comparisons			
Apixaban (5mg bd)	*2.18 (0.40 , 17.9)*	-	*2.18 (0.40 , 17.9)*
Dabigatran (150mg bd)	*2.11 (0.64 , 8.12)*	-	*2.11 (0.64 , 8.12)*
Rivaroxaban (15mg bd then 20mg od)	*6.81 (0.90 , 219)*	-	*6.81 (0.90 , 219)*

Table 133 Results for myocardial infarction (acute treatment of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*0.96 (0.09 , 8.47)*	*0.96 (0.09 , 8.47)*
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	*0.71 (0.08 , 4.49)*	*0.71 (0.08 , 4.49)*
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	*3.17 (0.17 , 145)*	*3.17 (0.17 , 145)*
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)	-	*0.74 (0.16 , 3.03)*	*0.74 (0.16 , 3.03)*
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	*3.27 (0.29 , 124)*	*3.27 (0.29 , 124)*
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	*4.44 (0.50 , 143)*	*4.44 (0.50 , 143)*

8.4.5 Major bleeding

The nine trials reported 228 major bleeding events, leading to a network of 13 interventions (Figure 88). These studies were judged to be at low risk of bias (Figure 89). There was strong evidence that apixaban (5 mg bd) and rivaroxaban (15mg bd then 20mg od) reduce risk of major bleeding compared with warfarin (INR 2-3) (Table 134). There was evidence that risk of major bleeding was higher for edoxaban (60 or 30 (17.6%) mg od) and dabigatran (150mg bd) compared with apixaban (5mg bd) (Table 135).

Figure 88 Network plot for major bleeding (acute treatment of VTE)

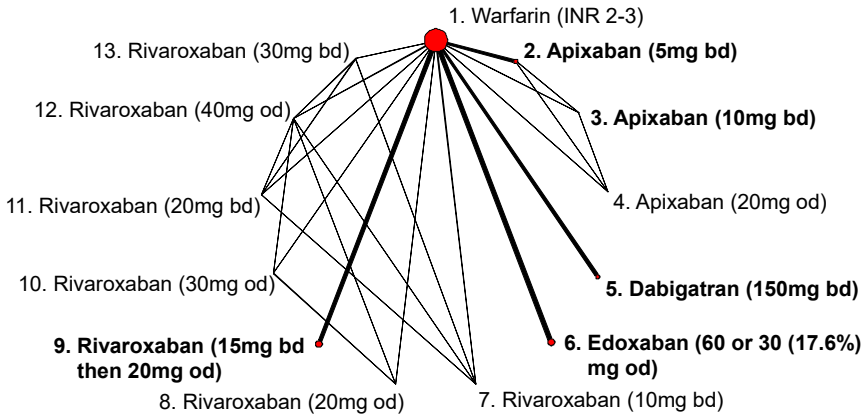


Figure 89 Included trials and risk of bias assessment for major bleeding (acute treatment of VTE)

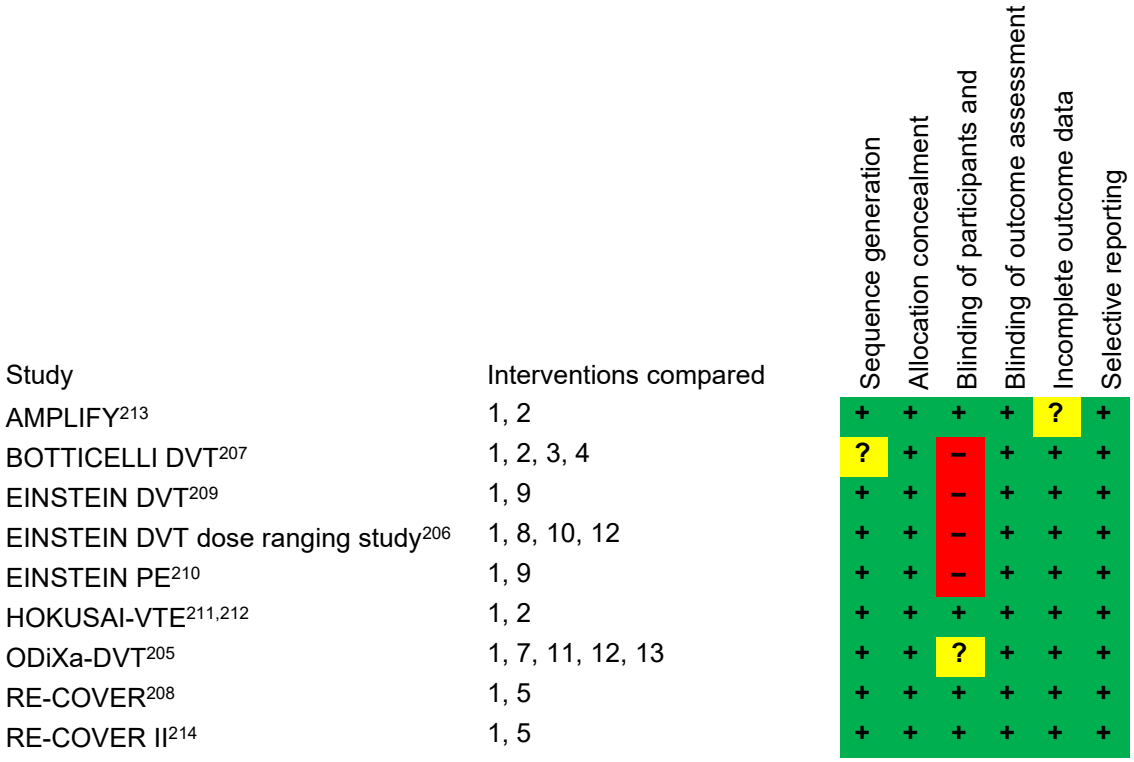


Table 134 Results for major bleeding (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd)	0.33 (0.18 , 0.56)	-	0.33 (0.18 , 0.56)
Dabigatran (150mg bd)	0.76 (0.48 , 1.18)	-	0.76 (0.48 , 1.18)
Edoxaban (60 or 30 (17.6%) mg od)	0.85 (0.59 , 1.22)	-	0.85 (0.59 , 1.22)
Rivaroxaban (15mg bd then 20mg od)	0.55 (0.37 , 0.80)	-	0.55 (0.37 , 0.80)
Imprecisely estimated comparisons			
Apixaban (10mg bd)	*0.18 (0 , 3.84)*	-	*0.18 (0 , 3.84)*
Apixaban (20mg od)	*1.79 (0.23 , 15.8)*	-	*1.79 (0.23 , 15.8)*
Rivaroxaban (10mg bd)	*1.86 (0.23 , 16)*	-	*1.86 (0.23 , 16)*
Rivaroxaban (20mg od)	*0.97 (0.07 , 9.40)*	-	*0.97 (0.07 , 9.40)*
Rivaroxaban (30mg od)	*1.81 (0.24 , 14.8)*	-	*1.81 (0.24 , 14.8)*
Rivaroxaban (20mg bd)	*1.90 (0.24 , 15.4)*	-	*1.90 (0.24 , 15.4)*
Rivaroxaban (40mg od)	*1.03 (0.18 , 6.02)*	-	*1.03 (0.18 , 6.02)*
Rivaroxaban (30mg bd)	*3.58 (0.65 , 26.6)*	-	*3.58 (0.65 , 26.6)*

Table 135 Results for major bleeding (acute treatment of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	1.68 (0.85 , 3.40)	1.68 (0.85 , 3.40)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	2.60 (1.35 , 5.21)	2.60 (1.35 , 5.21)
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)	-	1.12 (0.63 , 1.98)	1.12 (0.63 , 1.98)
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	0.72 (0.40 , 1.30)	0.72 (0.40 , 1.30)
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	0.64 (0.38 , 1.10)	0.64 (0.38 , 1.10)
Imprecisely estimated comparisons			
Apixaban (10mg bd) vs Apixaban (5mg bd)	*0.54 (0 , 12.1)*	-	*0.54 (0 , 12.1)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*2.32 (1.15 , 4.86)*	*2.32 (1.15 , 4.86)*
Dabigatran (150mg bd) vs Apixaban (10mg bd)	-	*4.31 (0.19 , 2090)*	*4.31 (0.19 , 2090)*
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (10mg bd)	-	*4.84 (0.22 , 2300)*	*4.84 (0.22 , 2300)*
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (10mg bd)	-	*3.12 (0.14 , 1470)*	*3.12 (0.14 , 1470)*

8.4.6 Clinically relevant bleeding

Eight studies reported 2365 clinically relevant bleeding events, leading to a network of 10 interventions (Figure 90). These studies were mostly judged to be at low risk of bias (Figure 91), with some concerns about lack of blinding of participants and personnel. There was evidence that apixaban (5mg bd), dabigatran (150mg bd) and edoxaban (60 or 30 (17.6%) mg od) reduce risk of clinically relevant bleeding compared with warfarin (INR 2-3) (Table 136). There was some evidence that rivaroxaban (15mg bd then 20mg od) reduces risk of clinically relevant bleeding compared with warfarin (INR 2-3). There was evidence that risk of clinically relevant bleeding is higher with dabigatran (150mg bd), edoxaban (60 or 30 (17.6%) mg od) and rivaroxaban (15mg bd then 20mg od) compared with apixaban (5mg bd). (Table 137). There was evidence that risk of clinically relevant bleeding is higher with edoxaban (60 or 30 (17.6%) mg od) and rivaroxaban (15mg bd then 20mg od) compared with dabigatran (150mg bd).

Figure 90 Network plot for clinically relevant bleeding (acute treatment of VTE)

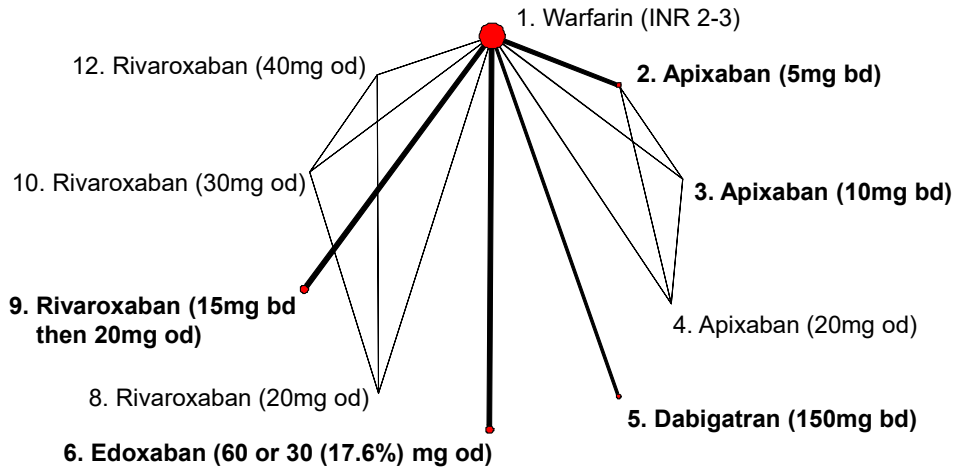


Figure 91 Included trials and risk of bias assessment for clinically relevant bleeding (acute treatment of VTE)

Study	Interventions compared	Sequence generation	Allocation concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AMPLIFY[213]	1, 2	+	+	+	+	?	+
BOTTICELLI DVT[207]	1, 2, 3, 4	?	+	–	+	+	+
EINSTEIN DVT[209]	1, 9	+	+	–	+	+	+
EINSTEIN DVT dose ranging study[206]	1, 8, 10, 12	+	+	–	+	+	+
EINSTEIN PE[210]	1, 9	+	+	–	+	+	+
HOKUSAI-VTE[211,212]	1, 2	+	+	+	+	+	+
RE-COVER[208]	1, 5	+	+	+	+	+	+
RE-COVER II[214]	1, 5	+	+	+	+	+	+

Table 136 Results for clinically relevant bleeding (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd)	0.44 (0.35 , 0.55)	-	0.44 (0.35 , 0.55)
Apixaban (10mg bd)	0.36 (0.12 , 0.87)	-	0.36 (0.12 , 0.87)
Apixaban (20mg od)	0.76 (0.34 , 1.61)	-	0.76 (0.34 , 1.61)
Dabigatran (150mg bd)	0.61 (0.49 , 0.76)	-	0.61 (0.49 , 0.76)
Edoxaban (60 or 30 (17.6%) mg od)	0.81 (0.70 , 0.94)	-	0.81 (0.70 , 0.94)
Rivaroxaban (15mg bd then 20mg od)	0.93 (0.80 , 1.08)	-	0.93 (0.80 , 1.08)
Rivaroxaban (20mg od)	0.54 (0.20 , 1.39)	-	0.54 (0.20 , 1.39)
Rivaroxaban (30mg od)	0.56 (0.21 , 1.43)	-	0.56 (0.21 , 1.43)
Imprecisely estimated comparisons			
Rivaroxaban (40mg od)	*0.17 (0.04 , 0.58)*	-	*0.17 (0.04 , 0.58)*

Table 137 Results for clinically relevant bleeding (acute treatment of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (10mg bd) vs Apixaban (5mg bd)	0.81 (0.28 , 2.00)	-	0.81 (0.28 , 2.00)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	1.39 (1.02 , 1.90)	1.39 (1.02 , 1.90)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	1.84 (1.41 , 2.40)	1.84 (1.41 , 2.40)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	2.12 (1.63 , 2.76)	2.12 (1.63 , 2.76)
Dabigatran (150mg bd) vs Apixaban (10mg bd)	-	1.72 (0.68 , 5.02)	1.72 (0.68 , 5.02)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (10mg bd)	-	2.27 (0.91 , 6.56)	2.27 (0.91 , 6.56)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (10mg bd)	-	2.62 (1.05 , 7.55)	2.62 (1.05 , 7.55)
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)	-	1.32 (1.01 , 1.73)	1.32 (1.01 , 1.73)
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	1.52 (1.17 , 1.99)	1.52 (1.17 , 1.99)
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	1.15 (0.93 , 1.42)	1.15 (0.93 , 1.42)

8.4.7 All-cause mortality

Eight studies reported 662 all-cause mortality events, leading to a network of ten interventions (Figure 92). These studies were mostly judged to be at low risk of bias (Figure 93), with some concerns about lack of blinding of participants and personnel. There was little evidence that risk of all cause mortality differed for any of the NOAC interventions compared with warfarin (INR 2-3) (Table 138). Neither was there evidence that risk of all cause mortality differed between licensed doses of NOACs (Table 139).

Figure 92 Network plot for all-cause mortality (acute treatment of VTE)

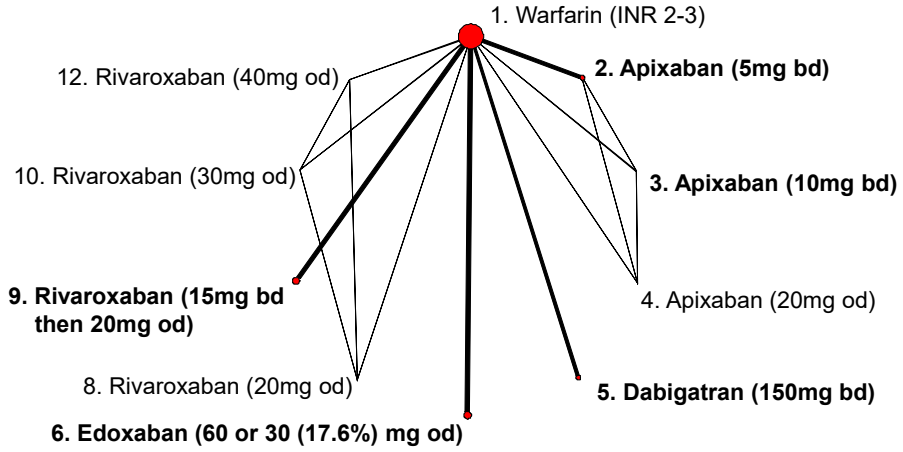


Figure 93 Included trials and risk of bias assessment for all-cause mortality (acute treatment of VTE)

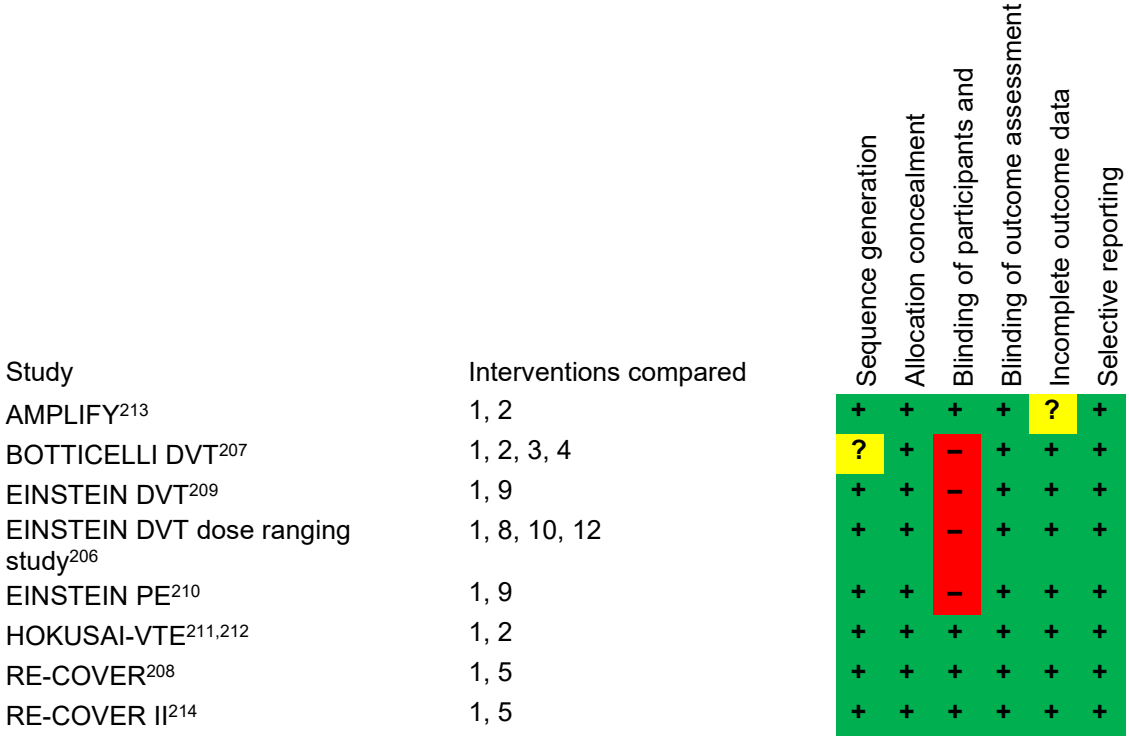


Table 138 Results for all-cause mortality (acute treatment of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd)	0.85 (0.57 , 1.27)	-	0.85 (0.57 , 1.27)
Dabigatran (150mg bd)	1.00 (0.66 , 1.52)	-	1.00 (0.66 , 1.52)
Edoxaban (60 or 30 (17.6%) mg od)	1.05 (0.82 , 1.35)	-	1.05 (0.82 , 1.35)
Rivaroxaban (15mg bd then 20mg od)	0.96 (0.73 , 1.29)	-	0.96 (0.73 , 1.29)
Imprecisely estimated comparisons			
Apixaban (10mg bd)	*0.58 (0.05 , 3.74)*	-	*0.58 (0.05 , 3.74)*
Apixaban (20mg od)	*0.61 (0.05 , 3.87)*	-	*0.61 (0.05 , 3.87)*
Rivaroxaban (20mg od)	*0.80 (0.18 , 3.16)*	-	*0.80 (0.18 , 3.16)*
Rivaroxaban (30mg od)	*1.73 (0.55 , 5.88)*	-	*1.73 (0.55 , 5.88)*
Rivaroxaban (40mg od)	*0.35 (0.04 , 1.82)*	-	*0.35 (0.04 , 1.82)*

Table 139 Results for all-cause mortality (acute treatment of VTE): NOACs (licensed doses only)

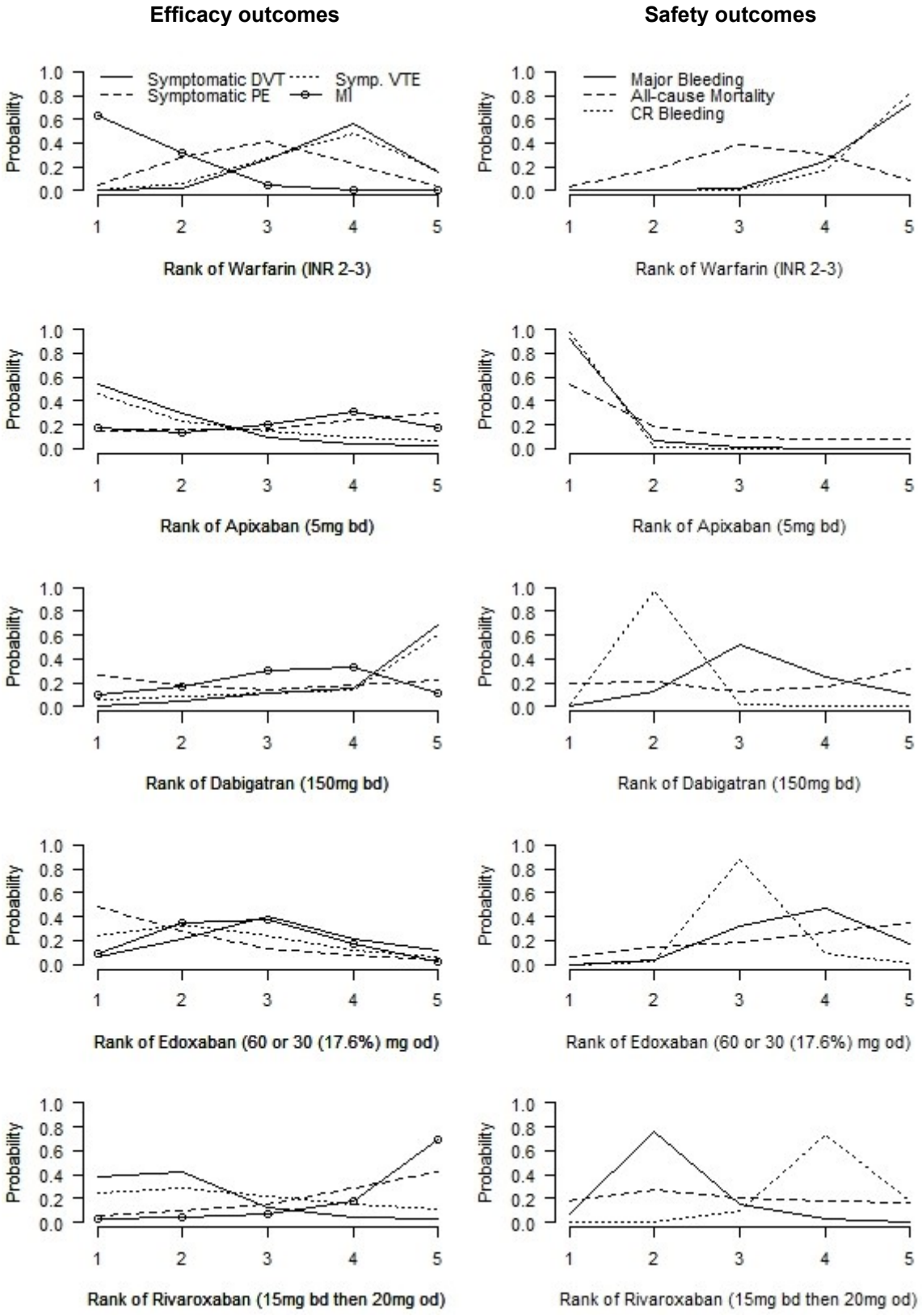
Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	1.18 (0.66 , 2.12)	1.18 (0.66 , 2.12)
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (5mg bd)	-	1.24 (0.77 , 1.99)	1.24 (0.77 , 1.99)
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (5mg bd)	-	1.14 (0.70 , 1.87)	1.14 (0.70 , 1.87)
Edoxaban (60 or 30 (17.6%) mg od) vs Dabigatran (150mg bd)	-	1.05 (0.65 , 1.70)	1.05 (0.65 , 1.70)
Rivaroxaban (15mg bd then 20mg od) vs Dabigatran (150mg bd)	-	0.97 (0.58 , 1.59)	0.97 (0.58 , 1.59)
Rivaroxaban (15mg bd then 20mg od) vs Edoxaban (60 or 30 (17.6%) mg od)	-	0.92 (0.63 , 1.34)	0.92 (0.63 , 1.34)
Imprecisely estimated comparisons			
Apixaban (10mg bd) vs Apixaban (5mg bd)	*0.68 (0.05 , 4.47)*	-	*0.68 (0.05 , 4.47)*
Dabigatran (150mg bd) vs Apixaban (10mg bd)	-	*1.73 (0.25 , 22.6)*	*1.73 (0.25 , 22.6)*
Edoxaban (60 or 30 (17.6%) mg od) vs Apixaban (10mg bd)	-	*1.82 (0.27 , 23.2)*	*1.82 (0.27 , 23.2)*
Rivaroxaban (15mg bd then 20mg od) vs Apixaban (10mg bd)	-	*1.67 (0.25 , 21.4)*	*1.67 (0.25 , 21.4)*

8.4.8 Summary of results and ranking of interventions

There was little evidence that risk of symptomatic VTE, symptomatic DVT or symptomatic PE differed for any of the NOAC interventions compared with warfarin (INR 2-3). Neither was there evidence that risk of these outcomes differed between licensed doses of NOACs. However there was evidence of substantial reductions in risk of both major bleeding and clinically relevant bleeding for apixaban (5 mg bd) compared with warfarin (INR 2-3). There was also evidence that other NOACs reduced bleeding compared with warfarin (INR 2-3). In comparisons between licensed doses of NOACs, there was evidence that apixaban (5 mg bd) reduced major bleeding risk compared with some other NOACs. With regards to model appraisal, we did not identify any instance of lack of convergence among the Markov chains, poor model fit or inconsistency.

Figure 94 presents the rankogram for all licensed interventions and all seven outcomes examined in this review. There was a high probability that warfarin (INR 2-3) is ranked worst for major bleeding and clinically relevant bleeding. There was a high probability that apixaban 5mg bd is ranked best for major bleeding and clinically relevant bleeding, and this intervention also had a high probability of being ranked best or second best for symptomatic DVT, symptomatic VTE and all-cause mortality.

Figure 94 Rankogram for licensed interventions examined in acute treatment of VTE



CR: clinically relevant

9. Clinical results (4): Secondary prevention of venous thromboembolism

9.1 Included studies

Ten completed randomised controlled trials with eleven references[223,230-239], one ongoing trial[240] and one trial reported in insufficient detail to include in the quantitative synthesis[241] met the eligibility criteria for the review (Figure 58). A summary of the characteristics of the ten studies included in the analyses is presented in Table 140. All were multicentre and many were conducted across countries in North and South America, Europe, Asia, and Australia, New Zealand, South Africa, Russia and Israel. All were phase III trials. A total of 10,390 patients were included: the number of patients randomised ranged from 162 to 2,866. Four studies, with a randomised total of 7,902 patients, examined a NOAC (against placebo in three studies and against warfarin in one study). Four studies, with a randomised total of 1,263 patients, examined warfarin (against placebo in two studies and against no treatment in two studies). Two studies, with a randomised total of 1,225 patients, examined aspirin against placebo.

Eligibility criteria were similar across the studies, all patients having already been treated for first ever objectively confirmed symptomatic DVT and/or PE. The mean age of patients was similar across studies that compared NOACs, ranging from 54.7 to 58 years. The mean age of patients across all the ten included studies ranged from 53 to 67.3 years. The percentage of male patients was similar across studies that compared NOACs, ranging from 55.5% to 61% although this information was not reported in one of the studies. The percentage of males across the ten studies ranged from 52.8% to 63.9%. Mean body mass index was reported in only three studies[233,236,238] and ranged from 27.1 to 29.9 kg/m^2 across study arms. Mean body weight ranged from 83.7kg to 86.1kg across study arms where data were reported. The proportion of patients with comorbidities was not well reported. Three studies[233,239] reported the proportion of patients who were diabetic, which ranged from 6.7% to 10.5%. Two studies reported proportions with hypertension and cancer[238,239], which ranged from 36.3% to 41.3% and 1% to 4% respectively. Half of the studies that reported each comorbidity examined a NOAC.

Two studies examined dabigatran 150mg twice daily: against standard intensity warfarin (INR 2-3) in one study and against placebo in the other. One study examined each of apixaban 2.5mg and 5mg twice daily, and rivaroxaban 20mg once daily, against placebo in both studies. Two studies examined aspirin 100mg once daily against placebo. Four studies examined warfarin; against placebo in two studies, and against no treatment in two studies. Three of these four studies examined standard intensity warfarin and one study examined low intensity warfarin (INR 1.5-2). Mean time in therapeutic range for standard intensity warfarin arms was reported in only one study[232] and was 83%.

The duration of treatment varied across studies, ranging from six to 36 months in the NOAC studies, 24 to 48 months in the aspirin studies, and three to 51.6 months in the warfarin studies. Efficacy and safety outcomes reported across studies were similar irrespective of the intervention examined, and were reported at the end of the treatment periods. All ten studies reported data on symptomatic VTE and major bleeding. Nine studies each reported data on symptomatic DVT, symptomatic PE, and all-cause mortality. Six studies reported data on clinically relevant bleeding, and five studies reported data on myocardial infarction. Only the four NOACs studies were sponsored by a pharmaceutical company. Four other studies were conducted with funding from more than one source: mainly medical research councils or institutes. In all sponsored studies, the sponsors were responsible for study design and data collection, and in the majority of cases data analysis (particularly the pharmaceutical company funded studies). Funding source was not declared in two studies.

Table 140 Characteristics of ten included randomised trials in secondary prevention of VTE

Study (Centre type) [Countries]	Sponsor (sponsor's role)	Age eligibility (Mean age) [% Male]	Clinical condition	No. rand.	Interventions compared	Tmt duration (months)	Outcomes	Time of outcome assessment (months)
AMPLIFY-EXT[238] (Multicentre) [North and South America, Europe, Russia, Israel, Australia, Asia, South Africa]	Pfizer and Bristol-Myers Squibb ("The sponsors collected and maintained the data; the academic authors had access to the data at all times, through the sponsors")	≥18 yrs. (56.7 yrs.) [57.4%]	Already treated for a first-ever objectively confirmed, symptomatic DVT or PE (with or without DVT)	2486	**Apixaban** 1. 2.5mg bd 2. 5mg bd 3. **Placebo** bd	12	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE, fatal PE Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, MI, death (cardiovascular), death (all causes)	12
ASPIRE[237] (Multicentre) [Argentina, Australia, New Zealand, Asia]	National Health and Medical Research Council Australia and others (not specified) ("The funder was responsible for the collection, maintenance, integrity, and confidentiality of all data")	≥18 yrs. (54.5 yrs.) [54.4%]	Already treated for a first-ever unprovoked episode of objectively diagnosed symptomatic DVT or an acute PE.	822	**Aspirin** 1. 100mg od 2. **Placebo** od	Up to 48	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic distal DVT, symptomatic proximal DVT, symptomatic PE, fatal PE Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, MI, all stroke, death (cardiovascular), death (all causes)	37.2 (median)

EINSTEIN-EXTENSION[223,234,235] (Multicentre) [North and South America, Europe, Israel, Australia, New Zealand, Asia, South Africa]	Bayer Healthcare ("The data were collected and maintained by the sponsor")	≥18 yrs. (58 yrs.) [NR]	Already treated for mixed (first-ever and ≥1 previous VTE) confirmed symptomatic PE or DVT	1197	**Rivaroxaban** 1. 20mg od 2. **Placebo** od	6-12	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE, fatal PE Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, fatal bleeding, death (all causes)	6.2 (mean)
LAFIT[230] (Multicentre) [Canada & USA]	Supported by a grant from Dupont Pharma, Wilmington, Del., and by the Medical Research Council of Canada, the Heart and Stroke Foundation of Canada and the Ministry of Health of Ontario (Not declared)	Adults (59 yrs.) [60%]	Already treated for a first-ever episode of idiopathic VTE	162	**Warfarin** 1. INR 2-3 (Mean ttr: 64%) 2. **Placebo** od	24	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE, fatal PE Safety: All bleeding, major bleeding, minor bleeding, death (all causes)	24

PREVENT[233] (Multicentre) [USA]	National Heart, Lung, and Blood Institute USA (Note: Study drug and placebo were supplied without fee by Bristol-Myers Squibb) ("The funder appointed an independent data and safety monitoring committee that monitored the primary end point of recurrent venous thromboembolism")	≥30 yrs. (Median-53 yrs.) [52.8%]	Already treated for idiopathic VTE. VTE episode is not clearly reported but texts suggest this may be a first-ever event	508	**Warfarin** 1. INR 1.5-2 (Mean ttr: NR) 2. **Placebo** od	51.6 (mean 25.2)	Efficacy: Symptomatic VTE, fatal PE Safety: Major bleeding, minor bleeding, MI, death (all causes)	51.6 (mean 25.2)
RE-MEDY[239] (Multicentre) [North and South America, Europe, Russia, Israel, Australia, New Zealand, Asia, New Zealand, South Africa]	Boehringer Ingelheim ("Study was designed, conducted, and data analysed by the funder in conjunction with the steering committee")	≥18 yrs. (54.7 yrs.) [61%]	Already treated for mixed (first-ever and ≥1 previous) objectively confirmed, symptomatic, proximal DVT or PE	2866	**Dabigatran** 1. 150mg bd **Warfarin** 2. INR 2-3 (Median ttr: 65.3%)	6-36	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE Safety: All bleeding, major bleeding, composite clinically relevant bleeding, intracranial bleeding, MI, death (all causes)	36

RE-SONATE[239] (Multicentre) [North America, Europe, Russia, Australia, New Zealand, Asia, & South Africa]	Boehringer Ingelheim ("Study was designed, conducted, and data analysed by the funder in conjunction with the steering committee")	≥18 yrs. (55.8 yrs.) [55.5%]	Already treated for mixed (first-ever and ≥1 previous) objectively confirmed, symptomatic, proximal DVT or PE. A small proportion (<1%) had ≥1 previous	1353	**Dabigatran** 1. 150mg bd 2. **Placebo** bd	6	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE Safety: All bleeding, major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, MI	6
WARFASA[236] (Multicentre) [Austria & Italy]	University of Perugia, Italy and others (not specified) ("Data were collected, maintained, and analysed by the Clinical Research Unit of the University of Perugia")	≥18 yrs. (62 yrs.) [63.9%]	Already treated for a first-ever, objectively confirmed, symptomatic, unprovoked, proximal DVT, PE, or both	403	**Aspirin** 1. 100mg od 2. **Placebo** od	24	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic PE, fatal PE, arterial event Safety: Major bleeding, clinically relevant non-major bleeding, composite clinically relevant bleeding, death (all causes)	24
WODIT-DVT[231] (Multicentre) [Italy]	Not declared	15-85 yrs. (67.3 yrs.) [57.9%]	Already treated for a first-ever episode of symptomatic objectively confirmed idiopathic proximal DVT	267	**Warfarin** 1. INR 2-3 (Mean ttr: 81%) 2. **No treatment**	9	Efficacy: Symptomatic VTE, symptomatic DVT, symptomatic non-fatal PE, fatal PE Safety: Major bleeding, fatal bleeding, death (cardiovascular), death (all causes)	33

WODIT-PE[232] (Multicentre) [Italy]	Not declared	15-85 yrs. (62 yrs.) [59.5%]	Already treated for a first-ever episode of symptomatic, objectively confirmed PE	326	**Warfarin** 1. INR 2-3 (Mean ttr: NR) 2. **No treatment**	3	Efficacy: Symptomatic VTE, symptomatic PE, symptomatic non-fatal PE, symptomatic DVT, fatal PE Safety: All bleeding, major bleeding, fatal bleeding, death (cardiovascular), death (all causes)	3

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; MI = myocardial infarction; INR = international normalized ratio; rand = randomised; od = once daily; bd = twice daily; Tmt = treatment; ttr = time in therapeutic range; NR = Not reported

9.2 Time in therapeutic range for warfarin interventions

Table 141 shows the comparator interventions, target INR and (where reported) mean time in therapeutic range for the five studies that included a warfarin intervention arm. Three (60%) of these studies reported mean time in therapeutic range, which was 64%in LAFIT, 65.3% in RE-MEDY and 81% in WODIT-DVT.

Table 141 Mean time in therapeutic range for warfarin in secondary prevention of VTE

Study	Interventions that were compared with warfarin	Warfarin INR	Mean time in therapeutic range (INR)
LAFIT[230]	Placebo od, warfarin	2-3	64%
PREVENT[233]	Placebo od	1.5-2	NR
RE-MEDY[239]	Dabigatran 150mg bd	2-3	65.3% (median)
WODIT-DVT[231]	No treatment	2-3	81%
WODIT-PE[232]	No treatment	2-3	NR

VTE = venous thromboembolism; INR = international normalized ratio; NR = not reported, od = once daily; bd = twice daily

9.3 Risk of bias in included studies

Table 142 shows detailed risk of bias assessments for each included study for each domain of the Cochrane assessment tool. Generally, the studies were judged to be at low risk of bias for sequence generation, blinding of outcome assessment and incomplete outcome data. However one study did not describe how the randomisation sequence was generated. Eight studies described how treatment allocation was concealed: these studies were judged to be at low risk of bias for this domain. One study provided insufficient information to enable a judgement on allocation concealment and one study provided no information on this domain: these studies were judged to be at unclear and high risk of bias respectively. Overall, the risk of bias due to selective reporting was judged to be low. Three studies were open-label and so were judged to be at a high risk of bias for blinding of participants and personnel.

Table 142 Risk of bias assessments for ten included randomised trials in secondary prevention of VTE

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AMPLIFY-EXT[238]	L-"Randomization was performed with the use of an interactive voice-response system and was stratified according to the initial diagnosis (deep-vein thrombosis or pulmonary embolism) and participation or no participation in the AMPLIFY trial"	L-"Randomization was performed with the use of an interactive voice-response system AMPLIFY trial"	U-"We conducted a randomized, double-blind study". "Patients were assigned, in a 1:1:1 ratio, to receive 2.5 mg of apixaban, 5 mg of apixaban, or placebo, all given twice daily".	L-"An independent committee, whose members were unaware of the study-group assignments, adjudicated the qualifying initial diagnosis (deep-vein thrombosis or pulmonary embolism) and all suspected outcomes"	L-All patients were included in the analyses	L-All outcomes reported as per study protocol
ASPIRE[237]	L-"Randomization was performed through a central Web-based randomization system, with stratification according to centre and duration of initial oral anticoagulation therapy (≤26 weeks or >26 weeks)"	L-"Randomization was performed through a central web-based randomization system"	L-"Enteric-coated aspirin, in L00-mg tablets, and matching placebo were provided without charge by Bayer Health-Care Pharmaceuticals"	L-"All primary and secondary events were adjudicated by an independent event adjudication committee whose members were unaware of the group assignments"	L-Very few missing outcome data but these almost balance out across intervention groups, with similar reasons for missing data. However, analysis was by intension to treat	L-All outcomes reported as per study protocol

EINSTEIN-EXTENSION[234,235]	L-"This was a randomized, double-blind, placebo-controlled superiority study in which patients who completed the first 6–12 months of oral anticoagulant treatment with VKA or with rivaroxaban (if previously enrolled in the EINSTEIN-DVT or EINSTEIN-PE studies)". Since this study is related to EINSTEIN DVT and PE studies where randomisation was by use of computerised voice-response system, it is assumed that randomisation was done.	L-Since this study is related to EINSTEIN DVT and PE studies, it is assumed that there was central allocation of treatment	H-Since this study is related to EINSTEIN DVT and PE studies, both of open-label type, it is assumed that participants and personnel may not have been blinded	L-"All suspected outcome events were classified by a central adjudication committee whose members were unaware of the treatment assignments"	L-For all outcomes (except bleeding outcomes): No missing outcome data-analysis was by intention to treat L-For bleeding outcomes: Very minimal missing data - unlikely to influence outcome	L-All outcomes reported as per study protocol
LAFIT[230]	L-"A computer algorithm, with a randomly determined block size of two or four within each stratum, had previously determined whether the patient received warfarin or placebo"	L-"Patients were provided with consecutively numbered supplies of study drug"	L-"We performed a double-blind, randomized trial. Patients were provided with consecutively numbered supplies of study drug either tablets containing 5 mg of warfarin or identical-appearing placebo"	L-"Information on all suspected outcome events and deaths was reviewed and classified by a central adjudication committee whose members were unaware of the treatment assignments"	L-All patients were included in the analyses	U-Study protocol not found
PREVENT[233]	L-"Randomization was stratified according to clinical site, time since the index event (≤6	L-Randomization to low-intensity warfarin (Coumadin,	L-"To ensure blinding, sham dose adjustments were made in the placebo	L-"All end points were reviewed by a committee of physicians who were unaware of	L-All patients were included in the analyses	L-All outcomes reported as per study protocol

	months or >6 months), and whether or not the index event was the patient's first venous thromboembolism" Randomization to low-intensity warfarin (Coumadin, provided without charge by Bristol-Myers Squibb; target INR, 1.5 to 2.0) or to matching placebo was performed centrally.	provided without charge by Bristol-Myers Squibb; target INR, 1.5 to 2.0) or to matching placebo was performed centrally.	group. These devices were altered electronically to provide a coded INR value that was transmitted in a double-blind fashion to the data coordinating centre"	treatment-group assignments"		
RE-MEDY[239]	L-"Patients underwent randomization by means of an interactive voice-response system. The true or sham INR was then obtained by means of an interactive voice-response system with a central computer that had been programmed with the randomization schedule"	L-"Patients underwent randomization by means of an interactive voice-response system"	L-"A randomized, double-blind design. Patients were assigned in a 1:1 ratio to receive active dabigatran (at a fixed dose of 150 mg twice daily) and a warfarin-like placebo or active warfarin and a dabigatran-like placebo"	L-"Central committees, whose members were not aware of the treatment assignments, adjudicated suspected cases of recurrent venous thromboembolism, bleeding, death, acute coronary events, and liver function abnormalities"	L-All patients were included in the analyses	L-All outcomes reported as per study protocol
RE-SONATE[239]	L-"Patients underwent randomization by means of an interactive voice-response system. Randomization was stratified according to the presence or absence of active cancer" and according	L-"Patients underwent randomization by means of an interactive voice-response system"	U-"A randomized, double-blind design" "patients were assigned in a 1:1 ratio to receive dabigatran (at a fixed dose of 150 mg twice daily) or a matching Placebo"	L-"Central committees, whose members were not aware of the treatment assignments, adjudicated suspected cases of recurrent venous thromboembolism, bleeding, death, acute	L-All patients were included in the analyses	L-All outcomes reported as per study protocol

	to study centre in the placebo-control study.			coronary, and liver function abnormalities"		
WARFASA[236]	L-"WARFASA was a multicenter, investigator-initiated, randomized, double-blind clinical trial. Eligible patients were randomly assigned to aspirin, 100 mg once daily, or placebo for 2 years, with the option of extending the study treatment. Randomization occurred within 2 weeks after vitamin K antagonists had been withdrawn."	U-Not enough information on whether or not treatment allocation was concealed. "Eligible patients were randomly assigned to aspirin, 100 mg once daily, or placebo for 2 years, with the option of extending the study treatment."	U-"WARFASA was a multicentre, investigator-initiated, randomized, double-blind clinical trial"	L-"All suspected study outcome events were assessed by a central, independent adjudication committee whose members were unaware of the group assignments and who reviewed the imaging results"	L-All patients were included in the analyses	L-All outcomes reported as per study protocol
WODIT-DVT[231]	U-"The Warfarin Optimal Duration Italian Trial was a randomized, multicentre, open trial"	H-No information on allocation concealment	H-"The Warfarin Optimal Duration Italian Trial was a randomized, multicentre, open trial"	L-"All suspected outcome events and all deaths were reviewed centrally, for both the interim and final analyses, by an independent, external adjudication committee whose members were unaware of the treatment group assignments"	L-All patients were included in the analyses	U-Study protocol not found
WODIT-PE[232]	L-"Randomization was performed centrally in permuted blocks of six"	L-"Randomization was performed centrally in permuted blocks of six"	H-"Our study, like other studies with oral anticoagulant therapy, was not a placebo-controlled, double-blind trial"	L-"All suspected outcome events and all deaths were reviewed centrally by an independent, external adjudication committee whose members were unaware of the	L-All patients were included in the analyses	U-Study protocol not found

		treatment group assignments”	

L = low risk; H = high risk; U = unclear risk; VTE = venous thromboembolism; DVT = deep vein thrombosis, PE = pulmonary embolism; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; Note: quotations are denoted by inverted commas

9.4 Results of clinical effectiveness and safety

This review included ten trials comparing a total number of nine interventions (Table 143). The outcomes reported in the ten studies, along with the number of events per outcome, are displayed in Table 144 and Table 145. We performed network meta-analyses for seven outcomes: symptomatic DVT, symptomatic PE, symptomatic VTE, myocardial infarction, major bleeding, clinically relevant bleeding and all-cause mortality.

Results are presented as follows for each of the six outcomes. First, we provide network plots to illustrate the comparisons of interventions made in the different trials. Second, we illustrate the risk of bias assessments specific to the outcome for each trial included in the network. Third, we present results tables for each intervention compared with the reference treatment (placebo). Fourth, we present for each NOAC intervention compared with aspirin and warfarin. Fifth, we present results tables for pairwise comparisons among licensed doses of the NOACs. For all sets of results tables, posterior median odds ratios and 95% credible intervals from Bayesian fixed-effect analyses are shown, although we refer to the latter as confidence intervals for convenience. In these tables we present results separately for any available direct evidence, for any indirect comparisons that can be made (excluding the direct evidence) and for the network meta-analysis (which combines the direct and the indirect evidence). Comparisons from the NMA with a ratio between interval limits exceeding nine were considered “imprecisely estimated” and are presented at the bottom of each table (note that calculation of indirect evidence was not undertaken for imprecisely estimated comparisons). A summary of results across outcomes is provided at the end, in the form of a ‘rankogram’, which illustrates the probability that each treatment is best, second best, and so on, for each outcome. Last, forest plots of all contributing data, with odds ratios calculated using standard frequentist methods, are included in Appendix 5.

Table 143 List of distinct interventions examined by included randomised trials in secondary prevention of VTE

1 Placebo	6 Apixaban (2.5mg bd)
2 No treatment	7 Apixaban (5mg bd)

3 Aspirin (100mg od)	8 Dabigatran (150mg bd)
4 Warfarin (INR 1.5-2)	9 Rivaroxaban (20mg od)
5 Warfarin (INR 2-3)	

1

Table 144 Efficacy outcomes reported by ten included randomised trials in secondary prevention of VTE: number of events for each outcome in each trial

Study	Study size	Symptomatic DVT	Symptomatic proximal DVT	Symptomatic distal DVT	Symptomatic PE	Fatal PE	Symptomatic non-fatal PE	Symptomatic VTE	Cardiovascular deaths	All-cause mortality
AMPLIFY-EXT[238]	2482	67				0	27	101	15	25
ASPIRE[237]	822	82	68	25	48	2		130	12	34
EINSTEIN-EXTENSION[223,234,235]	1188	36				1	15	50		3
LAFIT[230]	162	11				1	6	18		4
PREVENT[233]	508					2		51		12
RE-MEDY[239]	2856	30					15	44		36
RE-SONATE[239]	1343	24					15	38		
WARFASA[236]	402	44			25	2		71		11
WODIT-DVT[231]	267	34				0	8	42	6	14
WODIT-PE[232]	326	14			12	2	10	33	3	19

Table 145 Safety outcomes reported by ten included randomised trials in secondary prevention of VTE: number of events for each outcome in each trial

Study	Study size	MI	Arterial event	All bleeding	Minor bleeding	Major bleeding	Fatal bleeding	Intracranial bleeding	Clinically relevant non-major bleeding	Clinically relevant bleeding
AMPLIFY-EXT[238]	2482	9				7	0		78	84
ASPIRE[237]	822	8		22		14	2		8	22
EINSTEIN-EXTENSION[223,234,235]	1188					4	0		39	43
LAFIT[230]	162			10	7	3				
PREVENT[233]	508	5			94	7				
RE-MEDY[239]	2856	11		650		38		6		225
RE-SONATE[239]	1343	2		111		2			46	48
WARFASA[236]	402		13			2			6	8
WODIT-DVT[231]	267					6	2			

WODIT-PE[232]	326	11	4	0

9.4.1 Symptomatic venous thromboembolism

All ten studies reported on symptomatic VTE (578 events), leading to a network of all nine interventions (Figure 95). The included studies were judged to be at mostly low risk of bias, with concerns only about lack of blinding of participants and personnel in some studies (Figure 96). There was evidence that aspirin (100 mg od) decreased the risk of symptomatic VTE compared with placebo (Table 146). Both warfarin (INR 1.5-2) and warfarin (INR 2-3) substantially reduced risk of symptomatic VTE compared with placebo. All NOACs at the doses included in the network substantially reduced risk of symptomatic VTE compared with placebo. Risk of symptomatic VTE was lower for all NOACs at doses included in the network compared with aspirin (Table 147). However there was no clear evidence that risk of symptomatic VTE differed between these NOAC interventions and warfarin (INR 2-3), although most comparisons were imprecisely estimated (Table 148). There was no clear evidence that risk of of symptomatic VTE differed between licensed doses of NOACs (Table 149), although all comparisons were imprecisely estimated.

Figure 95 Network plot for symptomatic VTE (secondary prevention of VTE)

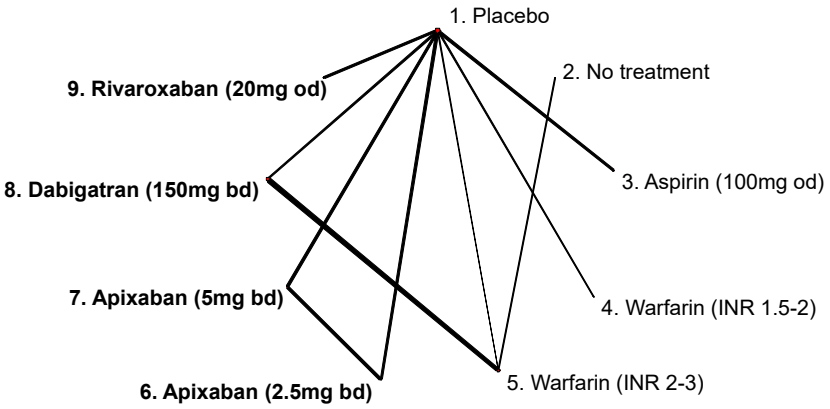


Figure 96 Included trials and risk of bias assessment for symptomatic VTE (secondary prevention of VTE)

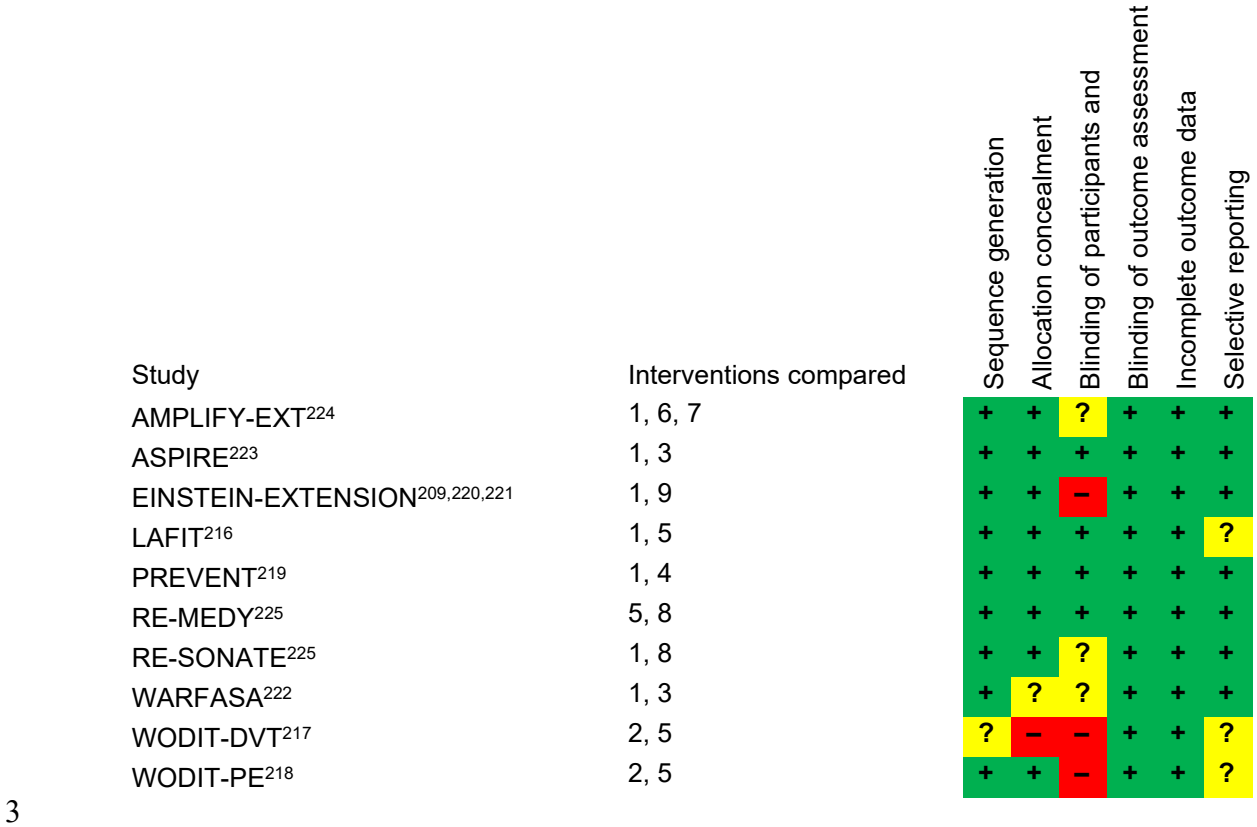


Table 146 Results for symptomatic VTE (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Aspirin (100mg od)	0.68 (0.50 , 0.92)	-	0.68 (0.50 , 0.92)
Warfarin (INR 1.5-2)	0.33 (0.17 , 0.63)	-	0.33 (0.17 , 0.63)
Apixaban (2.5mg bd)	0.17 (0.09 , 0.30)	-	0.17 (0.09 , 0.30)
Apixaban (5mg bd)	0.18 (0.09 , 0.31)	-	0.18 (0.09 , 0.31)
Dabigatran (150mg bd)	0.07 (0.02 , 0.18)	-	0.07 (0.02 , 0.18)
Rivaroxaban (20mg od)	0.17 (0.07 , 0.35)		0.17 (0.07 , 0.35)
Imprecisely estimated comparisons			
No treatment	-	*0.05 (0.01 , 0.17)*	*0.05 (0.01 , 0.17)*
Warfarin (INR 2-3)	*0.05 (0.01 , 0.14)*	-	*0.05 (0.01 , 0.14)*

Table 147 Results for symptomatic VTE (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	-	0.25 (0.13 , 0.48)	0.25 (0.13 , 0.48)
Apixaban (5mg bd)	-	0.26 (0.13 , 0.50)	0.26 (0.13 , 0.50)
Rivaroxaban (20mg od)	-	0.25 (0.10 , 0.55)	0.25 (0.10 , 0.55)
Imprecisely estimated comparisons			
Dabigatran (150mg bd)	-	*0.10 (0.03 , 0.28)*	*0.10 (0.03 , 0.28)*

Table 148 Results for symptomatic VTE (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd)	1.36 (0.67 , 2.80)	-	1.36 (0.67 , 2.80)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*2.10 (0.42 , 14.0)*	*2.10 (0.42 , 14.0)*
Apixaban (5mg bd)	-	*2.96 (0.64 , 19.1)*	*2.96 (0.64 , 19.1)*
Rivaroxaban (20mg od)	-	*3.01 (0.55 , 20.4)*	*3.01 (0.55 , 20.4)*

Table 149 Results for symptomatic VTE (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	1.04 (0.48 , 2.22)	-	1.04 (0.48 , 2.22)
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	0.99 (0.36 , 2.6)	0.99 (0.36 , 2.6)
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	0.96 (0.35 , 2.48)	0.96 (0.35 , 2.48)
Imprecisely estimated comparisons			
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*0.41 (0.11 , 1.29)*	*0.41 (0.11 , 1.29)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*0.40 (0.11 , 1.25)*	*0.40 (0.11 , 1.25)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	*2.41 (0.67 , 9.93)*	*2.41 (0.67 , 9.93)*

We conducted a supplementary analysis using hazard ratios for symptomatic recurrent VTE. The structure of the network was exactly the same as that presented in Figure 95. Results, presented in Table 150, Table 151, Table 152 and Table 153, were similar to those based on odds ratios.

Table 150 Results for recurrent VTE (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	HR (95% CI)
Aspirin (100mg od)	0.68 (0.51 , 0.90)
Warfarin (INR 1.5-2)	0.36 (0.19 , 0.68)
Warfarin (INR 2-3)	0.05 (0.02 , 0.16)
Apixaban (2.5mg bd)	0.17 (0.10 , 0.31)
Apixaban (5mg bd)	0.18 (0.10 , 0.32)
Dabigatran (150mg bd)	0.08 (0.03 , 0.22)
Rivaroxaban (20mg od)	0.18 (0.09 , 0.37)
Imprecisely estimated comparisons	
No treatment	*0.06 (0.02 , 0.23)*

Table 151 Results for recurrent VTE (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	HR (95% CI)
Apixaban (2.5mg bd)	0.25 (0.13 , 0.49)
Apixaban (5mg bd)	0.26 (0.14 , 0.51)
Dabigatran (150mg bd)	0.11 (0.04 , 0.34)
Rivaroxaban (20mg od)	0.27 (0.12 , 0.58)

Table 152 Results for recurrent VTE (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	HR (95% CI)
Dabigatran (150mg bd)	1.45 (0.80 , 2.60)
Imprecisely estimated comparisons	
Apixaban (2.5mg bd)	*3.24 (0.92 , 11.4)*
Apixaban (5mg bd)	*3.36 (0.95 , 11.7)*
Rivaroxaban (20mg od)	*3.41 (0.88 , 12.6)*

Table 153 Results for recurrent VTE (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	HR (95% CI)
Imprecisely estimated comparisons	
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*0.57 (0.14 , 1.94)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*0.48 (0.01 , 6.79)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	*0.86 (0.02 , 13.0)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	*0.85 (0.02 , 13.4)*
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	*1.54 (0.04 , 25.7)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	*1.79 (0.03 , 121)*

9.4.2 Symptomatic deep vein thrombosis

Nine studies reported 342 symptomatic DVT events, leading to a network of eight interventions (Figure 97). These studies were mostly judged to be at low risk of bias (Figure 98), with some concerns about lack of blinding of participants and personnel. There was no clear evidence that aspirin (100 mg od) reduced risk of symptomatic DVT compared with placebo (Table 154). There was evidence that warfarin (INR 2-3) and all NOACs at doses included in the network substantially reduced risk of symptomatic DVT compared with placebo. These NOAC interventions substantially reduced risk of symptomatic DVT compared with aspirin (Table 155). By contrast, there was no clear evidence that risk of symptomatic DVT differed between these NOACs and warfarin (INR 2-3), although comparisons were imprecisely esti4mated (Table 156). There was no clear evidence that risk of symptomatic DVT differed between NOACs at licensed doses, although all comparisons were imprecisely estimated (Table 157).

Figure 97 Network plot for symptomatic DVT (secondary prevention of VTE)

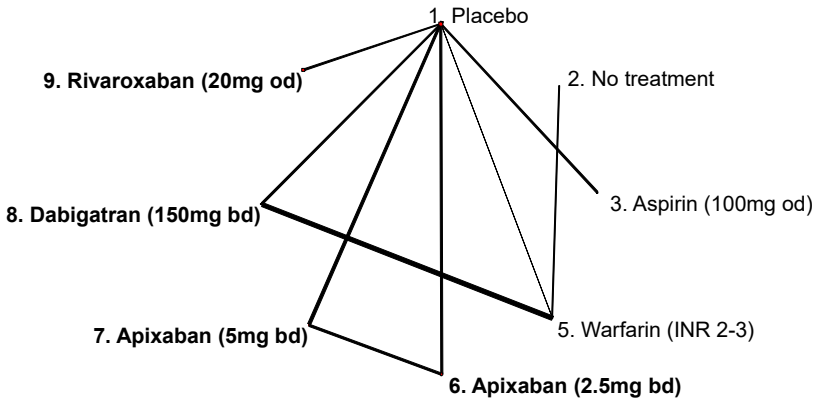


Figure 98 Included trials and risk of bias assessment for symptomatic DVT (secondary prevention of VTE)

Study	Interventions compared	Sequence generation	Allocation concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AMPLIFY-EXT[224]	1, 6, 7	+	+	?	+	+	+
ASPIRE[223]	1, 3	+	+	+	+	+	+
EINSTEIN-EXTENSION[209,220,221]	1, 9	+	+	–	+	+	+
LAFIT[216]	1, 5	+	+	+	+	+	?
RE-MEDY[225]	5, 8	+	+	+	+	+	+
RE-SONATE[225]	1, 8	+	+	?	+	+	+
WARFASA[222]	1, 3	+	?	?	+	+	+
WODIT-DVT[217]	2, 5	?	–	–	+	+	?
WODIT-PE[218]	2, 5	+	+	–	+	+	?

Table 154 Results for symptomatic DVT (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Aspirin (100mg od)	0.74 (0.51 , 1.07)	-	0.74 (0.51 , 1.07)
Apixaban (2.5mg bd)	0.1 (0.04 , 0.22)	-	0.1 (0.04 , 0.22)
Apixaban (5mg bd)	0.14 (0.06 , 0.28)	-	0.14 (0.06 , 0.28)
Rivaroxaban (20mg od)	0.14 (0.05 , 0.34)	-	0.14 (0.05 , 0.34)
Imprecisely estimated comparisons			
No treatment	-	*0.05 (0.01 , 0.22)*	*0.05 (0.01 , 0.22)*
Warfarin (INR 2-3)	*0.05 (0.01 , 0.17)*	-	*0.05 (0.01 , 0.17)*
Dabigatran (150mg bd)	*0.07 (0.01 , 0.21)*	-	*0.07 (0.01 , 0.21)*

Table 155 Results for symptomatic DVT (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	-	0.14 (0.05 , 0.32)	0.14 (0.05 , 0.32)
Apixaban (5mg bd)	-	0.19 (0.08 , 0.42)	0.19 (0.08 , 0.42)
Rivaroxaban (20mg od)	-	0.19 (0.06 , 0.51)	0.19 (0.06 , 0.51)
Imprecisely estimated comparisons			
Dabigatran (150mg bd)	-	*0.09 (0.02 , 0.30)*	*0.09 (0.02 , 0.30)*

Table 156 Results for symptomatic DVT (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*2.10 (0.42 , 14.0)*	*2.10 (0.42 , 14.0)*
Apixaban (5mg bd)	-	*2.96 (0.64 , 19.1)*	*2.96 (0.64 , 19.1)*
Dabigatran (150mg bd)	*1.36 (0.67 , 2.80)*	-	*1.36 (0.67 , 2.80)*
Rivaroxaban (20mg od)	-	*3.01 (0.55 , 20.4)*	*3.01 (0.55 , 20.4)*

Table 157 Results for symptomatic DVT (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*1.40 (0.48 , 4.37)*	-	*1.40 (0.48 , 4.37)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*0.65 (0.10 , 3.04)*	*0.65 (0.10 , 3.04)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*1.44 (0.37 , 5.36)*	*1.44 (0.37 , 5.36)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*0.46 (0.07 , 1.98)*	*0.46 (0.07 , 1.98)*
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	*1.02 (0.28 , 3.46)*	*1.02 (0.28 , 3.46)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	*2.21 (0.43 , 14.2)*	*2.21 (0.43 , 14.2)*

9.4.3 Symptomatic pulmonary embolism

Three studies reported symptomatic PE events, and a further six reported symptomatic non-fatal and fatal PE events, which were added together. The studies reported a total 173 symptomatic PE events, leading to a network comparing eight interventions (Figure 99). The included studies were mostly judged to be at low risk of bias (Figure 100), with some concerns about lack of blinding of participants and personnel. There was evidence that warfarin (INR 2-3), apixaban (5mg bd), dabigatran (150mg bd) and rivaroxaban (20mg od) substantially reduce risk of symptomatic PE compared with placebo (Table 158). There was evidence that dabigatran (150mg bd) and rivaroxaban (20mg od) reduce risk of symptomatic PE compared with aspirin (Table 159). There was evidence that risk of symptomatic PE was higher for apixaban (2.5mg bd) compared with warfarin (INR 2-3) (Table 160). There was weak evidence that risk of symptomatic PE was lower for dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd) (Table 161).

Figure 99 Network plot for symptomatic PE (secondary prevention of VTE)

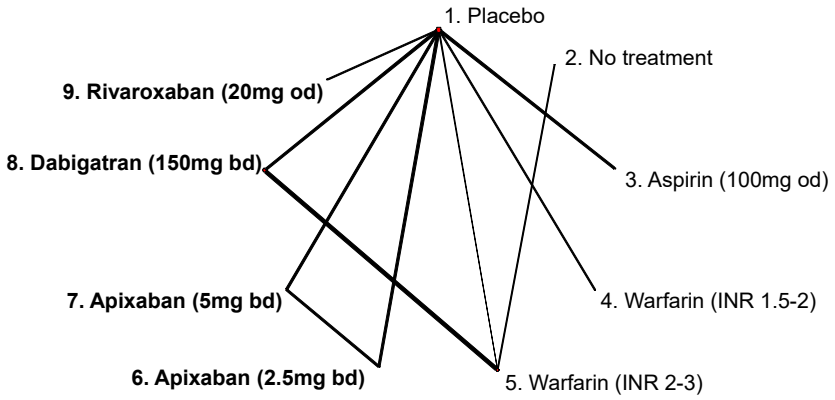


Figure 100 Included trials and risk of bias assessment for symptomatic PE (secondary prevention of VTE)

Study	Interventions compared	Sequence generation	Allocation concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AMPLIFY-EXT[224]	1, 6, 7	+	+	?	+	+	+
ASPIRE[223]	1, 3	+	+	+	+	+	+
EINSTEIN-EXTENSION[209,220,221]	1, 9	+	+	–	+	+	+
LAFIT[216]	1, 5	+	+	+	+	+	?
RE-MEDY[225]	5, 8	+	+	+	+	+	+
RE-SONATE[225]	1, 8	+	+	?	+	+	+
WARFASA[222]	1, 3	+	?	?	+	+	+
WODIT-DVT[217]	2, 5	?	–	–	+	+	?
WODIT-PE[218]	2, 5	+	+	–	+	+	?

Table 158 Results for symptomatic PE (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Aspirin (100mg od)	0.63 (0.38 , 1.02)	-	0.63 (0.38 , 1.02)
Imprecisely estimated comparisons			
No treatment	-	*0.05 (0.01 , 0.32)*	*0.05 (0.01 , 0.32)*
Warfarin (INR 2-3)	*0.05 (0.01 , 0.24)*	-	*0.05 (0.01 , 0.24)*
Apixaban (2.5mg bd)	*0.51 (0.20 , 1.21)*	-	*0.51 (0.20 , 1.21)*
Apixaban (5mg bd)	*0.25 (0.07 , 0.71)*	-	*0.25 (0.07 , 0.71)*
Dabigatran (150mg bd)	*0.09 (0.01 , 0.35)*	-	*0.09 (0.01 , 0.35)*
Rivaroxaban (20mg od)	*0.12 (0.02 , 0.45)*	-	*0.12 (0.02 , 0.45)*

Table 159 Results for symptomatic PE (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	-	0.81 (0.29 , 2.19)	0.81 (0.29 , 2.19)
Imprecisely estimated comparisons			
Apixaban (5mg bd)	-	*0.40 (0.10 , 1.28)*	*0.40 (0.10 , 1.28)*
Dabigatran (150mg bd)	-	*0.14 (0.02 , 0.61)*	*0.14 (0.02 , 0.61)*
Rivaroxaban (20mg od)	-	*0.19 (0.03 , 0.78)*	*0.19 (0.03 , 0.78)*

Table 160 Results for symptomatic PE (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd)	1.76 (0.64 , 5.24)	-	1.76 (0.64 , 5.24)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*10.1 (1.66 , 102)*	*10.1 (1.66 , 102)*
Apixaban (5mg bd)	-	*4.94 (0.66 , 53.6)*	*4.94 (0.66 , 53.6)*
Rivaroxaban (20mg od)	-	*2.29 (0.19 , 28.4)*	*2.29 (0.19 , 28.4)*

Table 161 Results for symptomatic PE (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*0.49 (0.13 , 1.62)*	-	*0.49 (0.13 , 1.62)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*0.18 (0.02 , 0.92)*	*0.18 (0.02 , 0.92)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*0.23 (0.03 , 1.18)*	*0.23 (0.03 , 1.18)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*0.36 (0.04 , 2.38)*	*0.36 (0.04 , 2.38)*
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	*0.47 (0.05 , 3.04)*	*0.47 (0.05 , 3.04)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	*1.31 (0.12 , 14.0)*	*1.31 (0.12 , 14.0)*

9.4.4 Myocardial infarction

Five studies reported 35 myocardial infarction events, leading to a network of seven interventions (Figure 101). These studies were judged to be at low risk of bias (Figure 102). All comparisons were imprecisely estimated (Table 162, Table 163, Table 164 and Table 165).

Figure 101 Network plot for myocardial infarction (secondary prevention of VTE)

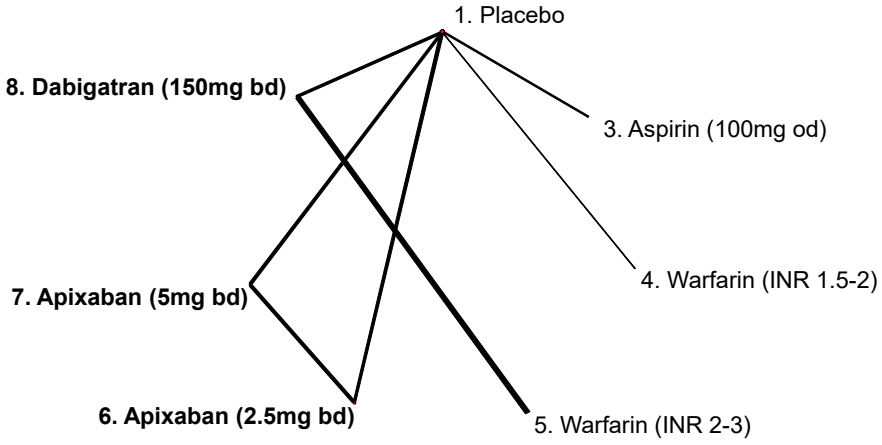


Figure 102 Included trials and risk of bias assessment for myocardial infarction (secondary prevention of VTE)

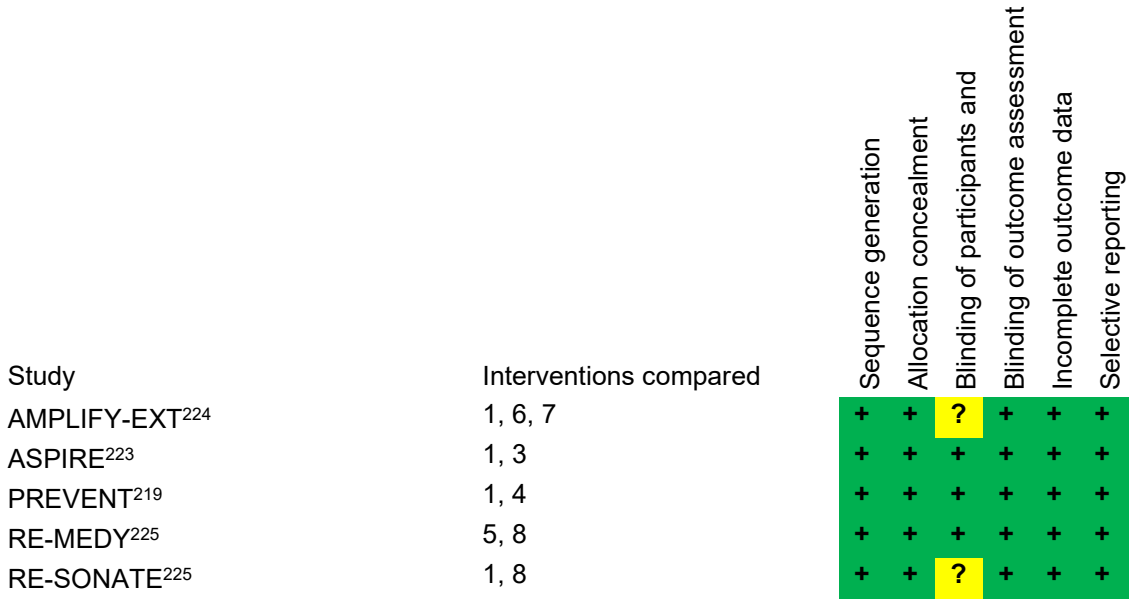


Table 162 Results for myocardial infarction (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Aspirin (100mg od)	*0.29 (0.04 , 1.37)*	-	*0.29 (0.04 , 1.37)*
Warfarin (INR 1.5-2)	*1.57 (0.24 , 14.0)*	-	*1.57 (0.24 , 14.0)*
Warfarin (INR 2-3)	*0.06 (0 , 3.26)*	-	*0.06 (0 , 3.26)*
Apixaban (2.5mg bd)	*0.45 (0.06 , 2.51)*	-	*0.45 (0.06 , 2.51)*
Apixaban (5mg bd)	*0.74 (0.13 , 3.59)*	-	*0.74 (0.13 , 3.59)*
Dabigatran (150mg bd)	*0.90 (0.02 , 29.8)*	-	*0.90 (0.02 , 29.8)*

Table 163 Results for myocardial infarction (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*1.57 (0.12 , 21.7)*	*1.57 (0.12 , 21.7)*
Apixaban (5mg bd)	-	*2.60 (0.26 , 33.1)*	*2.60 (0.26 , 33.1)*
Dabigatran (150mg bd)	-	*3.19 (0.05 , 174)*	*3.19 (0.05 , 174)*

Table 164 Results for myocardial infarction (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	*-*	*7.48 (0.08 , 1220)*	*7.48 (0.08 , 1220)*
Apixaban (5mg bd)	*-*	*12.6 (0.15 , 2000)*	*12.6 (0.15 , 2000)*
Dabigatran (150mg bd)	*13.6 (2.26 , 409)*	*-*	*13.6 (2.26 , 409)*

Table 165 Results for myocardial infarction (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*1.65 (0.25 , 14.2)*	*-*	*1.65 (0.25 , 14.2)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*-*	*2.06 (0.03 , 117)*	*2.06 (0.03 , 117)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	*-*	*1.22 (0.02 , 57.5)*	*1.22 (0.02 , 57.5)*

9.4.5 Major bleeding

All ten studies reported on major bleeding (87 events), leading to a network of nine interventions (Figure 103). These studies were mostly judged to be at low risk of bias (Figure 104), with some concerns about lack of blinding of participants and personnel. There was evidence that risk of major bleeding is higher for warfarin (INR 2-3) and rivaroxaban (20mg od) compared with placebo, although these comparisons were imprecisely estimated (Table 166). Comparisons of the risk of major bleeding for NOACs compared with aspirin were imprecisely estimated (Table 167). There was evidence that risk of major bleeding is lower with dabigatran (150mg bd), apixaban (2.5mg bd) and apixaban (5mg bd) compared with warfarin (INR 2-3) (Table 168). There was evidence that risk of major bleeding is higher with dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd and 5mg bd) (Table 169).

Figure 103 Network plot for major bleeding (secondary prevention of VTE)

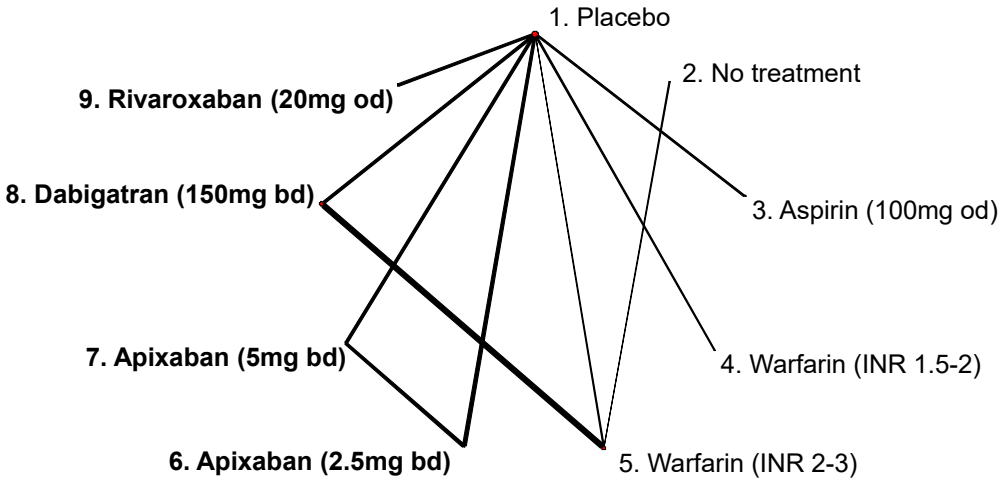
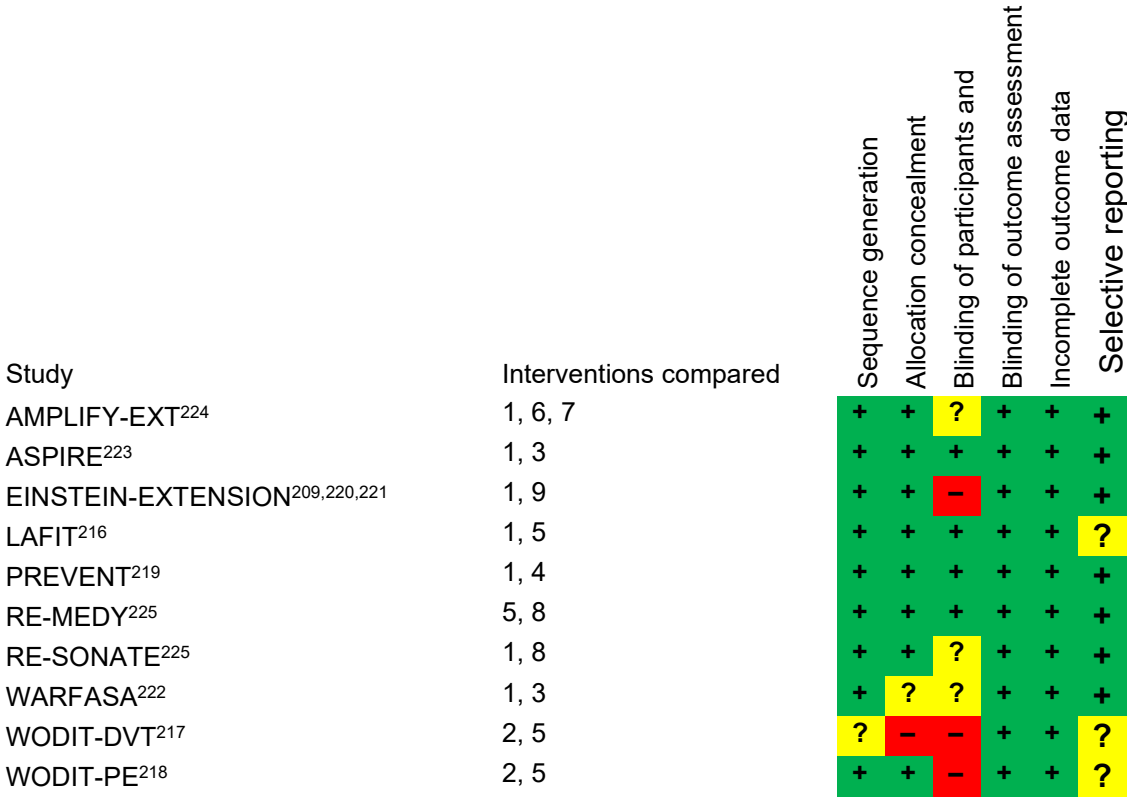


Figure 104 Included trials and risk of bias assessment for major bleeding (secondary prevention of VTE)



Study	Interventions compared	Sequence generation	Allocation concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
AMPLIFY-EXT[224]	1, 6, 7	+	+	?	+	+	+
ASPIRE[223]	1, 3	+	+	+	+	+	+
EINSTEIN-EXTENSION[209,220,221]	1, 9	+	+	–	+	+	+
LAFIT[216]	1, 5	+	+	+	+	+	?
PREVENT[219]	1, 4	+	+	+	+	+	+
RE-MEDY[225]	5, 8	+	+	+	+	+	+
RE-SONATE[225]	1, 8	+	+	?	+	+	+
WARFASA[222]	1, 3	+	?	?	+	+	+
WODIT-DVT[217]	2, 5	?	–	–	+	+	?
WODIT-PE[218]	2, 5	+	+	–	+	+	?

Table 166 Results for major bleeding (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Aspirin (100mg od)	1.3 (0.47 , 3.76)	-	1.3 (0.47 , 3.76)
Imprecisely estimated comparisons			
No treatment	-	*4.93 (0.36 , 142)*	*4.93 (0.36 , 142)*
Warfarin (INR 1.5-2)	*2.78 (0.55 , 22.2)*	-	*2.78 (0.55 , 22.2)*
Warfarin (INR 2-3)	*12.0 (1.66 , 279)*	-	*12.0 (1.66 , 279)*
Apixaban (2.5mg bd)	*0.45 (0.06 , 2.57)*	-	*0.45 (0.06 , 2.57)*
Apixaban (5mg bd)	*0.19 (0.01 , 1.56)*	-	*0.19 (0.01 , 1.56)*
Dabigatran (150mg bd)	*6.11 (0.83 , 145)*	-	*6.11 (0.83 , 145)*
Rivaroxaban (20mg od)	*17.8 (1.25 , 8340)*		*17.8 (1.25 , 8340)*

Table 167 Results for major bleeding (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*0.34 (0.03 , 2.60)*	*0.34 (0.03 , 2.60)*
Apixaban (5mg bd)	-	*0.14 (0 , 1.54)*	*0.14 (0 , 1.54)*
Dabigatran (150mg bd)	-	*4.81 (0.50 , 126)*	*4.81 (0.50 , 126)*
Rivaroxaban (20mg od)	-	*13.9 (0.78 , 6690)*	*13.9 (0.78 , 6690)*

Table 168 Results for major bleeding (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd)	0.51 (0.25 , 0.98)	-	0.51 (0.25 , 0.98)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*0.03 (0 , 0.53)*	*0.03 (0 , 0.53)*
Apixaban (5mg bd)	-	*0.01 (0 , 0.29)*	*0.01 (0 , 0.29)*
Rivaroxaban (20mg od)	-	*1.52 (0.03 , 712)*	*1.52 (0.03 , 712)*

Table 169 Results for major bleeding (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*0.43 (0.01 , 5.42)*	-	*0.43 (0.01 , 5.42)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*14.7 (0.96 , 582)*	*14.7 (0.96 , 582)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*44.8 (1.60 , 24100)*	*44.8 (1.60 , 24100)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*37.1 (1.70 , 2980)*	*37.1 (1.70 , 2980)*
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	*116 (2.87 , 92100)*	*116 (2.87 , 92100)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	*3.01 (0.05 , 1390)*	*3.01 (0.05 , 1390)*

9.4.6 Clinically relevant bleeding

Six studies reported 430 clinically relevant bleeding events across trials, leading to a network of seven interventions (Figure 105). These studies were mostly judged to be at low risk of bias (Figure 106) with some concerns about lack of blinding of participants and personnel. There was evidence that risk of clinically relevant bleeding is substantially higher with warfarin (INR 2-3), dabigatran (150 mg od) and rivaroxaban (20 mg od) compared with placebo (Table 170) and that risk of clinically relevant bleeding is higher with rivaroxaban (20 mg od) compared with aspirin (Table 171). There was evidence that risk of clinically relevant bleeding is lower with apixaban (2.5mg or 5mg bd) and dabigatran (150mg bd) compared with warfarin (INR 2-3) (Table 172). All comparisons between NOACs at licensed doses were imprecisely estimated, but there was evidence that risk of clinically relevant bleeding is higher with dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd and 5mg bd) (Table 173).

Figure 105 Network plot for clinically relevant bleeding (secondary prevention of VTE)

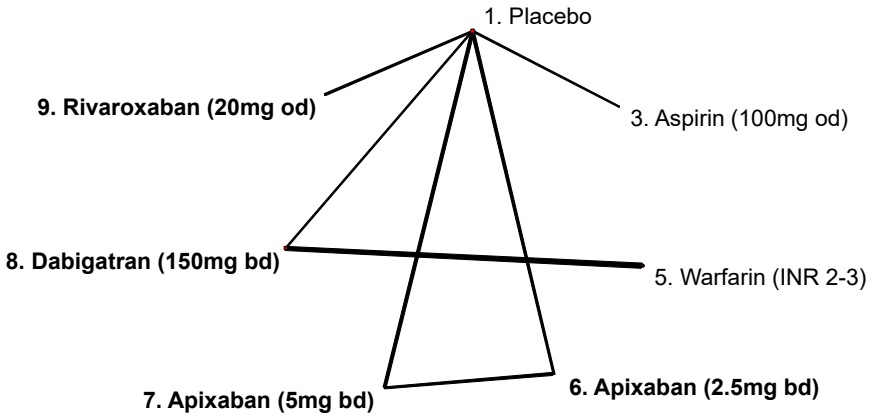


Figure 106 Included trials and risk of bias assessment for clinically relevant bleeding (secondary prevention of VTE)

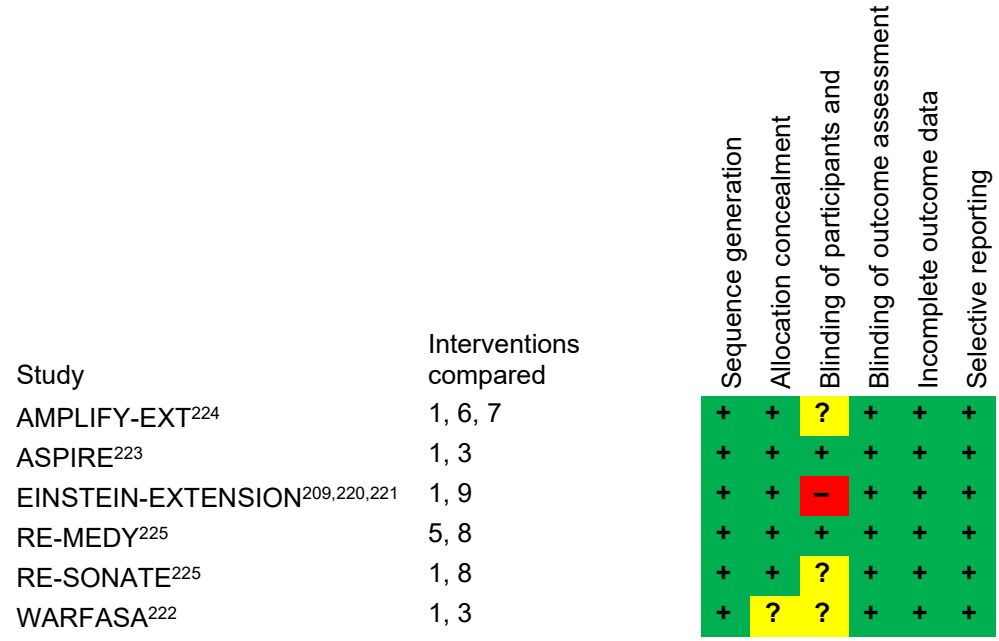


Table 170 Results for clinically relevant bleeding (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Aspirin (100mg od)	1.51 (0.72 , 3.27)	-	1.51 (0.72 , 3.27)
Warfarin (INR 2-3)	5.85 (2.93 , 12.6)	-	5.85 (2.93 , 12.6)
Apixaban (2.5mg bd)	1.22 (0.69 , 2.19)	-	1.22 (0.69 , 2.19)
Apixaban (5mg bd)	1.66 (0.96 , 2.89)	-	1.66 (0.96 , 2.89)
Dabigatran (150mg bd)	3.05 (1.62 , 6.25)	-	3.05 (1.62 , 6.25)
Rivaroxaban (20mg od)	5.56 (2.58 , 14.0)		5.56 (2.58 , 14.0)

Table 171 Results for clinically relevant bleeding (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	-	0.81 (0.31 , 2.08)	0.81 (0.31 , 2.08)
Apixaban (5mg bd)	-	1.10 (0.43 , 2.78)	1.10 (0.43 , 2.78)
Dabigatran (150mg bd)	-	2.03 (0.75 , 5.66)	2.03 (0.75 , 5.66)
Rivaroxaban (20mg od)	-	3.70 (1.25 , 12.0)	3.70 (1.25 , 12.0)

Table 172 Results for clinically relevant bleeding (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Apixaban (2.5mg bd)	-	0.21 (0.08 , 0.52)	0.21 (0.08 , 0.52)
Apixaban (5mg bd)	-	0.28 (0.11 , 0.69)	0.28 (0.11 , 0.69)
Dabigatran (150mg bd)	0.52 (0.39 , 0.69)	-	0.52 (0.39 , 0.69)
Rivaroxaban (20mg od)	-	0.95 (0.32 , 3.01)	0.95 (0.32 , 3.01)

Table 173 Results for clinically relevant bleeding (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*0.43 (0.01 , 5.42)*	-	*0.43 (0.01 , 5.42)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*14.7 (0.96 , 582)*	*14.7 (0.96 , 582)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*44.8 (1.60 , 24100)*	*44.8 (1.60 , 24100)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*37.1 (1.70 , 2980)*	*37.1 (1.70 , 2980)*
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	*116 (2.87 , 92100)*	*116 (2.87 , 92100)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	*3.01 (0.05 , 1390)*	*3.01 (0.05 , 1390)*

9.4.7 Bleeding (sensitivity analysis)

We conducted a supplementary analysis based on hazard ratios for bleeding events reported in some studies. We extracted hazard ratios for clinically relevant bleeding, or for major bleeding if that was the only information available. The structure of this resulting network is presented in Figure 107. Results are similar to those for clinically relevant bleeding (Table 174, Table 175, Table 176 and Table 177).

Figure 107 Network plot for bleeding (secondary prevention of VTE)

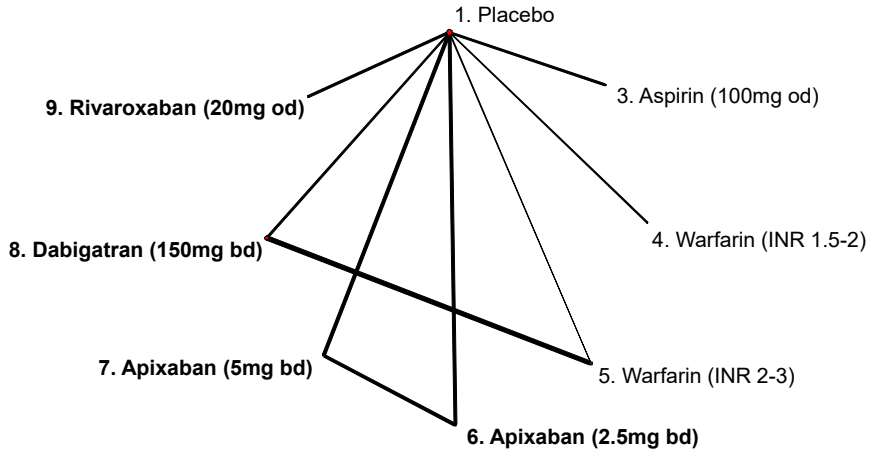


Table 174 Results for bleeding (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Network meta-analysis HR (95% CI)
Aspirin (100mg od)	1.48 (0.70 , 3.09)
Warfarin (INR 2-3)	5.39 (2.64 , 10.8)
Apixaban (2.5mg bd)	1.29 (0.72 , 2.33)
Apixaban (5mg bd)	1.82 (1.05 , 3.17)
Dabigatran (150mg bd)	2.91 (1.51 , 5.54)
Rivaroxaban (20mg od)	5.19 (2.28 , 11.6)
Imprecisely estimated comparisons	
Warfarin (INR 1.5-2)	*2.54 (0.48 , 13.1)*

Table 175 Results for bleeding (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Network meta-analysis HR (95% CI)
Apixaban (2.5mg bd)	0.87 (0.34 , 2.25)
Apixaban (5mg bd)	1.23 (0.48 , 3.14)
Dabigatran (150mg bd)	1.97 (0.73 , 5.25)
Rivaroxaban (20mg od)	3.51 (1.17 , 10.5)

Table 176 Results for bleeding (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Network meta-analysis HR (95% CI)
Apixaban (2.5mg bd)	0.24 (0.09 , 0.61)
Apixaban (5mg bd)	0.34 (0.14 , 0.84)
Dabigatran (150mg bd)	0.54 (0.41 , 0.71)
Rivaroxaban (20mg od)	0.96 (0.33 , 2.82)

Table 177 Results for bleeding (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Network meta-analysis HR (95% CI)
Imprecisely estimated comparisons	
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	*1.65 (0.25 , 14.2)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	*2.06 (0.03 , 117)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	*1.22 (0.02 , 57.5)*

9.4.8 All-cause mortality

Nine studies reported 158 all-cause mortality events, leading to a network of nine interventions (Figure 108). These studies were mostly judged to be at low risk of bias (Figure 109), with some concerns about lack of blinding of participants and personnel. All comparisons of risk of all-cause mortality with placebo, except that for aspirin (100 mg od), were imprecisely estimated (Table 178). However there was evidence that risk of all-cause mortality was lower for apixaban (5mg bd) compared with placebo. Comparisons of NOACs with aspirin were imprecisely estimated, although there was weak evidence that risk of all-cause mortality is lower with apixaban (5mg bd) compared with aspirin (Table 179). There was no evidence that risk of all-cause mortality differed for NOACs compared with warfarin (INR 2-3), although all comparisons except that with dabigatran (150mg bd) were imprecisely estimated (Table 180). Comparisons of risk of all-cause mortality between NOACs at licensed doses were imprecisely estimated (Table 181).

Figure 108 Network plot for all-cause mortality (secondary prevention of VTE)

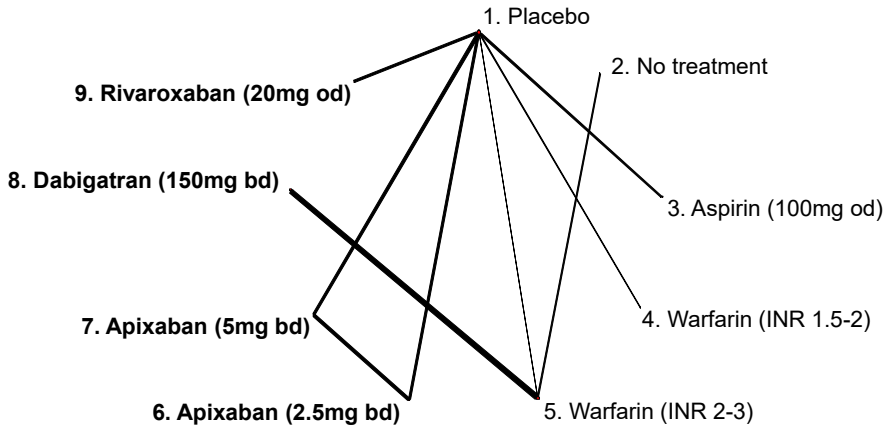


Figure 109 Included trials and risk of bias assessment for all-cause mortality (secondary prevention of VTE)

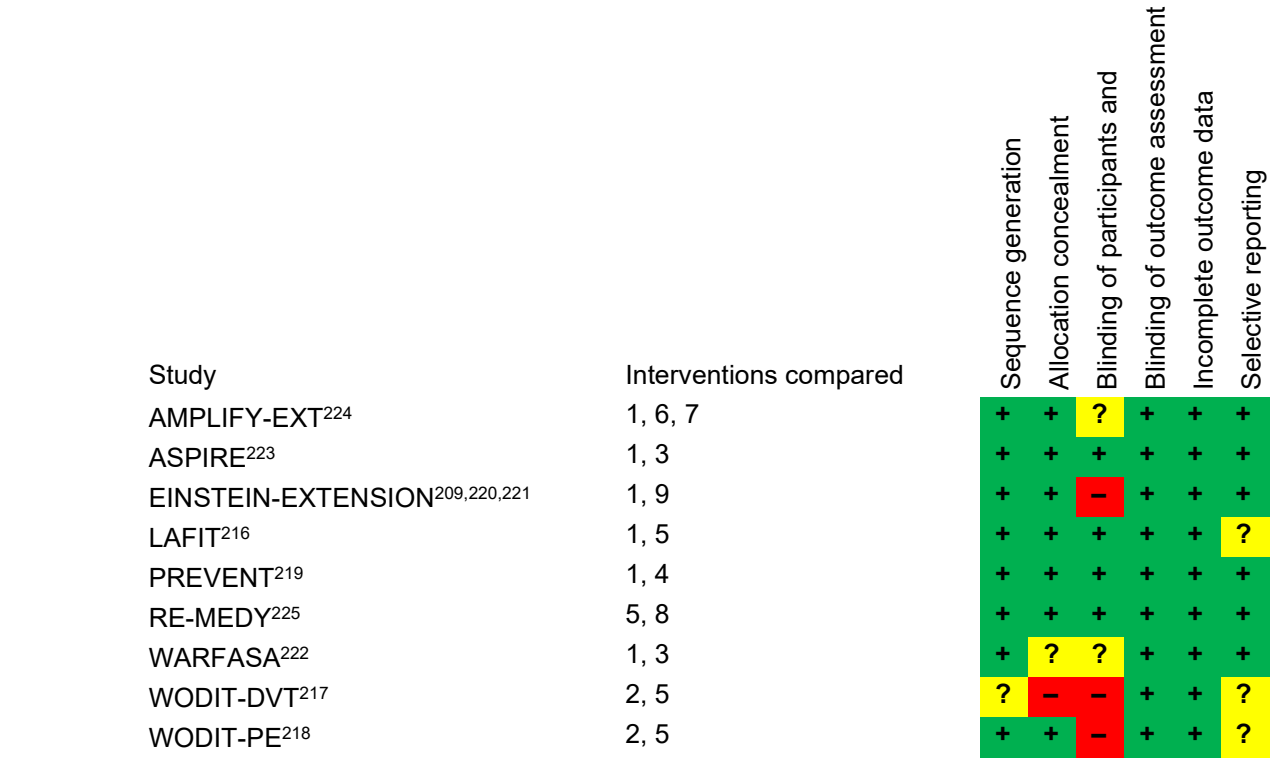


Table 178 Results for all-cause mortality (secondary prevention of VTE): Comparisons with placebo

Comparisons with placebo	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Aspirin (100mg od)	0.94 (0.52 , 1.73)	-	0.94 (0.52 , 1.73)
Apixaban (2.5mg bd)	0.48 (0.18 , 1.17)	-	0.48 (0.18 , 1.17)
Imprecisely estimated comparisons			
No treatment	-	*0.20 (0.01 , 2.03)*	*0.20 (0.01 , 2.03)*
Warfarin (INR 1.5-2)	*0.47 (0.12 , 1.54)*	-	*0.47 (0.12 , 1.54)*
Warfarin (INR 2-3)	*0.28 (0.01 , 2.47)*	-	*0.28 (0.01 , 2.47)*
Apixaban (5mg bd)	*0.27 (0.07 , 0.78)*	-	*0.27 (0.07 , 0.78)*
Dabigatran (150mg bd)	*0.25 (0.01 , 2.50)*	-	*0.25 (0.01 , 2.50)*
Rivaroxaban (20mg od)	*0.41 (0.01 , 5.21)*	-	*0.41 (0.01 , 5.21)*

Table 179 Results for all-cause mortality (secondary prevention of VTE): Comparisons with aspirin

Comparisons with aspirin	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*0.50 (0.16 , 1.49)*	*0.50 (0.16 , 1.49)*
Apixaban (5mg bd)	-	*0.29 (0.07 , 0.98)*	*0.29 (0.07 , 0.98)*
Dabigatran (150mg bd)	-	*0.26 (0.01 , 2.87)*	*0.26 (0.01 , 2.87)*
Rivaroxaban (20mg od)	-	*0.43 (0.01 , 5.90)*	*0.43 (0.01 , 5.90)*

Table 180 Results for all-cause mortality (secondary prevention of VTE): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Dabigatran (150mg bd)	0.89 (0.45 , 1.73)	-	0.89 (0.45 , 1.73)
Imprecisely estimated comparisons			
Apixaban (2.5mg bd)	-	*1.71 (0.15 , 60.6)*	*1.71 (0.15 , 60.6)*
Apixaban (5mg bd)	-	*0.97 (0.08 , 35.1)*	*0.97 (0.08 , 35.1)*
Rivaroxaban (20mg od)	-	*1.52 (0.03 , 98.3)*	*1.52 (0.03 , 98.3)*

Table 181 Results for all-cause mortality (secondary prevention of VTE): NOACs (licensed doses only)

Licensed NOACs only	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Imprecisely estimated comparisons			
Apixaban (5mg bd) vs Apixaban (2.5mg bd)	-	*0.57 (0.14 , 1.94)*	*0.57 (0.14 , 1.94)*
Dabigatran (150mg bd) vs Apixaban (2.5mg bd)	-	*0.51 (0.01 , 6.39)*	*0.51 (0.01 , 6.39)*
Rivaroxaban (20mg od) vs Apixaban (2.5mg bd)	-	*0.85 (0.02 , 12.9)*	*0.85 (0.02 , 12.9)*
Dabigatran (150mg bd) vs Apixaban (5mg bd)	-	*0.91 (0.02 , 13.0)*	*0.91 (0.02 , 13.0)*
Rivaroxaban (20mg od) vs Apixaban (5mg bd)	-	*1.52 (0.04 , 26.3)*	*1.52 (0.04 , 26.3)*
Rivaroxaban (20mg od) vs Dabigatran (150mg bd)	-	*1.79 (0.03 , 121)*	*1.79 (0.03 , 121)*

9.4.9 Summary of results

Our analyses of a network of ten randomized controlled trials found evidence that warfarin (INR 2-3), apixaban (2.5mg bd), apixaban (5mg bd), dabigatran (150mg bd) and rivaroxaban (20mg od) reduce risk of recurrent VTE, symptomatic DVT and symptomatic PE compared with placebo. Some of these reductions were substantial. We also found evidence that aspirin (100mg od) and warfarin (INR 1.5-2) reduce risk of recurrent VTE. The risk of recurrent VTE and symptomatic DVT is generally lower for NOACs at doses included in the network than for aspirin (100mg od). However, there was little evidence that risks of recurrent VTE and symptomatic DVT differ comparing NOACs with warfarin (INR 2-3), nor that the risk of these outcomes differs between licensed doses of NOACs. There was evidence that risk of symptomatic PE is higher with apixaban (2.5mg bd) compared with warfarin (INR 2-3) and lower with dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd).

By contrast, the risk of major bleeding and clinically relevant bleeding is higher with warfarin (INR 2-3), dabigatran (150 mg od) and rivaroxaban (20 mg od) compared with placebo. However, the risk of these outcomes is lower for dabigatran (150mg bd), apixaban (2.5mg bd) and apixaban (5mg bd) compared with warfarin (INR 2-3). There was evidence that the risk of major bleeding and clinically relevant bleeding is higher with dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd and 5mg bd). However, results should be interpreted with caution because many comparisons were imprecisely estimated: for this reason it was not possible to derive a rankogram for this network.

For some outcomes there was evidence that patients who remained untreated had lower outcome risks than those on active interventions. This counterintuitive finding is based on the from WODIT-DVT and WODIT-PE trials. With regards to model appraisal, we did not identify any instance of lack of convergence among the Markov chains, poor model fit or inconsistency.

10. Clinical results (5): Combined safety analyses

In this chapter, we present network plots and pairwise comparisons from network meta-analyses using the information from all four reviews. These should not be regarded as main results, but as a set of supplementary analyses in which we aimed to gain power by combining all databases in a single network for each of the following outcomes: myocardial infarction; major bleeding; clinically relevant bleeding and all-cause mortality.

A number of decisions were made in order to define the list of relevant nodes (e.g., interventions). We excluded the TOPIC-1, TOPIC-2 and ARDEPARIN ATHROPLASTY STUDY trials, as for the analyses of primary prevention of VTE. We also excluded several individual interventions that were not considered to provide relevant information and were not necessary to keep our networks connected. These were warfarin arms with a subtherapeutic INR range, arms combined dabigatran and aspirin (only considered in PETRO), no treatment arms (only found in WODIT-DVT and WODIT-PE and compared to warfarin), LMWH (Nadroparin 3800 IU anti-Xa od, only implemented in PROTECHT and compared to placebo), and warfarin with INR range 3-4 (only considered in AFASAK and compared to aspirin). If the intervention had been implemented in a two-arm trial, then the trial was excluded from these analyses.

We also made several decisions in order to reduce the number of intervention arms compared. The reference treatment in our networks was warfarin (INR 2-3), which may include other vitamin-K antagonist interventions, as was described for the analyses of atrial fibrillation. The antiplatelet interventions were defined as in the atrial fibrillation review (e.g., <150mg od and ≥150mg od). The standard dose of LMWH was as in the review of primary prevention of VTE, and LMWH administered to non-surgical patients was combined with post-operative LMWH. We merged some NOAC intervention doses and labelled these according to total daily dose. The edoxaban (60mg) intervention included one arm from the review of acute VTE treatment in which 17% of patients received 30mg instead. The list of interventions included in the networks is presented in Table 182.

Results are presented as follows for each outcome. First, we provide network plots. Second, we present results tables for each intervention compared with the reference treatment (warfarin (INR range 2-3)). These tables show posterior median odds ratios and 95% credible intervals from Bayesian fixed-effect analyses are shown, but we refer to the latter as confidence intervals for convenience. We present results separately for any available direct evidence, for any indirect comparisons that can be made and for the network meta-analysis (which combines the direct and the indirect evidence). Comparisons from the NMA with a ratio between interval limits exceeding nine were considered to be imprecisely estimated and are presented at the bottom of each table (back-calculation of indirect evidence was not done for imprecisely estimated comparisons).

Table 182 List of distinct interventions examined in the combined safety analyses

Warfarin (INR 2-3)	Dabigatran (100-150mg)
LMWH Post-op (standard dose)	Dabigatran (220mg)
LMWH Pre-op (standard dose)	Dabigatran (300-600mg)
LMWH (Enoxaparin 20mg bd)	Edoxaban (5-15mg)
Antiplatelet (<150mg od)	Edoxaban (30-45mg)
Antiplatelet (≥150mg od)	Edoxaban (60mg)
Placebo	Edoxaban (90-120mg)
Apixaban (5mg)	Rivaroxaban (5mg)
Apixaban (10mg)	Rivaroxaban (10mg)
Apixaban (20mg)	Rivaroxaban (20-30mg)
Betrixaban (30-60mg)	Rivaroxaban (40-60mg)
Betrixaban (80mg)	

10.1 Myocardial infarction

A total of 34 trials reported on myocardial infarction across the four reviews, leading to a network of 18 interventions (Figure 110). The total number of events was 1489. Comparisons with the reference interventions (warfarin (INR 2-3)), presented in Table 183, suggest that risk of myocardial infarction is higher with dabigatran (220mg daily), dabigatran (300-600mg daily) and edoxaban (30-45mg daily) compared with warfarin (INR 2-3).

Figure 110 Network plot for myocardial infarction (combined analysis)

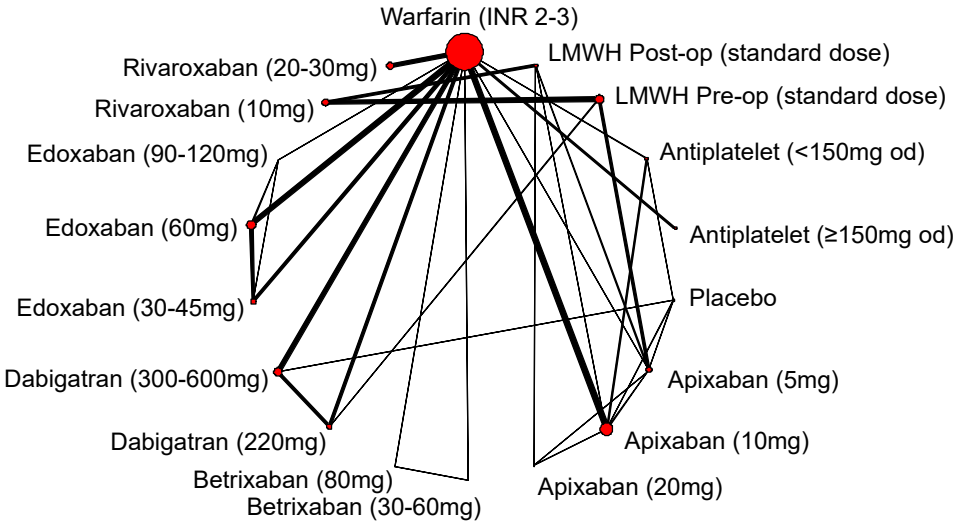


Table 183 Results for myocardial infarction (combined analysis): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
Antiplatelet (<150mg)	1.01 (0.63 , 1.60)	-	1.01 (0.63 , 1.60)
Antiplatelet (≥150mg)	1.36 (0.88 , 2.13)	-	1.36 (0.88 , 2.13)
Placebo	-	2.23 (0.79 , 6.72)	2.23 (0.79 , 6.72)
Apixaban (10mg)	0.90 (0.69 , 1.18)	-	0.90 (0.69 , 1.18)
Dabigatran (220mg)	1.39 (1.03 , 1.89)	-	1.39 (1.03 , 1.89)
Dabigatran (300-600mg)	1.44 (1.08 , 1.91)	-	1.44 (1.08 , 1.91)
Edoxaban (30-45mg)	1.25 (1.00 , 1.56)	-	1.25 (1.00 , 1.56)
Edoxaban (60mg)	1.01 (0.81 , 1.26)	-	1.01 (0.81 , 1.26)
Rivaroxaban (20-30mg)	0.84 (0.64 , 1.09)	-	0.84 (0.64 , 1.09)
Imprecisely estimated comparisons			
LMWH Post-op (standard dose)	-	*2.17 (0.50 , 9.72)*	*2.17 (0.50 , 9.72)*
LMWH Pre-op (standard dose)	-	*0.82 (0.19 , 3.42)*	*0.82 (0.19 , 3.42)*
Apixaban (5mg)	-	*1.33 (0.40 , 4.46)*	*1.33 (0.40 , 4.46)*
Apixaban (20mg)	-	*0.46 (0.01 , 4.23)*	*0.46 (0.01 , 4.23)*
Edoxaban (90-120mg)	*0.19 (0 , 2.61)*	-	*0.19 (0 , 2.61)*
Rivaroxaban (10mg)	-	*0.60 (0.13 , 2.80)*	*0.60 (0.13 , 2.80)*

10.2 Major bleeding

A total of 71 trials reported on major bleeding across the four reviews, leading to a network of 23 interventions (Figure 111). In total there were 5335 major bleeding events. The pairwise comparisons with warfarin, shown in Table 184, suggest that the risk of major bleeding is similar for both pre-operative and post-operative LMWH compared with warfarin (INR 2-3). However, there was notable inconsistency between the directly and indirectly estimated odds ratios. There was evidence that risk of major bleeding is lower for NOAC interventions compared with warfarin (INR 2-3), in agreement with the results from the atrial fibrillation review. This applies to the apixaban (10mg daily), dabigatran (100-150mg and 220mg daily) and edoxaban interventions. Risk of major bleeding appeared higher with rivaroxaban (10mg and 30-40mg daily) compared with warfarin (INR 2-3), a finding that might stem from the evidence on primary prevention of VTE.

Figure 111 Network plot for major bleeding (combined analysis)

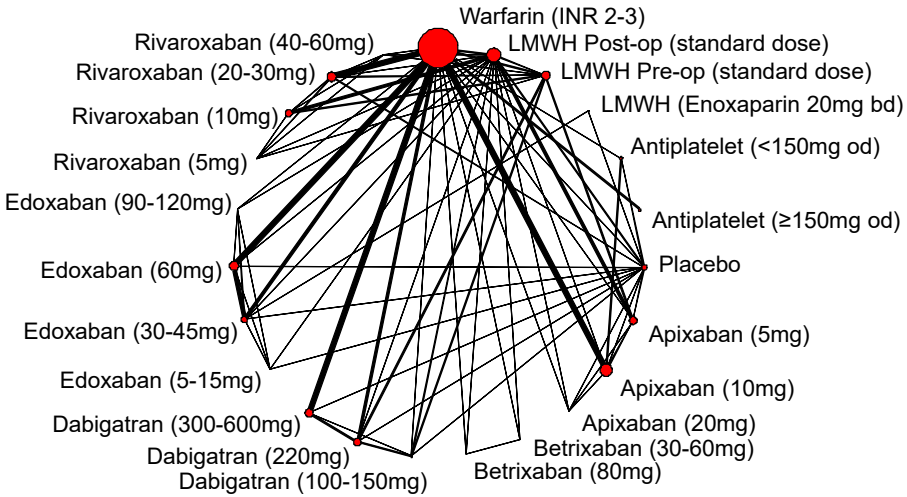


Table 184 Results for major bleeding (combined analysis): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Post-op (standard dose)	1.65 (1.11 , 2.44)	0.61 (0.41 , 0.89)	0.99 (0.75 , 1.29)
LMWH Pre-op (standard dose)	2.14 (1.36 , 3.36)	0.62 (0.45 , 0.89)	0.99 (0.75 , 1.3)
LMWH (Enoxaparin 40mg)	-	0.61 (0.21 , 1.84)	0.61 (0.21 , 1.84)
Antiplatelet (<150mg)	1.01 (0.57 , 1.80)	0.62 (0.41 , 0.93)	0.73 (0.52 , 1.03)
Antiplatelet (≥150mg)	1.07 (0.82 , 1.41)	-	1.07 (0.82 , 1.41)
Placebo	0.60 (0.36 , 0.99)	-	0.60 (0.36 , 0.99)
Apixaban (5mg)	-	0.89 (0.60 , 1.31)	0.89 (0.60 , 1.31)
Apixaban (10mg)	0.67 (0.59 , 0.77)	-	0.67 (0.59 , 0.77)
Apixaban (20mg)	1.77 (0.84 , 3.76)	-	1.77 (0.84 , 3.76)
Dabigatran (100-150mg)	-	0.62 (0.39 , 0.97)	0.62 (0.39 , 0.97)
Dabigatran (220mg)	0.82 (0.71 , 0.94)	-	0.82 (0.71 , 0.94)
Dabigatran (300-600mg)	0.91 (0.80 , 1.04)	-	0.91 (0.80 , 1.04)
Edoxaban (30-45mg)	0.47 (0.40 , 0.54)	-	0.47 (0.40 , 0.54)
Edoxaban (60mg)	0.80 (0.70 , 0.90)	-	0.80 (0.70 , 0.90)
Edoxaban (90-120mg)	2.43 (0.97 , 5.76)	-	2.43 (0.97 , 5.76)
Rivaroxaban (5mg)	-	0.65 (0.22 , 1.55)	0.65 (0.22 , 1.55)
Rivaroxaban (10mg)	-	1.71 (1.14 , 2.57)	1.71 (1.14 , 2.57)
Rivaroxaban (20-30mg)	1.01 (0.88 , 1.15)	-	1.01 (0.88 , 1.15)
Rivaroxaban (40-60mg)	1.18 (0.45 , 3.12)	3.53 (2.00 , 6.22)	2.67 (1.63 , 4.36)
Imprecisely estimated comparisons			
Betrixaban (30-60mg)	-	*0.09 (0 , 2.87)*	*0.09 (0 , 2.87)*
Betrixaban (80mg)	-	*0.10 (0 , 3.07)*	*0.10 (0 , 3.07)*
Edoxaban (5-15mg)	-	*0.63 (0.10 , 2.64)*	*0.63 (0.10 , 2.64)*

10.3 Clinically relevant bleeding

A total of 51 trials reported on clinically relevant bleeding, leading to a network of 22 interventions (Figure 112). These trials reported a total of 14324 clinically relevant bleeding events. Comparisons with the reference intervention (warfarin (INR 2-3)), presented in Table 185, suggest that risk of clinically relevant bleeding was lower with LMWH compared with warfarin (INR 2-3). The risk of clinically relevant bleeding was also lower for antiplatelets and placebo compared with warfarin (INR 2-3), as found in the atrial fibrillation and VTE secondary prevention reviews. Among the NOAC interventionss, risk of clinically relevant bleeding was lower with apixaban (5mg and 10mg daily), betrixaban (30-60mg daily), dabigatran, edoxaban (30-45mg and 60mg daily) and rivaroxaban (5mg and 10mg daily) compared with warfarin (INR 2-3), but higher with edoxaban (90mg daily). These findings are generally in agreement with those from the atrial fibrillation and VTE treatment reviews.

Figure 112 Network plot for clinically relevant bleeding (combined analysis)

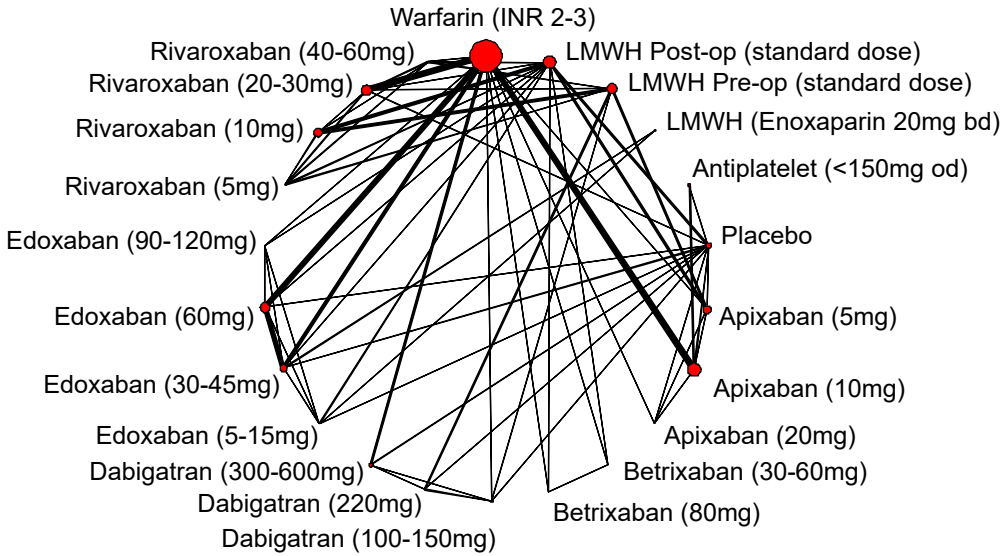


Table 185 Results for clinically relevant bleeding (combined analysis): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Post-op (standard dose)	-	0.39 (0.29 , 0.53)	0.39 (0.29 , 0.53)
LMWH Pre-op (standard dose)	-	0.48 (0.36 , 0.66)	0.48 (0.36 , 0.66)
LMWH (Enoxaparin 40mg)	-	0.52 (0.31 , 0.86)	0.52 (0.31 , 0.86)
Antiplatelet (<150mg)	-	0.52 (0.40 , 0.67)	0.52 (0.40 , 0.67)
Placebo	0.28 (0.21 , 0.37)	-	0.28 (0.21 , 0.37)
Apixaban (5mg)	0.40 (0.30 , 0.54)	-	0.40 (0.30 , 0.54)
Apixaban (10mg)	0.61 (0.55 , 0.67)	-	0.61 (0.55 , 0.67)
Apixaban (20mg)	0.74 (0.40 , 1.38)	-	0.74 (0.40 , 1.38)
Betrixaban (30-60mg)	0.24 (0.08 , 0.64)	-	0.24 (0.08 , 0.64)
Betrixaban (80mg)	0.45 (0.16 , 1.21)	-	0.45 (0.16 , 1.21)
Dabigatran (100-150mg)	0.54 (0.37 , 0.78)	-	0.54 (0.37 , 0.78)
Dabigatran (220mg)	-	0.57 (0.39 , 0.82)	0.57 (0.39 , 0.82)
Dabigatran (300-600mg)	0.62 (0.52 , 0.73)	-	0.62 (0.52 , 0.73)
Edoxaban (5-15mg)	-	0.53 (0.25 , 1.08)	0.53 (0.25 , 1.08)
Edoxaban (30-45mg)	0.59 (0.54 , 0.64)	-	0.59 (0.54 , 0.64)
Edoxaban (60mg)	0.83 (0.78 , 0.89)	-	0.83 (0.78 , 0.89)
Edoxaban (90-120mg)	2.04 (1.15 , 3.62)	0.82 (0.27 , 2.52)	1.69 (1.00 , 2.80)
Rivaroxaban (5mg)	-	0.42 (0.21 , 0.80)	0.42 (0.21 , 0.80)
Rivaroxaban (10mg)	-	0.72 (0.53 , 0.98)	0.72 (0.53 , 0.98)
Rivaroxaban (20-30mg)	1.00 (0.93 , 1.07)	-	1.00 (0.93 , 1.07)
Rivaroxaban (40-60mg)	0.23 (0.06 , 0.85)	1.46 (0.97 , 2.21)	1.24 (0.84 , 1.83)

10.4 All-cause mortality

In total 59 trials reported on all-cause mortality, leading to a network of 23 interventions (Figure 113). The total number of deaths was 8508. Comparisons with the reference intervention (warfarin (INR 2-3)), shown in Table 186, suggest that risk of all-cause mortality was higher with antiplatelet therapy (≥150mg daily) compared with warfarin (INR 2-3). Risk of all-cause mortality was generally lower among the NOAC interventions (estimated odds ratios compared with warfarin (INR 2-3) were between 0.87 and 0.93).

Figure 113 Network plot for all-cause mortality (combined analysis)

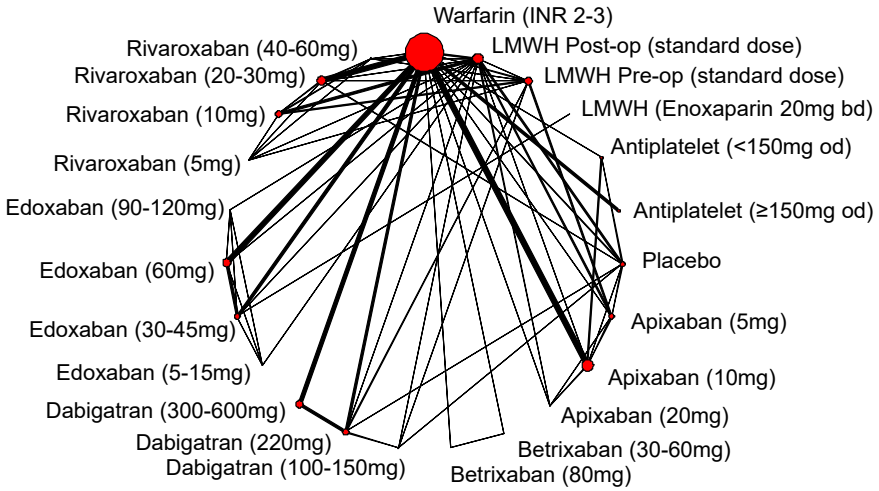


Table 186 Results for all-cause mortality (combined analysis): comparisons with warfarin (INR 2-3)

Comparisons with warfarin (INR 2-3)	Direct evidence OR (95% CI)	Indirect evidence OR (95% CI)	Network meta-analysis OR (95% CI)
LMWH Pre-op (standard dose)	-	1.70 (0.84 , 3.50)	1.70 (0.84 , 3.50)
LMWH Post-op (standard dose)	0.68 (0.32 , 1.47)	1.26 (0.80 , 1.98)	1.07 (0.72 , 1.6)
Antiplatelet (<150mg)	1.02 (0.76 , 1.37)	1.13 (0.87 , 1.47)	1.08 (0.88 , 1.32)
Antiplatelet (≥150mg)	1.23 (1.02 , 1.48)	-	1.23 (1.02 , 1.48)
Placebo	1.15 (0.77 , 1.71)	-	1.15 (0.77 , 1.71)
Apixaban (5mg)	-	1.07 (0.54 , 2.08)	1.07 (0.54 , 2.08)
Apixaban (10mg)	0.87 (0.78 , 0.97)	-	0.87 (0.78 , 0.97)
Dabigatran (220mg)	0.92 (0.81 , 1.04)	-	0.92 (0.81 , 1.04)
Dabigatran (300-600mg)	0.89 (0.79 , 1.01)	-	0.89 (0.79 , 1.01)
Edoxaban (30-45mg)	0.88 (0.79 , 0.97)	-	0.88 (0.79 , 0.97)
Edoxaban (60mg)	0.93 (0.85 , 1.02)	-	0.93 (0.85 , 1.02)
Rivaroxaban (10mg)	-	1.10 (0.70 , 1.72)	1.10 (0.70 , 1.72)
Rivaroxaban (20-30mg)	0.87 (0.75 , 1.02)	-	0.87 (0.75 , 1.02)
Imprecisely estimated comparisons			
Apixaban (20mg)	*0.67 (0.17 , 2.34)*	-	*0.67 (0.17 , 2.34)*
Betrixaban (30-60mg)	*0.71 (0.07 , 10.2)*	-	*0.71 (0.07 , 10.2)*
Betrixaban (80mg)	*0.19 (0 , 5.78)*	-	*0.19 (0 , 5.78)*
Dabigatran (100-150mg)	-	*1.36 (0.32 , 5.00)*	*1.36 (0.32 , 5.00)*
Edoxaban (5-15mg)	-	*0.76 (0.06 , 4.54)*	*0.76 (0.06 , 4.54)*
Edoxaban (90-120mg)	-	*0.16 (0 , 2.30)*	*0.16 (0 , 2.30)*
Rivaroxaban (40-60mg)	*0.27 (0.04 , 1.03)*	-	*0.27 (0.04 , 1.03)*

11. Cost-effectiveness results (2): venous thromboembolism

11.1 Introduction

In this chapter we present the results of the cost-effectiveness analysis for first line secondary prevention, acute treatment and primary prevention of venous thromboembolic disease. The decision questions, populations, interventions, outcomes, model structures, cost and utility inputs have been previously described in chapter 4. In this chapter we begin by describing clinical effectiveness inputs to the models, including relative treatment effects based on the evidence identified in the systematic reviews (chapters 7, 8 and 9), transition probabilities on the reference treatment on which relative effects are applied, other state transition probabilities based on evidence from longitudinal studies, and mortality. We then present the results from our cost-effectiveness model, together with sensitivity analyses to key assumptions made.

11.2 Model inputs: VTE secondary prevention

11.2.1 Overview

The state transition parameters that inform the secondary prevention model have two components. The relative effects of the different treatments come from the network meta-analyses of the studies identified in the systematic review (chapter 9). The transition parameters under standard care (i.e. no pharmacological treatment) are taken from longitudinal studies that provide information on the natural history of VTE.

11.2.2 Relative treatment efficacy

Hazard ratios for the relative treatment effects of aspirin, warfarin and three NOACs (apixaban, dabigatran and rivaroxaban) compared to placebo are derived from the network meta-analysis (Table 150). These hazard ratios were applied to the risk of symptomatic VTE on the reference treatment (no pharmacotherapy) to estimate the efficacy of each intervention. The network meta-analysis revealed inconsistent results between the WODIT trials which used a no treatment control arm and other trials which used a placebo control arm. The estimated hazard for no treatment lacked face validity as it was much lower than placebo and aspirin and was similar to the NOACs.

Therefore, we decided that aspirin, warfarin and NOAC efficacy relative to placebo was the more reliable estimate for the cost-effectiveness model.

Given a recurrent VTE event, we estimated the probability that it is a DVT, which can be subtracted from 1 to give the probability that it is a PE. If the recurrent VTE is a PE, we estimated the probability that is a non-fatal PE. Due to very small numbers of events in the secondary prevention RCTs, we are unable to estimate relative treatment effects for these conditional probabilities and assumed that they are treatment independent. We therefore treat each arm of each trial as an independent source of information on (i) the probability of a DVT-only given a recurrent VTE event and (ii) the probability of a non-fatal PE given a PE event. Eight out of the ten studies in the systematic review were included in this analysis; two studies did not record counts of DVT, non-fatal PE and fatal PE. The counts of VTE, DVT, non-fatal PE and fatal PE are in Table 144. Both fixed and random effects single arm meta-analyses were explored (including study arms with zero events). The random effects models did not show evidence of a better fit compared to the fixed effect models. We therefore used the results from the fixed effect meta-analysis to estimate conditional probabilities and uncertainty using Beta distributions (Table 187).

Table 187 Estimated risk for DVT given VTE recurrence and non-fatal PE given PE.

Event	Proportion	Alpha	Beta	Distribution
DVT given recurrent VTE	0.626	268	160	Beta
Non-fatal PE given PE	0.919	147	13	Beta

11.2.3 Relative treatment safety

The criteria for and classification of bleeding events is not uniform across RCTs and is the subject of wider debate[242]. Our model distinguishes between fatal bleeds, non-fatal intra-cranial haemorrhage (ICH) and other clinically relevant bleeds (those which require an intervention or hospital admission). Minor bleeds, identified through close monitoring in RCTs, that do not require intervention are not considered clinically relevant and have not been included in the model due to the minimal impact on quality of life and costs.

The incidence of ICH was not commonly reported in the secondary prevention VTE RCTs. Therefore the relative treatment effects of the NOACs compared to warfarin for ICH were derived from RCTs conducted in the AF population (Table 52). These trials included all NOAC and dose combinations compared in the secondary prevention of VTE. We assumed that the relative treatment effect of no pharmacotherapy and aspirin compared to warfarin for ICH are similar to those estimated for clinically relevant bleeding (Table 174).

The VTE secondary prevention RCTs did not provide sufficient information to determine what proportion of ICHs are fatal. Therefore the proportion of non-fatal ICHs was estimated from a study that investigated ICHs in patients with AF[243] using data from the RE-LY trial[112]. In total there were 56 fatal and 98 non-fatal ICHs. The relative treatment effects for other clinically relevant bleeding, compared to the reference group (no pharmacotherapy), for the interventions were estimated in a network meta-analysis (Table 174).

11.2.4 Transition probabilities with usual care (no pharmacotherapy)

A rapid literature review was conducted to identify long term follow up studies in a patient population with VTE to inform the natural history of VTE with usual care (no pharmacotherapy). The initial search identified 3,915 abstracts. After abstract selection and full paper review of the most relevant subset of papers, the following three studies, based in the same region of Italy, were selected as most relevant to parameterise the secondary prevention model.

Prandoni et al[244] recruited 528 patients with a first episode of venography proven DVT in a prospective cohort study conducted in a single centre in Italy. Patients were treated initially with unfractioned heparin or LMWH and then warfarin (INR target 2.0 to 3.0) for at least 3 months. Patients were advised to wear compression stockings for at least two years and followed up every 6 months for up to eight years. The aim of the study was to assess VTE recurrence, PTS incidence and mortality. The results of this study were used to parameterise the rate of mild/moderate and severe PTS.

Prandoni et al[245] broadened their previous work and reported on a prospective cohort of 1,626 patients recruited in three centres in Italy. Patients with a previous, imaging confirmed, symptomatic proximal DVT or a PE after discontinuation of anticoagulation (warfarin for on average 3 months) treatment were eligible. Patients were followed up in clinic or by telephone at least once every 6 months for a maximum of 10 years (median 50 months). The study estimated the cumulative incidence of symptomatic recurrent VTE, confirmed by imaging and we used these results to estimate the risk of recurrent VTE with no anticoagulation in our model.

Pengo et al[246] estimated the incidence of chronic thromboembolic pulmonary hypertension (CTPH) in a prospective cohort of 223 patients with a first episode of acute PE in one Italian centre. Patients initially received heparin and then oral anticoagulation for at least 6 months (target INR 2.0 to 3.0). Follow up was performed at least every 6 months during the first 2 years and then annually for up to 10 years; mean follow up was 94.3 months. CTPH was diagnosed in patients with unexplained persistent dyspnea, with supportive evidence on pulmonary angiography and mean pulmonary artery pressures. We used these findings to estimate transition from 'post PE' and 'post PE DVT' to CTPH in our model.

Parameters informing the risk of recurrent VTE in the usual care group (no long-term pharmacotherapy) were derived from Prandoni et al[245]. Individual patient data was reconstructed from the cumulative risk plot and exponential and Weibull parametric distributions were fitted to this data. The Akaike information criterion (AIC)[247] was used to determine the best fitting curve for the within study period (preferring models with lower AIC) and a visual examination determined the validity of the extrapolation. The best fitting curve for the within study period was the Weibull distribution (Figure 114, Table 188).

The risk of a clinically relevant bleed in the reference group was estimated based on PREVENT[233]. The PREVENT trial had a follow up of up to 4.3 years with a mean of 2.1 years. The observed rate of major bleeding, requiring hospitalisation or transfusion, in the placebo arm was 4 per 1,000 person years. Patients not receiving pharmacotherapy are assumed to be at equal risk of bleeds as placebo.

Figure 114 Parametric distributions for recurrent VTE baseline risk fitted to results reported in Prandoni et al[245]

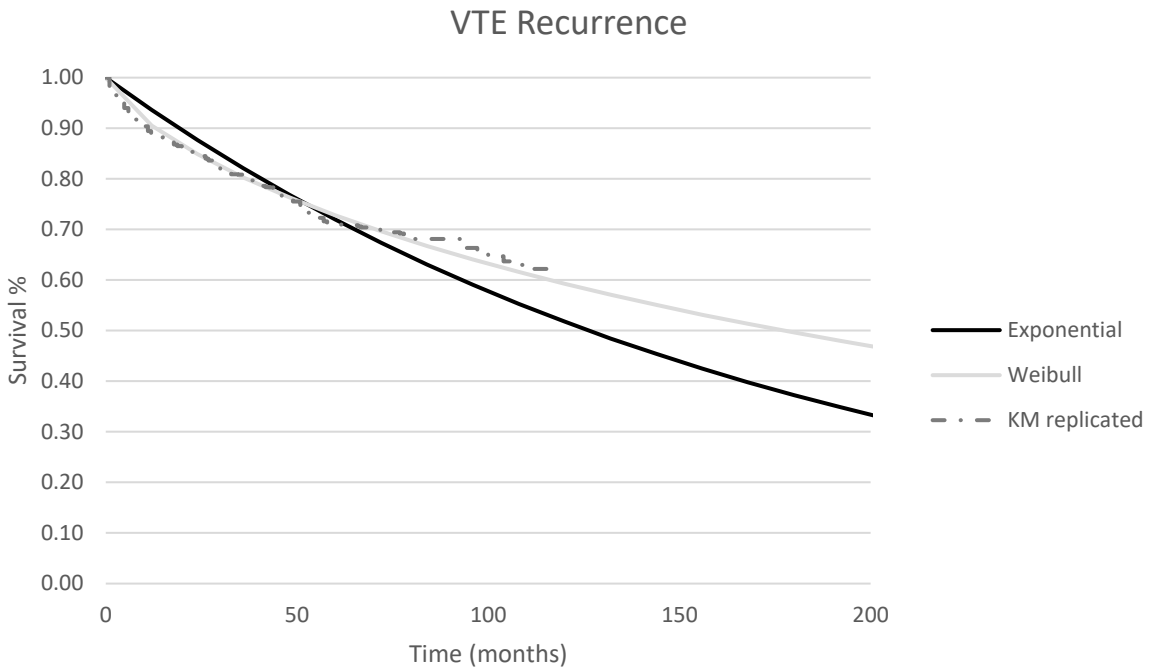


Table 188 Parameters and Akaike Information Criterion (AIC) for recurrent VTE baseline risk based on Prandoni et al[245]

Distribution	Scale	Shape	AIC
Exponential	0.005487	-	2758.604
Weibull	0.016565	0.721213	2702.246

11.2.5 Future VTE-related events

A proportion of patients develop PTS after a DVT. The incidence of PTS, stratified by mild/moderate or severe was derived from Prandoni et al[244] which provides a plot of the cumulative incidence of all PTS and severe PTS. Data from this plot were extracted using WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/) to estimate the yearly incidence of severe PTS and mild/moderate PTS (Table 189). The cumulative incidence of PTS levels off two years after the index VTE event and we assume that patients have no additional risk of PTS after that time. The rate of CTPH given a PE was taken from Pengo et al[246]. In total seven of 223 patients developed symptoms of CTPH, all seven events occurred in the initial two years (Table 190).

Table 189 Cumulative PTS rates given DVT

Year	Cumulative incidence PTS (95% confidence interval)	Cumulative incidence severe PTS (95% confidence interval)	Source
1	0.172 (0.135 to 0.215)	0.029 (0.009 to 0.044)	Prandoni[244]
2	0.231 (0.180 to 0.277)	0.062 (0.032 to 0.090)	Prandoni[244]

Table 190 Incidence of CTPH given PE

Month	Cumulative incidence of CTPH	Confidence interval	Source
12	0.031	0.007 to 0.055	Pengo 2004[246]
24	0.038	0.011 to 0.065	Pengo 2004[246]

11.2.6 Mortality

In the model, patients can die from a fatal PE, an ICH or other, all-cause, mortality. The rates of recurrent VTE and ICH including fatal PE and ICH events are described previously. We assumed that ICH was the cause of all of the fatal bleeding events. Seven trials[230-233,235,237,239] reported on fatal bleeds; all had low counts and four had zero events. We assumed that sudden fatal PEs do not accure a cost and non-sudden fatal PE accure the full cost of treating a PE. This proportion of sudden fatal PEs was assumed to be 74.4% as recorded in Prandoni et al[245].

All-cause mortality rates are applied to every health state in the model to incorporate other causes of death. These were obtained from the office of national statistics (ONS) [13] stratified by gender and age to match our population Appendix 10.

11.3 Model inputs: VTE acute treatment

11.3.1 Overview

Relative treatment effects for the probabilities in the first line acute treatment decision tree model have been derived from three network meta-analyses and a pair wise meta-analysis (described below) for the following four events: 1) Recurrent VTE; 2) Non-fatal ICH (pairwise meta-analysis); 3) Other clinically relevant bleeding; 4) Non VTE related mortality.

11.3.2 Relative treatment efficacy

The odds ratios of four NOACs (apixaban, dabigatran, edoxaban, rivaroxaban) compared to warfarin were derived from the network meta-analysis (Table 126). The probabilities of DVT given recurrent VTE and non-fatal PE given PE were, as with secondary prevention, assumed to be treatment independent and derived from single arms from all nine studies in the acute treatment review using a fixed effect meta-analysis (Table 192; Table 124).

Table 191 Odds ratios of VTE recurrence on acute treatment: all ORs are compared with warfarin

Intervention	OR	95% CI	Distribution
Dabigatran	1.09	0.75 to 1.59	MCMC posterior simulations
Rivaroxaban	0.90	0.67 to 1.21	MCMC posterior simulations
Apixaban	0.83	0.58 to 1.18	MCMC posterior simulations

Table 192 Estimated risk of DVT given VTE recurrence and non-fatal PE given PE

Event	Proportion	Alpha	Beta	Distribution
DVT given recurrent VTE	0.47	341	387	Beta
Non-fatal PE given a PE event	0.73	283	104	Beta

11.3.3 Relative treatment safety

Four out of the nine studies identified in the literature review reported non-fatal ICH. The incidence was low, 38 patients out of 21,916 experienced an event, and there was not enough data to perform a network meta-analysis. Instead we assumed all NOACs have a similar risk, and performed a pair-wise meta-analysis for all NOACs combined compared with warfarin. Fixed and random effect pair wise meta-analyses were

explored resulting in deviance information criterion (DIC)[26] values of 40.31 and 39.54, respectively. We preferred models with lower DIC where differences of at least 3 are considered to be meaningful. On this basis the fixed effect model was used to estimate the odds ratio and uncertainty (Table 193). This assumption was explored in a sensitivity analysis where we assumed the risk of non-fatal ICH for NOACs is the same as the risk on warfarin. The relative treatment effects for individual NOACs compared with warfarin for other clinically relevant bleeds were estimated in Table 136 and are provided below (Table 194).

11.3.4 Mortality

To derive the mortality in the six months of acute treatment a network meta-analysis was performed. The counts are the reported all-cause mortality with VTE related mortality deducted. Eight out of the nine studies identified in the literature review reported all-cause mortality and VTE related mortality separately (table 64). The data used in the network meta-analysis is in Appendix 9. The results relative to warfarin are in Table 195.

11.3.5 Transition probabilities with usual care (warfarin)

The risk of experiencing recurrent VTE, non-fatal ICH, CR bleed and non-VTE related mortality on usual care (warfarin) have been estimated from a single arm fixed effect meta-analysis model for each outcome using all the warfarin arms identified in the systematic review (including study arms with zero counts). The fixed effect model was chosen over random effects model on the basis of lower DIC. Each of the outcomes is considered to be independent and so are modelled separately to estimate parameters and Beta distributions representing uncertainty (Table 196).

Table 193 Odds ratios of non-fatal ICH in the acute treatment: NOACs combined compared with warfarin

Intervention	OR	95% CI	Distribution
NOACs	0.395	0.189 to 0.790	MCMC posterior simulations

Table 194 Odds ratios of clinically relevant bleeds in acute treatment: all ORs are compared with warfarin

Intervention	OR	95% CI	Distribution
Dabigatran	0.61	0.49 to 0.76	MCMC posterior simulations

Rivaroxaban	0.93	0.81 to 1.08	MCMC posterior simulations
Edoxaban	0.81	0.70 to 0.94	MCMC posterior simulations
Apixaban	0.44	0.35 to 0.55	MCMC posterior simulations

Table 195 Odds ratios of non-VTE/ICH related mortality in acute treatment: all ORs are compared with warfarin

Intervention	OR	95% CI	Distribution
Dabigatran	0.98	0.64 to 4.84	MCMC posterior simulations
Rivaroxaban	0.96	0.71 to 1.30	MCMC posterior simulations
Edoxaban	1.06	0.81 to 1.39	MCMC posterior simulations
Apixaban	0.87	0.54 to 1.39	MCMC posterior simulations

Table 196 Estimated risk on warfarin for recurrent VTE, non-fatal ICH, clinically relevant bleeding and non-VTE related mortality.

Event	Proportion	Alpha	Beta	Distribution
Recurrent VTE	0.027	378	13,474	Beta
Non-fatal ICH	0.002	27	10,930	Beta
Clinically relevant bleed	0.097	1319	12,288	Beta
Non-VTE related mortality	0.018	244	13,496	Beta

11.4 Model inputs: VTE primary prevention

11.4.1 Overview

Absolute probabilities of VTE, clinically relevant bleeds and mortality on reference treatment (LMWH) are estimated from the LMWH arms of the primary prevention trials identified in our systematic review, and these probabilities differ between THR and TKR populations (due to different length of time on treatment). All the relative effects of NOACs have been derived from network meta-analyses, and the MCMC simulations are used directly as inputs to our probabilistic model, retaining all correlations between parameter estimates. We stratified relative effects of NOACs compared to LMWH by THR and TKR populations. However due to sparse data for adverse events, and for consistency with the clinical effectiveness results, we assumed that relative effects are common across THR and TKR populations for CR bleeds and all cause mortality.

11.4.2 Relative treatment efficacy

The proportion of patients that experience a symptomatic VTE event was derived from network meta-analyses stratified by post THR and TKR reported in Table 94 and Table

96 respectively. The reference comparator for these two populations is post-operative LMWH. We pooled relative treatment effects over the THR and TKR populations in a sensitivity analysis.

11.4.3 Relative treatment safety

ICH was only reported in 12 primary prevention studies. Within these studies the total count of ICH is six out of 32,879 patients (it may also be the case that studies which did not report ICH did not observe any events, which would mean the risk is even lower). Patients receiving primary prevention (for up to 35 days) are at much lower risk of ICH than patients receiving acute treatment (up to 6 months) or long-term secondary prevention. Due to extremely low incidence, this outcome has not been incorporated into the primary prevention model. The relative treatment effects for clinically relevant bleeding compared to post-operative LMWH are reported in Table 116.

11.4.4 Mortality

Relative treatment effects for all-cause mortality have been derived from the network meta-analysis. This includes fatal VTE events, so to avoid double counting VTE related mortality, only the rates from all-cause mortality informed the transition to death in the model. The results relative to post-operative LMWH are given in Table 118. The mortality rates for patients that do not experience a symptomatic VTE and enter the two stage Markov model were taken from the ONS all-cause mortality Appendix 10.

11.4.5 Transition probabilities with usual care (LMWH)

Usual care in the primary prevention model is post-operative LMWH[11]. The risk of experiencing each event (VTE, CR bleed and mortality) on the reference treatment was estimated from single arm fixed effect meta-analyses for each outcome and population (THR or TKR), using reference treatment arms identified in the systematic review (including studies with zero events). The outcomes are considered to be independent and so are modelled separately. The absolute risk of recurrent VTE and all cause mortality on LMWH was estimated separately for the THR and TKR populations, since THR patients remain on treatment for longer. There was not enough information on other clinically relevant bleeding in the THR population to estimate an absolute risk; we therefore pooled over TKR and THR populations. We fitted a random

effects model over the pooled TKR and THR population for CR bleeds due to the substantial heterogeneity; random effects model giving a DIC of 22.7 compared to 43.0 for a fixed effect model. The resulting parameter estimates and Beta distributions that represent the uncertainty in these estimates are given in Table 197.

Table 197 Estimated risk on LMWH for VTE, clinically relevant bleeding and mortality minus VTE related mortality. Beta distributions, Beta (alpha,beta), representing uncertainty in the estimates are given.

Event	Proportion	Alpha	Beta	Distribution
Recurrent VTE THR	0.035	65	1,787	Beta
Recurrent VTE TKR	0.023	36	1,527	Beta
Mortality THR	0.019	53	2,619	Beta
Mortality TKR	0.004	16	4,342	Beta
Event	**Proportion**	**LB**	**UB**	**Distribution**
Clinically relevant bleed	0.029	0.005	0.121	MCMC simulations

11.5 Sensitivity analyses

We tested the robustness of the models' results to some of the model parameters in one way sensitivity analyses, listed below.

Proportion of VTE events that are fatal and non-fatal PE (secondary prevention): We varied the proportion of DVT, non-fatal PE and fatal PE when a patient experienced a recurrent VTE event in the secondary prevention model. Having a large proportion of non-fatal recurrent VTE events has a small effect on quality of life compared to having a large proportion of fatal events. We used a beta distribution with proportions estimated in Prandoni et al[244]; 101 recurrent events consisting of 80 DVTs, 10 non-fatal PE and 11 fatal PE.

Risk of CR bleed on warfarin (secondary prevention): The rate used in the base case was the observed rate for major bleeds in a secondary prevention RCT (PREVENT[233]). This could be an underestimate due to only including major and not clinically relevant minor bleeds. In sensitivity analysis we instead use the odds of experience a CR bleed taken from the AF population (section 6.2.4).

Rate of non-fatal ICH (acute treatment): We did not have enough data to perform a network meta-analysis on this outcome. In the base case we assumed all NOACs have the same relative treatment effect compared with warfarin. We tested this assumption by instead assuming the rate of non-fatal ICH is equal among NOACs and Warfarin in this sensitivity analysis.

Cost of edoxaban (acute treatment): Edoxaban does not currently have a list price in the UK. For the base case we assume a cost similar to the list price of other NOACs, and test this assumption in a sensitivity analysis. We do this through a threshold analyses to see what the cost of edoxaban would have to be for it to be considered cost effective at a willingness to pay threshold of £20,000 per QALY. We begin by assuming a zero drug cost for edoxaban, noting that if it is not found to be cost-effective at a zero cost, then increasing the cost will not change our results.

Changing the time on treatment (acute treatment): In the majority of trials in our review patients receive acute treatment for six months, however NICE guidance recommends three months in acute treatment, with an additional three months treatment if necessary. We assume six months treatment in our base case, and reduce this to three months in a sensitivity analysis. Note that due to a lack of evidence, we assume relative treatment efficacy is unchanged if given for 3 months rather than 6 months, however absolute event rates for adverse events decrease with time on treatment, and treatment costs are reduced.

Pooling post THR and post TKR populations for relative treatment effect of VTE (primary prevention): We pooled THR and TKR populations to estimate relative treatment effects of VTE in primary prevention in this sensitivity analysis. The relative treatment effects are in Appendix 11.

Dabigatran dose for elderly patients (primary prevention): In this sensitivity analysis we costed dabigatran at a lower dose in the primary prevention models to match the dose recommended for the elderly in the BNF; 150mg once daily.

Cost of treatment related adverse events (all models): We varied the cost of treatment related adverse events by +/-50%. These included CR bleeds, ICH and post ICH.

Cost of VTE events (all models): We varied the cost of VTE events by +/-50%. These included DVT, PE, mild moderate PTS, severe PTS and CTPH.

Utility decrements of treatment related adverse events (all models): We varied the utility decrement of treatment related adverse events by +/-50%. These included CR bleeds, ICH and post ICH.

Utility decrements of VTE events (all models): We varied the utility decrement of VTE events by +/-50%. These included DVT, PE, mild moderate PTS, severe PTS and CTPH.

Cost of warfarin (all models): We assess sensitivity of our results to administration and montitoring cost of warfarin through a threshold analysis to see what the cost of warfarin would have to be for it to be considered cost effective at a willingness to pay threshold of £20,000 per QALY. We begin by assuming a zero cost for warfarin, noting that if it is not found to be cost-effective at a zero cost, then increasing the cost will not change our results.

11.6 Results of the cost effectiveness model: VTE secondary prevention

We estimated expected costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000 for first line prevention therapy (Table 198). The cheapest comparator is aspirin (total expected cost £20,671). No pharmacotherapy is the next cheapest treatment with benefits similar to aspirin. Warfarin and the NOACs all have substantially higher costs than aspirin and no pharmacotherapy, and the NOACs are more expensive than warfarin. Dabigatran and apixaban (5mg) have marginally higher expected QALYs compared to no pharmacotherapy. Apixaban (2.5mg) has the lowest expected QALYs followed by warfarin. Apixaban (2.5mg) has the highest hazard ratio for the risk of ICH, albeit estimated imprecisely. Although the NOACs and warfarin prevent more

recurrent VTEs than no pharmacotherapy or aspirin, the rate of recurrent VTE is low, and the rate of adverse events (ICH and clinically relevant bleeds), which can have a long-term impact on quality of life, are generally higher for the NOACs than aspirin or no pharmacotherapy.

Aspirin has the highest expected net benefit at a willingness to pay per QALY threshold of £20,000 and £30,000 (Table 198). However the confidence interval for the incremental net benefit of aspirin includes zero indicating uncertainty about whether it is more cost-effective than no pharmacotherapy. All NOACs have negative expected incremental net benefits at the £20,000 and £30,000 thresholds, and all confidence intervals are negative at the £20,000 threshold, indicating that they are not cost-effective compared with no pharmacotherapy. Dabigatran, which had the lowest estimated hazard ratio for recurrent VTE and ICH of all the NOACs, also has the highest expected net benefit of any NOAC. However dabigatran is not cost effective relative to no pharmacotherapy even at the £30,000 threshold, as the incremental net monetary benefit is negative (-£3402; -£12,338 to £5424). Figure 115 shows that although there is uncertainty in the estimated costs and QALYs, it is clear that aspirin has lower costs and similar benefits in the majority of the samples. Over a wide range of willingness to pay per QALY thresholds, aspirin has the highest expected net benefit (Figure 117), and also the highest probability of being the most cost-effective (Figure 116), although there is a non-negligible probability that no pharmacotherapy is the most cost-effective intervention for secondary prevention of VTE at a threshold of £20,000 to £30,000. These results suggest that it is not cost effective to prescribe NOACs or warfarin for secondary prevention of VTE over the range of willingness to pay thresholds that we explored (up to £40,000 per QALY).

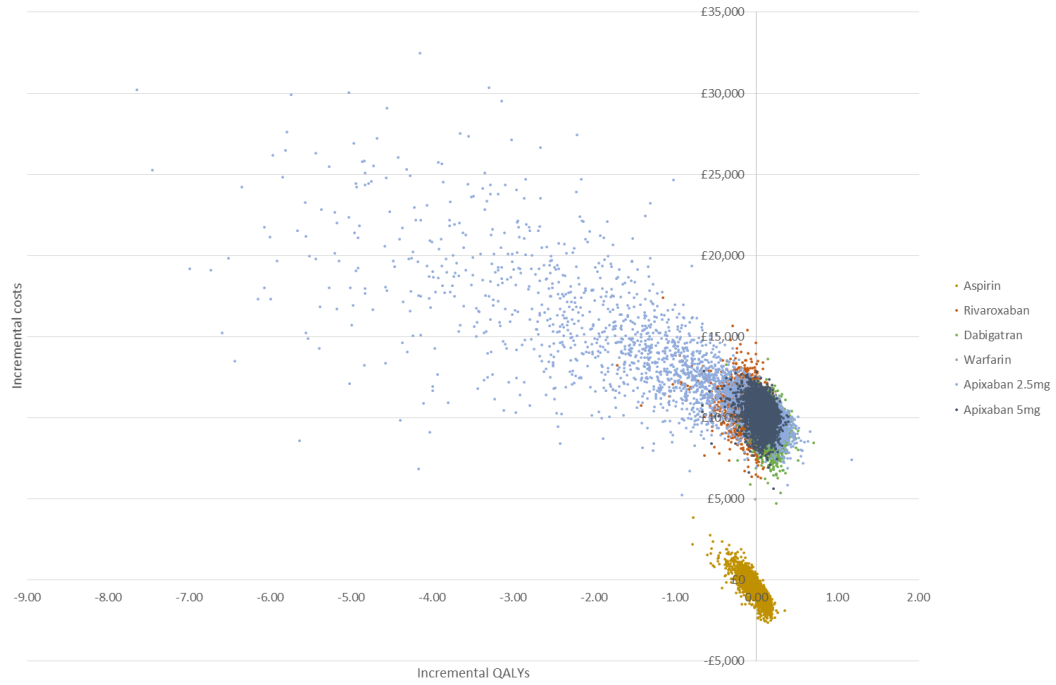
The estimated per-person expected value of perfect information was £757 at a willingness-to-pay of £20,000 and £1291 at £30,000. Assuming a VTE incidence of 183 per 100,000 in a European population,[10] and population of 65-70 year olds in England and Wales of approximately 3 million (2011 census), gives an estimated VTE incidence rate per year of 5490. Population EVPI over a 10 year time horizon, discounting at 3.5%, is approximately £36 million and £61 million at willingness-to-pay thresholds of £20,000 and £30,000 respectively.

Figure 118 shows the proportion of the EVPI that is attributable to different groups of parameters. The optimal decision is most sensitive to the relative treatment effects, suggesting that there may be value in running a large trial comparing a NOAC, with aspirin and no pharmacotherapy. Note however that due to low event rates a study powered to capture VTE events may be prohibitive.

Table 198 Results of the secondary prevention cost effectiveness analysis. Incremental results are relative to no pharmacotherapy. Figures are presented as mean (confidence interval)

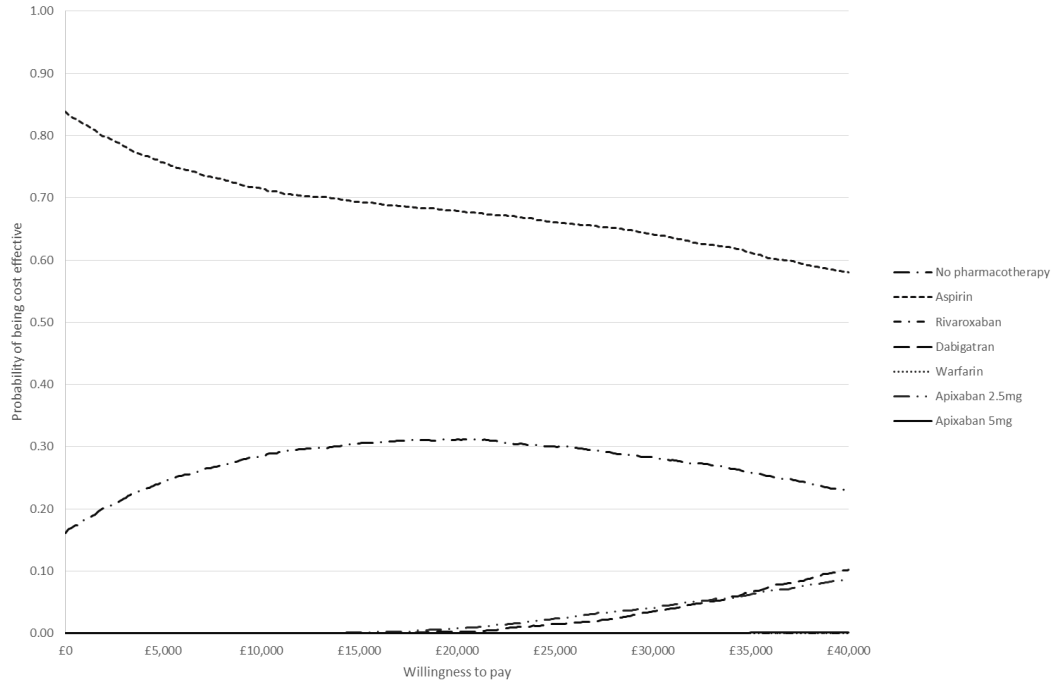
	No pharmacotherapy	Aspirin	Rivaroxaban	Dabigatran	Warfarin	Apixaban 2.5mg	Apixaban 5mg
Costs	£21,282 (£14,619 to £30,388)	£20,671 (£14,342 to £29,346)	£31,781 (£26,270 to £39,317)	£30,952 (£25,613 to £38,396)	£26,379 (£21,103 to £33,550)	£33,496 (£26,672 to £43,389)	£31,557 (£26,061 to £39,312)
QALYs	12.58 (12.16 to 12.94)	12.58 (12.05 to 12.99)	12.50 (11.97 to 12.91)	12.74 (12.32 to 13.09)	12.32 (11.67 to 12.78)	11.83 (8.1 to 13.07)	12.63 (12.17 to 13.00)
Incremental costs	-	£-611 (£-1,834 to £939)	£10,498 (£8,197 to £12,640)	£9,670 (£7,545 to £11,406)	£5,097 (£2,337 to £7,829)	£12,213 (£8,365 to £22,029)	£10,275 (£8,429 to £11,810)
Incremental QALYs	-	0.00 (-0.27 to 0.15)	-0.08 (-0.42 to 0.16)	0.16 (-0.05 to 0.36)	-0.26 (-0.71 to 0.03)	-0.75 (-4.40 to 0.39)	0.06 (-0.18 to 0.25)
Incremental net ,monetary benefit (at £20,000)		623 (-6,404 to 4,602)	£-12,119 (£-19,983 to £-6,238)	£-6,536 (£-1,1671 to £-1,513)	£-10,351 (£-20,582 to £-3,256)	£-27,180 (£-109,197 to £-1,272)	£-9,171 (£-14,548 to £-4,565)
Incremental net monetary benefit (at £30,000)	-	£629 (£-9,176 to £6,085)	£-13,740 (£-28,266 to £-3,216)	£-3,402 (£-12,388 to £5,424)	£-15,606 (£-34,467 to £-2,776)	£-42,146 (£-19,7897 to £6,442)	£-8,067 (£-18,012 to £294)

Figure 115 Incremental cost effectiveness plane for secondary prevention (No pharmacotherapy: reference)



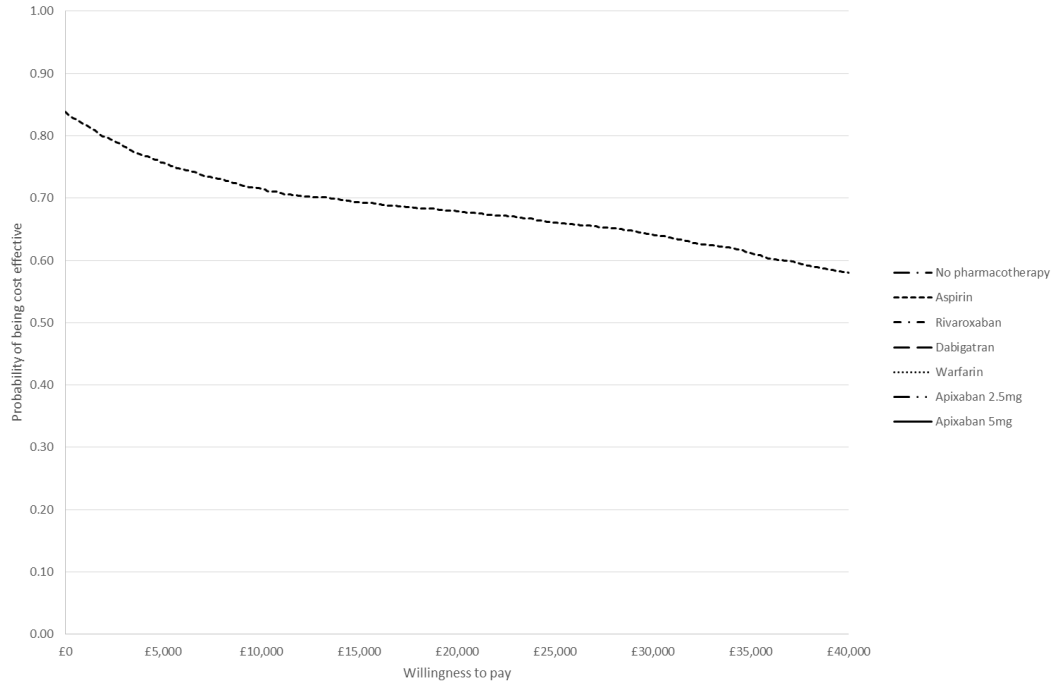
See section 4.5.3 for further details

Figure 116 Cost effectiveness acceptability curve for secondary prevention



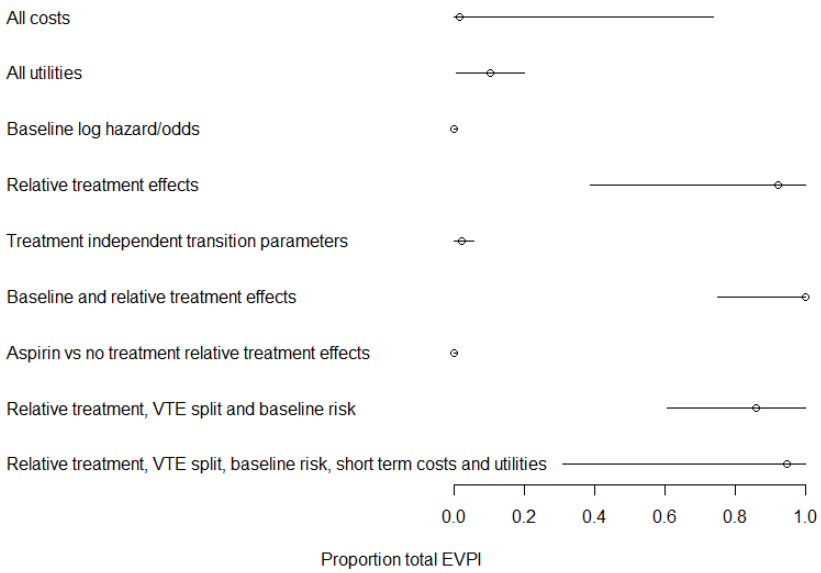
See section 4.5.3 for further details

Figure 117 Cost effectiveness acceptability frontier for secondary prevention



See section 4.5.3 for further details

Figure 118 Expected value of partial perfect information (EVPPI) for subsets of model input parameters in the VTE secondary prevention model, presented as a proportion of the total EVPI*



* SAVI estimated EVPPI scaled by EVPPI of all parameters as estimated by SAVI. 95% intervals are ±1.96×SE and are truncated above at 1 and below at 0.

11.7 Results of the cost effectiveness model: VTE acute treatment

We estimated expected costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000 for first line therapy (Table 199). Expected costs and benefits are similar across all treatments, because of the short (6 month) treatment duration and the small and imprecisely estimated effects of NOACs on VTE recurrence and adverse events compared to warfarin. Warfarin has the lowest expected cost (£19,651), followed by dabigatran, edoxaban, apixaban, and rivaoxaban the most expensive (£19,753). Apixaban had the highest expected QALYs (12.02), but this is only 0.04 QALYs greater than the interventions with the lowest expected QALYs (edoxaban, warfarin and dabigatran).

The expected net benefit is highest for apixaban at willingness to pay per QALY thresholds of £20,000 and £30,000. This is due to the marginally lower risk of recurrent VTE, clinically relevant bleeding and non-VTE related mortality with apixaban relative to other NOACs. However there is substantial uncertainty around this estimate. Rivaroxoban also has a positive incremental net benefit compared with warfarin. Confidence intervals for incremental net benefit are wide for all treatments, reflecting substantial uncertainty that is also seen in the incremental cost-effectiveness plane (Figure 119).

The cost-effectiveness acceptability curves (Figure 120) show that for very low willingness to pay per QALY, warfarin is the most cost-effective treatment (because it has lowest expected costs). For willingness to pay thresholds above £1,000, apixaban (5mg) has the highest expected net benefit (Figure 121) with a probability of being most cost-effective at £20,000 to £30,000 per QALY thresholds of approximately 0.54. However it is possible that rivaroxaban or dabigatran are the most cost-effective interventions, even at high willingness to pay thresholds.

The per-person expected value of perfect information was £365 at a willingness-to-pay of £20,000 and £579 at £30,000. Assuming a VTE incidence rate per year of 5490 (as for secondary prevention). Population EVPI over a 10 year time horizon,

discounting at 3.5%, is approximately £17million and £27million at willingness-to-pay of £20,000 and £30,000 respectively.

Figure 122 shows the proportion of the EVPI that is attributable to different groups of parameters. The optimal decision is most sensitive to uncertainty in the cost and utility model inputs. This suggests there may be value in conducting a study to estimate the utilities associated with VTE events and treatment related events. Since such a study is likely to be relatively inexpensive to conduct (compared with an RCT), and given the magnitude of likely benefits, this should be considered a research priority. The optimal decision is not very sensitive to event rates on the reference comparator (baseline risk), relative treatment effects for all comparators, relative treatment effects of apixaban versus warfarin (the two comparators with the highest probability of being cost effective at a willingness to pay of £20,000 per QALY), and treatment independent transition parameters.

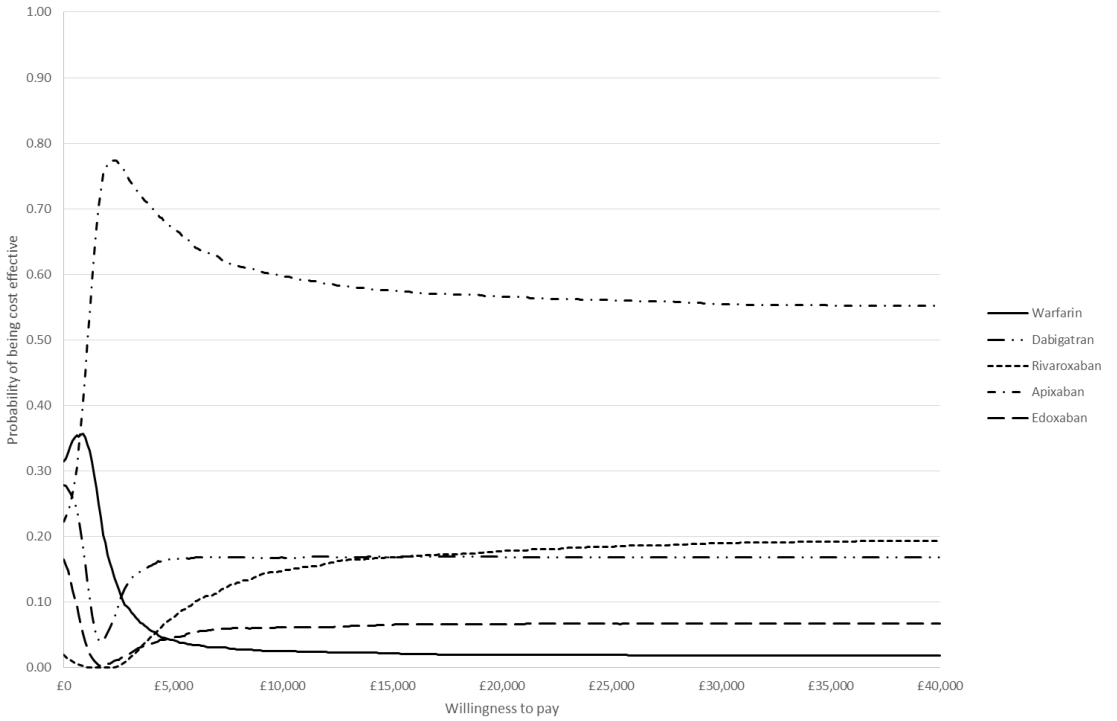
Table 199 Results of the acute treatment cost effectiveness analysis: Costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Costs	£19,651 (£13,543 to £27,667)	£19,663 (£13,522 to £27,695)	£19,753 (£13,579 to £27,819)	£19,683 (£13,543 to £27,801)	£19,675 (£13,557 to £27,732)
QALYs	11.98 (11.46 to 12.36)	11.98 (11.46 to 12.37)	11.99 (11.48 to 12.38)	12.02 (11.49 to 12.41)	11.98 (11.46 to 12.36)
Incremental costs		£12 (£-168 to £152)	£102 (£-22 to £211)	£31 (£-149 to £180)	£24 (£-99 to £133)
Incremental QALYs		0.00 (-0.10 to 0.08)	0.01 (-0.06 to 0.07)	0.04 (-0.07 to 0.12)	-0.01 (-0.07 to 0.05)
Incremental net monetary benefit (at £20,000)		£21 (£-1,885 to £1,498)	£196 (£-1,123 to £1,281)	£710 (£-1,322 to £2,185)	£-132 (£-1,369 to £920)
Incremental net monetary benefit (at £30,000)		£38 (£-2,903 to £2,324)	£344 (£-1,686 to £2,018)	£1,080 (£-2,059 to £3,351)	£-186 (£-2,084 to £1,434)

Figure 119 Incremental cost effectiveness plane for acute treatment (Warfarin: reference)

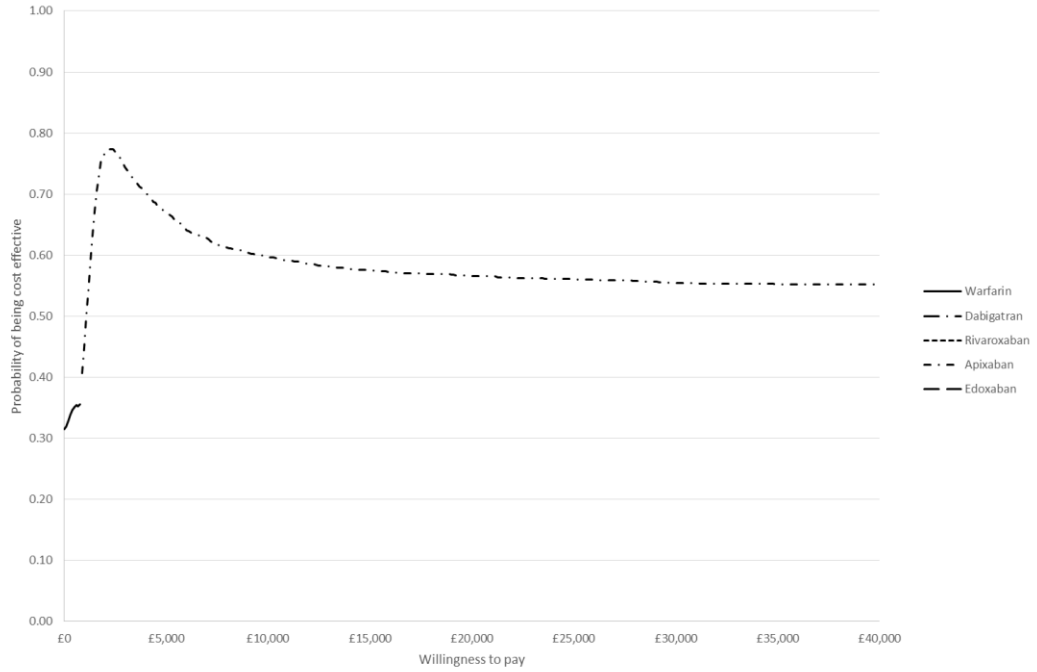
See section 4.5.3 for further details

Figure 120 Cost effectiveness acceptability curve for acute treatment



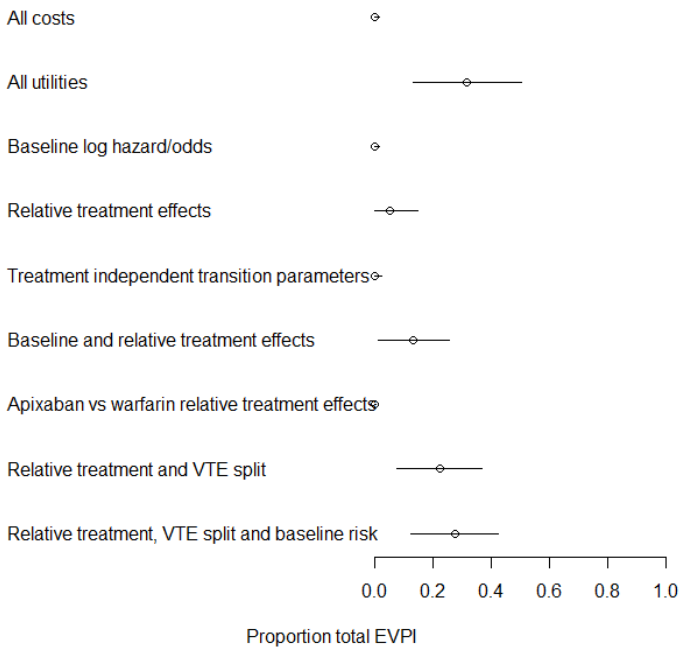
See section 4.5.3 for further details

Figure 121 Cost effectiveness acceptability frontier for acute treatment



See section 4.5.3 for further details

Figure 122 Expected value of partial perfect information (EVPPI) for subsets of parameters in the VTE acute treatment model, as a proportion of the total EVPI*



* SAVI estimated EVPPI scaled by EVPPI of all parameters as estimated by SAVI. 95% intervals are ±1.96×SE and are truncated above at 1 and below at 0.

11.8 Results of the cost effectiveness model: VTE primary prevention

11.8.1 Total hip replacement

The expected total costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000 for first line prevention therapy are reported in Table 200. The lowest expected total costs are for apixaban (£702) followed by rivaroxaban (£718), then dabigatran (£893). LMWH has the highest expected cost (£1,062). Expected benefits are highest for rivaroxaban and LMWH (9.10 QALYs), followed by dabigatran (9.04 QALYs) then apixaban (8.96 QALYs). At both £20,000 and £30,000 willingness to pay per QALY thresholds, rivaroxaban has the highest expected incremental net benefit, although confidence intervals around net benefit are wide (particularly for dabigatran) and also skewed (apixaban).

Rivaroxaban has the highest expected net benefit over the range of willingness to pay thresholds we explored (Figure 124), but with substantial uncertainty: its probability of being the most cost-effective was 0.35 for willingness to pay per QALY threshold £30,000 (Figure 125). Because of the very wide confidence limits for dabigatran, there is an apparently contradictory finding that it has the highest probability of being the most cost-effective NOAC (Figure 124) for thresholds above £14,000, but does not have the highest expected net benefit (Figure 125, Table 200). This phenomenon is documented in the literature, and in these circumstances the CEAF (Figure 125) is a better summary than CEAC (Figure 124)[248]. Note the general high degree of uncertainty as to which treatment is the most cost-effective.

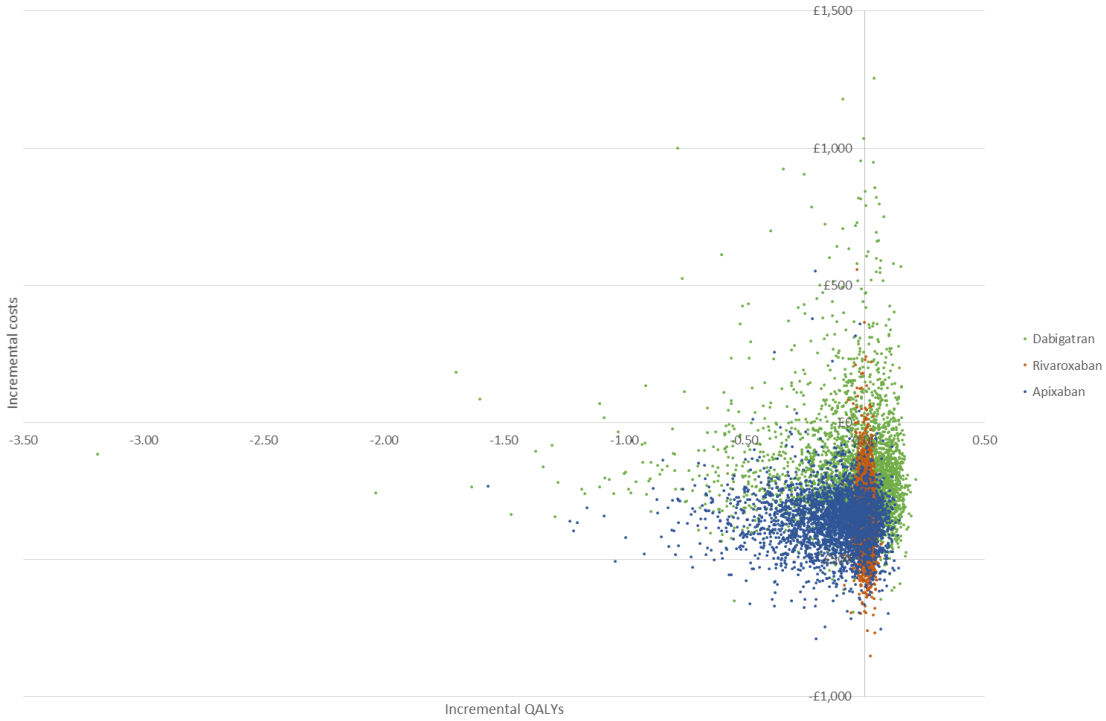
The per-person expected value of perfect information estimated was £730 at a willingness-to-pay of £20,000 and £1,138 at £30,000. Assuming an annual incidence of primary THR operations per year[72] of 76,000, population EVPI over a 10 year time horizon, discounting at 3.5%, is approximately £475million and £741million at willingness-to-pay of £20,000 and £30,000 respectively. These very high figures reflect the high per person EVPI (driven by the uncertainty in the available evidence) and also the large volume of primary THR operations that are conducted.

Figure 126 shows the proportion of the EVPI that is attributable to different groups of parameters. The optimal decision is most sensitive to uncertainty in the treatment independent transition parameters, and also sensitive to uncertainty in the cost parameters. The decision is not very sensitive to uncertainty in utility values, event rates on the reference comparator (baseline risk), relative treatment effects for all comparators, relative treatment effects of rivaroxaban versus LMWH (the two comparators with the highest probability of being cost effective at a willingness to pay of £20,000 per QALY), and the proportion of VTE events. This suggests that there may be value in running a longitudinal study examining the treatment independent transition parameters: rates of mild/moderate PTS, severe PTS, CTPH and the proportion split of VTE events.

Table 200 Results of the THR primary prevention cost effectiveness analysis: Costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit

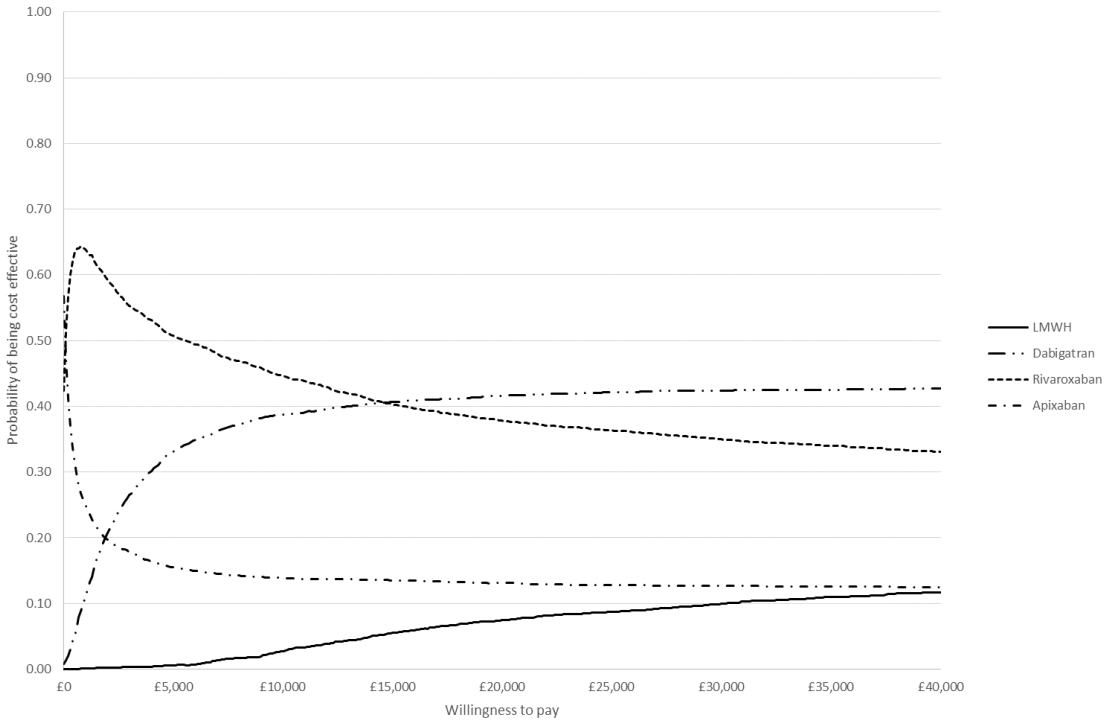
	LMWH	Dabigatran	Rivaroxaban	Apixaban
Costs	£1062 (£888 to £1311)	£893 (£635 to £1495)	£718 (£571 to £1045)	£702 (£573 to £953)
QALYs	9.1 (8.85 to 9.35)	9.04 (8.44 to 9.40)	9.10 (8.84 to 9.36)	8.96 (8.47 to 9.31)
Incremental costs		£-169 (£-430 to £345)	£-344 (£-558 to £-99)	£-360 (£-559 to £-156)
Incremental QALYs		-0.06 (-0.61 to 0.15)	0.01 (-0.04 to 0.04)	-0.13 (-0.57 to 0.09)
Incremental Net Monetary Benefit (at £20,000)		£-1066 (£-12127 to £3191)	£453 (£-485 to £1312)	£-2284 (£-11017 to £2085)
Incremental Net Monetary Benefit (at £30,000)		£-1684 (£-18241 to £4649)	£507 (£-883 to £1739)	£-3606 (£-16704 to £2917)

Figure 123 Incremental cost effectiveness plane for THR primary prevention (LMWH reference)



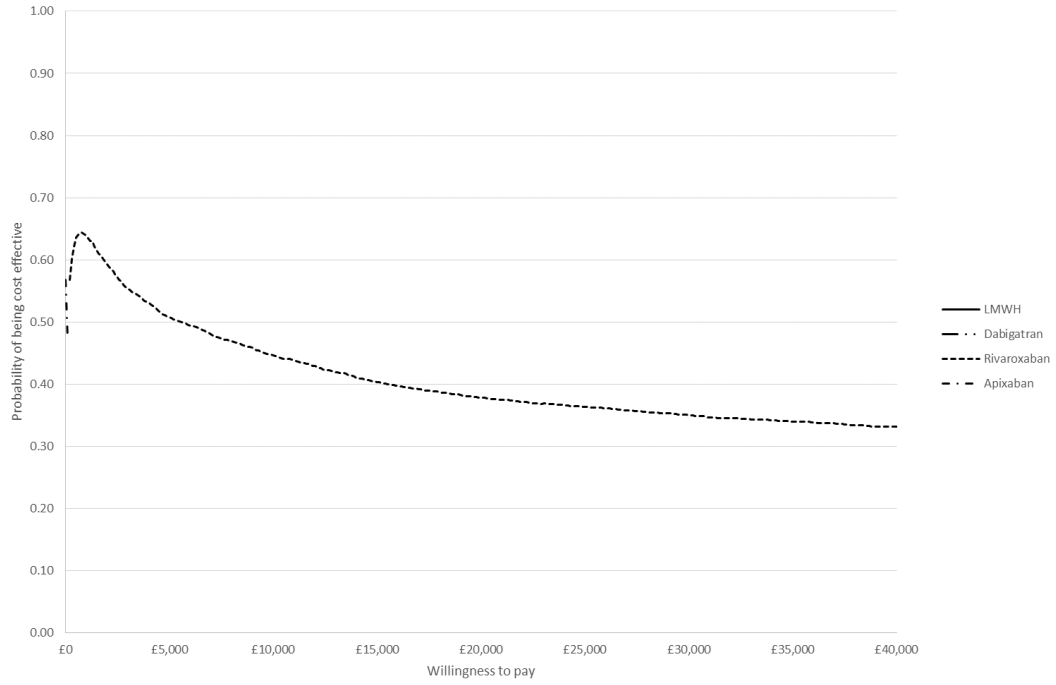
See section 4.5.3 for further details

Figure 124 Cost effectiveness acceptability curve for THR primary prevention



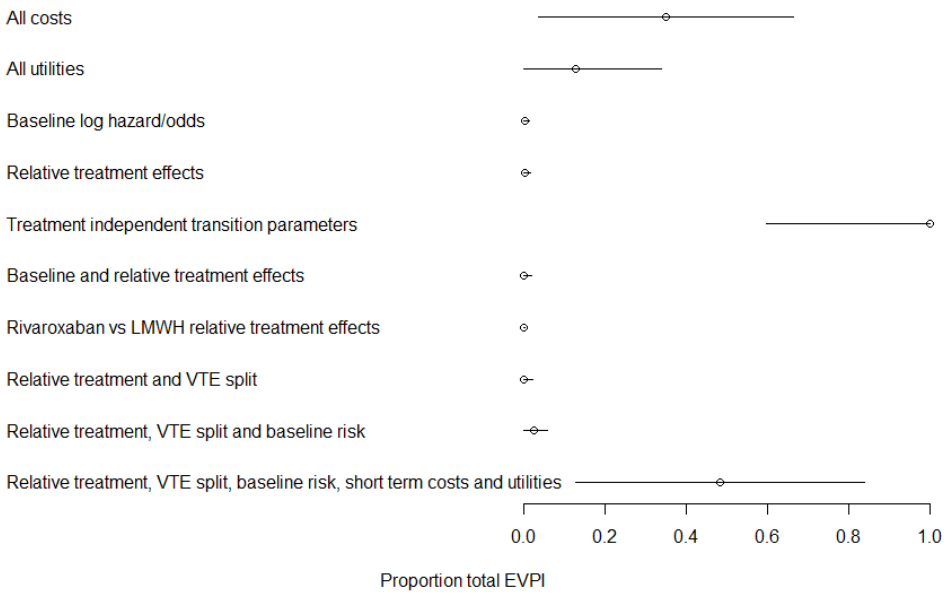
See section 4.5.3 for further details

Figure 125 Cost effectiveness acceptability frontier for THR primary prevention



See section 4.5.3 for further details

Figure 126 Expected value of partial perfect information (EVPPI) for subsets of model input parameters in the VTE primary prevention THR model, presented as a proportion of the total EVPI*



* SAVI estimated EVPPI scaled by EVPPI of all parameters as estimated by SAVI. 95% intervals are ±1.96×SE and are truncated above at 1 and below at 0.

11.8.2 Total knee replacement

The expected total costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000 for first line prevention therapy are reported in Table 201. Both benefits and uncertainty in the benefits are similar across interventions. Rivaroxaban has the lowest expected total costs (£834), followed by post-operative LMWH (£855) and dabigatran (£871), while apixaban has the highest expected total costs of £932. Rivaroxaban and LMH had similar incremental net benefit at willingness to pay per QALY thresholds of £20,000 and £30,000. Dabigatran and apixaban have negative incremental net benefit compared with post-operative LMWH.

The cost-effectiveness plane (Figure 127) and the cost-effectiveness acceptability curves (Figure 128) show substantial uncertainty around the relative costs and benefits of these interventions. Rivaroxaban has the highest expected net benefit over the range of willingness to pay thresholds we explored (Figure 129), and the highest probability of being the most cost-effective treatment for willingness to pay per QALY thresholds up to approximately £20,000 (Figure 128). Beyond that dabigatran has the highest probability of being the most cost-effective, but not the highest expected net benefit due to the high level of uncertainty around the cost-effectiveness of dabigatran (as seen also in the THR population). As previously noted we prefer the CEAF summary (Figure 129) in this situation. Note that there is a non-negligible chance that each of the treatments may be the most cost-effective, and this decision uncertainty increases as we increase our willingness to pay per QALY.

The per-person Expected Value of Perfect Information was £171 at a willingness-to-pay of £20,000 and £249 at £30,000, which is lower than that seen in other populations, reflecting the larger number of studies on this population. Assuming an annual incidence of primary TKR operations per year[72] of 76,000, population EVPI over a 10 year time horizon, discounting at 3.5%, is approximately £111million and £161million at willingness-to-pay of £20,000 and £30,000 respectively. These high figures reflect the large volume of primary TKR operations that are conducted.

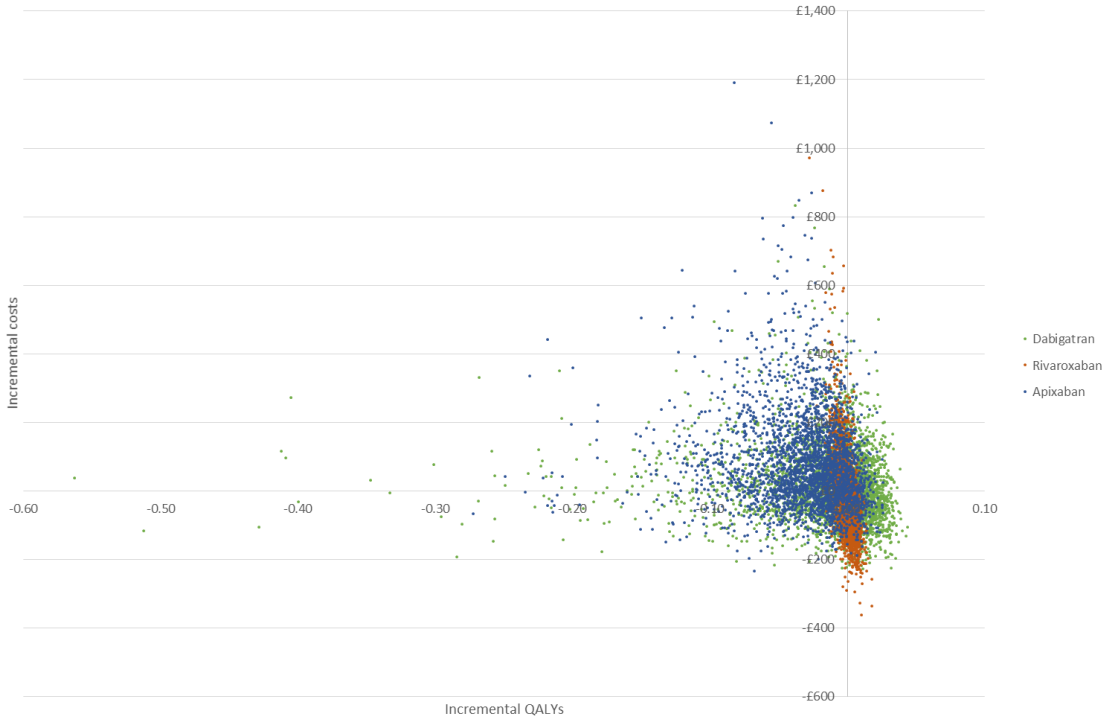
Figure 130 shows the proportion of the EVPI that is attributable to different groups of parameters. The optimal decision is most sensitive to uncertainty in the utilities,

relative treatment effects, and treatment independent transition parameters, and also sensitive to uncertainty in the cost parameters, but not to uncertainty in the risk on the reference comparator. This suggests that there may be value in running a large trial comparing NOACs and warfarin to reduce the uncertainty in the relative treatment effects. There may also be value in conducting a study to estimate the utility values associated with VTE events and treatment related eventsand a longitudinal study examining the treatment independent transition parameters: rates of mild/moderate PTS, severe PTS, CTPH and the proportion split of VTE events.

Table 201 Results of the TKR primary prevention cost effectiveness analysis: Costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000

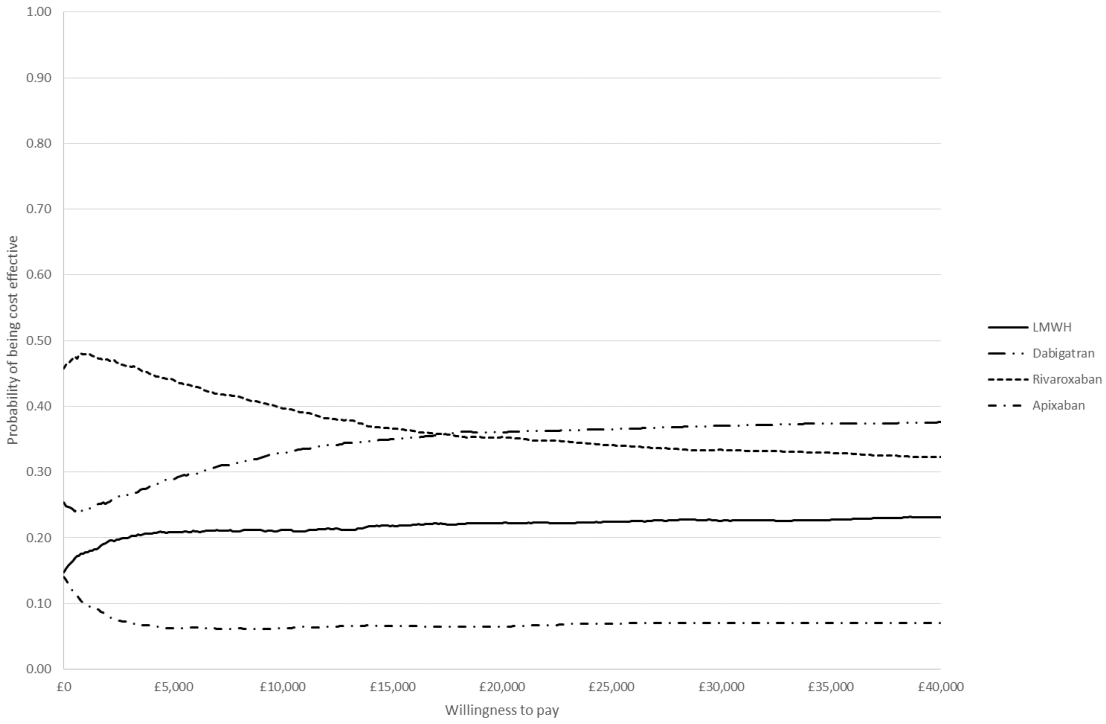
	LMWH	Dabigatran	Rivaroxaban	Apixaban
Costs	£855 (£706 to £1078)	£871 (£646 to £1252)	£834 (£632 to £1183)	£932 (£688 to £1388)
QALYs	9.25 (9.00 to 9.49)	9.24 (8.96 to 9.48)	9.25 (9.00 to 9.49)	9.22 (8.96 to 9.46)
Incremental costs		£16 (£-149 to £284)	£-20 (£-187 to £223)	£77 (£-113 to £417)
Incremental QALYs		-0.02 (-0.14 to 0.03)	0.00 (-0.01 to 0.01)	-0.03 (-0.12 to 0.01)
Incremental Net Monetary Benefit (at £20,000)		£-320 (£-2844 to £638)	£16 (£-406 to £329)	£-686 (£-2458 to £266)
Incremental Net Monetary Benefit (at £30,000)		£-472 (£-4214 to £919)	£13 (£-509 to £414)	£-991 (£-3658 to £375)

Figure 127 Incremental cost effectiveness plane for TKR primary prevention (LMWH: reference)



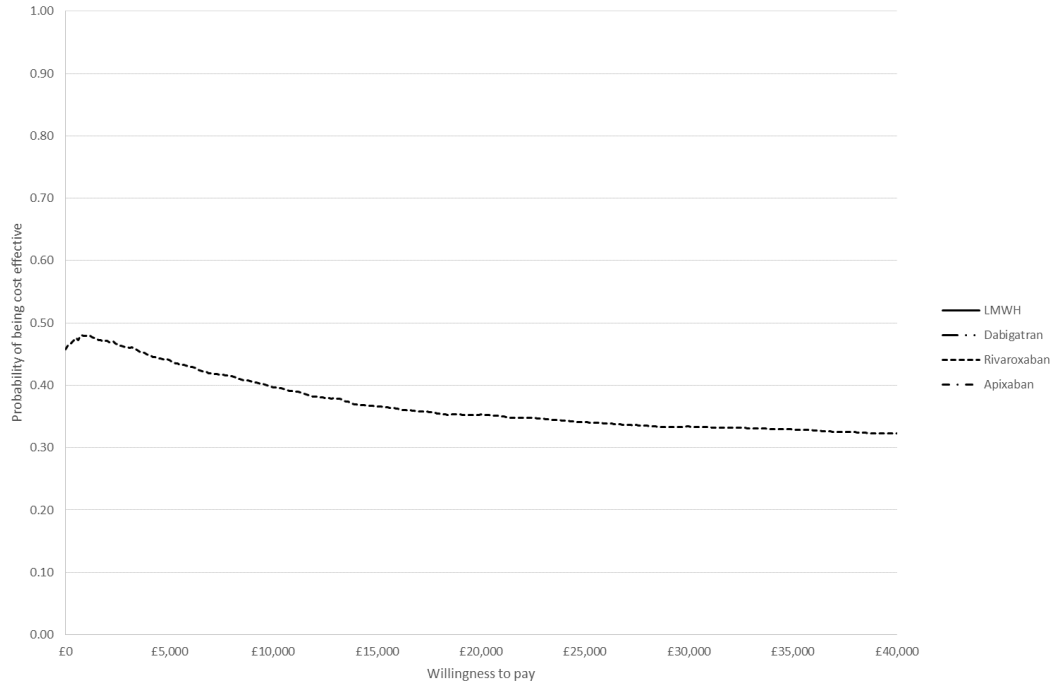
See section 4.5.3 for further details

Figure 128 Cost effectiveness acceptability curve for TKR primary prevention



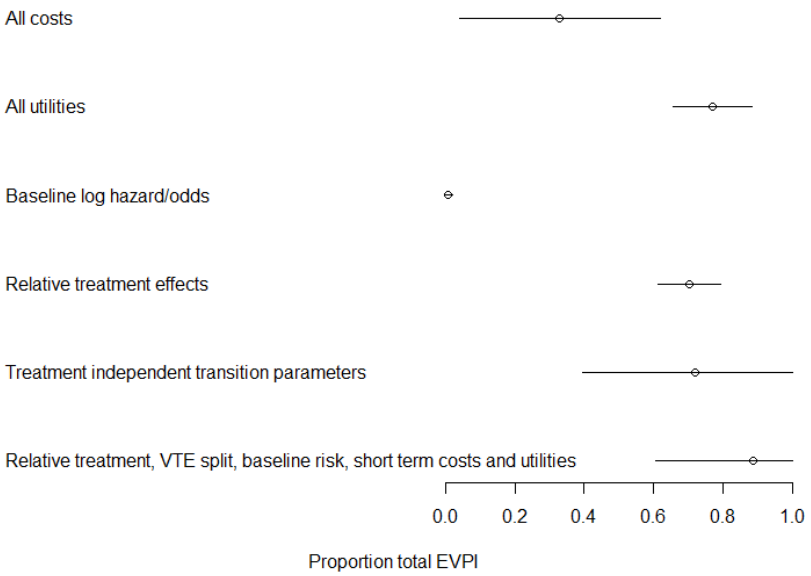
See section 4.5.3 for further details

Figure 129 Cost effectiveness acceptability frontier for TKR primary prevention



See section 4.5.3 for further details

Figure 130 Expected value of partial perfect information (EVPPI) for subsets of parameters in the VTE primary prevention TKR model, as a proportion of the total EVPI*



* SAVI estimated EVPPI scaled by EVPPI of all parameters as estimated by SAVI. 95% intervals are ±1.96×SE and are truncated above at 1 and below at 0.

11.9 Results of sensitivity analyses for secondary prevention model

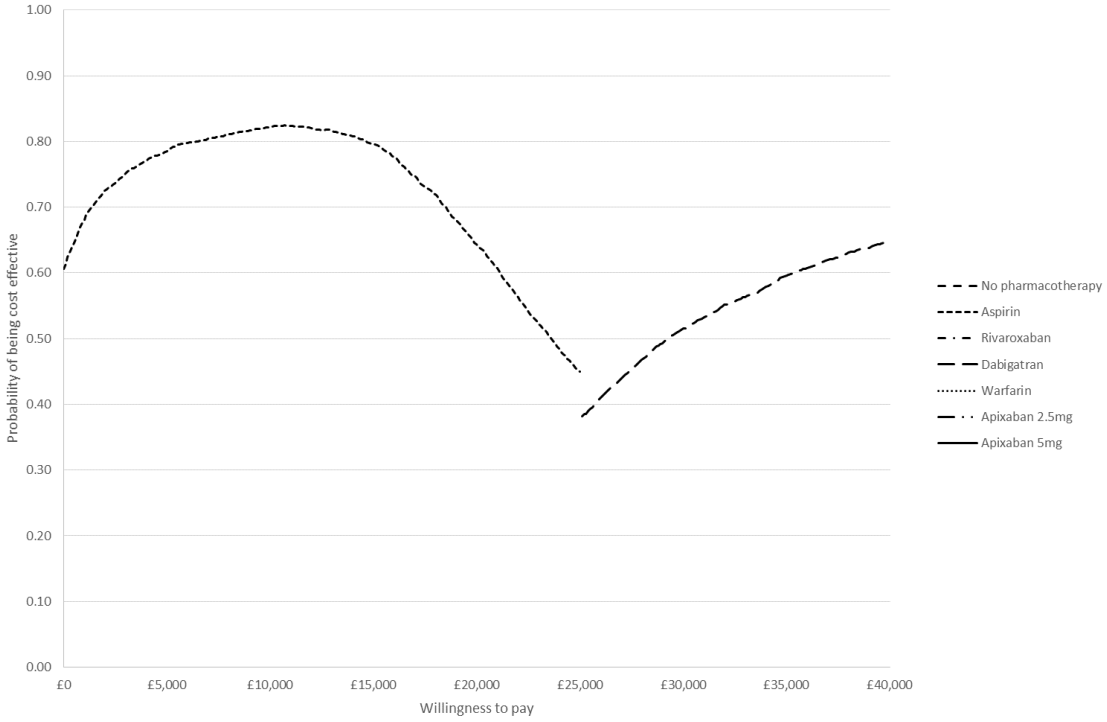
We varied the proportion of recurrent VTEs that are DVT, non-fatal PE and fatal PE using the proportions estimated in Prandoni et al[244] (79% DVT, 10% non-fatal PE and 11% fatal PE) rather than the proportions estimated from the RCTs included in the systematic review. At a willingness to pay of over £25,000 per QALY dabigatran becomes the most cost-effective treatment (Figure 131). This indicates that NOACs are more likely to be cost-effective in secondary prevention if the risk of fatal VTE is higher than we assumed in our base case analysis.

We varied the CR bleed rate to match that assumed in the AF model. The results were robust to this assumption, with aspirin having the highest expected net benefit over all willingness to pay thresholds that we explored. We explored sensitivity of results to a policy of switching patients to warfarin after a second VTE event and the sensitivity to the cost of warfarin by reducing the cost to £0 in one way sensitivity analyses. The results were robust to these assumptions (Appendix 12).

The results were robust to the seven sensitivity analyses where we varied the utilities of VTE and adverse events by +/-50%, the adverse event costs by +/-50% and the VTE costs by +50% (Appendix 12). When we reduced the cost of VTE events by 50%, no pharmacotherapy has the highest expected net benefit over willingness to pay thresholds we explored (Figure 132).

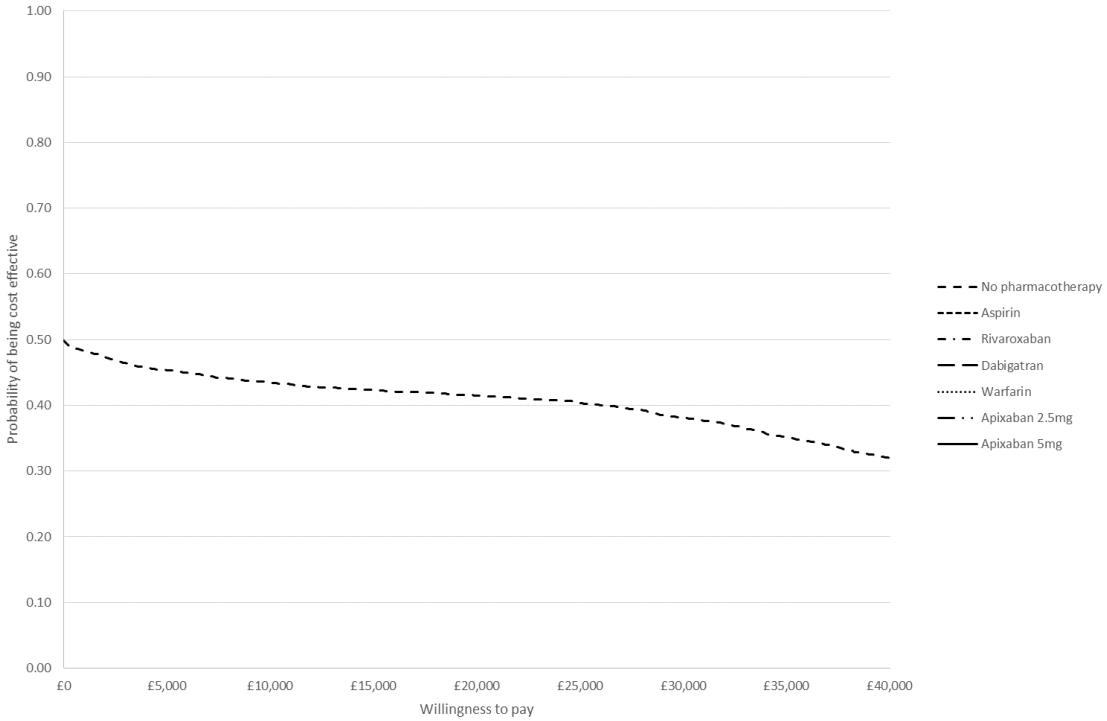
When the rate of ICH for no pharmacotherapy was assumed to be zero, no pharmacotherapy then had the highest probability of being cost-effective and the highest net benefit over a willingness to pay range of £0 to £40,000 (Figure 133). In this analysis the risk of having an ICH while on aspirin and NOACs outweighed the benefit gained from reduce recurrent VTE.

Figure 131 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: vary proportion of DVT, non-fatal PE and fatal PE of recurrent VTE



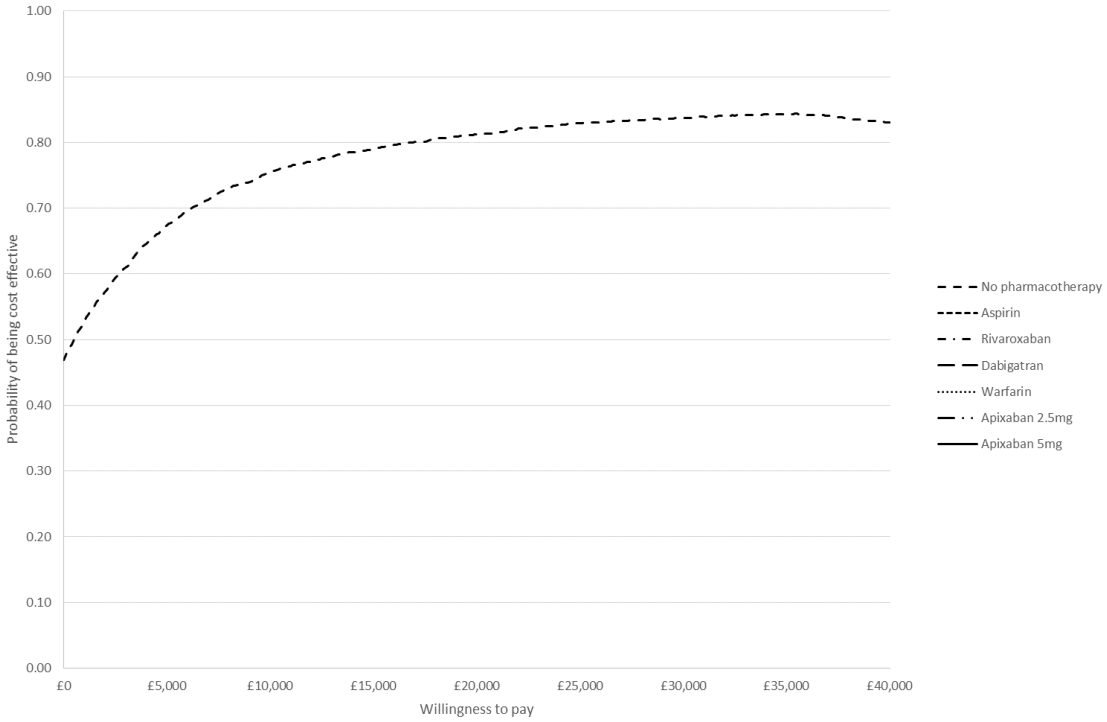
See section 4.5.3 for further details

Figure 132 Cost effectiveness acceptability frontier for secondary prevention sensitivity analyses: reduction in VTE costs by 50%



See section 4.5.3 for further details

Figure 133 Cost effectiveness acceptability frontier secondary prevention: risk of ICH for no pharmacotherapy is set to zero



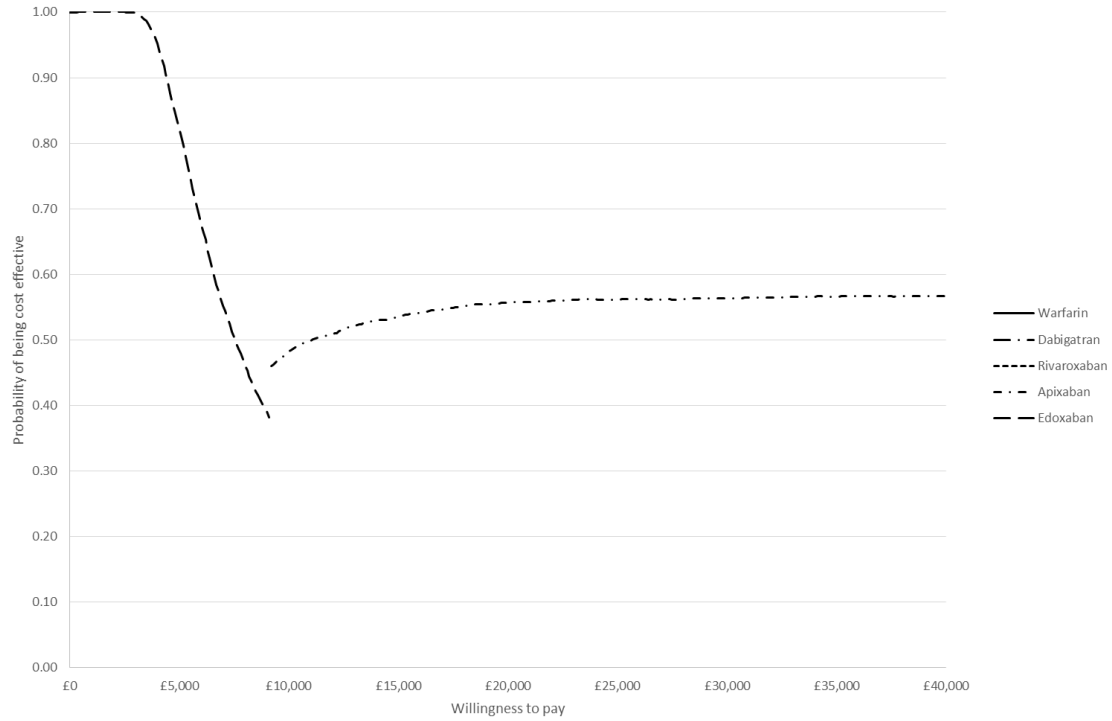
See section 4.5.3 for further details

11.10 Results of sensitivity analyses for acute treatment model

Changing the time on treatment from six months to three months and varying the cost and utilities by +/-50% over VTE events and adverse events did not alter the conclusion that apixaban was most likely to be cost-effective over a threshold of £1,000 (Appendix 12). The assumption that NOACs have the same non-fatal ICH rate as warfarin had little effect on the conclusion that apixaban has the highest expected net benefit at a willingness to pay per QALY thresholds of £20,000 and £30,000 (Appendix 12).

Assuming a zero cost for edoxaban we find that edoxaban has the highest expected net benefit and highest probability of being cost-effective at a willingness to pay threshold less than £10,000 per QALY. However, as willingness to pay per QALY increases above £10,000, apixaban is the most cost-effective treatment, due to the higher benefits (Table 199, Figure 134).

Figure 134 Cost effectiveness acceptability frontier acute treatment model: assuming a zero cost for edoxaban



See section 4.5.3 for further details

11.11 Results of sensitivity analyses for primary prevention model

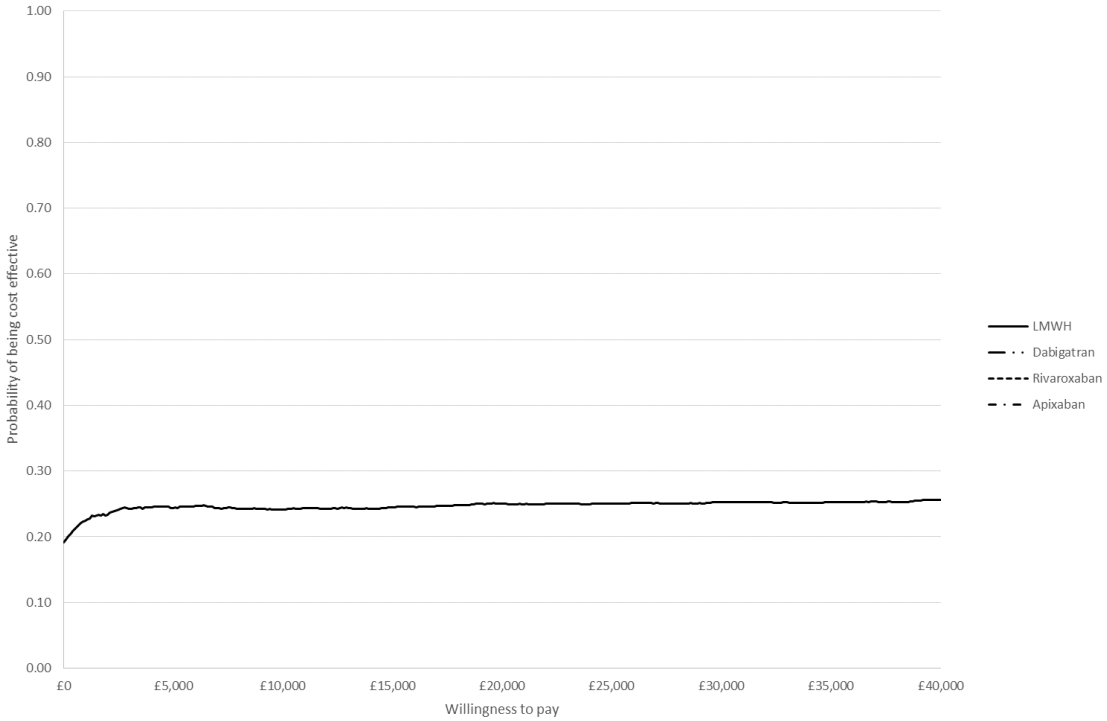
11.11.1 Total knee replacement

When we increased the adverse events utilities by 50% LMWH became the most cost-effective treatment at a willingness to pay of over £27,000 per QALY (Figure 135). Increasing the adverse event costs by 50% changed the comparators with the highest average net benefit from rivaroxaban to LMWH over willingness to pay thresholds we explored (Figure 136).

Decreasing the VTE event costs by 50% changed the comparators with the highest average net benefit from rivaroxaban to LMWH over willingness to pay thresholds we explored (Figure 137). When we decreasing the VTE utilities by 50% LMWH became the most cost effective comparator above a willingness to pay threshold of £20,000 (Figure 138).

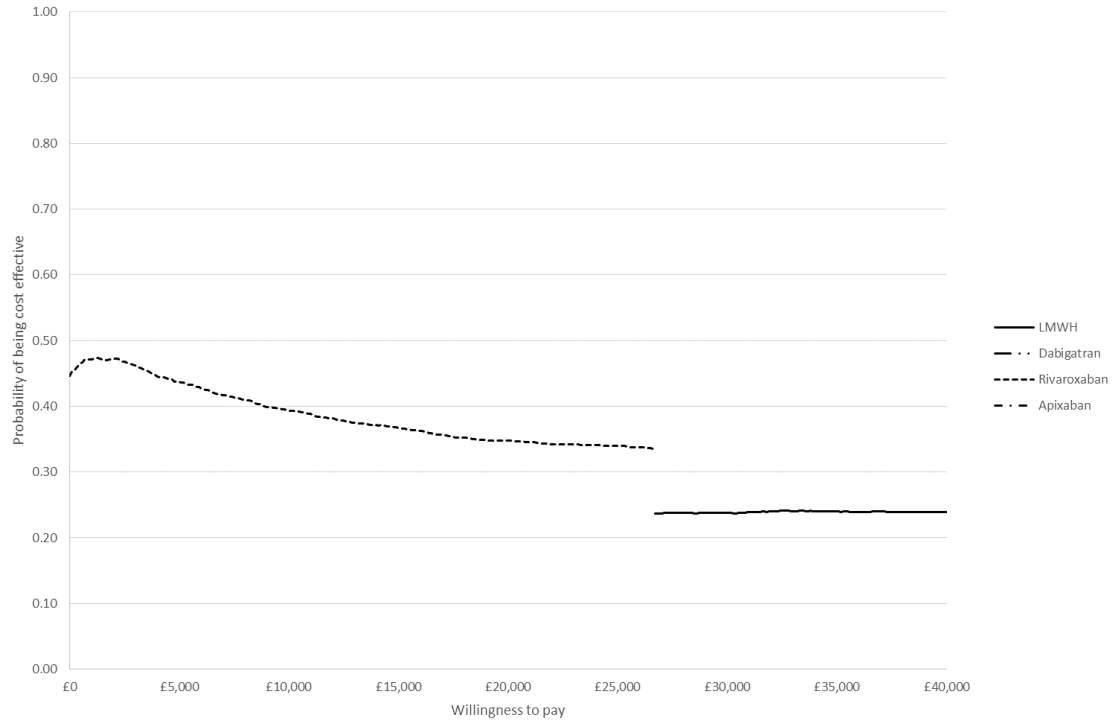
Our results were robust to all other sensitivity analyses conducted on the primary prevention populations; pooling post THR and post TKR populations for relative treatment effect of VTE costing dabigatran at a lower dose to match the licensed dose for an elderly population, decreasing the costs and utilities for adverse events and increasing the costs and utilities for VTE events by 50% (Appendix 12).

Figure 135 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: increasing AE costs by 50%



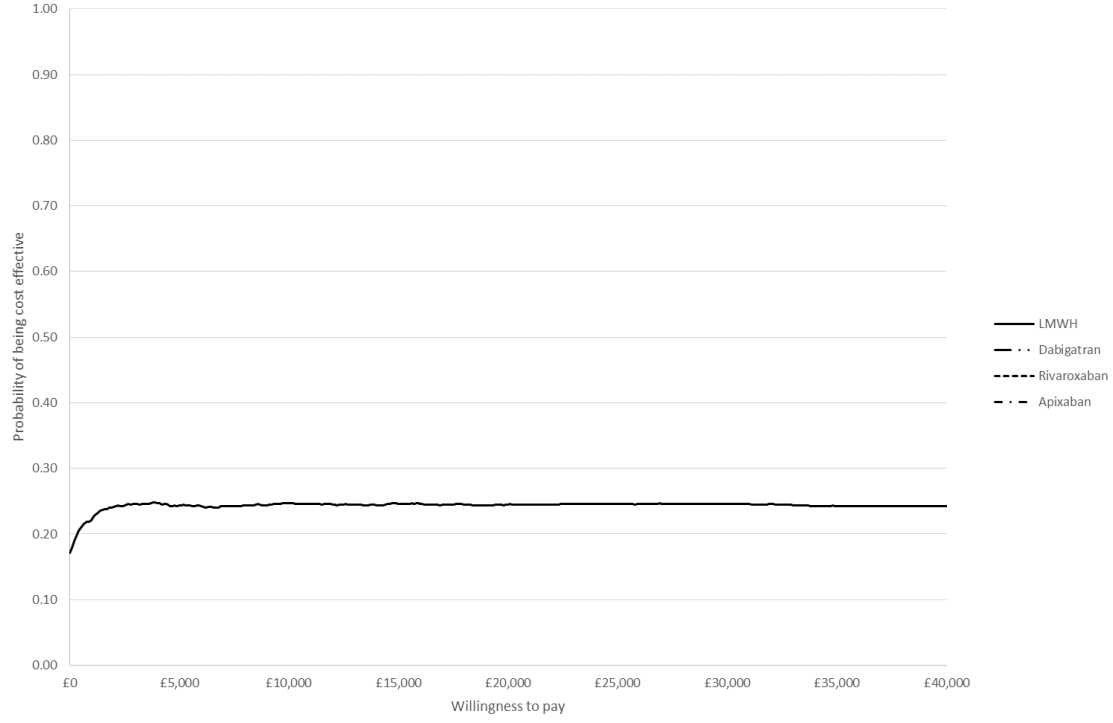
See section 4.5.3 for further details

Figure 136 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: increasing AE utilities by 50%



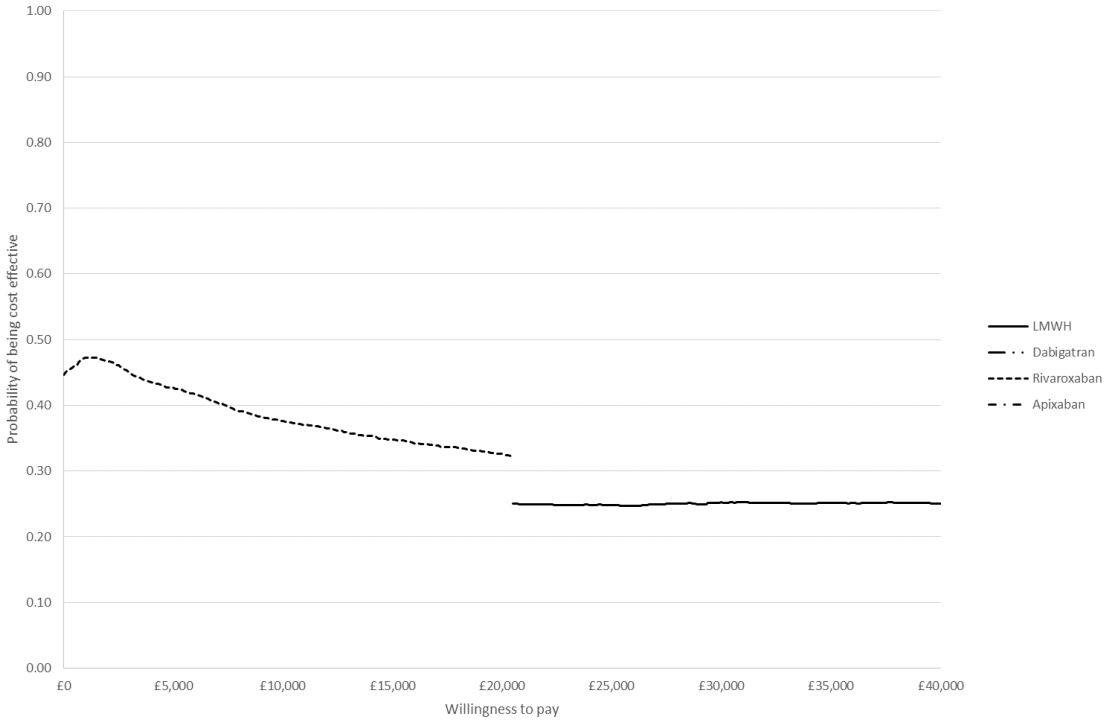
See section 4.5.3 for further details

Figure 137 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: decreasing VTE costs by 50%



See section 4.5.3 for further details

Figure 138 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: decreasing VTE utilities by 50%



See section 4.5.3 for further details

11.11.2 Total hip replacement

Our results were robust to all of the sensitivity analyses conducted on the primary prevention populations; pooling post THR and post TKR populations for relative treatment effect of VTE, costing dabigatran at a lower dose to match the licensed dose for an elderly population and varying the costs and utilities for VTE and adverse events by +/-50% (Appendix 12).

11.12 Summary of cost-effectiveness findings

The economic analyses of the use of NOACs in the prevention and treatment of VTE attempt to balance the costs of pharmacotherapy against the benefits of reducing VTE-related events and the risks of anti-coagulant related adverse events. To a large extent the findings of the economic analyses reflect the evidence and uncertainty identified by the network meta-analyses in previous chapters.

In secondary prevention, we found no strong evidence that NOACs (apixaban, dabigatran, and rivaroxaban) were more cost-effective than no pharmacotherapy or aspirin. The RCT evidence that NOACs reduce the risk of VTE was counterbalanced by the relatively low underlying risk of VTE, the low proportion of fatal VTE events and the potentially elevated risk of adverse events due to bleeding. Our base case analysis indicated that the relatively small benefits of NOACs compared to no pharmacotherapy or aspirin did not justify the high costs of long-term NOAC treatment. This finding was sensitive to assumptions about the incidence of fatal PE. We found that aspirin was most likely to be cost-effective for secondary prevention, although there was uncertainty as to whether no pharmacotherapy was more cost-effective, and choice between aspirin and no pharmacotherapy was particularly sensitive to assumptions around adverse events (ICH) under no pharmacotherapy, and costs associated with VTEs. Further research on the relative cost-effectiveness of aspirin and no pharmacotherapy would be of value.

In acute treatment, we found that NOACs, particularly apixaban, are likely to be cost-effective compared to warfarin at conventional NICE willingness to pay thresholds of £20,000 to £30,000 per QALY. Although there was little evidence that NOACs substantially reduced the risk of VTE compared to warfarin, the reduced risk of ICH and clinically relevant bleeding contributed to our finding that there was a relatively high probability (>0.5) that apixaban is the most cost-effective intervention in this setting. This finding was robust to sensitivity analyses on the model assumptions, although further research on the relative efficacy and safety of apixaban versus other NOACs would be valuable to increase the strength of evidence.

For primary prevention of VTE following hip surgery, expected clinical benefits were similar for rivaroxaban and LMWH, while the lower costs of intervention with rivaroxaban meant that it was the most cost-effective intervention at the usual NICE thresholds. For primary prevention of VTE following knee surgery there was little difference in clinical benefit between the interventions, while rivaroxaban and LMWH were similarly cost-effective. There is a substantial potential value of further research in both THR and TKR populations, partly due to the large volume of these operations meaning that a large population of patients may be given these treatments, but also due to the high levels of uncertainty in the relative treatment effects. This arises partly due to the fact that events are rare, and so very large studies are required to provide sufficient power to detect treatment differences where they exist, especially for adverse events which can have long-term consequences.

Our models make several assumptions (summarised in Table 202). In order to make the models tractable for each decision problem, we assumed that the most cost effective comparator in secondary prevention would be used after acute treatment and that the most cost effective comparator in acute treatment would be used after the failure of primary prevention. This assumes independence between treatments (i.e. the efficacy of secondary prevention does not depend on the therapy used for acute treatment). It also assumes that evidence from the wider acute/secondary prevention population (e.g including medical patients) provides valid evidence for those primary prevention (i.e. surgical) patients who require acute treatment and secondary prevention.

In our basecase secondary prevention model, we assumed that patients would only stop treatment after ICH. In reality patients may discontinue or switch treatment for various reasons. A proportion of patients will not comply with treatment due to side-effects or difficulty achieving a stable INR (on warfarin). Patients may also switch treatment after a recurrent symptomatic VTE event which may be interpreted as “treatment failure”. The secondary prevention RCTs, which have relatively short follow periods, provide very little evidence on long-term treatment compliance. Our finding that NOACs were not more cost-effective thatn aspirin or no pharmacotherapy were robust to a sensitivity analyses where patients switched to warfarin after a recurrent VTE, but may be sensitive to other treatment switching and non-compliance.

There is evidence that dabigatran is associated with myocardial infarction in the AF population. The VTE RCTs typically did not report MI as an outcome, and we did not include it in the VTE models. It is likely to be most influential in the secondary prevention of VTE where patients may be on therapy for prolonged periods. However, including the risk of MI in the secondary prevention model would not change our conclusion that none of the NOACs (including dabigatran) were cost-effective.

Edoxaban for the acute treatment of VTE is under review by NICE, but has not yet been approved or have a BNF list cost in the UK. We assumed that the cost would be similar to other NOACs and performed a threshold analysis on cost to see how price influenced cost-effectiveness in acute treatment. Because edoxaban had very similar efficacy to warfarin, with lower benefits to apixaban, we found that it was not cost-effective at willingness to pay per QALY values of £20,000 or £30,000 even at zero cost. When willingness to pay per QALY was low then it became cost-effective as the price went below that of warfarin, but such low threshold values are not used in practice.

Our systematic literature review identified evidence to inform model parameters for two primary prevention models (post THR and post TKR). We did not identify enough data to parameterise a model to estimate the cost-effectiveness of NOACs for patients hospitalised for medical treatment. These findings may not generalise to these patients and other patient groups.

Table 202 Main assumptions of the VTE models

Transition probabilities / model structure
Patients with asymptomatic VTE have no greater risk of symptomatic recurrent VTE than patients with no VTE event
VTE and bleeding events are independent
Patients cannot move out of the “PTS” or “CTPH” states, with the exception to the death state
All anticoagulation will be stopped for patients that have an intracranial haemorrhage
Proportion of VTE that is DVT versus non-fatal PE versus fatal PE is treatment independent
ICH relative safety from AF population
Quality of life & costs
Minor bleeds do not impact on quality of life and costs
Clinically relevant bleeds, DVT and non-fatal PE do not have a long term impact on quality of life

11.12.1 Comparisons with the literature

There have been relatively few previous cost-effectiveness analyses of NOACs for the prevention or treatment of VTE in the peer-reviewed literature. Most of the published studies focus on primary prevention after surgery and few compare more than one NOAC to LMWH[62,63,249,250]. The published comparisons of rivaroxaban, dabigatran and LMWH are based on direct trial evidence and conclude that, while rivaroxaban in particular may be cost-effective, there is great uncertainty about which strategy is the most cost effective[63,249,250]. One industry sponsored cost-effectiveness model comparing rivaroxaban to LMWH and a vitamin k antagonist, based on the EINSTEIN trial concluded that there was a high probability that rivaroxaban was cost-effective[251]. We also found that rivaroxaban was likely to be cost-effective for primary prevention after TKR and THR. However, despite including a larger number of trials in a network meta-analysis than previous cost-effectiveness models, our interpretation is tentative due imprecise estimates about effect and safety.

12. Discussion and conclusions

12.1 Main findings

In the following sections, we summarise the main findings for each therapeutic area, first summarising efficacy and safety comparisons of NOACs with established treatments, and then comparing individual NOACs with one another. We also summarise the results of the cost-effectiveness analyses.

12.1.1 Atrial fibrillation: results of clinical effectiveness analyses

There was evidence that apixaban (5mg bd), dabigatran (150mg bd), edoxaban (60mg od) and rivaroxaban (20mg od) all reduce the **risk of stroke or systemic embolism** compared with warfarin (INR 2-3). Among the NOACs, there was evidence of a higher risk of stroke or systemic embolism with edoxaban (60mg od) and rivaroxaban (20mg od) compared with dabigatran (150mg bd).

There was evidence that dabigatran (150mg bd) reduces the risk of **ischaemic stroke** compared with warfarin, whereas edoxaban (30mg od) increases that risk. There was little evidence that the risk of ischaemic stroke differed between licensed doses of NOACs

There was weak evidence that the **risk of MI** is higher with dabigatran (110mg bd), dabigatran (150mg bd) and edoxaban (30mg od) compared with warfarin (INR 2-3), and weak evidence that the risk of MI is lower with rivaroxaban (20mg od) compared with warfarin (INR 2-3). Among the NOACs, there was weak evidence that MI risk is higher with dabigatran (150mg bd) compared with apixaban (5mg bd), and lower with rivaroxaban (20mg od) compared with dabigatran (150mg bd).

There was evidence that apixaban (5mg bd), dabigatran (110mg bd), edoxaban (30mg od) and edoxaban (60mg od) all reduced **risk of major bleeding** compared with warfarin (INR 2-3). Among the NOACs, there was evidence that risk of major bleeding is higher with dabigatran (150mg bd) compared with apixaban (5mg bd), and with rivaroxaban (20mg od) compared with apixaban (5mg bd) and edoxaban (60mg od).

There was evidence that the **risk of clinically relevant bleeding** during antiplatelet therapy (aspirin <150mg od) is lower than with warfarin (INR 2-3). There was evidence that the risk of clinically relevant bleeding with apixaban (5mg bd), edoxaban (30mg od) and edoxaban (60mg od) is also lower than with warfarin (INR 2-3). However, edoxaban (30mg **bd**) and edoxaban (60mg **bd**) increased clinically relevant bleeding compared with warfarin (INR 2-3). In comparisons among NOACs, there was evidence that clinically relevant bleeding with edoxaban (60mg od) and rivaroxaban (20mg od) is higher than with apixaban (5mg bd) and that rivaroxaban (20mg od) increases clinically relevant bleeding compared with edoxaban (60mg od).

There was strong evidence that **risk of intracranial bleeding** was lower with apixaban (5mg bd), dabigatran (110mg bd), dabigatran (150mg bd), edoxaban (30mg od), edoxaban (60mg od) and rivaroxaban (20mg od) compared with warfarin (INR 2-3). For each of these NOACs and doses, except for rivaroxaban (20mg od), the estimated relative risk reduction for intracranial bleeding was more than 50%. There was weak evidence that risk of intracranial bleeding is higher with rivaroxaban (20mg od) compared with apixaban (5mg bd), dabigatran (150mg bd) and edoxaban (60mg od).

Risk of all-cause mortality was lower with apixaban (5mg bd), dabigatran (110mg bd), dabigatran (150mg bd), edoxaban (30mg od), edoxaban (60mg od) and rivaroxaban (20mg od)) compared with warfarin (INR 2-3), but there was little evidence of a difference between the licensed doses of NOACs for this outcome.

Apixaban (5mg bd) was ranked as being among the best interventions for a wide range of the outcomes evaluated including stroke or systemic embolism, MI, major bleeding, and all-cause mortality. Edoxaban (60mg od) was ranked second for major bleeding and all cause mortality. Except for all-cause mortality, outcomes for rivaroxaban (20mg od) were ranked less highly than several other NOACs. The non-NOAC interventions (warfarin (INR 2-3) and antiplatelet therapy (aspirin/clopidogrel≥150mg od)) were ranked worst for stroke or systemic embolism and were not among the best three interventions for any of the outcomes. We did not include apixaban (2.5mg bd) or betrixaban (40mg od), because comparisons involving these interventions were imprecisely estimated.

In our sensitivity analyses, results were similar when using HRs instead of ORs. Moreover, we found no evidence of effect modification according to mean time in therapeutic range for patients on warfarin. However, our meta-regression models assumed a common interaction effect across treatments: that assumption could not be empirically tested due to lack of replication for most comparisons. An important limitation is that primary studies did not report the mean time above or below therapeutic range for warfarin arms. Therefore, we were unable to address some clinically relevant questions regarding the impact of treatment settings for warfarin on stroke prevention as well as on bleeding and other adverse events.

12.1.2 Atrial fibrillation: results of cost effectiveness analyses

Dabigatran (150mg bd) has the lowest expected total cost (£23,064), followed by apixaban (5mg bd), edoxaban (60mg od), warfarin (INR 2-3), and rivaroxaban (20mg od) which had the highest expected total cost (£24,841). Expected costs are similar across all treatments, and there is a high degree of uncertainty around the costs for all treatments.

Apixaban (5mg bd) has the highest expected QALYs (5.49), followed by rivaroxaban (20mg od) (5.45), dabigatran (150mg bd) (5.42), edoxaban (60mg od) (5.41), and warfarin (INR 2-3) (5.17). The NOACs have similar expected QALYs, all of which are higher than for warfarin (INR 2-3). There is a high degree of uncertainty around the QALY estimates.

At a willingness to pay threshold of £20,000 per QALY, all NOACs have positive expected incremental net benefit compared to warfarin (INR 2-3), suggesting they may be a cost effective use of NHS resources. Apixaban (5mg bd) has the highest expected incremental net benefit (£7533), followed by dabigatran (150 mg bd) (£6365), rivaroxaban (20mg od) (£5279) and edoxaban (60mg od) (£5212). Apixaban (5mg bd) is the only NOAC for which the 95% confidence interval around incremental net benefit is positive, suggesting that apixaban is cost-effective compared with warfarin. These conclusions also hold at the higher threshold of £30,000. The key drivers of these results are the lower rates of MI, ICH and other CRB for apixaban (5mg bd).

The cost-effectiveness acceptability curve (CEAC) indicates that apixaban (5mg bd) has the highest probability of being the most cost-effective first line therapy for AF, close to 60% in the £20,000-30,000 range of willingness-to-pay thresholds generally considered by NICE. Dabigatran (150mg bd) has the highest probability of being cost-effective if the willingness-to-pay threshold is very low, due to having the lowest expected total costs. Warfarin (INR 2-3) and edoxaban (60mg od) are unlikely to be cost-effective. These results are further highlighted by the cost-effectiveness frontier (CEAF). Apixaban (5mg bd) has the highest expected net benefit at a wide range of willingness-to-pay thresholds. Apixaban (5mg bd) is likely to be the most cost-effective first line therapy for AF, under the assumptions of our model.

12.1.3 Primary prevention of venous thromboembolism: results of clinical effectiveness analyses

In *hip surgery patients* most treatment comparisons were imprecisely estimated, but there was evidence that **risk of symptomatic VTE** is lower with rivaroxaban (10mg od) compared with LMWH (pre-op, standard dose) but higher with LMWH (post-op, standard dose) and warfarin (INR 2-3) compared with LMWH (pre-op, standard dose). Comparisons between the licensed doses of NOACs were imprecisely estimated. For *knee surgery patients*, there was little evidence that risk of symptomatic VTE differed between apixaban (2.5mg bd), dabigatran (220mg od), or rivaroxaban (10mg od) compared with LMWH (post-op, standard dose). Comparisons between licensed doses of NOACs were also imprecisely estimated. For *medical patients* there was weak evidence that the risk of symptomatic VTE is lower with apixaban (2.5mg bd) compared with LMWH (standard dose), and also compared with rivaroxaban (10 mg od) although these comparisons were imprecisely estimated.

For **symptomatic DVT** all comparisons for *hip surgery patients* were imprecisely estimated, but there was evidence that risk of symptomatic DVT is higher for LMWH (post-op, standard dose) and warfarin (INR 2-3) compared with LMWH (pre-op, standard dose). All comparisons for *knee surgery patients* were imprecisely estimated but there was evidence that risk of symptomatic DVT was higher for LMWH pre-op (standard dose) compared with LMWH (post-op, standard dose). For *medical patients* all comparisons were imprecisely estimated, but there was evidence that risk of

symptomatic DVT is lower for apixaban (2.5mg bd) compared with LMWH (standard dose).

For **symptomatic PE** all comparisons for trials in *hip surgery, knee surgery and medical patients* were imprecisely estimated. For *knee surgery patients*, there was some evidence that the risk of symptomatic PE is lower with dabigatran (150mg od) and higher with apixaban (2.5mg bd) compared with LMWH (post-op, standard dose). Among licensed doses of NOACs the risk of symptomatic PE may be lower for rivaroxaban (10mg od) compared with apixaban (2.5mg bd).

For **myocardial infarction** all comparisons were imprecisely estimated, although there was some evidence that risk of MI is lower for rivaroxaban (10mg od) compared with LMWH (post-op, standard dose).

There was little evidence that **risk of major bleeding** differs between pre-operative and post-operative LMWH (standard dose). There was evidence that risk of major bleeding is lower with warfarin (INR 2-3) and higher with rivaroxaban (10mg od) compared with LMWH (post-op, standard dose). There was evidence that risk of major bleeding is higher with rivaroxaban (10mg od) compared with apixaban (2.5mg bd) and dabigatran (220mg od).

There was evidence that **risk of clinically relevant bleeding** is higher for pre-operative LMWH (standard dose) compared with post-operative LMWH (standard dose), and higher for dabigatran (150mg or 220mg od) and rivaroxaban (10mg od) compared with LMWH (post-op, standard dose). There was evidence that risk of clinically relevant bleeding is higher for dabigatran (220mg od) and rivaroxaban (10mg od) compared with apixaban (2.5mg bd).

There was little evidence that **risk of all-cause mortality** differed for any intervention compared with LMWH (post-op, standard dose). Comparisons between licensed doses of NOACs were imprecisely estimated.

Warfarin was ranked with high probability as the best intervention for major bleeding events and LMWH (post-op, standard dose) was ranked with high probability as best

or second-best intervention for clinically relevant bleeding. Rivaroxaban (10mg od) was ranked among the worst interventions for bleeding outcomes.

12.1.4 Primary prevention of venous thromboembolism following hip and knee surgery: results of cost effectiveness analyses

12.1.4.1 Total hip replacement

The lowest expected total costs are for apixaban (£702) followed by rivaroxaban (£718), then dabigatran (£893). LMWH has the highest expected cost (£1,062). Expected benefits are highest for rivaroxaban and LMWH (9.10 QALYs), followed by dabigatran (9.04 QALYs) then apixaban (8.96 QALYs). At both £20,000 and £30,000 willingness to pay per QALY thresholds, rivaroxaban has the highest expected incremental net benefit, although confidence intervals around net benefit are wide (particularly for dabigatran) and also skewed (apixaban). Rivaroxaban has the highest expected net benefit over the range of willingness to pay thresholds we explored, but with substantial uncertainty: its probability of being the most cost-effective was 0.35 for willingness to pay per QALY threshold £30,000.

12.1.4.2 Total knee replacement

Rivaroxaban has the lowest expected total costs (£834), followed by post-operative LMWH (£855) and dabigatran (£871), while apixaban has the highest expected total costs of £932. Rivaroxaban and LMWH had similar incremental net benefit at willingness to pay per QALY thresholds of £20,000 and £30,000. Dabigatran and apixaban have negative incremental net benefit compared with post-operative LMWH. The cost-effectiveness plane and the cost-effectiveness acceptability curves show substantial uncertainty around the relative costs and benefits of these interventions. Rivaroxaban has the highest expected net benefit over the range of willingness to pay thresholds we explored, and the highest probability of being the most cost-effective treatment for willingness to pay per QALY thresholds up to approximately £20,000.

12.1.5 Acute treatment of venous thromboembolic disease: results of clinical effectiveness analyses

The planned edoxaban dose in the HOKUSAI-VTE study was 60mg od, but 17.6% of the patients in that intervention arm received a lower dose of 30mg od. This intervention is denoted “Edoxaban (60 or 30 (17.6%) mg od).”

Compared with warfarin (INR 2-3), none of the NOACs reduced the **risk of symptomatic VTE, symptomatic DVT or symptomatic PE** on follow up, nor did the risk of any of these outcomes differ between licensed doses of NOACs.

For **risk of MI** all comparisons were imprecisely estimated.

There was strong evidence that apixaban (5 mg bd) and rivaroxaban (15mg bd then 20mg od) reduce **risk of major bleeding** compared with warfarin (INR 2-3). There was evidence that risk of major bleeding was higher for edoxaban (60 or 30 (17.6%) mg od) and dabigatran (150mg bd) compared with apixaban (5mg bd).

There was evidence that apixaban (5mg bd), dabigatran (150mg bd) and edoxaban (60 or 30 (17.6%) mg od) reduce **risk of clinically relevant bleeding** compared with warfarin (INR 2-3). There was some evidence that rivaroxaban (15mg bd then 20mg od) reduces risk of clinically relevant bleeding compared with warfarin (INR 2-3). There was evidence that risk of clinically relevant bleeding is higher with dabigatran (150mg bd), edoxaban (60 or 30 (17.6%) mg od) and rivaroxaban (15mg bd then 20mg od) compared with apixaban (5mg bd). There was evidence that risk of clinically relevant bleeding is higher with edoxaban (60 or 30 (17.6%) mg od) and rivaroxaban (15mg bd then 20mg od) compared with dabigatran (150mg bd).

There was little evidence that **risk of all cause mortality** differed for any of the NOAC interventions compared with warfarin (INR 2-3). Neither was there evidence that risk of all cause mortality differed between licensed doses of NOACs.

There was a high probability that warfarin (INR 2-3) is ranked worst for major bleeding and clinically relevant bleeding. There was a high probability that apixaban 5mg bd is ranked best for major bleeding and clinically relevant bleeding, and this intervention also had a high probability of being ranked best or second best for symptomatic DVT, symptomatic VTE and all-cause mortality.

12.1.6 Acute treatment of venous thromboembolic disease: results of cost effectiveness analyses

We estimated expected costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000. Expected costs and benefits are similar across all treatments, because of the short (6 month) treatment duration and the small and imprecisely estimated effects of NOACs on VTE recurrence and adverse events compared to warfarin. Warfarin has the lowest expected cost (£19,651), followed by dabigatran, edoxaban, apixaban, and rivaoxaban the most expensive (£19,753). Apixaban had the highest expected QALYs (12.02), but this is only 0.04 QALYs greater than the interventions with the lowest expected QALYs (edoxaban, warfarin and dabigatran).

The expected net benefit is highest for apixaban at willingness to pay per QALY thresholds of £20,000 and £30,000. This is due to the marginally lower risk of recurrent VTE, clinically relevant bleeding and non-VTE related mortality with apixaban relative to other NOACs. However there is substantial uncertainty around this estimate. Rivaroxoban also has a positive incremental net benefit compared with warfarin. Confidence intervals for incremental net benefit are wide for all treatments, reflecting substantial uncertainty that is also seen in the incremental cost-effectiveness plane.

The cost-effectiveness acceptability curves show that for very low willingness to pay per QALY, warfarin is the most cost-effective treatment (because it has lowest expected costs). For willingness to pay thresholds above £1,000, apixaban (5mg) has the highest expected net benefit, with a probability of being most cost-effective at £20,000 to £30,000 per QALY thresholds of approximately 0.54. However it is possible that rivaroxaban or dabigatran are the most cost-effective interventions, even at high willingness to pay thresholds.

12.1.7 Secondary prevention of venous thromboembolism: results of clinical effectiveness analyses

There was evidence that aspirin (100 mg od), warfarin (INR 1.5-2) and warfarin (INR 2-3) substantially reduced risk of symptomatic VTE compared with placebo. All NOACS at the doses included in the network also substantially reduced risk of

symptomatic VTE compared with placebo. Risk of symptomatic VTE was lower for all NOACs at doses included in the network compared with aspirin. However there was no clear evidence that risk of symptomatic VTE differed between these NOAC interventions and warfarin, although most comparisons were imprecisely estimated. There was no clear evidence that risk of symptomatic VTE differed between licensed doses of NOACs, although these comparisons were imprecisely estimated.

There was no clear evidence that aspirin (100 mg od) reduced **risk of symptomatic DVT** considered as an individual end-point compared with placebo. There was evidence that warfarin (INR 2-3) and all NOACs at doses included in the network substantially reduced risk of symptomatic DVT compared with placebo. These NOAC interventions substantially reduced risk of symptomatic DVT compared with aspirin. By contrast, there was no clear evidence that risk of symptomatic DVT differed between these NOACs and warfarin (INR 2-3), although comparisons were imprecisely estimated. There was no clear evidence that risk of symptomatic DVT differed between NOACs at licensed doses, although all comparisons were imprecisely estimated.

There was evidence that warfarin (INR 2-3), apixaban (5mg bd), dabigatran (150mg bd) and rivaroxaban (20mg od) substantially reduce risk of symptomatic PE compared with placebo. There was evidence that dabigatran (150mg bd) and rivaroxaban (20mg od) reduce risk of symptomatic PE compared with aspirin. There was evidence that risk of symptomatic PE was higher for apixaban (2.5mg bd) compared with warfarin (INR 2-3). There was weak evidence that risk of symptomatic PE was lower for dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd)

All comparisons of **risk of myocardial infarction** were imprecisely estimated.

There was evidence that **risk of major bleeding** is higher for warfarin (INR 2-3) and rivaroxaban (20mg od) compared with placebo, although these comparisons were imprecisely estimated. Comparisons of the risk of major bleeding for NOACs compared with aspirin were imprecisely estimated. There was evidence that risk of major bleeding is lower for dabigatran (150mg bd), apixaban (2.5mg bd) and apixaban

(5mg bd) compared with warfarin (INR 2-3). There was evidence that risk of major bleeding is higher with dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd and 5mg bd).

There was evidence that **risk of clinically relevant bleeding** is substantially higher with warfarin (INR 2-3), dabigatran (150 mg od) and rivaroxaban (20 mg od) compared with placebo, and that risk of clinically relevant bleeding is higher with rivaroxaban (20 mg od) compared with aspirin. There was evidence that risk of clinically relevant bleeding is lower with apixaban (2.5mg or 5mg bd) and dabigatran (150mg bd) compared with warfarin (INR 2-3). All comparisons between NOACs at licensed doses were imprecisely estimated, but there was evidence that risk of clinically relevant bleeding is higher with dabigatran (150mg bd) and rivaroxaban (20mg od) compared with apixaban (2.5mg bd and 5mg bd).

All comparisons of **risk of all-cause mortality** with placebo, except that for aspirin (100 mg od), were imprecisely estimated. However there was evidence that risk of all-cause mortality was lower for apixaban (5mg bd) compared with placebo. Comparisons of NOACs with aspirin were imprecisely estimated, although there was weak evidence that risk of all-cause mortality is lower with apixaban (5mg bd) compared with aspirin. There was no evidence that risk of all-cause mortality differed for NOACs compared with warfarin (INR 2-3), although all comparisons except that with dabigatran (150mg bd) were imprecisely estimated. Comparisons of risk of all-cause mortality between NOACs at licensed doses were imprecisely estimated.

12.1.8 Secondary prevention of venous thromboembolism: results of cost effectiveness analyses

We estimated expected costs, QALYs, incremental costs, incremental QALYs and incremental net monetary benefit at a willingness to pay of £20,000 and £30,000. The cheapest comparator is aspirin (total expected cost £20,671). No pharmacotherapy is the next cheapest treatment with benefits similar to aspirin. Warfarin and the NOACs all have substantially higher costs than aspirin and no pharmacotherapy, and the NOACs are more expensive than warfarin. Dabigatran and apixaban (5mg) have marginally higher expected QALYs compared to no pharmacotherapy. Apixaban

(2.5mg) has the lowest expected QALYs followed by warfarin. Apixaban (2.5mg) has the highest hazard ratio for the risk of ICH, albeit estimated imprecisely. Although the NOACs and warfarin prevent more recurrent VTEs than no pharmacotherapy or aspirin, the rate of recurrent VTE is low, and the rate of adverse events (ICH and clinically relevant bleeds), which can have a long-term impact on quality of life, are generally higher for the NOACs than aspirin or no pharmacotherapy.

Aspirin has the highest expected net benefit at a willingness to pay per QALY threshold of £20,000 and £30,000. However the confidence interval for the incremental net benefit of aspirin includes zero indicating uncertainty about whether it is more cost-effective than no pharmacotherapy. All NOACs have negative expected incremental net benefits at the £20,000 and £30,000 thresholds, and all confidence intervals are negative at the £20,000 threshold, indicating that they are not cost-effective compared with no pharmacotherapy. Dabigatran, which had the lowest estimated hazard ratio for recurrent VTE and ICH of all the NOACs, also has the highest expected net benefit of any NOAC. However dabigatran is not cost effective relative to no pharmacotherapy even at the £30,000 threshold, as the incremental net monetary benefit is negative (-£3402; -£12,388 to £5424). Although there is uncertainty in the estimated costs and QALYs, it is clear that aspirin has lower costs and similar benefits in the majority of the samples. Over a wide range of willingness to pay per QALY thresholds, aspirin has the highest expected net benefit, and also the highest probability of being the most cost-effective, although there is a non-negligible probability that no pharmacotherapy is the most cost-effective intervention for secondary prevention of VTE at a threshold of £20,000 to £30,000. These results suggest that it is not cost effective to prescribe NOACs or warfarin for secondary prevention of VTE over the range of willingness to pay thresholds that we explored (up to £40,000 per QALY).

12.1.9 Analyses of the value of information from future research

Value of information (VOI) analyses exploit the cost-effectivenss models to quantify and summarise the value (in cost terms) of evidence that could potentially be generated from future research studies.

For AF, the optimal decision regarding the most cost-effective NOAC is most sensitive to the hazard ratios comparing the NOACs, suggesting that a head-to-head trial comparing NOACs may be of value. The decision is also sensitive to costs, the effect of past events on future hazard ratios, and probabilities of treatment switching. A head to head trial could also provide information about baseline event rates, costs, and switching probabilities. However, a study powered to measure all of these outcomes with sufficient precision would require a very large sample size, which may be prohibitively expensive.

For VTE primary prevention in the total hip replacement population, the optimal decision is most sensitive to uncertainty in the treatment independent transition parameters, and also the cost parameters. This suggests that there may be value in running a longitudinal study examining the treatment independent transition parameters: rates of mild/moderate PTS, severe PTS, CTPH and the proportion split of VTE events.

For VTE primary prevention in the total knee replacement population, the optimal decision is most sensitive to uncertainty in the utilities, relative treatment effects, and treatment independent transition parameters, and is also sensitive to the cost parameters. This suggests that there may be value in running a large trial comparing NOACs and warfarin, which would reduce the uncertainty in the relative treatment effects. There may also be value in conducting a study to estimate the utility values associated with VTE events and treatment-related events and a longitudinal study examining the treatment independent transition parameters: rates of mild/moderate PTS, severe PTS, CTPH and the proportion split of VTE events.

For VTE acute treatment the optimal decision is most sensitive to uncertainty in the cost and utility model inputs. This suggests there may be value in conducting a study to estimate the utilities and costs associated with VTE events and treatment-related events. Since such a study is likely to be relatively inexpensive to conduct (compared with an RCT), and given the magnitude of likely benefits, this should be considered a research priority.

For VTE secondary prevention the optimal decision is most sensitive to the relative treatment effects, suggesting that there may be value in running a large trial comparing one or more NOACs with aspirin and no pharmacotherapy. However a study powered to capture VTE events may be prohibitively expensive, because event rates are low.

12.2 Strengths and limitations

12.2.1 Strengths

The strengths of this technology appraisal include its comprehensive coverage of all the therapeutic areas in which NOACS have been evaluated to date, using the same methodology. Previous analyses of comparative effectiveness have focused on individual therapeutic areas, making it more difficult to judge if one of the four licensed NOACs might emerge as a frontrunner in more than one therapeutic area. Additional strengths include: careful appraisal of study quality; focus on clinically relevant end-points; an evaluation of safety that considers evidence spanning all therapeutic areas together, to maximise power; the development of a possible treatment hierarchy for the different anticoagulant indications, where the data allowed it; and a cost-effectiveness analysis that is relevant to the NHS.

12.2.2 Limitations

The limitations of this technology appraisal relate mainly to shortfalls in the primary data, on which the overview is based. In particular:

- There were no direct head-to-head comparisons between different NOAC drugs: all such comparisons were therefore based on indirect evidence derived from the networks;
- Economic analyses for conditions like AF and VTE necessarily make long term projections on the basis of short term trial evidence, observational data and clinically informed assumptions about plausible treatment pathways and health state transitions. These assumptions and evidence limitations are discussed in previous sections (see 6.7 and 11.12).
- The profile of patients entering trials may not be the same as those treated in practice who may be older and have more co-morbidities. Treatment benefits in such patients may be smaller, and rates of harm higher, than estimated by trials;

- As for all new drugs, adverse effects that remained undetected during development may come to light with high volume use post licensing;
- It is possible that patients treated with warfarin in practice are at higher risk of bleeding complications than those in trials because of a greater number of co-morbidities and less stringent control of anticoagulation. However, concerns have also been raised previously that the time spent in the therapeutic range was suboptimal among patients in clinical trials assigned to warfarin. Thus clinical trials could have underestimated both the benefits and the risks of warfarin treatment.

For these reasons, guideline developers, prescribers and patients may wish to exercise caution when considering the prescription of new therapies over older, more established ones.

Several factors led to imprecision in the estimation of certain treatment effects. These included low rates of occurrence of certain end-points, particularly in trials evaluating the safety and efficacy of NOACs in the primary and secondary prevention of VTE; widespread use of composite end-points, with low rates of occurrence of certain (more clinically relevant) components of the composite; as well as substantial inconsistency in the reporting of end-points in different trials in the same therapeutic area, leading to a substantial amount of missing end-point data (see Table 22, Table 23, Table 92, Table 93, Table 124, Table 125, Table 144 and Table 145). Due to the low event rates and lack of substantial replication of specific comparisons across studies, we used fixed-effect models for the network meta-analysis. This does not account for heterogeneity in treatment effects. Under fixed-effect models, our Bayesian analyses with vague priors will produce results very similar to frequentist analyses.

The evidence base for established antiplatelet and anticoagulant treatments in primary prevention of VTE among hospitalised patients extends to groups of patients beyond those evaluated in this report, where comparisons were focused on patients undergoing hip and knee surgery. No trials of NOACS were identified among patients undergoing neurosurgery, gastroenterological surgery or gynaecological surgery. For this reason, conclusions about the comparative effectiveness of NOACs versus established antiplatelet and anticoagulant medications for primary prevention of VTE should be limited to hip and knee surgery patients.

The apparent efficacy of NOACs when compared to warfarin could be inflated if control of the INR was suboptimal among patients randomised to warfarin. For this reason many of the studies reported time spent in the therapeutic range (TTR), as an index of anticoagulant control. This is a potentially important issue for the studies of stroke prevention in AF, for which 16 (73%) of the 22 studies that included a warfarin intervention arm reported mean TTR. There was substantial variation in TTR (from 45.1% to 83%) between these studies. For acute treatment of VTE eight (89%) of the nine studies that included a warfarin intervention arm reported mean TTR, but variation between them was less marked than for the AF studies (56.9% to 63.5%). For secondary prevention of VTE, mean TTR was reported in three (60%) of the 5 studies that included a warfarin intervention arm. The pre-specified protocol for this health technology appraisal specified TTR as a potential modifier of NOAC treatment effect in trials where warfarin was the comparator. We plan future analyses that address this issue.

The clinical effectiveness analyses reported are based on relative rather than absolute risk differences. However, event rates for different safety and efficacy endpoints were estimated within and contributed to the cost-effectiveness analyses.

Factors beyond those considered in this technology appraisal could influence the choice of the optimal anticoagulant in each of the therapeutic areas evaluated.

In some situations the need for anticoagulation monitoring with warfarin treatment may be viewed as a useful means to confirm adherence to anticoagulant therapy rather than as an inconvenience.

Recent studies have suggested that the efficacy and safety of dabigatran could be improved by monitoring of achieved drug levels, because these exhibit wide inter-individual variation. This may reduce the convenience of this NOAC and increase its cost compared to warfarin or other NOACs but we did not model this in the current report. Only one of the studies included in our reviews considered whether monitoring improves the efficacy and safety of NOACs: in a subsample of 9183 patients in the RE-LY trial, ischaemic stroke and major bleeding both correlated with dabigatran

plasma concentrations[16]. Specific tests to measure the anticoagulation effects of NOACs are being developed but are not yet widely available[252] and routine coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are of limited use[253,254]. It is therefore currently unclear whether the efficacy and safety profiles of NOACs can be improved by monitoring and dose adjustment. Monitoring may be particularly helpful in certain clinical situations (e.g. emergency surgery or patients presenting with bleeding[254]) and patient groups (advanced age, renal impairment).

Finally, therapeutic decision making may be influenced by recognition that effective treatments for reversal of anticoagulation with NOACs are still in the developmental phase. For example:

- Aripazine (PER-977; PER 977; ciraparantag) is a synthetic cationic molecule that binds unfractionated and low molecular weight heparin, the factor Xa inhibitors edoxaban, rivaroxaban and apixaban, and the factor II inhibitor dabigatran, but not to warfarin[255]. In a phase 1 trial involving 80 healthy volunteers, intravenous PER977 reversed the prolongation of whole blood clotting time induced by a single oral dose of edoxaban 60mg in a dose-dependent fashion, within 10-30 minutes of administration[256]. Phase 2 clinical studies of this agent are in progress.
- Andexanet alpha (PRT4445; PRT064445) is a recombinant modified factor Xa molecule that acts as an antidote to factor Xa inhibitors through a decoy mechanism. A number of phase 3 studies of this agent are underway[257,258].
- Idarucizumab (BI 655075) is a humanised monoclonal antibody fragment that binds dabigatran to reverse its anticoagulant activity[259,260]. Phase 1/2 studies of this agent have been completed. A phase 3 study investigating reversal of anticoagulation in patients receiving dabigatran who have uncontrolled bleeding or who require emergency surgery or invasive procedures is underway.

12.3 Research needs

Evidence on the comparative efficacy of NOACs in this review has come exclusively from indirect comparisons, because of the lack of head-to-head trials. Among patients with AF, a long-term condition, the trials have also been of relatively short duration. A

different manufacturer has developed each of the agents evaluated in this review and it is therefore unlikely that any head-to-head trials trials will be initiated by industry.

Reliable estimation of the cost effectiveness of NOACs in different clinical scenarios requires high quality data on absolute event rates for the various efficacy and safety outcomes. NHS health record data could provide a rich source for information, but so far health record data has been insufficiently utilised for this purpose.

Although NOACs were developed in part to supersede warfarin by obviating the need for therapeutic monitoring of anticoagulation, to improve convenience, recent studies[16] have suggested that monitoring of drug levels may improve safety and efficacy of dabigatran treatment. Whether this is also the case for other NOACs is not known.

The requirement for therapeutic drug monitoring with warfarin also serves as a means to assess adherence. Thus far, long-term adherence rates for NOACs e.g. among patients with AF who may require anticoagulation for many years have not been evaluated.

For secondary prevention of VTE, use of NOACs in high risk patients is a potential area for further study. Further research is needed to clarify whether aspirin or no treatment should be standard of care in this setting.

The research needs identified by this review are therefore as follows:

- To complete calculations of the Expected Value of Sample Information, in order to clarify whether it is justifiable to conduct one or more trials making direct comparisons between the most promising NOACs and NOAC doses, in situations typical of NHS clinical practice.
- To consider the merits of conducting cohort studies that reduce uncertainties in costs, utilities and transition probabilities in order to improve estimates of relative cost-effectiveness, in particular in the context of primary prevention of VTE in total hip replacement and total knee replacement, and acute treatment of VTE.
- Information on long-term rates of the main efficacy and safety outcomes among patients receiving anticoagulants for AF e.g. from registries or health record data.

- Information on the role (if any) of therapeutic monitoring to enhance the safety and efficacy of NOACs.
- Information on long-term adherence rates in patients receiving NOACs for AF.
- Development of tools to stratify risk of recurrent VTE.
- Further research is also needed to establish whether the secondary prevention of VTE with aspirin or other agents is cost-effective, with an adequate safety margin, in patients identified as being at particularly high risk of recurrence by validated risk stratification tools.

12.4 Implications for practice

This health technology appraisal was conducted to help guideline developers, doctors and patients decide when a NOAC might be preferred to an established anticoagulant and, when a NOAC is preferred to warfarin, if there is sufficient evidence to support the use of one particular NOAC over another. The evidence provided by this health technology appraisal indicates:

- NOACs have advantages over warfarin in patients with AF and, of the available NOACs, apixaban 5mg bd offers the best balance between efficacy and safety and has the highest probability of being most cost-effective.
- NOACs offer no efficacy advantage over warfarin in the acute treatment of VTE, but have a lower rate of bleeding complications albeit at a higher cost. For a willingness to pay threshold of >£5000, apixaban 5mg bd emerges as the most cost effective alternative to warfarin.
- Neither the clinical nor cost effectiveness analysis provided strong evidence that NOACs replace post-operative LMWH in primary prevention of VTE in patients undergoing hip or knee surgery.
- If secondary prevention after 3-6 months of anticoagulation for a first episode of VTE is to be considered (this is not currently established practice), NOACs provide no advantage over aspirin 100mg od.

13. Patient perspective

Anticoagulation Europe (Ace) is a charity that provides education, information and support to patients requiring anticoagulation therapy in the UK.

Patients requiring anticoagulants for the treatment and prevention of venous thromboembolism are given vitamin K antagonists (VKAs) warfarin, heparin and low – molecular weight heparin (LMWH). These treatments are effective and are now joined by newer technologies that work differently to warfarin.

The novel oral anticoagulants (NOACS) have become available to be used in the prevention of stroke in non-vavular atrial fibrillation and the treatment and secondary prevention of deep vein thrombosis and pulmonary embolism, complementing existing treatments.

In the UK, The National Institute of Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) have produced guidelines that recommend the new agents. The benefits to patients and clinicians are that there is now a broader range of treatment options available to treat and prevent blood clots.

Anticoagulation Europe has welcomed the opportunity to participate in this project and have contributed the patient perspective of current anticoagulation practice as captured by the experiences and feedback derived from their patient databases.

In our role as a dedicated anticoagulation charity, we have highlighted the need for equality of access to all the anticoagulation therapies as recommended by NICE and SMC. We advocate that patients should be adequately informed of the benefits and risks of all anticoagulation treatments in order that they can make an informed choice around their therapy options with the appropriate healthcare professionals.

AntiCoagulation Europe anticipates that this comprehensive study will provide a helpful and informative reference resource for clinicians when considering and presenting the most effective and safe anticoagulation treatment options to the patient for their condition.

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14.1 Data sharing statement

All study data will be available from the corresponding author on request, once papers reporting the study findings have been published. Corresponding author's contact details – School of Social and Community Medicine, Canynge Hall, University of Bristol, Bristol, UK.

14.2 Contributions of Authors

PNB, PAB, PAD, JAL, GNO and HHT worked for substantial periods of time on the project, and are listed alphabetically. Other authors (DMC, SD, DE, JPTH, WH, CS, JS, RS, AS, and NJW) apart from the first author (JACS) and last author (ADH) are then listed alphabetically.

Prof Jonathan Sterne (Professor of Medical Statistics and Epidemiology) co-conceived the project, led the grant application, led the project, contributed to statistical analyses and finalized the report.

Dr Pritesh Bodalia (Principal Pharmacist) contributed to the grant application, extracted data and assessed risk of bias for the AF review, checked these aspects for the VTE reviews, and provided pharmaceutical expertise.

Peter Bryden (Research Associate in Health Economics Modelling) developed and analysed the economic models for VTE reviews, and drafted relevant parts of the report.

Dr Philippa Davies (Research Associate in Evidence Synthesis/Systematic Reviewing) extracted and checked data, assessed risk of bias, and contributed to writing the report.

Dr Jose Lopez-Lopez (Research Associate in Medical Statistics) undertook the statistical analyses of clinical effectiveness and safety, and drafted relevant parts of the report.

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Dr Howard Thom (Research Associate in Health Economic Modelling) developed and analysed the economic models for the AF review, and drafted relevant parts of the report.

Dr Deborah Caldwell (Lecturer in Public Health Research) contributed to the grant application, contributed to the systematic review and planning of network meta-analyses.

Dr Sofia Dias (Research Fellow) contributed to the statistical analyses.

Diane Eaton (Project Manager, Anticoagulation Europe) provided a patient perspective.

Prof Julian Higgins (Professor of Evidence Synthesis) contributed to the grant application, contributed to the network meta-analyses of clinical effectiveness and safety, contributed to management of the project, and contributed to writing the report.

Prof Will Hollingworth (Professor of Health Economics) contributed to the grant application, contributed to the cost-effectiveness analyses and contributed to writing the report.

Prof Chris Salisbury (Professor in Primary Health Care) contributed to the grant application and provided clinical expertise.

Dr Jelena Savovic (Research Fellow) contributed to the grant application and contributed to the systematic review.

Dr Reecha Sofat (Senior Lecturer) provided clinical expertise and contributed to writing the report.

Annya Stephens-Boal (Executive Officer, Thrombosis UK) provided a patient perspective.

Dr Nicky Welton (Reader in Statistical and Health Economic Modelling) contributed to the grant application, contributed to the statistical and cost-effectiveness analyses and contributed to writing the report.

Prof Aroon Hingorani (Professor of Genetic Epidemiology) co-conceived the project, provided clinical expertise, and contributed to writing the report.

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Appendix 1 Medline search strategy

Appendix 1: Medline search strategy used for scoping reviews

Venous thromboembolism

Database: Medline 1950 to present (Search date: 20/03/14)

Search Strategy:

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1 exp Venous Thrombosis/ (43921)

2 exp Pulmonary Embolism/ (30904)

3 thromboembolism/ or venous thromboembolism/ (24405)

4 ((venous or vein$) adj3 (thrombus$ or thrombo$)).ti,ab. (45827)

5 (DVT or VTE).ti,ab. (9537)

6 (thrombophlebitis or thromboprophylaxis or thrombo-prophylaxis or thrombophlebitides).ti,ab. (7132)

7 ((pulmonary or lung or lungs) adj3 embol$).ti,ab. (27169)

8 ((leg or legs) adj3 (embol$ or thrombo$ or thrombus$)).ti,ab. (1141)

9 or/1-8 (111695)

10 exp *Anticoagulants/ (94334)

11 exp *Coumarins/ (24282)

12 Warfarin/ (14323)

13 exp Vitamin K/ai [Antagonists & Inhibitors] (1537)

14 Thrombin/ai [Antagonists & Inhibitors] (3372)

15 Factor Xa/ai [Antagonists & Inhibitors] (2203)

16 Aspirin/ (37741)

17 (anticoagula$ or anti-coagula$).ti. (20512)

18 (oral anticoagula$ or oral anti-coagula$).ti,ab. (7048)

19 (coumarin$ or coumadin$ or warfarin or marevan or dicoumarol or dicoumarin or dicumarin or dicumarol or acenocoumarol or phenindione or aldocumar).ti,ab. (24194)

20 (factor Xa adj2 (antagonist$ or inhibitor$)).ti,ab. (1356)

21 (factor 10a adj2 (antagonist$ or inhibitor$)).ti,ab. (2)

22 (factor IIa adj2 (antagonist$ or inhibitor$)).ti,ab. (25)

23 ((vitamin K or vitamin-k) adj2 (antagonist$ or inhibitor$)).ti,ab. (1830)

24 (dabigatram or pradaxa or BIBR1048 or Apixaban or Eliquis or BMS-562247-01 or Edoxaban or Lixiana or savaysa or DU-176b or betrixaban or PRT-054021 or PRT0504021 or rivaroxaban or xarelto or BAY-59739 or Erixaban or D0913).ti,ab. (1015)

25 (NOAC or NOACS).ti,ab. (86)

26 (aspirin or acetyl-salicylic acid or acetylsalicylic acid).ti,ab. (40463)

27 or/10-26 (170042)

28 *heparin/ or exp heparin, low-molecular-weight/ or heparinoids/ (33841)

29 (Dalteparin or fragmin$ or enoxaparin or clexane or lovenox or tinzaparin or innohep or bemiparin or badyket or hepadren or hibor or ivor or ivorat or zibor or certoparin or mono-embolex or sandoparin$ or nadroparin$ or fraxiparin$ or parnaparin or fluxum or reviparin or clivarine or lowmorin).ti,ab. (4597)

30 (LMWH$ or heparinoid$ or danaparoid or orgaran).ti,ab. (4469)

31 (low$ molecular adj2 heparin$).ti,ab. (9114)

32 or/28-31 (37314)

33 27 or 32 (173069)

34 9 and 33 (22835)

35 letter/ (803375)

36 editorial/ (333336)

37 news/ (151695)

38 exp historical article/ (318208)

39 Anecdotes as topic/ (4506)

40 comment/ (528857)

41 case report/ (1665228)

42 (letter or comment$).ti. (84259)

43 or/35-42 (3214189)

44 randomized controlled trial/ or Randomized Controlled Trials as Topic/ or random$.ti,ab. (774175)

45 43 not 44 (3185399)

46 animals/ not humans/ (3810079)

47 exp Animals, Laboratory/ (714848)

48 exp Animal Experimentation/ (6196)

49 exp Models, Animal/ (407481)

50 exp rodentia/ (2630754)
51 (rat or rats or mouse or mice).ti. (1065119)
52 or/45-51 (7547456)
53 34 not 52 (16525)
54 meta-analysis/ (45670)
55 meta-analysis as topic/ (13522)
56 (meta analy$ or metaanaly$ or metanaly$ or meta regression).ti,ab. (54350)
57 ((systematic$ or evidence$) adj2 (review$ or overview$)).ti,ab. (61810)
58 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab. (22477)
59 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (24122)
60 (search$ adj4 literature).ab. (23275)
61 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (71805)
62 cochrane.jw. (9850)
63 ((multiple treatment$ or indirect or mixed) adj2 comparison).ti,ab. (813)
64 or/54-63 (169922)
65 randomized controlled trial.pt. or randomized controlled trial/ or Randomized Controlled Trials as Topic/ (452316)
66 controlled clinical trial.pt. (87802)
67 randomi#ed.ab. (318385)
68 placebo.ab. (143748)
69 drug therapy.fs. (1675613)
70 randomly.ab. (189528)
71 trial.ab. (275251)
72 groups.ab. (1220973)
73 or/65-72 (3169503)
74 clinical trials as topic.sh. (168638)
75 trial.ti. (114737)
76 or/65-68,70,74-75 (899851)
77 64 or 76 (1015181)
78 53 and 77 (4596)
79 limit 78 to yr="2008 -Current" (1408)

80 atrial fibrillation.ti. (19641)
81 *atrial fibrillation/ (25973)
82 80 or 81 (26290)
83 79 not 82 (1281)

Atrial Fibrillation
Database: Medline In-process - Current week, Medline 1950 to present
(Search date: 20/03/14)
Search Strategy:
---
1 tachycardia, supraventricular/ or tachycardia, ectopic atrial/ (5440)
2 atrial fibrillation/ (33510)
3 ((atrial or atrium or auricular) adj3 fibrillat$).ti,ab. (38980)
4 heart fibrillat$.ti,ab. (42)
5 (supraventricul$ adj3 (arrhythmi$ or tachycardia$)).ti,ab. (7547)
6 ((atrial or atrium) adj3 (tachycardia$ or arrhythmi$)).ti,ab. (6888)
7 (atrial adj3 tachyarrhythmi$).ti,ab. (1210)
8 Atrial Flutter/ (4944)
9 ((atrial or auricular) adj3 flutter$).ti,ab. (5382)
10 or/1-9 (59756)
11 exp *Anticoagulants/ (94278)
12 exp *Coumarins/ (24265)
13 Warfarin/ (14307)
14 exp Vitamin K/ai [Antagonists & Inhibitors] (1534)
15 Thrombin/ai [Antagonists & Inhibitors] (3370)
16 Factor Xa/ai [Antagonists & Inhibitors] (2197)
17 Aspirin/ (37712)
18 (anticoagula$ or anti-coagula$).ti. (21584)
19 (oral anticoagula$ or oral anti-coagula$).ti,ab. (7768)
20 (coumarin$ or coumadin$ or warfarin or marevan or dicoumarol or dicoumarin or dicumarin or dicumarol or acenocoumarol or phenindione or aldocumar).ti,ab. (26479)
21 (factor Xa adj2 (antagonist$ or inhibitor$)).ti,ab. (1502)

22 (factor 10a adj2 (antagonist$ or inhibitor$)).ti,ab. (2)
23 (factor IIa adj2 (antagonist$ or inhibitor$)).ti,ab. (29)
24 ((vitamin K or vitamin-k) adj2 (antagonist$ or inhibitor$)).ti,ab. (2080)
25 (dabigatram or pradaxa or BIBR1048 or Apixaban or Eliquis or BMS-562247-01 or Edoxaban or Lixiana or savaysa or DU-176b or betrixaban or PRT-054021 or PRT0504021 or rivaroxaban or xarelto or BAY-59739 or Erixaban or D0913).ti,ab. (1330)
26 (NOAC or NOACS).ti,ab. (152)
27 (aspirin or acetyl-salicylic acid or acetylsalicylic acid).ti,ab. (42763)
28 or/11-27 (175520)
29 10 and 28 (6721)
30 letter/ (829317)
31 editorial/ (348841)
32 news/ (159814)
33 exp historical article/ (318220)
34 Anecdotes as topic/ (4506)
35 comment/ (572414)
36 case report/ (1665104)
37 (letter or comment$).ti. (94907)
38 or/30-37 (3300100)
39 randomized controlled trial/ or Randomized Controlled Trials as Topic/ or random$.ti,ab. (835720)
40 38 not 39 (3270043)
41 animals/ not humans/ (3807926)
42 exp Animals, Laboratory/ (714413)
43 exp Animal Experimentation/ (6188)
44 exp Models, Animal/ (407073)
45 exp rodentia/ (2629200)
46 (rat or rats or mouse or mice).ti. (1097935)
47 or/40-46 (7662407)
48 29 not 47 (5201)
49 systematic review/ (0)
50 meta analysis/ (45623)
51 (meta analy$ or metaanaly$ or metanaly$ or meta regression).ti,ab. (61909)

52 ((systematic$ or evidence$) adj2 (review$ or overview$)).ti,ab. (71965)
53 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab. (24936)
54 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (26492)
55 (search$ adj4 literature).ab. (26789)
56 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or cinahl or science citation index or bids or cancerlit).ab. (82698)
57 cochrane.jw. (10337)
58 ((multiple treatment$ or indirect or mixed) adj2 comparison).ti,ab. (901)
59 or/49-58 (186127)
60 randomized controlled trial.pt. or randomized controlled trial/ or Randomized Controlled Trials as Topic/ (452445)
61 controlled clinical trial.pt. (87837)
62 randomi#ed.ab. (343274)
63 placebo.ab. (151447)
64 drug therapy.fs. (1674296)
65 randomly.ab. (208182)
66 trial.ab. (297177)
67 groups.ab. (1328911)
68 or/60-67 (3312451)
69 clinical trials as topic.sh. (168554)
70 trial.ti. (123158)
71 or/60-63,65,69-70 (946554)
72 59 or 71 (1075719)
73 48 and 72 (1764)
74 limit 73 to yr="2010 -Current" (728)

Appendix 2 Forest plots: Stroke prevention in atrial fibrillation

Table 203 provides the reference numbers that correspond to the trial names for the review of stroke prevention in AF, so that readers can easily trace the results presented in the forest plots along this section.

Table 203 List of trial names and reference numbers (stroke prevention in AF)

Trial name	Reference(s)	Trial name	Reference(s)
ACTIVE-W	103	BAFTA	106
AFASAK	98	Chinese ATAFS	102
AFASAK II	100	ENGAGE AF-TIMI 48	114, 134
AF-ASA-VKA-CHINA	138	EXPLORE-Xa	131
AF-DABIG-VKA-JAPAN	113	J-ROCKET AF	123
AF-EDOX-VKA-ASIA	118	PATAF	101
AF-EDOX-VKA-JAPAN	121	PETRO	105
AF-EDOX-VKA-MULTI	111	RE-LY	107, 112
AF-VKA-ASA-CHINA	125	ROCKET AF	109, 115, 126, 132
ARISTOTLE	110, 117, 122, 127-130, 133, 135-137	SPAF II	99
ARISTOTLE-J	116	WASPO	104
AVERROES	108, 119, 120, 124		

Figure 139 Forest plot for stroke or systemic embolism [1/4] (stroke prevention in AF)

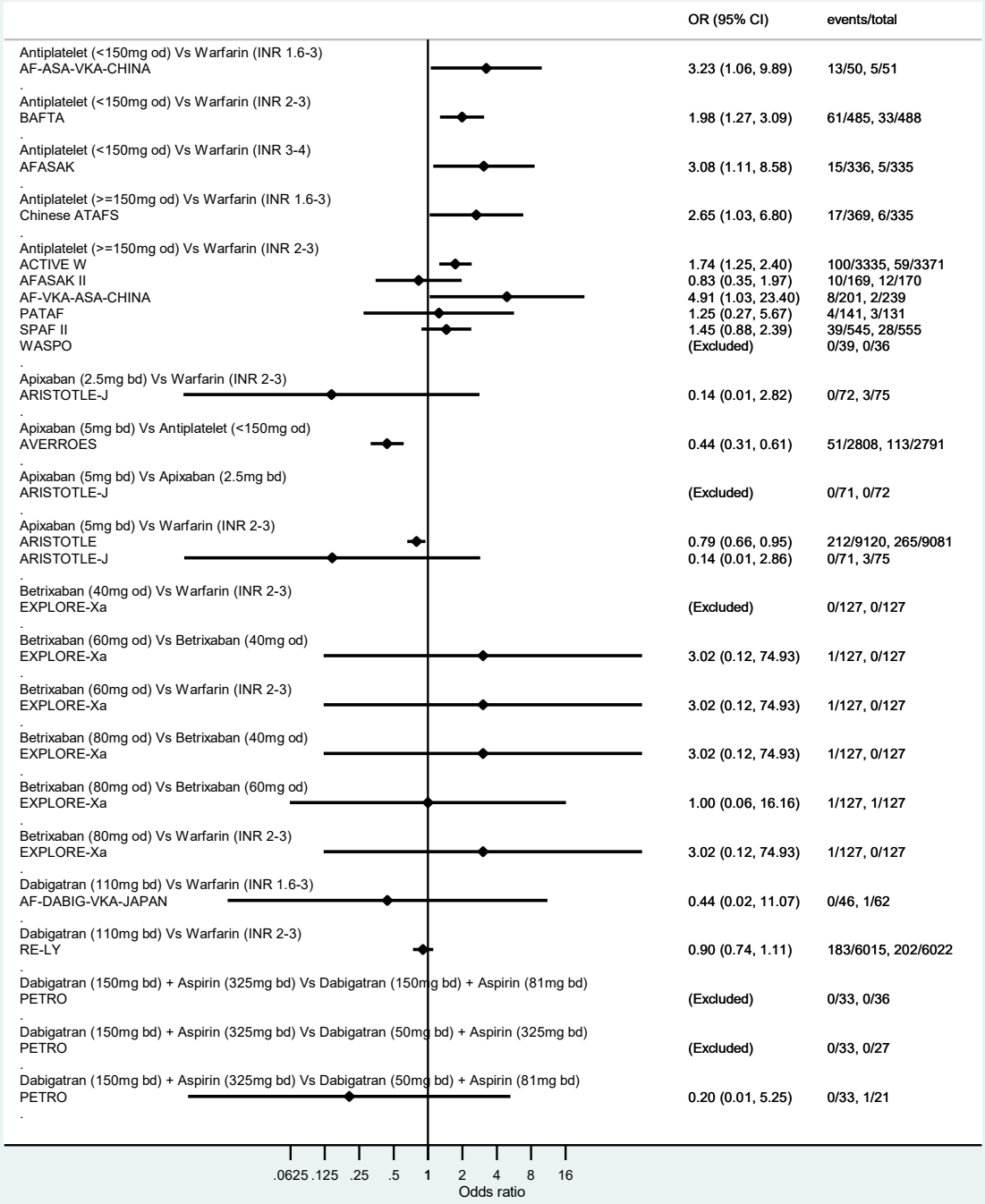


Figure 140 Forest plot for stroke or systemic embolism [2/4] (stroke prevention in AF)

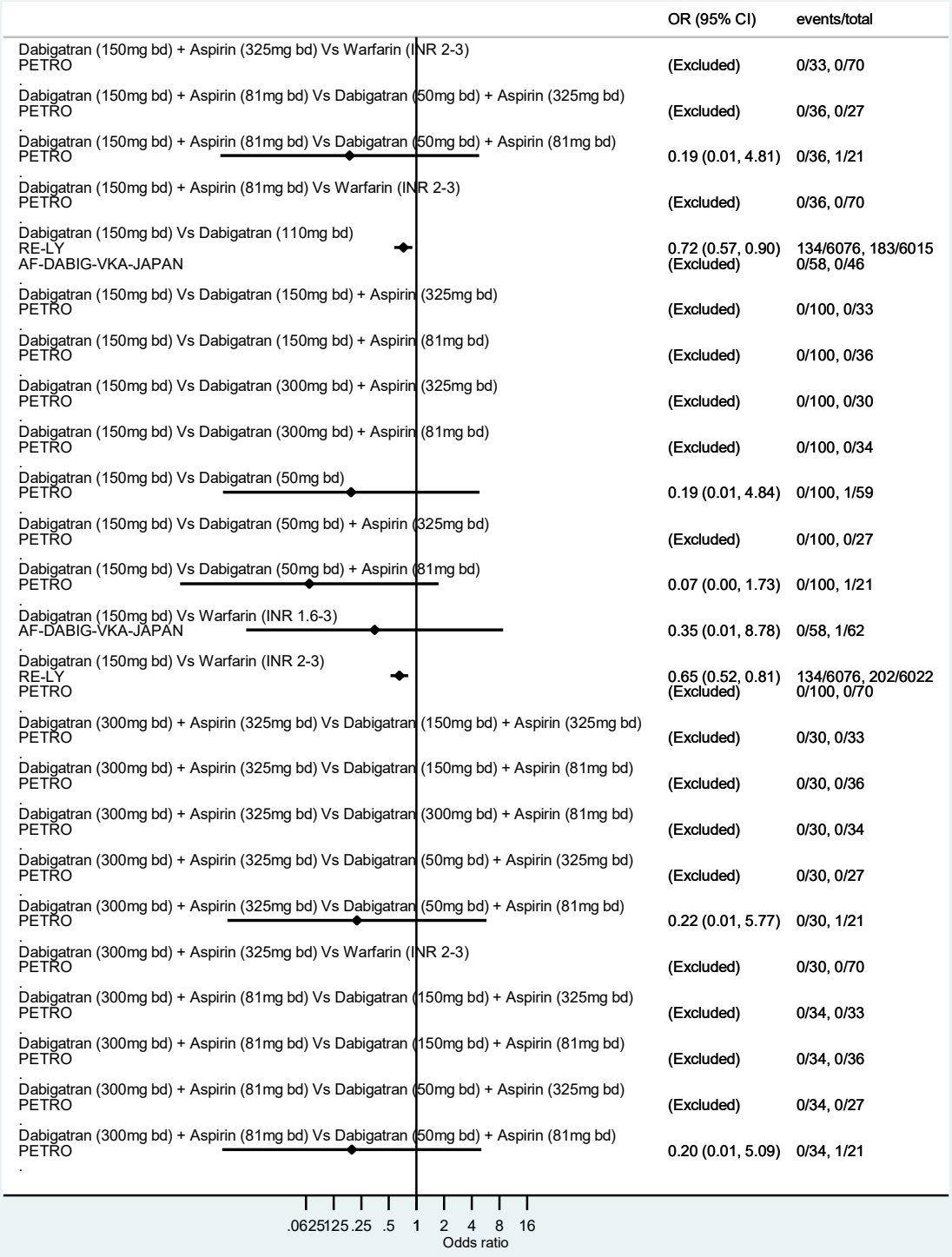


Figure 141 Forest plot for stroke or systemic embolism [3/4] (stroke prevention in AF)

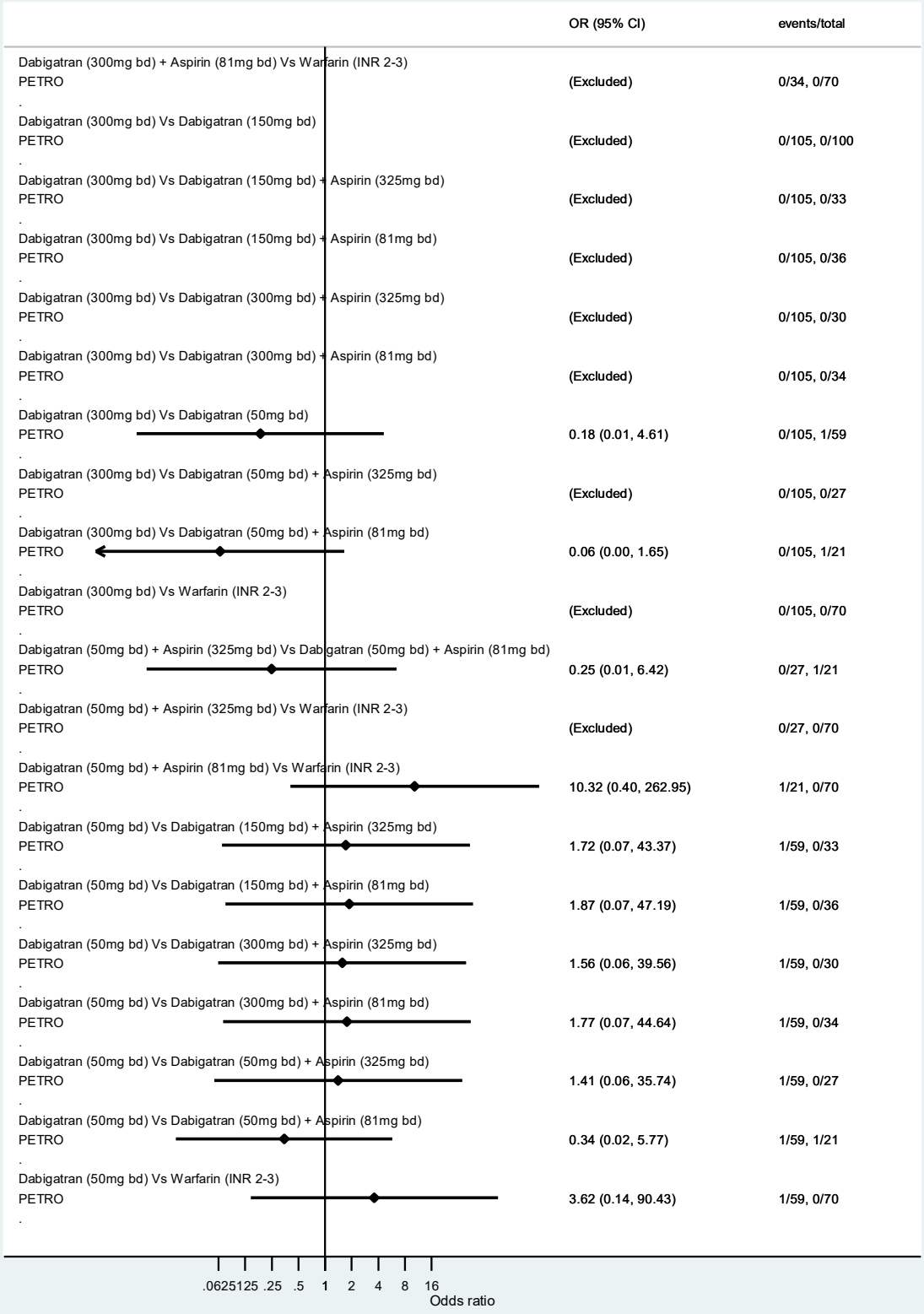


Figure 142 Forest plot for stroke or systemic embolism [4/4] (stroke prevention in AF)

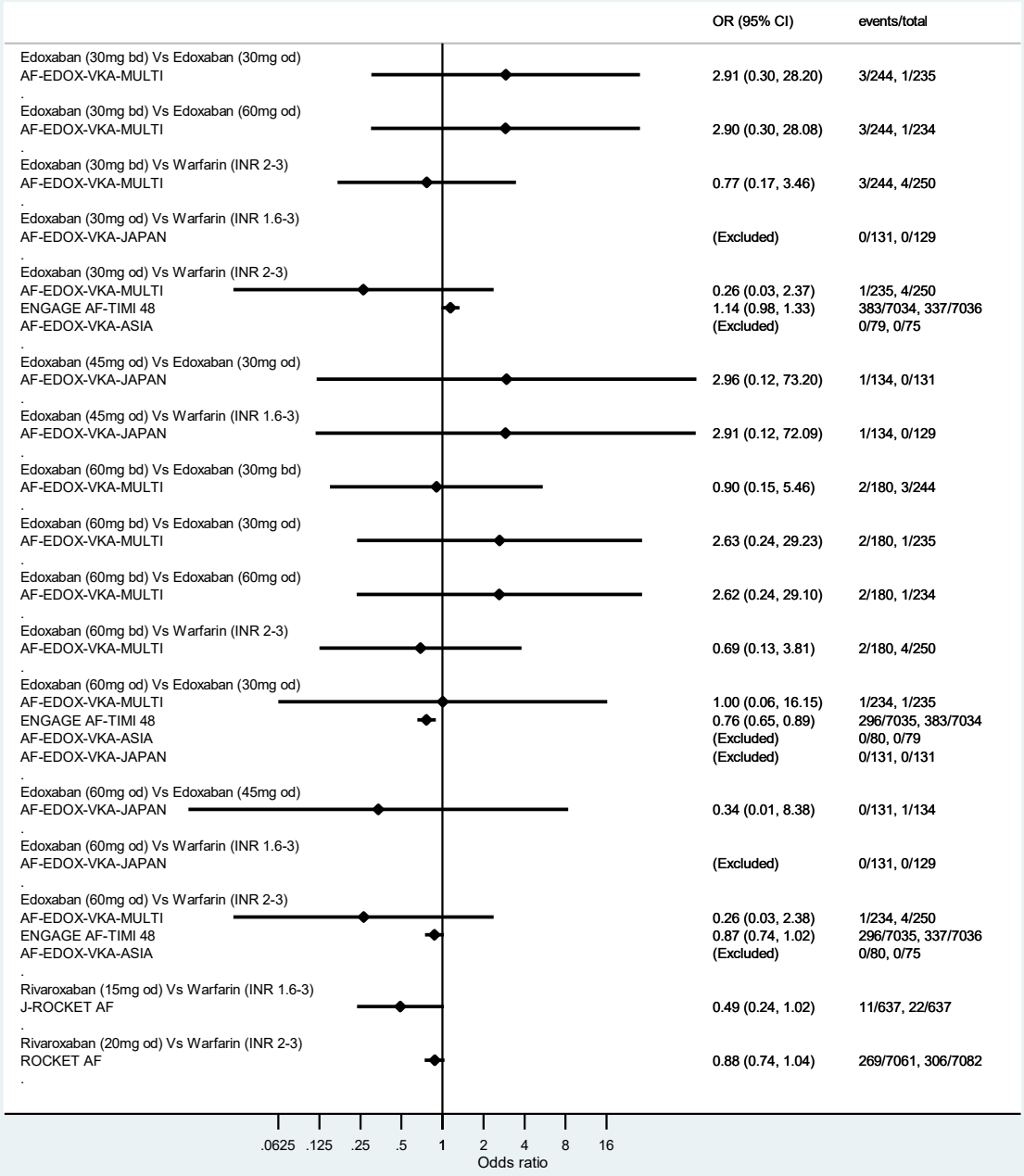


Figure 143 Forest plot for ischaemic stroke (stroke prevention in AF)

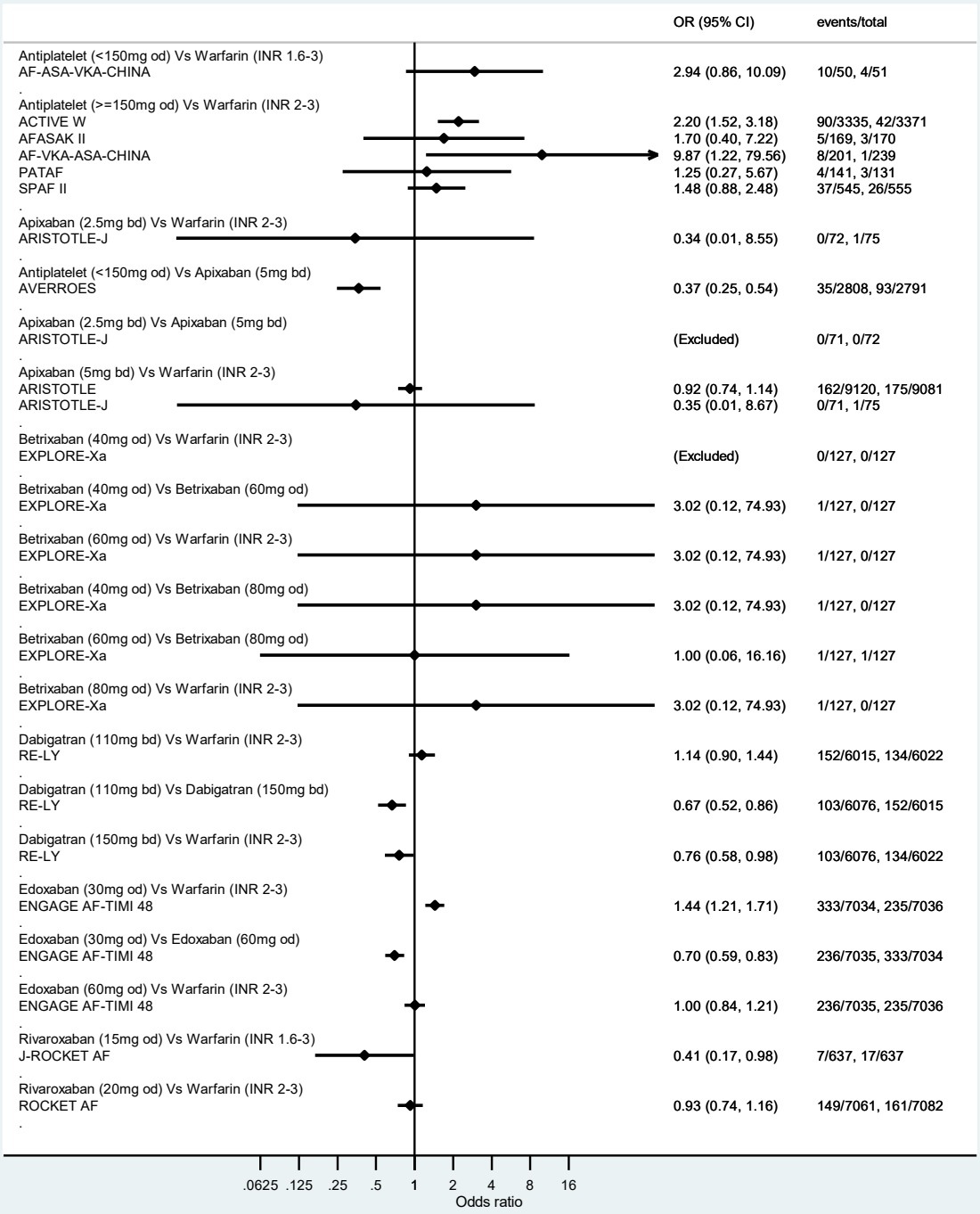


Figure 144 Forest plot for myocardial infarction (stroke prevention in AF)

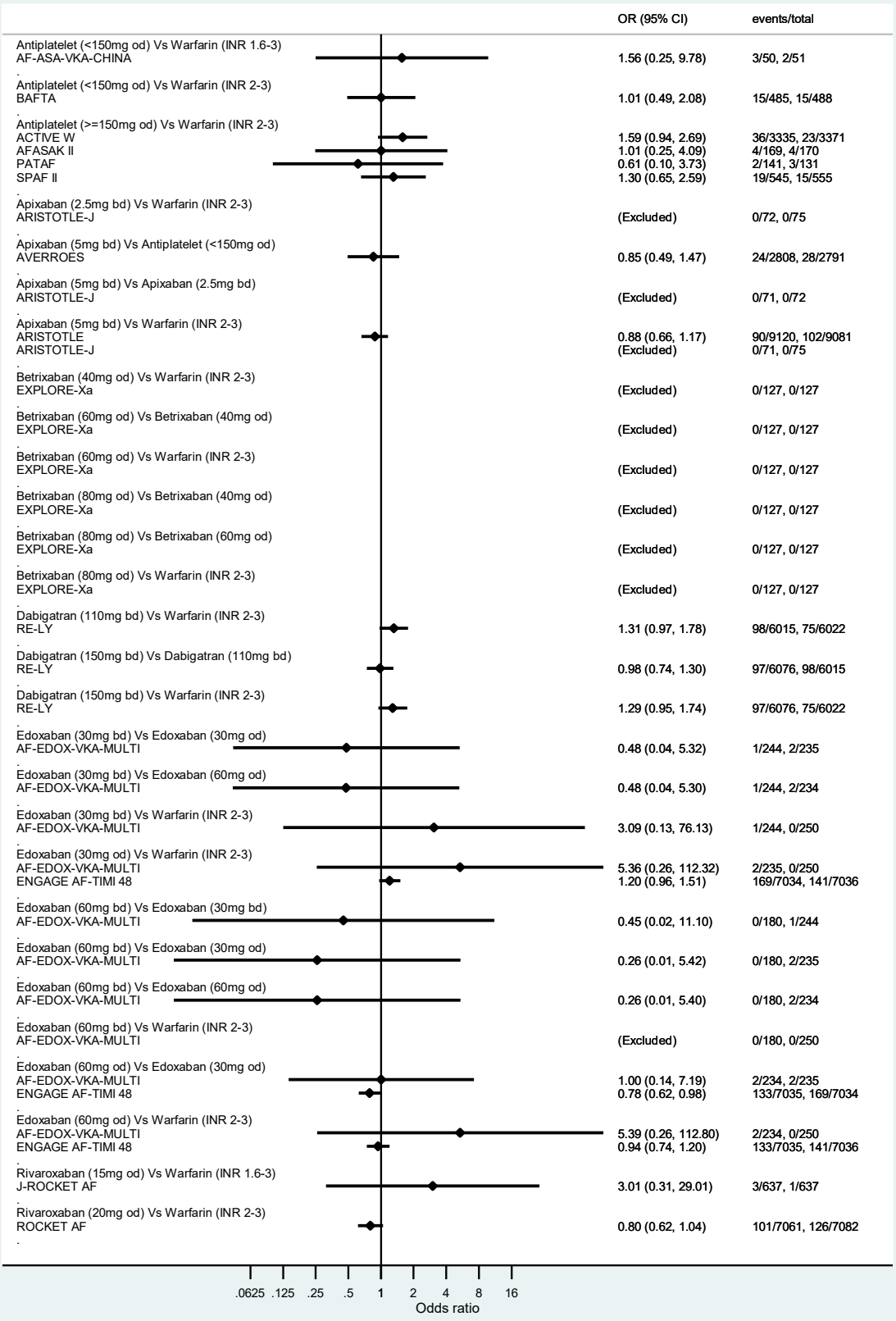


Figure 145 Forest plot for major bleeding [1/4] (stroke prevention in AF)

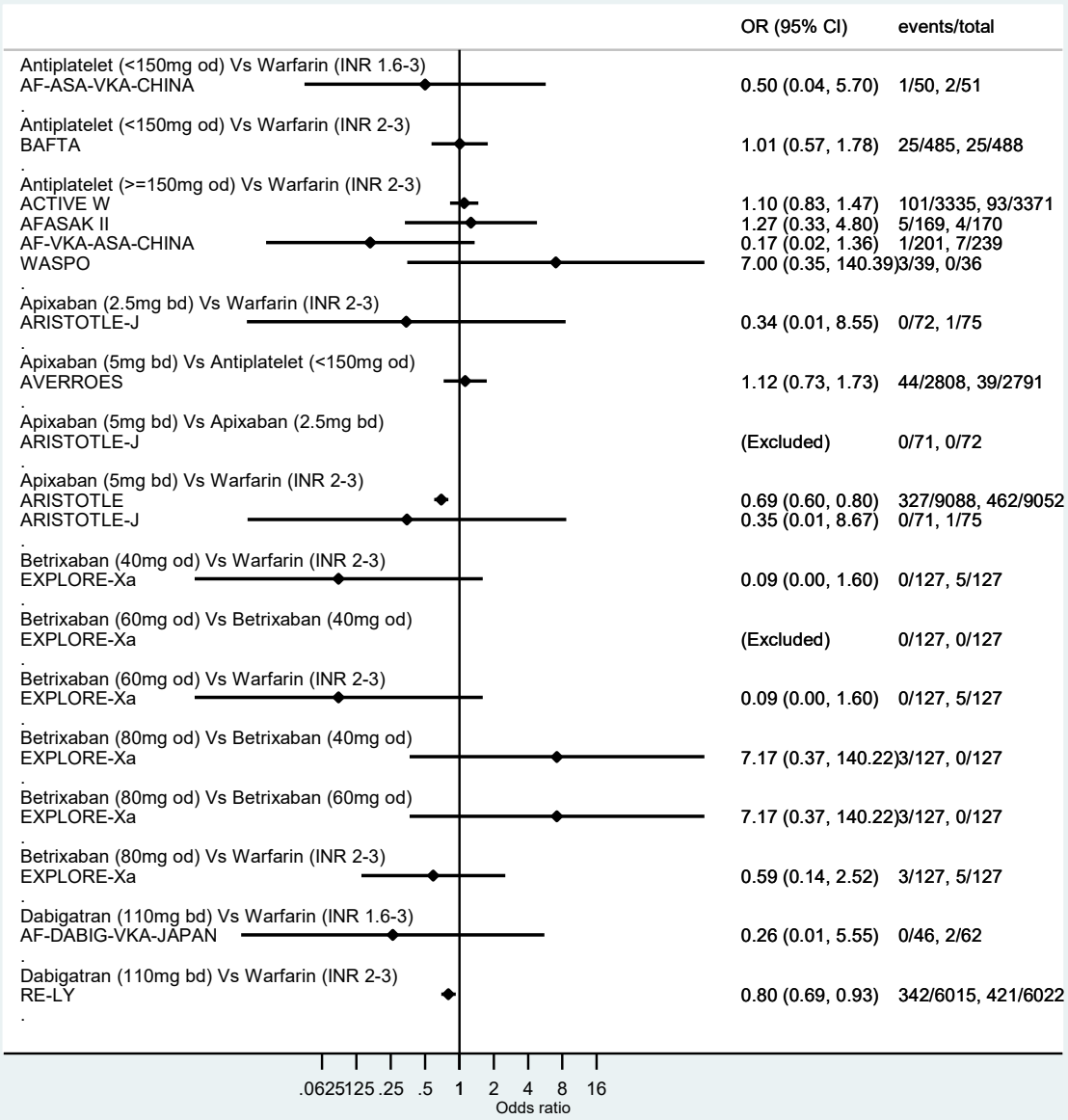


Figure 146 Forest plot for major bleeding [2/4] (stroke prevention in AF)

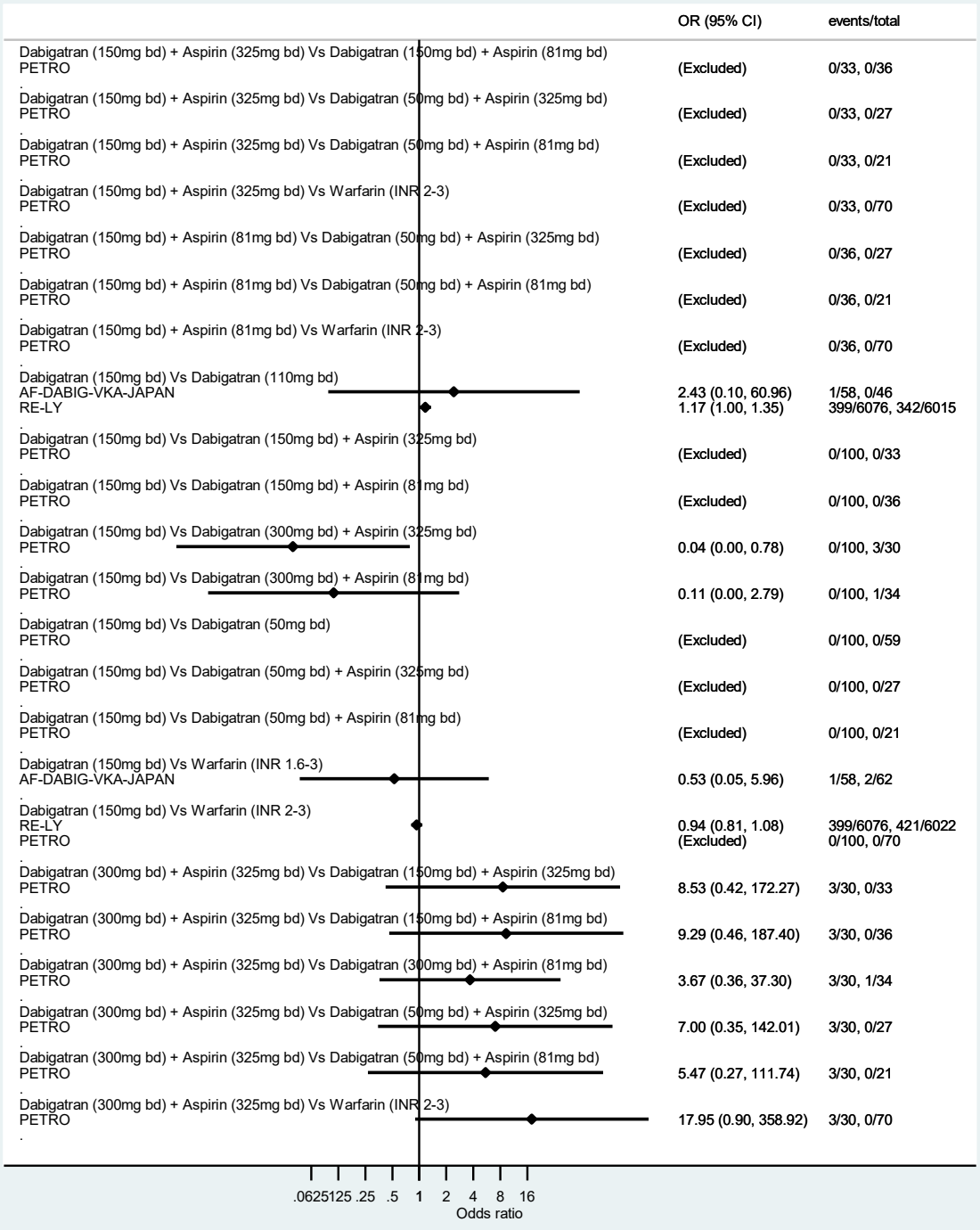


Figure 147 Forest plot for major bleeding [3/4] (stroke prevention in AF)

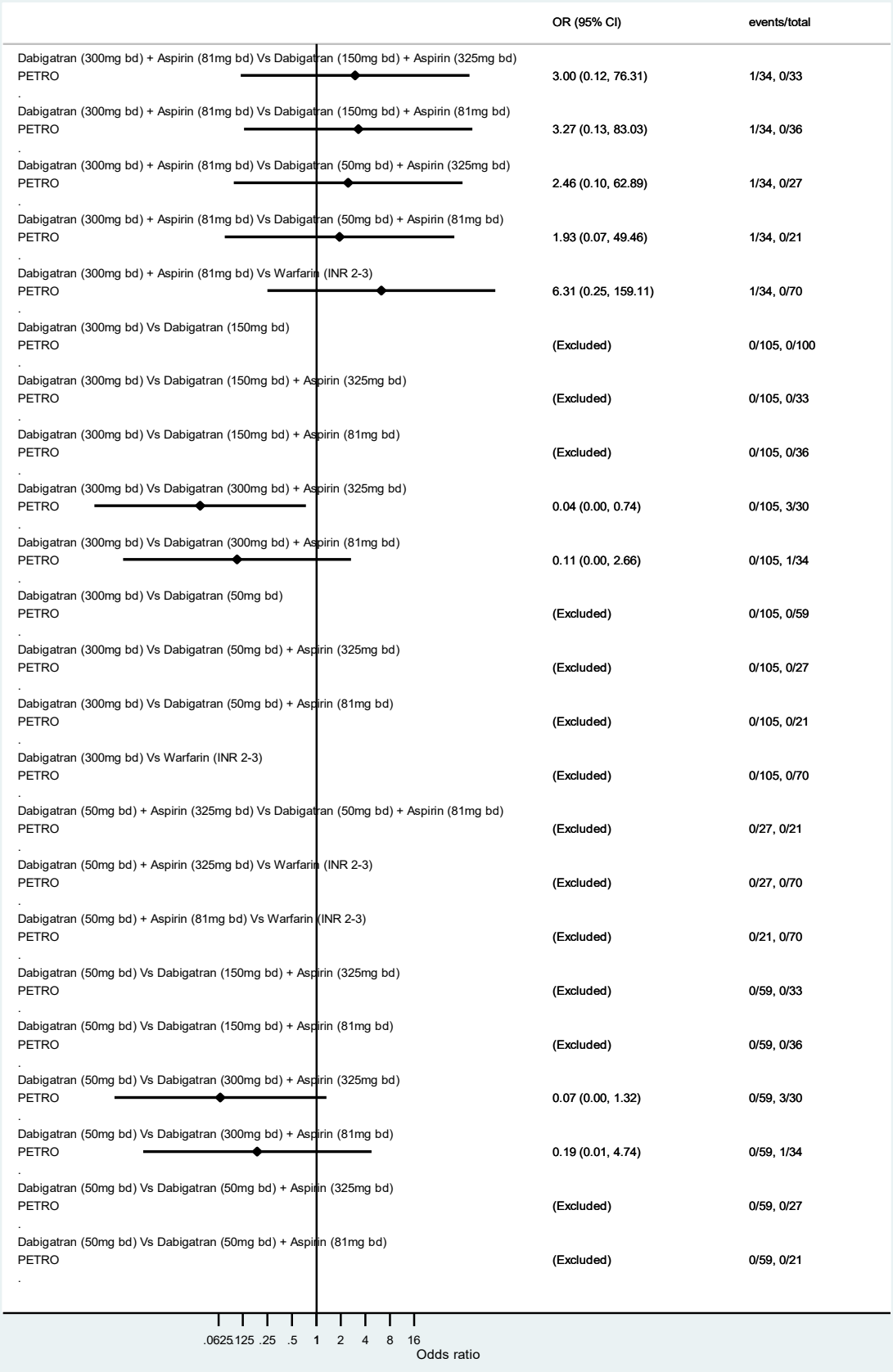


Figure 148 Forest plot for major bleeding [4/4] (stroke prevention in AF)

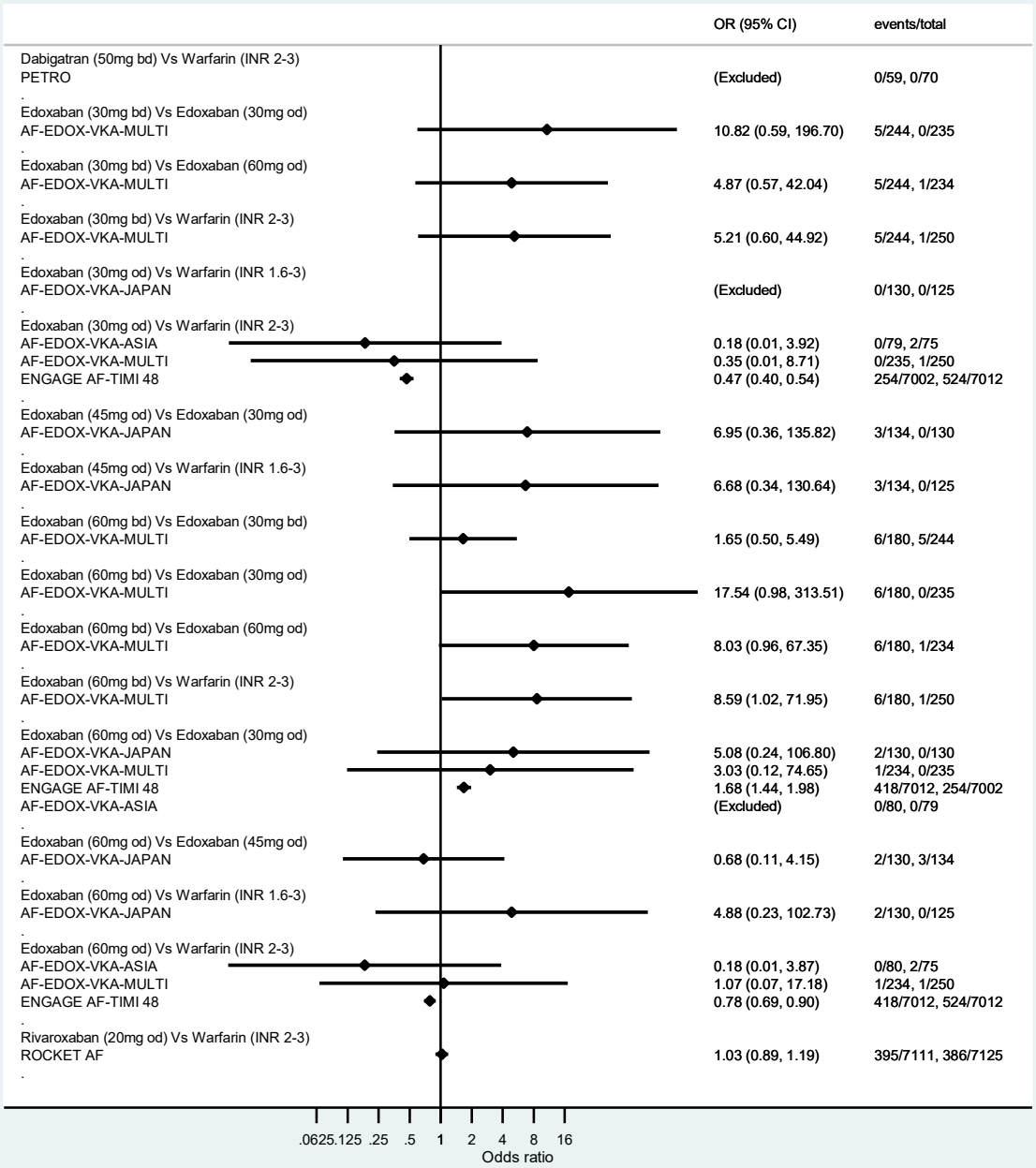


Figure 149 Forest plot for clinically relevant bleeding [1/3] (stroke prevention in AF)

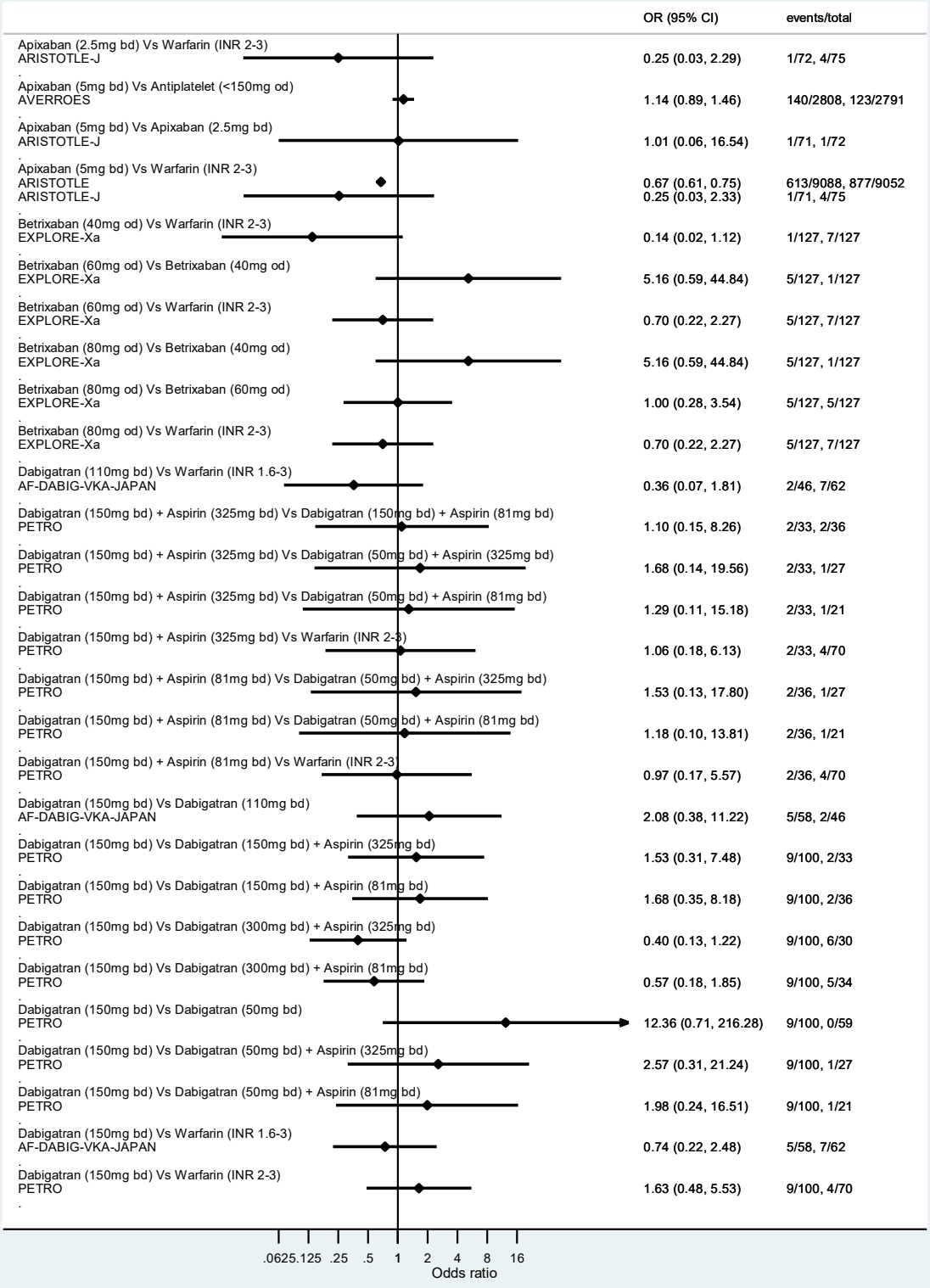


Figure 150 Forest plot for clinically relevant bleeding [2/3] (stroke prevention in AF)

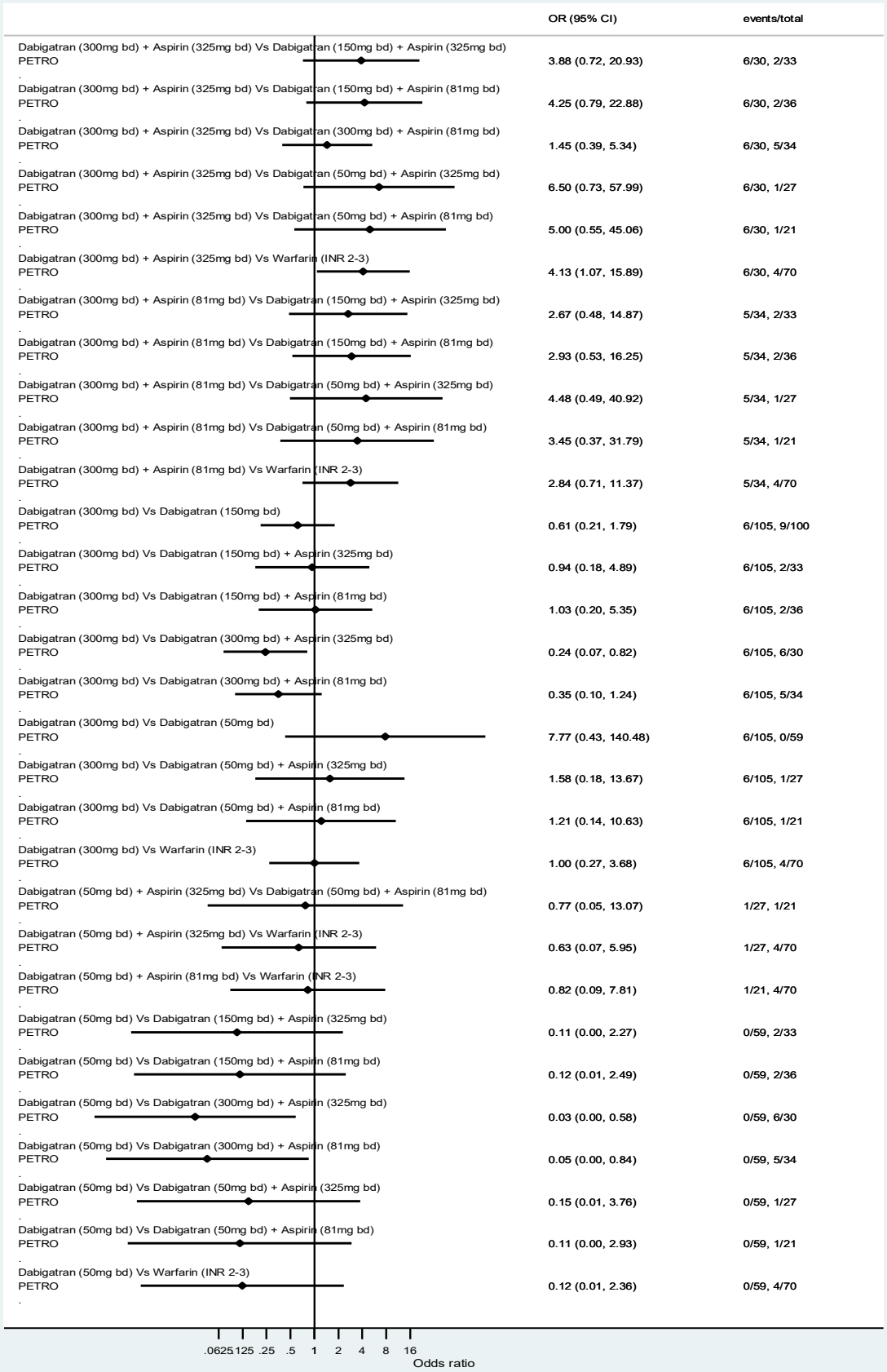


Figure 151 Forest plot for clinically relevant bleeding [3/3] (stroke prevention in AF)

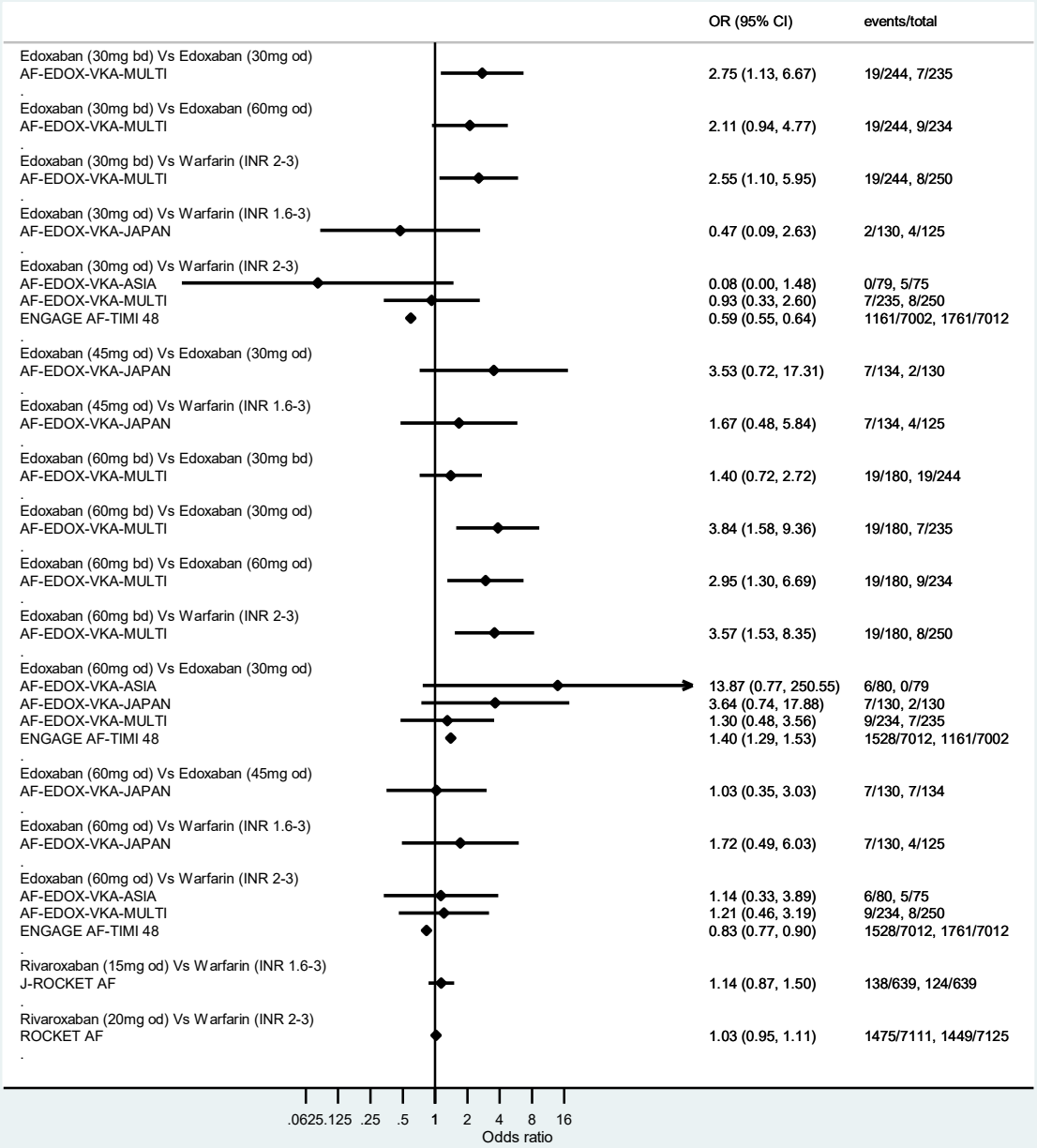


Figure 152 Forest plot for intracranial bleeding (stroke prevention in AF)

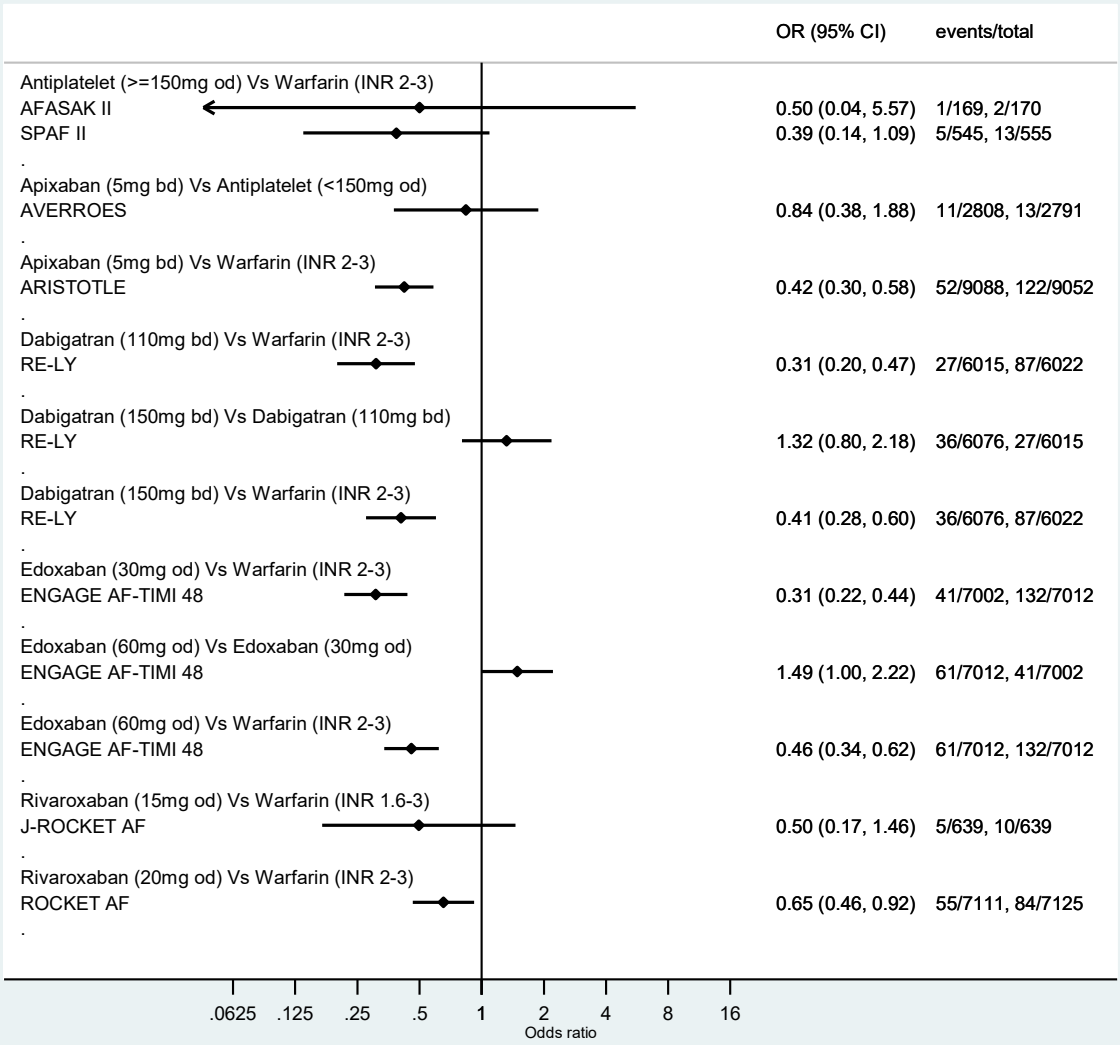
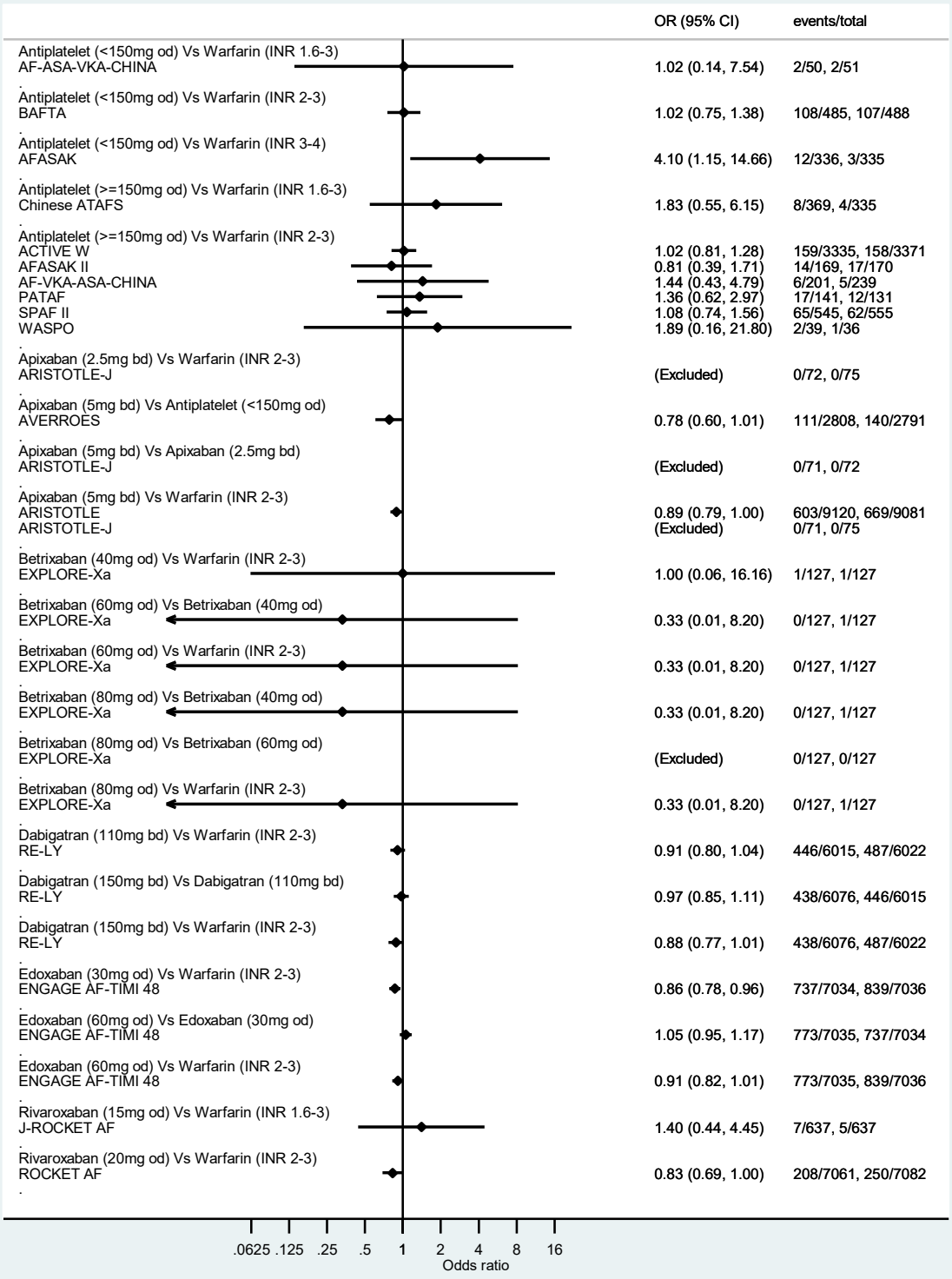


Figure 153 Forest plot for all-cause mortality (stroke prevention in AF)



Appendix 3 Forest plots: Primary prevention of venous thromboembolism

Table 204 provides the reference numbers that correspond to the trial names for the review of primary prevention of VTE, so that readers can trace the results presented in the forest plots.

Table 204 List of trial names and reference numbers (primary prevention of VTE)

Trial name	Reference(s)	Trial name	Reference(s)
ADOPT	193	RE-MODEL	166
ADVANCE-1	176	RE-NOVATE	165
ADVANCE-2	183	RE-NOVATE II	188, 194
ADVANCE-3	181	STARS E-3	187
APROPOS	167	STARS J-1	177, 185
ARDEPARIN ATHROPLASTY STUDY	201	STARS J-2	179
		STARS J-4	186, 198
BISTRO II	200	STARS J-V	184
EXPERT	173	TOPIC-1	202
LIFENOX	190	TOPIC-2	202
MAGELLAN	189, 196	VTE-APIX-PLACEBO-USACAN	195
ODiXa-HIP	199	VTE-DABIG-LMWH-GREECE	192
ODiXa-HIP2	164	VTE-DABIG-PLAC-JAPAN	180
ODiXa-KNEE	162	VTE-EDOX-LMWH-MULTI	182
ODiXa-OD.HIP	163	VTE-LMWH-PLAC-CAN	174
PROTECHT	175	VTE-LMWH-PLAC-JAPAN	191
RECORD 1	170	VTE-RIVAROX-LMWH-BRAZIL	169
RECORD 2	171	VTE-RIVAROX-LMWH-CHINA	197
RECORD 3	168	VTE-VKA-LMWH-CANADA	157
RECORD 4	178	VTE-VKA-LMWH-US	158
RE-MOBILISE	172	VTE-VKA-LMWH-US-2	159

Figure 154 Forest plot for symptomatic DVT [1/3] (primary prevention of VTE)

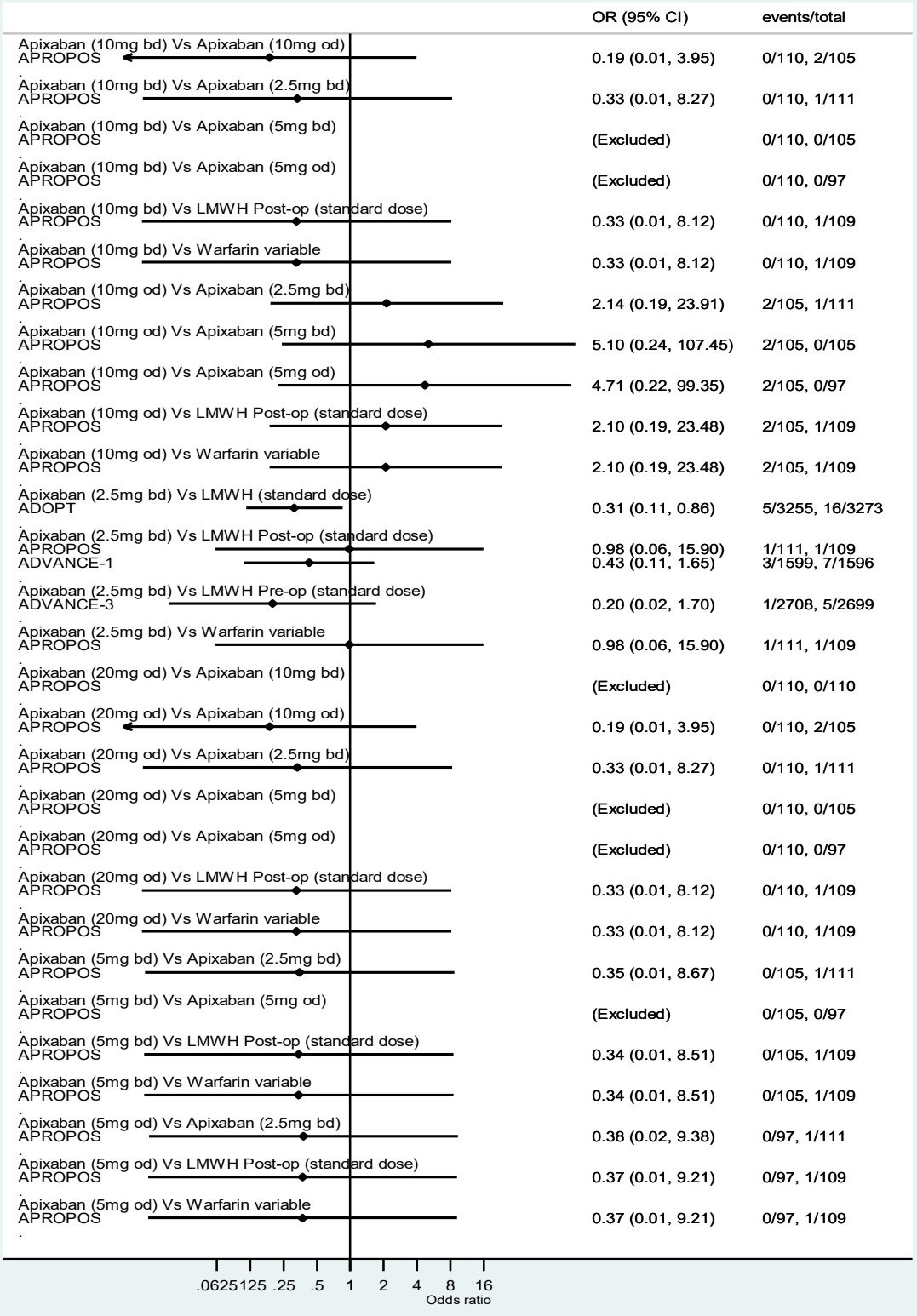


Figure 155 Forest plot for symptomatic DVT [2/3] (primary prevention of VTE)

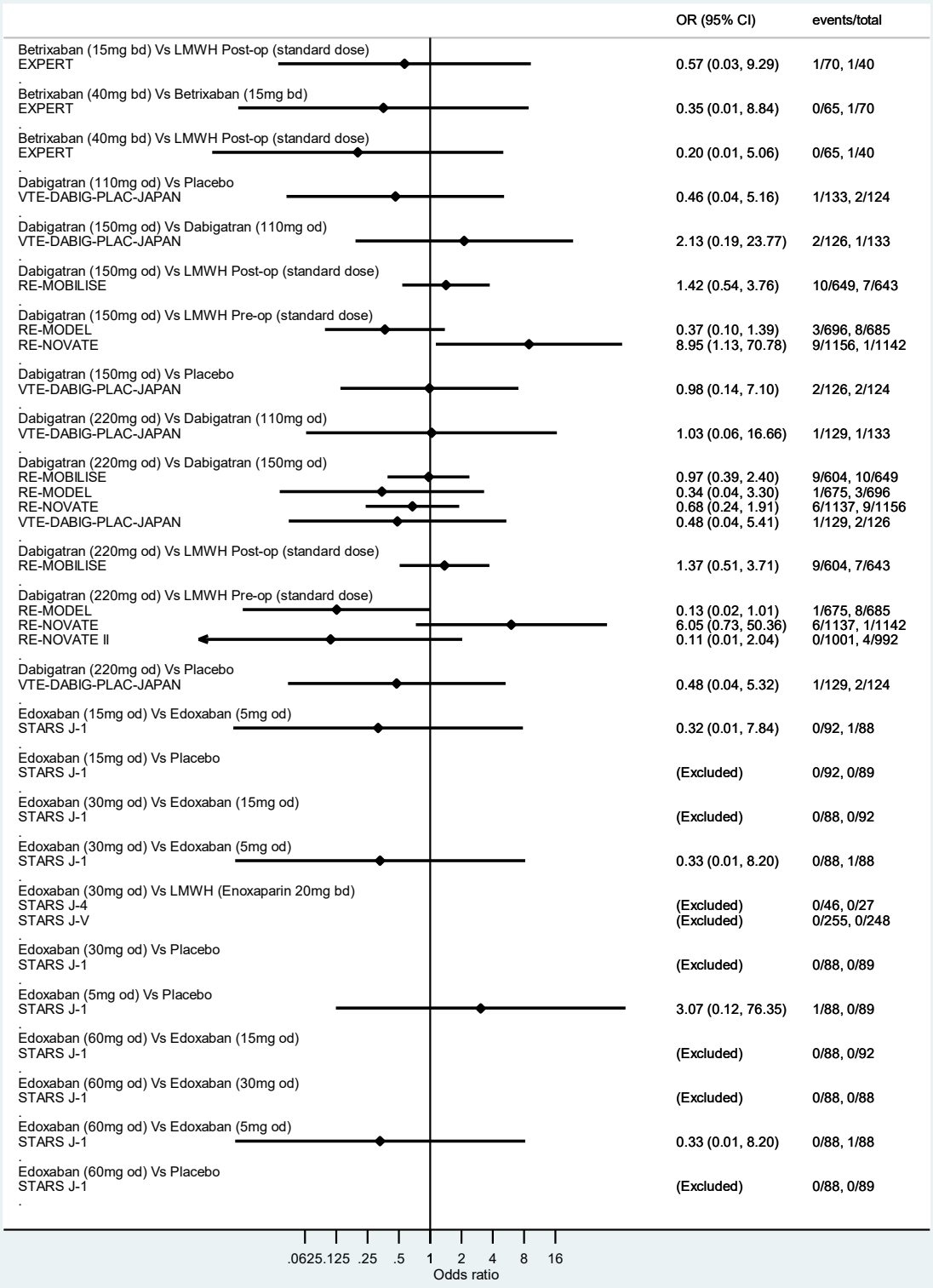


Figure 156 Forest plot for symptomatic DVT [3/3] (primary prevention of VTE)

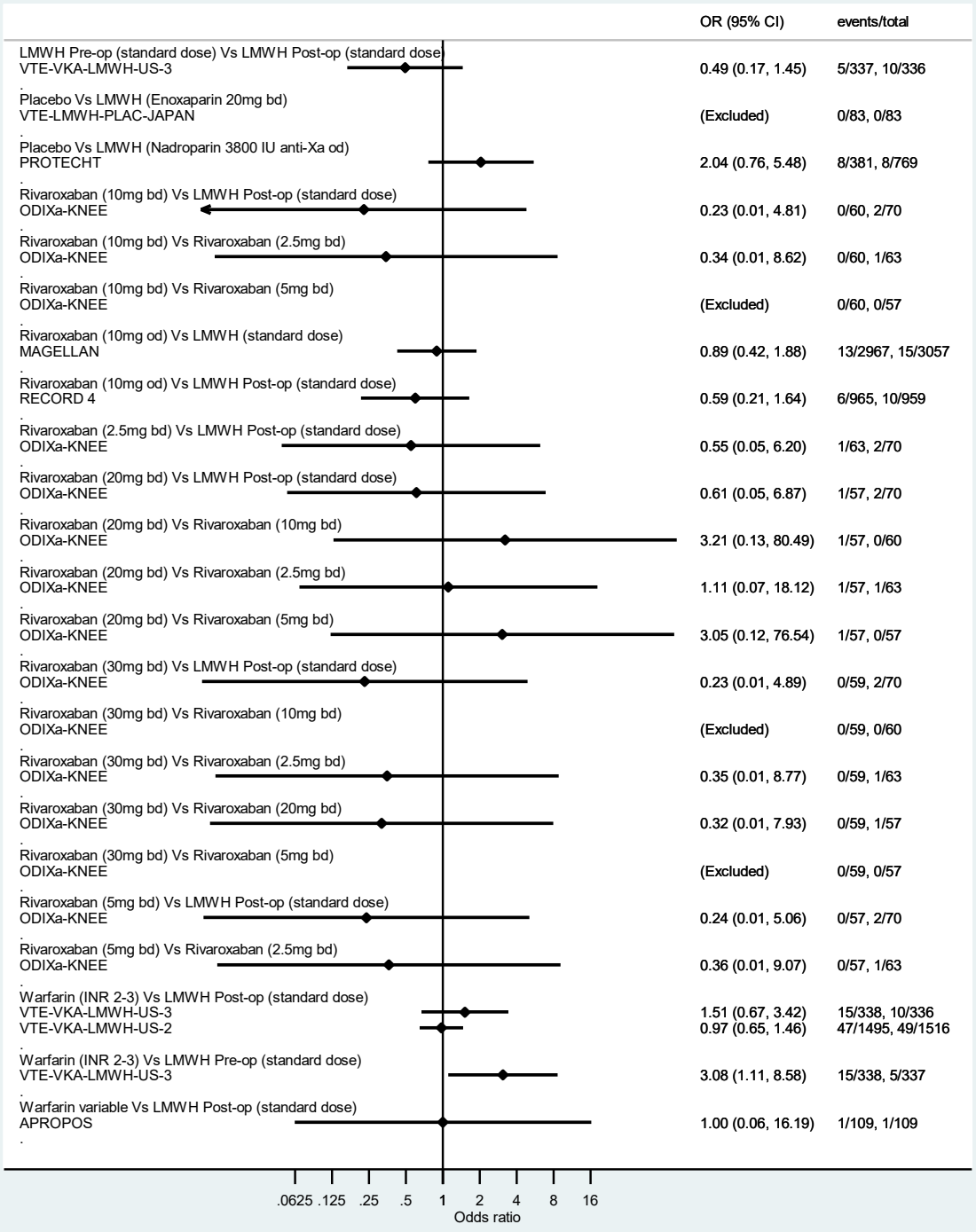


Figure 157 Forest plot for symptomatic PE [1/4] (primary prevention of VTE)

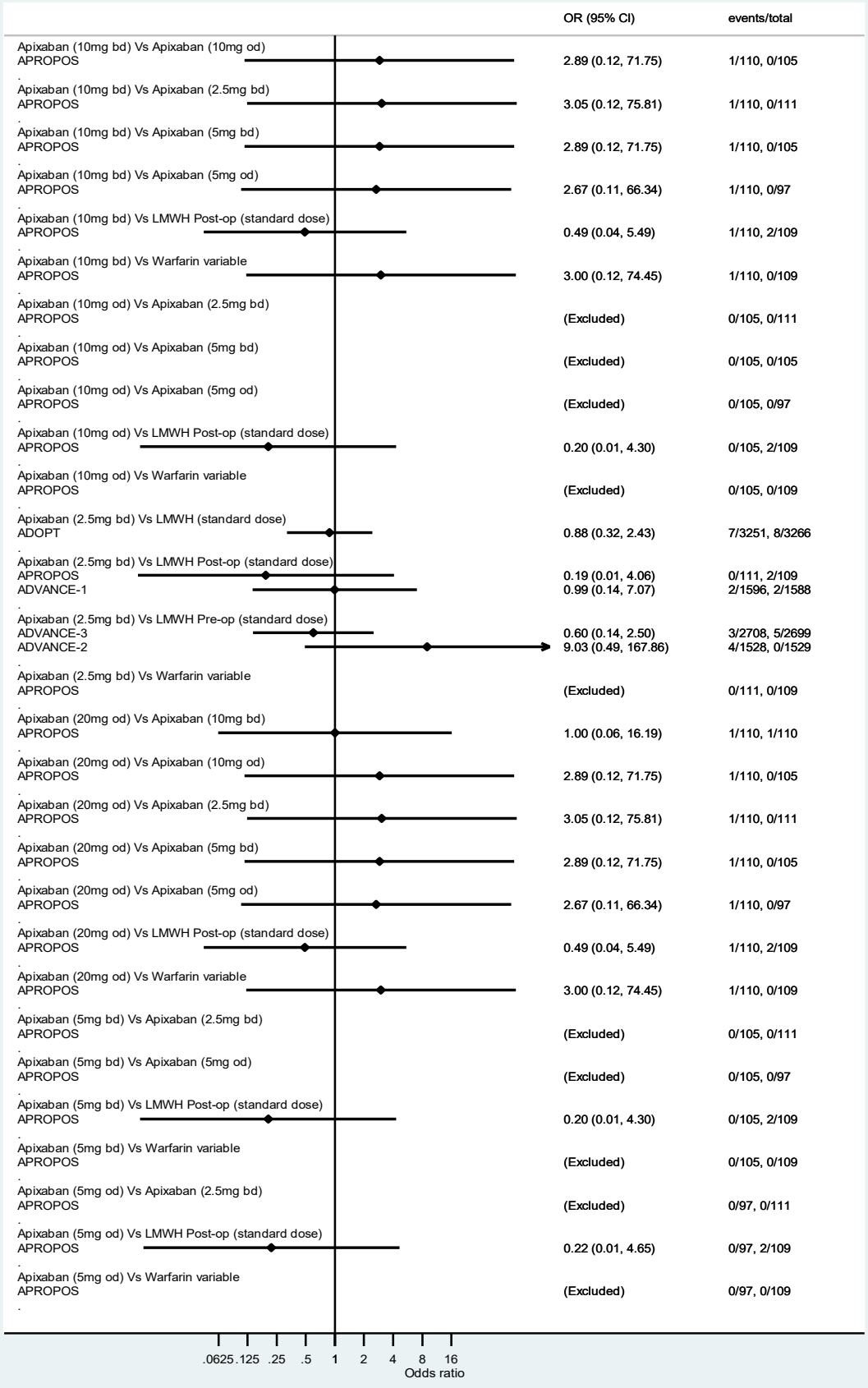
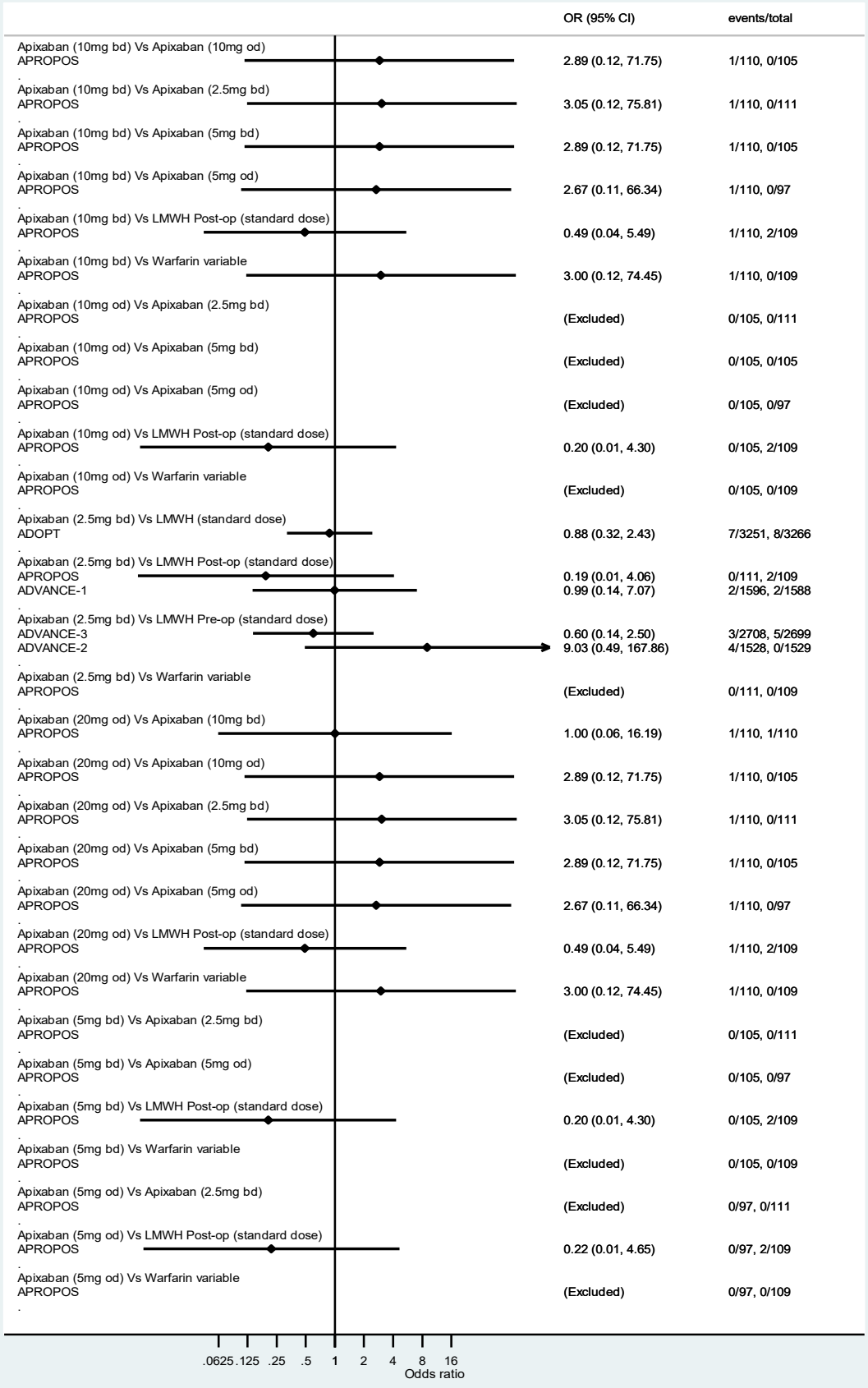


Figure 158 Forest plot for symptomatic PE [2/4] (primary prevention of VTE)



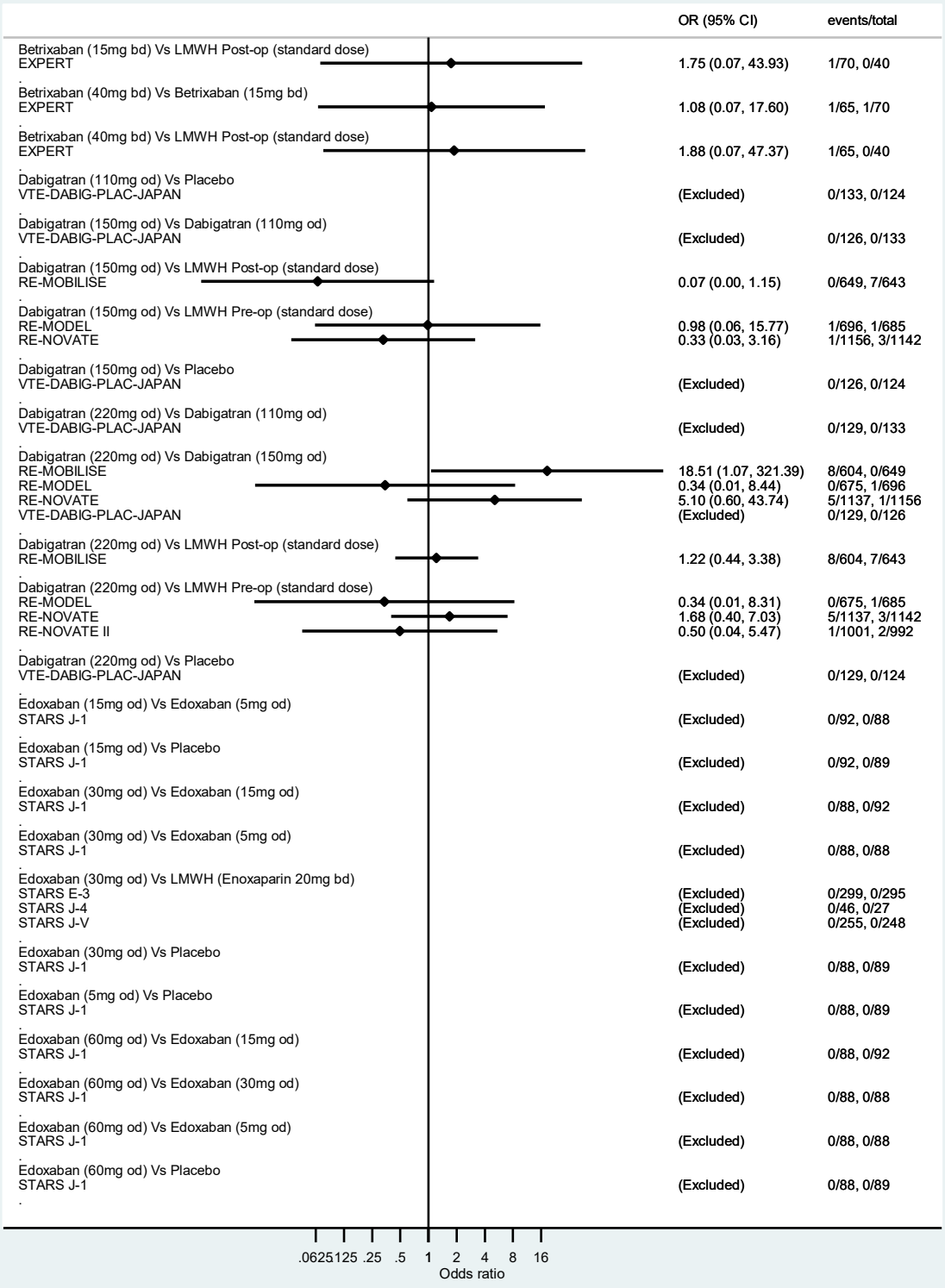
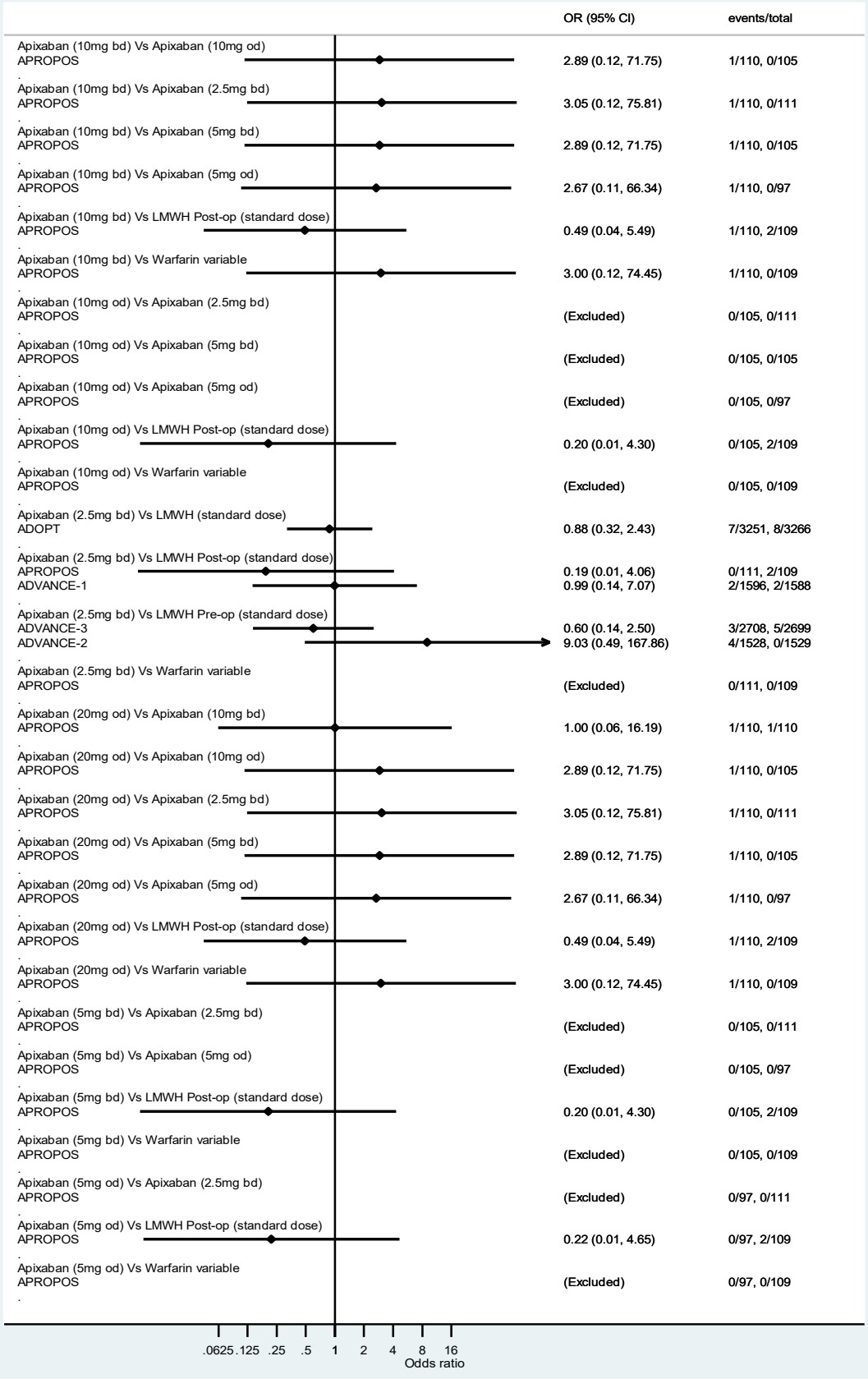

OR (95% CI)
events/total
Betrixaban (15mg bd) Vs LMWH Post-op (standard dose)
EXPERT 1.75 (0.07, 43.93) 1/70, 0/40
Betrixaban (40mg bd) Vs Betrixaban (15mg bd)
EXPERT 1.08 (0.07, 17.60) 1/65, 1/70
Betrixaban (40mg bd) Vs LMWH Post-op (standard dose)
EXPERT 1.88 (0.07, 47.37) 1/65, 0/40
Dabigatran (110mg od) Vs Placebo
VTE-DABIG-PLAC-JAPAN (Excluded) 0/133, 0/124
Dabigatran (150mg od) Vs Dabigatran (110mg od)
VTE-DABIG-PLAC-JAPAN (Excluded) 0/126, 0/133
Dabigatran (150mg od) Vs LMWH Post-op (standard dose)
RE-MOBILISE 0.07 (0.00, 1.15) 0/649, 7/643
Dabigatran (150mg od) Vs LMWH Pre-op (standard dose)
RE-MODEL 0.98 (0.06, 15.77) 1/696, 1/685
RE-NOVATE 0.33 (0.03, 3.16) 1/1156, 3/1142
Dabigatran (150mg od) Vs Placebo
VTE-DABIG-PLAC-JAPAN (Excluded) 0/126, 0/124
Dabigatran (220mg od) Vs Dabigatran (110mg od)
VTE-DABIG-PLAC-JAPAN (Excluded) 0/129, 0/133
Dabigatran (220mg od) Vs Dabigatran (150mg od)
RE-MOBILISE 18.51 (1.07, 321.39) 8/604, 0/649
RE-MODEL 0.34 (0.01, 8.44) 0/675, 1/696
RE-NOVATE 5.10 (0.60, 43.74) 5/1137, 1/1156
VTE-DABIG-PLAC-JAPAN (Excluded) 0/129, 0/126
Dabigatran (220mg od) Vs LMWH Post-op (standard dose)
RE-MOBILISE 1.22 (0.44, 3.38) 8/604, 7/643
Dabigatran (220mg od) Vs LMWH Pre-op (standard dose)
RE-MODEL 0.34 (0.01, 8.31) 0/675, 1/685
RE-NOVATE 1.68 (0.40, 7.03) 5/1137, 3/1142
RE-NOVATE II 0.50 (0.04, 5.47) 1/1001, 2/992
Dabigatran (220mg od) Vs Placebo
VTE-DABIG-PLAC-JAPAN (Excluded) 0/129, 0/124
Edoxaban (15mg od) Vs Edoxaban (5mg od)
STARS J-1 (Excluded) 0/92, 0/88
Edoxaban (15mg od) Vs Placebo
STARS J-1 (Excluded) 0/92, 0/89
Edoxaban (30mg od) Vs Edoxaban (15mg od)
STARS J-1 (Excluded) 0/88, 0/92
Edoxaban (30mg od) Vs Edoxaban (5mg od)
STARS J-1 (Excluded) 0/88, 0/88
Edoxaban (30mg od) Vs LMWH (Enoxaparin 20mg bd)
STARS E-3 (Excluded) 0/299, 0/295
STARS J-4 (Excluded) 0/46, 0/27
STARS J-V (Excluded) 0/255, 0/248
Edoxaban (30mg od) Vs Placebo
STARS J-1 (Excluded) 0/88, 0/89
Edoxaban (5mg od) Vs Placebo
STARS J-1 (Excluded) 0/88, 0/89
Edoxaban (60mg od) Vs Edoxaban (15mg od)
STARS J-1 (Excluded) 0/88, 0/92
Edoxaban (60mg od) Vs Edoxaban (30mg od)
STARS J-1 (Excluded) 0/88, 0/88
Edoxaban (60mg od) Vs Edoxaban (5mg od)
STARS J-1 (Excluded) 0/88, 0/88
Edoxaban (60mg od) Vs Placebo
STARS J-1 (Excluded) 0/88, 0/89
.0625 .125 .25 .5 1 2 4 8 16
Odds ratio

Figure 159 Forest plot for symptomatic PE [3/4] (primary prevention of VTE)



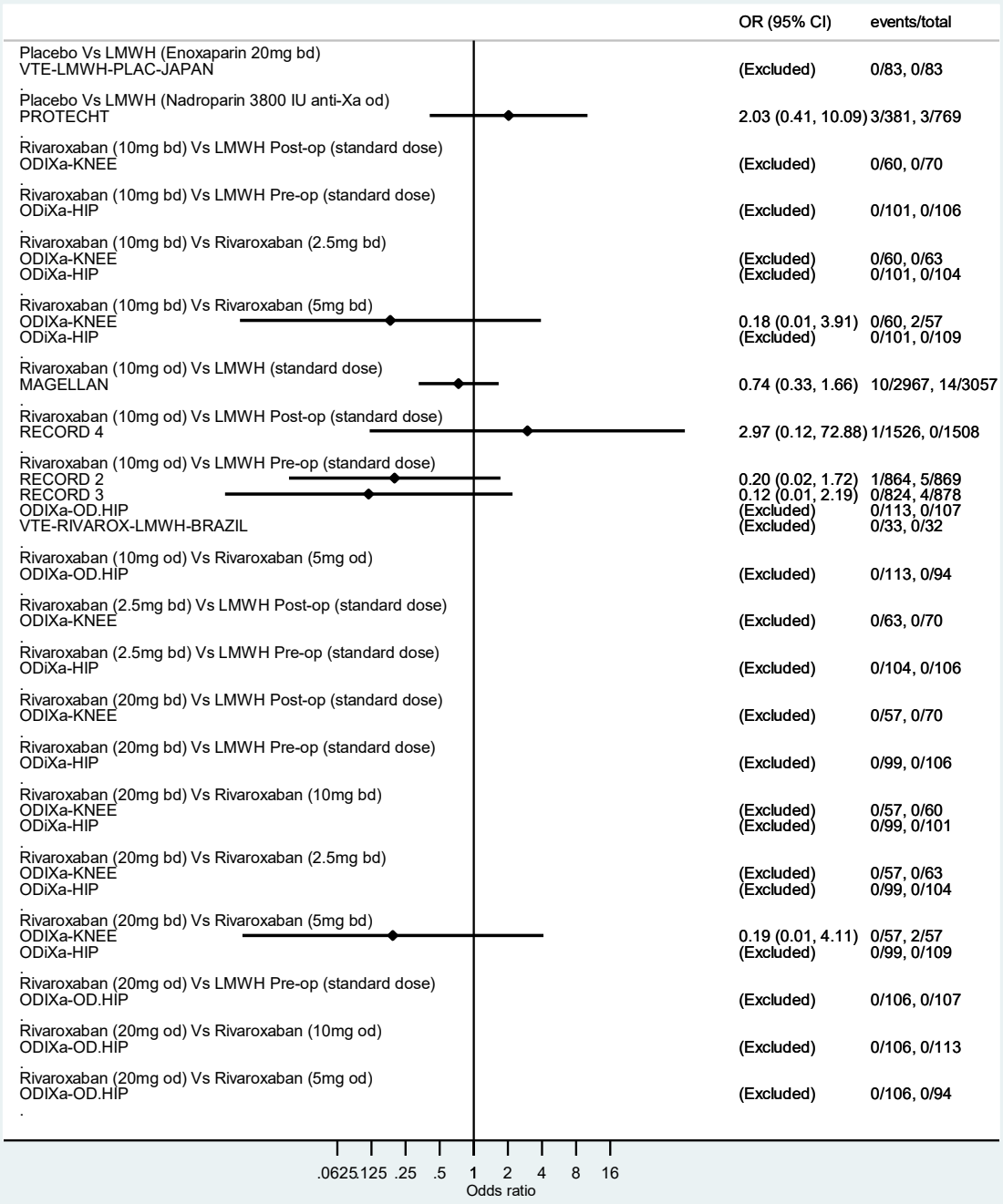
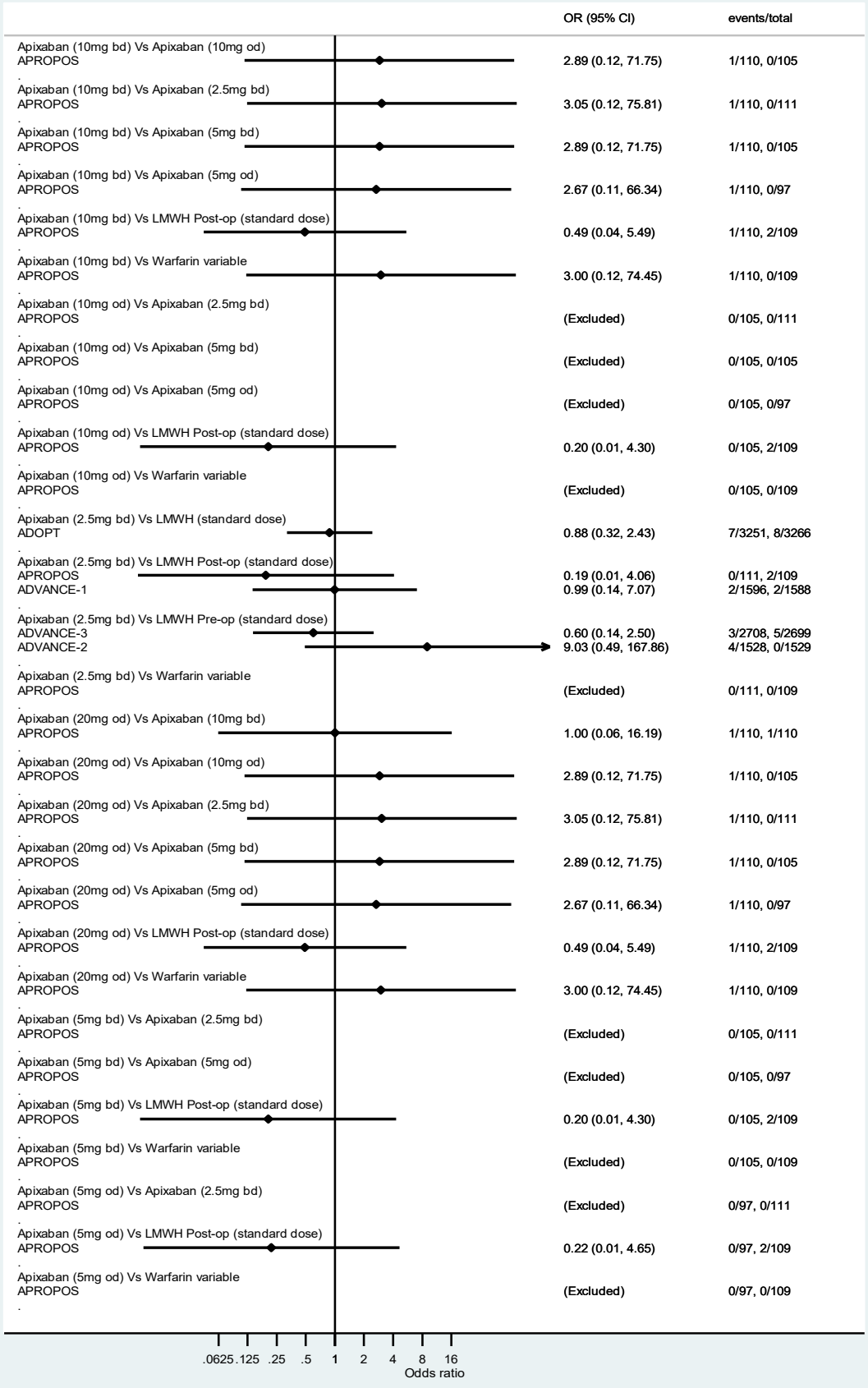

OR (95% CI)
events/total
Placebo Vs LMWH (Enoxaparin 20mg bd)
VTE-LMWH-PLAC-JAPAN (Excluded) 0/83, 0/83
Placebo Vs LMWH (Nadroparin 3800 IU anti-Xa od)
PROTECHT 2.03 (0.41, 10.09) 3/381, 3/769
Rivaroxaban (10mg bd) Vs LMWH Post-op (standard dose)
ODIXa-KNEE (Excluded) 0/60, 0/70
Rivaroxaban (10mg bd) Vs LMWH Pre-op (standard dose)
ODiXa-HIP (Excluded) 0/101, 0/106
Rivaroxaban (10mg bd) Vs Rivaroxaban (2.5mg bd)
ODIXa-KNEE (Excluded) 0/60, 0/63
ODiXa-HIP (Excluded) 0/101, 0/104
Rivaroxaban (10mg bd) Vs Rivaroxaban (5mg bd)
ODIXa-KNEE 0.18 (0.01, 3.91) 0/60, 2/57
ODiXa-HIP (Excluded) 0/101, 0/109
Rivaroxaban (10mg od) Vs LMWH (standard dose)
MAGELLAN 0.74 (0.33, 1.66) 10/2967, 14/3057
Rivaroxaban (10mg od) Vs LMWH Post-op (standard dose)
RECORD 4 2.97 (0.12, 72.88) 1/1526, 0/1508
Rivaroxaban (10mg od) Vs LMWH Pre-op (standard dose)
RECORD 2 0.20 (0.02, 1.72) 1/864, 5/869
RECORD 3 0.12 (0.01, 2.19) 0/824, 4/878
ODIXa-OD.HIP (Excluded) 0/113, 0/107
VTE-RIVAROX-LMWH-BRAZIL (Excluded) 0/33, 0/32
Rivaroxaban (10mg od) Vs Rivaroxaban (5mg od)
ODIXa-OD.HIP (Excluded) 0/113, 0/94
Rivaroxaban (2.5mg bd) Vs LMWH Post-op (standard dose)
ODIXa-KNEE (Excluded) 0/63, 0/70
Rivaroxaban (2.5mg bd) Vs LMWH Pre-op (standard dose)
ODiXa-HIP (Excluded) 0/104, 0/106
Rivaroxaban (20mg bd) Vs LMWH Post-op (standard dose)
ODIXa-KNEE (Excluded) 0/57, 0/70
Rivaroxaban (20mg bd) Vs LMWH Pre-op (standard dose)
ODiXa-HIP (Excluded) 0/99, 0/106
Rivaroxaban (20mg bd) Vs Rivaroxaban (10mg bd)
ODIXa-KNEE (Excluded) 0/57, 0/60
ODiXa-HIP (Excluded) 0/99, 0/101
Rivaroxaban (20mg bd) Vs Rivaroxaban (2.5mg bd)
ODIXa-KNEE (Excluded) 0/57, 0/63
ODiXa-HIP (Excluded) 0/99, 0/104
Rivaroxaban (20mg bd) Vs Rivaroxaban (5mg bd)
ODIXa-KNEE 0.19 (0.01, 4.11) 0/57, 2/57
ODiXa-HIP (Excluded) 0/99, 0/109
Rivaroxaban (20mg od) Vs LMWH Pre-op (standard dose)
ODIXa-OD.HIP (Excluded) 0/106, 0/107
Rivaroxaban (20mg od) Vs Rivaroxaban (10mg od)
ODIXa-OD.HIP (Excluded) 0/106, 0/113
Rivaroxaban (20mg od) Vs Rivaroxaban (5mg od)
ODIXa-OD.HIP (Excluded) 0/106, 0/94
.0625 .125 .25 .5 1 2 4 8 16
Odds ratio

Figure 160 Forest plot for symptomatic PE [4/4] (primary prevention of VTE)



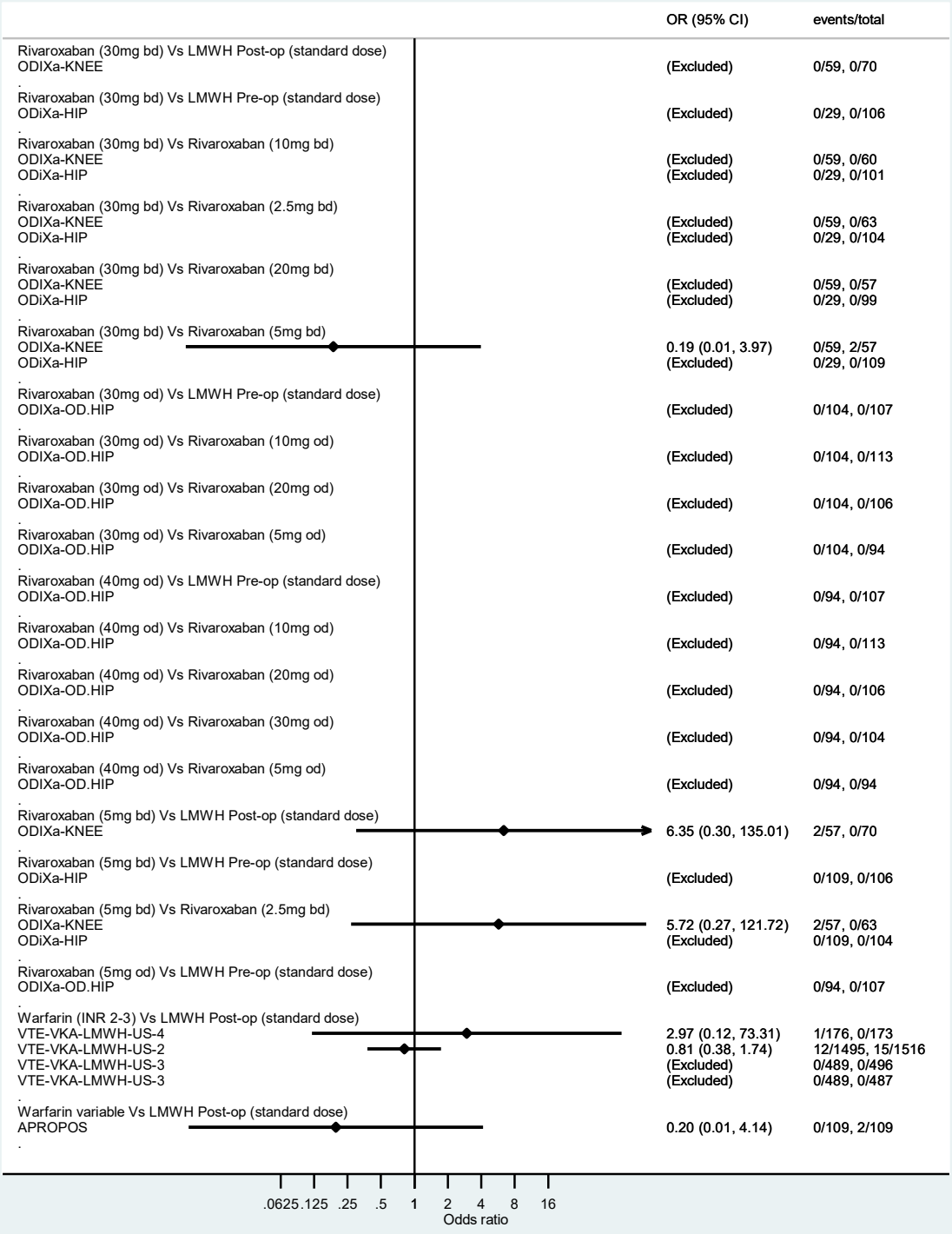

OR (95% CI)
events/total
Rivaroxaban (30mg bd) Vs LMWH Post-op (standard dose)
ODIXa-KNEE (Excluded) 0/59, 0/70
Rivaroxaban (30mg bd) Vs LMWH Pre-op (standard dose)
ODiXa-HIP (Excluded) 0/29, 0/106
Rivaroxaban (30mg bd) Vs Rivaroxaban (10mg bd)
ODIXa-KNEE (Excluded) 0/59, 0/60
ODiXa-HIP (Excluded) 0/29, 0/101
Rivaroxaban (30mg bd) Vs Rivaroxaban (2.5mg bd)
ODIXa-KNEE (Excluded) 0/59, 0/63
ODiXa-HIP (Excluded) 0/29, 0/104
Rivaroxaban (30mg bd) Vs Rivaroxaban (20mg bd)
ODIXa-KNEE (Excluded) 0/59, 0/57
ODiXa-HIP (Excluded) 0/29, 0/99
Rivaroxaban (30mg bd) Vs Rivaroxaban (5mg bd)
ODIXa-KNEE 0.19 (0.01, 3.97) 0/59, 2/57
ODiXa-HIP (Excluded) 0/29, 0/109
Rivaroxaban (30mg od) Vs LMWH Pre-op (standard dose)
ODIXa-OD.HIP (Excluded) 0/104, 0/107
Rivaroxaban (30mg od) Vs Rivaroxaban (10mg od)
ODIXa-OD.HIP (Excluded) 0/104, 0/113
Rivaroxaban (30mg od) Vs Rivaroxaban (20mg od)
ODIXa-OD.HIP (Excluded) 0/104, 0/106
Rivaroxaban (30mg od) Vs Rivaroxaban (5mg od)
ODIXa-OD.HIP (Excluded) 0/104, 0/94
Rivaroxaban (40mg od) Vs LMWH Pre-op (standard dose)
ODIXa-OD.HIP (Excluded) 0/94, 0/107
Rivaroxaban (40mg od) Vs Rivaroxaban (10mg od)
ODIXa-OD.HIP (Excluded) 0/94, 0/113
Rivaroxaban (40mg od) Vs Rivaroxaban (20mg od)
ODIXa-OD.HIP (Excluded) 0/94, 0/106
Rivaroxaban (40mg od) Vs Rivaroxaban (30mg od)
ODIXa-OD.HIP (Excluded) 0/94, 0/104
Rivaroxaban (40mg od) Vs Rivaroxaban (5mg od)
ODIXa-OD.HIP (Excluded) 0/94, 0/94
Rivaroxaban (5mg bd) Vs LMWH Post-op (standard dose)
ODIXa-KNEE 6.35 (0.30, 135.01) 2/57, 0/70
Rivaroxaban (5mg bd) Vs LMWH Pre-op (standard dose)
ODiXa-HIP (Excluded) 0/109, 0/106
Rivaroxaban (5mg bd) Vs Rivaroxaban (2.5mg bd)
ODIXa-KNEE 5.72 (0.27, 121.72) 2/57, 0/63
ODiXa-HIP (Excluded) 0/109, 0/104
Rivaroxaban (5mg od) Vs LMWH Pre-op (standard dose)
ODIXa-OD.HIP (Excluded) 0/94, 0/107
Warfarin (INR 2-3) Vs LMWH Post-op (standard dose)
VTE-VKA-LMWH-US-4 2.97 (0.12, 73.31) 1/176, 0/173
VTE-VKA-LMWH-US-2 0.81 (0.38, 1.74) 12/1495, 15/1516
VTE-VKA-LMWH-US-3 (Excluded) 0/489, 0/496
VTE-VKA-LMWH-US-3 (Excluded) 0/489, 0/487
Warfarin variable Vs LMWH Post-op (standard dose)
APROPOS 0.20 (0.01, 4.14) 0/109, 2/109
.0625 .125 .25 .5 1 2 4 8 16
Odds ratio

Figure 161 Forest plot for symptomatic VTE [1/3] (primary prevention of VTE)

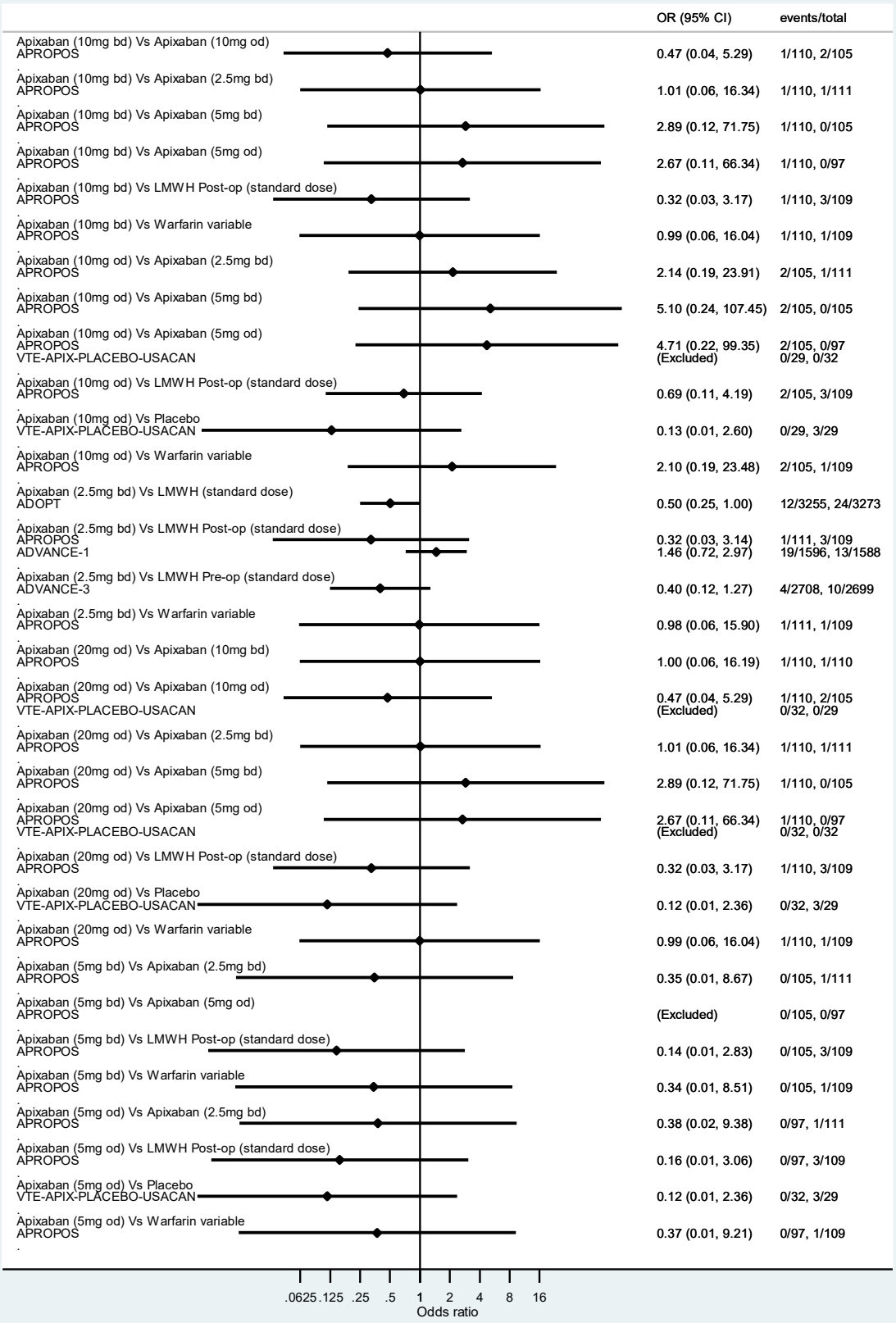


Figure 162 Forest plot for symptomatic VTE [2/3] (primary prevention of VTE)

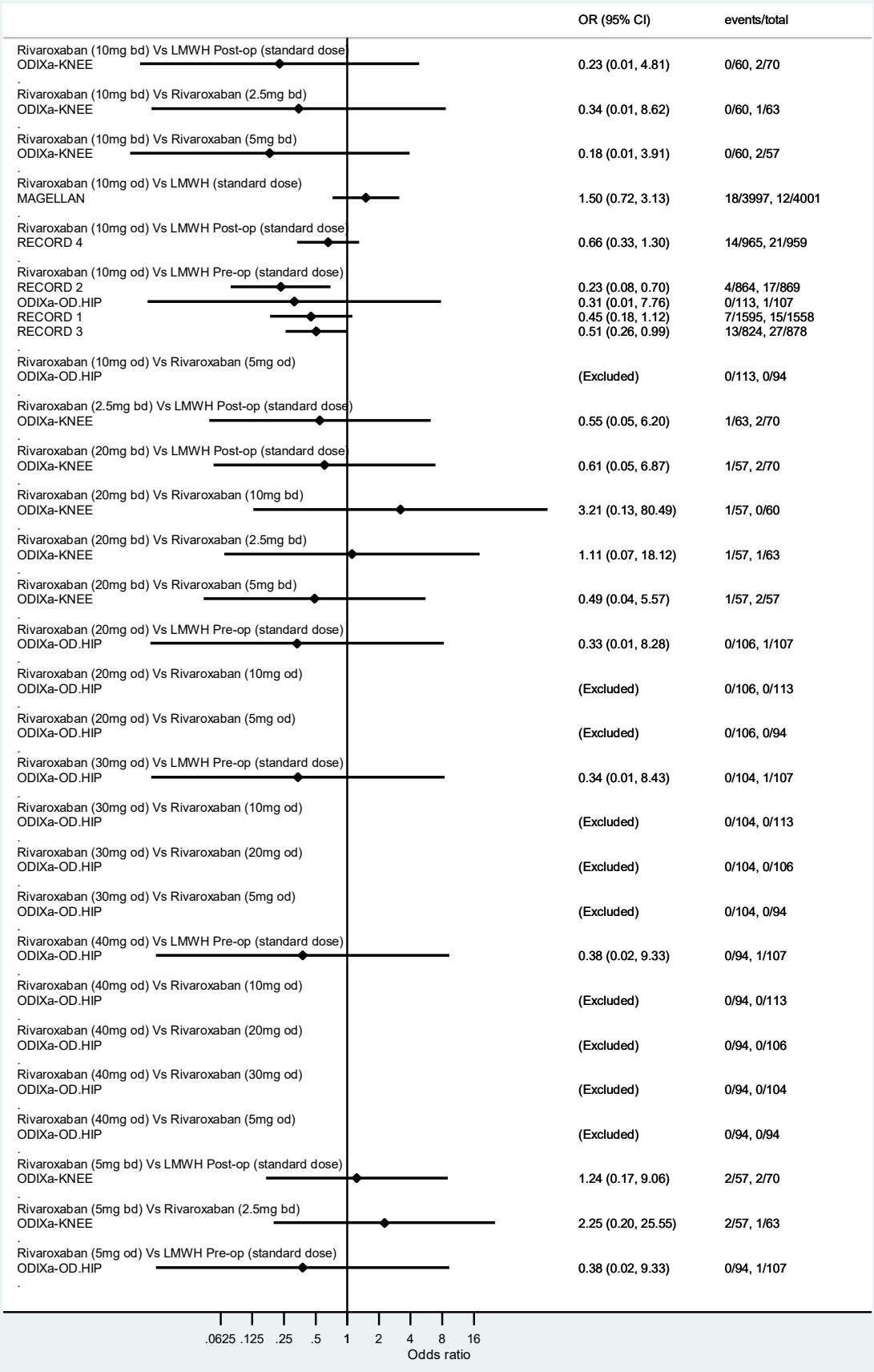


Figure 163 Forest plot for symptomatic VTE [3/3] (primary prevention of VTE)

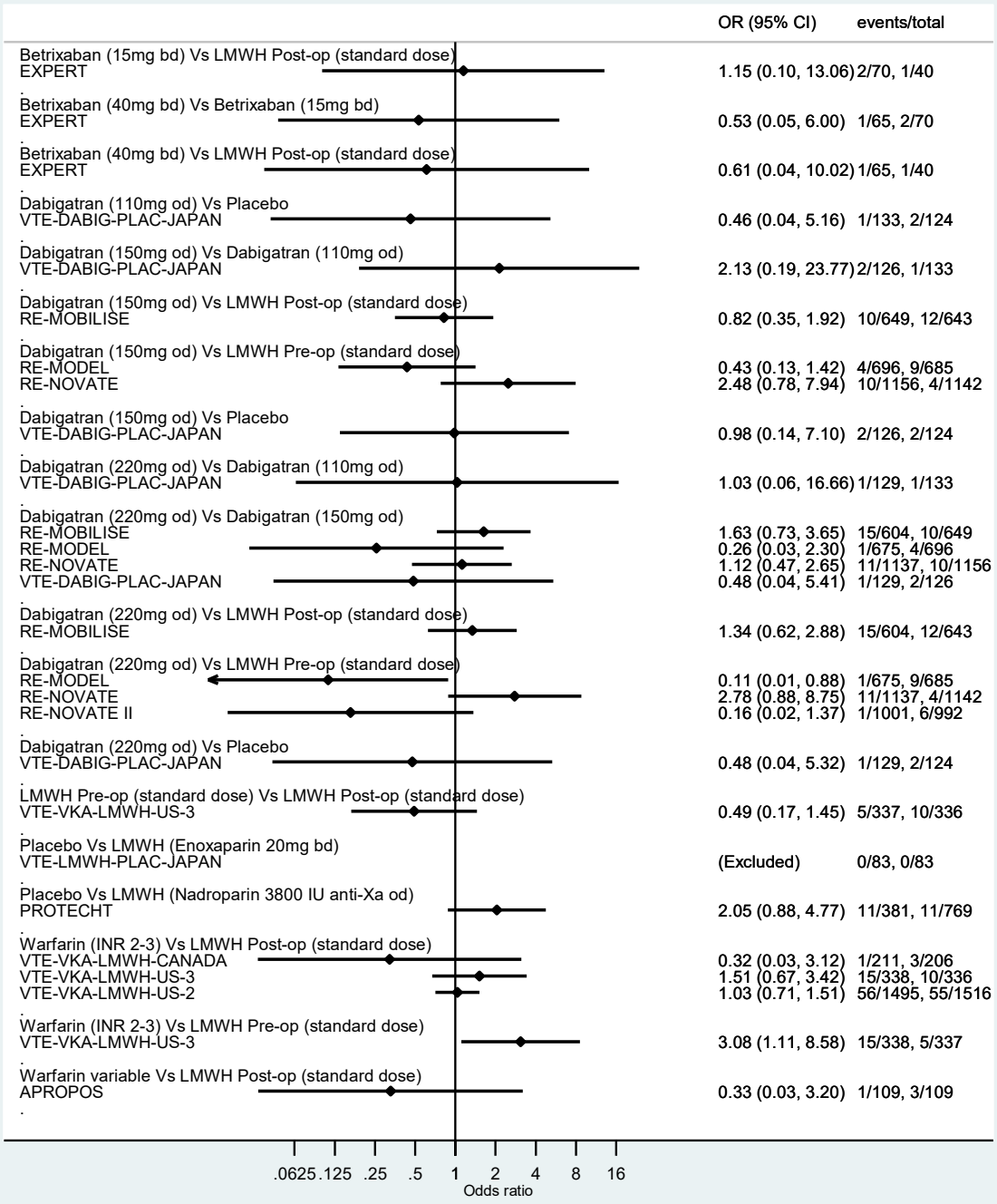


Figure 164 Forest plot for myocardial infarction (primary prevention of VTE)

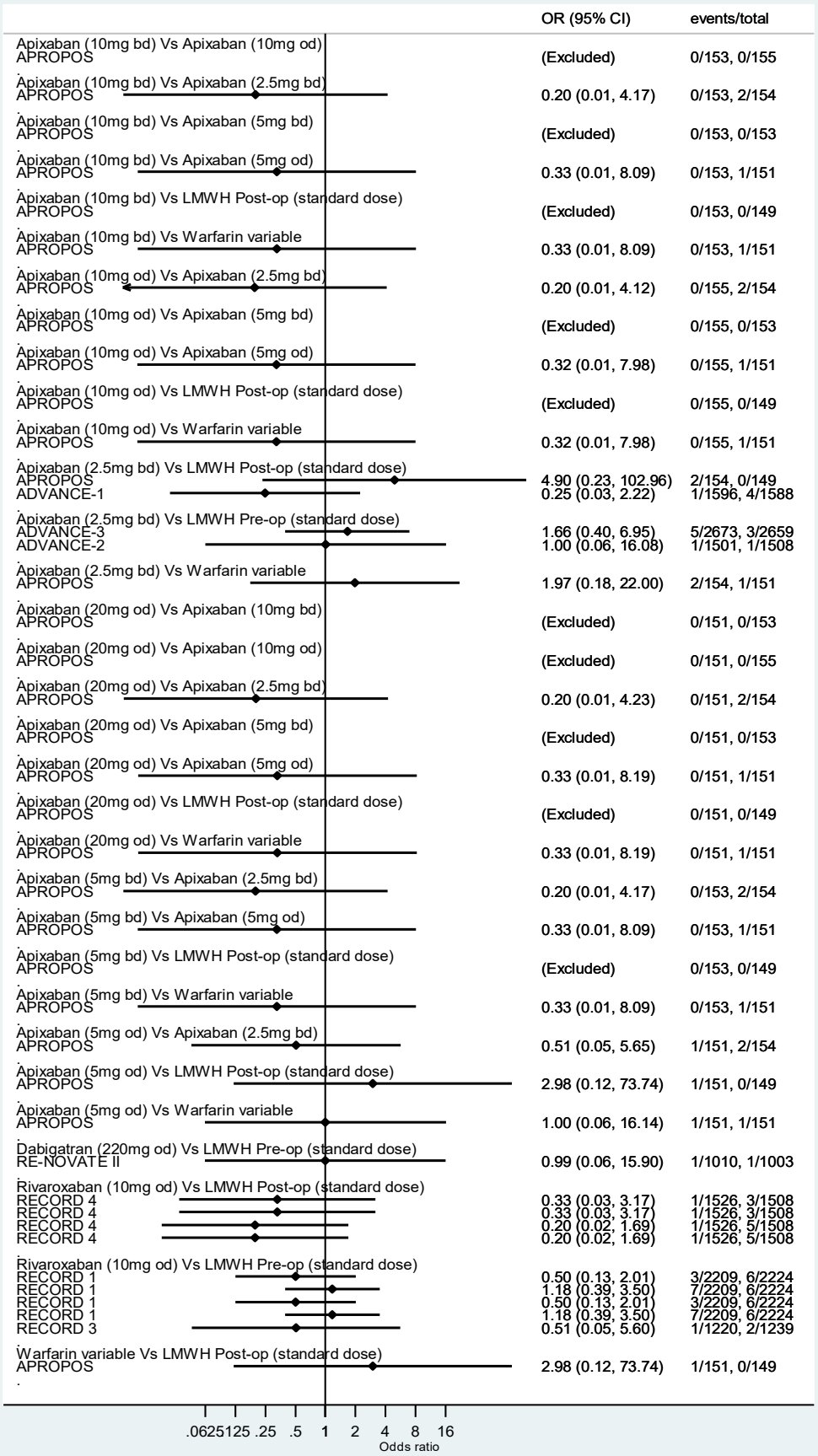


Figure 165 Forest plot for major bleeding [1/4] (primary prevention of VTE)

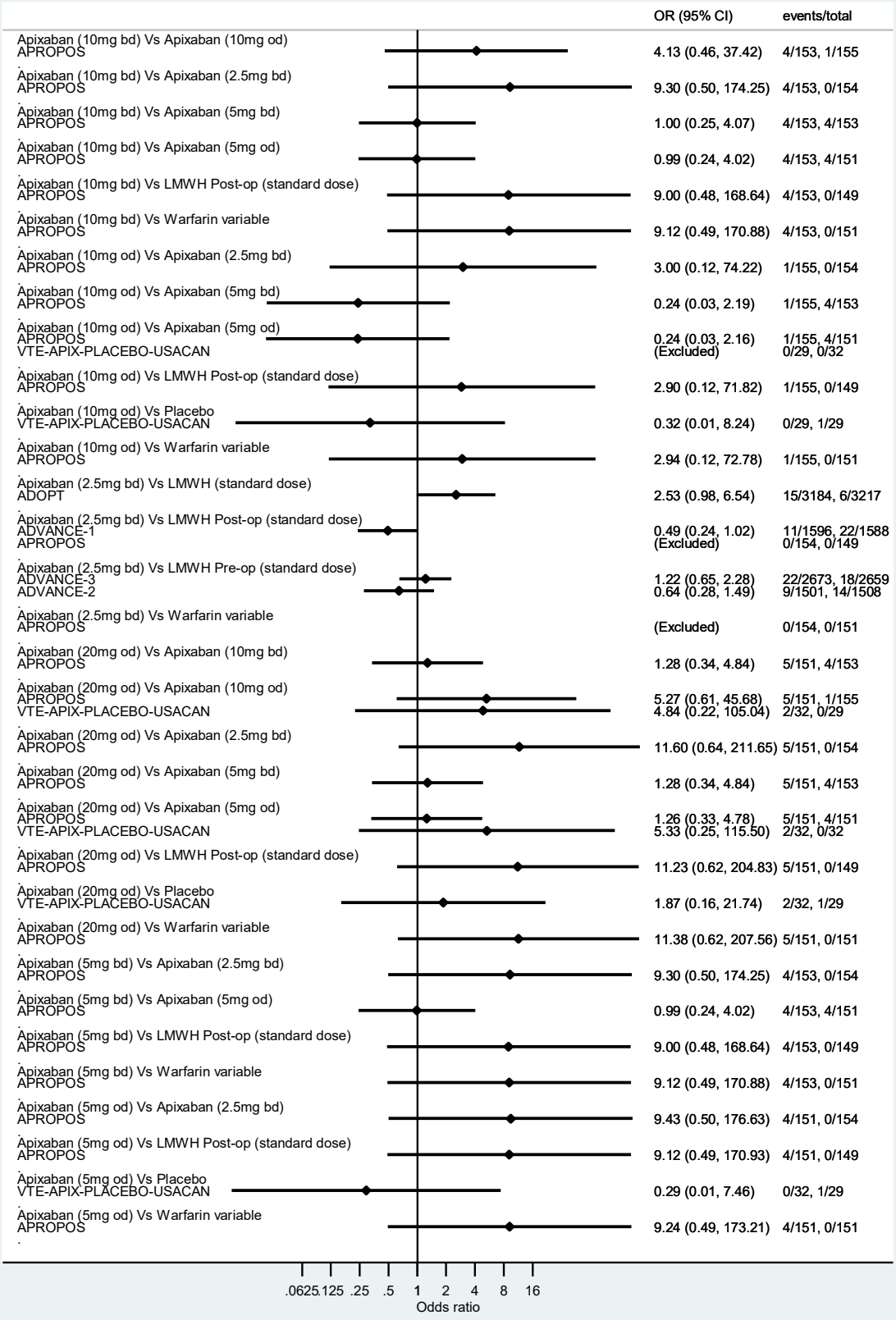


Figure 166 Forest plot for major bleeding [2/4] (primary prevention of VTE)

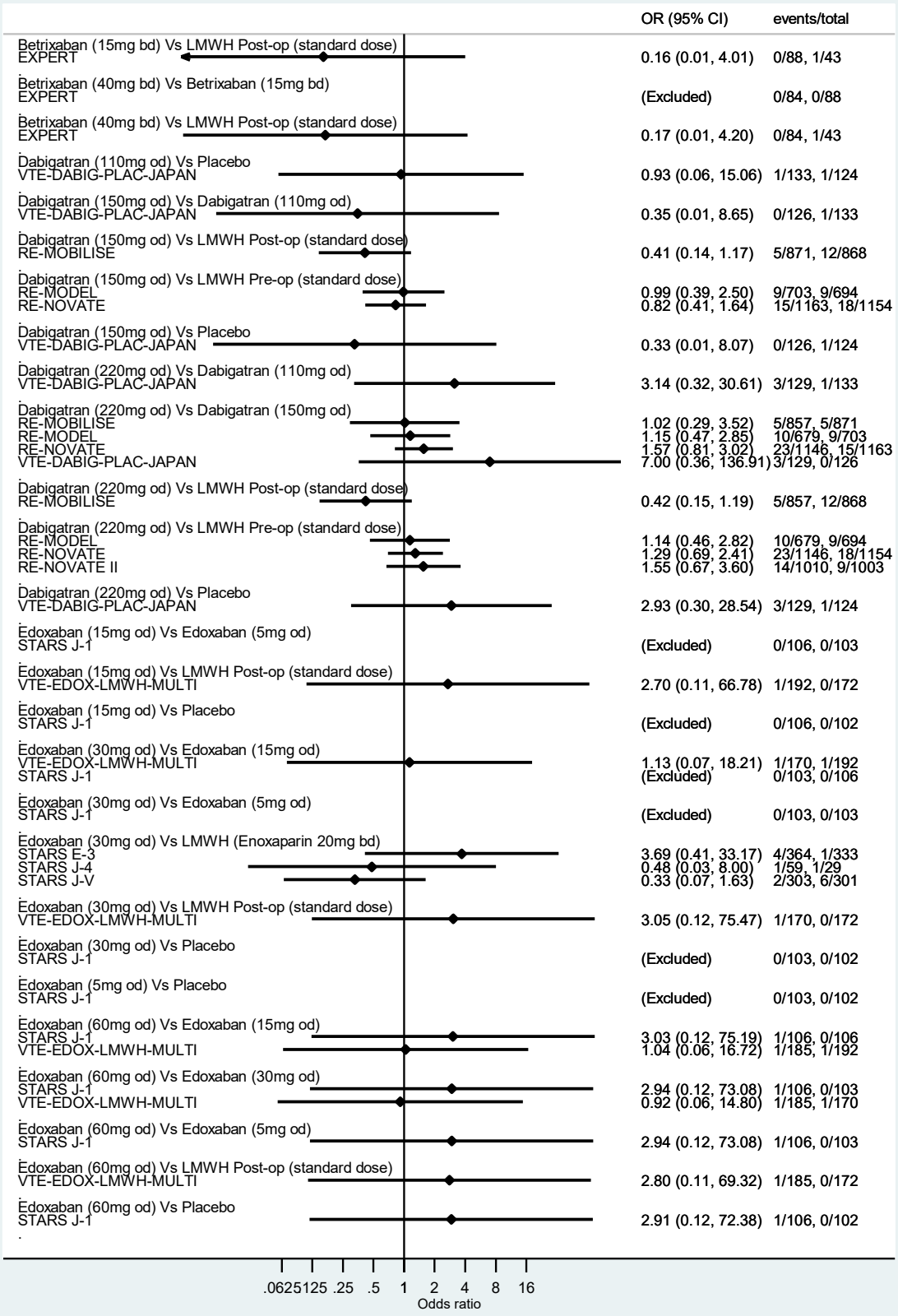


Figure 167 Forest plot for major bleeding [3/4] (primary prevention of VTE)

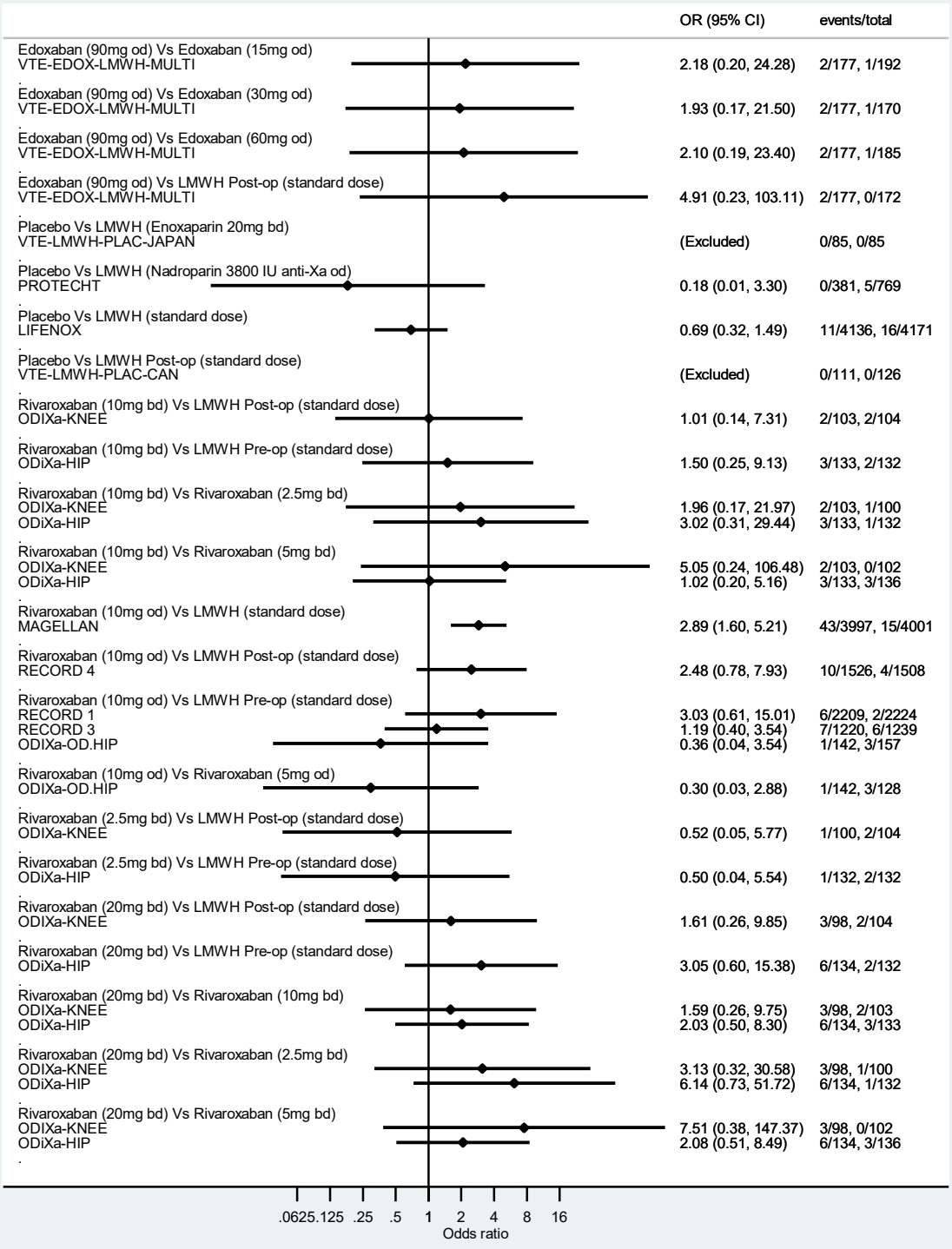


Figure 168 Forest plot for major bleeding [4/4] (primary prevention of VTE)

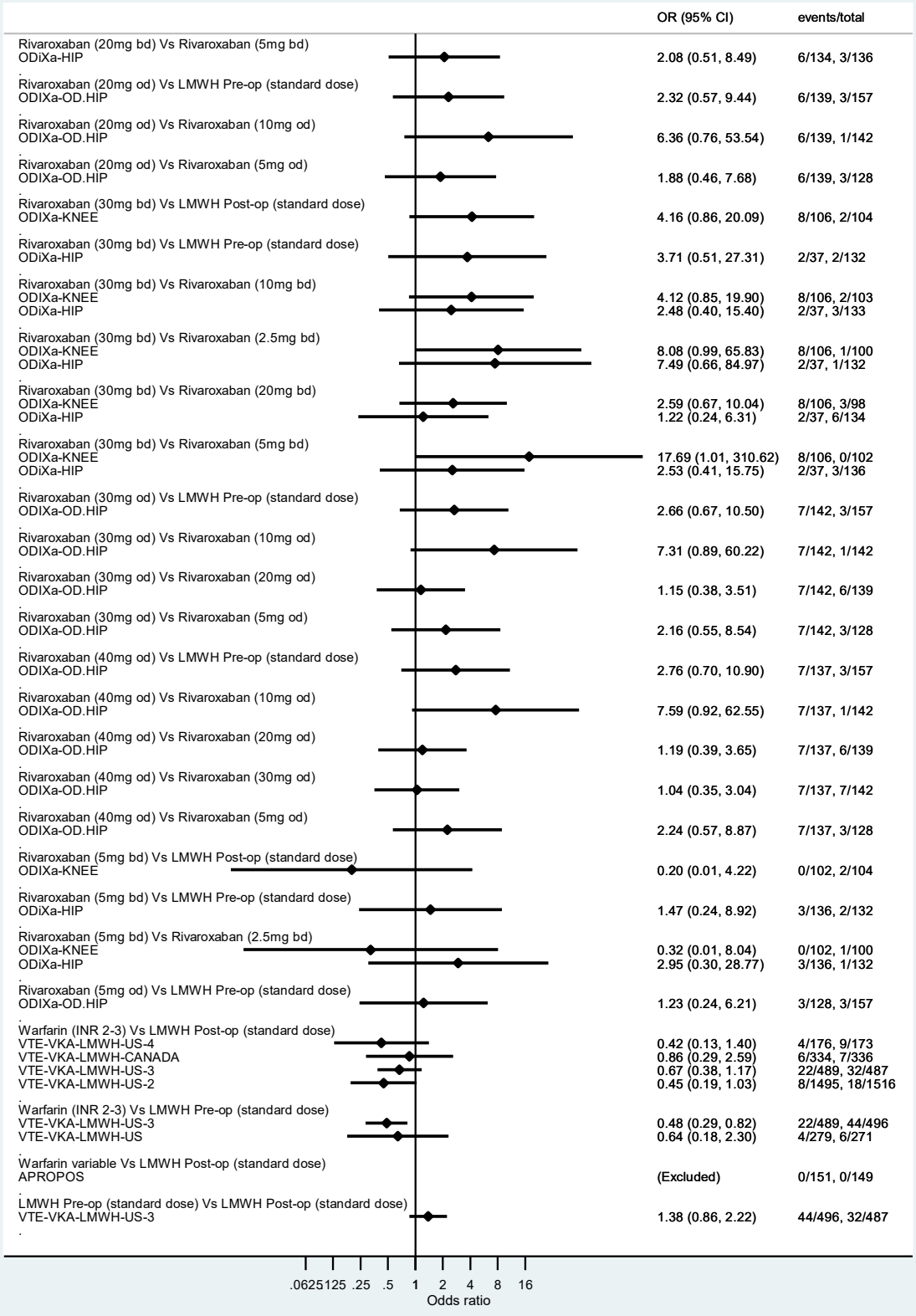


Figure 169 Forest plot for clinically relevant bleeding [1/2] (primary prevention of VTE)

)

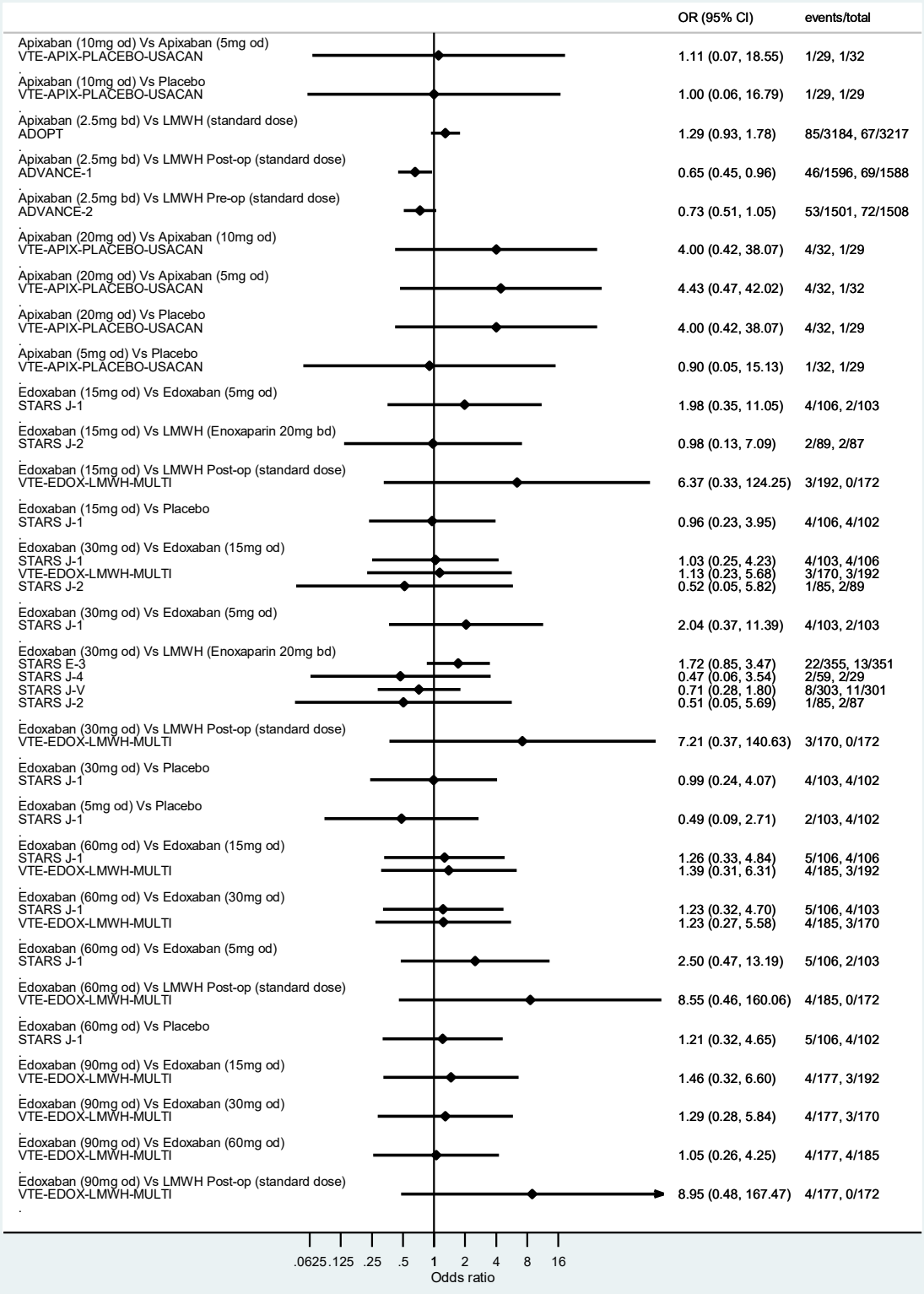


Figure 170 Forest plot for clinically relevant bleeding [2/2] (primary prevention of VTE)

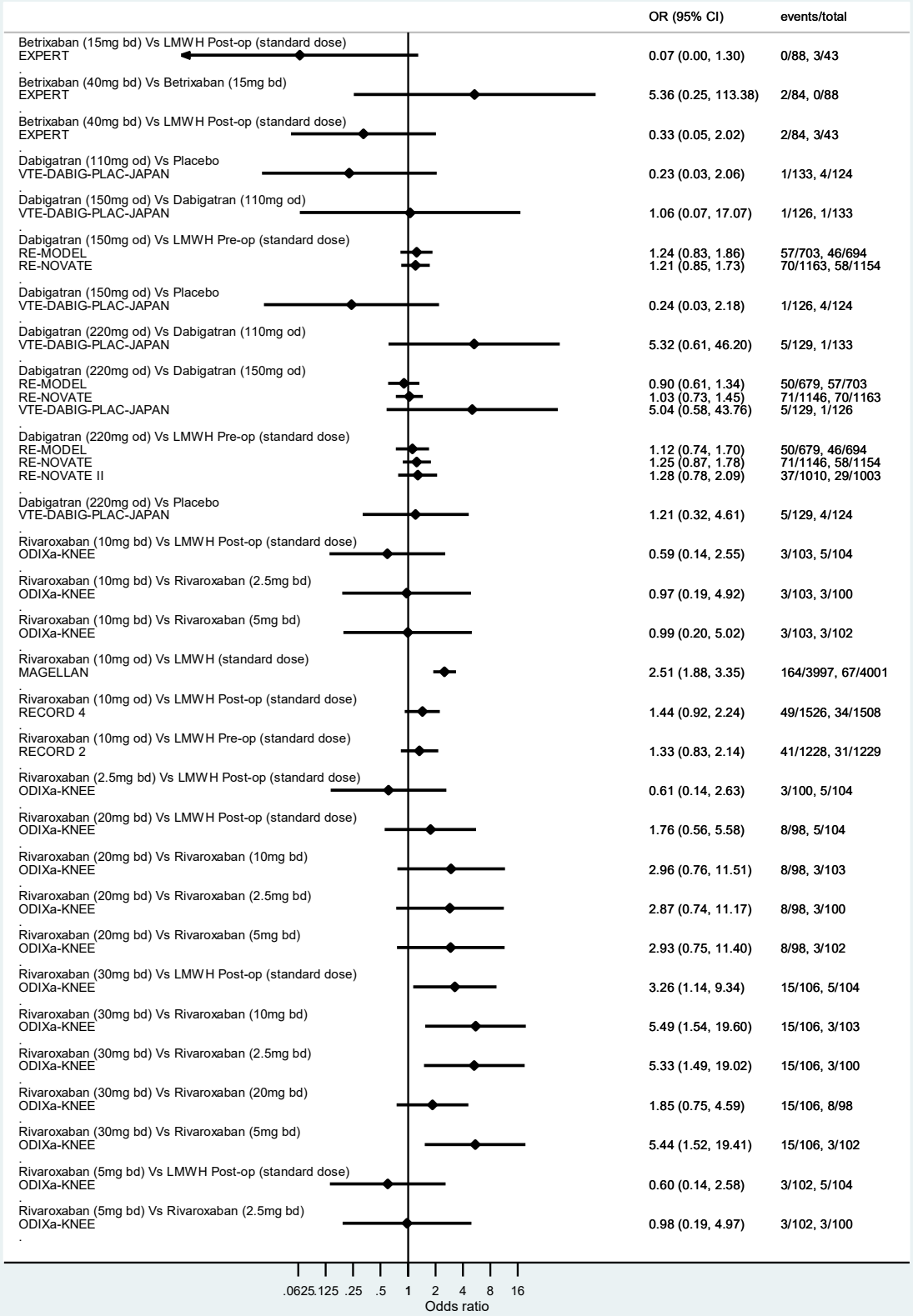


Figure 171 Forest plot for all-cause mortality [1/3] (primary prevention of VTE)

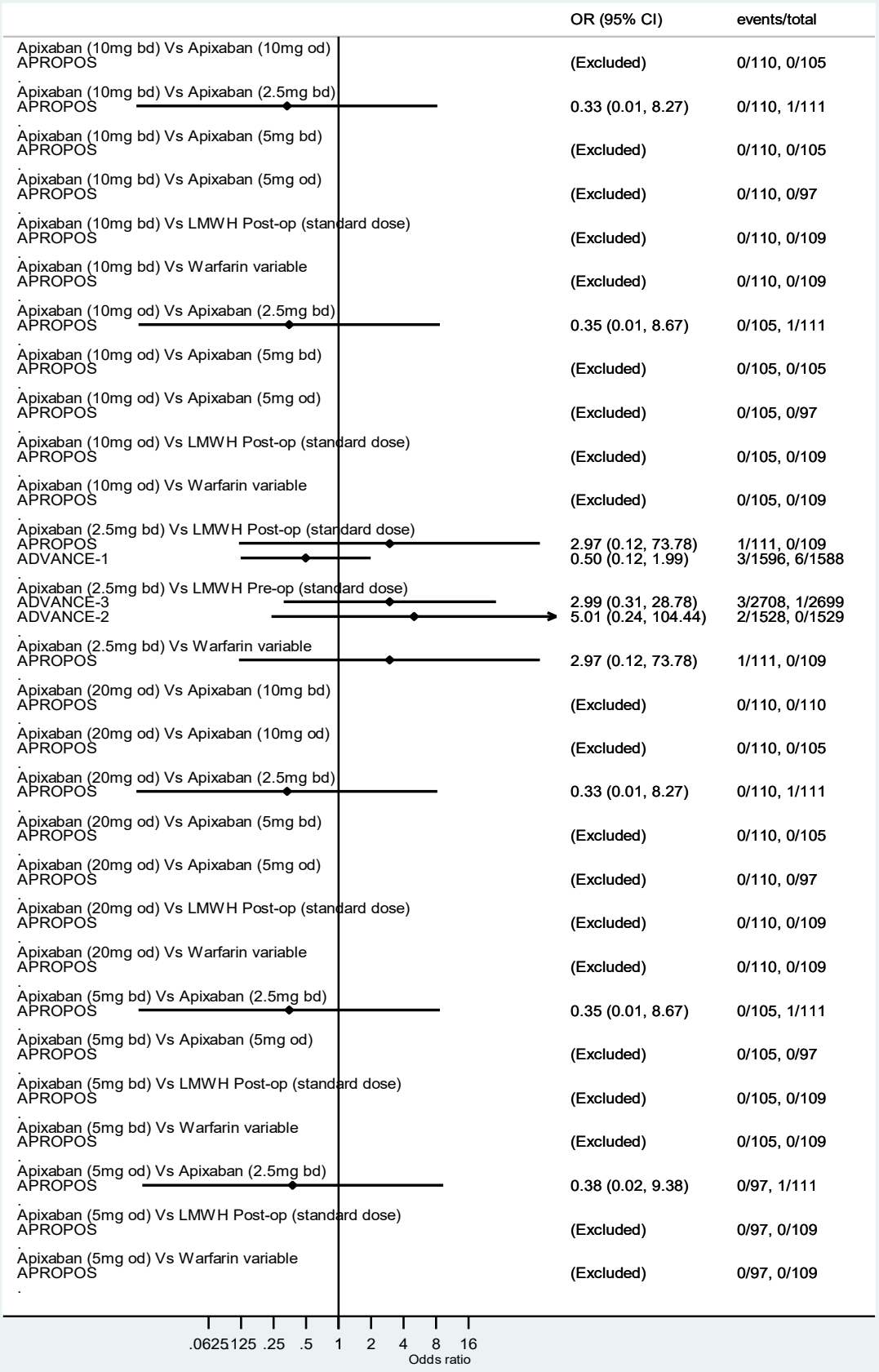


Figure 172 Forest plot for all-cause mortality [2/3] (primary prevention of VTE)

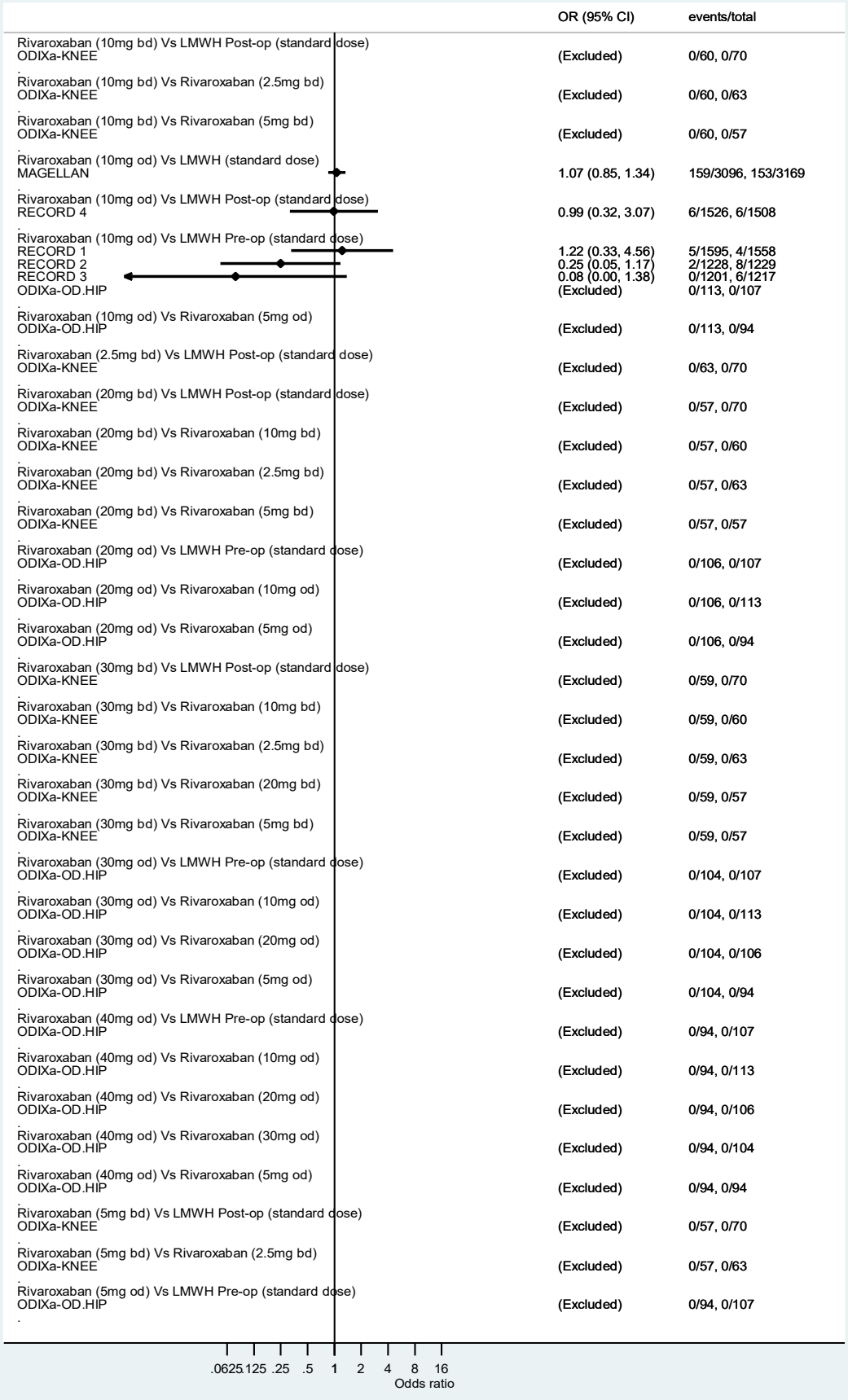
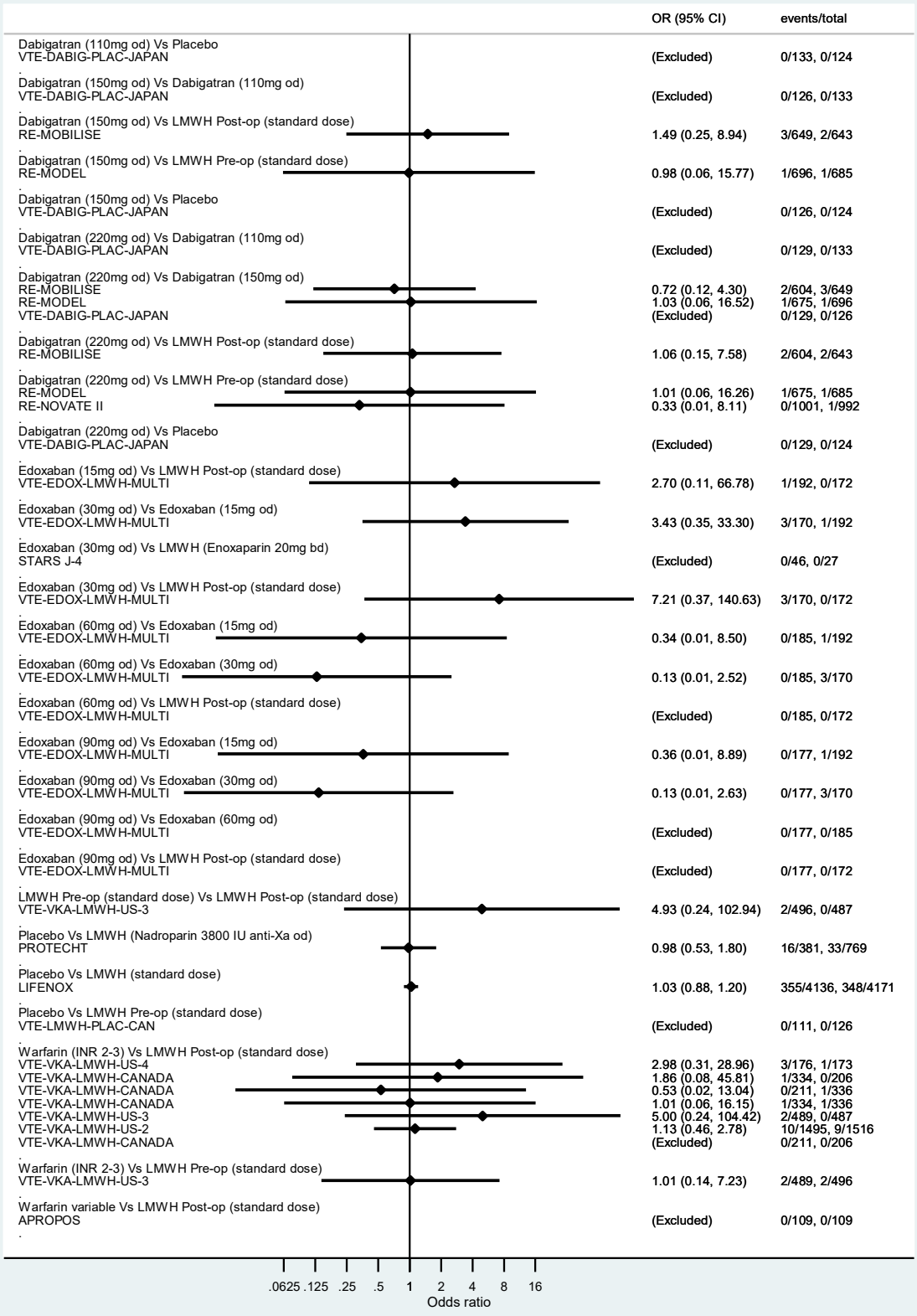


Figure 173 Forest plot for all-cause mortality [3/3] (primary prevention of VTE)



Appendix 4 Forest plots: Acute treatment of venous thromboembolism

Table 205 provides the reference numbers that correspond to the trial names for the review of acute treatment of VTE, so that readers can easily trace the results displayed in the forest plots along this section.

Table 205 List of trial names and reference numbers (acute treatment of VTE)

Trial name	Reference(s)	Trial name	Reference(s)
AMPLIFY	215	HOKUSAI-VTE	213, 214
BOTTICELLI DVT	209	ODiXa-DVT	207
EINSTEIN DVT	211	RE-COVER	210
EINSTEIN DVT dose ranging study	208	RECOVER II	216
EINSTEIN PE	212		

Figure 174 Forest plot for symptomatic DVT (acute treatment of VTE)

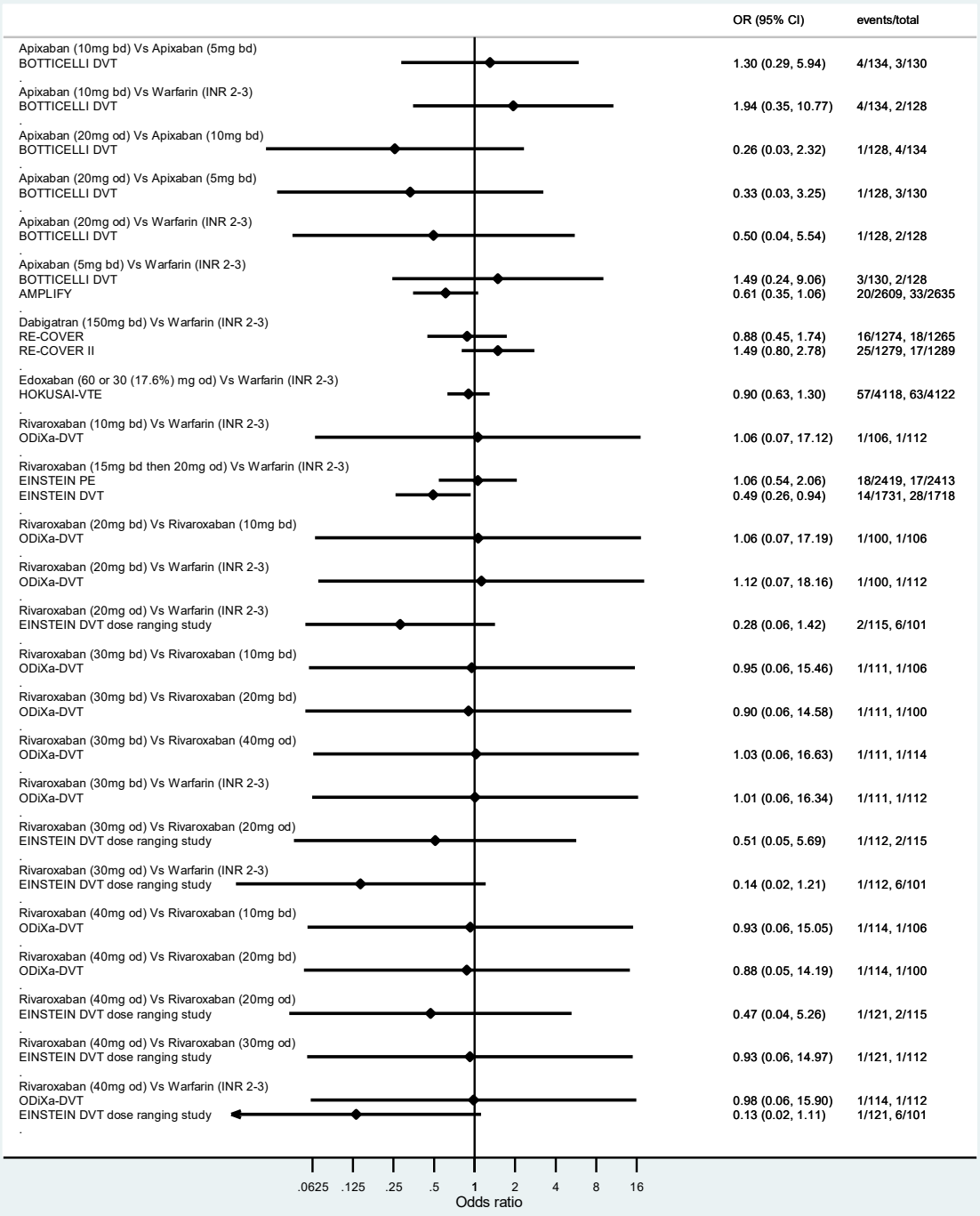


Figure 175 Forest plot for symptomatic PE (acute treatment of VTE)

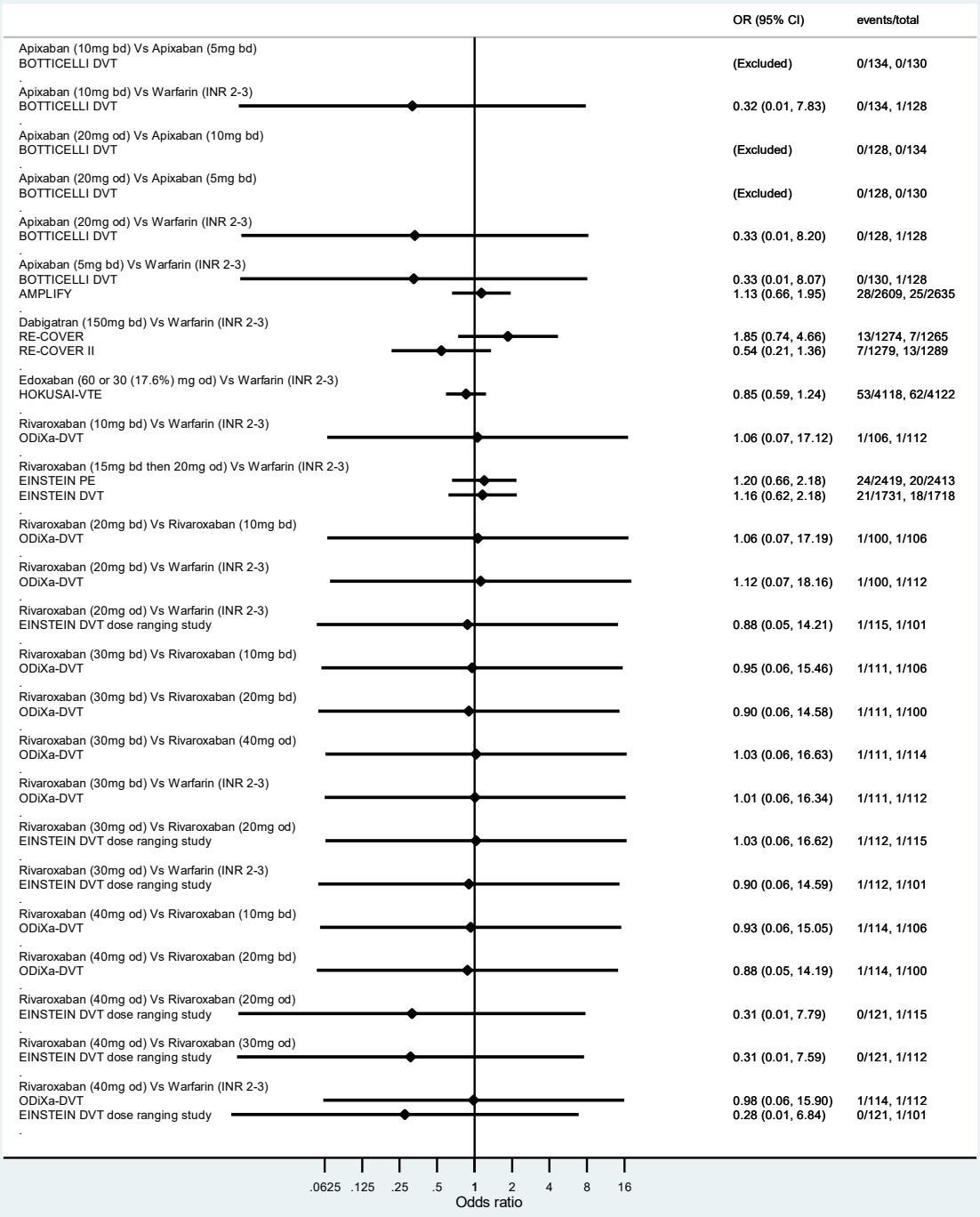


Figure 176 Forest plot for symptomatic VTE (acute treatment of VTE)

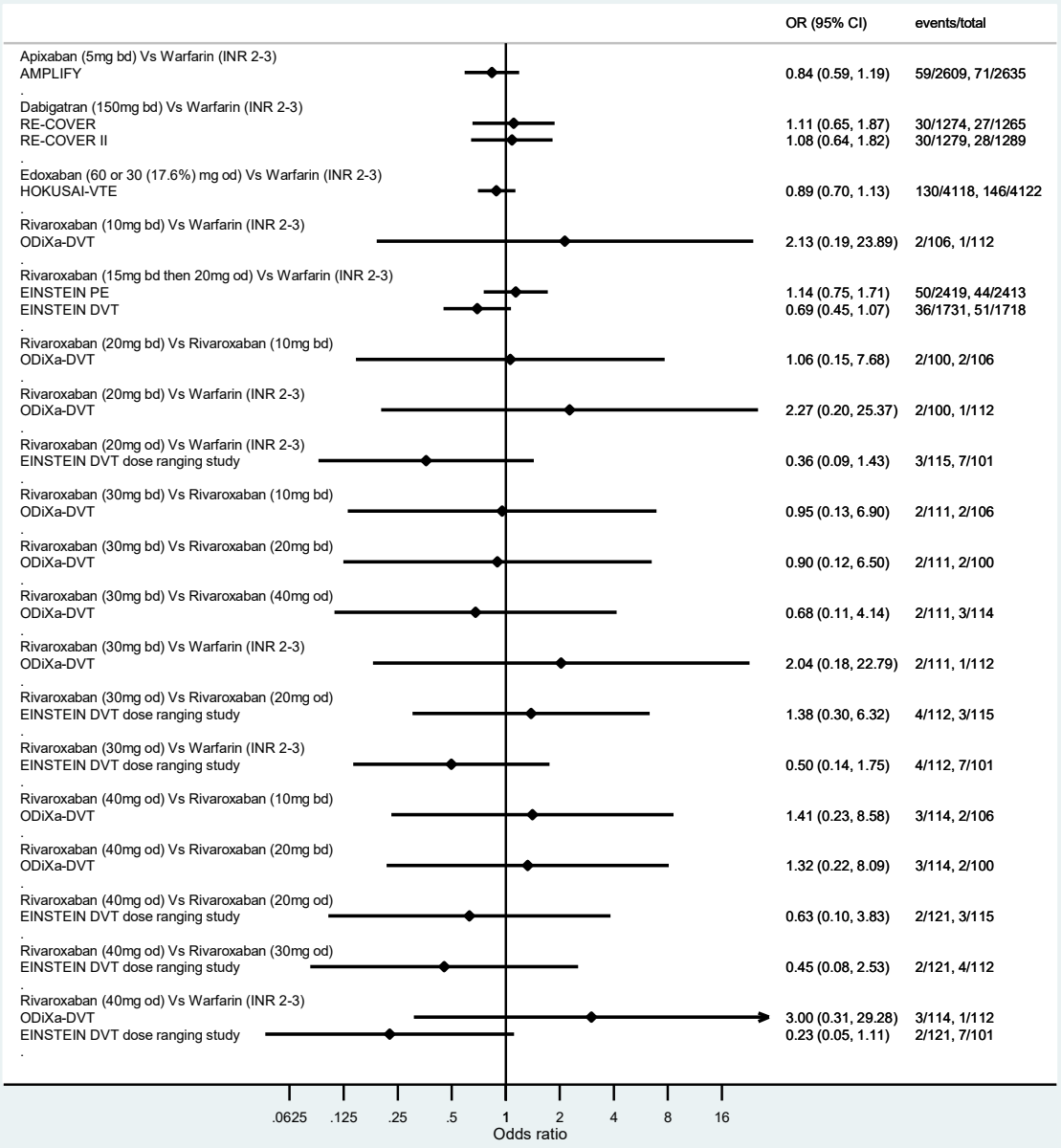


Figure 177 Forest plot for myocardial infarction (acute treatment of VTE)

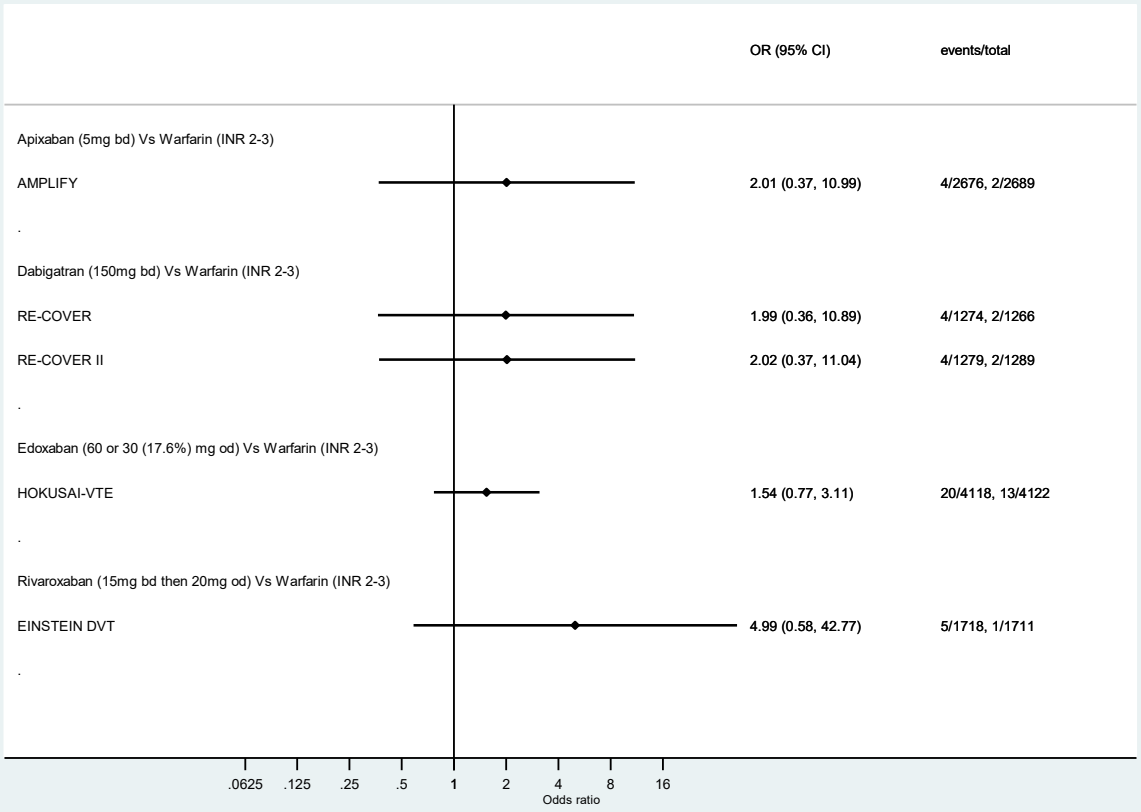


Figure 178 Forest plot for major bleeding (acute treatment of VTE)

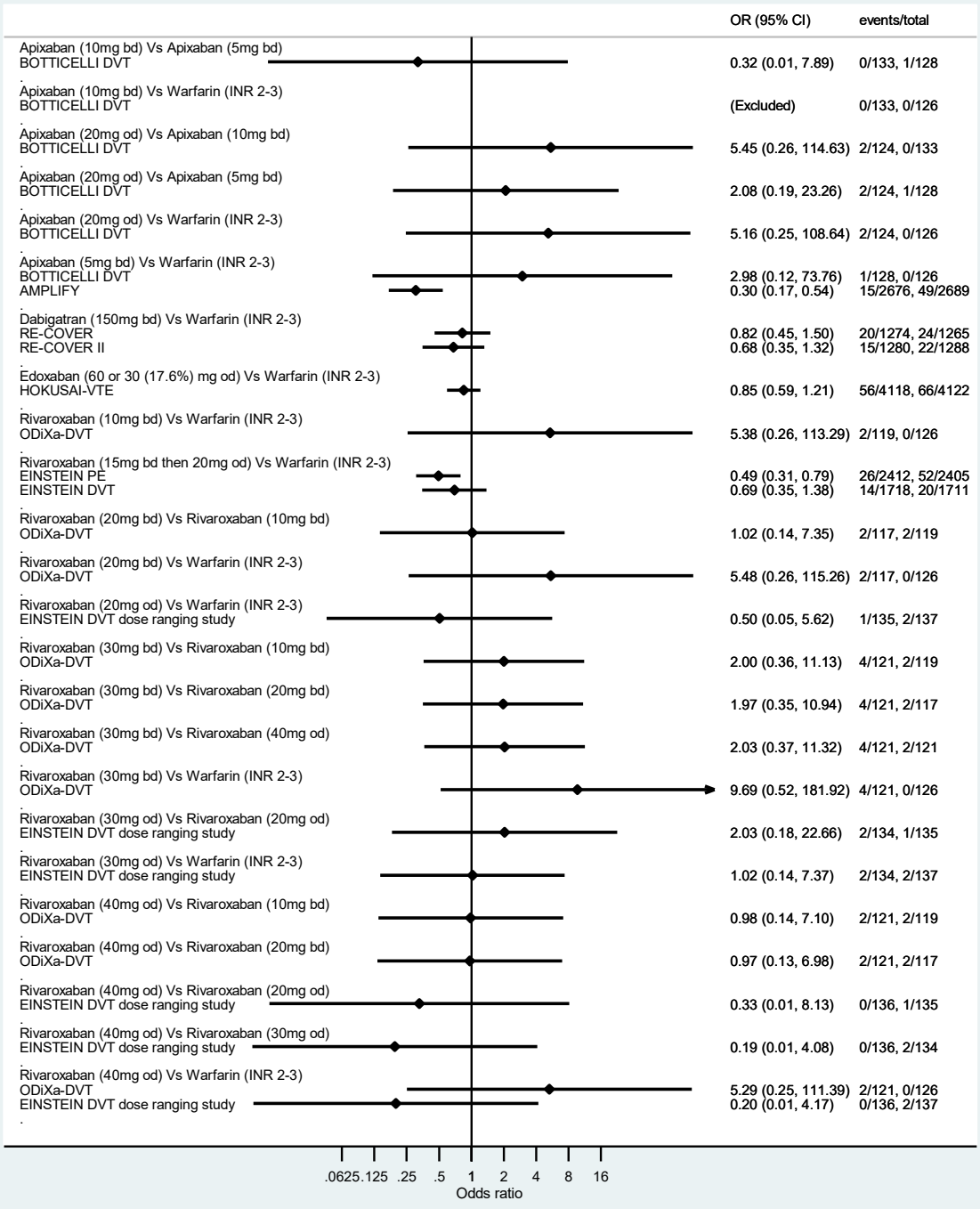


Figure 179 Forest plot for clinically relevant bleeding (acute treatment of VTE)

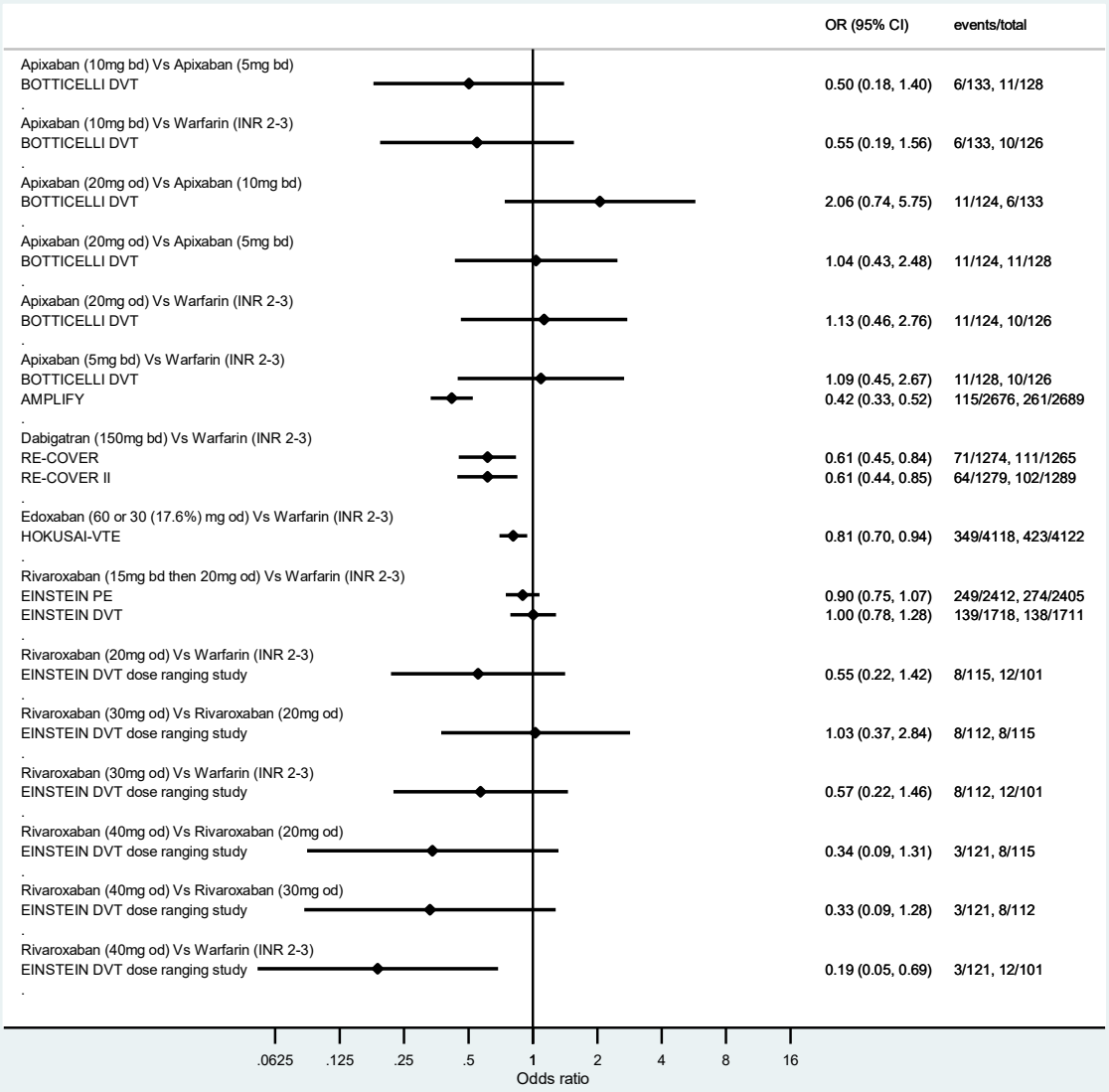
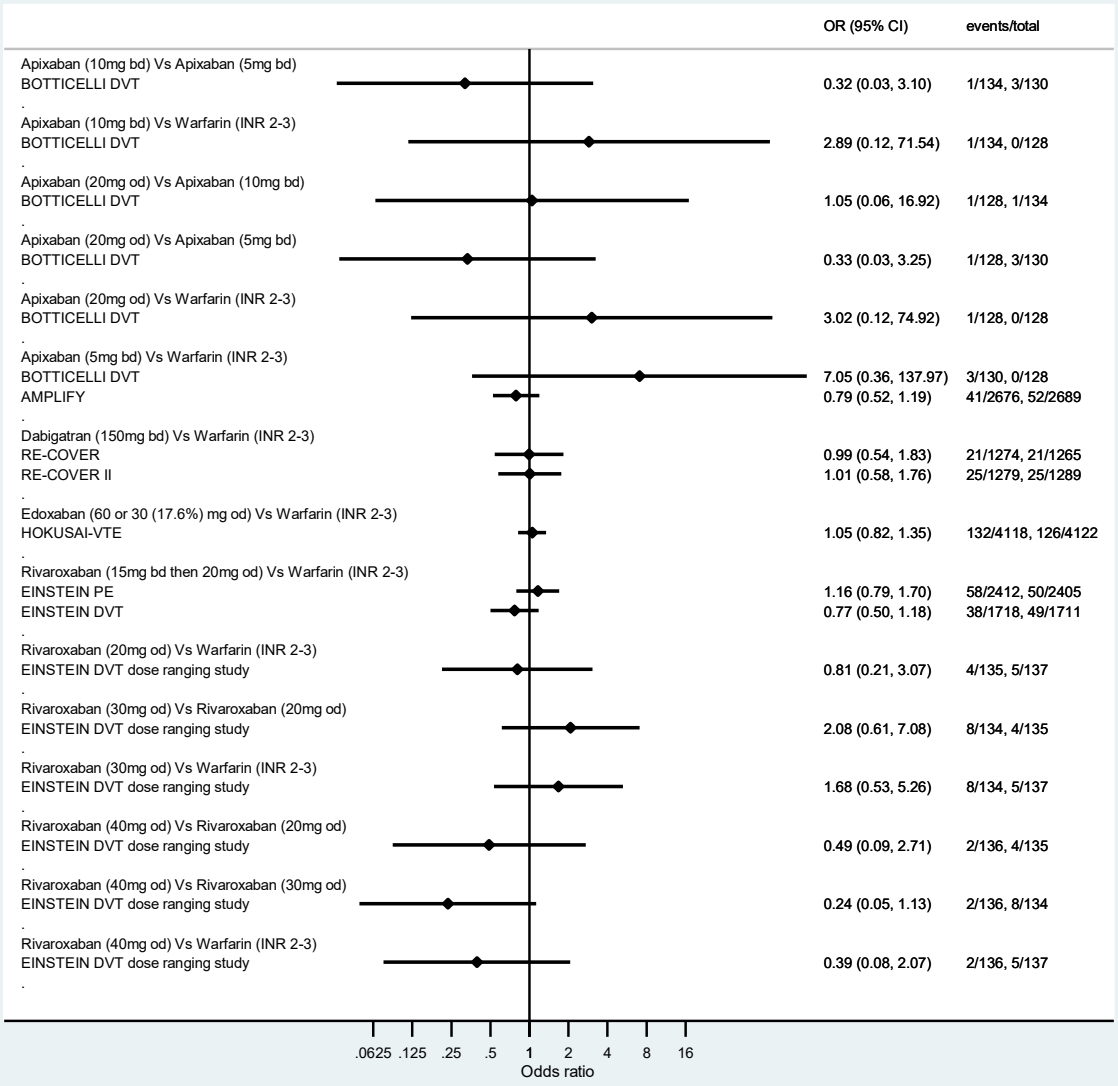


Figure 180 Forest plot for all-cause mortality (acute treatment of VTE)



Appendix 5 Forest plots: Secondary prevention of venous thromboembolism

Table 206 provides the reference numbers that correspond to the trial names for the review of secondary prevention of VTE, so that readers can easily trace the results displayed in the forest plots presented throughout this section.

Table 206 List of trial names and reference numbers (secondary prevention of VTE)

Trial name	Reference(s)	Trial name	Reference(s)
AMPLIFY-EXT	226	RE-MEDY	227
ASPIRE	225	RE-SONATE	227
EINSTEIN-EXTENSION	211, 222, 223	WARFASA	224
LAFIT	218	WODIT-DVT	219
PREVENT	221	WODIT-PE	220

Figure 181 Forest plot for symptomatic DVT (secondary prevention of VTE)

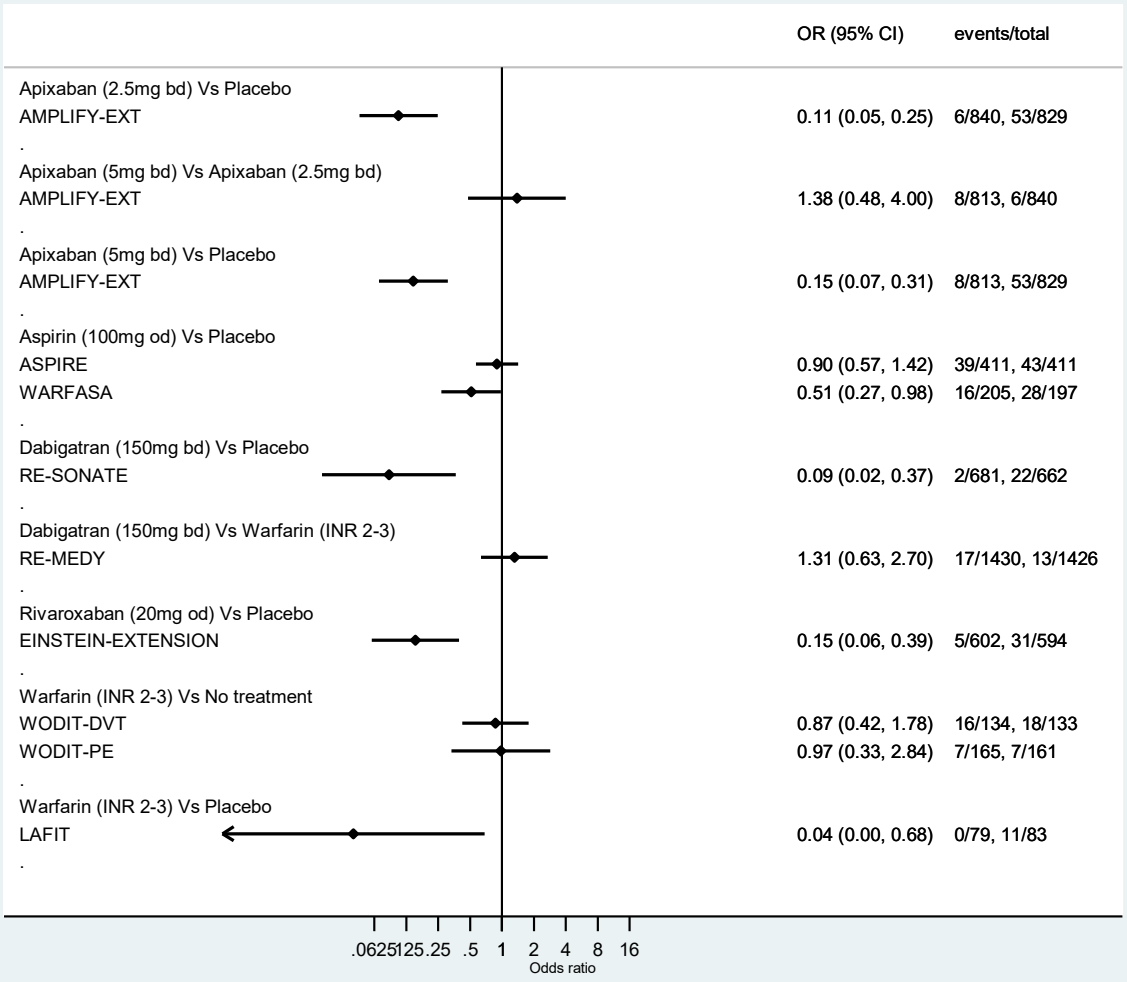


Figure 182 Forest plot for symptomatic PE (secondary prevention of VTE)

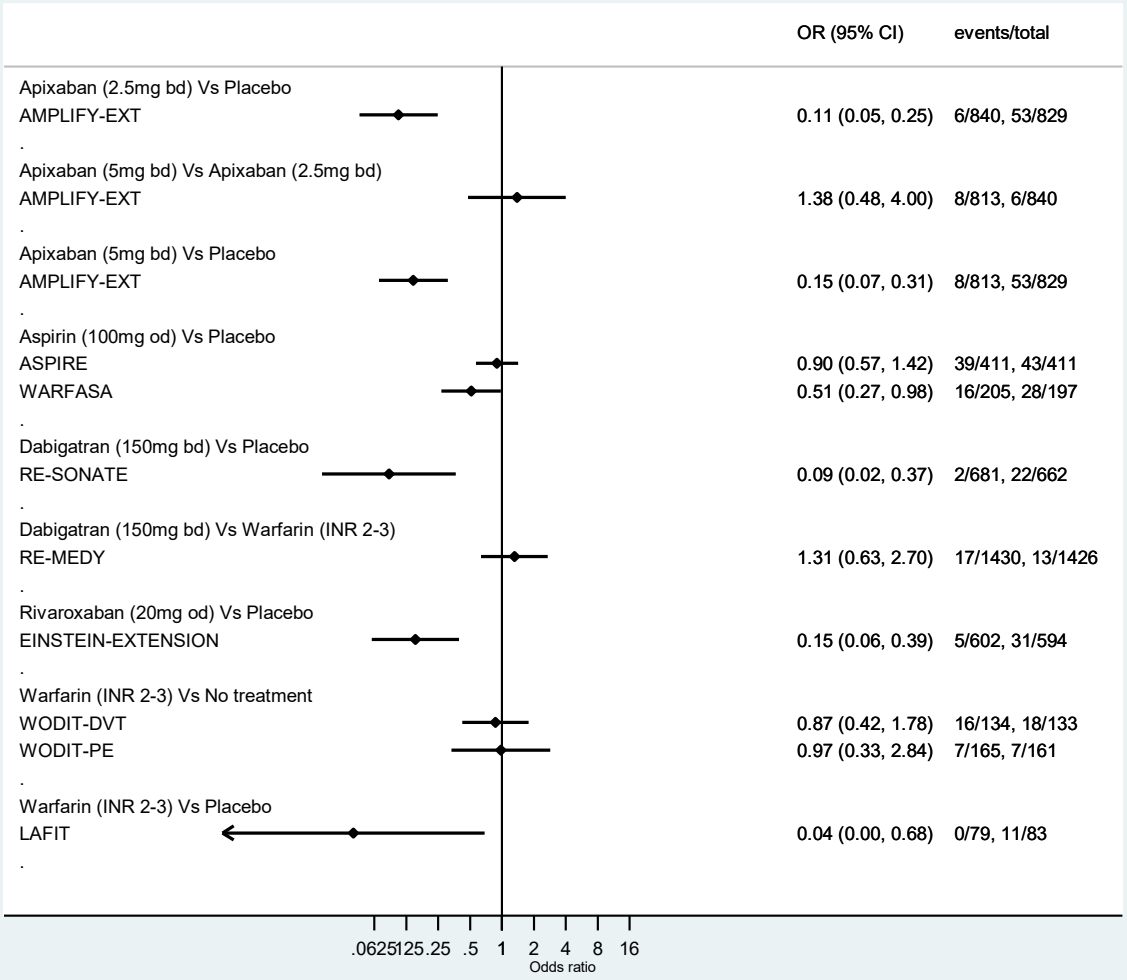


Figure 183 Forest plot for symptomatic VTE (secondary prevention of VTE)

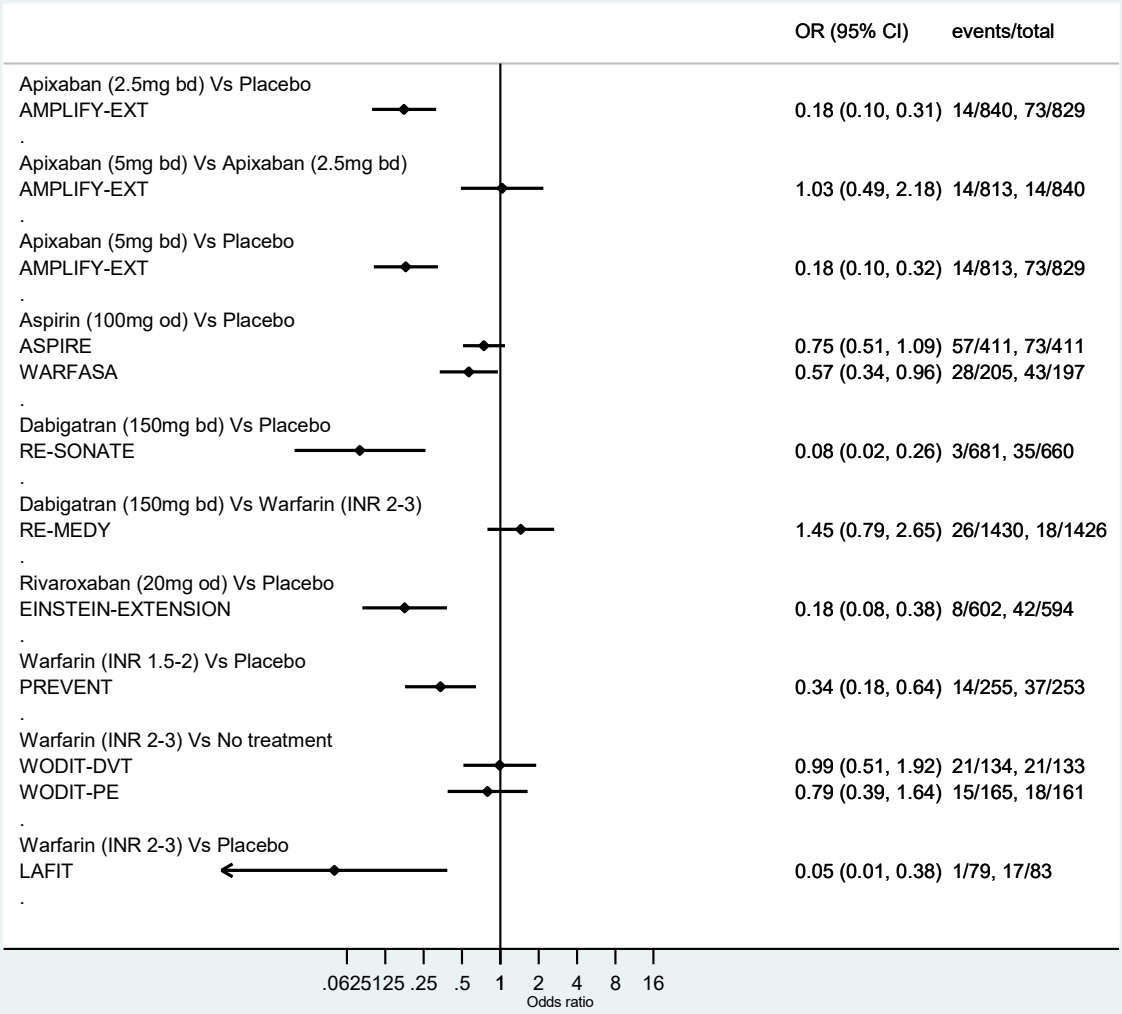


Figure 184 Forest plot for myocardial infarction (secondary prevention of VTE)

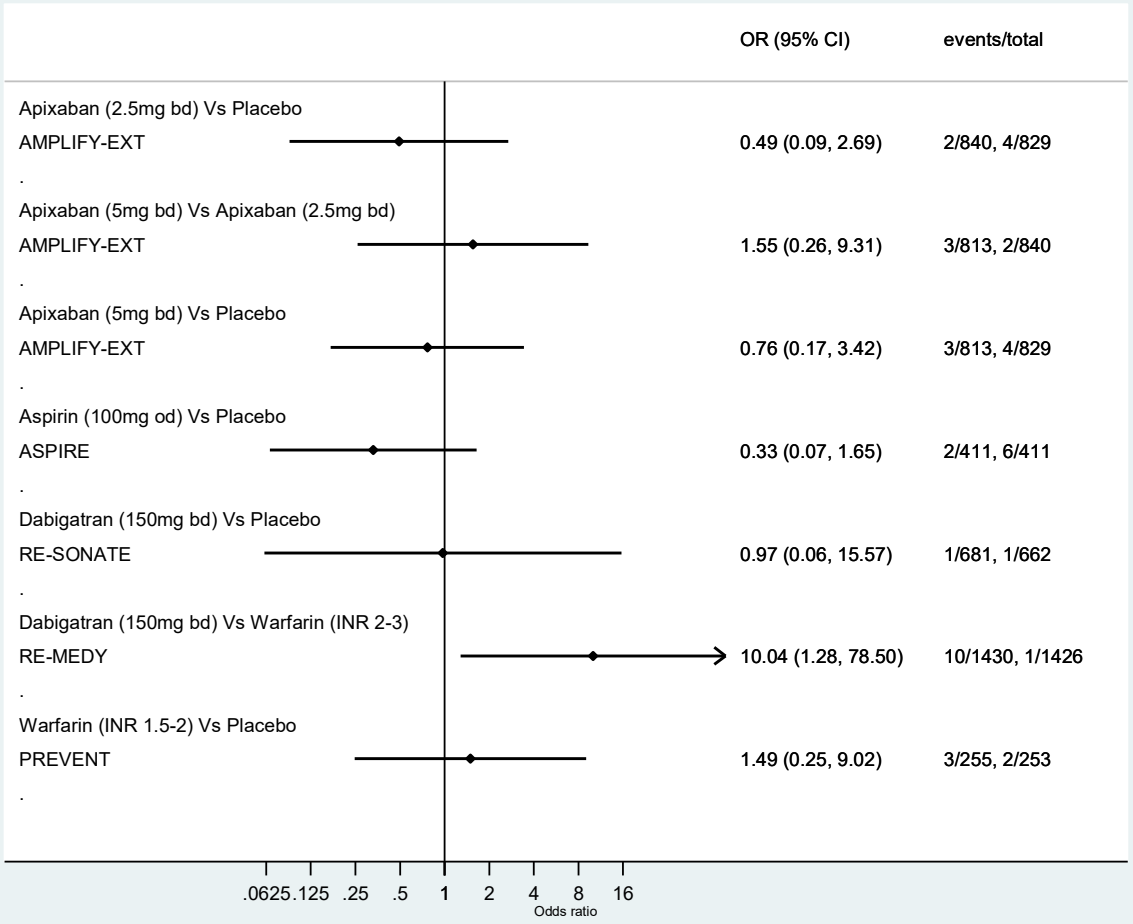


Figure 185 Forest plot for major bleeding (secondary prevention of VTE)

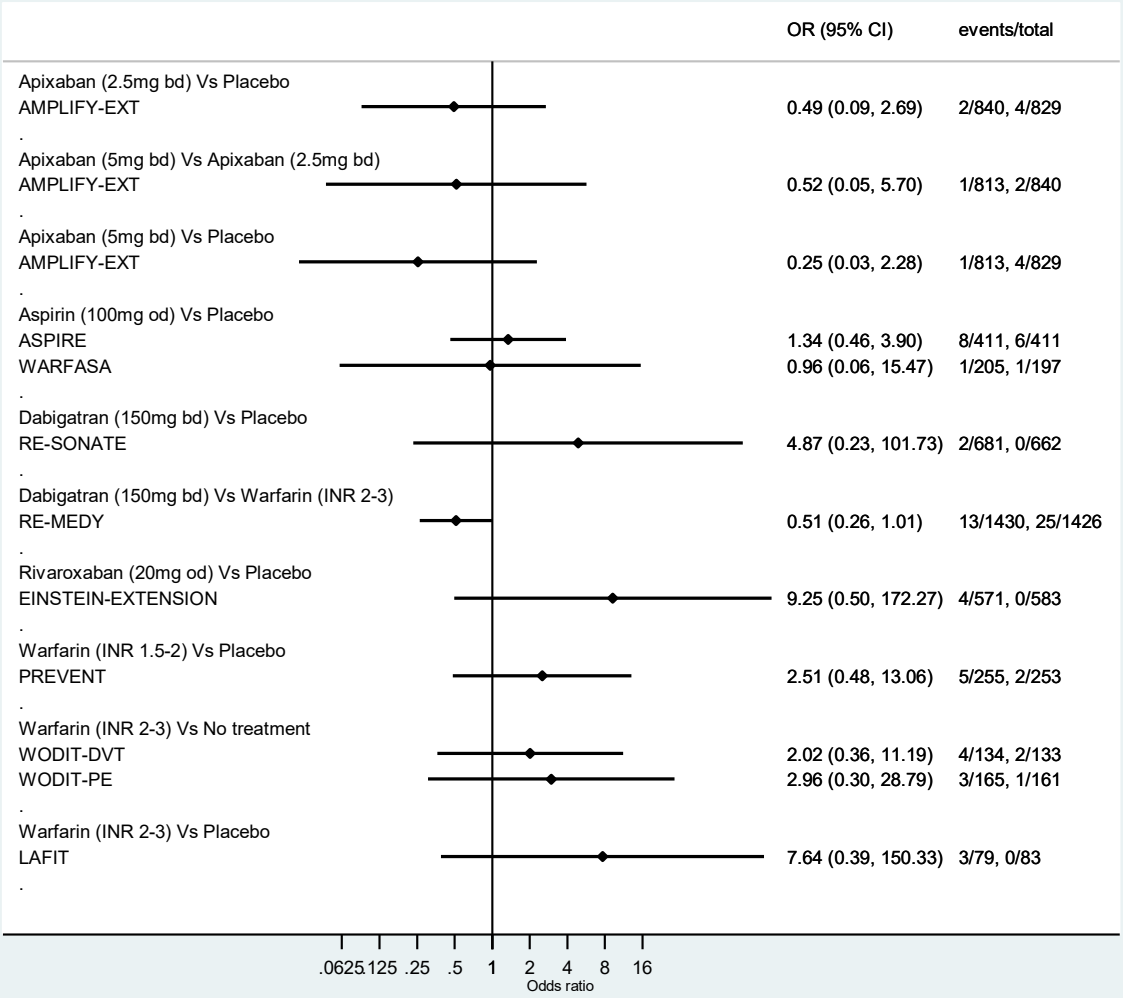


Figure 186 Forest plot for clinically relevant bleeding (secondary prevention of VTE)

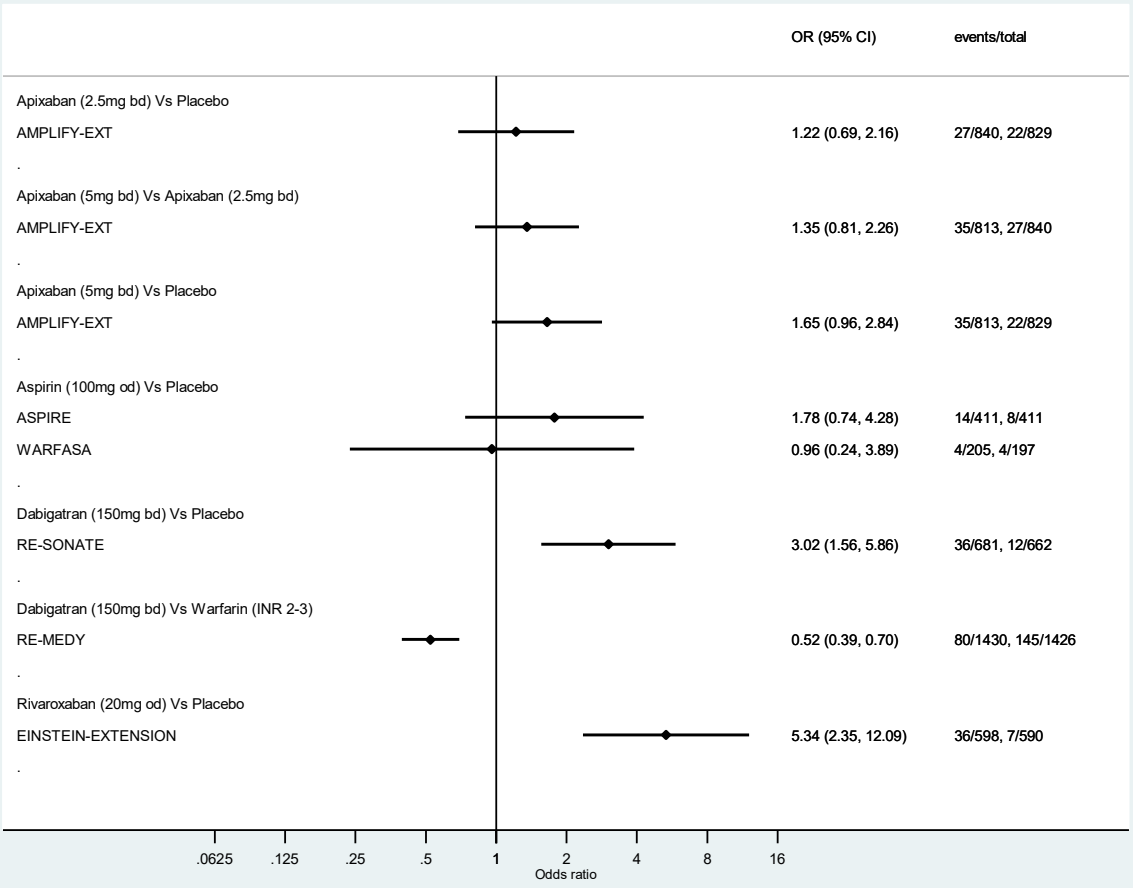
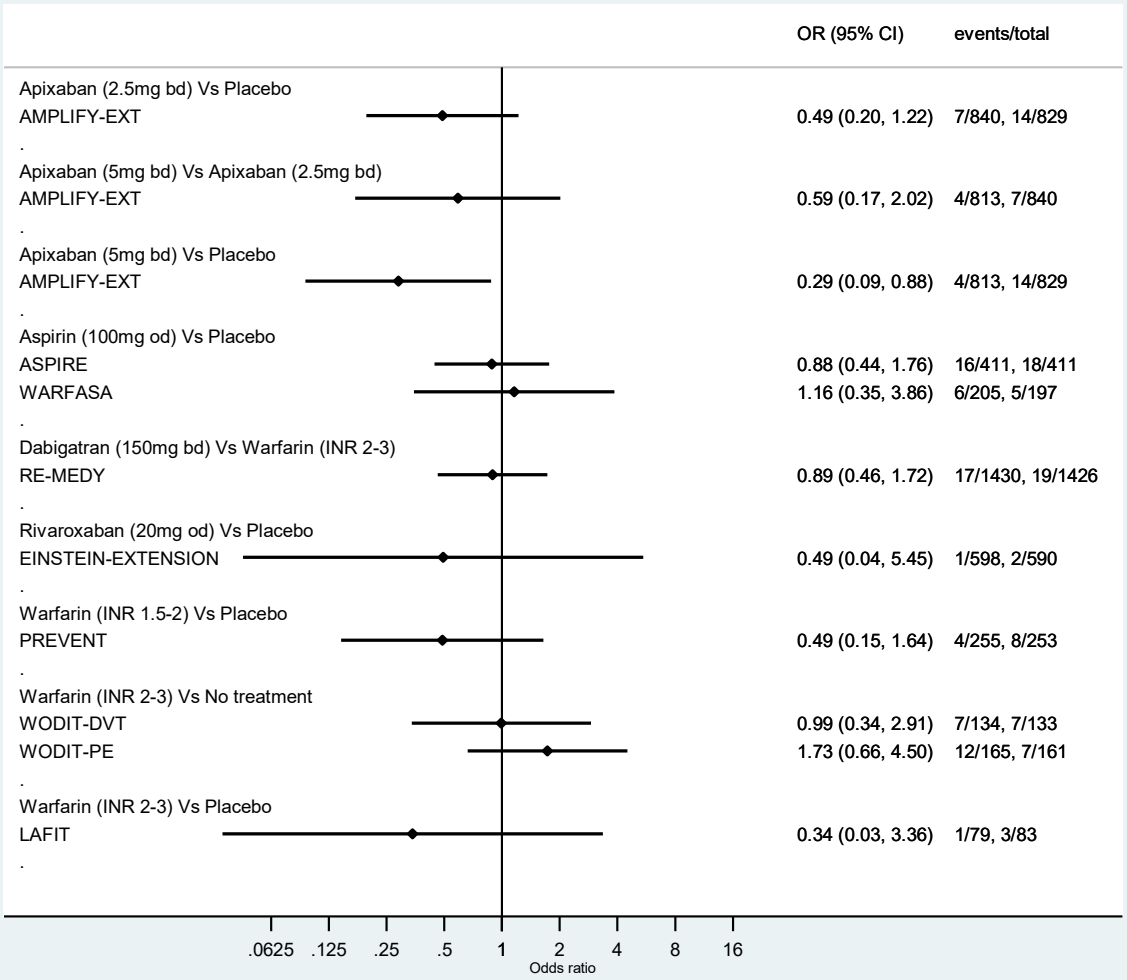


Figure 187 Forest plot for all-cause mortality (secondary prevention of VTE)



Appendix 6 Discussion of previous economic models

The earliest model we identified was developed by Gage et al. in 1995 [35]. This used a Markov model comparing warfarin, Aspirin and no therapy. States, such as "Second Stroke", were used to record the event history of patients and this history had an effect on risks of future events, costs and utilities. Strokes, ICH, and TIA were included, while MI and extracranial bleeds were not. The time horizon was 10 years and the cycle length was one month. The RIND state (reversible ischaemic neurologic deficit) was used to represent recovery from a temporary stroke or TIA. Patients were assumed to switch treatments from warfarin to Aspirin if they experienced a bleed and from Aspirin to warfarin if they experienced a stroke. In common with this model, we will adopt a Markov modelling framework with states that record event histories to account for their effect on risks, costs and utilities. In our model, we include all of the events in this model, although we rename haemorrhage as a bleed and model it in more detail, categorised by severity. We also account for the possibility of treatment switching. We also model the general RIND state in more detail, recording specific event histories, such as history of both MI and stroke.

One of the first published models in the UK setting was that by Lightowlers and McGuire in 1998 [36]. They used a very simple decision tree with a 10-year time horizon to assess the cost-effectiveness of different monitoring strategies for warfarin compared to each other and to no treatment for over 75 year olds. They included bleeding as an adverse event but made the simplifying assumption that it was roughly twice as likely in the warfarin group as in the no-treatment group. Our model will be more sophisticated than this decision tree approach. Our Markov model structure will allow us to evaluate lifetime cost-effectiveness as we can account for recurring events and long-term treatment effects, costs and utilities.

Recently, some more complicated model structures have been explored. The Bayer submission to NICE on rivaroxaban in 2011 used a 22-state Markov model to compare treatments for non-valvular AF in the 73 year old population in the UK [37], similar to our target population. The cycle length for the Markov model was 3 months and, as in our model, they used a life-time time horizon. The model accounted for treatment switching and for discontinuation of treatment, both of which be accounted for in our

model. In a similar fashion to our model and that of Gage 1995, patient history was accounted for by memory states, such as the “Post Minor Stroke” states. Unlike in Gage 1995, ICH and minor/major bleed were distinguished and, under clinical advisement, this is a distinction we will also make. The model also separated SE and stroke, a distinction we will adopt. The evidence used to inform the model was a mixture of trial data (ROCKET-AF) and the results of a Bayesian NMA comparing rivaroxaban 20 mg once daily, dabigatran 110mg, dabigatran 150mg, warfarin, aspirin and placebo. We do not have access to individual patient trial data but will use a Bayesian NMA of aggregate data from RCTs to inform a majority of our model’s transition probabilities.

Several recent publications have been largely based on the template set down by Gage in 1995. The models by Shah et al in 2011 [38], Freeman et al 2011 [39], two by Lee et al 2012[40,41] separately looking at rivaroxaban and apixaban, and by Harrington 2013 [42] all used a similar structure to Gage 1995 [35] but with updated input evidence, extra states, and different treatments. As in our model, these models used longer time horizons (up to 35 years). Due to the availability of superior data, some of these models used shorter cycle lengths (2 weeks). They additionally used TIA itself rather than RIND to represent a non-disabling minor stroke, a choice we will adopt in accordance with clinician advice, and some of the models included an MI event, using evidence of adverse treatment effect on MI rate of dabigatran 110mg and 150mg compared to warfarin from the RE-LY trial and the Framingham study. As in Gage 1995, memory states were used to record event histories but these models also included a history of both stroke and ICH, a choice we will extend by including states with a history of up to four events (stroke, bleed, ICH, MI). Kamel et al. 2012 [43] used a similar structure to the Lee et al. models, with evidence from the ARISTOTLE trial, but investigated apixaban and warfarin for the prevention of only secondary stroke. Our model will be interested in primary, secondary, and any subsequent stroke, so this is not a model of particular interest. Harrington 2013, in the USA setting, is the latest of this series of models and its parameters are based on the results of the ARISTOTLE, RE-LY, and ROCKET-AF studies of the novel oral anticoagulants.

A highly complex model was published by the Canadian agency for drugs and technologies in health (CADTH) comparing rivaroxaban, dabigatran and apixaban with

each other and with warfarin in the Canadian setting. As in our model and previous AF models, this was a Markov model [80]. The model used a cycle length of 3 months and base case time horizon of 40 years. CADTH analysed populations stratified by risk of stroke, assessed by CHADS2, and by age (<75 and ≥75 years) and allowed event rates to vary with the age of the cohort, an important feature that we will adopt for our model. A difference from our model is that CADTH included fatal and non-fatal pulmonary embolism (PE), an event we will not include as clinical advice was that PE was not a to AF treatment. The CADTH model was informed by a broad evidence base, combining results from RE-LY, ARISTOTLE, and ROCKET-AF via a NMA conducted in both the Bayesian and Frequentist setting.

Wisloff et al 2013 used a decision tree followed by an 8-state Markov model to compare dabigatran, apixaban and rivaroxaban with warfarin for populations with a range of ages in the Norwegian setting [45]. The model used eight health states, notably including gastrointestinal bleeding as the only possible bleed type. We grouped all clinically relevant bleeding events as clinical advice was that they would have similar sequelae and effects on risks of future bleeds and other events. The cycle length of the Wisloff 2013 model was 12 months as shorter cycle lengths of only 1 month was led to spurious results, most likely due to limited data, although the model was based on the results of ROCKET-AF, RE-LY and ARISOTLE. A lifetime time horizon was used but a cut-off at 105 years was imposed. Our model will adopt a similar cut-off at 100 years. The Wisloff 2013 study is significant as it was one of the few to conduct a value of information analysis.

Discrete Event Simulation was used by Pink et al. in 2011 as an alternative to Markov modelling[50]. This modelled similar events to our model, including stroke, MI, ICH, TIA, and major bleeding, and simulated 50,000 individuals over a lifetime time horizon in the UK to compare dabigatran and warfarin. The model primarily used the RE-LY trial to inform its parameters. Although discrete event simulation has the advantage over Markov models of modelling events in continuous time and modelling individual patients, we decided this extra level of detail was unnecessary and that the available data was in any case insufficient.

A recent model of dabigatran for stroke prevention in AF in the UK setting was published by Kansal et al. in 2012 [46]. This was a Markov model which built on a

previous model by Sorensen et al. 2009 [261]. This model used a 3 month cycle length and lifetime time horizon, with a cut-off at 100 years, as in our model. The model used an NMA of Roskel et al 2010 [262] to inform its clinical parameters. Although we will use a separate NMA, and other long-term sources, for clinical parameters, the costs and utilities in our model will largely follow those used in this Kansal et al. 2012 model [46], although we will update or inflate to today's prices where possible. Kansal et al. found that dabigatran was both more effective and less costly than warfarin for the prevention of stroke in AF, although they assumed that dabigatran did not require monitoring and the results may be very sensitivity to this assumption.

Appendix 7 Competing risks network meta-analysis for hazard ratios of events

All event types reported in the systematic literature review must be included to account for correlation and competing risks, giving a total of 17 types of events, although all trials report only a subset of these events.

1. Ischaemic stroke
2. Bleeding
3. Minor bleeding
4. Fatal bleeding
5. MI
6. Death (all causes)
7. Transient ischaemic attack (TIA)
8. Fatal stroke
9. Composite Clinically relevant bleeding
10. Hospital admission
11. Death (cardiovascular)
12. Arterial event
13. Pulmonary embolism
14. Extracranal minor bleeding
15. Systemic embolism (SE)) (obtained by subtracting “All Stroke” from “Stroke or systemic embolism” in trials that report both)
16. Intracranial bleeding (ICH) (to which we added haemorrhagic stroke, under clinical advice)
17. Clinically relevant bleeding (a combination of major bleeding and clinically relevant non-major bleeding)

Events of interest to our model are death (All causes), MI, TIA, clinically relevant bleeding, ischaemic stroke, SE and ICH.

In all of the following models, λ_i is the rate of events of type i, which is modelled on the log-scale. The data are reported in three different ways, which we describe in turn below. The interpretation of the λ_i's is the same across different data types and can be estimated in a shared parameter model.

For each study *j*, arm *k*, and outcome *i*, the log of the hazard λ_{jki} is related to the study-specific baseline hazard μ_{ji} and log hazard ratio of the treatment in arm k (t_{jk}) relative to the treatment in arm 1 (t_{j1})

$$\log(\lambda_{jki}) = \mu_{ji} + d_{t_{jk}i} - d_{t_{j1}i}$$

The baseline hazards μ_{ji} are treated as nuisance parameters and vague priors are placed on them

$$\mu_{ji} \sim N(0, 0.0001)$$

Vague priors are also placed on the log hazard ratios for all outcomes *i* and treatments *t*

$$d_{ti} \sim N(0, 0.0001)$$

1. Number of first events

Here, only the first event is recorded for each individual, and they are assumed censored at the point at which the first event occurs. The outcomes are therefore competing risks, and need to be modelled jointly.

Let $r_1, r_2, ..., r_m$ be the number of individuals with first event being of type *i*, for *i=1,…,m*, and $R = \sum_{i=1}^{m} r_i$. Let E be the observed person years at risk. Then the likelihood is:

$$R \sim Po\left(E \sum_{i=1}^{m} \lambda_i \right) \qquad \text{and conditional on } R$$

$$\left(r_1, r_2, ..., r_m\right) \sim Multinomial\left(\left(\frac{\lambda_1}{\sum_{i=1}^{m} \lambda_i}, ..., \frac{\lambda_m}{\sum_{i=1}^{m} \lambda_i} \right); R \right)$$

There are 5 studies which report in this format, of which 4 report the mean follow-up time. The observed person years at risk can be obtained from the mean follow up time by multiplying by the number of individuals randomised. In one study median follow-up and also study duration are reported, but not mean follow-up. Median follow-up is just over half that of study duration, due to censoring. If we assume mean follow-up is approximately equal to median follow-up, then we can obtain the person years at risk as if mean follow-up were reported.

2. Number of individuals experiencing at least 1 event of a given type

Here, the number of individuals experiencing at least one event of a given type are recorded. Each individual may count towards more than one event type, but only once for each event type. We need to consider mortality slightly differently to other event types, because this can only happen once. The model is the same as that presented in Chapter X.

Now let r_i be the number of individuals with at least one event of type i, and r_m the number of mortalities.

The likelihood for the number of mortalities is:

$$r_m \sim Po(E\lambda_m)$$

The likelihood for other events is approximately (assuming an average follow-up time, $\bar{t}$, for each individual, and number randomised *n*):

$$r_i \sim Bin(p_i, n)$$

where p_i is the probability that an individual has 1 or more event of type i over follow-up period $\bar{t}$:

giving:

$$c\log\log(p_i) = \log(\bar{t}) + \log(\lambda_i)$$

where $c\log\log(p_i) = \log(-\log(1-p_i))$

There are 14 studies reporting outcomes in this format. Of these only 3 report mean follow-up time, $\bar{t}$, which can be used in the likelihood as described above. 2 studies report median follow-up time, which we can use if we assume that the mean follow-up time is approximately equal to the median follow-up. One study does not report any information on follow-up, and so has to be excluded from the analysis.

The remaining 8 studies report only the study duration, which we know from those studies reporting both study duration and mean or median follow-up greatly over-estimates mean follow-up time. In studies that report both, the mean follow-up time, as a proportion of the study duration ranges from 36% to 69%. We used a prior for this proportion, π, then set $\bar{t} = \pi$t (where t=study duration). This allowed us to include these studies, but reflected our uncertainty in the mean follow-up time.

3. Total number of events

Here we have total number of events of type i for given person years at risk E.

Now let r_i be the number events of type i, including repeat events within individuals.

The likelihood is:

$$r_i \sim Po(E\lambda_i)$$

There are 3 studies reporting results in this format. Of these, one reports mean follow-up time from which we can derive E. The other two report median follow-up time, which we can use if we assume mean follow-up time is approximately equal to median follow-up time.

Estimating mean follow-up time from median follow-up time

If censoring follows an Exponential distribution, then mean = median/log(2) giving mean > median. However in the only study that reports both, they are very similar. This is probably due to the various different censoring mechanisms (mortality, lost-to-follow up). We will therefore make the assumption that our analyses can use the median follow-up when the mean follow-up is not available.

Appendix 8 Competing risks model for hazard in warfarin arms of trials

The natural history model on standard care (warfarin (INR 2-3)) requires estimates of the baseline log hazard, rather than hazard ratios, of events of interest. As in the treatment effects NMA, there are three types of outcomes data to be incorporated into the model. The main difference is that a common, random effect, baseline log hazard for the warfarin arm (labelled 1) is assumed across studies with m_i and precision ω_i

For each study *j* with a warfarin arm and outcome *i*, the log of the hazard λ_{ji} is

$$\log(\lambda_{ji}) = \mu_{ji}$$

The trial specific baseline hazards are related to the across trial baseline hazard

$$\mu_{ji} \sim N(m_i, \omega_i)$$

A vague prior is placed on the mean of baseline hazard

$$m_i \sim N(0, 0.0001)$$

A vague prior is placed on the precision of the baseline hazard, on the standard deviation scale

$$\frac{1}{\sqrt{\omega_i}} \sim Uniform(0,5)$$

The rest of the model is identical to that presented in Appendix 7.

Appendix 9 All-cause mortality minus VTE related mortality data (acute treatment of VTE)

Table 207 All-cause mortality minus VTE related mortality data (acute treatment of VTE)

Study	Comparator	N	All-cause mortality minus VTE related mortality
AMPLIFY[227]	Apixaban 2 x 5mg	2691	0
AMPLIFY[227]	Warfarin	2704	37
BOTTICELLI DVT[221]	Apixaban 2 x 5mg	130	3
BOTTICELLI DVT[221]	Apixaban 2 x 10mg	134	1
BOTTICELLI DVT[221]	Apixaban 1 x 20mg	128	1
BOTTICELLI DVT[221]	Warfarin	128	0
EINSTEIN DVT[223]	Rivaroxaban 2x15 mg (first 21 days), then 1x20mg	1731	36
EINSTEIN DVT[223]	Warfarin	1718	43
EINSTEIN DVT dose ranging study[220]	Rivaroxaban 1 x 20 mg	115	4
EINSTEIN DVT dose ranging study[220]	Rivaroxaban 1 x 30 mg	112	6
EINSTEIN DVT dose ranging study[220]	Rivaroxaban 1 x 40 mg	121	1
EINSTEIN DVT dose ranging study[220]	Warfarin	101	0
EINSTEIN PE[224]	Rivaroxaban 2x15 mg (first 21 days), then 1x20mg	2419	48
EINSTEIN PE[224]	Warfarin	2413	44
HOKUSAI-VTE[225,226]	Edoxaban 60 or 30 (17.6%) mg	4118	108
HOKUSAI-VTE[225,226]	Warfarin	4122	102
RE-COVER[222]	Dabigatran 2 x 150 mg	1274	20
RE-COVER[222]	Warfarin	1265	18
RE-COVER II[228]	Dabigatran 2 x 150 mg	1279	22
RE-COVER II[228]	Warfarin	1289	25

Appendix 10 ONS life tables stratified by age and gender

Table 208 ONS life tables stratified by age and gender

Age	Males	Females
55	0.0052	0.0034
56	0.0059	0.0038
57	0.0062	0.0042
58	0.0069	0.0045
59	0.0074	0.0050
60	0.0082	0.0054
61	0.0090	0.0059
62	0.0098	0.0064
63	0.0105	0.0068
64	0.0115	0.0075
65	0.0124	0.0081
66	0.0142	0.0092
67	0.0155	0.0101
68	0.0167	0.0109
69	0.0190	0.0123
70	0.0213	0.0139
71	0.0235	0.0150
72	0.0257	0.0169
73	0.0279	0.0183
74	0.0311	0.0206
75	0.0340	0.0228
76	0.0380	0.0257
77	0.0420	0.0290
78	0.0470	0.0327
79	0.0516	0.0368
80	0.0581	0.0416
81	0.0657	0.0471
82	0.0735	0.0531
83	0.0817	0.0608
84	0.0915	0.0685
85	0.1019	0.0766
86	0.1130	0.0866
87	0.1263	0.0959
88	0.1386	0.1082
89	0.1570	0.1217
90	0.1694	0.1392
91	0.1840	0.1507
92	0.1974	0.1672
93	0.2147	0.1792

94	0.2382	0.2028
95	0.2594	0.2240
96	0.2830	0.2455
97	0.3041	0.2631
98	0.3240	0.2828
99	0.3424	0.3056
100	0.3654	0.3252

1

2

3

Appendix 11 Log odds ratios relative to LMWH

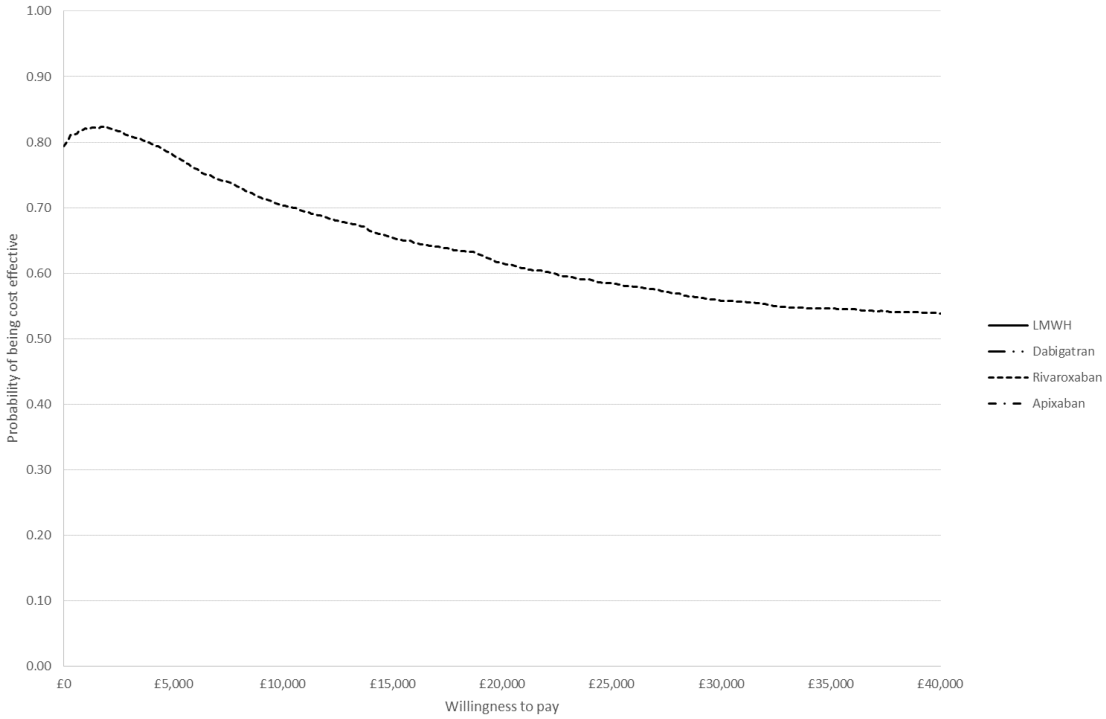
Table 209 Estimated (posterior mean) log odds ratios relative to LMWH post-operative (standard dose): pooled surgical primary population

Treatment	Log-odds ratio	95% CI	Distribution
Apixaban (2.5mg bd)	-0.05	-0.63 to 0.52	MCMC posterior simulations
Dabigatran (220mg od)	-0.02	-0.60 to 0.56	MCMC posterior simulations
Rivaroxaban (10mg od)	-0.67	-1.18 to -0.18	MCMC posterior simulations

Appendix 12 VTE sensitivity analyses

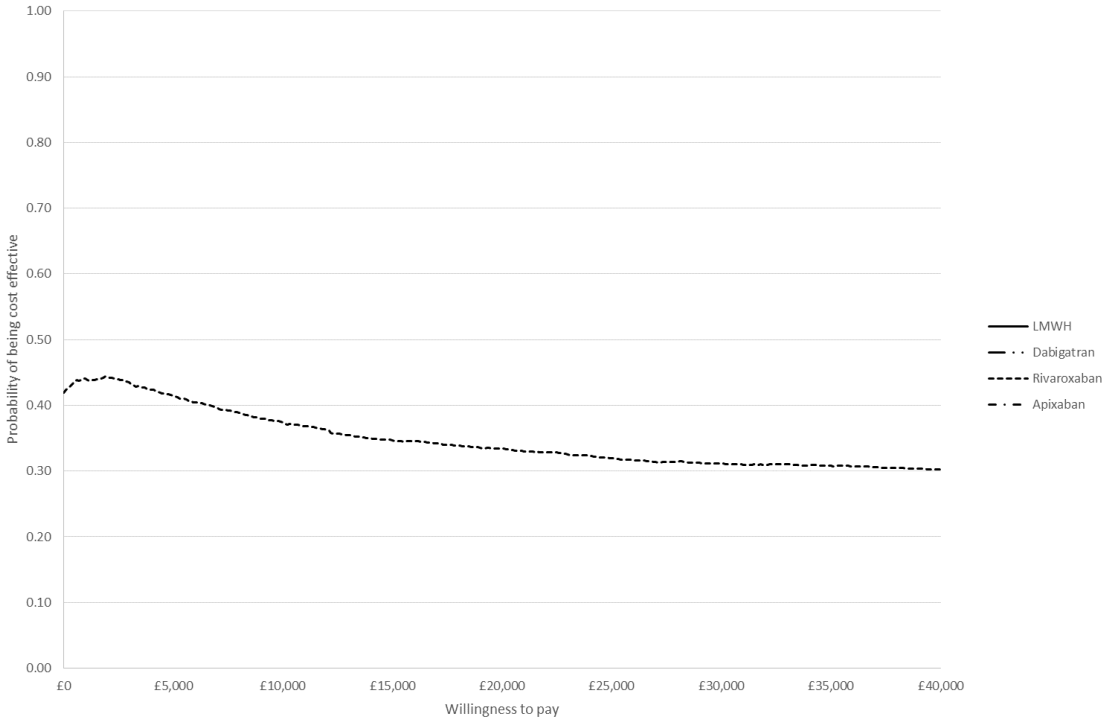
Primary prevention of venous thromboembolism: Total knee replacement

Figure 188 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: pooling post THR and post TKR populations for relative treatment effect of VTE



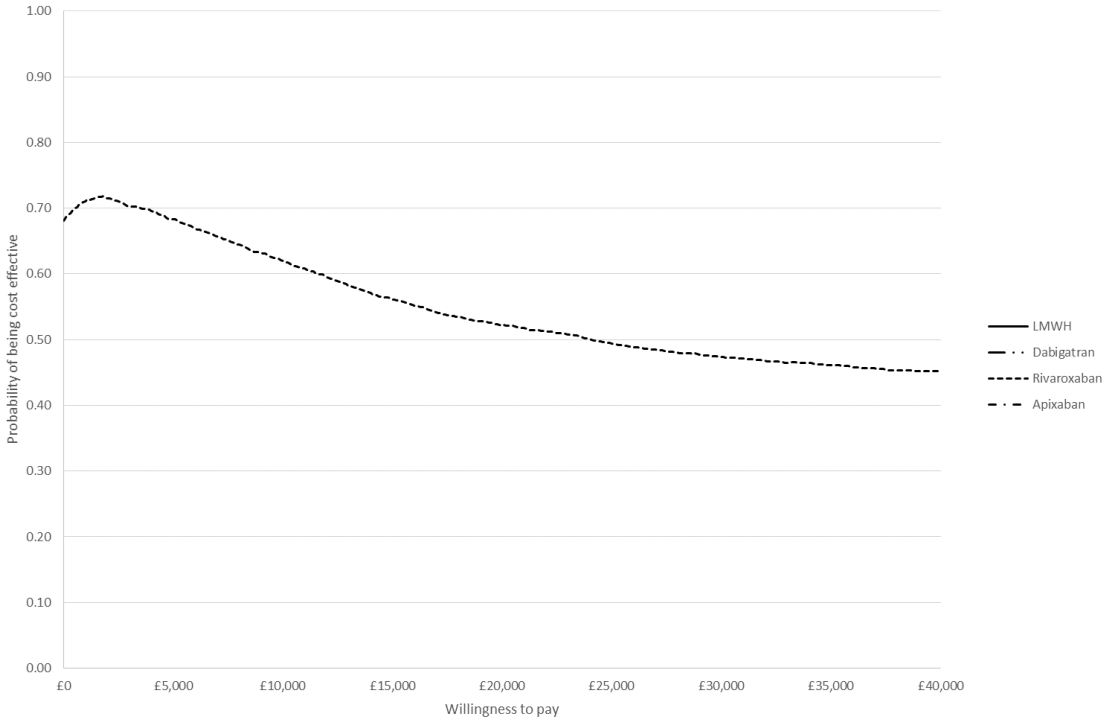
See section 4.5.3 for further details

Figure 189 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: setting the cost of dabigatran to 150mg once daily



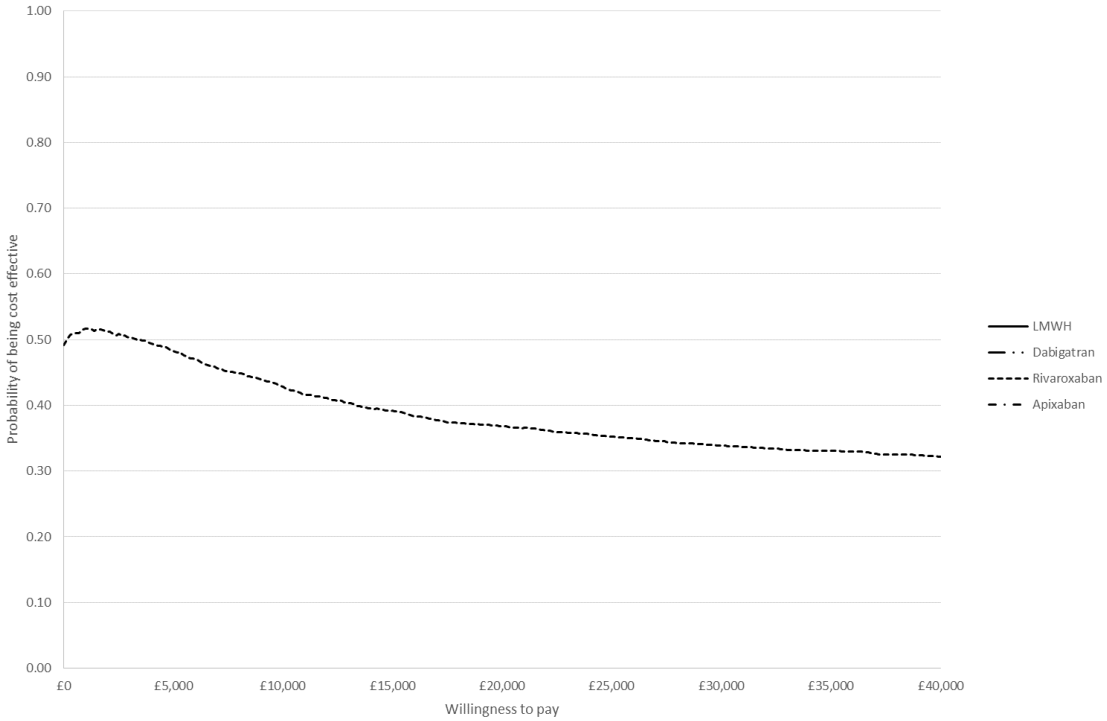
See section 4.5.3 for further details

Figure 190 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: pooling over surgical population for VTE relative treatment effects



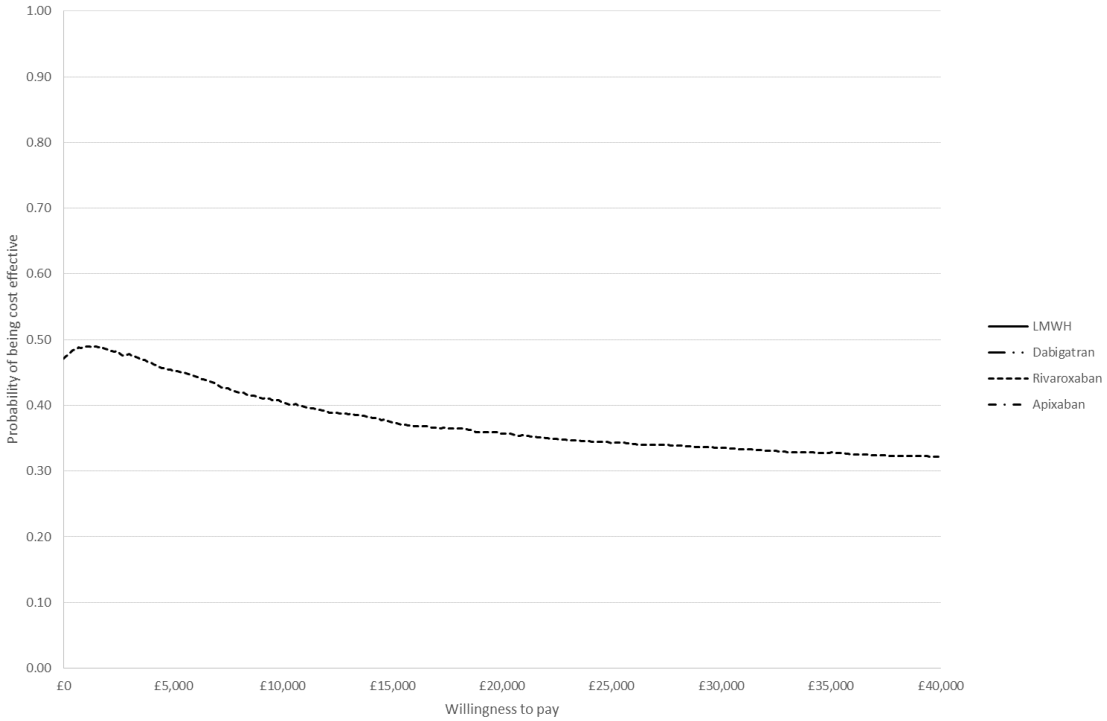
See section 4.5.3 for further details

Figure 191 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: decreasing AE costs by 50%

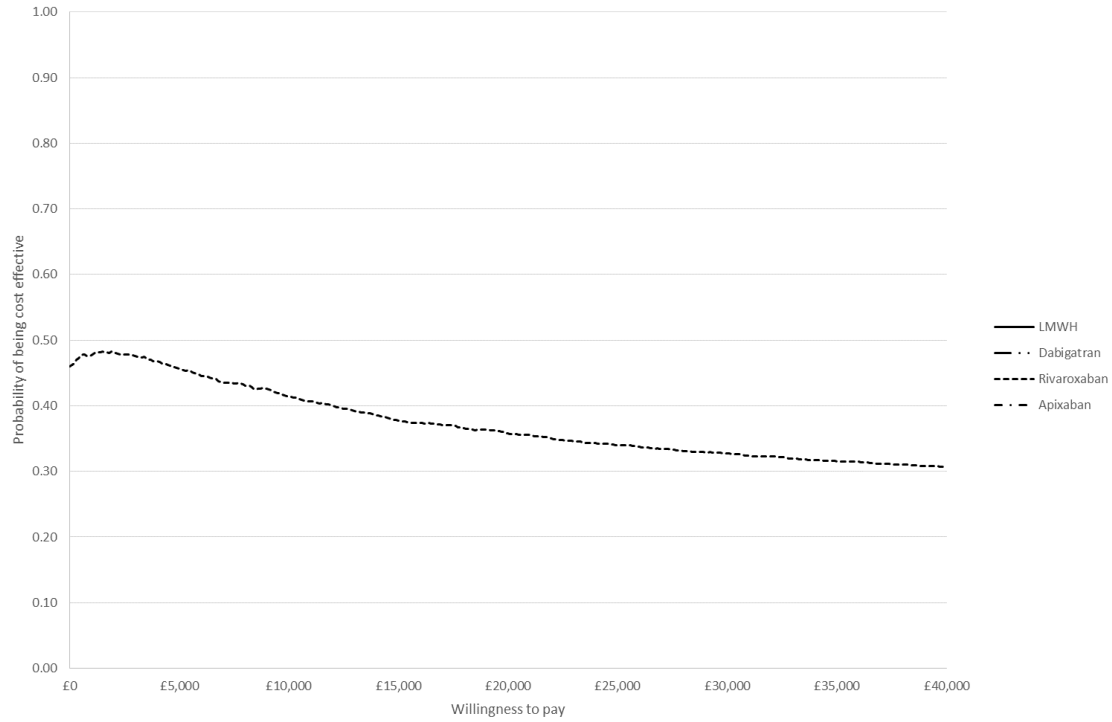


See section 4.5.3 for further details

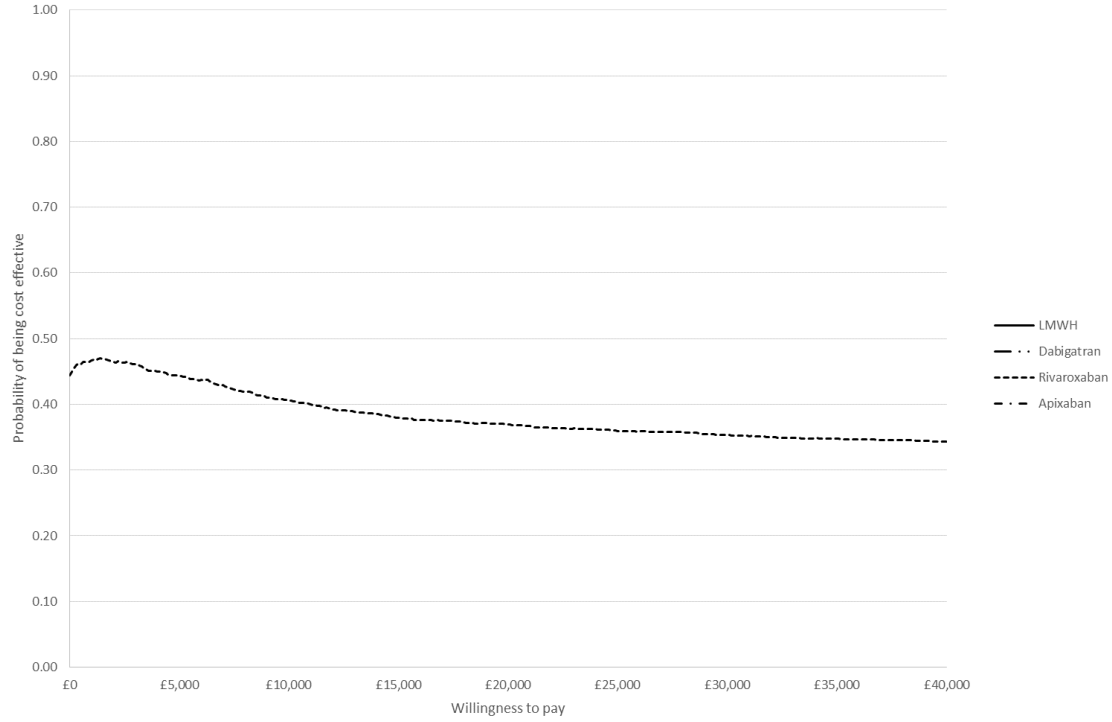
Figure 192 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: decreasing AE utilities by 50%



See section 4.5.3 for further details**Figure 193 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: increasing VTE costs by 50%**

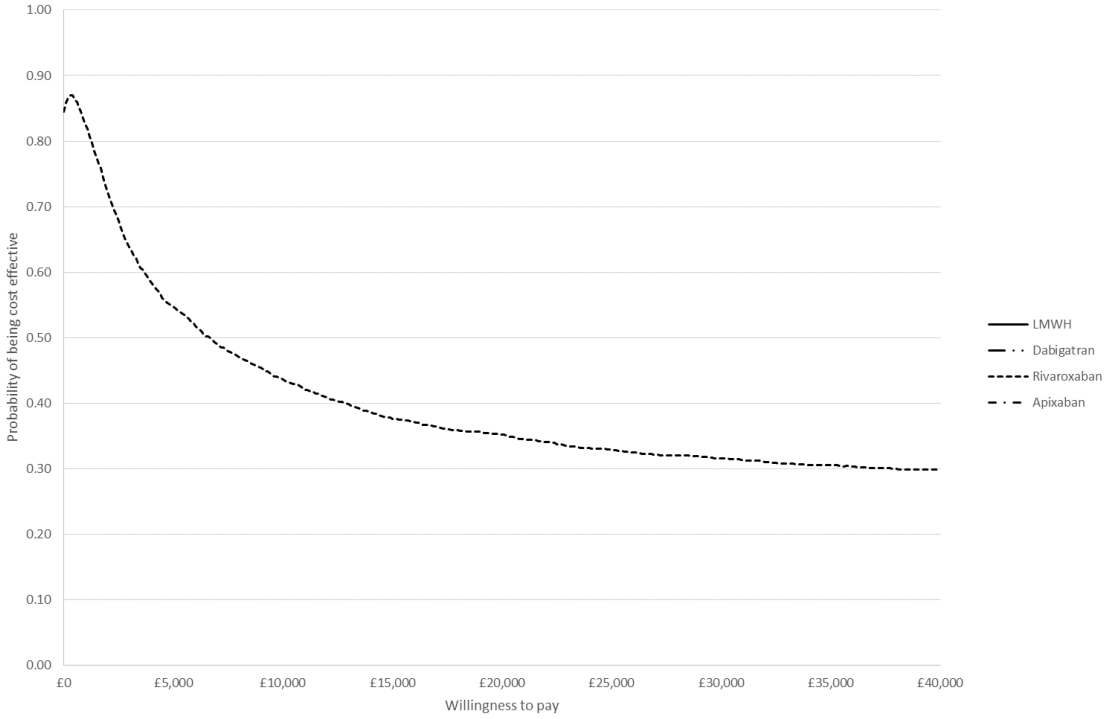


See section 4.5.3 for further details**Figure 194 Cost effectiveness acceptability frontier for TKR primary prevention sensitivity analysis: increasing VTE utilities by 50%**



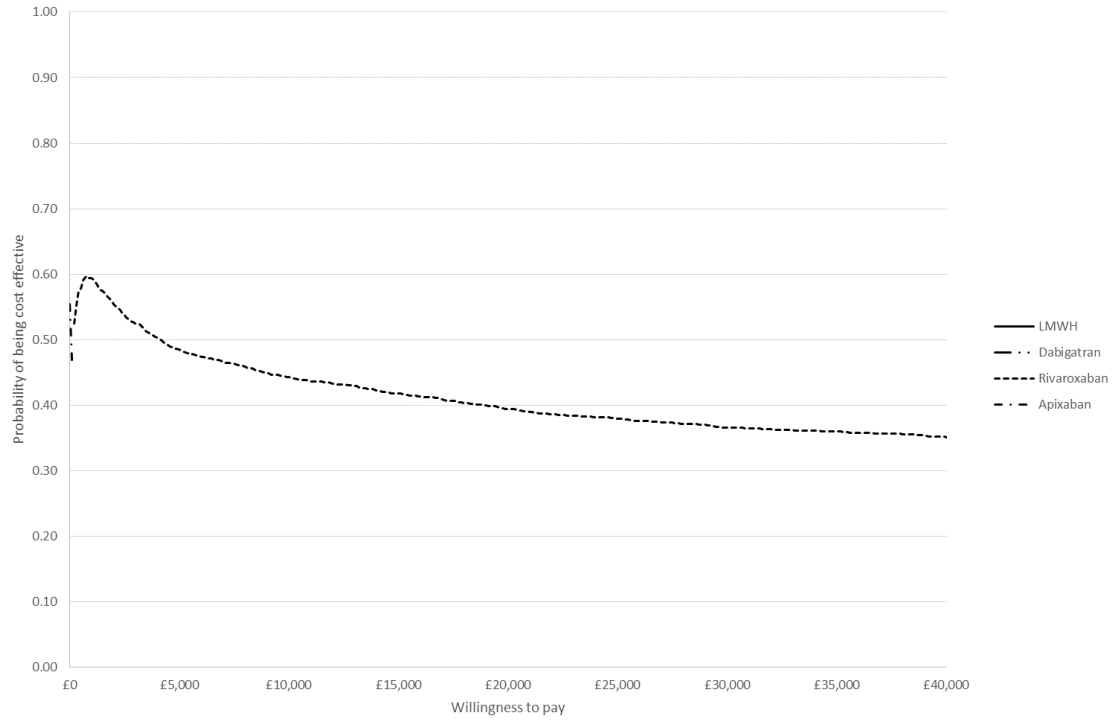
See section 4.5.3 for further detailsPrimary prevention of venous thromboembolism: Post hip replacement surgery

Figure 195 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: pooling post THR and post TKR populations for relative treatment effect of VTE



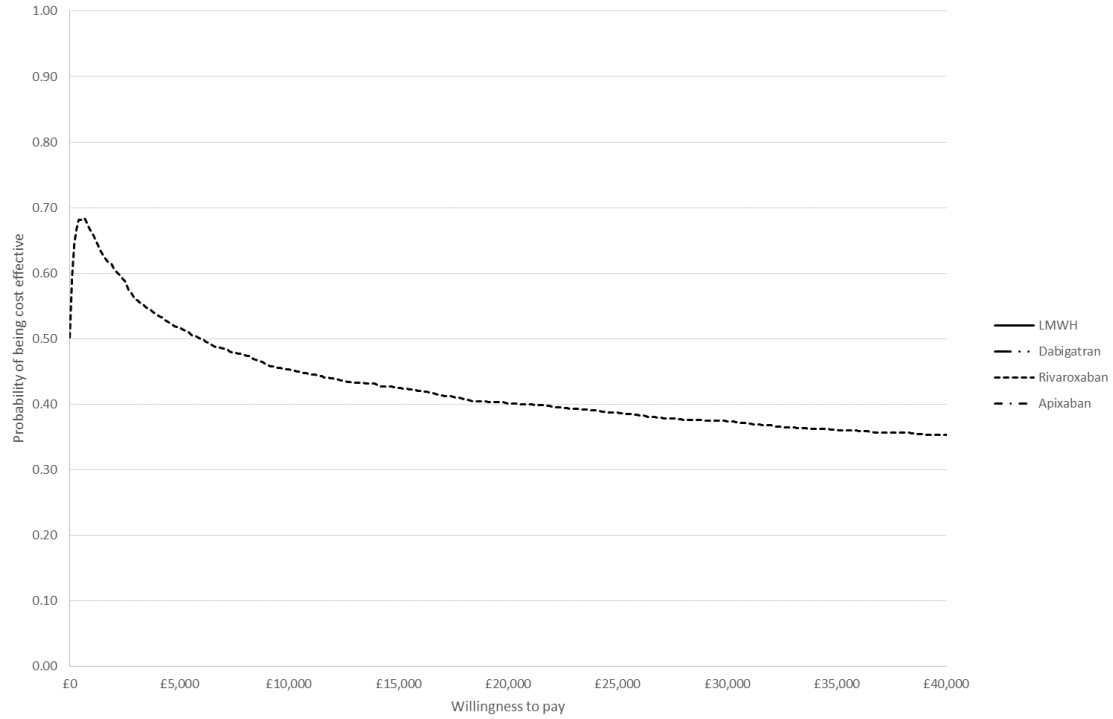
See section 4.5.3 for further details

Figure 196 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: setting the cost of dabigatran to 150mg once daily



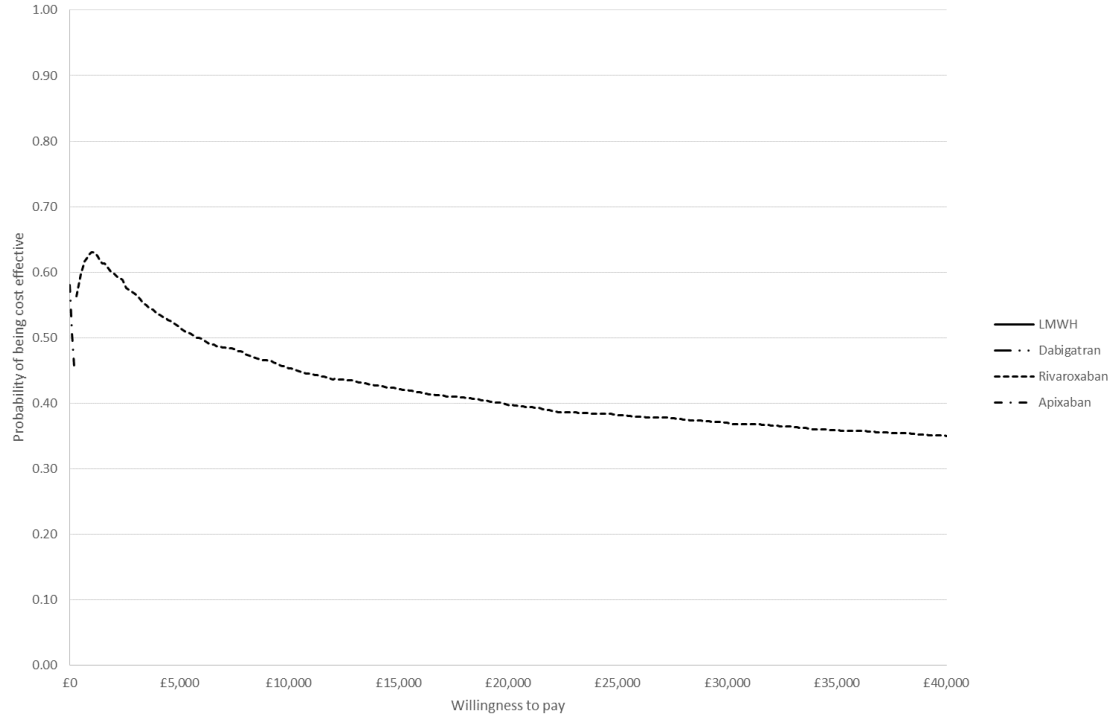
See section 4.5.3 for further details

Figure 197 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: decreasing AE costs by 50%



See section 4.5.3 for further details

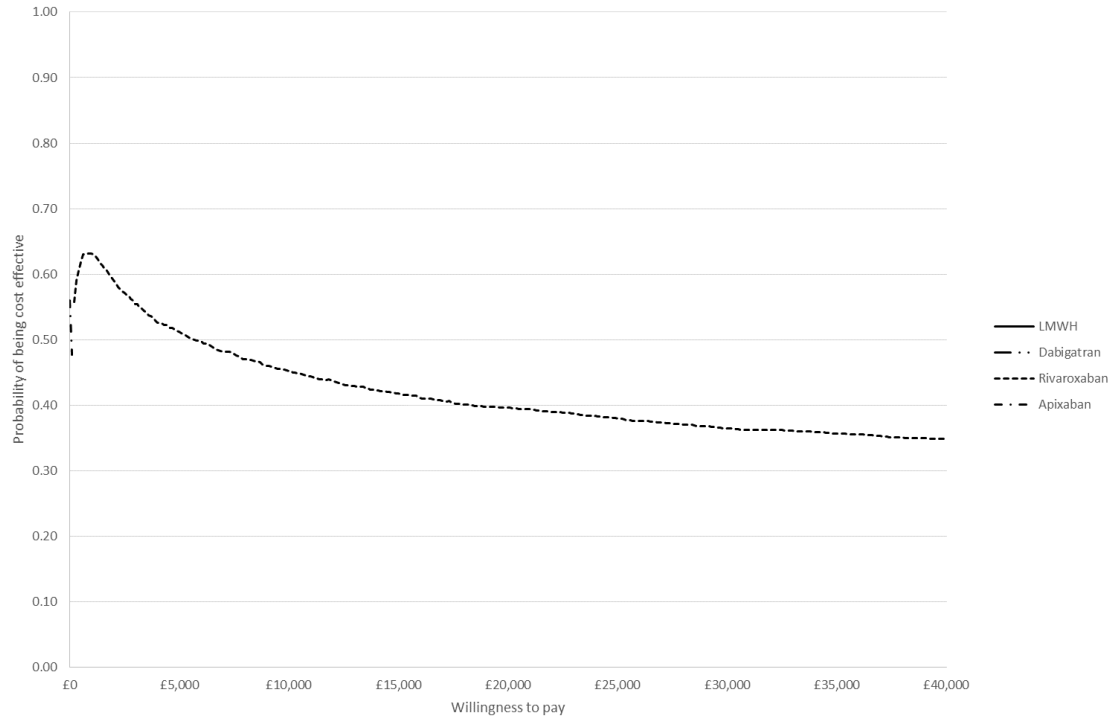
Figure 198 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: increasing AE costs by 50%



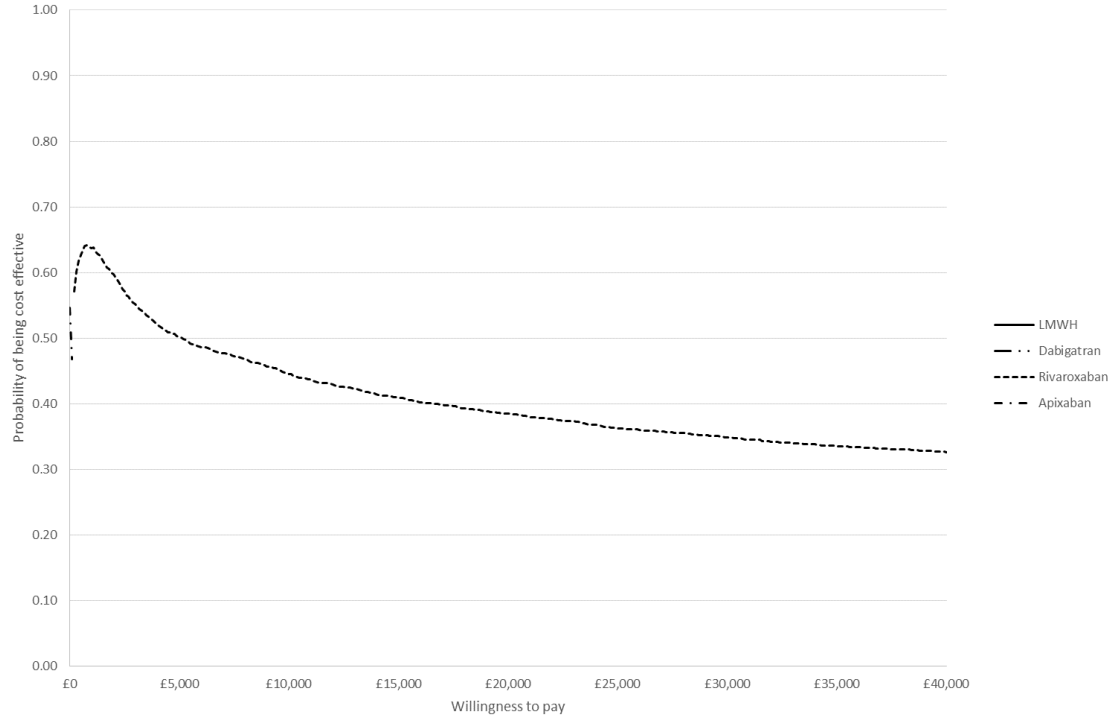
See section 4.5.3 for further details

Figure 199 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: decreasing AE utilities by 50%

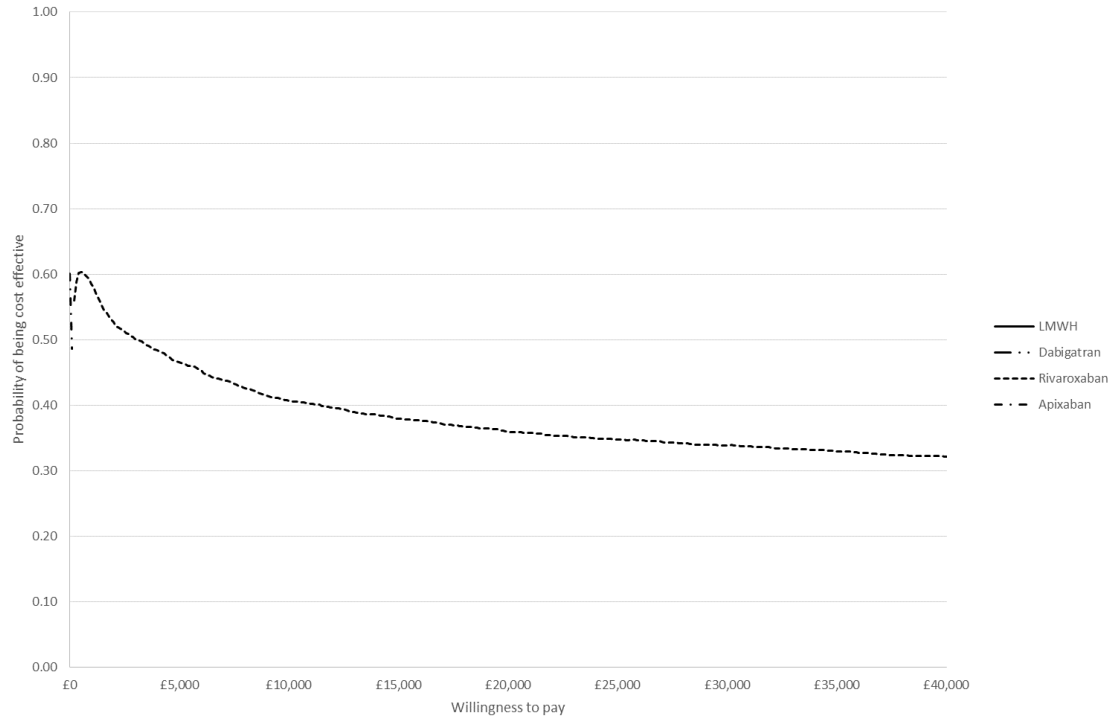
1



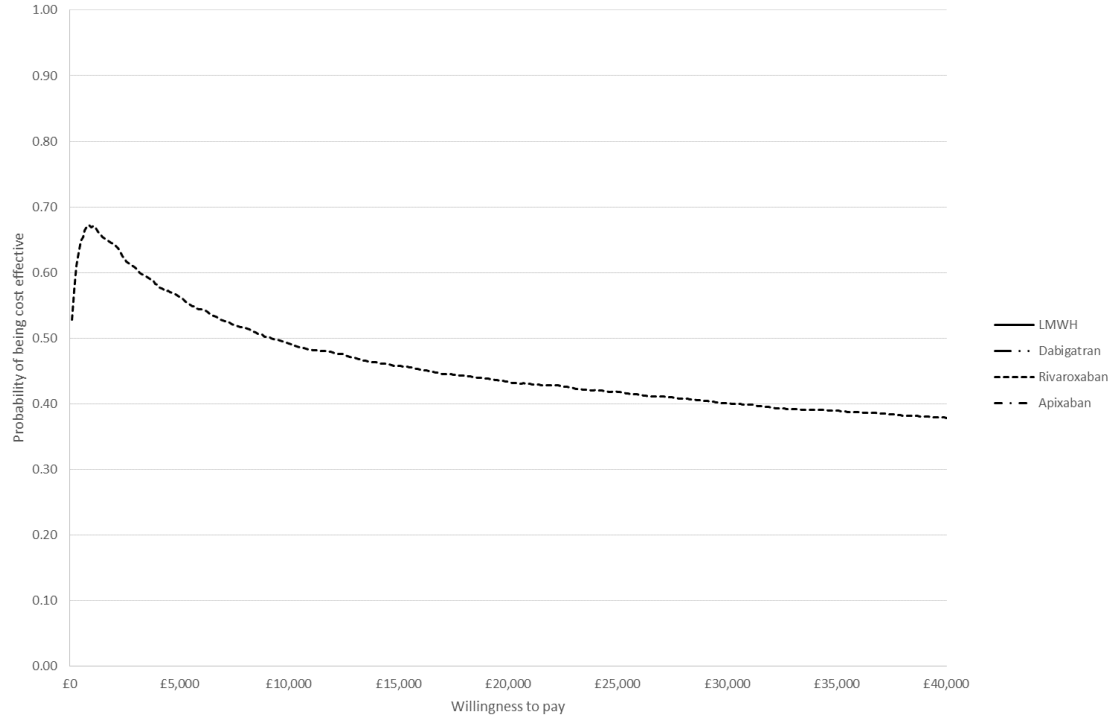
See section 4.5.3 for further details Figure 200 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: increasing AE utilities by 50%



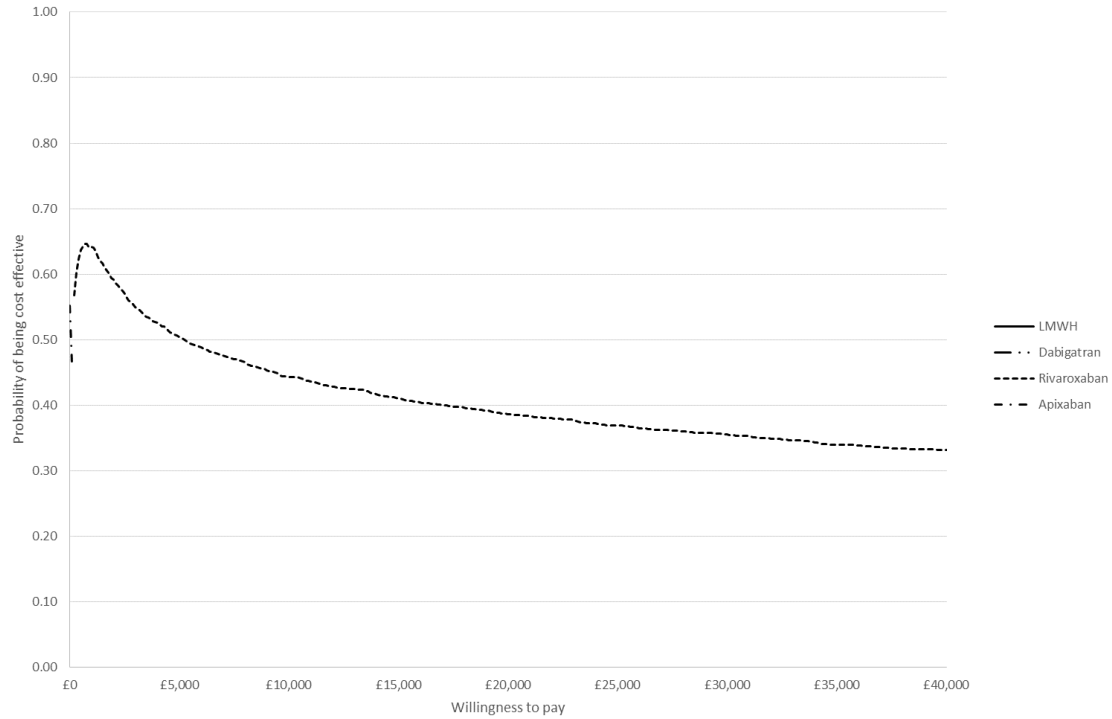
See section 4.5.3 for further details Figure 201 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: decreasing VTE costs by 50%



See section 4.5.3 for further detailsFigure 202 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: increasing VTE costs by 50%

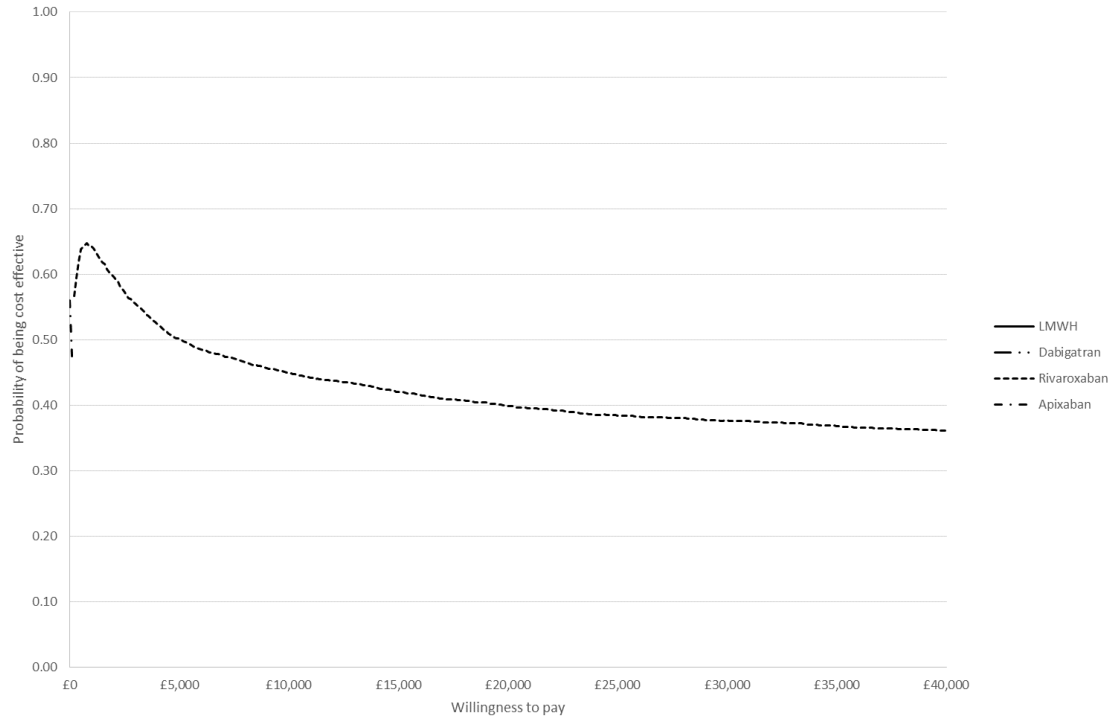


See section 4.5.3 for further detailsFigure 203 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: decreasing VTE utilities by 50%



See section 4.5.3 for further details

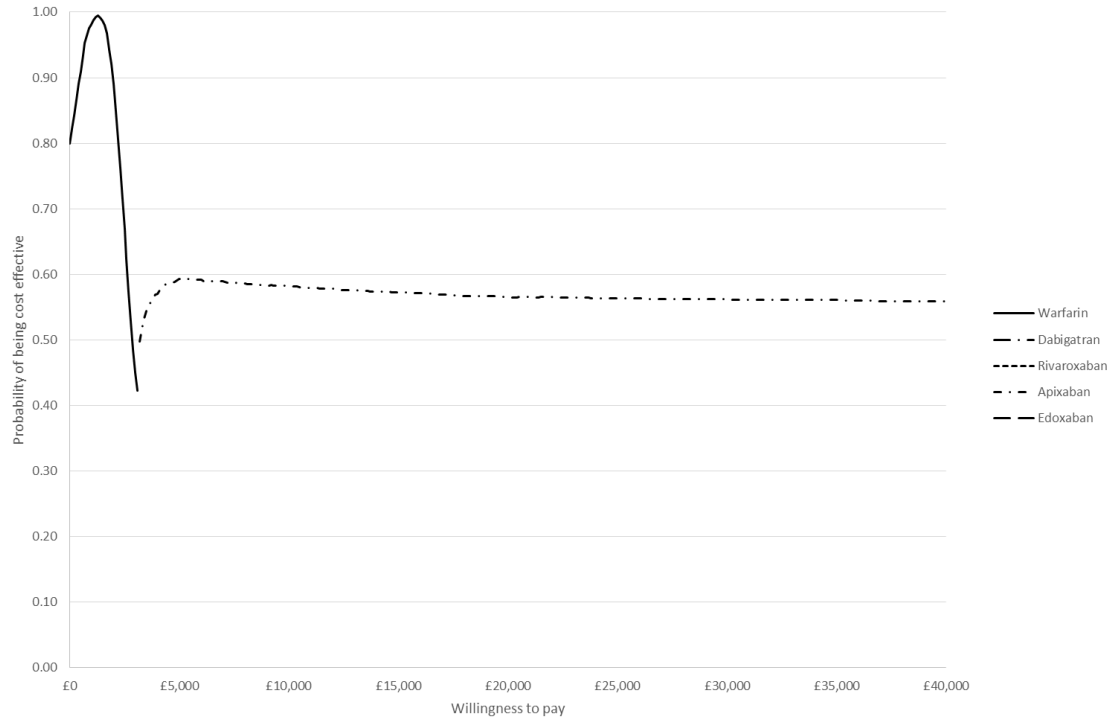
Figure 204 Cost effectiveness acceptability frontier for THR primary prevention sensitivity analysis: increasing VTE utilities by 50%



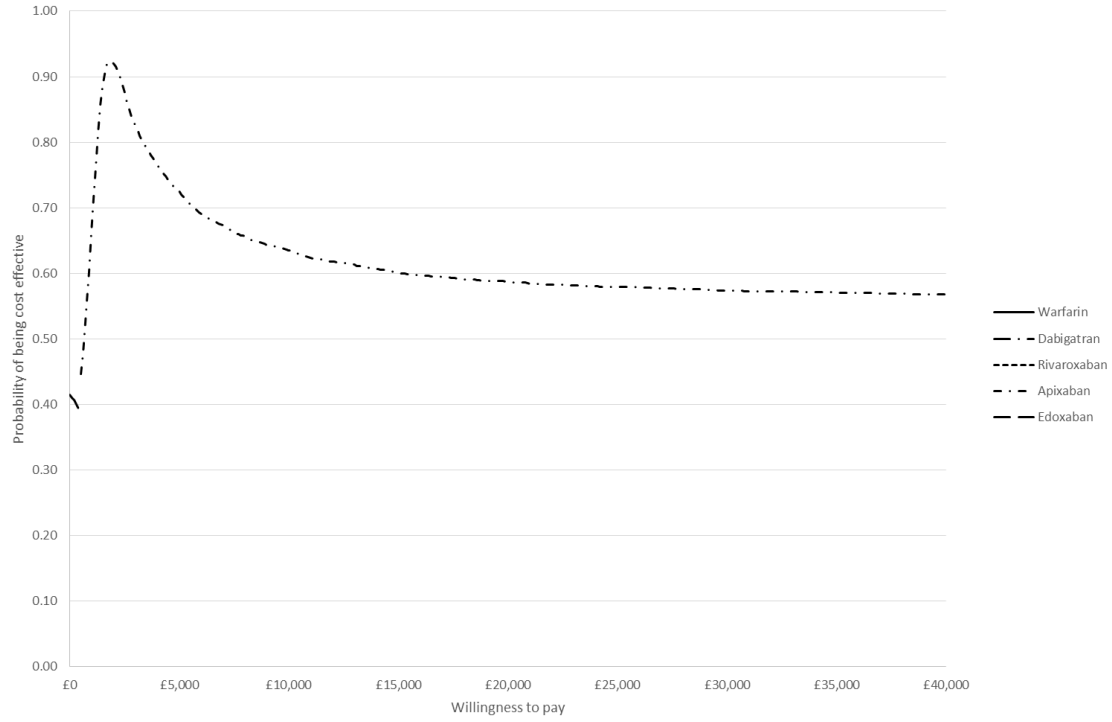
See section 4.5.3 for further details

Acute treatment of venous thromboembolism

Figure 205 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: decreasing AE cost by 50%

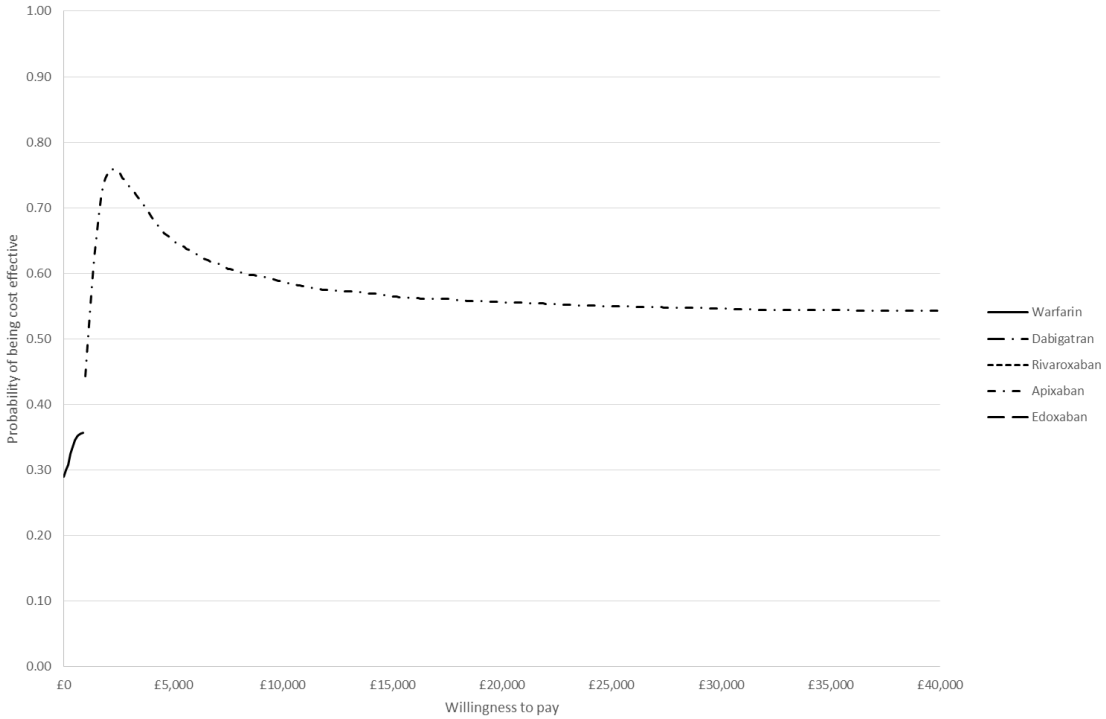


See section 4.5.3 for further details**Figure 206 Cost effectiveness acceptability frontier acute treatment model: increasing adverse event costs by 50%**



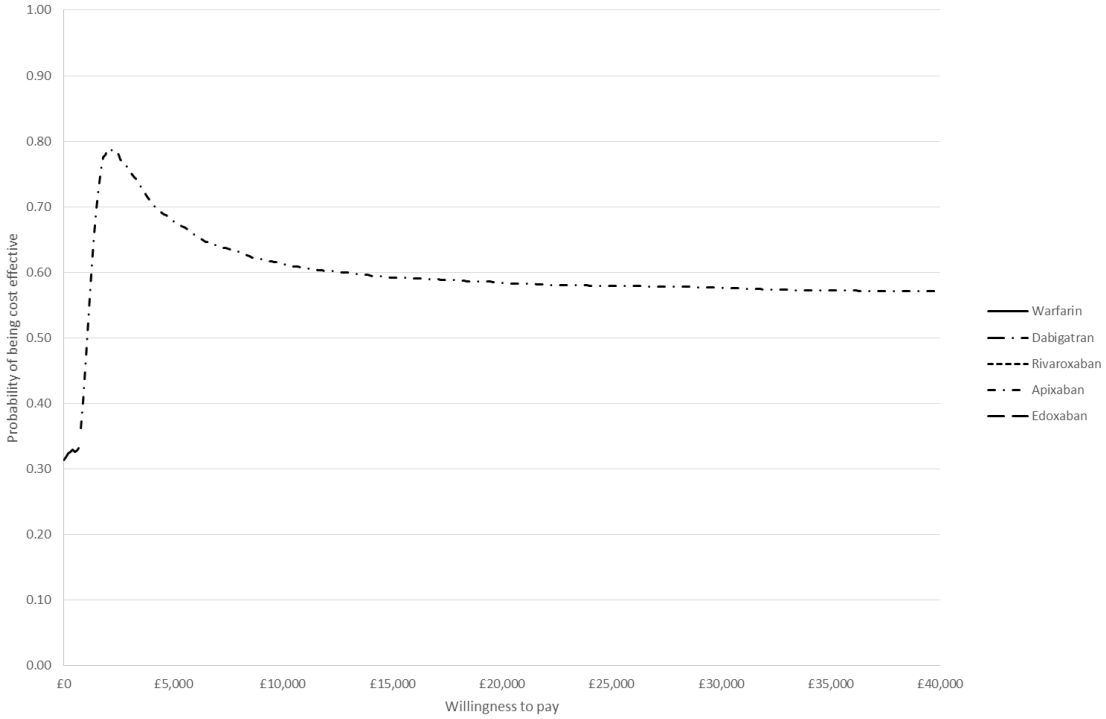
See section 4.5.3 for further details

Figure 207 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: decreasing AE utility by 50%

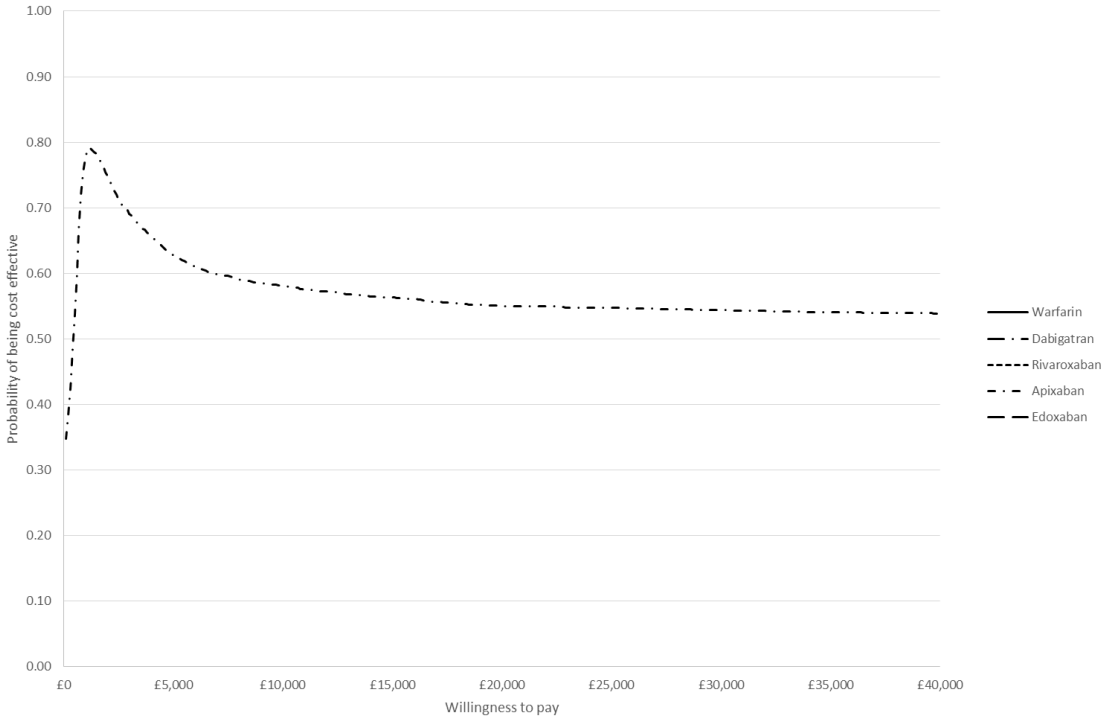


See section 4.5.3 for further details

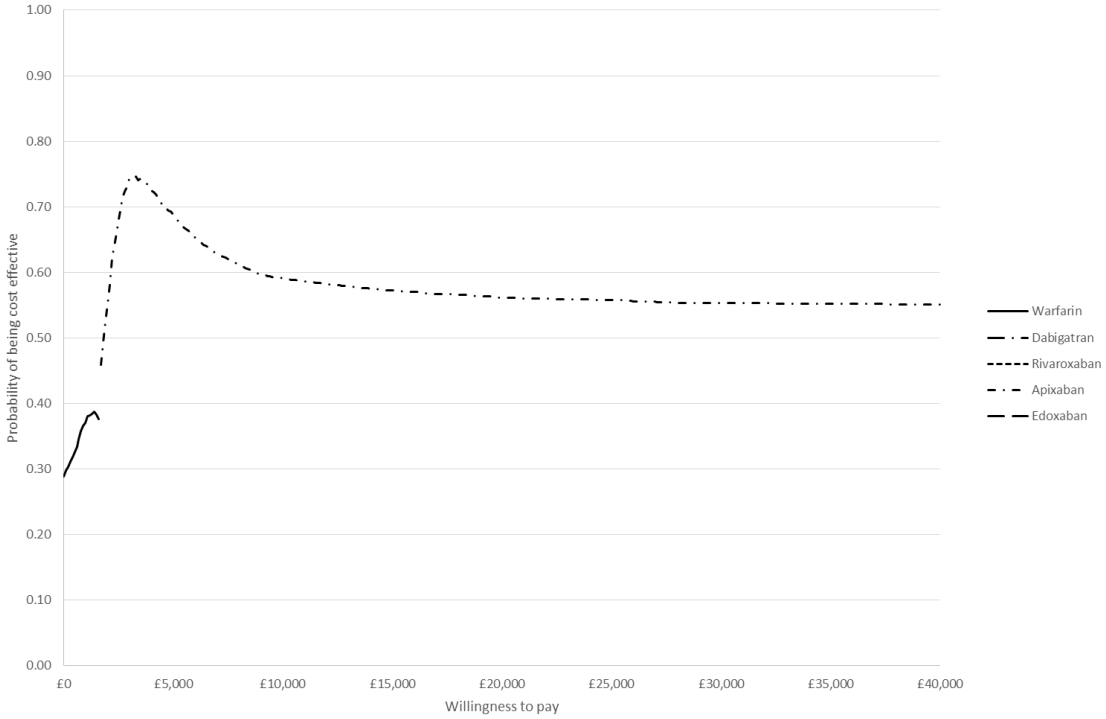
Figure 208 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: increasing AE utility by 50%



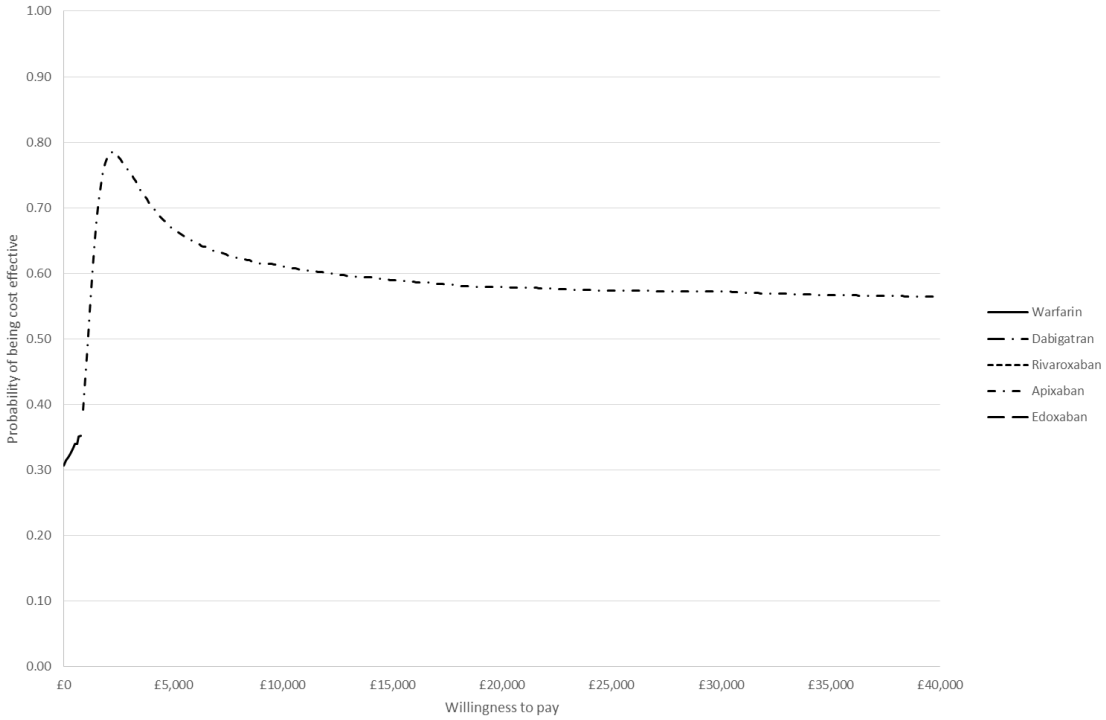
See section 4.5.3 for further details**Figure 209 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: decreasing VTE cost by 50%**



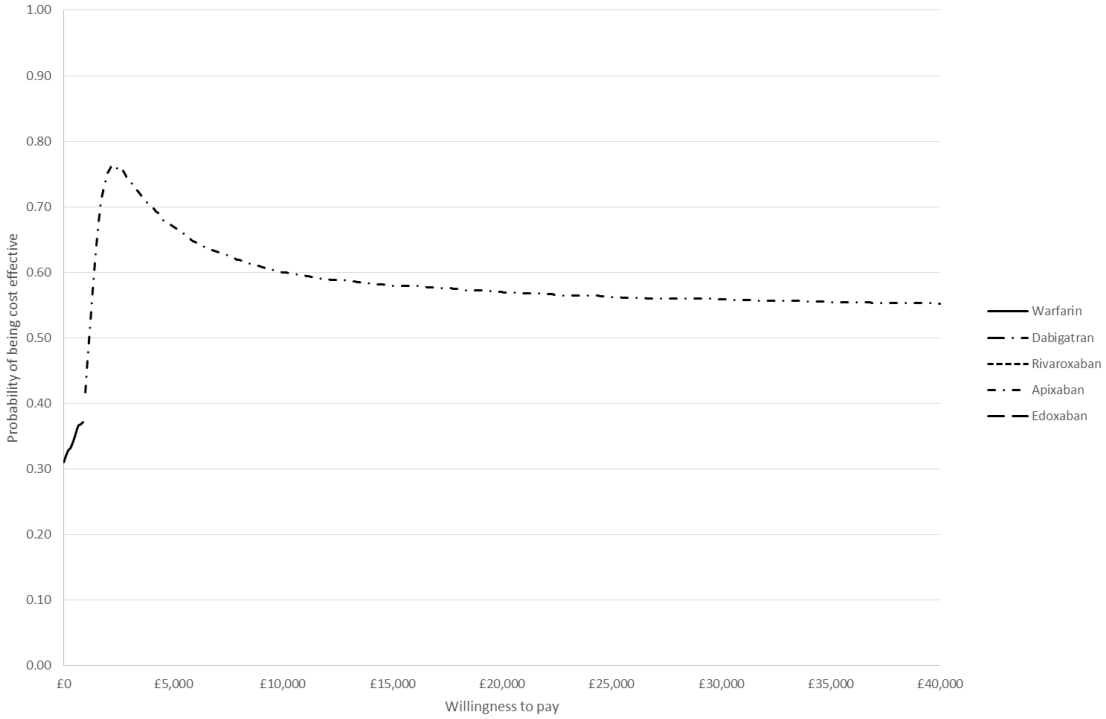
See section 4.5.3 for further details**Figure 210 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: increasing VTE cost by 50%**



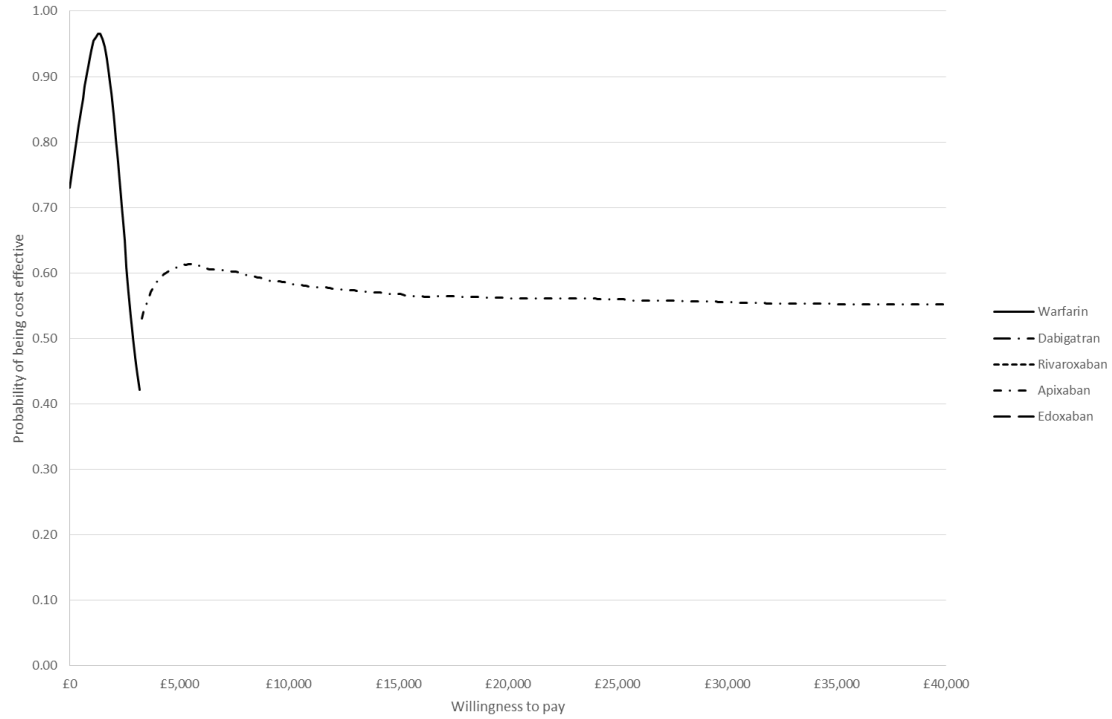
See section 4.5.3 for further details**Figure 211 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: decreasing VTE utility by 50%**



See section 4.5.3 for further details**Figure 212 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: increasing VTE utility by 50%**

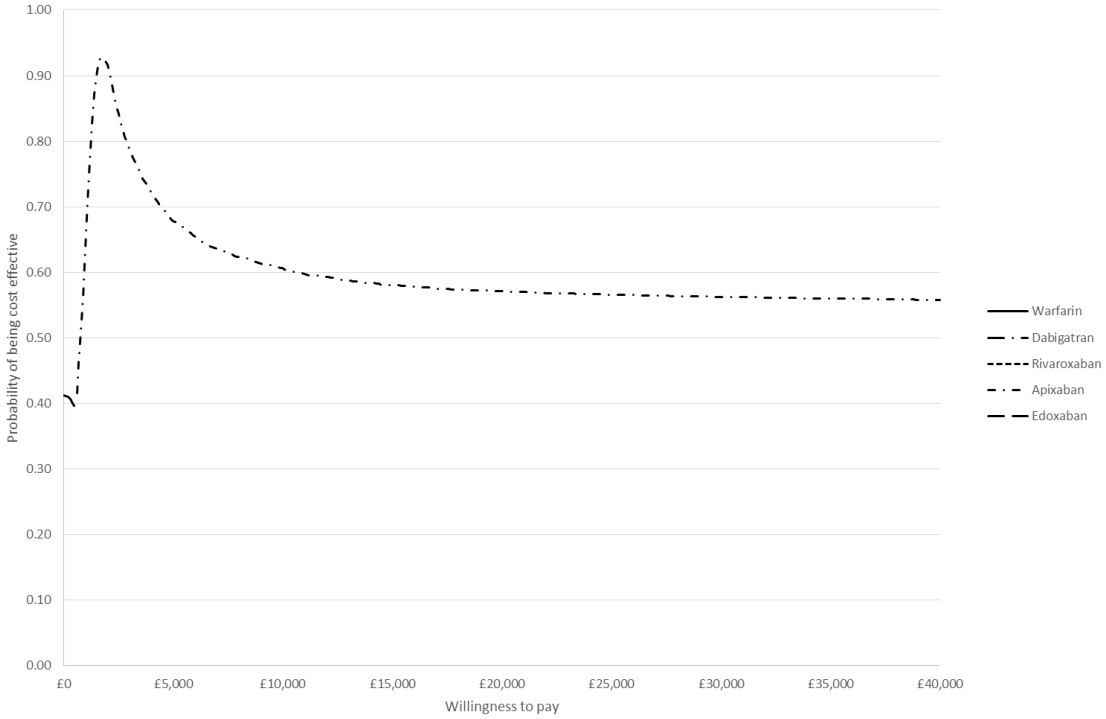


See section 4.5.3 for further details**Figure 213 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: NOACs rate of non-fatal ICH rate equal to warfarin**



See section 4.5.3 for further details

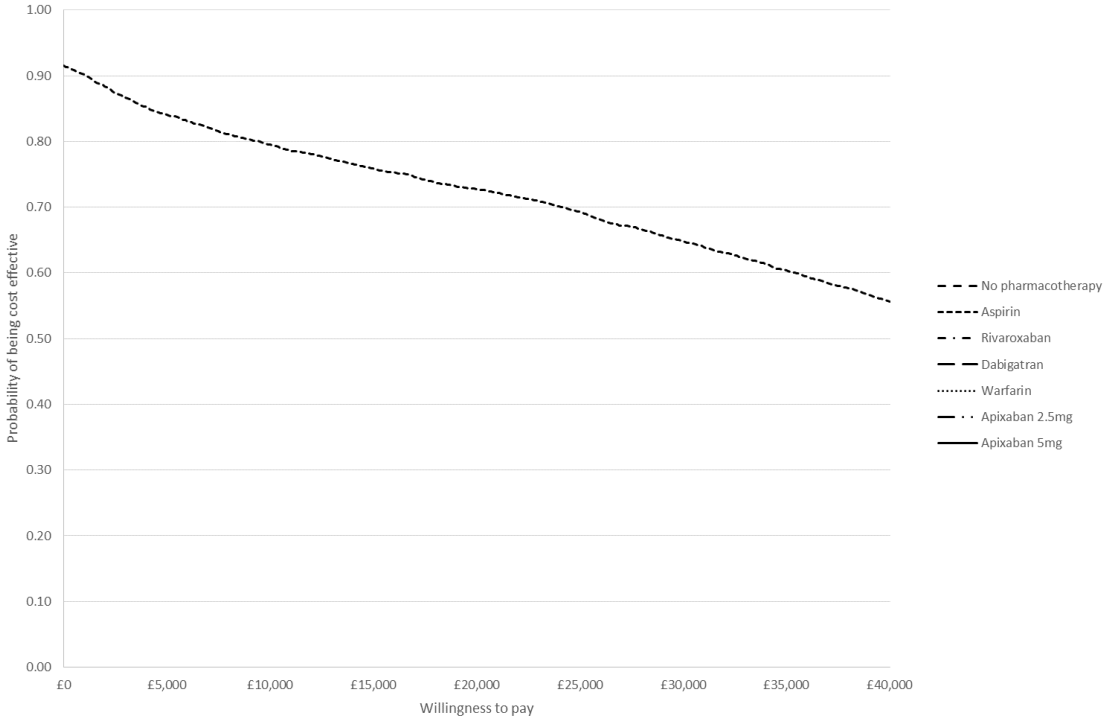
Figure 214 Cost effectiveness acceptability frontier for acute treatment sensitivity analysis: Changing time on treatment from six months to three months



See section 4.5.3 for further details

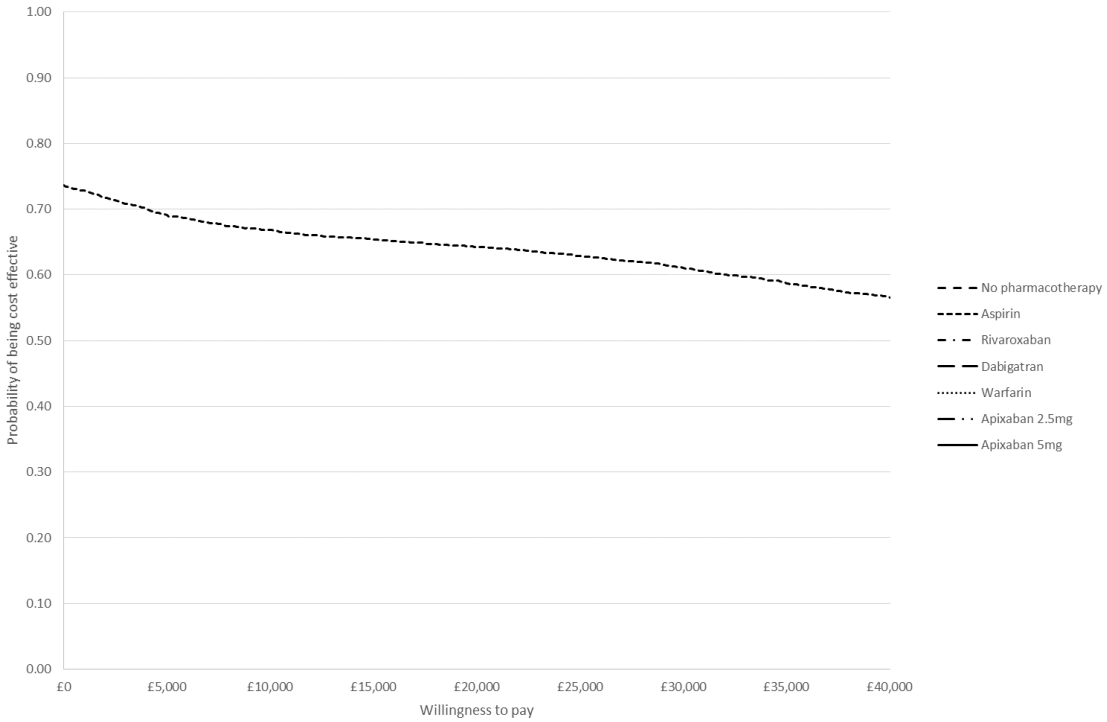
Secondary prevention of venous thromboembolism

Figure 215 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: Patients on no pharmacotherapy and aspirin receive warfarin after a second VTE event

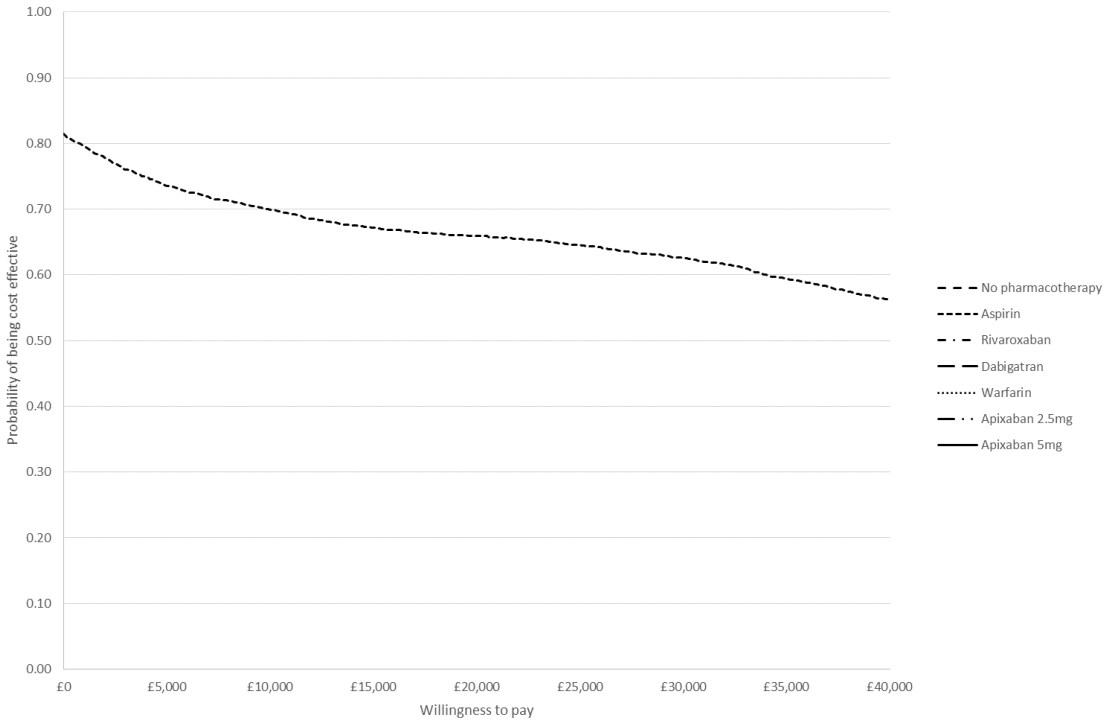


See section 4.5.3 for further details

Figure 216 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: change bleed base rate

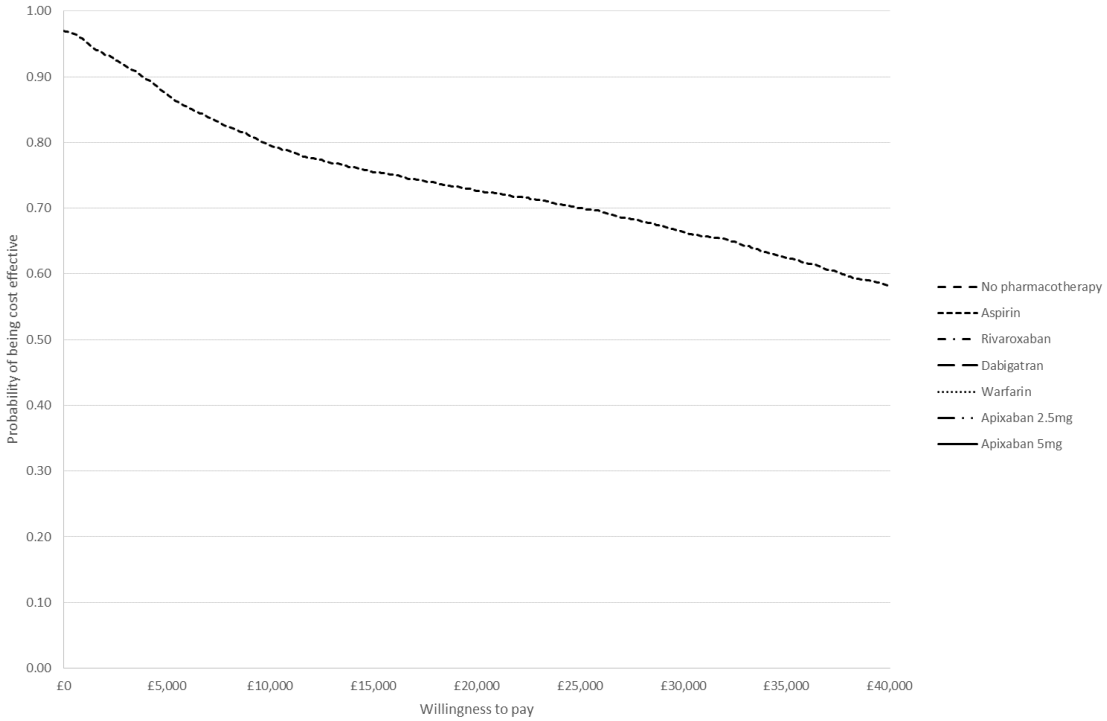


See section 4.5.3 for further details**Figure 217 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: setting the cost of warfarin to £0**

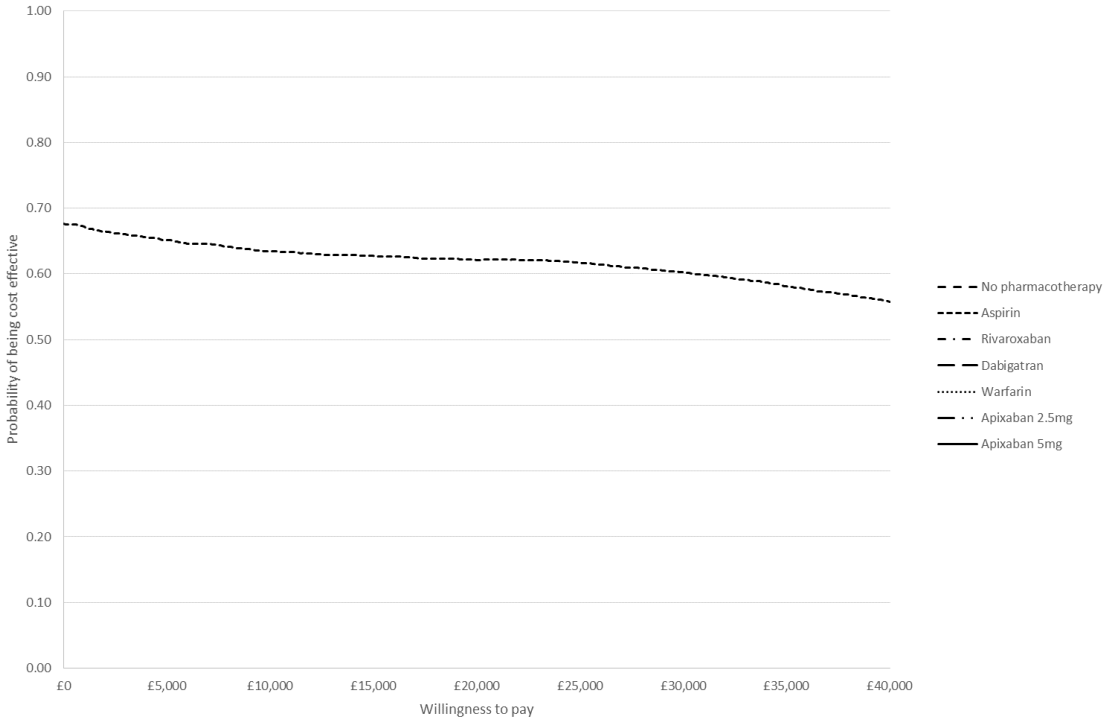


See section 4.5.3 for further details

Figure 218 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: decreasing the AE cost by 50%

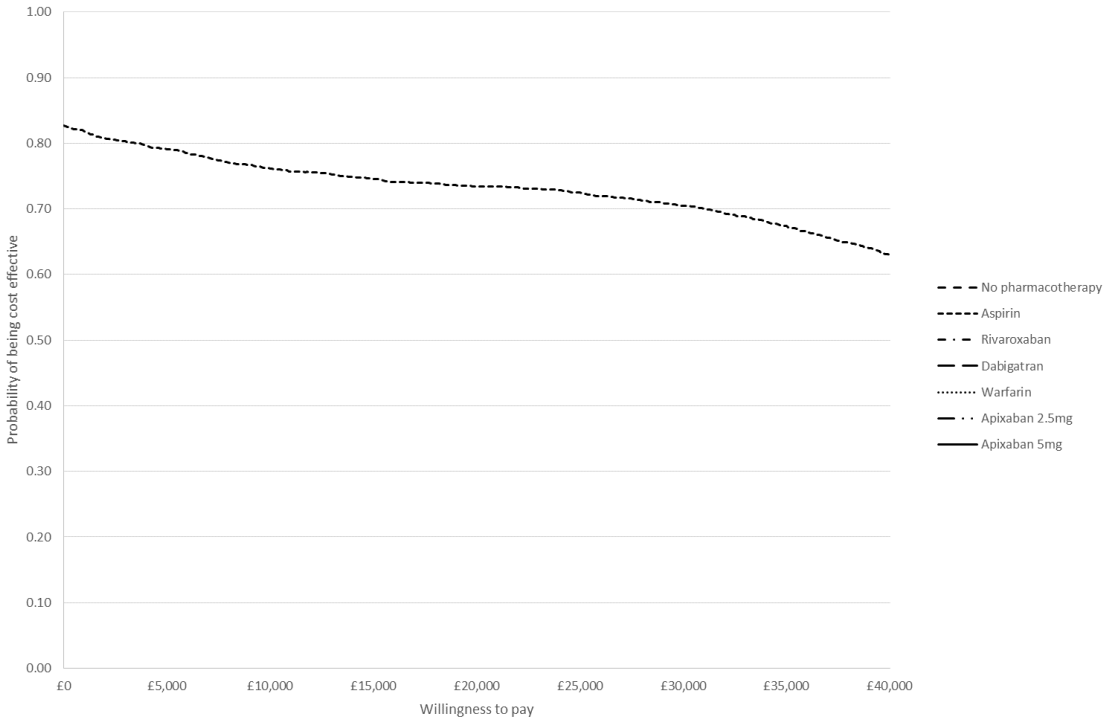


See section 4.5.3 for further details**Figure 219 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: increasing the AE cost by 50%**

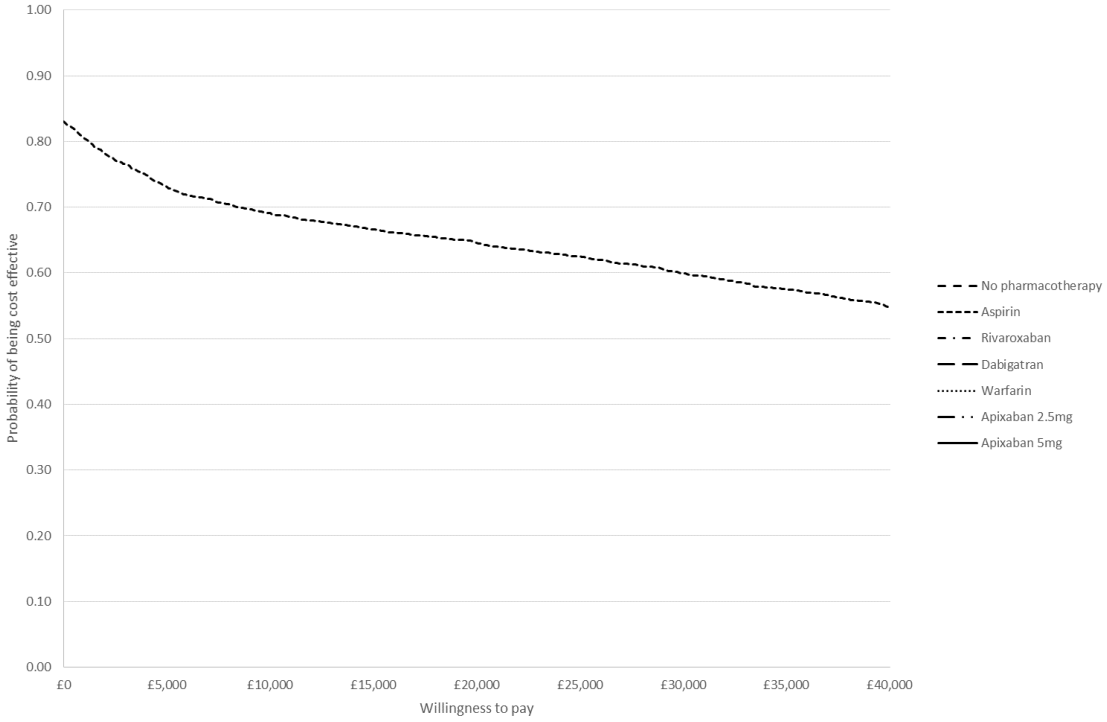


See section 4.5.3 for further details

Figure 220 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: decreasing the AE utility by 50%

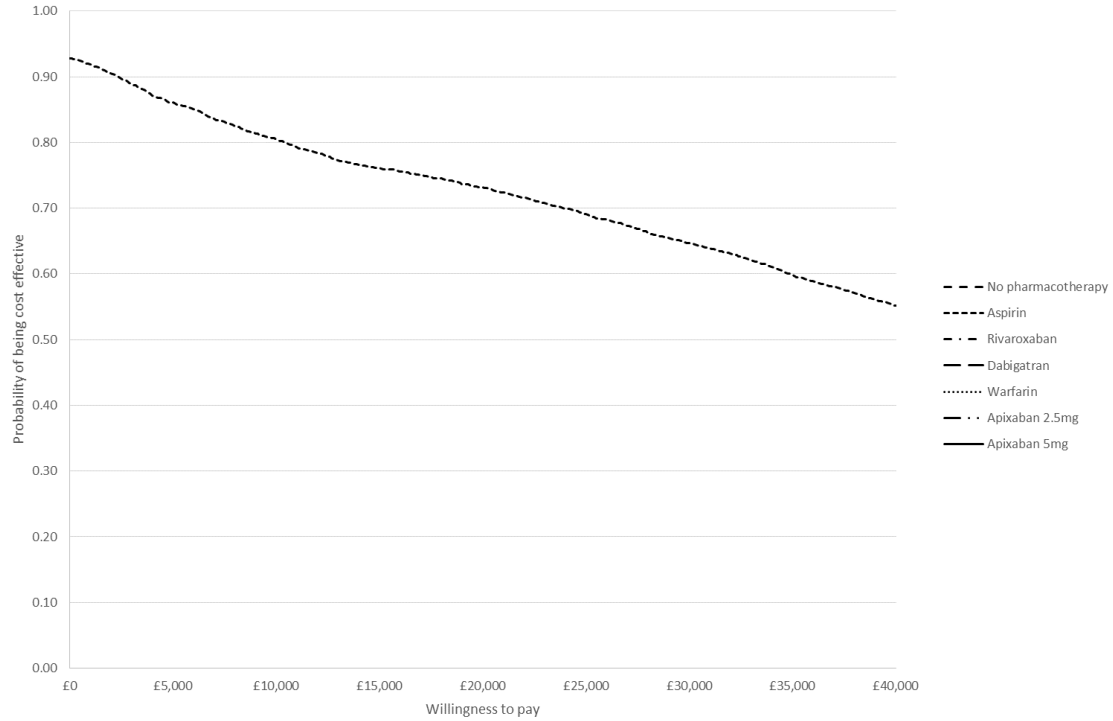


See section 4.5.3 for further details**Figure 221 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: increasing the AE utility by 50%**

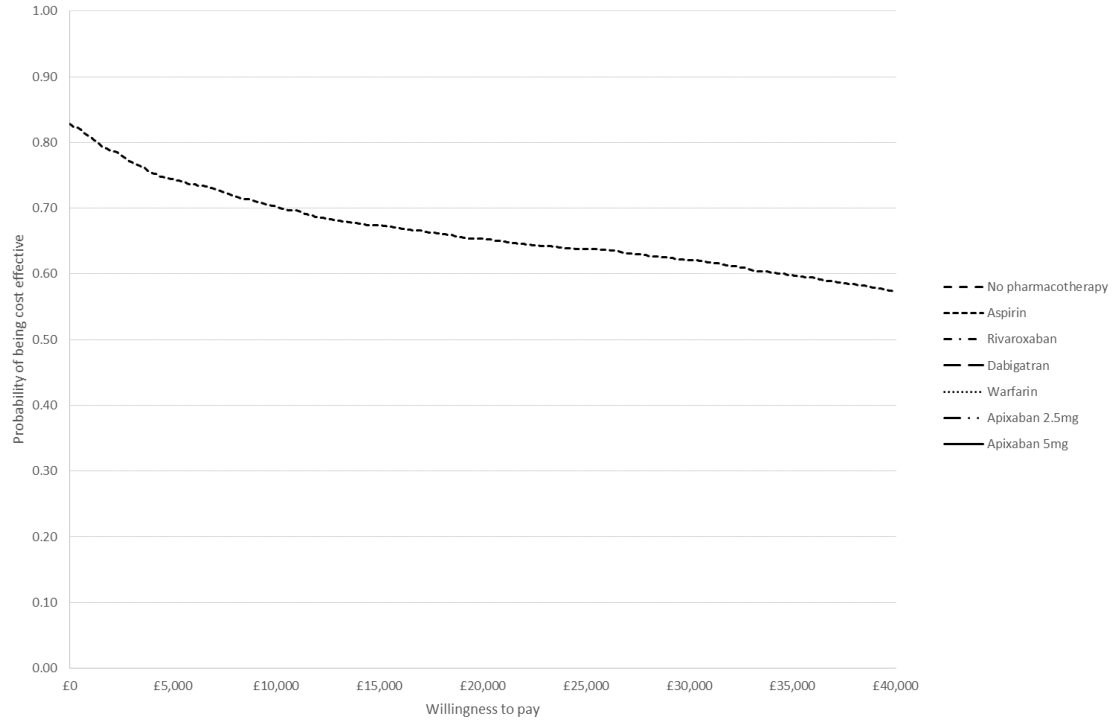


See section 4.5.3 for further details

Figure 222 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: increasing the cost of VTE events by 50%

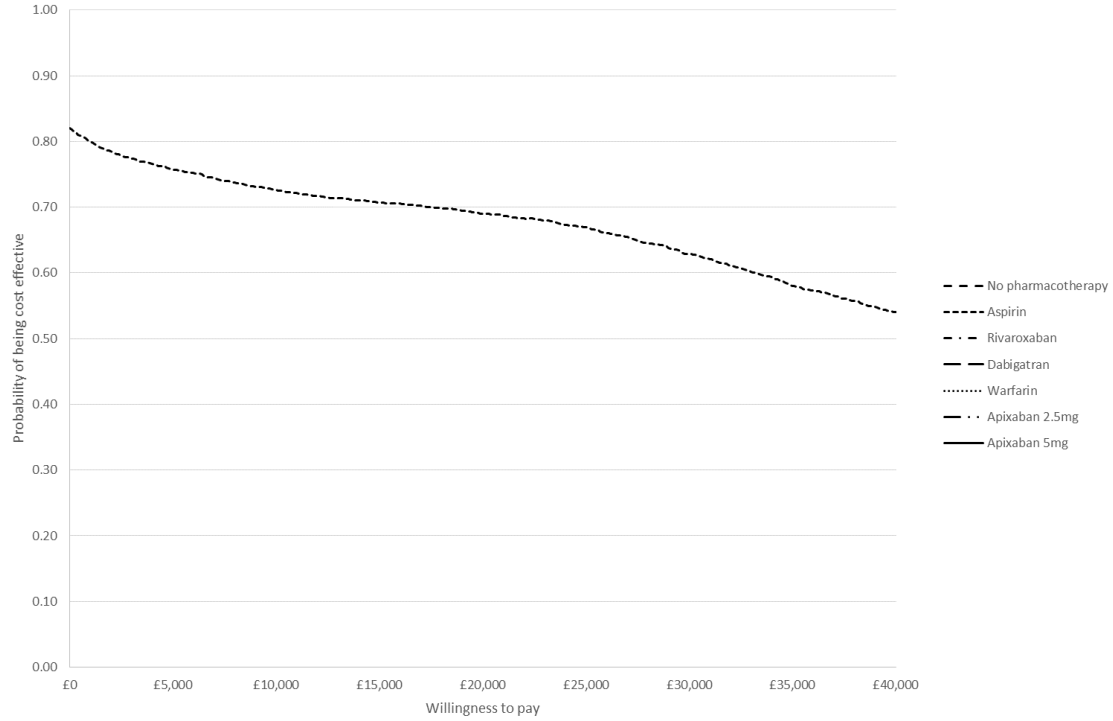


See section 4.5.3 for further details **Figure 223 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: decreasing VTE utility by 50%**



See section 4.5.3 for further details **Figure 224 Cost effectiveness acceptability frontier for secondary prevention sensitivity analysis: increasing VTE utility by 50%**

1



2

3 See section 4.5.3 for further details