National Institute for Health and Care Excellence

Final

Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

[D] Evidence reviews for pharmacological treatment in people with suspected or confirmed deep vein thrombosis and/or pulmonary embolism

NICE guideline NG158

Evidence reviews underpinning recommendations 1.3.1 to 1.3.21, 1.4.1, 1.4.7 to 1.4.11 and research recommendations in the guideline

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Final version

These evidence reviews were developed by the NICE Guideline Updates Team

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1. What is the clinical and cost effectiveness of different pharmacological treatments for people with suspected DVT prior to confirmed diagnosis?

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Introduction

DVT is thrombus in the venous system of the leg. Early complications may include inflammation and pulmonary embolism (PE) whilst late complications include circulation problems such as post-thrombotic syndrome (PTS). Pulmonary embolism (PE) requires immediate treatment because it can be life-threatening. Additionally, it is associated with serious comorbid conditions such as chronic thromboembolic pulmonary hypertension (CTEPH).

In suspected cases of DVT or PE, treatment with anticoagulants is often given in the interim period between initial presentation (based on a composite of symptoms, personal history, an initial D-dimer test and/or evaluation of Wells' criteria) and confirmatory diagnostic tests. The standard of care in patients suspected of having a venous thromboembolism has been the use of low molecular weight heparin. However, with the recent development of direct-acting oral anticoagulants (DOACs), alternative therapies may be considered. This review aims to determine which pharmacological treatment(s) are the most clinical and cost effective for people with suspected PE or DVT. It identified studies that fulfilled the conditions specified in Table 1 and Table 2. For full details of the review protocol, see appendix A.

PICO tables

Table 1 PICO for pharmacological treatment of suspected DVT

Population	Adults (18+ years) with suspected DVT Suspected DVT is defined as DVT suspected on the basis of clinical symptoms and/or D-dimer test, but before confirmation by ultrasound imaging or equivalent.
Intervention	• Apixaban • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) Note that intravenous LMWH will not be included. • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasaccharides
Comparator	• To each other • Placebo/no treatment
Outcomes	• All-cause mortality • VTE-related mortality • Length of hospital stay • Quality of life

	○ Generic and disease-specific measures will be reported ○ Overall score will be reported (data on subscales will not be reported) • Adverse events ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis) ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis) ○ Intracranial haemorrhage ○ Liver injury ○ Heparin induced thrombocytopenia

Table 2 PICO table for pharmacological treatments for suspected PE.

Population	Adults (18+ years) with suspected PE Suspected DVT is defined as PE suspected on the basis of clinical symptoms and/or D-dimer test, but before confirmation by CTPA or equivalent.
Intervention	• Apixaban • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) Note that intravenous LMWH will not be included. • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides
Comparator	• To each other • Placebo/no treatment
Outcomes	• All-cause mortality • VTE-related mortality • Length of hospital stay • Quality of life ○ Generic and disease-specific measures will be reported ○ Overall score will be reported (data on subscales will not be reported) • Adverse events ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis) ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis) ○ Intracranial haemorrhage ○ Liver injury ○ Heparin induced thrombocytopenia

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in Appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviation

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the 2012 NICE VTE guideline (CG144). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews (SRs) was conducted for this review and the accompanying review on the effectiveness of pharmacological treatments for confirmed venous thromboembolism. This returned 9,318 references (see appendix C for literature search strategy). Based on title and abstract screening against the review protocol 9,023 references were excluded, and 295 references were ordered for screening based on their full texts.

Of the 295 references screened as full texts, 0 references met the inclusion criteria specified in the review protocol for this question (appendix A). The clinical evidence study selection is presented as a diagram in appendix D.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened on title and abstract. Four references were identified for pharmacological treatment for suspected and confirmed VTE but none of these met the criteria for inclusion in this review for suspected VTE.

Excluded studies

See appendix M for a list of references for excluded studies, with reasons for exclusion and appendix N for the full references.

Economic evidence

A systematic search was carried out to cover all questions within this evidence review. The search returned 3,811 records. In addition, 8 papers were identified from the 2012 guideline. Of these records, 3,811 were excluded based on the basis of title and abstract. The remaining 8 papers were inspected in full and found not to be relevant to this review question. The excluded references are listed, with reasons for their exclusion, in appendix M and as full references in appendix N

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single rerun search covering all questions in the guideline. This search returned 2,013 records in total, all of which were excluded on title and abstract for this review question.

Economic model

It was anticipated that the amount of evidence informing the best pharmacological agent to treat individuals awaiting a formal VTE diagnosis would be insufficient to allow for formal

economic modelling. Also, because interim treatment is typically provided for a short period (24 hours), recommendations would most likely not have a significant resource impact. It was also the committee's opinion that recommendations resulting from this review question would likely be based on clinical and economic evidence on pharmacological treatments in patients with confirmed VTE, as well as practical considerations (i.e. some treatments may be more appropriate than others for delivery over a short time period). Therefore, no economic modelling was undertaken specifically in people with suspected DVT or PE; the economic model for people with confirmed DVT or PE is described below.

Evidence statements

Clinical evidence statements

No relevant evidence was identified for this review question.

Economic evidence statements

No relevant economic evidence was identified for this review question.

Pharmacological treatments for confirmed venous thromboembolism (VTE)

Review question

3. What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of DVT?

4. What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of PE?

Introduction

DVT is thrombus in the venous system of the leg. Early complications may include inflammation and pulmonary embolism (PE) whilst late complications include circulation problems such as post-thrombotic syndrome (PTS). Pulmonary embolism (PE) requires immediate treatment because it can be life-threatening. Additionally, it is associated with serious comorbid conditions such as chronic thromboembolic pulmonary hypertension (CTEPH).

The standard of care for the treatment of DVT has been the use of a combination of low-molecular-weight heparin (LMWH) and Warfarin. LMWH is typically administered subcutaneously for 5-7 days and has the potential for outpatient administration. Warfarin therapy is typically initiated during or immediately after the immediate LMWH phase and is administered orally.

Although warfarin is administered orally, it requires frequent monitoring - which can be done in a clinic or using self-monitoring, or a combination of both - to ensure that the person's international normalised ratio (INR) is within a specified range. Recently, several direct-acting oral anticoagulants (DOACs) have become available (rivaroxaban, apixaban, edoxaban and dabigatran) which do not require monitoring to confirm therapeutic anticoagulation. This development has the potential to improve the convenience of treatment for people with a VTE and, as a result, improve quality of life.

Anticoagulants prevent clot formation by interrupting the coagulation cascade. This mode of action leads to an increased risk of bleeding, including intracranial bleeding, which can adversely impact quality of life and can be fatal in some cases. Therefore, any decision about treatment must balance these benefits and harms, and the importance that the person with VTE places on each of them.

The initial treatment period for acute VTE is typically 3 months in duration. After this time the aim of therapy changes from treatment to secondary prevention of further VTE events and a decision is made about whether the individual would benefit from receiving extended medication.

This review aims to determine which pharmacological treatment(s) are the most clinical and cost effective for people with confirmed PE or DVT for both the initial treatment of acute VTE and for extended therapy when it is required. It identified studies that fulfilled the conditions specified in Table 3 and Table 4. For full details of the review protocol, see appendix A.

PICO tables

Table 3 PICO table for pharmacological treatments for people with confirmed DVT.

Population	Adults (18+ years) with confirmed DVT
Intervention	• Edoxaban • Apixaban • Dabigatran • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) - Note that intravenous LMWH will not be included as it is not licensed in the UK • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides • Vitamin K antagonists • Aspirin (extended therapy only) Combinations of treatments (simultaneous and sequential) will be considered.
Comparator	• To each other • Placebo/no treatment

Outcomes	• All-cause mortality
	• VTE-related mortality
	• Length of hospital stay
	• Post-thrombotic syndrome
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury
	  ○ Heparin induced thrombocytopenia

Table 4 PICO table for pharmacological treatments for people with confirmed PE.

Population	Adults (18+ years) with confirmed PE
Intervention	• Edoxaban • Dabigatran • Apixaban • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) Note that intravenous LMWH will not be included. • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides • Vitamin K antagonists • Aspirin (extended therapy only)

Comparator	• To each other • Placebo/no treatment

Outcomes	• All-cause mortality
	• VTE-related mortality
	• Length of hospital stay
	• Quality of life
	• Chronic thromboembolic pulmonary hypertension
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury
	  ○ Heparin induced thrombocytopenia

Methods and process

This evidence review was developed using the methods and process described in developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A and the methods section in Appendix B.

This review involved the use of Network Meta-Analyses (NMAs) to help determine the most effective treatments for the initial and extended time periods because:

- there are multiple treatment options for both initial treatment and extended therapy of VTE and the committee wanted to investigate the relative effectiveness of these treatments
- there was an absence of clinical trials that directly compared the DOACs
- the use of NMAs would allow indirect comparisons of effectiveness of all treatment options.

Numerous published NMAs were identified during screening, however, it was decided that none of these was completely suitable for use by the committee. This was typically due to the analyses only reporting a limited number of outcomes (usually VTE-recurrence and Major-bleeding only), a limited number of drug comparisons or the absence of recently published studies. As a result, a series of NMAs (with a novel economic model) were carried out by NICE to help inform decision making.

This review adopted the following additional definitions, key outcomes and methods:

1. Data was available for effects on:
    - initial treatment (treatment between 3 and 12 months),
    - extended therapy (which is aimed at secondary prevention and is defined in this review as treatment in participants that have already received anticoagulation treatment for between 3 and 12 months at the time of enrolment and who continued on treatment for a further period of time)

    These groups were analysed separately in both the pairwise and NMAs analyses.

2. The endpoints reported in the studies included in this review varied between numerous different time points. Within the pairwise analyses, these were all kept separate with the exception of “initial” events, which took place during the initial heparin treatment. Due to various factors (such as the duration of initial heparin treatment differing between trials and the time period reported sometimes including several days following heparin cessation) data pertaining to events that occurred within the first 14 days following the first administration of a study drug were grouped together.
3. The committee advised that dose-finding trials, such as the rivaroxaban dosing trial (Agnelli 2007) should not be included in this review as they contained doses that are not used in clinical practice and therefore do not contain useful comparisons. These trials are listed in the excluded studies table in appendix M.
4. The majority of outcomes listed in the review protocol were reported as dichotomous event data and/or hazard ratios (HRs). In cases where both types of data were available, HR data was prioritised for extraction because some of the studies had several different treatment durations in the intervention arm and HRs take into account the timing of each event to give risk at any point in time, while risk ratios summarise cumulative risk over the duration of the study. (The assumption of proportional hazards was checked for the included studies that reported HR data.)
5. For safety outcomes (major and clinically relevant non-major bleeding), the committee were primarily concerned with the likelihood of bleeding whilst taking the drug and the comparative safety profiles of the different drugs when taken correctly. Therefore, data reported as occurring “on-treatment”, which only included events occurring whilst the participant is taking the study drug (or within a window of up to 7 days following drug cessation, depending on the study), were prioritised for extraction. However, the committee indicated that bleeds occurring during an intention-to-treat duration are also of relevance as these are likely to reflect bleeding rates in real life setting. Therefore, in the absence of on-treatment data for safety outcomes, intention-to-treat data were extracted.
6. For VTE-recurrence and mortality outcomes, the committee were primarily concerned with effectiveness, specifically the effect of the drugs on outcomes when taken as they are likely to be taken in real-life settings. Therefore, for these outcomes, only intention-to-treat data were permitted.
7. DVT or PE-occurrence in this chapter refers to a DVT or PE developing in a person who already has confirmed VTE (DVT and/or PE). Unless otherwise stated, it is not clear whether the person had specifically a DVT or a PE as the index event. Subgroup analyses by index event were carried out where data was available.
8. Subgroup analyses were carried out for people with cancer, obesity, or chronic kidney disease and people aged 65 years or older. No data were available for the other subgroups listed in the protocol. For the obesity subgroup, data were reported for people with a BMI of 30kg/m^2 or above (see protocol deviation below). No data were available for people with restricted movement. For chronic kidney disease, data were reported for people with a creatinine clearance of less than 30 ml/min.
9. The cancer subgroup analysis reported in HOKUSAI-VTE was excluded from the analysis for people with VTE and cancer due to issues with poor reporting; the study only reported data at 12 months, irrespective of the participants intended or actual treatment duration (which could have been as low as 3 months) meaning that these data were neither intention to treat as required for VTE recurrence and mortality or on-treatment (as required for bleeding outcomes).
10. On the basis of committee input, LMWH alone (given for a duration of at least 3 months) was included as a potential treatment option for VTE in people with cancer, in part because of the ease of treatment in people concurrently receiving chemotherapy or undergoing procedures and operations, and because the committee were aware that several trials have demonstrated reduced rates of VTE-recurrence with LMWH compared

to LMWH+VKA in cancer patients. However, this was not considered to be a viable treatment option for the general population of people with VTE and was excluded from the analyses for this group of people.

11. Data were available for studies recruiting people with PE, DVT or unspecified VTE. The committee envisaged making similar recommendations for DVT and PE. As a result, and to allow the inclusion of the unspecified VTE data, the pairwise analysis was carried out with the data stratified by DVT, PE and unspecified VTE (studies including a mix of people with DVT, PE or both) in the forest plots. Pooled results were also displayed.
12. The GRADE tables for the pairwise data present the results for all of the strata with the pooled result, even where subgroup differences are not detected. The results were presented in this manner in case the committee decided to make separate recommendations for the PE and DVT groups.
13. Published NMAs were not used as a source of data for this review as new NMAs were carried out to combine all the existing evidence and look at the outcomes of interest identified by the committee. Instead, they were used to provide evidence to support or contrast with the findings of this review.
14. The choice of outcomes to model in the NMAs was based on committee prioritisation of the outcomes they required for decision making and the available data. The committee prioritised VTE mortality, VTE-recurrence, major-bleeding and clinically relevant non-major bleeding. However, as there was a shortage of data for VTE mortality, all-cause mortality was analysed as well.
15. The committee advised that the individual comparisons between each of the DOACs was important and therefore the DOACs should be entered into the network individually. However, other treatments (including VKAs, LMWH and UFH) were assessed at the class level due to the different members of these classes having comparable effectiveness/efficacy. Non-DOAC treatments were entered into the NMA under the drug class to which they belong.
16. Since the committee envisaged making similar recommendations for PE and DVT, they agreed that it was appropriate to carry out NMAs for VTE overall, which pooled the DVT, PE and unspecified VTE data. These NMAS were prioritised, but NMAs were also conducted separately for DVT and PE where data was available.
17. For bleeding outcomes, only data that related to endpoints that occurred whilst participants were receiving treatment (or up to 7 days post-treatment cessation) were used in the models.
18. The durations of the studies identified for the initial treatment analysis varied from 2 weeks to 12 months. Many of the studies comparing LMWH+VKA to UFH+VKA reported endpoints at 3 months, whereas the DOAC trials reported endpoints between 6 months and 12 months. Data for the different timepoints were combined in a single analysis in the NMA models. If there were multiple time points for the initial treatment, then we selected the latest time point reported that matched our criteria for that outcome. These analyses assumed that the relative efficacy of the comparisons remains constant over time. However, after assessing Kaplan-Meier curves for the included studies, it was apparent that this assumption was broken for those trials that only reported results in the very early stages of the initial treatment phase. As a result, the committee agreed that trials with endpoints within the first month of treatment (typically reported within the first 2-3 weeks) would be excluded from the network.
19. For the NMAs, the use of cloglog models enabled HR and event data to be combined. HR data was extracted instead of event data if a trial reported both outcome measures. In situations where no HR data was available then logit models that synthesised event data only were used. The models we used did not take into account differences in duration of treatment as it was not thought that this factor would impact the results in this case.

20. The cloglog models used in the review were based on the TSU models used in Oba (2018). The NMA models for dichotomous outcomes were based on models from the NICE Decision Support Unit (DSU) technical support document 2 (models 1c and 1d). The models are shown in appendix O.
21. The cloglog models generate results in the form of HRs. To enable direct comparisons between the pairwise and NMA data to be made in the relative effectiveness charts, event data was converted to HR data for each trial that did not report HRs. These calculations are based on the methods described by Watkins et al. (2018) and are shown in appendix J. The resulting HRs are shown also in forest plots, which are clearly labelled to show that the data is converted from event data.
22. A continuity correction was used where the data contained zero events in 1 arm of a trial, but not the other, but only if there were problems running the model. The continuity correction was used to help the models converge. This involved adding 0.5 to the zero event arm and its matching comparator arm and 1 to the denominator for both arms. The use of a continuity correction is noted in the model fit table.
23. Where the data for the NMA for a dichotomous outcome (for example discontinuation) included trials with 0 events in both arms, these trials were not included as part of the analysis because trials with 0 events in both arms do not contribute evidence on the relative treatment effects in pairwise or NMA.
24. The DSU code presents the results of dichotomous outcomes as Odds ratios (ORs). Pairwise results were presented as Risk ratios (RRs) as these were more easily understood by the committee than ORs. Therefore, for consistency, results from the NMAs that were obtained in the form of ORs were converted to RRs by the NICE Guideline Updates Team using the event rate in the reference treatment arm (treatment coded 1 for model output) for each dichotomous outcome. The event rate was taken from the largest trial with the relevant treatment arm for that outcome and time point.
25. Results were reported as the posterior median and 95% credible interval from the NMA model with the best fit to the data based on the NICE Guideline Updates team criteria for model choice detailed in appendix B.
26. For multi-arm trials (trials with 3 or more arms), to account for the covariance between arms, the model included a calculation of “V”, the covariance between the log(HR)s of the comparisons between A-B and A-C using the below formula:

$$V = [\ Var(\log(HR_{Avs.B})) + Var(\log(HR_{Avs.C})) - Var(\log(HR_{Bvs.C}))\ ] / 2$$

Var(log(HR)) was calculated using the upper and lower limits of the 95% confidence intervals for the HR:

$$Var(\log(HR)) = (\ [\ \log(\text{upper limit}) - \log(\text{lower limit})\ ] / 3.92\ )\ \hat{}\ 2$$

27. For Clog-log models, histograms are based on the rk[] node, whereas for event rate only models histograms are based on the RR[] node. The rk[] node is calculated based on the d[]’s, while the RR[] node is calculated based on the d[]’s as well as the baseline input used to convert ORs to RRs.
28. Inconsistency checking of the NMAs was carried (see appendix P) in cases where the models contained loops of evidence. These analyses relaxed the NMA assumption that the data from trials within a loop was consistent. These analyses did not identify any networks with inconsistency.
29. Although there were studies at high risk of bias included in the NMA, sensitivity analyses excluding these studies were not carried out because sensitivity analyses for the pair wise data either did not alter the interpretation of the effects of the treatments, or would have resulted in the loss of a treatment node completely due to their only being a single study for that particular treatment option.
30. The NMAs were graphically summarised using network diagrams, caterpillar plots, histograms and mileage charts. Network diagrams depict the direct comparisons between

treatment that were entered into each model, with thicker lines representing greater numbers of studies included for that comparison. Caterpillar plots depict the relative effectiveness of each drug compared a common comparator (typically LMWH+VKA or placebo). Histograms depict the probability of each treatment being ranked first to last among the drugs in each network. (For some outcomes, for example mortality, being ranked last may be the best, whereas for others being ranked in position 1 is best. To make this clear the figure legends state which position is best.) Mileage charts display the HR or RR for each comparison in the network and also contain each direct comparison obtained from the pairwise data either as reported directly by the clinical trial or after conversion from event data to HRs where appropriate.

31. The treatment network was explored using network diagrams. The networks were similar in shape; mainly star shaped, linked by a single common treatment with few, if any, loops and this made the assessment of inconsistency impossible for most comparisons within a network.

We would like to acknowledge the Technical Support Unit, at University of Bristol, particularly Nicky Welton and Caitlin Daly for providing advice, models, inconsistency checking and quality assurance for the network meta-analyses included in this review.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Protocol deviation

The planned subgroup analysis for the effectiveness of pharmacological treatments for people who were classified as obese was based on a BMI of 40 kg/m^2 or more in the review protocol, but no studies were identified that reported data on this group of people. However, data was reported for people who had a BMI of 30 kg/m^2 or more and the committee agreed that it was appropriate to include this data to inform recommendations for the pharmacological treatment of obese people.

Priority screening was not used for this review. All references returned by the search were screened at title and abstract level.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the 2012 NICE VTE guideline (CG144). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews (SRs) was conducted for this review and the accompanying review on the effectiveness of pharmacological treatments for suspected venous thromboembolism. This returned 9,318 references (see appendix C for literature search strategy). Based on title and abstract screening against the review protocol, 9,021 references were excluded, and 297 references were ordered for screening based on their full texts.

Of the 297 references screened as full texts, 54 references met the inclusion criteria specified in the review protocol for this question (appendix A). A single additional reference was identified through reference searching of included studies, making a total of 55 references included in the review. The clinical evidence study selection is presented as a diagram in appendix D. Systematic reviews were used as a source of primary studies and were then excluded.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches returned 6,272 references in total for all the questions included in the update, and these were screened on title and abstract. Four references were identified for pharmacological treatment for suspected and confirmed VTE and 1 reference was included after full text screening for this review question, meaning that in total, 56 references were included in this review.

Please see appendix E for the full evidence tables. The references of individual included studies are listed in appendix N.

Excluded studies

See Appendix M for a list of references for excluded studies, with reasons for exclusion, and appendix N for the full references.

Summary of clinical studies included in the evidence review

This review identified 57 trials in 56 references of pharmacological treatment for VTE. The studies are summarised in Table 5 for the initial treatment of VTE, with full details provided in the evidence tables in appendix E. The included studies for the cancer subgroup analysis of initial treatment and longer-term treatment (also called extended therapy or treatment) and are summarised in Table 7 and Table 6 respectively.

In total, 34 unique trials compared regimens for the initial treatment of VTE, 16 compared regimens for the extended therapy of VTE (in people who have already received at least 3 months anticoagulation), and 13 compared regimens for the initial treatment of VTE in people with cancer. (Some of the trials included subgroup analyses for people with cancer as well as the complete study population and some papers presented more than 1 trial in a single reference.)

This review also identified a number of published NMAs, looking at the three key areas covered in this review: initial treatment of VTE, initial treatment of VTE in people with cancer and the extended therapy of VTE. These NMAs were not used for data extraction in this review, but were instead used as a reference to ensure that no relevant studies were missed during screening and then excluded from further analyses with the exception of two recent NMAs (Sterne 2017 and Wang 2018) that were of particular relevance to this review. The quality appraisal and summary of characteristics of these studies can be found in the clinical evidence tables for Published NMAs. Sterne (2017) covered evidence for both the initial and extended therapy of VTE and Wang (2018) covered evidence for the extended therapy of VTE. The results of these published NMAs were used to compare and contrast the results of our own NMAs to look for consistency of results.

Table 5 Studies looking at the initial treatment of venous thromboembolism

Author (year)	Sample size	Interventions	% unprovoked VTE	Treatment period
AMPLIFY (2013)	5,395	• Apixaban • LMWH + VKA (enoxaparin 1.0 mg/kg twice daily)	89.8%	6 months
Buller (2003)	2,213	• UFH + VKA (5000 IU bolus then 1250 IU/hr followed by VKA INR 2.0-3.0) • Fondaparinux + VKA (5-10mg)	Not reported	3 months

Buller (2004)	2,205	• LMWH + VKA (enoxaparin 1.0 mg/kg twice daily followed by warfarin INR 2.0-3.0) • Fondaparinux + VKA (5-10mg)	Not reported	3 months
Buller (2008)	520	• LMWH + VKA *(tinzaparin 175 IU/kg, enoxaparin 1.5 mg/kg once-daily or 1.0 mg/kg twice-daily or fondaparinux followed by warfarin INR 2.0-3.0* • Apixaban (dose finding study: only 5mg twice daily retained in analysis)	Not reported	3 months
Decousus (1998)	400	• LMWH + VKA (enoxaparin 1.0mg/kg followed by warfarin INR 2.0-3.0) • UFH + VKA (5000 IU bolus then 500 IU/kg per day, with warfarin INR 2.0-3.0 from day 4)	Not reported	3 months
EINSTEIN-DVT (2010)	3,449	• Rivaroxaban • LMWH + VKA	62%	Up to 12 months
EINSTEIN-PE (2012)	4,832	• Rivaroxaban • LMWH + VKA	64.5%	Up to 12 months
Fiessinger (1996)	268	• LMWH + VKA • UFH + VKA	Not reported	3 months
Findik (2002)	59	• LMWH + VKA • UFH + VKA	Not reported	3 months
Hisatake (2017)	50	• Fondaparinux • Edoxaban with parenteral AC	Not reported	7 days
HOKUSAI-VTE (2013)	8,240	• LMWH + VKA • Edoxaban plus parenteral AC	65.7%	Up to 12 months
Kakkar (2003)	297	• LMWH + VKA • UFH + VKA	Not reported	3 months
Kearon (1999)	162	• LMWH + VKA • UFH + VKA	100%	3 months
Kearon (2006)	708	• LMWH + VKA • UFH + VKA	Not reported	3 months
Koopman (1996)	400	• LMWH + VKA • UFH + VKA	Not reported	3 months
Levine (1996)	500	• LMWH + VKA • UFH + VKA	Not reported	3 months
Lindmarker (1994)	204	• LMWH + VKA • UFH + VKA	Not reported	3 months
Lopaciuk (1992)	149	• LMWH + VKA • UFH + VKA	Not reported	3 months
Luomanmaki (1996)	330	• LMWH + VKA • UFH + VKA	Not reported	3 months
Merli (2001)	900	• LMWH + VKA • UFH + VKA	Not reported	3 months
Meyer (1995)	60	• LMWH + VKA • UFH + VKA	Not reported	3 months
Nakamura (2015)	80	• Apixaban • UFH + VKA	Not reported	5.5 months

Ninet (1991)	166	• LMWH + VKA • UFH + VKA	Not reported	3 months
Piazza (2016)	85	• LMWH + VKA • Edoxaban without parenteral AC	58%	3 months
Prandoni (1992)	170	• LMWH + VKA • UFH + VKA	Not reported	3 months
Prandoni (2004)	720	• LMWH + VKA • UFH + VKA	Not reported	3 months
Ramacciotti (2004)	201	• LMWH + VKA • UFH + VKA	Not reported	3 months
RE-COVER I (2009)	2,564	• LMWH + VKA • Dabigatran plus parenteral AC	Not reported	6 months
RE-COVER II (2014)	2,589	• LMWH + VKA • Dabigatran plus parenteral AC	Not reported	6 months
Simonneau (1993)	134	• LMWH + VKA • UFH + VKA	Not reported	3 months
Simonneau (1997)	612	• LMWH + VKA • UFH + VKA	Not reported	3 months
Ucar (2015)	121	• LMWH + VKA • UFH + VKA	Not reported	3 months
J-EINSTEIN (2015)	94	• Rivaroxaban • UFH + VKA	51.5%	22 days
Leizorovicz (2011)	401	• LMWH + VKA • UFH + VKA	Not reported	3 months

Table 6 Studies looking at the initial treatment of venous thromboembolism in people with cancer

Author (year)	Sample size	Interventions	% unprovoked VTE	Treatment period
AMPLIFY (2013)	167	Apixaban (10mg twice daily for 7 days then 5mg twice daily) LMWH+VKA	0%	6 months
CATCH (2015)	900	LMWH+VKA (tinzaparin 175IU/kg once daily for 5-10 days followed by VKA) LMWH alone (tinzaparin 175IU/kg once daily)	0%	6 months
CLOT (2003)	676	LMWH+VKA (dalteparin 200 IU/kg for 5-7 days followed by VKA) LMWH alone (dalteparin 200 IU/kg once daily for one month followed by 150 IU/kg once daily for 5 months))	0%	6 months
Deitcher (2006)	102	LMWH+VKA LMWH alone (enoxaparin 1.0mg/kg or 1.5mg/kg, both once daily)	0%	6 months
EINSTEIN-DVT (2010) and EINSTEIN-PE (2012)	462	Rivaroxaban (15mg twice daily for first 3 weeks followed by 20 mg once daily) LMWH+VKA	0%	3-12 months

Author (year)	Sample size	Interventions	% unprovoked VTE	Treatment period
HOKUSAI-Cancer (2018)	1,046	Edoxaban (30 or 60mg/kg depending on creatinine clearance and body weight) preceded by heparin for at least 5 days LMWH alone (dalteparin 200IU/kg for 30 days followed by 150IU/kg)	0%	Up to 12 months (data extracted at 6 months for VTE-recurrence and mortality)
Hull (2006)	200	LMWH+VKA UFH+VKA	0%	3 months
Meyer (2002)	146	LMWH+VKA (enoxaparin 1.5mg/kg once daily for >4 days followed by VKA) LMWH alone (enoxaparin 1.5mg/kg)	0%	3 months
RE-COVER I (2009) and RE-COVER II (2013)	221	Dabigatran (150mg twice daily preceded by heparin for at least 5 days) LMWH+VKA	0%	6 months
Romera (2009)	69	LMWH+VKA (tinzaparin 175IU/kg initial therapy followed by warfarin 2.0-3.0 INR) LMWH alone (tinzaparin 175IU/kg once daily)	0%	6 months
SELECT-D (2018)	406	Rivaroxaban (15mg twice first 3 weeks followed by 20mg once daily) LMWH alone (dalteparin 200 IU/Kg once daily for 30 days followed by 150 IU/kg once daily)	0%	6 months

Table 7 Studies looking at the extended therapy of venous thromboembolism

Author (year)	Sample size	Interventions	Prior treatment for VTE	Treatment period	% unprovoked VTE
AMPLIFY-EXT (2013)	2,482	Apixaban (2.5mg) Apixaban (5mg) Placebo	6-12 months Apixaban or VKA	12 months	91.7%
ASPIRE (2012)	822	Aspirin 100mg Placebo	6 weeks to 24 months	Up to 48 months	100%
Cohen (2016)	115	Rivaroxaban (20mg once daily) Warfarin (2.0-3.0)	≥ 3 months VKA	180 days (some outcomes were reported at 210 days)	Not reported
Crowther (2003	114	Warfarin (2.0-3.0) Warfarin (3.1-4.0)	Unclear length of prior treatment	Mean 2.65 years follow-up	Not reported
EINSTEIN-CHOICE (2017)	3,365	Rivaroxaban (20mg once daily)	6-12 months	Up to 24 months	41.3%

Author (year)	Sample size	Interventions	Prior treatment for VTE	Treatment period	% unprovoked VTE
		Rivaroxaban (10mg once daily) Aspirin (100mg once daily)			
EINSTEIN-EXT (2010)	1,197	Rivaroxaban (20mg once daily) Placebo	6-12 months VKA or rivaroxaban	6-12 months	73.7%
ELATE (2003)	738	Warfarin (INR 2.0-3.0) Warfarin (INR 1.5-1.9)	≥ 3 months VKA	Mean 26 months	100%
Kearon (1999)	162	Warfarin (INR 2.0-3.0) Placebo	≥ 3 months VKA	24 months	100% (DVT only)
PADIS-DVT (2019)	104	Warfarin (INR 2.0-3.0) Placebo	≥ 6 months VKA	18 months	100% (DVT only)
PADIS-PE (2015)	374	Warfarin (INR 2.0-3.0) Placebo	≥ 6 months VKA	18 months	100% (PE, with or without DVT)
PREVENT (2006)	508	Warfarin (INR 1.5-2.5) Placebo	≥ 3 months VKA	Up to 4.3 years	100%
RE-MEDY (2013)	2,866	Dabigatran (150mg twice daily) Warfarin (INR 2.0-3.0)	3-12 months VKA or dabigatran	6-36 months	Not reported
RE-SONATE (2013)	1,353	Dabigatran (150mg twice daily) Placebo	6-18 months VKA or dabigatran	6 months	Not reported
WARFASA (2012)	403	Aspirin 100mg Placebo	6-18 months with a VKA	Up to 24 months	100%
WODIT-DVT (2001)	267	Warfarin (INR 2.0-3.0) Discontinued therapy	≥ 3 months VKA	9 months	100% (DVT-only)
WODIT-PE (2003)	326	Warfarin (INR 2.0-3.0) Discontinued therapy	≥ 3 months VKA	Up to 9 months	56.2% (PE, with or without DVT)

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies, appendix F for forest plots and appendix G for GRADE tables. Please refer to the evidence statement section for an overall summary of the evidence.

Economic evidence

Included studies

A systematic search was carried out to cover all questions within this evidence review. The search returned 3,811 records. In addition, 8 papers were identified from the 2012 guideline. Of these records, 3,774 were excluded on basis of title and abstract for this review question. The remaining 45 papers were screened in full, and 6 were found to be relevant to this review question. A number of UK-based analyses were identified, so only studies using an NHS perspective were included.

An additional search was conducted at the end of the guideline development process to capture economic evidence published while the guideline was being developed. This was conducted as a single rerun search covering all questions in the guideline. The search returned 2,013 records in total, of which 2,007 were excluded on title and abstract for this review question. The remaining 6 papers were screened in full, and 1 was found to be relevant to this review question. Therefore, a total of 7 studies were included in this economic evidence review.

Excluded studies

Details of the studies excluded at full text review are given in appendix M, with the full references in appendix N.

Summary of studies included in the economic evidence review

Bamber et al. (2015) conducted a cost-utility analysis comparing rivaroxaban with LMWH/VKA in patients with a DVT or PE, based on results of the EINSTEIN DVT and EINSTEIN PE studies. The evaluation used a lifetime horizon and was conducted from the perspective of the NHS. Separate analyses were conducted for patients receiving 3, 6, or 12 months, or lifetime anticoagulation.

The authors used a Markov structure to model VTE treatment, which modelled relevant outcomes (recurrent DVT and PE, major extracranial bleeding, major intracranial bleeding, clinically relevant non-major bleeding, chronic thromboembolic pulmonary hypertension [CTEPH], and post-thrombotic syndrome [PTS]) for patients on and off treatment. Event data were taken from the EINSTEIN DVT and EINSTEIN PE trials for patients on treatment, and from published observational studies for patients off treatment. Separate on-treatment probabilities of recurrent VTE, major bleeding, and non-major clinically relevant bleeding (NMCRB) were used for LMWH/VKA and rivaroxaban, stratified according to whether patients had an index DVT or PE, and intended treatment duration. Mortality was implemented as both a background death rate and as a probability of death associated with certain model states (PE, major extracranial bleed, major intracranial bleed, and CTEPH).

The authors included costs of anticoagulants, monitoring healthcare visits, recurrent DVT/PE, bleeding events, PTS and CTEPH in the model. Unit costs were taken from standard NHS sources. Utilities were implemented by assigning an age-adjusted baseline QoL score to the cohort, from which utility decrements were subtracted for patients experiencing model events (DVT, PE, bleeding events, PTS, and CTEPH).

Results showed that rivaroxaban dominates LMWH/VKA (is less costly and produces more QALYs) for patients with an index DVT or PE for 3-, 6- and 12-month treatment durations. Rivaroxaban produces an ICER of £8,677 and £7,072 for DVT and PE respectively in

patients receiving lifetime anticoagulation. Probabilistic sensitivity analysis showed that the probability of rivaroxaban being cost effective at a threshold of £20,000 per QALY was greater than 81% across all groups.

This study was classified as being partially applicable as it only considered 2 of the interventions of interest. It was categorised as having potentially serious limitations due to a potential conflict of interest (the study was funded by the manufacturer of rivaroxaban). A number of model assumptions are potentially favourable towards rivaroxaban, such as a high number of monitoring appointments for LMWH/VKA, a high probability of death from a PE, and a low probability of treatment discontinuation.

Lanitis et al. (2016) conducted a cost-utility analysis assessing the cost effectiveness of 6 months of apixaban, rivaroxaban, dabigatran, or LMWH/VKA in patients with a VTE. The evaluation used a lifetime horizon and was conducted from the perspective of the NHS.

The authors used a Markov structure, which modelled relevant outcomes (recurrent DVT and PE, major extracranial bleeding, major intracranial bleeding, CRNMB, CTEPH, and PTS) for patients on and off treatment. Baseline and natural history data were mostly taken from the AMPLIFY trial, supplemented with data from observational studies. Treatment effects on recurrent VTE, major bleeding, non-major clinically relevant bleeding, and treatment discontinuation were derived from a network meta-analysis (NMA) of DOAC trials and were applied to event probabilities for patients on treatment. Mortality was implemented as both a background death rate and as a probability of death associated with certain model states (PE, major extracranial bleed, major intracranial bleed, and CTEPH).

The authors included costs of anticoagulant drugs, monitoring healthcare visits, recurrent DVT/PE, bleeding events, PTS and CTEPH in the model. Unit costs were taken from standard NHS sources. Utilities were implemented by assigning an age-adjusted baseline QoL score to the cohort, from which utility decrements were subtracted for patients experiencing model events (DVT, PE, bleeding events, PTS, and CTEPH).

Base case results showed that apixaban dominates rivaroxaban and dabigatran, and produces an ICER of £2,520 per QALY compared to LMWH/VKA. Probabilistic sensitivity analysis showed that apixaban had a high probability of being cost effective at a threshold of £20,000 per QALY (>85%). A subgroup analysis in patients with either an index DVT or PE showed that apixaban remains cost effective for both groups individually. An exploratory analysis of treatment duration found that apixaban remains cost-effective at 3-month, 12-month, and lifetime treatment durations.

This study was classified as being partially applicable as it did not include all DOACs (edoxaban was not included). It was categorised as having potentially serious limitations, due to a potential conflict of interest (the study was funded by the manufacturer of apixaban).

Lanitis et al. (2017) conducted a cost-utility analysis comparing 12 months of apixaban with either 6 months or 12 months of LMWH/VKA in patients with a VTE. The study used a lifetime time horizon, and was conducted from the perspective of the NHS.

The authors used a similar methodology to Lanitis et al. (2016), with the difference that only outcomes from the AMPLIFY trial were used to inform treatment effects in the first 6 months, and outcomes from the AMPLIFY-EXT trial were used to inform the relative effectiveness of apixaban, LMWH/VKA, and no treatment in the second 6 months.

Base case results showed that 12 months of treatment with apixaban was cost effective compared to 6 months of treatment with LMWH/VKA (ICER of £6,692 per QALY) and compared to 12 months of treatment with LMWH/VKA (ICER of £8,528 per QALY).

Probabilistic sensitivity analysis showed that extended therapy with apixaban has a 94% probability of being cost effective at a threshold of £20,000 per QALY.

This study was classified as being partially applicable, as it only assessed 2 of the regimens of interest. It was categorised as having potentially serious limitations, due to a potential conflict of interest (the study was funded by the manufacturer of apixaban). In addition, the authors did not include all the relevant comparators required to demonstrate the cost effectiveness of extended apixaban treatment; 12 months of apixaban is not compared to 6 months of apixaban, only to 6 and 12 months of LMWH/VKA.

Jugrin et al. (2015) conducted a cost-utility analysis comparing dabigatran with LMWH/warfarin in patients with VTE, based on results of the RE-COVER I and II trials. The study used a lifetime time horizon, and was conducted from the perspective of the NHS. Separate analyses were conducted for patients receiving up to 6 months of anticoagulation and patients receiving extended, up to 24 months anticoagulation.

The authors used a Markov structure, which included relevant outcomes (recurrent DVT and PE, major extracranial bleeding, major intracranial bleeding, CRNMB, CTEPH, and PTS) for patients on and off treatment. Clinical data were taken from the warfarin arm of RE-COVER and RE-COVER II trials, supplemented with published observational data to inform the incidence of recurrent VTE while off treatment and the incidence of PTS and CTEPH. Treatment effects on VTE recurrence and major/non-major clinically relevant bleeding (also from the RE-COVER I and II trials) were used to inform event probabilities for Dabigatran while on treatment.

The authors included costs of anticoagulant drugs, monitoring healthcare visits, recurrent DVT/PE, bleeding events, PTS and CTEPH in the model. Utility values were mostly derived from the RE-COVER I and II trials, supplemented with utility decrements from the literature for severe PTS, CTEPH and long-term disability from intracranial bleeding.

Base case results showed that Dabigatran produces an ICER of £767 per QALY compared to LMWH/warfarin in the population treated for up to 6 months, and an ICER of £7,877 per QALY in the population treated for up to 24 months. The ICER remained below £20,000 per QALY for patients sub-grouped by type of index VTE (DVT or PE). Probabilistic sensitivity analysis showed that Dabigatran has a relatively high probability of being cost effective across all subgroups (79%-94%).

This study was classified as being partially applicable as it only considered 2 of the interventions of interest. It was categorised as having potentially serious limitations due to a potential conflict of interest (the study was funded by the manufacturer of dabigatran).

Jugrin et al. (2016) conducted a cost-utility analysis comparing dabigatran with rivaroxaban in patients with VTE. The study used a lifetime time horizon and was conducted from the perspective of the NHS. Separate analyses were conducted for patients treated with 6 months of anticoagulation and extended anticoagulation (additional 6-12 months treatment).

The authors used a similar methodology to Jugrin et al. (2015), with the difference that treatment effects were informed by an indirect comparison of rivaroxaban and dabigatran, using outcomes from the RE-COVER, RE-COVER II, EINSTEIN PE, and EINSTEIN DVT trials.

Base case results showed that dabigatran dominates rivaroxaban (is less costly and produces more QALYs) for both treatment durations, and for DVT and PE subgroups individually. However, probabilistic sensitivity analysis results showed that there is a

reasonable amount of uncertainty around this finding; dabigatran has a 61%-88% probability of being cost effective at a threshold of £20,000 per QALY.

This study was classified as being partially applicable as it only considers 2 of the interventions of interest. It was categorised as having potentially serious limitations due to a potential conflict of interest (the study was funded by the manufacturer of dabigatran).

Sterne et al. (2017) conducted a cost-utility analysis evaluating the cost effectiveness of LMWH/warfarin, dabigatran, rivaroxaban, apixaban and edoxaban for the acute treatment of VTE (6 months anticoagulation), and the cost-effectiveness of warfarin, rivaroxaban, dabigatran, apixaban 2.5 mg bd, apixaban 5 mg bd, aspirin and "no pharmacotherapy" for the secondary prevention of VTE (lifetime anticoagulation). The study used a lifetime horizon and was conducted from the perspective of the NHS.

The authors used a short-term decision tree structure followed by a long-term Markov structure to model relevant outcomes (recurrent VTE, intracranial bleeding, other clinically relevant bleeding, CTEPH, and PTS). Treatment effects were taken from NMAs of DOAC trials. Baseline/natural history data were taken from published observational sources, although recurrent VTE data were taken from the "no pharmacotherapy" arm of the NMA.

The authors included costs of anticoagulant drugs, monitoring healthcare visits, recurrent DVT/PE, bleeding events, PTS and CTEPH in the model. Unit costs were taken from standard NHS sources where available. Utilities were implemented by assigning an age-adjusted baseline QoL score to the cohort, from which utility decrements were subtracted for patients experiencing model events.

Base case results for acute treatment showed that apixaban is cost effective at a threshold of £20,000 per QALY, with an ICER of £800 compared to LMWH/warfarin (calculated from absolute costs and QALYs reported by authors). All other treatments are simply or extendedly dominated. Probabilistic sensitivity analysis showed that apixaban has a ~54% probability of being cost effective at a threshold of £20,000-£30,000 per QALY. All other treatments have a probability of <25%. Base case results for secondary prevention showed that dabigatran has an ICER of £64,660 per QALY compared to aspirin. All other treatments are dominated. Probabilistic sensitivity analysis showed that only aspirin and "no pharmacotherapy" have non-trivial probabilities of being cost effective at a £20,000 per QALY threshold (~70% and ~30%, respectively).

This study was classified as being directly applicable. It was categorised as having potentially serious limitations due to a number of methodological issues. First, due to a lack of RCT data to inform the acute treatment model, the assumption was made that the probability of non-fatal intracranial bleeding is the same across all DOACs. Second, in the secondary prevention model, treatment effects on intracranial bleeding were taken from atrial fibrillation studies. Third, the acute treatment model incorporates NMA results for the effect of treatment on all-cause mortality. This unnecessarily produces a large amount of uncertainty in results, since the 95% confidence intervals are very wide for all treatments. Fourth, the authors make the assumption that all bleeding-related mortality is due to intracranial bleeding. Fifth, no list price was available for edoxaban at the time of the analysis and was assumed to be the same as dabigatran.

Clay et al. (2018) developed a cost-utility analysis assessing the cost effectiveness of edoxaban compared to warfarin for treatment of VTE using data from the Hokusai-VTE trial. The index VTE was treated for 6 months and recurrent VTEs with lifelong anticoagulation. The analysis used a lifetime horizon and was conducted from the perspective of the NHS.

The authors used a Markov structure with 1-month cycle length and modelled VTE recurrence, major intracranial and extracranial bleeding, CRNMB and death. PTS, CTEPH and disability following major intracranial bleeds were modelled as simultaneous states.

Baseline VTE recurrence and bleeding rates were derived from a post-hoc analysis of the Hokusai-VTE trial. The probability of developing a recurrent VTE while off treatment, CTEPH, PTS and disability after a major intracranial bleed were sourced from the literature. Background mortality was based on UK life tables while condition-specific mortality following a PE, CTEPH or a major intracranial bleed were also based on published estimates.

Costs were identified from standard NHS sources and included drug costs, recurrence, appointments and admissions, bleeding events, disability following major intracranial bleeds, PTS and CTEPH. Utilities were implemented by assigning an age-adjusted baseline QoL score to the cohort, from which utility decrements were subtracted for patients experiencing events in the model.

The base-case analysis showed that edoxaban dominated LMWH/warfarin as it was less expensive (-£55) and generated more QALYs (0.033). Probabilistic sensitivity analysis showed that edoxaban had a 99.5% probability of being cost effective at a threshold of £20,000/QALY.

This study was classified as being partially applicable as it only includes 2 of the comparators of interest. It was categorised as having potentially serious limitations due to a potential conflict of interest (study sponsored by the manufacturer of edoxaban).

Economic model

The 7 published economic evaluations included in the review only partially address the review question about the best pharmacological treatment for confirmed VTE. Despite considering the UK context, none of the analyses includes all the comparators available to NHS patients, particularly for the extended phase of treatment. Most of the economic analyses were often informed by individual trials comparing low molecular weight heparin (LMWH) followed by a vitamin K antagonist (VKA) to a direct-acting oral anticoagulant (DOAC) in the initial 6-months post VTE, which was then extrapolated to a longer time horizon. Six of the 7 studies were funded by manufacturers of individual DOACs, raising potential conflicts of interest. The committee considered this to be an area of high economic uncertainty and prioritised it for *de novo* economic modelling. The model was constructed as a cost-utility analysis from an NHS/personal social services perspective. A summary of the model structure and key results is provided below. A detailed description of the model with full results and sensitivity analyses is provided in a separate economic modelling report (evidence review G).

Population

Adults with a confirmed diagnosis of PE or DVT; a subgroup analysis was run for people with cancer.

Comparators

The model was divided into an initial treatment phase (first 3 to 6 months following a DVT or PE) and an extended therapy phase aimed at secondary prevention. The assumption about the duration of treatment in the model depended on whether the VTE was provoked or unprovoked.

In the base case, the model assumed that people remained on the same treatment in the initial and extended phases and compared the following 7 strategies:

1. LMWH/VKA
2. UFH/VKA
3. Fondaparinux/VKA
4. Apixaban
5. Rivaroxaban
6. Dabigatran
7. Edoxaban

The first 3 comparators reflect different bridging therapies for VKA, which were assumed to be administered on average for 10 days, after which time the VKA would be continued on its own. For the purposes of the model, the VKA was assumed to be warfarin. As per their labels, dabigatran and edoxaban were started after 5 days of parenteral anticoagulation, which was assumed to be LMWH in the model.

For extended therapy, additional comparators were identified for inclusion in the NMAs, giving rise to the potential to model a wider set of strategies if treatment switching was allowed between the initial and extended phases. The sequencing analysis included the 7 comparators above for initial treatment and 10 comparators for extended therapy, yielding a total of 70 potential sequences of initial treatment and extended therapy. However, the committee noted that a number of these sequences were unlikely to be relevant to current clinical practice. In particular, the committee felt that a person would not normally switch from a DOAC as initial treatment to warfarin as extended therapy unless there were specific clinical concerns. It was agreed in advance of running the model that the clinical plausibility of these treatment sequences would be taken into account by presenting incremental cost-effectiveness results both with and without these strategies. The 10 comparators of interest for extended therapy in the sequencing analysis included:

1. No treatment
2. VKA low (INR 1.5-2.0)
3. VKA standard (INR 2.0-3.0)
4. Aspirin
5. Apixaban (2.5 mg twice daily)
6. Apixaban (5 mg twice daily)
7. Dabigatran
8. Edoxaban
9. Rivaroxaban (10 mg)
10. Rivaroxaban (20 mg)

For the cancer subgroup analysis, data were only available to estimate relative treatment effects from trials conducted in the initial phase following a VTE and so these were applied for the entire duration of treatment in the model. A total of 8 strategies were modelled in the cancer subgroup, including the 7 strategies listed in the base case above plus the addition of LMWH alone.

Methods

Model structure

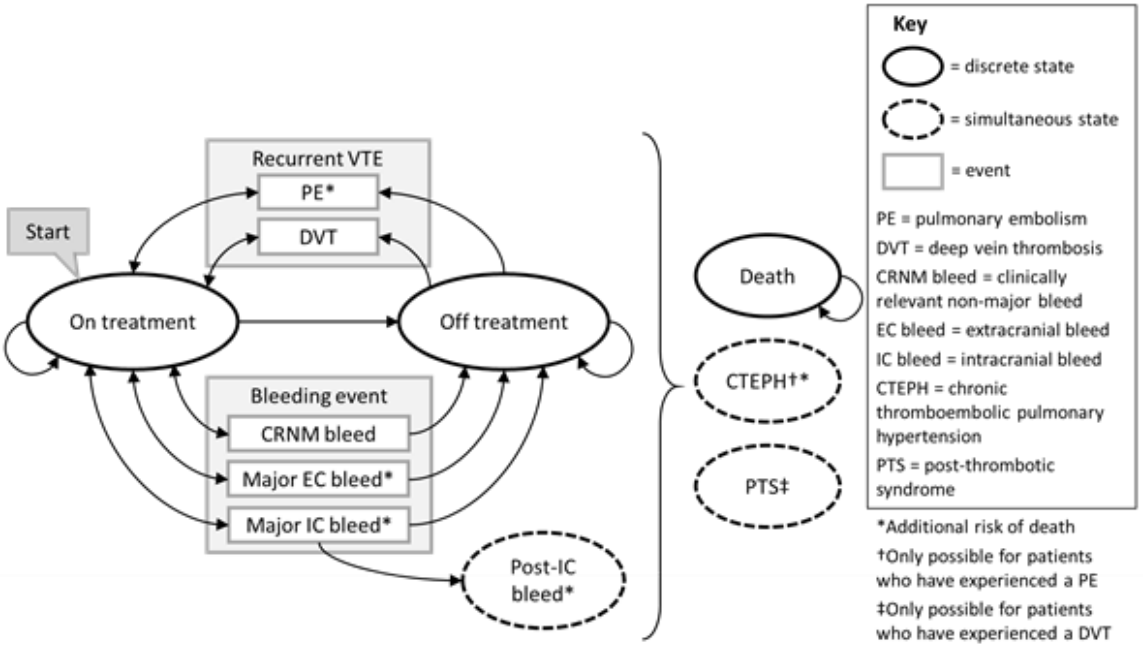
A Markov model was used to represent key events associated with management of a DVT or PE including VTE recurrence, major bleeding events, clinically relevant non-major bleeding (CRNMB) events and downstream sequelae such as chronic thromboembolic pulmonary

hypertension (CTEPH), post-thrombotic syndrome (PTS) and long-term disability associated with intracranial bleeds.

Separate cohorts were run for people who had experienced a DVT as the index event and people who had experienced a PE as the index event but in both cases the same model structure was used. The cohort starts in the "on treatment" state where individuals are at risk of both VTE recurrence and bleeding events. Individuals can transition to the "off treatment" state if their intended treatment course ends, they discontinue due to a bleeding event, or they discontinue for another reason ("spontaneous" discontinuation). While off treatment, people remain at risk of having a recurrent VTE (and the risk is higher than if they had continued treatment) but they are no longer at risk of bleeding events. People who have had a PE are at risk of developing CTEPH and people who have had a DVT are at risk of developing PTS. CTEPH and PTS are both modelled as simultaneous states, which track the proportion of people with these conditions over time while they are inhabiting one of the other discrete states in the model. A simultaneous state is also used to track the long-term impact of disability following a major intracranial bleed.

In the model, people can die at any point from background mortality. There is a one-off immediate risk of death associated with the following events: recurrent PE, major extracranial bleeding and major intracranial bleeding. There is also a long-term increased risk of death associated with CTEPH and with being in the post-intracranial bleed state.

Figure 1: Structure of the Markov model



The cohort is weighted to reflect the proportion of people who experience a provoked versus an unprovoked VTE and the model estimates the risk of recurrence separately for these populations. Unprovoked VTEs are associated with a higher risk of recurrence and are generally treated for longer. In the base case, committee consensus was that people with a provoked VTE would receive treatment for 3 months (this was assumed irrespective of the number of prior provoked events because it was not possible to track this at the individual level) and people with an unprovoked VTE would receive long-term treatment of an indefinite duration.

People who experience a recurrent VTE while off treatment are assumed to return to the same treatment that they received for the index event at the start of the model. People who experience a recurrent VTE while on treatment are assumed to switch to another treatment. For simplicity, this was modelled as a weighted average of the costs and effectiveness of all treatment comparators.

The model uses a 3-month cycle length and adopts a lifetime horizon with a discount rate of 3.5%. Observational data showed that the probability of VTE recurrence and bleeding decrease over time before plateauing, so the model uses a series of tunnel states to track the first 6 cycles since a VTE event.

Results

Results are reported for the following:

- **Base-case analysis** – people remain on the same treatment for the initial and extended phases
- **Sequencing analysis** – considers treatment switching between the initial and extended phases
- **Cancer subgroup analysis**

For each analysis, results are reported separately for DVT and PE index events. Incremental results are presented by ordering strategies from the least to most expensive and incremental cost-effectiveness ratios (ICERs) are calculated for strategies that are not dominated or extendedly dominated. Probabilistic results are presented graphically as cost-effectiveness acceptability curves (CEACs), which show the probability of each strategy being cost effective over a range of threshold values.

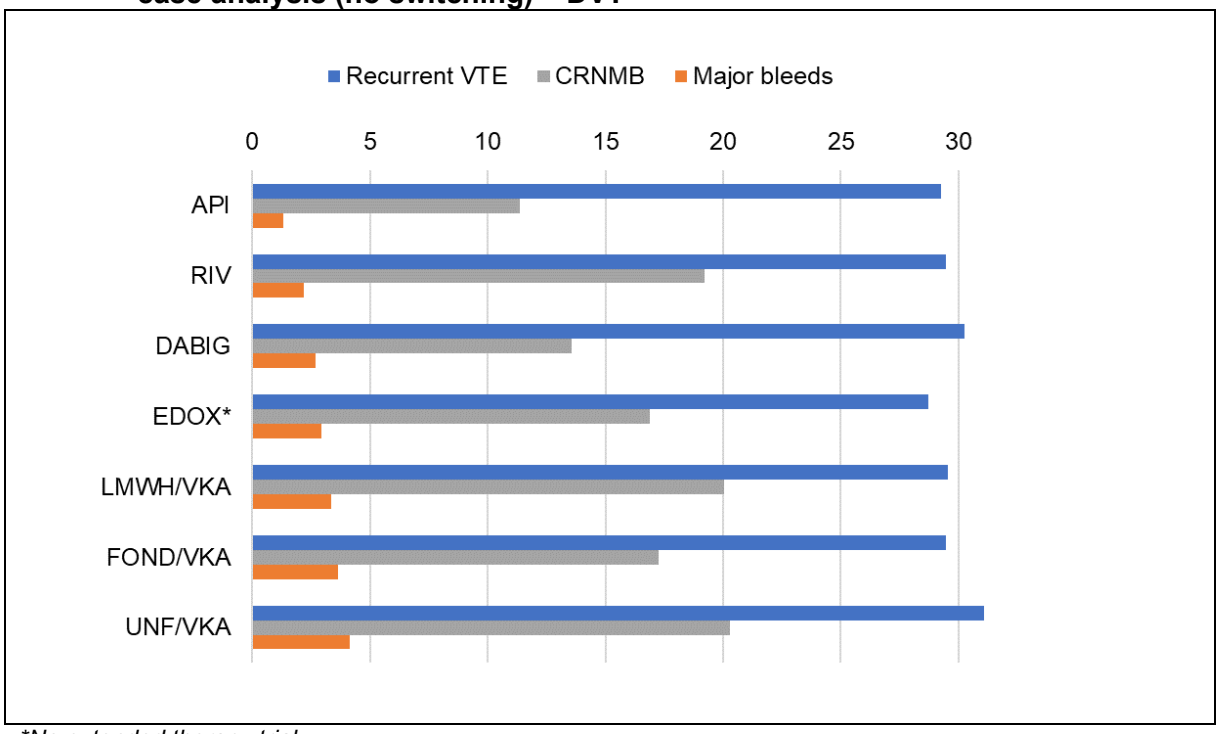
Base-case analysis

Base-case analysis (no switching) – DVT

Figure 2 shows the number of VTE recurrences, major bleeds and CRNMB events for each treatment over the lifetime horizon per 100 patients entering the model following an index DVT event. The number of VTE recurrences for all treatments is similar, with edoxaban having the lowest number (28.7) and UFH/VKA the highest (31.1). Apixaban has the lowest number of both major bleeding and CRNMB events. For all strategies, the absolute number of major bleeding events is low compared to the number of VTE recurrences but the impact of major bleeds in terms of mortality, quality of life and costs in the model is high.

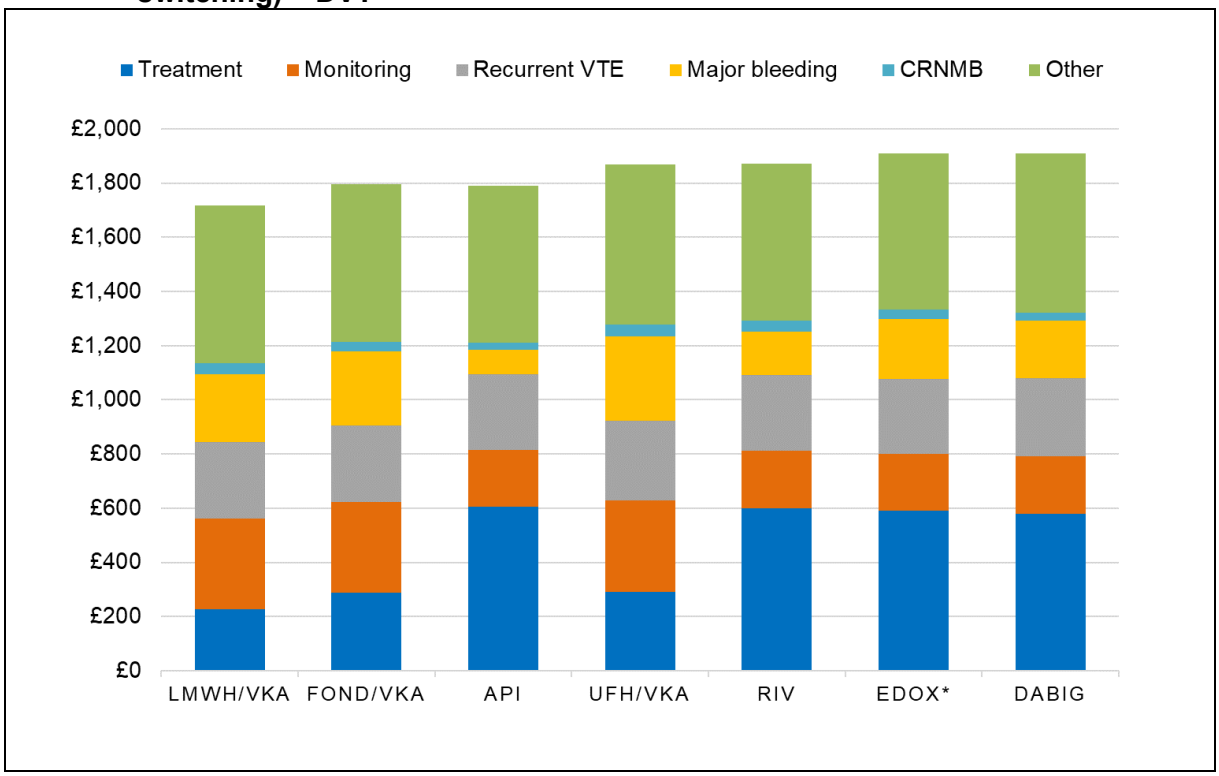
Figure 3 shows a breakdown of costs by category. Compared to VKA-based strategies, the DOACs all have higher treatment costs but lower monitoring costs and lower costs associated with bleeding events. The category ‘other’ includes the cost of managing sequelae such as PTS and CTEPH.

Figure 2: Number of VTE recurrences and bleeding events per 100 people in the base-case analysis (no switching) – DVT



*No extended therapy trial

Figure 3: Summary of undiscounted costs by category in the base-case analysis (no switching) – DVT



*No extended therapy trial

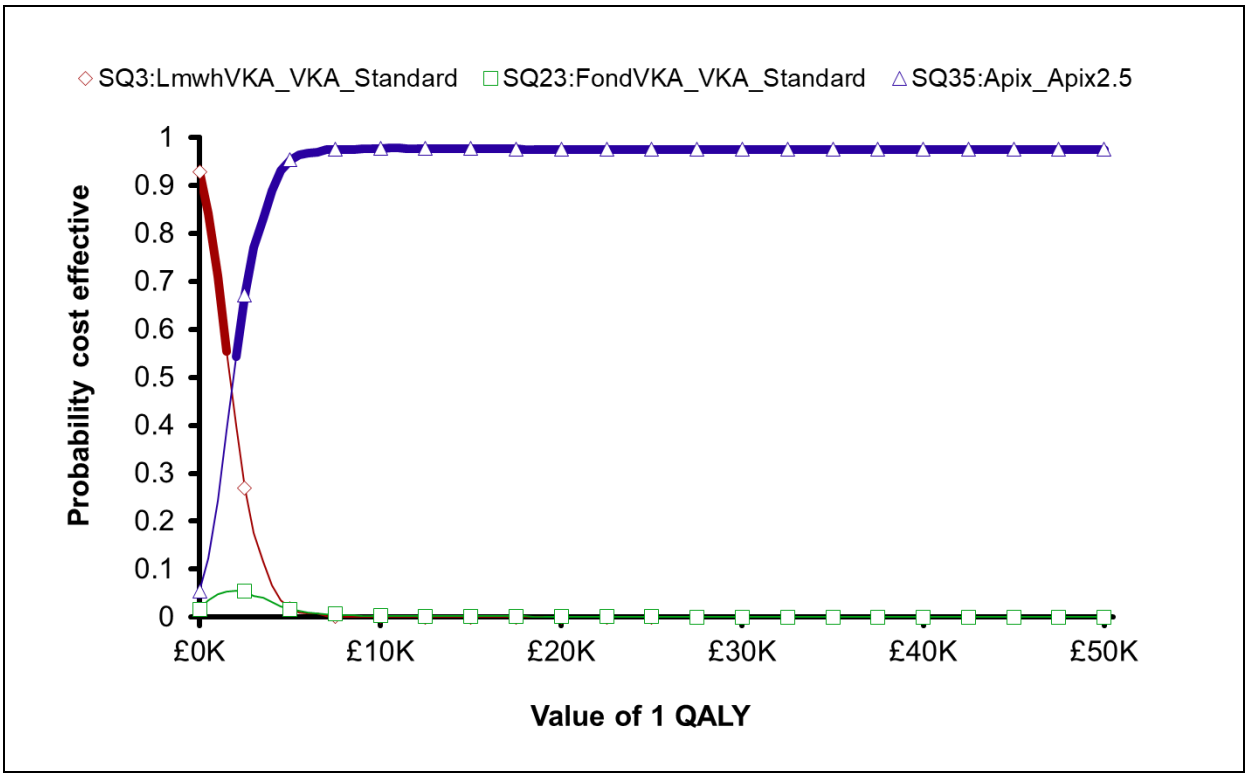
Deterministic cost-effectiveness results are shown in Table 8. Apixaban generates the most QALYs with an ICER of £1,802/QALY compared to LMWH/VKA. All other strategies are dominated. The CEAC in Figure 4 shows that apixaban has a high probability of being cost effective (97.5% at a threshold value of £20,000/QALY).

Table 8: Deterministic incremental cost-effectiveness results for the base-case analysis (no treatment switching) - DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA	£1,445	7.504			
Fondaparinux/VKA	£1,519	7.498	£74	-0.006	dominated
Apixaban	£1,527	7.550	£82	0.045	£1,802
UFH/VKA	£1,585	7.482	£59	-0.067	dominated
Rivaroxaban	£1,601	7.531	£74	-0.019	dominated
Edoxaban	£1,631	7.516	£104	-0.034	dominated
Dabigatran	£1,632	7.518	£106	-0.032	dominated

(a) No extended therapy trial

Figure 4: Cost-effectiveness acceptability curve for the base-case analysis (no treatment switching) – DVT

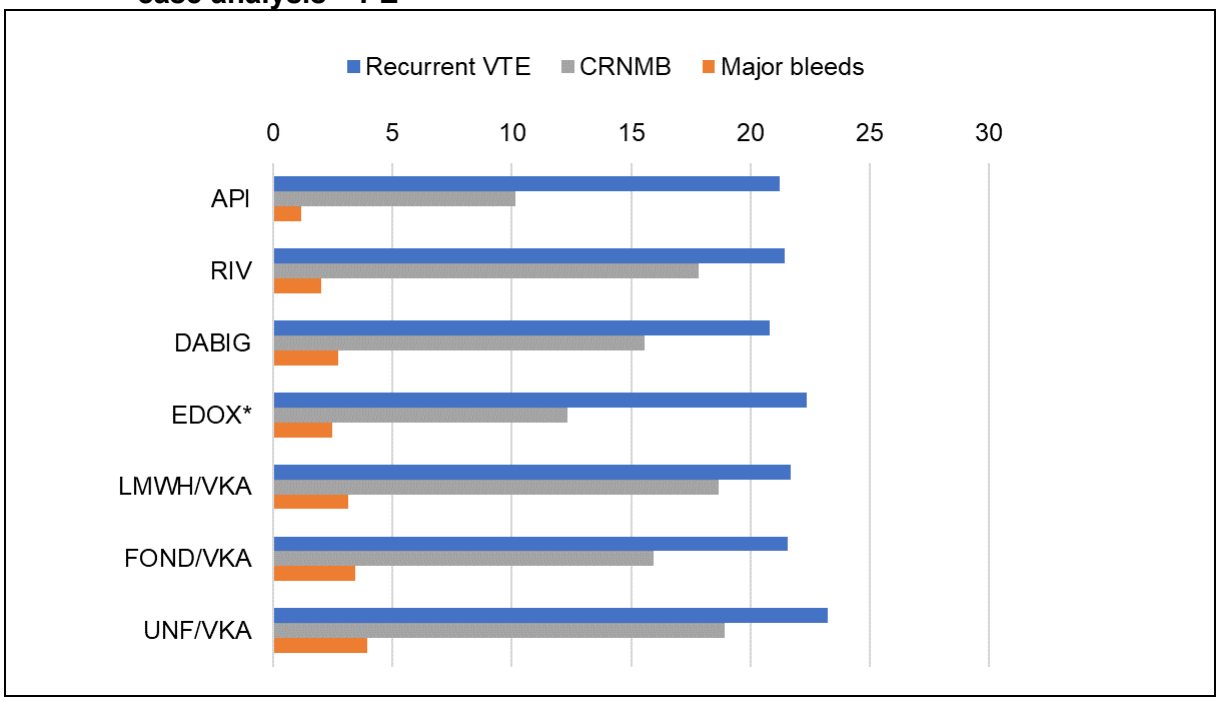


Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Base-case analysis (no switching) – PE

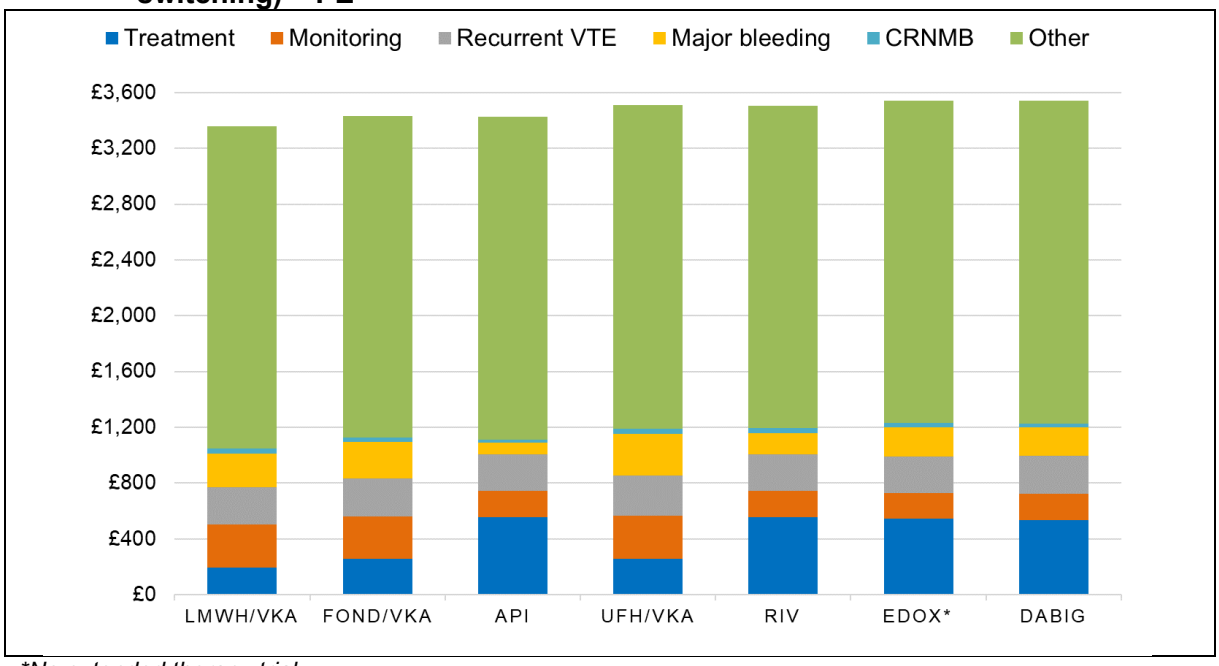
Figure 5 and Figure 6 show the number of VTE recurrence and bleeding events and costs for the base-case analysis in people with a PE. The results for PE are consistent with those for DVT.

Figure 5: Number of VTE recurrences and bleeding events per 100 people in the base-case analysis – PE



No extended therapy trial

Figure 6: Summary of undiscounted costs by category in the base-case analysis (no switching) – PE



No extended therapy trial

Apixaban generates the most QALYs and an ICER of £1,660/QALY compared to LMWH/VKA (Table 9). There is a 97% probability that apixaban is cost effective at a threshold value of £20,000/QALY (

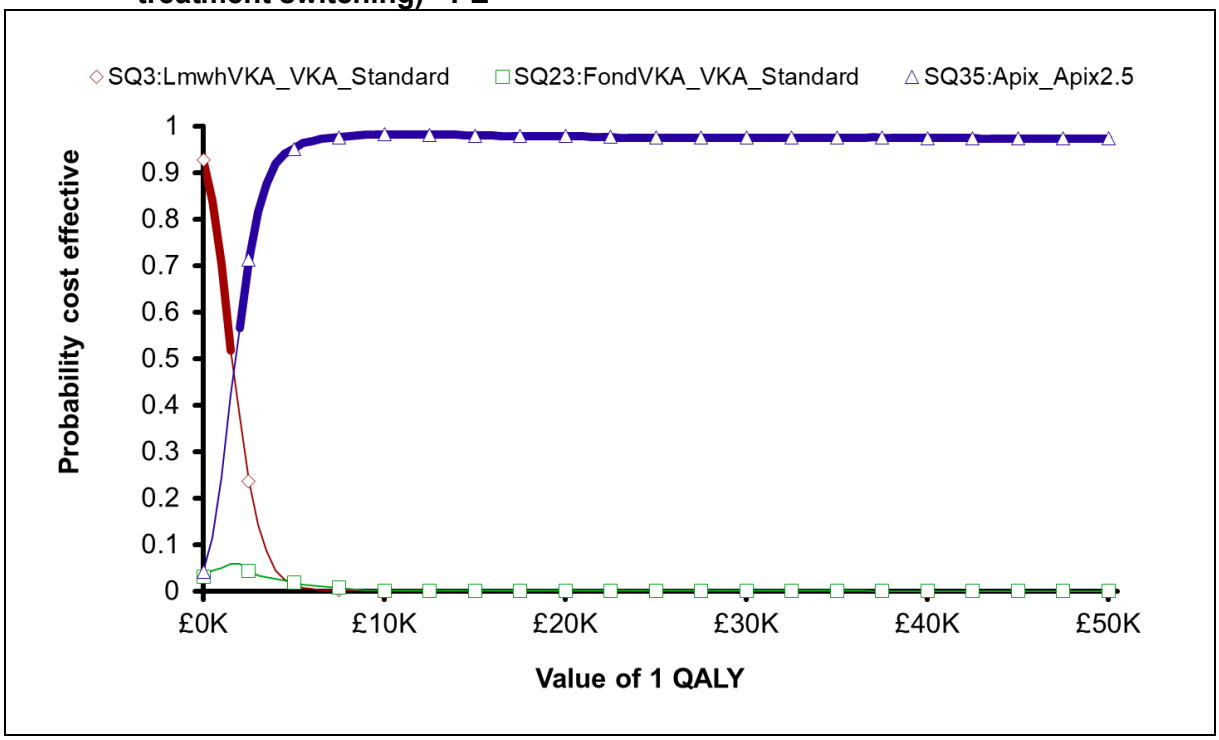
Figure 7).

Table 9: Deterministic incremental cost-effectiveness results for the base-case analysis (no treatment switching) - PE

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA	£2,968	7.401			
Fondaparinux/VKA	£3,039	7.395	£72	-0.006	dominated
Apixaban	£3,044	7.447	£77	0.046	£1,660
UFH/VKA	£3,107	7.375	£63	-0.072	dominated
Rivaroxaban	£3,116	7.427	£71	-0.019	dominated
Edoxaban	£3,143	7.414	£98	-0.032	dominated
Dabigatran	£3,149	7.412	£104	-0.035	dominated

(a) No extended therapy trial

Figure 7: Cost-effectiveness acceptability curve for the base-case analysis (no treatment switching) - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis

Sequencing analysis (all strategies) - DVT

Table 10 shows the deterministic incremental cost-effectiveness results for all 70 strategies assuming treatment switching from any initial treatment to any extended therapy is possible following a DVT index event. The sequence of apixaban as initial treatment followed by apixaban (5 mg twice daily) in the extended therapy phase generates the most QALYs. The QALY differences between strategies that begin with the same initial treatment are generally

very small. The sequences of apixaban as initial treatment followed by no treatment, aspirin and VKA standard in the extended therapy phase all generate similar QALYs and the strategies apixaban followed by apixaban (5 mg twice daily) and apixaban followed by apixaban (2.5 mg twice daily) generate virtually identical costs as well as QALYs. The ICER for the sequence apixaban followed by apixaban (5 mg) versus apixaban followed by VKA standard is £26,161/QALY. At a threshold value of £20,000/QALY, the strategy with the highest net monetary benefit is the sequence apixaban followed by VKA standard although this is not the strategy with the highest probability of being cost effective. In line with the small incremental differences in costs and QALYs between strategies, Figure 8 shows there is considerable uncertainty in these results. No strategy achieves >50% probability of being cost effective over the range of threshold values shown.

Table 10: Deterministic incremental cost-effectiveness results for the sequencing analysis (all strategies) - DVT

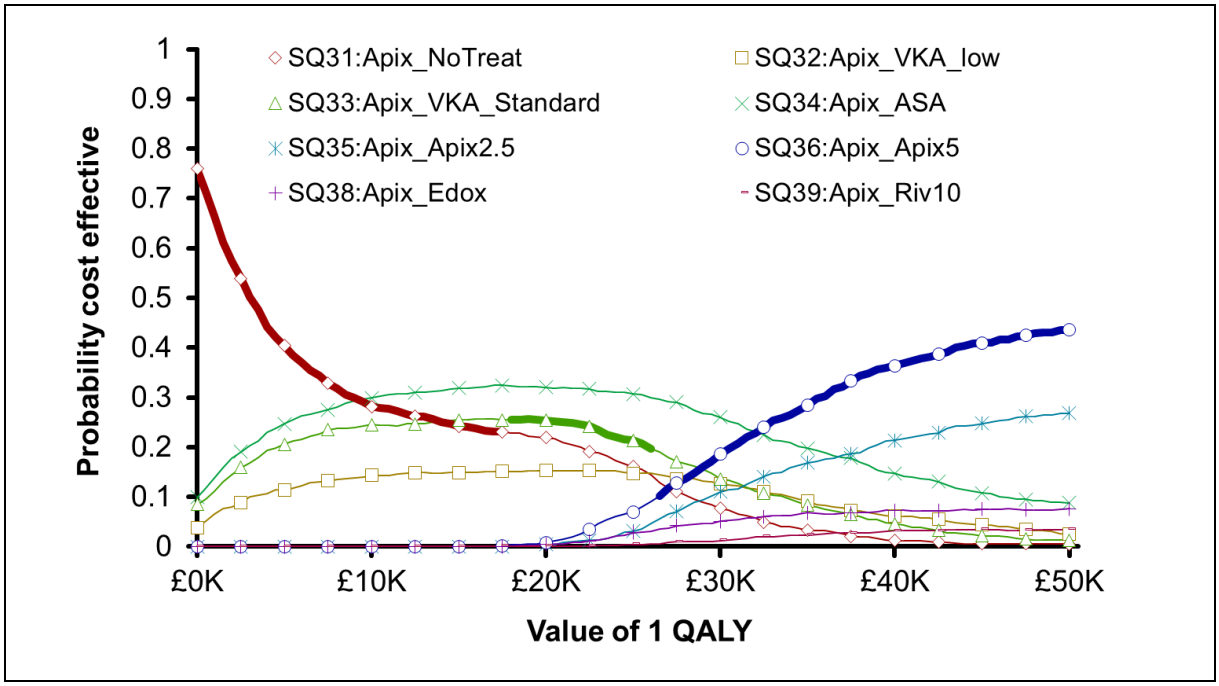
Strategy	Absolute		Incremental			Rank NMB[(a)]
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)	
SQ31:Apix_NoTreat	£1,341	7.543				2
SQ33:Apix_VKA_Standard	£1,351	7.543	£10	0.001	£12,052	1
SQ34:Apix_ASA	£1,358	7.543	£7	0.000	dominated	3
SQ32:Apix_VKA_low	£1,361	7.541	£10	-0.002	dominated	6
SQ61:Riv_NoTreat	£1,410	7.529	£59	-0.014	dominated	12
SQ63:Riv_VKA_Standard	£1,420	7.530	£69	-0.013	dominated	11
SQ64:Riv_ASA	£1,427	7.530	£75	-0.014	dominated	13
SQ62:Riv_VKA_low	£1,429	7.528	£78	-0.015	dominated	16
SQ1:LmwhVKA_NoTreat	£1,435	7.504	£84	-0.040	dominated	40
SQ3:LmwhVKA_VKA_Standard	£1,445	7.504	£94	-0.039	dominated	39
SQ51:Edox_NoTreat	£1,448	7.514	£97	-0.029	dominated	22
SQ4:LmwhVKA_ASA	£1,451	7.504	£100	-0.039	dominated	41
SQ2:LmwhVKA_VKA_low	£1,454	7.502	£103	-0.041	dominated	45
SQ53:Edox_VKA_Standard	£1,458	7.515	£107	-0.029	dominated	21
SQ41:Dabig_NoTreat	£1,461	7.514	£110	-0.030	dominated	25
SQ54:Edox_ASA	£1,465	7.515	£113	-0.029	dominated	23
SQ52:Edox_VKA_low	£1,467	7.513	£116	-0.031	dominated	29
SQ43:Dabig_VKA_Standard	£1,471	7.514	£120	-0.029	dominated	24
SQ44:Dabig_ASA	£1,477	7.514	£126	-0.029	dominated	26
SQ42:Dabig_VKA_low	£1,480	7.512	£129	-0.031	dominated	32
SQ21:FondVKA_NoTreat	£1,510	7.497	£158	-0.046	dominated	51
SQ37:Apix_Dabig	£1,517	7.547	£166	0.003	ext. dom.	7
SQ23:FondVKA_VKA_Standard	£1,519	7.498	£168	-0.045	dominated	50
SQ24:FondVKA_ASA	£1,526	7.498	£175	-0.045	dominated	4
SQ36:Apix_Apix5	£1,526	7.550	£175	0.007	£26,161	52
SQ38:Apix_Edox	£1,527	7.545	£1	-0.005	dominated	5
SQ35:Apix_Apix2.5	£1,527	7.550	£1	0.000	dominated	8
SQ22:FondVKA_VKA_low	£1,528	7.496	£2	-0.054	dominated	56

Strategy	Absolute		Incremental			Rank NMB[(a)]
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)	
SQ39:Apix_Riv10	£1,535	7.544	£9	-0.006	dominated	9
SQ40:Apix_Riv20	£1,544	7.541	£18	-0.009	dominated	10
SQ11:UnfVKA_NoTreat	£1,576	7.482	£50	-0.069	dominated	62
SQ67:Riv_Dabig	£1,583	7.533	£57	-0.017	dominated	17
SQ13:UnfVKA_VKA_Standard	£1,585	7.482	£60	-0.068	dominated	61
SQ66:Riv_Apix5	£1,592	7.537	£66	-0.013	dominated	14
SQ14:UnfVKA_ASA	£1,592	7.482	£66	-0.068	dominated	18
SQ68:Riv_Edox	£1,592	7.531	£66	-0.019	dominated	63
SQ65:Riv_Apix2.5	£1,593	7.536	£67	-0.014	dominated	15
SQ12:UnfVKA_VKA_low	£1,594	7.480	£68	-0.070	dominated	66
SQ69:Riv_Riv10	£1,601	7.531	£75	-0.020	dominated	19
SQ7:LmwhVKA_Dabig	£1,606	7.507	£80	-0.043	dominated	47
SQ70:Riv_Riv20	£1,610	7.528	£84	-0.022	dominated	20
SQ6:LmwhVKA_Apix5	£1,614	7.511	£88	-0.039	dominated	43
SQ8:LmwhVKA_Edox	£1,615	7.506	£89	-0.044	dominated	44
SQ5:LmwhVKA_Apix2.5	£1,615	7.510	£89	-0.040	dominated	48
SQ57:Edox_Dabig	£1,621	7.518	£95	-0.032	dominated	33
SQ9:LmwhVKA_Riv10	£1,623	7.505	£97	-0.045	dominated	49
SQ56:Edox_Apix5	£1,630	7.521	£104	-0.029	dominated	27
SQ58:Edox_Edox	£1,631	7.516	£105	-0.034	dominated	28
SQ55:Edox_Apix2.5	£1,631	7.521	£105	-0.029	dominated	35
SQ10:LmwhVKA_Riv20	£1,632	7.502	£106	-0.048	dominated	34
SQ47:Dabig_Dabig	£1,632	7.518	£106	-0.033	dominated	53
SQ59:Edox_Riv10	£1,639	7.515	£113	-0.035	dominated	37
SQ46:Dabig_Apix5	£1,641	7.521	£115	-0.029	dominated	30
SQ48:Dabig_Edox	£1,641	7.516	£115	-0.034	dominated	36
SQ45:Dabig_Apix2.5	£1,642	7.521	£116	-0.029	dominated	31
SQ60:Edox_Riv20	£1,648	7.513	£122	-0.037	dominated	42
SQ49:Dabig_Riv10	£1,650	7.515	£124	-0.035	dominated	38
SQ50:Dabig_Riv20	£1,659	7.513	£133	-0.038	dominated	46
SQ27:FondVKA_Dabig	£1,680	7.501	£154	-0.049	dominated	57
SQ26:FondVKA_Apix5	£1,689	7.505	£163	-0.045	dominated	54
SQ28:FondVKA_Edox	£1,690	7.499	£164	-0.051	dominated	55
SQ25:FondVKA_Apix2.5	£1,690	7.504	£164	-0.046	dominated	58
SQ29:FondVKA_Riv10	£1,698	7.499	£172	-0.051	dominated	59
SQ30:FondVKA_Riv20	£1,707	7.496	£181	-0.054	dominated	60
SQ17:UnfVKA_Dabig	£1,742	7.485	£216	-0.065	dominated	67
SQ16:UnfVKA_Apix5	£1,750	7.489	£224	-0.061	dominated	64
SQ18:UnfVKA_Edox	£1,751	7.484	£225	-0.066	dominated	65
SQ15:UnfVKA_Apix2.5	£1,751	7.488	£225	-0.062	dominated	68

Strategy	Absolute		Incremental			Rank NMB[(a)]
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)	
SQ19:UnfVKA_Riv10	£1,759	7.483	£233	-0.067	dominated	69
SQ20:UnfVKA_Riv20	£1,767	7.480	£241	-0.070	dominated	70

(a) Based on net monetary benefit at £20,000/QALY

Figure 8: Cost-effectiveness acceptability curve for the sequencing analysis (all strategies) - DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) – DVT

Prior to running the model, the committee noted that a person would not normally switch from a DOAC as initial treatment to a VKA as extended therapy unless there were specific tolerability concerns. This is because switching to a VKA would require the introduction of INR monitoring visits that patients may find inconvenient and unacceptable. Table 11 presents the incremental cost-effectiveness results for non-dominated strategies if treatment strategies that involve switching from a DOAC to a VKA are removed from the decision space. In addition, given the virtually identical costs and QALYs for the different apixaban doses in extended therapy, only strategies at the licensed dose of 2.5 mg twice daily for extended therapy have been retained to simplify interpretation of the CEACs (Figure 9).

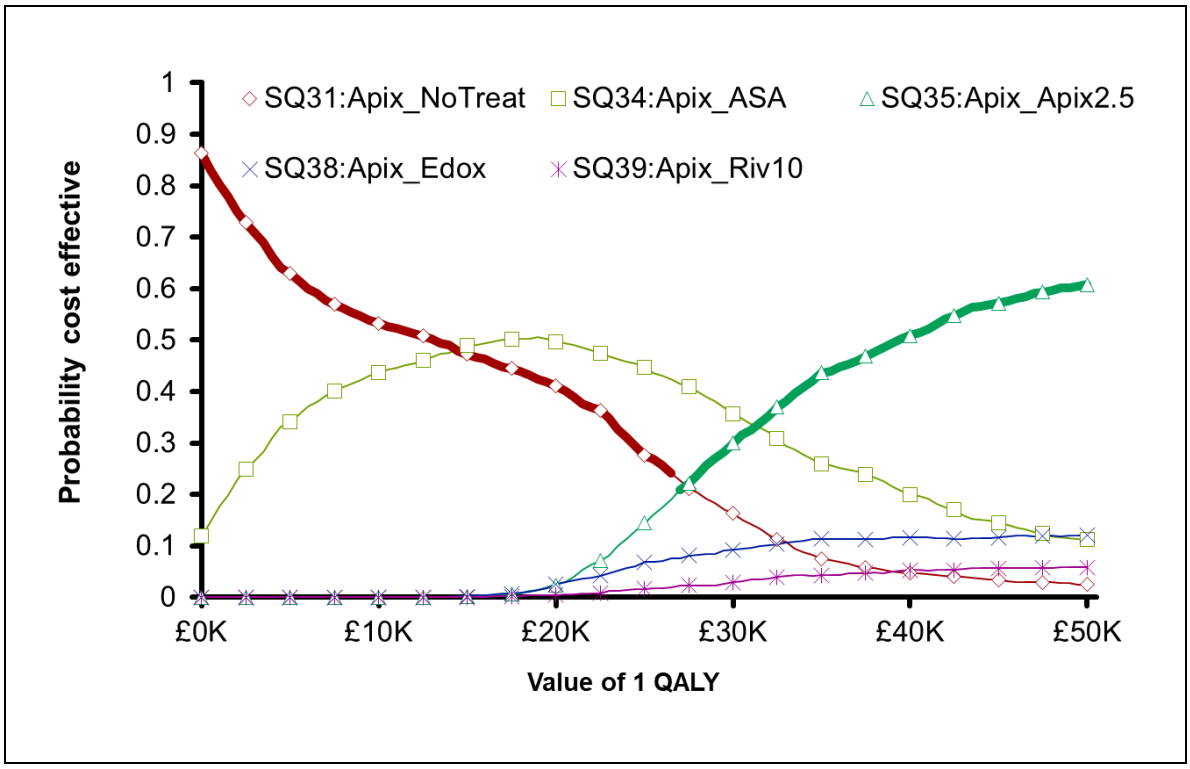
In this scenario, the least costly strategy is still apixaban followed by no treatment. Apixaban followed by apixaban (2.5 mg) is the only strategy that is not dominated with an ICER of £26,009/QALY.

The strategy apixaban followed by aspirin is not on the cost-effectiveness frontier in the deterministic analysis because it is extendedly dominated but at a threshold value of £20,000/QALY, it is the strategy with the highest probability of being cost effective.

Table 11: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, no VKA after DOAC) - DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ31:Apix_NoTreat	£1,341	7.543			
SQ35:Apix_Apix2.5	£1,527	7.550	£185	0.007	£26,009

Figure 9: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) - DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – DVT

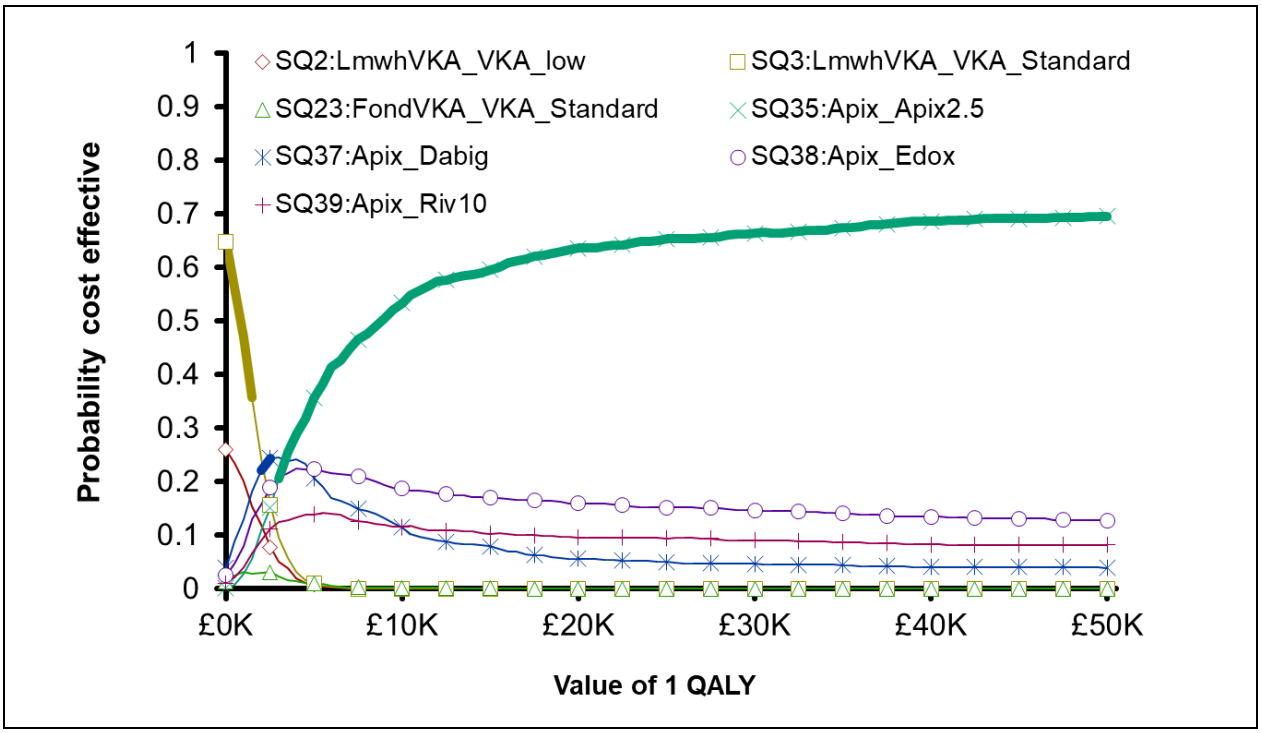
Results of the extended therapy NMAs showed that aspirin was less effective for the outcome VTE recurrence than the DOACs or warfarin and the committee felt that in clinical practice, aspirin would not be an appropriate option for long-term secondary prevention in all patients, particularly those who have had more than one VTE and are at higher risk of recurrence. Similarly, no treatment is unlikely to be an appropriate option for these people in the extended phase. Table 12 presents the non-dominated incremental cost-effectiveness results when strategies containing no treatment or aspirin in the extended phase are also removed from the decision space. The least costly strategy is now LMWH/VKA followed by

VKA standard. Apixaban followed by apixaban (2.5 mg twice daily) remains the strategy that generates the most QALYs, with an ICER of £3,035/QALY compared to apixaban followed by dabigatran. The CEAC for this scenario in Figure 10 shows that the strategy of starting on apixaban as initial treatment and remaining on apixaban for extended therapy has a 63% probability of being cost effective at a threshold value of £20,000/QALY.

Table 12: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – DVT

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ3:LmwhVKA_VKA_Standard	£1,445	7.504			
SQ37:Apix_Dabig	£1,517	7.547	£72	0.042	£1,709
SQ35:Apix_Apix2.5	£1,527	7.550	£10	0.003	£3,035

Figure 10: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (separate incremental results for strategies starting with LMWH/VKA, apixaban, dabigatran, edoxaban or rivaroxaban) – DVT

The committee was also interested in understanding what is the most cost-effective treatment for a given initial treatment. Table 13 reports incremental cost-effectiveness results separately for strategies beginning with LMWH/VKA, apixaban, dabigatran, edoxaban or rivaroxaban as the initial treatment. As above, these results omit strategies that were deemed by the committee not to be clinically relevant for the majority of patients and exclude the following extended therapy options: VKA after DOACs, aspirin and no treatment. Apixaban 5mg was also omitted to simplify interpretation of the ICERs because it produced identical results to apixaban 2.5mg. When LMWH/VKA is used as the initial treatment, the

strategy of switching to apixaban in the extended therapy phase generates the most QALYs, with an ICER of £27,826/QALY in comparison to the strategy of remaining on a VKA. That is to say, if a person starts on LMWH/VKA in the initial treatment phase, switching to any DOAC in the extended phase is unlikely to be cost effective. For strategies that start with a DOAC as initial treatment, apixaban 2.5 mg is the most cost-effective extended therapy option.

Table 13: Deterministic incremental cost-effectiveness results presented separately by initial treatment – DVT

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
LMWH/VKA as initial treatment					
SQ3:LmwhVKA_VKA_Standard	£1,445	7.504			
SQ2:LmwhVKA_VKA_low	£1,454	7.502	£9	-0.002	dominated
SQ7:LmwhVKA_Dabig	£1,606	7.507	£161	0.003	ext. dom.
SQ8:LmwhVKA_Edox	£1,615	7.506	£170	0.001	dominated
SQ5:LmwhVKA_Apix2.5	£1,615	7.510	£170	0.006	£27,826
SQ9:LmwhVKA_Riv10	£1,623	7.505	£8	-0.006	dominated
SQ10:LmwhVKA_Riv20	£1,632	7.502	£17	-0.008	dominated
Apixaban as initial treatment					
SQ37:Apix_Dabig	£1,517	7.547			
SQ38:Apix_Edox	£1,527	7.545	£10	-0.002	dominated
SQ35:Apix_Apix2.5	£1,527	7.550	£10	0.003	£3,035
SQ39:Apix_Riv10	£1,535	7.544	£8	-0.006	dominated
SQ40:Apix_Riv20	£1,544	7.541	£17	-0.008	dominated
Dabigatran as initial treatment					
SQ47:Dabig_Dabig	£1,632	7.518			
SQ48:Dabig_Edox	£1,641	7.516	£9	-0.002	dominated
SQ45:Dabig_Apix2.5	£1,642	7.521	£9	0.003	£3,043
SQ49:Dabig_Riv10	£1,650	7.515	£8	-0.006	dominated
SQ50:Dabig_Riv20	£1,659	7.513	£17	-0.008	dominated
Edoxaban as initial treatment					
SQ57:Edox_Dabig	£1,621	7.518			
SQ58:Edox_Edox	£1,631	7.516	£9	-0.002	dominated
SQ55:Edox_Apix2.5	£1,631	7.521	£10	0.003	£3,045
SQ59:Edox_Riv10	£1,639	7.515	£8	-0.006	dominated
SQ60:Edox_Riv20	£1,648	7.513	£17	-0.008	dominated
Rivaroxaban as initial treatment					
SQ67:Riv_Dabig	£1,583	7.533			
SQ68:Riv_Edox	£1,592	7.531	£9	-0.002	dominated
SQ65:Riv_Apix2.5	£1,593	7.536	£10	0.003	£3,039
SQ69:Riv_Riv10	£1,601	7.531	£8	-0.006	dominated
SQ70:Riv_Riv20	£1,610	7.528	£17	-0.008	dominated

Sequencing analysis (all strategies) - PE

Table 14 shows the deterministic cost-effectiveness results for all 70 potential strategies assuming treatment switching from any initial treatment to any extended therapy is possible following a PE index event. The sequence of apixaban as initial treatment followed by apixaban (5 mg twice daily) in the extended therapy phase generates the most QALYs. Similar to the results for DVT, the sequence of apixaban as initial treatment followed by no treatment in the extended therapy phase is the least costly strategy. The next least costly strategy is the sequence apixaban followed by VKA standard, with an ICER of £4,300/QALY compared to apixaban followed by no treatment. The ICER for the sequence apixaban followed by apixaban (5 mg) versus apixaban followed by VKA standard is £27,247/QALY

Similar to the results for DVT, the QALY differences between strategies that begin with the same initial treatment are very small. In particular, the strategies apixaban followed by apixaban (5 mg) and apixaban followed by apixaban (2.5 mg) generate virtually identical costs and QALYs.

At a threshold value of £20,000/QALY, the strategy with the highest net monetary benefit and the highest probability of being cost effective is the sequence apixaban followed by VKA standard but Figure 11 shows there is considerable uncertainty in the results; no strategy achieves >50% probability of being cost effective at threshold values above £2,000/QALY.

Table 14: Deterministic incremental cost-effectiveness results for the sequencing analysis (all strategies) - PE

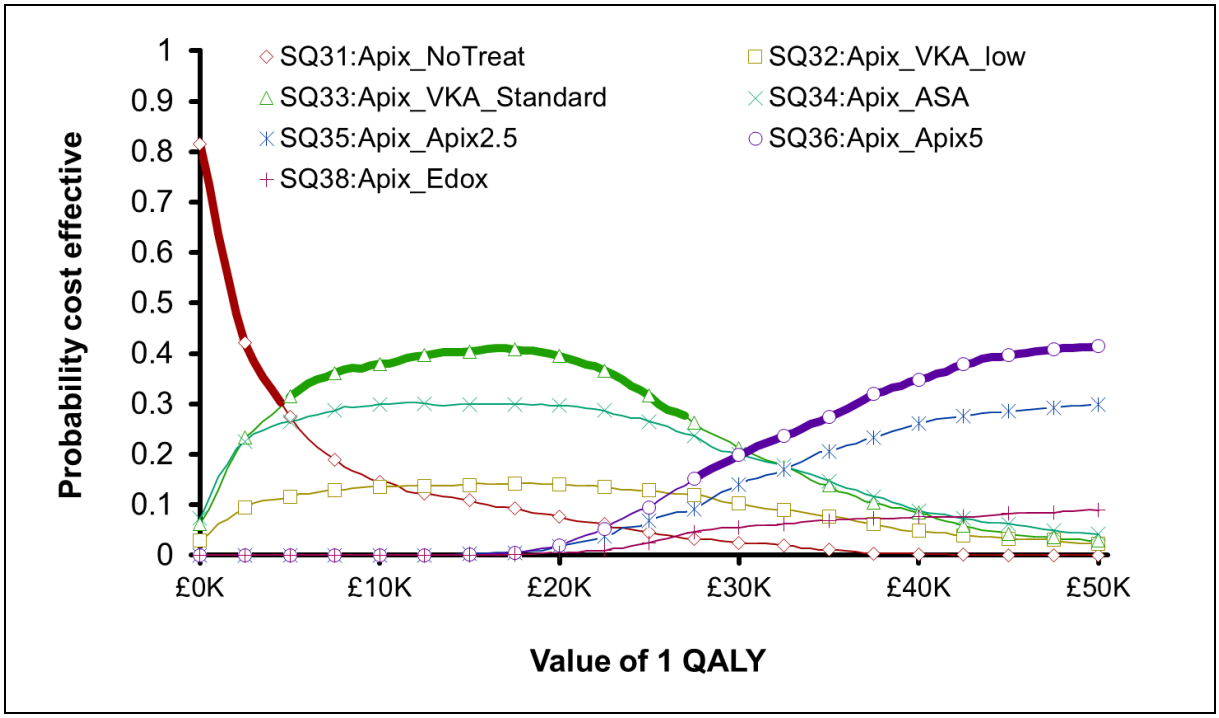
Strategy	Absolute		Incremental			Rank NMB[(a)]
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)	
SQ31:Apix_NoTreat	£2,863	7.438				3
SQ33:Apix_VKA_Standard	£2,874	7.441	£12	0.003	£4,300	1
SQ34:Apix_ASA	£2,878	7.440	£3	-0.001	dominated	2
SQ32:Apix_VKA_low	£2,882	7.439	£8	-0.002	dominated	6
SQ61:Riv_NoTreat	£2,930	7.425	£55	-0.016	dominated	13
SQ63:Riv_VKA_Standard	£2,941	7.427	£67	-0.014	dominated	11
SQ64:Riv_ASA	£2,945	7.426	£70	-0.015	dominated	12
SQ62:Riv_VKA_low	£2,949	7.425	£74	-0.016	dominated	16
SQ1:LmwhVKA_NoTreat	£2,956	7.398	£82	-0.043	dominated	42
SQ51:Edox_NoTreat	£2,964	7.410	£90	-0.031	dominated	23
SQ3:LmwhVKA_VKA_Standard	£2,968	7.401	£93	-0.040	dominated	39
SQ4:LmwhVKA_ASA	£2,971	7.399	£97	-0.042	dominated	41
SQ2:LmwhVKA_VKA_low	£2,975	7.398	£101	-0.043	dominated	21
SQ53:Edox_VKA_Standard	£2,975	7.413	£101	-0.028	dominated	45
SQ54:Edox_ASA	£2,979	7.412	£105	-0.029	dominated	22
SQ41:Dabig_NoTreat	£2,981	7.407	£107	-0.034	dominated	30
SQ52:Edox_VKA_low	£2,983	7.411	£109	-0.030	dominated	26
SQ43:Dabig_VKA_Standard	£2,992	7.409	£118	-0.032	dominated	27
SQ44:Dabig_ASA	£2,996	7.408	£121	-0.033	dominated	29
SQ42:Dabig_VKA_low	£3,000	7.407	£125	-0.034	dominated	34
SQ21:FondVKA_NoTreat	£3,028	7.392	£154	-0.049	dominated	53

Strategy	Absolute		Incremental			Rank NMB[(a)]
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)	
SQ37:Apix_Dabig	£3,035	7.444	£161	0.003	ext. dom.	7
SQ23:FondVKA_VKA_Standard	£3,039	7.395	£165	-0.046	dominated	50
SQ24:FondVKA_ASA	£3,043	7.394	£168	-0.047	dominated	51
SQ36:Apix_Apix5	£3,044	7.447	£169	0.006	£27,247	4
SQ38:Apix_Edox	£3,044	7.442	£0	-0.005	dominated	5
SQ35:Apix_Apix2.5	£3,044	7.447	£1	0.000	dominated	8
SQ22:FondVKA_VKA_low	£3,047	7.393	£3	-0.055	dominated	56
SQ39:Apix_Riv10	£3,052	7.441	£8	-0.006	dominated	9
SQ40:Apix_Riv20	£3,060	7.439	£16	-0.008	dominated	10
SQ11:UnfVKA_NoTreat	£3,096	7.373	£52	-0.075	dominated	63
SQ67:Riv_Dabig	£3,099	7.430	£55	-0.017	dominated	17
SQ13:UnfVKA_VKA_Standard	£3,107	7.375	£63	-0.072	dominated	61
SQ66:Riv_Apix5	£3,108	7.433	£64	-0.014	dominated	14
SQ68:Riv_Edox	£3,108	7.429	£64	-0.019	dominated	18
SQ65:Riv_Apix2.5	£3,109	7.433	£65	-0.014	dominated	15
SQ14:UnfVKA_ASA	£3,110	7.374	£67	-0.073	dominated	62
SQ12:UnfVKA_VKA_low	£3,114	7.373	£70	-0.074	dominated	66
SQ69:Riv_Riv10	£3,116	7.427	£72	-0.020	dominated	19
SQ7:LmwhVKA_Dabig	£3,123	7.403	£79	-0.044	dominated	47
SQ70:Riv_Riv20	£3,124	7.425	£80	-0.022	dominated	20
SQ6:LmwhVKA_Apix5	£3,132	7.407	£88	-0.041	dominated	43
SQ8:LmwhVKA_Edox	£3,132	7.402	£88	-0.045	dominated	48
SQ5:LmwhVKA_Apix2.5	£3,133	7.406	£89	-0.041	dominated	44
SQ57:Edox_Dabig	£3,134	7.416	£90	-0.031	dominated	28
SQ9:LmwhVKA_Riv10	£3,140	7.401	£96	-0.046	dominated	49
SQ56:Edox_Apix5	£3,143	7.419	£99	-0.028	dominated	24
SQ58:Edox_Edox	£3,143	7.414	£99	-0.033	dominated	25
SQ55:Edox_Apix2.5	£3,143	7.419	£100	-0.028	dominated	32
SQ10:LmwhVKA_Riv20	£3,148	7.398	£104	-0.049	dominated	52
SQ47:Dabig_Dabig	£3,149	7.412	£105	-0.035	dominated	36
SQ59:Edox_Riv10	£3,151	7.413	£107	-0.034	dominated	35
SQ46:Dabig_Apix5	£3,157	7.415	£114	-0.032	dominated	31
SQ48:Dabig_Edox	£3,157	7.411	£114	-0.037	dominated	38
SQ45:Dabig_Apix2.5	£3,158	7.415	£114	-0.032	dominated	33
SQ60:Edox_Riv20	£3,159	7.411	£115	-0.036	dominated	37
SQ49:Dabig_Riv10	£3,165	7.410	£121	-0.038	dominated	40
SQ50:Dabig_Riv20	£3,173	7.407	£129	-0.040	dominated	46
SQ27:FondVKA_Dabig	£3,195	7.398	£152	-0.049	dominated	57
SQ26:FondVKA_Apix5	£3,204	7.401	£160	-0.046	dominated	54
SQ28:FondVKA_Edox	£3,204	7.396	£160	-0.051	dominated	58

Strategy	Absolute		Incremental			Rank NMB[(a)]
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)	
SQ25:FondVKA_Apix2.5	£3,205	7.401	£161	-0.047	dominated	55
SQ29:FondVKA_Riv10	£3,212	7.395	£168	-0.052	dominated	59
SQ30:FondVKA_Riv20	£3,220	7.393	£176	-0.054	dominated	60
SQ17:UnfVKA_Dabig	£3,259	7.378	£215	-0.069	dominated	67
SQ18:UnfVKA_Edox	£3,267	7.376	£223	-0.071	dominated	64
SQ16:UnfVKA_Apix5	£3,267	7.381	£223	-0.066	dominated	68
SQ15:UnfVKA_Apix2.5	£3,268	7.381	£224	-0.067	dominated	65
SQ19:UnfVKA_Riv10	£3,275	7.375	£231	-0.072	dominated	69
SQ20:UnfVKA_Riv20	£3,283	7.373	£239	-0.074	dominated	70

(a) Based on net monetary benefit at £20,000/QALY

Figure 11: Cost-effectiveness acceptability curve for the sequencing analysis (all strategies) - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) - PE

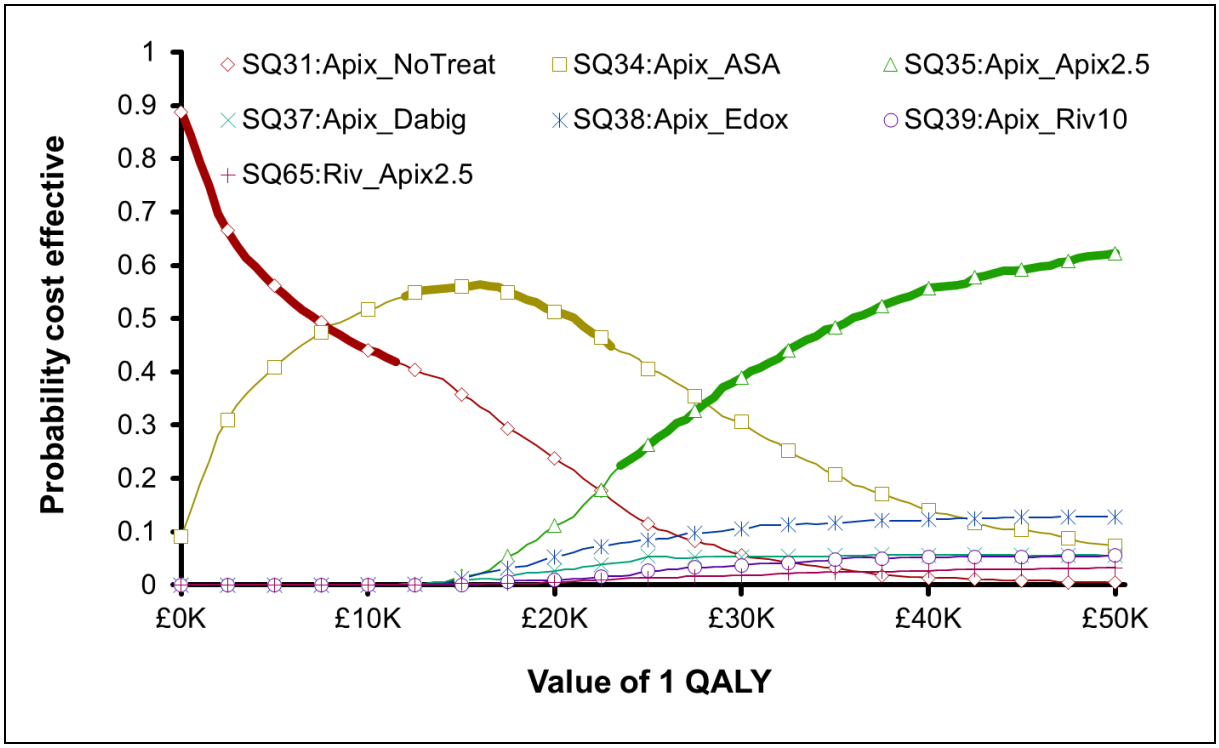
Table 15 presents the non-dominated incremental cost-effectiveness results if all treatment strategies that involve switching from a DOAC to a VKA are removed from the decision space. In addition, given the virtually identical costs and QALYs for the different apixaban doses in extended therapy, only strategies at the licensed dose of 2.5 mg twice daily for extended therapy have been retained to simplify interpretation of the CEACs (Figure 12).

The least costly strategy is still apixaban followed by no treatment. Compared to the least costly strategy, apixaban followed by aspirin has an ICER of £11,134/QALY. Apixaban followed by apixaban (2.5 mg twice daily) is the only other strategy that is not dominated, with an ICER of £23,035/QALY compared to apixaban followed by aspirin.

Table 15: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) - PE

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
SQ31:Apix_NoTreat	£2,863	7.438			
SQ34:Apix_ASA	£2,878	7.440	£15	0.001	£11,134
SQ35:Apix_Apix2.5	£3,044	7.447	£167	0.007	£23,035

Figure 12: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC) - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – PE

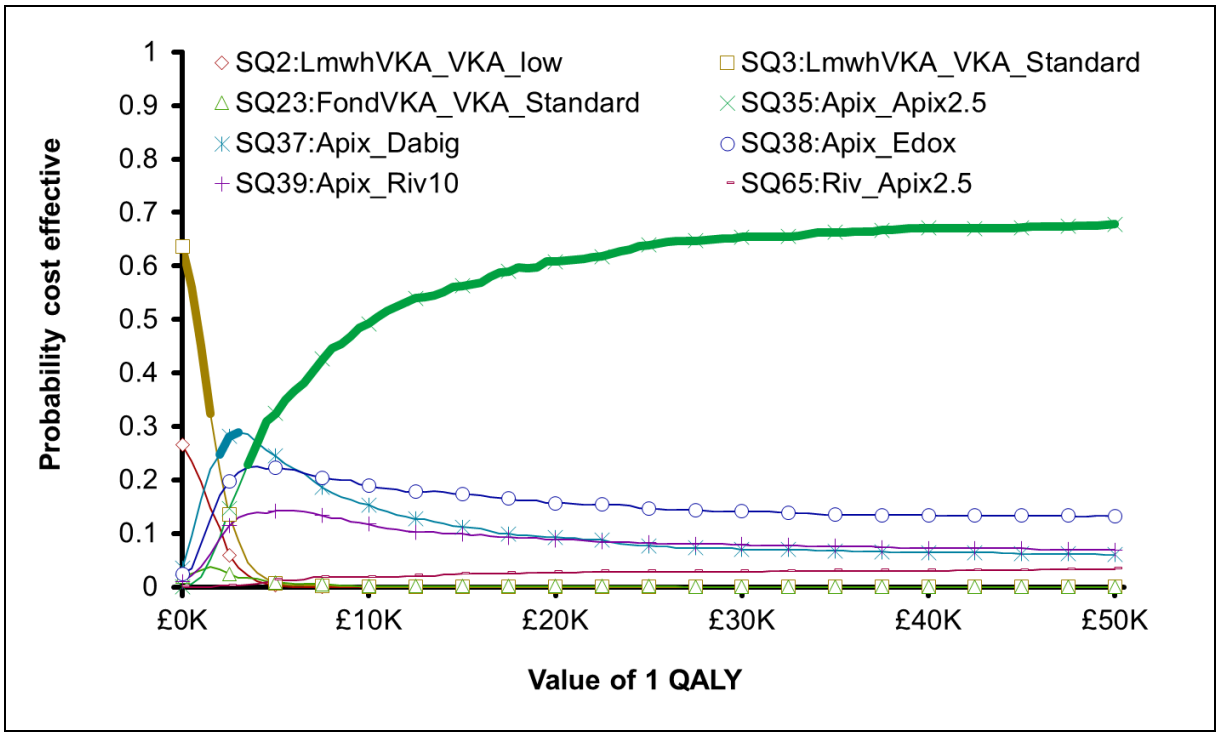
Table 16 presents the non-dominated incremental cost-effectiveness results when strategies containing no treatment or aspirin in the extended phase are also removed from the decision space. The least costly strategy is now LMWH/VKA followed by VKA standard. Apixaban followed by apixaban (2.5 mg twice daily) remains the most cost-effective strategy, with an ICER of £3,283/QALY compared to apixaban followed by dabigatran.

Figure 13 shows the CEAC for this scenario, with apixaban followed by apixaban 2.5 mg having 61% probability of being cost effective.

Table 16: Deterministic incremental cost-effectiveness results showing non-dominated strategies only for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – PE

	Absolute		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
SQ3:LmwhVKA_VKA_Standard	£2,968	7.401			
SQ37:Apix_Dabig	£3,035	7.444	£67	0.043	£1,551
SQ35:Apix_Apix2.5	£3,044	7.447	£10	0.003	£3,283

Figure 13: Cost-effectiveness acceptability curve for the sequencing analysis (excluding apixaban 5 mg, VKA after DOAC, no treatment, aspirin) – PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Sequencing analysis (separate incremental results for strategies starting with LMWH/VKA, apixaban, dabigatran, edoxaban or rivaroxaban) – PE

Table 17 shows separate incremental cost-effectiveness results for strategies starting with LMWH/VKA, apixaban, dabigatran, edoxaban or rivaroxaban in PE. The results are consistent with those for DVT.

Table 17: Deterministic incremental cost-effectiveness results presented separately by initial treatment – PE

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
LMWH/VKA as initial treatment					
SQ3:LmwhVKA_VKA_Standard	£2,968	7.401			
SQ4:LmwhVKA_ASA	£2,971	7.399	£3	-0.001	dominated
SQ2:LmwhVKA_VKA_low	£2,975	7.398	£7	-0.002	dominated
SQ7:LmwhVKA_Dabig	£3,123	7.403	£156	0.003	ext. dom.
SQ8:LmwhVKA_Edox	£3,132	7.402	£164	0.001	dominated
SQ5:LmwhVKA_Apix2.5	£3,133	7.406	£165	0.006	£28,969
SQ9:LmwhVKA_Riv10	£3,140	7.401	£7	-0.005	dominated
Apixaban as initial treatment					
SQ37:Apix_Dabig	£3,035	7.444			
SQ38:Apix_Edox	£3,044	7.442	£9	-0.002	dominated
SQ35:Apix_Apix2.5	£3,044	7.447	£10	0.003	£3,283
SQ39:Apix_Riv10	£3,052	7.441	£7	-0.006	dominated
SQ40:Apix_Riv20	£3,060	7.439	£16	-0.008	dominated
Dabigatran as initial treatment					
SQ47:Dabig_Dabig	£3,149	7.412			
SQ48:Dabig_Edox	£3,157	7.411	£9	-0.002	dominated
SQ45:Dabig_Apix2.5	£3,158	7.415	£9	0.003	£3,291
SQ49:Dabig_Riv10	£3,165	7.410	£7	-0.005	dominated
SQ50:Dabig_Riv20	£3,173	7.407	£15	-0.008	dominated
Edoxaban as initial treatment					
SQ57:Edox_Dabig	£3,134	7.416			
SQ58:Edox_Edox	£3,143	7.414	£9	-0.002	dominated
SQ55:Edox_Apix2.5	£3,143	7.419	£10	0.003	£3,292
SQ59:Edox_Riv10	£3,151	7.413	£7	-0.006	dominated
SQ60:Edox_Riv20	£3,159	7.411	£15	-0.008	dominated
Rivaroxaban as initial treatment					
SQ67:Riv_Dabig	£3,099	7.430			
SQ68:Riv_Edox	£3,108	7.429	£9	-0.002	dominated
SQ65:Riv_Apix2.5	£3,109	7.433	£9	0.003	£3,287
SQ69:Riv_Riv10	£3,116	7.427	£7	-0.005	dominated
SQ70:Riv_Riv20	£3,124	7.425	£16	-0.008	dominated

Subgroup analysis

Cancer population – DVT

Figure 14 presents key events for the cancer population with an index DVT. Rivaroxaban has the lowest number of VTE recurrences while apixaban has the lowest number of major bleeding events. Figure 15 shows that LMWH used on its own is by far the most expensive treatment. The category 'other' includes the cost of managing sequelae such as PTS and CTEPH. Costs of cancer treatment are included in the cost-effectiveness analysis but are excluded from Figure 15.

Table 18 reports the incremental cost-effectiveness results. Apixaban produces the most QALYs with an ICER of £12,727 compared to LMWH/VKA, although this was associated with considerable uncertainty. LMWH alone has a 0% probability of being cost effective because although it produces similar QALYs to rivaroxaban, it is much more costly compared to all other treatments.

Figure 14: Number of VTE recurrences and bleeding events per 100 people in the cancer subgroup analysis – DVT

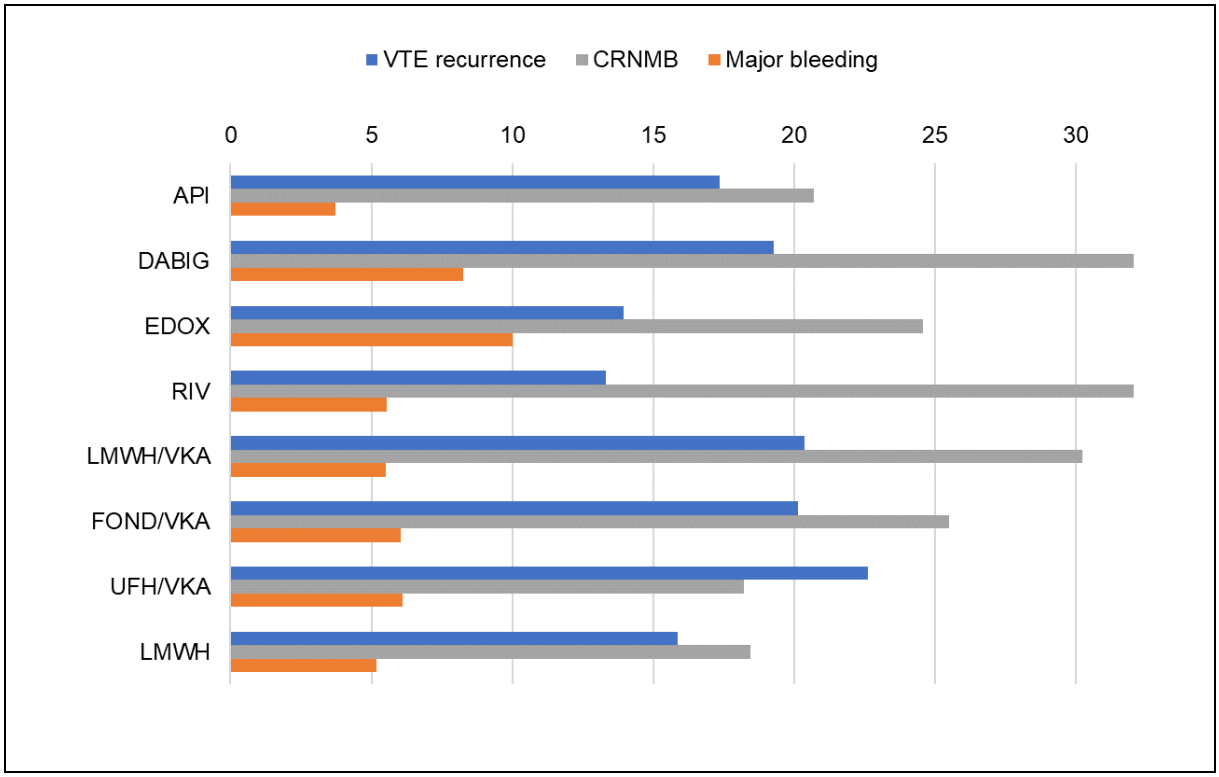


Figure 15: Summary of undiscounted costs by category (excluding cancer-related costs) in the cancer subgroup analysis – DVT

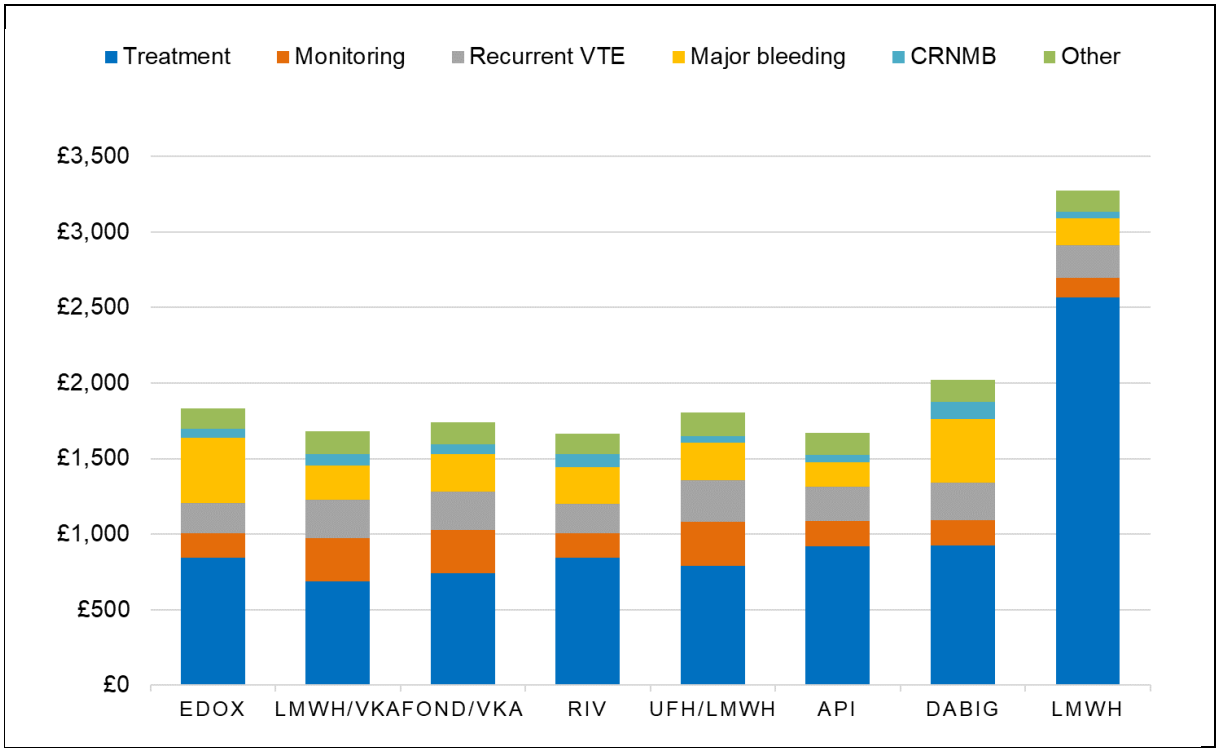
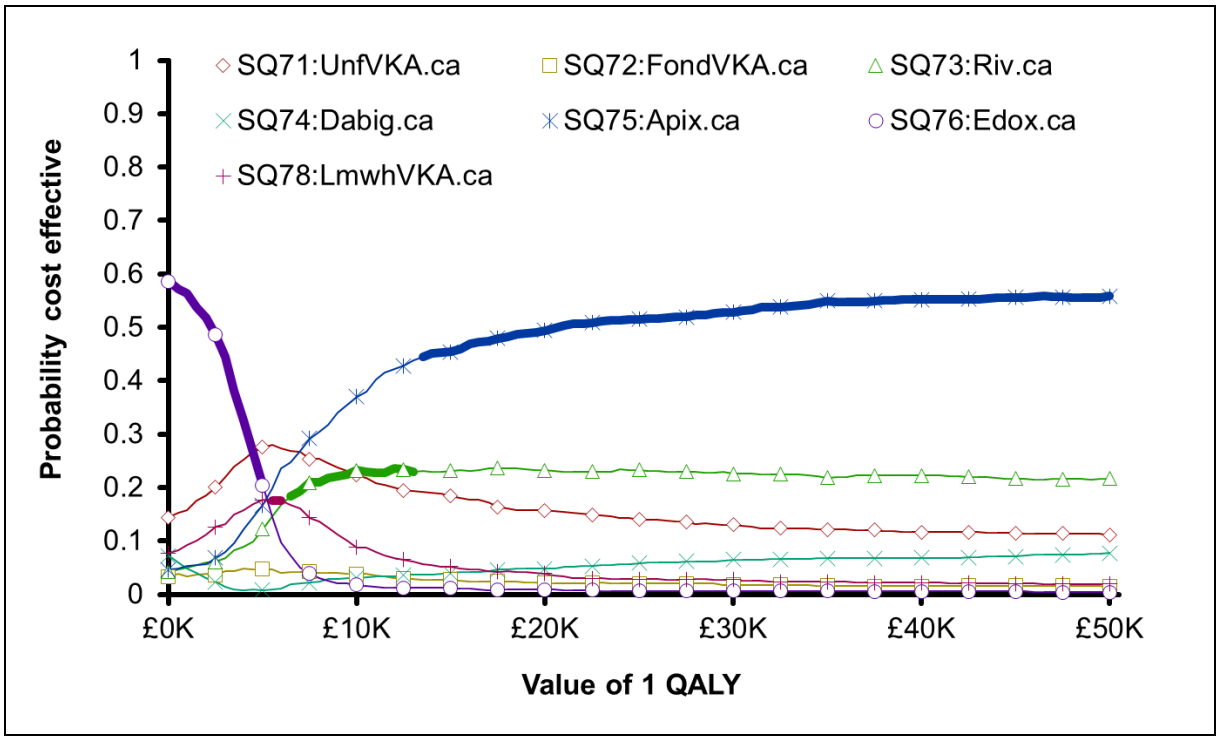


Table 18: Deterministic incremental cost-effectiveness results for the cancer population - DVT

	Absolute		Incremental		
Strategy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER (£/QALY)**
Edoxaban	£19,538	1.390			
LMWH/VKA	£19,650	1.412	£112	0.022	£5,080
Fondaparinux/VKA[(a)]	£19,678	1.409	£28	-0.003	dominated
Rivaroxaban	£19,697	1.418	£47	0.006	£7,716
UFH/VKA	£19,713	1.407	£16	-0.011	dominated
Apixaban	£19,794	1.426	£97	0.008	£12,728
Dabigatran	£19,803	1.396	£9	-0.030	dominated
LMWH	£21,287	1.418	£1,494	-0.008	dominated

(a) No data in the cancer population

Figure 16: Cost-effectiveness acceptability curve for the cancer subgroup - DVT



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Cancer population – PE

Figure 17 and Figure 18 present key events and costs for the cancer population with an index PE. Results for PE are consistent with those for DVT. Table 19 shows that apixaban generates the most QALYs and has an ICER of £15,378/QALY compared to rivaroxaban.

Figure 17: Number of VTE recurrences and bleeding events per 100 people in the cancer subgroup analysis – PE

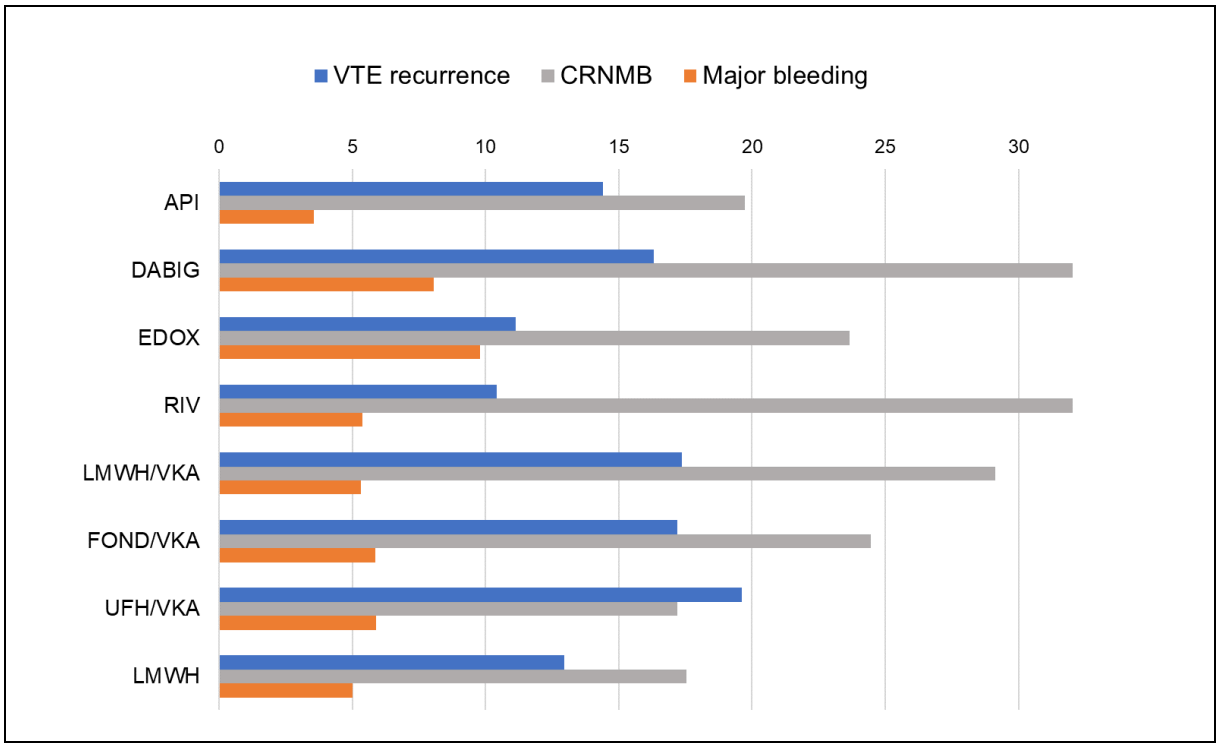


Figure 18: Summary of undiscounted costs by category (excluding cancer-related costs) in the cancer subgroup analysis – PE

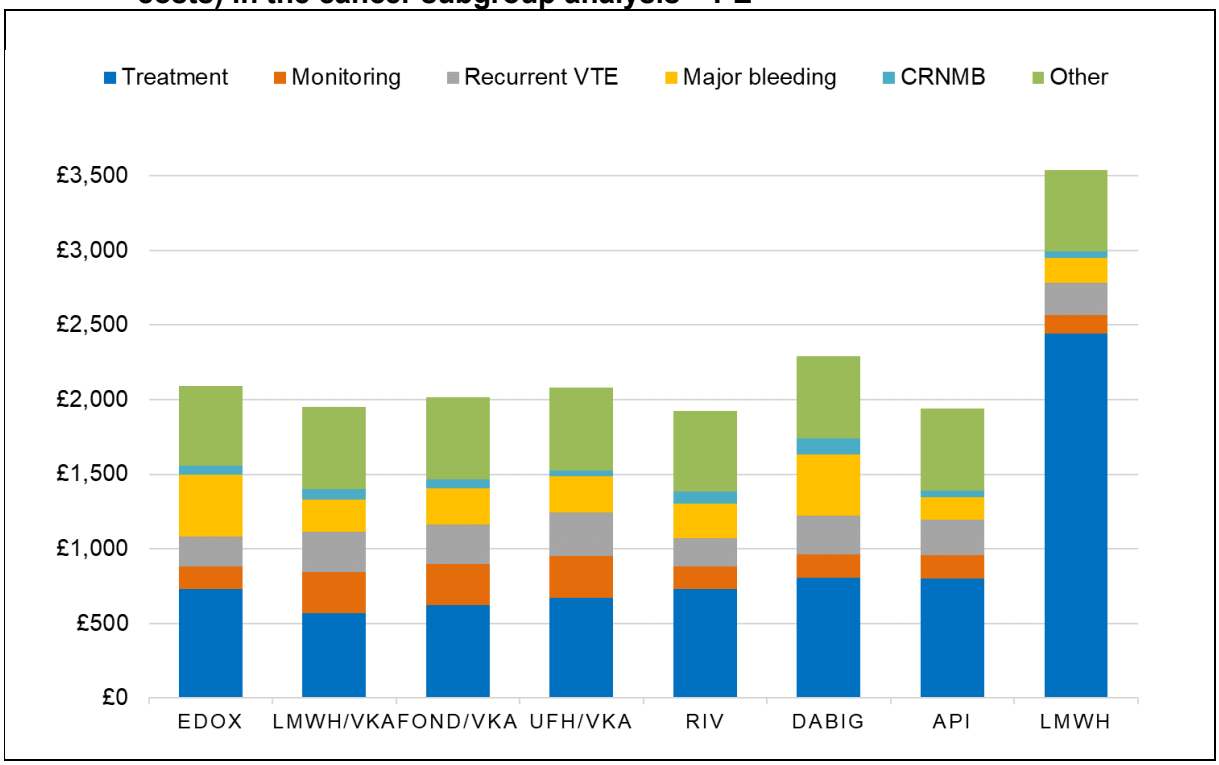
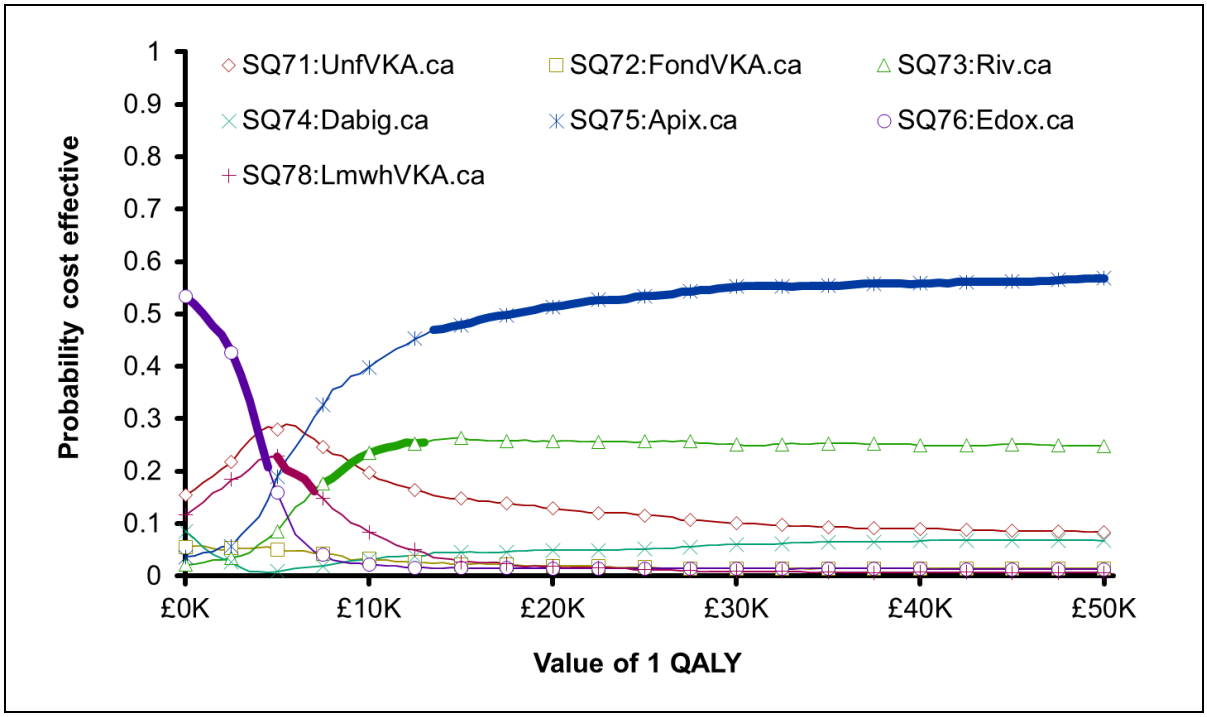


Table 19: Deterministic incremental cost-effectiveness results for the cancer population - PE

Strategy	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER (£/QALY)
Edoxaban	£19,363	1.368			
LMWH/VKA	£19,440	1.386	£78	0.018	£4,340
Fondaparinux/VKA[(a)]	£19,469	1.383	£29	-0.003	dominated
UFH/VKA	£19,493	1.379	£52	-0.007	dominated
Rivaroxaban	£19,521	1.397	£81	0.010	£7,826
Dabigatran	£19,598	1.371	£77	-0.025	dominated
Apixaban	£19,599	1.402	£78	0.005	£15,378
LMWH	£21,094	1.395	£1,496	-0.007	dominated

(a) No data in the cancer population

Figure 19: Cost-effectiveness acceptability curve for the cancer subgroup - PE



Note: Only strategies that have a >3% probability of being cost effective are shown on the graph

Summary of findings

Results of the base-case cost-effectiveness analysis, in which people are assumed to remain on the same treatment in the initial treatment and extended therapy phases, show that apixaban has a high probability of being cost effective. This is because apixaban achieves the biggest reduction in both major bleeding and CRNMB as well as having a favourable effect on VTE recurrence and as a consequence generates the most QALYs. Compared to LMWH/VKA, apixaban has a higher acquisition cost but these costs are partially offset through fewer monitoring visits and lower resource use associated with managing major bleeding events, resulting in an ICER of £1,802/QALY for DVT index events and £1,660/QALY for PE index events.

If the analysis is expanded to consider the option of switching from any initial treatment to any extended therapy, the sequence of apixaban followed by VKA standard had the highest net monetary benefit but probabilistic sensitivity analyses for both DVT and PE showed that there was considerable uncertainty around this result. In addition, prior to running the model, the committee noted that this sequence was unlikely to be relevant to current clinical practice because a person would not normally switch from a DOAC as initial treatment to warfarin as extended therapy unless there were specific clinical concerns. When all sequences of a DOAC followed by a VKA were removed from the decision space, the sequence apixaban followed by aspirin had the highest probability of being cost effective. Although aspirin was not as effective as a VKA or DOACs for the outcome VTE recurrence, it also did not significantly increase the risk of major bleeding compared to placebo and has a low acquisition cost compared to other treatments. When strategies with aspirin, no treatment and switching from a DOAC to a VKA were removed from the decision space, the strategy with the highest probability of being cost effective was to start on apixaban as initial treatment and remain on apixaban in the extended therapy phase. It was noted that the difference in QALYs for all sequences beginning with the same initial treatment were generally very small. This is because there is greater uncertainty surrounding relative treatment effects in the extended phase and because the choice of treatment in the initial treatment phase (when the baseline risk of both VTE recurrence and bleeding are highest) has a much bigger impact on total QALYs.

In people with cancer and VTE, apixaban generated the most QALYs and had the highest probability of being cost effective for both DVTs and PEs but there was more uncertainty in these results compared to the base-case analysis in the overall VTE population. LMWH used on its own was more costly compared to all other treatments and it had a 0% probability of being cost effective for both DVTs and PEs. If compared to LMWH/VKA, LMWH alone generates more QALYs but produces an ICER of approximately £268,000/QALY for DVT and £189,000/QALY for PE.

Evidence statements

Clinical evidence statements for pairwise results for the initial treatment of VTE

Please refer to appendix B for an explanation of the format of the pairwise evidence statements.

Fondaparinux + VKA v LMWH + VKA for the initial treatment of DVT

Low to moderate quality evidence from 1 RCT with 2,205 people **could not differentiate** the following outcomes between people offered fondaparinux + VKA and people offered LMWH + VKA:

- VTE recurrence (overall or PE/DVT-occurrence specifically)
- Major bleeding in the first 14 days of treatment and at 3 months
- Clinically relevant non-major bleeding at 3 months
- VTE-related mortality at 3 months
- All-cause mortality at 3 months

Fondaparinux + VKA v UFH + VKA for the initial treatment of PE.

Low quality evidence from 1 RCT with 2,213 people **found a reduction** in clinically relevant non-major bleeding during the initial 14 days of treatment and at 3 months in people offered fondaparinux + VKA compared to LMWH+VKA.

Very-low to low quality evidence from 1 RCT with 2,213 people **could not differentiate** the following outcomes between people offered fondaparinux + VKA and people offered LMWH + VKA:

- VTE recurrence (overall or PE or DVT-occurrence specifically) at 3 months
- Major bleeding in the first 14 days of treatment and at 3 months
- VTE-related mortality at 3 months
- All-cause mortality at 3 months

LMWH + VKA vs. UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Low to moderate quality evidence from up to 15 RCTs with up to 5,753 people found **a reduction** in major bleeding at 14 days (in all people with a VTE and people with DVT-only) and **reduced** VTE recurrence (for all people with a VTE, and for people specifically with DVT only), all-cause mortality and major bleeding (specifically in people with a DVT-only) at 3 months in people offered LMWH compared to UFH.

Very-low to low quality evidence from up to 15 RCTs with up to 5,753 people **could not differentiate** the following outcomes between people offered LMWH + VKA and people offered UFH + VKA:

- VTE recurrence in the first 14 days and at 3 months (overall, for specifically those with an index PE, those specifically with CrCl≤30ml/min and those specifically with CrCl>30ml/min).

- Major bleeding in the first 14 days (in those specifically with PE) of treatment and at 3 months (overall, in people with any VTE and those specifically with a PE, those specifically with CrCl≤30ml/min and those specifically with CrCl>30ml/min).
- Clinically relevant non-major bleeding at 3 months
- VTE-related mortality at 3 months
- All-cause mortality at 14 days
- Serious adverse event at 3 months

Sensitivity analyses

Sensitivity analyses were carried out to remove studies at high risk of bias from the prioritised outcomes. These analyses did not lead to any meaningful changes in the interpretation of the evidence for any outcomes except for the following, for which there was previously an effect but now **could not differentiate**:

- VTE-recurrence at 3 months (for all participants with VTE and those specifically with an index DVT)
- All-cause mortality at 3 months (for all participants with VTE)

Publication bias

There was no evidence indicating that publication bias influenced the results of any of the outcomes for this comparison.

LMWH + VKA vs. UFH + VKA for the initial treatment of DVT in elderly people with impaired renal function

Low quality evidence from one RCT with people **found an increase** in all-cause mortality in people given LMWH+VKA compared to UFH+VKA.

Apixaban (5/10mg twice daily for 7 days followed by 5mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

High quality evidence from up to 1 RCT with 5,365 people **found a reduction in** major bleeding and clinically relevant non-major bleeding at 6 months in people offered apixaban compared to LMWH+VKA.

High quality evidence from up to 1 RCT with 5,365 people **found no difference** in serious adverse events at 6 months between people offered apixaban and people offered LMWH+VKA.

Very-low to moderate quality evidence from up to 2 RCTs with up to 5,649 people **could not differentiate** the following outcomes between people offered apixaban and people offered LMWH+VKA:

- VTE recurrence (overall or DVT/PE specifically) at 3 months and at 6 months specifically in those with a BMI< 30kg/m^2 BMI ≥30 kg/m^2, those aged <65 years or those aged ≥65 years.
- Major bleeding at 3 months
- Clinically relevant non-major bleeding at 3 months

- All-cause mortality at 3 months
- VTE-recurrence (Overall, for all patients and those specifically with an index DVT and those specifically with an index PE) at 6 months
- Intracranial bleeding at 6 months
- Fatal bleeds at 6 months
- All-cause mortality at 6 months
- VTE-related mortality at 6 months

Apixaban (10mg twice daily for 7 days followed by 5mg twice daily) versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Very-low to low quality evidence from 1 RCTs with up to 79 people **could not differentiate** the following outcomes between people offered apixaban and people offered UFH + VKA:

- VTE recurrence (Overall and PE specifically) at 5.5 months.
- Major bleeding at 5.5 months.
- Clinically relevant non-major bleeding (for all patients and those specifically with an index PE and those specifically with an index DVT) at 5.5 months.
- Serious adverse events at 5.5 months.

Edoxaban (30/60mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Moderate quality evidence from 1 RCT with 8,240 people **found a reduction** in clinically relevant non-major bleeding at 3 months whilst on treatment in those people offered Edoxaban compared to LMWH + VKA.

Moderate quality evidence from 1 RCT with 8,240 people **found a reduction** in clinically relevant non-major bleeding during the treatment period (between 3 and 12 months) in people offered Edoxaban compared to LMWH + VKA but the point estimates were less than the defined individual minimal clinically important differences.

Moderate quality evidence from 1 RCT with 8,240 people **found no difference** in serious adverse events during the treatment period between people offered Edoxaban and people offered LMWH + VKA.

Very -low to moderate quality evidence from 1 RCT with up to 8,240 people **could not differentiate** the following outcomes between people offered Edoxaban and people offered LMWH + VKA:

- VTE-recurrence (overall or DVT/PE specifically; for all people with a VTE or those with a PE specifically) at 3 months and overall during the on-treatment phase (between 3 and 12 months).
- Major bleeding (all major bleeds, intracranial bleeds and fatal bleeds) at 3 months and overall during the on-treatment phase (between 3 and 12 months)
- All-cause mortality during the on-treatment phase (between 3 and 12 months)
- VTE-related mortality during the on-treatment phase (between 3 and 12 months

Very-low quality evidence from 1 RCT with 84 people **could not differentiate** clinically relevant non major bleeding and VTE-recurrence at 3 months between people offered Edoxaban and people offered LMWH + VKA.

Edoxaban (30/60mg once daily) versus Fondaparinux + VKA for the initial treatment of VTE (DVT and/or PE)

Very-low quality evidence from 1 RCT with 50 people **could not differentiate** major bleeding or VTE-recurrence (VTE generally or PE specifically) at 7 days between people offered Edoxaban and people offered LMWH + VKA for the treatment of VTE.

Dabigatran (150mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

High quality evidence from 1 RCT with 5,107 people found a **reduction** in clinically relevant non-major bleeding at 6 months in people offered dabigatran compared to LMWH + VKA.

High quality evidence from 2 RCT with 5,107 people **found no difference** in serious adverse events during the treatment period between people offered Dabigatran and people offered LMWH + VKA.

Low quality evidence on up to 2 RCTs with up to 5,107 people **could not differentiate** the following outcomes between people offered Dabigatran and people offered LMWH + VKA:

- VTE-recurrence (overall or DVT/PE specifically; for all people with a VTE and those specifically with DVT-only, BMI< 30kg/m^2 BMI ≥30 kg/m^2, those aged <65 years or those aged ≥65 years.) at 6 months
- Major bleeding (all major bleeds, intracranial bleeds only and fatal bleeds only) at 6 months
- All-cause mortality at 6 months or at 7months (6 months treatment plus a 30-day follow-up post-treatment)
- VTE-related mortality at 6 months or at 7months (6 months treatment plus a 30-day follow-up post-treatment)
- Major or clinically relevant non-major bleeding event

Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Moderate to high quality evidence from 1 RCT with 3,449 participants **found a reduction in** DVT-occurrence (specifically in those participants with a DVT-only index event) during the on-treatment phase (between 3 and 12 months) in people offered rivaroxaban compared to LMWH + VKA.

Low quality evidence from up to 2 RCTs with up to 8,266 participants **found a reduction in** major-bleeding during the on-treatment phase (in all people with a VTE generally and those with specifically a DVT-only and those with a PE specifically) between 3 and 12 months in people offered rivaroxaban compared to LMWH + VKA.

Very-low quality evidence from two studies reporting data on up to 3,701 people **found a lower** mean score for self-reported treatment burdens at 15 days, 1 months, 2 months, 3 months, 6 months, 12 months and overall, and reported a greater mean score for treatment benefits at 15 days, 1 months, 2 months, 3 months, 6 months and overall, in people offered rivaroxaban compared to LMWH + VKA.

Low to moderate quality evidence from up to 2 RCTs with 8,266 participants **found no difference** in clinically relevant non-major bleeding (In all people with a VTE and those with a PE specifically) or serious adverse events (In all people with a VTE and those with a PE

specifically) during the on-treatment phase (between 3 and 12 months) between people offered rivaroxaban and people offered LMWH + VKA.

Very-low to moderate quality evidence from up to 2 RCTs with up to 8,266 **could not differentiate** the following outcomes between people offered rivaroxaban compared to LMWH + VKA:

- VTE-recurrence (In all people with a VTE or those with DVT or PE specifically, those with a BMI< 30kg/m^2 , BMI ≥30 kg/m^2, those aged <65 years or those aged ≥65 years) on-treatment phase (between 3 and 12 months).
- PE-occurrence during the on-treatment phase (between 3 and 12 months).
- DVT-occurrence (specifically in those people with PE or those with VTE generally) during the on-treatment phase (between 3 and 12 months).
- Intracranial bleeds (in people with PE with or without DVT) during the on-treatment phase (between 3 and 12 months).
- Fatal bleeds during the on-treatment phase (between 3 and 12 months).
- Clinically relevant non-major bleeding (in people with DVT only) during the on-treatment phase (between 3 and 12 months)
- All-cause mortality (in all people with a VTE or those with DVT-only or those with PE with or without a DVT) during the on-treatment phase (between 3 and 12 months)
- VTE-related mortality (in all people with a VTE or those with DVT-only or those with PE with or without a DVT) during the on-treatment phase (between 3 and 12 months)
- Mean score on the anti-clot benefits scale reported at 12 month

Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus UFH + VKA for the initial *treatment* of VTE (DVT and/or PE*)*

Very-low quality evidence from 1 RCT containing data on 71 people **could not differentiate** VTE recurrence (overall or DVT/PE specifically) between those given rivaroxaban and those given UFH+VKA.

Clinical evidence statements for pairwise results for the initial treatment of VTE in people with cancer

Please refer to appendix B for an explanation of the format of the pairwise evidence statements.

LMWH + VKA vs. LMWH alone for the initial treatment of VTE

Moderate to high quality evidence from up to 4 RCTs with up to 1,703 people found **an increase in** VTE-recurrence, DVT-occurrence and clinically relevant non-major bleeding up to 6 months in people offered LMWH +VKA compared to LMWH alone.

Low to moderate quality evidence from up to 3 RCTs with up to 1,643 people **could not differentiate** the following outcomes between people offered LMWH + VKA and people offered UFH + VKA:

- VTE recurrence up to 6 months (for specifically those with renal function of CrCl≤30 mL/min and those specifically with renal function CrCl>30 mL/min).
- PE-occurrence.

- Major bleeding up to 3 months and up to 6 months (for all participants, those specifically with creatinine clearance levels ≤30 mL/min and those specifically with levels >30 mL/min, and when only including intracranial bleeds).
- Clinically relevant non-major bleeding (for people specifically with creatinine clearance levels ≤30 mL/min and those specifically with levels >30 mL/min)
- All-cause mortality up to 3 months and up to 6 months (for all participants, those specifically with creatinine clearance levels ≤30 mL/min and those specifically with levels >30 mL/min)
- VTE-related mortality up to 6 months
- Serious adverse events

UFH + VKA versus LMWH alone for the initial treatment of VTE in people with cancer

Very low quality evidence from 1 RCT with 200 participants **could not differentiate** the following outcomes between people offered UFH+VKA and people offered LMWH alone:

- VTE-recurrence up to 3 months
- Major bleeding up to 3 months
- Clinically relevant non-major bleeding up to 3 months
- All-cause mortality up to 3 months

Apixaban versus LMWH+VKA for the initial treatment of VTE in people with cancer

Very low quality evidence from 1 RCT with up to 167 participants **could not differentiate** the following outcomes between people offered apixaban and people offered LMWH+VKA:

- VTE-recurrence up to 6 months
- Major bleeding up to 6 months
- Clinically relevant non-major bleeding up to 6 months
- All-cause mortality up to 6 months

Rivaroxaban versus LMWH+VKA for the initial treatment of VTE in people with cancer

Very low quality evidence from 1 RCT with up to 462 participants **could not differentiate** the following outcomes between people offered rivaroxaban and people offered LMWH+VKA:

- VTE-recurrence up to 12 months
- Major bleeding up to 12 months
- Clinically relevant non-major bleeding up to 12 months
- All-cause mortality up to 12 months

Rivaroxaban versus LMWH alone for the initial treatment of VTE in people with cancer

Moderate to high quality evidence from 1 RCT with 406 participants found **a reduction** in VTE-recurrence and **an increase** in clinically relevant non-major bleeding during the on-treatment phase (up to 6 months) in people offered rivaroxaban compared to LMWH alone.

Low to moderate quality evidence from 1 RCT with 406 participants **could not differentiate** the following outcomes between people offered rivaroxaban and people offered LMWH+VKA:

- DVT-occurrence up to 6 months
- PE-occurrence up to 6 months

- Major bleeding up to 6 months
- All-cause mortality up to 6 months

Dabigatran versus LMWH+VKA for the initial treatment of VTE in people with cancer

Very low quality evidence from 1 RCT with up to 221 participants **could not differentiate** the following outcomes between people offered dabigatran and people offered LMWH+VKA:

- VTE-recurrence up to 6 months
- Major bleeding up to 6 months
- Clinically relevant non-major bleeding up to 6 months
- All-cause mortality up to 6 months
- VTE-related mortality up to 6 months

Edoxaban versus LMWH alone for the initial treatment of VTE in people with cancer

Low quality evidence from 1 RCT with 1046 participants found **an increase** in major bleeding and clinically relevant non-major bleeding during the on-treatment phase (up to 12 months) in people offered edoxaban compared to LMWH alone.

Very low quality evidence from 1 RCT with up to 1046 participants **could not differentiate** the following outcomes between people offered dabigatran and people offered LMWH+VKA:

- VTE-recurrence up to 6 months
- All-cause mortality up to 6 months

Clinical evidence statements for pairwise results for the extended therapy of VTE

Please refer to appendix B for an explanation of the format of the pairwise evidence statements.

Apixaban (2.5mg twice daily) versus apixaban (5mg twice daily) versus placebo for the extended therapy of VTE

Moderate to high quality evidence from 1 RCT with 1,669 participants **found a reduction in** VTE-recurrence (in all people with a VTE generally and those specifically with DVT-only and those with a PE specifically, those aged <65 years and those aged ≥65 years), serious adverse events and DVT-occurrence during up to 12 months of extended therapy in people offered apixaban (2.5mg) compared to placebo.

Very-low to moderate quality evidence from 1 RCT with up to 2,482 **could not differentiate** the following outcomes during up to 12 months of extended therapy between people offered apixaban 2.5mg and people offered placebo:

- VTE-recurrence
- Major bleeding
- Clinically relevant non-major bleeding
- All-cause mortality
- VTE-related mortality
- Serious adverse events
- DVT-occurrence
- PE-occurrence

Moderate to high quality evidence from 1 RCT with 1,642 participants **found a reduction in** VTE-recurrence (in all people with a VTE generally and those specifically with DVT-only and those with a PE specifically, those aged <65 years and those aged ≥65 years), all-cause mortality, serious adverse events, PE-occurrence and DVT-occurrence during up to 12 months of extended therapy in people offered apixaban (5mg) compared to placebo.

Moderate quality evidence from 1 RCT with 1,642 participants **found an increase in** clinically relevant non-major bleeding during up to 12 months of extended therapy in people offered apixaban (5mg) compared to placebo.

High quality evidence from 1 RCT with 1,115 participants **found an increase in** VTE-recurrence in people aged <65 years during up to 12 months of extended therapy in people offered apixaban (5mg) compared to apixaban (2.5mg).

High quality evidence from 1 RCT with 1,115 participants **found an increase in** VTE-recurrence in people aged ≥65 years during up to 12 months of extended therapy in people offered apixaban (2.5mg) compared to apixaban (5mg).

Very-low to moderate quality evidence from 1 RCT with up to 2,482 **could not differentiate** the following outcomes during up to 12 months of extended therapy between people offered apixaban 2.5mg and people offered 5mg:

- VTE-recurrence
- Major bleeding
- Clinically relevant non-major bleeding
- All-cause mortality
- VTE-related mortality
- Serious adverse events
- DVT-occurrence
- PE-occurrence

Rivaroxaban (20mg once daily) versus placebo for the extended therapy of VTE

High quality evidence from 1 RCT with up to 1,196 participants **found a reduction in** VTE-recurrence (overall and specifically in those aged ≥ 65 years, DVT-occurrence and PE-occurrence during up to 12 months of extended therapy in people offered rivaroxaban compared to placebo.

High quality evidence from 1 RCT with up to 1,188 participants **found an increase in** clinically relevant non-major bleeding during up to 12 months of extended therapy in people offered rivaroxaban compared to placebo.

Low to moderate quality evidence from 1 RCT with up to 1,196 **could not differentiate** the following outcomes during up to 12 months of extended therapy between people offered rivaroxaban and people offered placebo:

- Major bleeding
- All-cause
- VTE-related mortality

Dabigatran versus warfarin for the extended therapy of VTE

Moderate quality evidence from 1 RCT with up to 2,856 participants **found a decrease in** clinically relevant non-major bleeding during up to 36 months of extended therapy in people offered dabigatran compared to warfarin.

High quality evidence from 1 RCT with up to 2,856 participants **found no meaningful difference in** serious adverse events by the end of the 36 months treatment period between people offered dabigatran and people offered warfarin.

Low to moderate quality evidence from 1 RCT with up to 1,196 **could not differentiate** the following outcomes during up to 36 months of extended therapy between people offered dabigatran and people offered warfarin:

- VTE-recurrence (in all people with a VTE generally, those specifically with a DVT-only, specifically with a PE, those aged ≥ 65 years or those aged <65 years).
- DVT-occurrence
- PE-occurrence
- Non-fatal PE
- Serious adverse events in the 30 days following treatment cessation
- Major bleeding
- All-cause mortality
- VTE-related mortality

Dabigatran versus placebo for the extended therapy of VTE

High quality evidence from 1 RCT with up to 1,343 participants **found a decrease in** VTE-recurrence (in all people with a VTE generally, those specifically with a DVT-only, specifically with a PE, those aged ≥ 65 years and those aged <65 years), DVT-occurrence, PE-occurrence during up to 6 months of extended therapy in people offered dabigatran compared to placebo.

Moderate quality evidence from 1 RCT with up to 1,343 participants **found an increase in** clinically relevant non-major bleeding during up to 6 months of extended therapy in people offered dabigatran compared to placebo.

Low to moderate quality evidence from 1 RCT with up to 1,196 **could not differentiate** the following outcomes during up to 6 months of extended therapy between people offered dabigatran and people offered placebo:

- Major bleeding
- Serious adverse events

Warfarin (INR 2.0-3.0) versus discontinuation of anticoagulation for the extended therapy of VTE

Very-low quality evidence from 1 RCT with 267 participants **could not differentiate** the following outcomes during up to 9 months of extended therapy between people offered warfarin and people for whom anticoagulant therapy was discontinued:

- VTE recurrence during the on-treatment phase (up to 9 months)

- Major bleeding (all major bleeds and specifically fatal bleeds) during the on-treatment phase (up to 9 months)

Low-intensity warfarin (INR 1.5-2.0) versus placebo for the extended therapy of VTE

Low quality evidence from 1 RCT with 508 participants **found a decrease in** VTE-recurrence (in all people with a VTE generally) during up to 4.3 years of extended therapy in people offered warfarin compared to placebo.

Very-low quality evidence from 1 RCT with up to 508 participants **could not differentiate** the following outcomes during up to 4.3 years of extended therapy between people offered warfarin and people offered placebo:

- Major bleeding
- All-cause mortality

Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of DVT

High quality evidence from up to 2 RCTs with up to 266 participants **found a decrease in** VTE-recurrence (overall and in those people with a BMI<30kg/m^2, DVT-occurrence during up to 24 months of extended therapy in people offered warfarin compared to placebo.

Low to moderate quality evidence from 1 RCT with 162 participants **could not differentiate** the following outcomes during up to 24 months of extended therapy between people offered warfarin and people offered placebo:

- PE-occurrence
- Major bleeding
- All-cause mortality

Low to moderate quality evidence from 1 RCT with 104 participants **could not differentiate** the following outcomes during up to 18 months of extended therapy between people offered warfarin and people offered placebo:

- VTE-recurrence in those people with a BMI≥30kg/m^2
- PE-occurrence
- All-cause mortality
- VTE-related mortality

Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of PE

High quality evidence from 1 RCT with 371 participants **found a decrease in** VTE-recurrence (overall and specifically those with a BMI <30 kg/m^2), DVT-occurrence and PE-occurrence during up to 9 months of extended therapy in people offered warfarin compared to placebo in participants with PE.

Low to moderate quality evidence from 1 RCT with 371 participants **could not differentiate** the following outcomes during up to 9 months of extended therapy between people offered warfarin and people offered placebo:

- VTE-recurrence in those with a BMI ≥30kg/m^2
- Major bleeding

- All-cause mortality

Warfarin (INR 2.0-3.0) versus low intensity warfarin for the extended therapy of VTE

Moderate to high quality evidence from 1 RCT with 738 participants **found a decrease in** VTE-recurrence, during up to 2.2 years of extended therapy in people offered warfarin compared to low-intensity warfarin.

Low to moderate quality evidence from 1 RCT with 738 participants **could not differentiate** the following outcomes during up to 2.2 years of extended therapy between people offered warfarin and people offered low-intensity warfarin:

- VTE-recurrence (in those specifically with an DVT-only index event, those specifically with PE [with or without DVT as the index event], those aged ≥ 65 years or those aged <65 years)
- Major bleeding (overall, those aged ≥ 65 years or those aged <65 years)
- All-cause mortality

Rivaroxaban (20mg) versus rivaroxaban (10mg) versus aspirin (100mg) for the extended therapy of VTE

Moderate to high quality evidence from 1 RCT with up to 2,225 participants **found a reduction in** VTE-recurrence (in all people with a VTE generally, those specifically with DVT-only, those with a BMI <30kg/m^2, those with a BMI ≥30kg/m2, those aged <65 years and those aged ≥ 65 years), DVT-occurrence and PE-occurrence during up to 12 months of extended therapy in people offered rivaroxaban 20mg compared to aspirin 100mg.

Low to moderate quality evidence from 1 RCT with up to 2,225 **could not differentiate** the following outcomes during up to 12 months of extended therapy between people offered rivaroxaban 20mg compared to aspirin 100mg:

- VTE-recurrence (specifically in people with PE [with or without DVT] as the index event)
- Major bleeding
- Clinically relevant non-major bleeding
- All-cause mortality
- VTE-related mortality

High quality evidence from 1 RCT with up to 2,225 participants **found a reduction in** VTE-recurrence (in all people with a VTE generally and those specifically with DVT-only, those specifically with PE [with or without DVT], those with a BMI <30kg/m^2, those aged <65 years and those aged ≥ 65 years), DVT-occurrence and PE-occurrence during up to 12 months of extended therapy in people offered rivaroxaban 10mg compared to aspirin 100mg.

Low to moderate quality evidence from 1 RCT with up to 2,225 **could not differentiate** the following outcomes during up to 12 months of extended therapy between people offered rivaroxaban 10mg compared to aspirin 100mg:

- VTE recurrence in those with a BMI ≥30kg/m2
- Major bleeding
- Clinically relevant non-major bleeding
- All-cause mortality

- VTE-related mortality

Low to moderate quality evidence from 1 RCT with up to 2,225 **could not differentiate** the following outcomes during up to 12 months of extended therapy between people offered rivaroxaban 20mg compared to rivaroxaban 10mg:

- VTE-recurrence (overall, specifically those with DVT-only, those with PE [with or without DVT], those with a BMI <30kg/m^2, those with a BMI ≥30kg/m2, those aged <65 years and those aged ≥ 65 years)
- DVT-occurrence
- PE-occurrence
- Major bleeding
- Clinically relevant non-major bleeding
- All-cause mortality
- VTE-related mortality

Aspirin (100mg) versus placebo for the extended therapy of VTE

Low to moderate quality evidence from up to 2 RCTs with up to 1,224 participants found **a decrease in** VTE-recurrence (overall and specifically those aged <65 years) and DVT-occurrence during up to 2 years of extended therapy in people offered aspirin compared to placebo.

Very low to low quality evidence from up to 2 RCTs with up to 1,224 participants **could not differentiate** the following outcomes during extended therapy between people offered aspirin compared to placebo:

- VTE recurrence up to 4 years (overall, and specifically those with DVT-only, those with PE [with or without DVT], those with a BMI <30kg/m^2, those with a BMI ≥30kg/m2 and those aged ≥ 65 years)
- Major bleeding up to 2 years and up to 4 years
- Clinically relevant non-major bleeding up to 2 years and up to 4 years
- All-cause mortality up to 2 years and up to 4 years
- VTE-related mortality up to 4 years
- DVT-occurrence up to 2 years
- PE-occurrence up to 2 years

Rivaroxaban versus warfarin (INR 2.0-3.0) for the extended therapy of VTE (DVT and/or PE) associated with antiphospholipid syndrome

Very-low quality evidence from 1 RCT with 115 participants **could not differentiate** the following outcomes between people offered rivaroxaban and people offered warfarin:

- Quality of life (health utility component of ED-5Q-5L score) at day 180
- Clinically relevant non-major bleeding at day 210
- Serious adverse events at day 210

Low quality evidence from 1 RCT reporting data on 115 participants **could not estimate** an effect for VTE-recurrence or Major bleeding at day 210 as both arms reported 0 events.

Low quality evidence from 1 RCT with 11 participants found **an increase** in quality of life (on the Health state VAS component of the ED-5Q-5L score) in people offered rivaroxaban compared to warfarin, but the effect may not be clinically important.

High intensity warfarin (INR 3.1-4.0) versus standard intensity warfarin (INR 2.0-3.0) for the extended therapy of VTE (DVT and/or PE) associated with antiphospholipid syndrome

Very low-quality evidence from 1 RCT with 87 participants **could not differentiate** VTE-recurrence in the long-term between those given high intensity warfarin and low-intensity warfarin.

Clinical evidence statements for NMA results

The format of the evidence statements is explained in the methods in appendix B.

Initial treatment NMAs

Please refer to the summary of the results for the initial treatment NMAs in appendix I.

VTE networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Low quality data from 1 NMA with 37,857 participants found **a reduction** in VTE-recurrence in people offered:
  - LMWH+VKA, apixaban, edoxaban or rivaroxaban versus UFH + VKA.
- Moderate quality data from 1 NMA with 35,880 participants found a **reduction** in major bleeding in people offered:
  - apixaban or rivaroxaban versus UFH + VKA, LMWH+VKA and fondaparinux+VKA.
  - apixaban also showed improvements compared to edoxaban and dabigatran.
- Low quality data from 1 NMA with 33,489 participants found a **reduction** in clinically relevant non-major bleeding in people offered:
  - apixaban, dabigatran or edoxaban versus LMWH + VKA.
  - apixaban or dabigatran versus UFH + VKA, edoxaban and rivaroxaban.
  - apixaban also showed improvements compared to fondaparinux + VKA
- Moderate quality data from 1 NMA with 37,359 participants found a **reduction** in all-cause mortality in people offered:
  - LMWH + VKA or rivaroxaban versus fondaparinux+VKA.

The remaining NMAs **could not differentiate** between interventions (see Table 107 for remaining comparisons).

DVT networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Moderate quality data from 1 NMA with 19,107 participants found **a reduction** in VTE-recurrence in people offered:
  - LMWH+VKA, apixaban or rivaroxaban versus UFH + VKA.
- Moderate quality data from 1 NMA with 11,682 participants found **a reduction** in major bleeding in people offered:

    - LMWH+VKA, apixaban or rivaroxaban versus UFH + VKA.
- Moderate quality data from 1 NMA with 8,492 participants found **a reduction** in all-cause mortality in people offered:
    - LMWH+VKA or rivaroxaban versus UFH + VKA.
    - rivaroxaban also showed improvements versus fondaparinux + VKA.

The remaining NMAs could not differentiate between interventions (see Table 108 for remaining comparisons).

PE networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Low quality data from 1 NMA with 12,821 participants found **a reduction** in major bleeding in people offered:
    - apixaban or rivaroxaban versus UFH + VKA, LMWH+VKA and fondaparinux+VKA.
    - apixaban also showed improvements versus rivaroxaban.

The remaining NMAs **could not differentiate** between interventions (see Initial treatment of PE

Table 109 for remaining comparisons).

Obesity and elderly subgroup networks

The NMAs **could not differentiate** between any interventions (see Table 110 and Table 111 for comparisons).

Initial treatment of VTE in people with cancer NMAs

Please refer to the summary of the results for the initial treatment of VTE in people with cancer NMAs in appendix I.

VTE networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Moderate quality data from 1 NMA with 4,197 participants found **a reduction** in VTE-recurrence in people offered:
    - LMWH alone, rivaroxaban or edoxaban compared with LMWH+VKA.
- Very-low quality data from 1 NMA with 4,291 participants found a **reduction** in major bleeding in people offered:
    - LMWH alone compared with edoxaban.
- Low quality data from 1 NMA with 3,385 participants found a **reduction** in clinically relevant non major bleeding in people offered:
    - LMWH alone or UFH+VKA compared with LMWH+VKA, rivaroxaban or dabigatran.
    - LMWH alone also showed improvements compared with edoxaban.

The remaining NMAs could not differentiate between interventions (see Table 112 for remaining comparisons).

Extended therapy NMAs

Please refer to the summary of the results for the extended therapy NMAs in appendix I.

VTE networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Moderate quality data from 1 NMA with 14,637 participants found **a reduction** in VTE-recurrence in people offered:
  - rivaroxaban (10mg and 20mg), warfarin (standard and low-intensity), apixaban (2.5mg and 5mg), dabigatran or aspirin compared with placebo.
  - rivaroxaban (10mg and 20mg), warfarin (standard and low-intensity), apixaban (2.5mg and 5mg) and dabigatran also showed improvements compared with aspirin.
  - dabigatran and warfarin standard also showed improvements compared with warfarin-low intensity.
  - warfarin standard also showed improvements compared to discontinuation of treatment.
- Low quality data from 1 NMA with 14,840 participants found a **reduction** in major bleeding in people offered:
  - placebo or apixaban (2.5mg or 5mg) compared with warfarin (standard and low-intensity) and rivaroxaban (20mg).
  - apixaban (5mg) also showed improvements compared with rivaroxaban (10mg).
- High quality data from 1 NMA with 12,458 participants found a **reduction** in clinically relevant non-major bleeding in people offered:
  - placebo, dabigatran or apixaban (2.5mg or 5mg) compared with warfarin (standard intensity).
  - apixaban (2.5 mg and 5mg) and placebo also showed improvements compared with rivaroxaban (20mg).
  - placebo also showed improvements compared with rivaroxaban (10mg), apixaban 5mg, dabigatran and aspirin.
- High quality data from 1 NMA with 12,913 participants found a **reduction** in all-cause mortality in people offered:
  - rivaroxaban (10mg), apixaban (5mg) or warfarin (standard intensity) compared with placebo.
  - rivaroxaban (10mg) also showed improvements compared with aspirin and rivaroxaban (20mg).

The remaining NMAs **could not differentiate** between interventions (see Table 113 for remaining comparisons).

DVT networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Moderate quality data from 1 NMA with 7,719 participants with DVT-only found a **reduction** in VTE-recurrence in people offered:
  - dabigatran, warfarin (standard and low intensity), apixaban (2.5mg and 5mg), rivaroxaban (20mg and 10mg) or aspirin compared with placebo.
  - Dabigatran, warfarin (standard-intensity), apixaban (2.5mg and 5mg) and rivaroxaban (20mg and 10mg) also showed improvements compared with aspirin.

The remaining NMAs **could not differentiate** between interventions (see Table 114 for remaining comparisons).

PE networks

Based on the NMAs, the following differences in effectiveness were obtained:

- High quality data from 1 NMA with 4,697 participants with PE (with or without DVT) found a **reduction** in VTE-recurrence in people offered:
    - dabigatran, warfarin (standard intensity), apixaban (2.5mg and 5mg) or rivaroxaban (20mg and 10mg) compared with placebo.
    - dabigatran, warfarin (standard-intensity), apixaban (5mg) or rivaroxaban (20mg and 10mg) also showed improvements compared with aspirin.

The remaining NMAs **could not differentiate** between interventions (see Table 115 for remaining comparisons).

Elderly subgroup networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Moderate quality data from 1 NMA with 4,707 participants with VTE found a **reduction** in VTE-recurrence in people offered:
    - dabigatran, warfarin (low and standard intensity), apixaban (2.5mg and 5mg), rivaroxaban (20mg and 10mg) or aspirin compared with placebo.
    - dabigatran, warfarin (low- and standard-intensity), apixaban (5mg), dabigatran or rivaroxaban (20mg and 10mg) also showed improvements compared with aspirin.
    - warfarin (standard-intensity), apixaban (5mg) or dabigatran also showed improvements compared with apixaban (2.5mg).
    - warfarin (standard-intensity) or dabigatran also showed improvements compared with rivaroxaban (10mg and 20mg).

The remaining NMAs **could not differentiate** between interventions (see Table 116 for remaining comparisons).

Obesity subgroup networks

Based on the NMAs, the following differences in effectiveness were obtained:

- Moderate quality data from 1 NMA with 1,553 participants with VTE found a **reduction** in VTE-recurrence in people offered:
    - warfarin (standard intensity) or rivaroxaban (20mg and 10mg) compared with placebo.
    - rivaroxaban (20mg) also showed improvements compared with aspirin.

The remaining NMAs **could not differentiate** between interventions (see Table 117 for remaining comparisons).

Published NMAs

Initial treatment

Moderate quality evidence from 1 published network meta-analysis containing 28,803 participants (adults aged ≥ 18 years who have received a new or recurrent objectively confirmed diagnosis of acute symptomatic VTE) found that there was evidence of substantial reductions in risk of both major bleeding and CRB for apixaban (5 mg bd) compared with warfarin (INR 2–3). There was also evidence that other DOACs reduced bleeding compared with warfarin (INR 2–3). In comparisons between licensed doses of DOACs, there was evidence that apixaban (5 mg bd) reduced major bleeding risk compared with some other DOACs. The evidence was partially applicable because the NMA did not cover all of the outcomes of interest.

Extended therapy

Moderate quality evidence from 1 published network meta-analysis (Sterne 2017) containing 10,390 participants (adults aged ≥ 18 years who have completed a minimum of 3 months of anticoagulant treatment for objectively confirmed first VTE without recurrence) found that the risk of major bleeding and CRB was higher with warfarin (INR 2–3), dabigatran (150 mg od) and rivaroxaban (20 mg od) than placebo. However, the risk of these outcomes was lower for dabigatran (150 mg bd), apixaban (2.5 mg bd) and apixaban (5 mg bd) than warfarin (INR 2–3). There was evidence that the risk of major bleeding and CRB was higher with dabigatran (150 mg bd) and rivaroxaban (20 mg od) than apixaban (2.5 mg bd and 5 mg bd). The evidence was partially applicable because the NMA did not cover all of the outcomes of interest.

Moderate quality evidence from 1 published network meta-analysis (Wang 2018) containing 22,396 participants (studies on extended therapy for secondary prevention of VTE) found that low-intensity VKAs and standard-intensity VKAs were associated with a higher risk of major bleeding. Compared with aspirin, standard-intensity VKAs was associated with a significant risk of major bleeding. Compared with placebo or observation, standard-intensity VKAs and low-dose factor Xa inhibitors were associated with a reduced risk of all-cause mortality. The evidence was partially applicable because the NMA did not cover all outcomes of interest and some interventions were merged.

Economic evidence statements

A partially applicable study with potentially serious limitations (Bamber et al., 2015) assessed the cost effectiveness of rivaroxaban versus LMWH/VKA, and found that rivaroxaban produces an ICER of £8,677/QALY for patients with a DVT, and an ICER of £7,072 in patients with a PE. Probabilistic sensitivity analysis showed a high degree of certainty around this finding (>81%).

A partially applicable study with potentially serious limitations (Lanitis et al., 2016) assessed the cost effectiveness of apixaban, rivaroxaban, dabigatran, and LMWH/VKA in patients with a VTE. Results showed that apixaban dominates rivaroxaban and dabigatran, and produces an ICER of £2,520/QALY compared with LMWH/VKA. Probabilistic sensitivity analysis showed a high degree of certainty that apixaban is cost effective at a threshold of £20,000/QALY (>85%).

A partially applicable study with potentially serious limitations (Lanitis et al., 2017) assessed the cost effectiveness of 12 months anticoagulation with apixaban versus 6 or 12 months anticoagulation with LMWH/VKA. Results showed that 12 months of apixaban produces an ICER of £6,692/QALY compared to 12 months of LMWH/VKA and an ICER of £8,528/QALY compared to 6 months of LMWH/VKA. Probabilistic sensitivity analysis showed a high degree of certainty that apixaban is cost effective at a threshold of £20,000/QALY (>94%).

A partially applicable study with potentially serious limitations (Jugrin et al., 2015) assessed the cost effectiveness of dabigatran versus LMWH/warfarin in patients anticoagulated for up to 6 months or up to 24 months. Results showed that dabigatran produces an ICER of £767/QALY in patients treated for up to 6 months, and an ICER of £7,877 in patients treated for up to 24 months. Dabigatran remained cost effective in DVT/PE subgroups for both treatment durations. Probabilistic sensitivity analysis showed a relatively high degree of certainty that dabigatran is cost effective at a threshold of £20,000/QALY across all subgroups (79%-94%).

A partially applicable study with potentially serious limitations (Jugrin et al., 2016) assessed the cost effectiveness of dabigatran versus rivaroxaban in patients treated with 6 months of anticoagulation or “extended anticoagulation” (additional 6-12 months treatment). Results showed that dabigatran dominates rivaroxaban in both treatment groups. Dabigatran remained cost effective in DVT/PE subgroups for both treatment durations. Probabilistic sensitivity analysis showed a moderate degree of uncertainty that dabigatran is cost effective at a £20,000/QALY threshold (61%-88% probability).

A directly applicable study with potentially serious limitations (Sterne et al., 2017) assessed the cost effectiveness of rivaroxaban, dabigatran, apixaban, edoxaban, and LMWH/warfarin during “acute treatment” (6 months anticoagulation) and the cost effectiveness of rivaroxaban, dabigatran, apixaban 2.5 mg bd, apixaban 5 mg bd, warfarin, aspirin, and no pharmacotherapy during “secondary prevention” (lifetime anticoagulation). For acute treatment, results showed that apixaban produces an ICER of £800/QALY compared to LMWH/warfarin, with all other treatments being dominated. For secondary prevention, results showed that dabigatran produces an ICER of £64,660 compared to aspirin, with all other treatments being dominated. Probabilistic sensitivity analysis showed a relatively high degree of uncertainty in results: apixaban has a probability of ~54% of being cost-effective at a threshold of £20,000-£30,000/QALY in the acute treatment analysis. Aspirin has a probability of ~70% of being cost effective at a £20,000/QALY threshold in the secondary prevention analysis.

A partially applicable study with potentially serious limitations (Clay et al., 2018) assessed the cost effectiveness of edoxaban versus LMWH/VKA, and found that edoxaban was dominant. Probabilistic sensitivity analysis showed a high degree of certainty around this finding (>99%).

A directly applicable original economic model with minor limitations found that apixaban has a high probability of being cost effective if people remain on the same drug throughout initial treatment and extended therapy. Assuming a treatment duration of 3 months for provoked VTEs and indefinite (lifetime) treatment for unprovoked VTEs, results showed that compared to LMWH/VKA, apixaban produces an ICER of £1,802/QALY for patients with a DVT, and an ICER of £1,660/QALY for patients with a PE. If switching from any initial treatment to any extended therapy is allowed, there is greater uncertainty about the optimal sequence. However, the committee noted that some sequences of initial and extended therapy are not

clinically relevant for the majority of people with a VTE. When these sequences were excluded from the model, apixaban as initial treatment followed by apixaban as extended therapy remained the most cost-effective strategy. In people with cancer and VTE, apixaban has the highest probability of being cost effective but the results were more uncertain than in the overall VTE population. In people with cancer, LMWH alone is not cost effective due to the comparatively high acquisition cost.

The committee's discussion of the evidence

Terminology used in the recommendations

At the point of diagnosis or when people with suspected VTE are waiting for test results they may require a therapeutic dose of anticoagulant. The committee called this interim or immediate treatment to differentiate it firstly from treatment that lasts several months in duration (referred to as initial treatment in this document) following confirmed diagnosis and secondly from extended therapy aimed at preventing recurrence, which is long-term and may be life-long depending on the risk of VTE recurrence and major bleeding.

Interpreting the evidence

The outcomes that matter most

The committee noted that several outcomes are of particular importance to people with VTE. Major bleeding can be potentially fatal or require that anticoagulation be stopped, and a reversal agent administered. In addition, both major and clinically relevant non-major bleeding negatively impact the quality of life. VTE recurrence is also particularly important due to the impact this has on mortality and is likely indicative of treatment failure. Treatment for VTE is expected to improve both all-cause and VTE-related mortality.

In people with cancer, the committee advised that recurrence and bleeding outcomes are again important. However, they commented that all-cause mortality may be a poor measure of treatment effectiveness due to the high likelihood of death being cancer-related.

The committee advised that the relative importance of these outcomes changes over time as the risk of them occurring can vary. Following a diagnosis of a first VTE, the individual is at a particularly high risk of recurrence, while also being at risk of major bleeding due to anticoagulant treatment. However, after an initial course of treatment of several months the risk of VTE recurrence is reduced, but the risk of major bleeding associated with anticoagulation therapy remains constant.

The quality of the evidence

Issues that span treatment durations and population groups.

The studies included in this review were of low to high risk of bias. Where risk of bias was identified this was typically due to poor randomisation techniques/reporting, poor reporting of outcomes (and whether outcomes occur on or off-treatment) or a lack of blinding (of participants and assessors). The committee agreed that outcomes that are objectively assessed (such as mortality, VTE-recurrence and bleeding) are less likely to be affected by a lack of blinding. In addition, assessment of these outcomes was typically determined by a blinded committee. However, risk of bias is still present as for example, participants may

have been more likely to seek help for potential complications (such as bleeding) if they were aware that they were in the active treatment arm. The committee agreed with the risk of bias assessment of the included studies.

The committee noted that several trials (including the large DOAC trials) reported that on average, patients were in the therapeutic range (INR 2.0-3.0) less than 65% of the time (the target set in the UK). The committee discussed this as a potential directness issue and noted that there is likely to be variation in the quality of treatment given, including variance between countries in the time to therapeutic treatment range when administering warfarin. However, in the absence of sensitivity analyses stratified by treatment centre, it is difficult to determine what effect this would have on results. The committee agreed that the evidence should not be marked down for indirectness due to this issue as it is unclear how often this target is met in practice in the UK and as typically, studies included in this review were not more than 10% below the target time in therapeutic range (for example, the AMPLIFY trial reported that participants were in therapeutic range 61% of the time, the EINSTEIN-DVT trial 57.7% of the time and HOKUSAI-VTE 63.5% of the time).

The committee noted the differing definitions of VTE recurrence, with some trials offering vague definitions, some requiring that the VTE be a new occurrence that is different to the index event, and others including extensions of index events. Additionally, the committee advised that clinically, it can be difficult to differentiate an extended VTE from a new event.

The committee noted that the majority of trials were sponsored by pharmaceutical companies. They discussed the differences between the trials in depth, in particular, focusing that the DOAC trials differed in their inclusion and exclusion criteria, resulting in differences in study populations. For example, the AMPLIFY trials (for the initial and extended networks) had much stricter exclusion criteria when compared to the EINSTEIN trials. AMPLIFY used haematological variables in the exclusion criteria, such as a low haemoglobin and/or platelet count. These differences could potentially lead to a selection bias in favour of lower recurrence and bleeding rates in the commercial apixaban studies. However, the committee agreed that the study populations of the different DOAC trials were all relevant to the review question and that the trials should therefore not be marked down for indirectness. The committee agreed that it was appropriate to combine the different trials in the NMAs but agreed that there were still concerns with the heterogeneity of the populations in the included trials.

The committee were aware of post-hoc analyses (for example Beyer-Westendorf, 2017; see other references in Appendix N) which demonstrated that post-trial manipulation of the inclusion/exclusion criteria to select a subgroup of participants from the EINSTEIN trial to better match the AMPLIFY trial altered the risk of major bleeding and VTE-recurrence. However, the committee agreed that these post-hoc analyses were problematic, and they too were sponsored by or carried out by pharmaceutical companies. The selection of participants from one trial to match the inclusion criteria of another subverted randomisation, making it hard to interpret the results. The committee agreed that they could not make inferences based on the results of this study because this evidence did not meet our inclusion criteria and similar papers were not systematically identified for the other DOAC trials.

The studies included in this review also differed in treatment duration. Several trials (such as the EINSTEIN and HOKUSAI trials) allowed differing treatment durations within the same study. In the EINSTEIN trials, participants were allocated to 3, 6 or 12 months treatment duration; the authors reported Cox proportional hazard models that were stratified by

treatment duration. The HOKUSAI-VTE and cancer trials permitted 3-12 and 6-12 months treatment, respectively, but did not stratify results by intended treatment duration. Instead, the HOKUSAI trials reported outcomes occurring on-treatment and at 12 months after randomization (even for those participants with an intended treatment duration of less than 12 months).The HOKUSAI-Cancer trial reported outcome data at 6 months (including on-treatment reporting) and this was extracted instead of the 12 month outcome data because all participants in this trial had an intended treatment duration of at least 6 months. The HOKUSAI-VTE trial did not report data at the different time points for most outcomes and was downgraded for indirectness for VTE-recurrence and mortality outcomes as this review is concerned with events that occur during the intended treatment duration only. It was not downgraded for bleeding outcomes as these were reported on treatment. For recurrence and mortality outcomes reported as hazard ratios, this study was also marked down for risk of bias as events occurring off-treatment violate the proportional hazards assumption.

The studies also differed in the durations of time that they classified as initial treatment and when the extended therapy period began. Most studies for the initial treatment of VTE ranged from 3-12 months. Studies for the extended therapy of VTE ranged from 3-36 months in intended treatment and required that participants had already received at least 3 months anticoagulation (with some participants, such as those in the EINSTEIN-EXT, 2012 trial, having received up to 12 months). This means that there was overlap between initial and extended therapy periods across the studies, as some extended therapy studies (such as WODIT-DVT, 2001) were conducted on people who had received 3 months prior treatment and were randomized to another 9 months treatment but some initial treatment studies treated participants for up to 12 months (such as EINSTEIN-DVT, 2010). The intended treatment durations (for the initial treatment studies) and prior treatment durations (for extended therapy studies) are listed in the summary tables above.

The committee noted these differences in duration and the overlap between initial and extended therapy periods. The committee commented that the summary of product characteristics (SPCs) for apixaban and rivaroxaban include an initial treatment period of at least 6 months and then a change in dose for longer term treatment, reflecting the longer initial treatment period used in the trials for these DOACs compared to some of the other interventions.

The committee agreed that for analysis purposes initial treatment could be taken as treatment that lasted between 3 and 12 months after an acute event. They noted that the risk of VTE recurrence decreased over time and from around 3 months onwards the goal of therapy switched to secondary prevention of VTE recurrence rather than treatment for the acute VTE event. They therefore agree that all durations of extended therapy could be analysed together providing the participants that have already received anticoagulation treatment for at least 3 months at the time of enrolment because would exclude the initial 3 month treatment period (where there is higher risk of recurrence following an acute event). These groupings were used for both the pairwise meta-analyses and NMAs.

Common issues regarding the quality of the NMAs across all treatment durations and all population groups

The committee noted that the evidence base consisted typically of large trials that, when combined in an NMA, produced very-low to high quality data and were able to differentiate between treatments for several of the outcomes of interest to this review. The committee

agreed that the evidence from the NMAs allowed indirect comparisons between drugs that have not been directly compared in the same trial.

The committee agreed that NMAs could be conducted for all people with a VTE because they did not expect that the results would differ between people with DVT and PE and thought that they would make recommendations for VTE as a whole. Additionally, there was limited data available for people with a DVT or with a PE specifically and therefore conducting NMAs on people with VTE allowed for the inclusion of more trials and a more complex treatment network. However, the committee advised that where possible NMAs should also be conducted for PE and DVT separately to investigate whether there are differences in response to treatments between the groups.

The trials included in the NMAs reported data in different formats, with some reporting event data, others reporting hazard ratio data and some reporting both. To allow combination of these two types of data where necessary, a clog-log model was used. The use of this model assumed that beyond the very early part of initial treatment phase (up to 2 weeks) there is a roughly proportional hazard between the trial arms. The committee agreed that, based on their clinical experience, this assumption was reasonable for the outcomes of interest. This assumption was also checked by inspection of the Kaplan-Meier curves reported in the included trials at the different stages of treatment (initial and extended) and for the cancer subgroup. Additionally, pairwise event data were converted to HR data to enable direct comparisons between the pairwise and NMA data to be made in the relative effectiveness charts using a method described in Watkins et al. (2018) (see appendix J). The committee also agreed that the treatment data of varying durations could be combined because the risk/hazard of an event occurring was expected to be constant over these time periods. For the initial treatment analyses this was 2 weeks to 12 months and for the extended therapy analyses this was 6 months up to 4.3 years.

Checking the NMA networks for inconsistency did not identify any loops with inconsistent results (see appendix P for more details) and therefore the assumption of consistency of results that underlies the use of NMAs was met.

Specific issues regarding the evidence for initial treatment of VTE in people with cancer

The committee advised that all-cause mortality may be a poor indication of a treatment effectiveness in people with cancer due to the high likelihood of death being cancer related in this population.

The data included in our analyses for initial treatment of VTE in people with cancer came from both studies that specifically recruited people with both cancer and VTE, and from subgroup analyses of the main DOAC studies, containing only those participants that had active cancer at baseline. Ideally, all of the studies would have been of the first type, but this was not the case. There are several issues related to the use of subgroup data from the main trials. Firstly, although the proportions of cancer that were metastatic were typically reported, it is often unclear whether this was balanced between groups and individual types of cancer were typically not reported or balanced between groups. Additionally, the number of participants in these trials who had cancer was very small and therefore statistically underpowered to detect a meaningful difference between the drugs. As a result, the committee agreed that the subgroup analyses could be downgraded for risk of bias.

Seven trials specifically recruited people with VTE and cancer. Four trials compared LMWH alone to LMWH+VKA for up to 6 months, one trial compared LMWH alone to Unfractionated heparin + VKA (UFH + VKA) and two trials compared DOACs (edoxaban and rivaroxaban) to LMWH alone. The HOKUSAI-CANCER (2018) trial reported data at 12 months, irrespective of whether the participants were allocated to a treatment duration of less than 12 months), consequently, the data for this trial was extracted at 6 months, as all participants had an intended treatment of at least 6 months.

As for the initial treatment analyses, NMAs were conducted for all participants with VTE, However, there were insufficient data to run NMAs for DVT and PE patients separately. Meaning that this level of granularity could not be achieved for this population.

The NMAs for people with cancer were of very-low to moderate quality due to the risk of bias (resulting typically from the studies being subgroup analyses and/or unblinded) of several included studies and due to visual inspection of the relative effectiveness charts identifying discrepancies between the pairwise and NMA comparisons. The committee were concerned with this low quality and the lack of certainty with these NMAs. In particular, apixaban and dabigatran comparisons were very underpowered, as evidence for these drugs came solely from subgroup analyses, and reasonable conclusions regarding the effectiveness of these drugs in people with cancer could not be made.

Specific issues regarding the evidence for extended therapy of VTE

The committee noted that there was an even greater degree of heterogeneity in evidence for extended therapy due to differences between studies in the prior length of anticoagulation participants were allowed to receive before entering the study. Additionally, participants in the extended DOAC trials were often recruited from the initial treatment DOAC studies and were eligible whether they had received VKA in that study or a DOAC. Therefore, studies differed not only with regards to the length of prior treatment and the length of extended therapy, but also in the drugs they had previously received.

Extended therapy studies have been conducted for apixaban, rivaroxaban and dabigatran but not for edoxaban. As such, the committee noted that there is an absence of evidence for the longer term effectiveness of this drug and it was not included in the extended therapy NMAs. It was however, included in the economic modelling of extended therapy (see the full economic modelling report in evidence review G and the economic model summary section above for details of the assumptions that were made to enable inclusion in the model).

The committee noted that the major bleeding NMA for the extended therapy of VTE was of low quality. This was primarily due to a very low number of major bleeds reported in the trials, In particular, the committee noted that it was unlikely that people taking apixaban (2.5mg 2 people/ 840; 5mg 1 person/ 813) would have fewer major bleeds than those taking a placebo (4 people /829; 4 people /829 respectively) because the mechanism of action of apixaban and the other anticoagulants makes bleeds more likely. They agreed that this result was probably due to random chance coupled with the very low event rate. The resulting risk ratios for apixaban reflect this uncertainty as they cross the line of no effect (apixaban 2.5mg RR 0.49 [0.09 to 2.69]; 5mg RR 0.25 [0.03 to 2.28]). The other treatments were also associated with low numbers of major bleeding events leading to wide 95% CIs in the pairwise analysis. This had a considerable impact on the imprecision of this network leading to wide 95% credible intervals (CrIs) in the NMA. The committee agreed there was still uncertainty surrounding the difference in risk of bleeding between anticoagulants during

extended therapy. Specific issues regarding the evidence for initial treatment of VTE in people with cancer

Benefits and harms

Interim anticoagulation treatment for suspected DVT or PE

There was an absence of evidence about the most effective treatment for people with suspected DVT or PE. Based on the existing recommendations in the diagnosis section of the guideline, these people would be offered interim treatment with anticoagulants at various points in the diagnosis pathway when tests could not be performed within the specified time frames (for example, if a proximal leg vein ultrasound scan cannot be done within 4 hours or if an urgent D-dimer test cannot be carried out within 4hrs). The committee agreed that it was important that treatment was not delayed under these circumstances as there would be an increased risk of disease progression for the people who do have DVT or PE and this could, in the worst-case scenario, be fatal. In contrast, the people who do not have PE or DVT would only receive a single dose or couple of doses until the test results return and they would have a short-term increased risk of bleeding and anxiety.

The committee recommended that clinicians do not wait for the results of baseline blood tests before starting interim anticoagulation treatment because the results of these tests could be relatively slow to arrive and it was more important to treat the person with anticoagulants at once if they could not be diagnosed within a short time frame (see below for additional information regarding the rationale for this part of the recommendation). However, they agreed that these tests should be reviewed within 24 hours of commencing anticoagulation to ensure that any required changes to the treatment regimen could be made quickly (for example if the individual had impaired renal function).

The committee agreed that there was a need for guidance about the types of anticoagulants to use in these circumstances. In the absence of any evidence to support a particular treatment they made a consensus recommendation to prescribe the anticoagulant treatment regimen that the person would be given if their diagnosis was confirmed, thus avoiding the person with VTE having to switch treatment later. However, the committee recognised that there may be reasons to prescribe a different anticoagulant while diagnosis is being confirmed and test results are yet to return (for example, if local protocols specify a particular treatment for suspected VTE or the choice of available drugs is limited at that point in time and location).They therefore included the caveat that if possible, the anticoagulant chosen should be the one that could be continued should diagnosis be confirmed.

The committee also included cross references to the relevant recommendations in the diagnosis sections for DVT and PE to make it clear under which circumstances interim treatment could be offered.

Initial anticoagulation treatment for confirmed DVT or PE

The committee agreed that based on the evidence and their clinical experience, they could make common recommendations for people with DVT and PE, with the exception of specific subgroups with additional complications such as renal impairment.

Once people have a confirmed diagnosis of proximal DVT or PE the committee agreed that it was important to offer them anticoagulant treatment immediately to reduce the risk of VTE recurrence. They chose to recommend this for at least 3 months in the first instance because

the majority of evidence for the effective treatment of VTE looked at event rates at 3 months or longer and the committee agreed that it was appropriate to have a review at 3 months to determine whether the person with VTE would benefit from longer term treatment or whether treatment could be discontinued. They noted that the balance of the benefits versus harms of treatment changed over time and were aware of evidence that suggested that a longer treatment duration was not beneficial for everyone with VTE (see the extended therapy section below for more details). An initial treatment period of at least 3 months is also part of established clinical practice.

The committee noted that certain groups of people with VTE may require different treatments and/or additional investigations and therefore it is important that these people are identified and treated appropriately. To ensure that these people are correctly identified the committee recommended that baseline blood tests including full blood count, renal and hepatic function, prothrombin time (PT) and activated partial thromboplastin time (APTT) are carried out at this time and that the results have been reviewed within 24 hours. However, despite recognising the importance of certain tests to identify certain populations, such as those with renal impairment, they agreed that the potential harm from not treating a confirmed VTE event immediately was likely to be greater than the harm of giving a single dose of anticoagulant while waiting for the test results in people who would otherwise be contraindicated for a specific treatment. They therefore made a recommendation to reflect this.

The committee agreed that it is important that each person with VTE is matched to a regimen that will work for them. The committee were aware that recommendations regarding patient preferences already exist in the guideline and agreed their importance. They included mention of comorbidities, contraindications (which should include any arising from potential drug-interactions) and preferences in the recommendations concerning pharmacological treatment to ensure that these issues are taken into account during the decision making process and that the person with VTE is able to access the most effective treatment regimen for their individual circumstances. The committee also were aware of the NICE guideline on medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. They agreed that the recommendations covering information about supporting patient involvement in making decisions about medicine, supporting adherence and reviewing medicines are relevant to this guideline at multiple stages of the pharmacological treatment pathway. These recommendations cover good practice points around communication, increasing patient involvement, providing information and ways to increase adherence and although they are generic the committee agreed that the points still apply to interactions between healthcare professionals and people with VTE. In addition, they noted that the recommendations in NICE's guideline on medicines optimisation that covered the use of patient decision aids are also relevant across the treatment pathway as they cover general good practice points to improve patient involvement in decision making as well as the use of patient decision aids. Finally, the committee noted that there are also relevant recommendations on shared decision making in the NICE guideline on patient experience in adult NHS services. The committee included cross references to these guidelines at the start of the anticoagulation treatment recommendations.

The committee made a separate recommendation concerning the choice of anticoagulant based on their assessment of the quality of the trials (as discussed in the section above), and the findings from the pairwise and NMA results.

For people with VTE, the pairwise and NMA analyses for the outcome of VTE-recurrence could not differentiate between any of the comparators, except for UFH + VKA, which was

shown in the NMA to have increased recurrences compared to LMWH + VKA , apixaban, edoxaban and rivaroxaban (see initial treatment summary tables for VTE, PE and DVT). Apixaban and rivaroxaban both reduced major bleeding compared to LMWH + VKA, fondaparinux + VKA and UFH+VKA, with apixaban also reducing major bleeds compared to dabigatran and edoxaban. In the NMA, apixaban, dabigatran and edoxaban all demonstrated reduced clinically relevant non-major bleeds compared to LMWH+VKA, UFH+ VKA and rivaroxaban. Apixaban and dabigatran also demonstrated clinically relevant reduced non - major bleeds compared to edoxaban. The NMA evidence could not differentiate mortality outcomes between any of the DOACs or other treatment alternatives, (LMWH + VKA, fondaparinux + VKA and UFH+VKA).

The committee discussed the difficulty of identifying the most clinically effective treatment option due to difficulties in balancing the benefits (of reduced recurrences) against the harms (bleeds) of each treatment option. They agreed that the economic model was helpful in synthesising these outcomes in a way that enabled them to look at the overall effect on the person with VTE using QALYs (quality adjusted life years) as a measure of benefit.

Apixaban was the most cost-effective option based on the results from the economic model (see the section on cost effectiveness and resource use below). Based on the inability of the included evidence to differentiate between treatments for effectiveness at reducing VTE recurrence (with the exception of UFH +VKA mentioned above), the increased effectiveness of apixaban in reducing both major and clinically relevant non-major bleeding, and the cost effectiveness results the committee agreed to recommend apixaban as a first choice for the initial treatment of VTE. However, as discussed above (see quality of the evidence section), the committee had concerns about differences in the inclusion criteria between the DOAC trials and, in particular, the narrower inclusion criteria in the apixaban trial in comparison to the rivaroxaban trial. Specifically, they were concerned that the stricter inclusion criteria in the apixaban trial and the greater proportion of people with unprovoked VTE might have reduced the number of bleeds compared to the EINSTEIN trial where there was a greater proportion of people with provoked VTE. This reduction in bleeding risk is a key parameter in the economic model that underlies the cost-effectiveness of apixaban.

The committee also decided to recommend rivaroxaban as a first choice treatment based on the clinical effectiveness of rivaroxaban, particularly the reduction in major bleeds compared to LMWH+VKA; the committee's concerns regarding the strict inclusion criteria of the apixaban trial; the very similar costs of apixaban and rivaroxaban and the results of the economic model (see the cost effectiveness and resource use section below for details). The committee concluded that due to the issues with the apixaban trial there was a greater degree of certainty that apixaban and rivaroxaban were better than alternative options rather than apixaban specifically being the best option.

The committee recognised that apixaban or rivaroxaban may not be suitable for everyone with VTE and, based on the pairwise and NMA results, they recommended alternative treatment options of dabigatran, edoxaban or LMWH concurrently with a vitamin K antagonist. Edoxaban and dabigatran were less preferable options than apixaban and rivaroxaban for the initial treatment of VTE due to having higher risks of major bleeding than apixaban and being less cost effective than both apixaban and rivaroxaban. However, NMA evidence suggests that dabigatran and edoxaban offer reduced clinically relevant non-major bleeding compared to LMWH+VKA; dabigatran also showed reduced clinically relevant non-major bleeding compared to rivaroxaban and UFH+VKA while edoxaban demonstrated reduced VTE-recurrences compared to UFH + VKA.

LMWH+VKA demonstrated reduced rates of all-cause mortality compared to fondaparinux+VKA and reduced rates of VTE-recurrence compared to UFH+VKA. LMWH +VKA has a long history of use in clinical practice and the frequent INR monitoring associated with this treatment means that its anticoagulant effect is very reliable. This treatment option might be suitable for people with VTE who are unable to take a DOAC for medical reasons and those who prefer a higher level of monitoring. The committee agreed that if LMWH is being used it is important it should be initiated as soon as possible and continued for at least 5 days or until the INR is at least 2.0 for at least 2 days, at which point VKA can be continued alone. The committee made recommendations to reflect this to help ensure best clinical practice is observed.

The committee noted that fondaparinux +VKA was previously recommended as an option for the treatment of VTE and was typically used for treating people that objected to the use of heparin due to its porcine origin. The committee noted that the NMA evidence showed that the people offered apixaban, dabigatran or rivaroxaban had lower risks of major bleeding and/ or CRNMB compared to those offered fondaparinux and that there was an increase in all-cause mortality in people offered fondaparinux +VKA compared to LMWH +VKA. Based on these findings, the committee agreed that fondaparinux should not be included in the list of treatment options. However, the committee did not want to make a specific recommendation that fondaparinux should not be used as there are still some rare circumstances under which it would be appropriate to use fondaparinux, such as if a person with VTE objects to the use of animal-derived anticoagulants and for people with VTE who prefer/require a parenteral therapy but have a reaction to heparin based products (such as people who have heparin-induced thrombocytopenia).

The committee commented that it is already current practice that UFH not be routinely used for the initial treatment of VTE (except for people with established renal failure [estimated creatinine clearance of less than 15 ml/min], hemodynamic instability or if they are at an increased risk of bleeding). The committee noted that the evidence showed that other recommended treatments were more clinically and cost effective. In people with VTE, the NMAs results showed that compared to UFH+VKA, people offered apixaban, rivaroxaban and edoxaban had lower risks of VTE recurrence; apixaban and rivaroxaban had lower risk of major bleeding and apixaban, dabigatran and edoxaban had lower risks of CRNMB. In addition, in the DVT subgroup analysis, the NMA results showed that people in the UFH +VKA group had increased all-cause mortality compared to LMWH+ VKA. The committee agreed that making an explicit recommendation that UFH should not be routinely used except in people with renal impairment or at an increased bleeding risk will reinforce good clinical practice.

The committee made a research recommendation aimed at addressing the issues of comparability between the DOAC trials. The research recommendation specified an analysis of individual patient data (IPD) from the existing RCTs involving DOACs and the other treatment options (see appendix Q for more details). They envisaged that this analysis would allow the selection of comparable participants from across the trials and that this data could be used in a series of NMAs to improve the estimation of relative clinical effectiveness, cost-effectiveness and safety between the DOACs and other treatment options. This would help to reduce the problems the committee had with differences in the inclusion criteria between the DOAC trials, in particular the AMPLIFY trial for apixaban. The committee did not make a research recommendation for an RCT directly comparing the DOACs in people with VTE because they agreed that it was unlikely that this trial would be feasible due to difficulties in obtaining funding when clinical trials of the DOACs already exist and that the manufacturers

of the individual DOACs would lack an incentive to test their products directly against a competitor's drug in case their DOAC was shown to be less clinically effective. However, they also acknowledged that it may be difficult to get the manufacturers of the DOACs and the authors of the clinical trials to provide IPD for re-analysis.

The committee made separate recommendations for people with PE with haemodynamic instability and people with DVT or PE with renal impairment, antiphospholipid syndrome or body weight less than 50kg or more than 120kg.

People with VTE at extremes of body weight (less than 50kg or more than 120kg)

The committee discussed the uncertainty about effective dosing strategies for people with VTE and obesity and the reasons underlying it. In particular, they noted that there are concerns about subtherapeutic anticoagulation due to uncertainty regarding the distribution of the anticoagulants in the body, peak concentration and elimination in these people.

The committee noted that there was a shortage of evidence for the relative effectiveness of different treatments in people with VTE at the extremes of weight. The committee noted that the evidence was for people with a BMI of at least 30 kg/m^2, rather than those specifically with class III obesity (BMI of at least 40 kg/m^2) for whom the problems above are more pronounced. The committee agreed that this evidence should not be marked down for indirectness because this grouping covers a wider range of people with obesity. There was evidence on 4 treatment options in people with VTE and obesity (LMWH+VKA, apixaban, rivaroxaban and dabigatran) however, evidence was typically limited to the outcome of VTE-recurrence and both the pairwise and NMA analyses could not differentiate between the different treatments for this outcome. As a result, they agreed that there are concerns about maintaining therapeutic anticoagulation using DOACs and uncertainty about effective dosing strategies.

The committee discussed the International Society on Thrombosis and Haemostasis consensus statement that highlights that DOACs should not be used in people weighing over 120kg. However, if they are used in obese people with VTE then the levels of anticoagulants need to be measured. They noted that not all hospitals in the UK (for example, district general hospitals) are capable of effectively measuring this and agreed that this approach is impractical in most cases.

The committee agreed that it was most likely that a person who was obese would be prescribed VKA to ensure that they are receiving sufficient anticoagulant to treat their VTE because the effects of VKA can be monitored (using INR monitoring). However, there are situations in which VKA is unsuitable, such as when the person has difficulty maintaining the INR within the therapeutic range and when the frequency of monitoring is too time-consuming or impractical. The committee agreed that although there was more uncertainty about the use of DOACs in people with obesity there are likely to be circumstances in which the DOACs are suitable.

The committee also noted that there is uncertainty surrounding effective treatments for people with low body weight and that the summary of product characteristics (SPCs) for several anticoagulants refer to absolute body weight rather than BMI when talking about dose adjustments for people at the extremes of body weight. The committee therefore decided to refer to absolute weight in their recommendation and agreed that low body weight (< 50kg) and high body weight (> 120kg) were appropriate categories to use to alert the

clinician to the need for a different treatment dose or monitoring. These reflect the categories used in some of the SPCs, although they do not all use the same cut-offs.

Taking these issues into account and using their clinical expertise, the committee agreed that it was more helpful not to make a specific recommendation for a particular anticoagulant for people at extremes of body weight, allowing the treating clinician to decide which anticoagulant to use for the individual with VTE. This choice should be based on the need for monitoring and dose adjustment listed in the SPCs and take into account locally agreed protocols or advice from a specialist or multidisciplinary team. However, they highlighted the need for monitoring to ensure therapeutic anticoagulation with whichever anticoagulant is used.

In addition, to try to address the limited evidence for effectiveness of DOACs in people with a body weight <50kg or >120kg , the committee agreed that these people should be included as subgroups in their research recommendation to compare the effectiveness of anticoagulants using individual patient data (see appendix Q for more details). The committee also noted the uncertainty surrounding the most effective dosing strategy for the DOACs and for the LMWH dalteparin, in people within these weight groups. However, as this was not within the scope of this review or the current guideline update, they were unable to make research recommendations to address these issues.

PE with haemodynamic instability

The results of the NMAs in people with VTE show that other treatments are more clinically and cost effective than UFH+VKA for the general population. However, based on their clinical expertise, the committee agreed only UFH+VKA is suitable for use in people with haemodynamically unstable PE and made recommendations to reflect this.

They agreed that in cases of highly unstable PE, when thrombolysis might be given, there are two key reasons to give UFH over LMWH or a DOAC:

1. Reversibility of treatment- People with haemodynamically unstable PE who go on to receive systemic thrombolysis are at an increased risk of bleeding. UFH treatment can be easily stopped and the anticoagulant effect it has wears off relatively quickly. Its action is therefore easily reversed if major or critical site bleeding occurs. In contrast, LMWH is given as a subcutaneous injection, has a longer half-life and is only partially reversible with protamine sulphate. In addition, the committee noted that the published literature on thrombolysis typically used UFH as the preceding treatment and that, in practice, most clinicians would prefer to use UFH prior to thrombolysis as a result.

2. Efficacy – people with hemodynamically unstable PE, and those in cardiovascular shock, have poor peripheral perfusion and as such there is concern that subcutaneous injection with LMWH will take too long (3-4 hours) to reach its peak effect and may result in subtherapeutic levels of anticoagulation due to absorption issues. As intravenous UFH is delivered directly into the blood stream and monitored continuously through measurement of the APTT ratio, there is a more measurable and rapid therapeutic effect, particularly if it is administered within medical areas that have expertise and familiarity, such as critical care units.

The committee also retained part of a 2012 recommendation (and cross reference to relevant section) to consider thrombolytic therapy in these people, as this is common practice and could be beneficial if their condition changes.

People with VTE and renal impairment

The committee agreed that it is particularly important to think about clearance of the anticoagulant in people with renal impairment because of the role of the kidneys in clearing drugs from the body. People with renal impairment have an increased risk of drug accumulation, which can lead to an increase in bleeding risk and may therefore require different treatment options to people with VTE who lack renal impairment.

There was very limited evidence on people with VTE and renal impairment from the pairwise results for the initial treatment of VTE, and there was not enough to run NMAs for any of the outcomes. Leizorovicz (2011) looked at LMWH + VKA versus UFH + VKA for the initial treatment of DVT in elderly people with impaired renal function (CrCl≤30 mL/min). People in the UFH+VKA arm of the trial had a reduced risk of all-cause mortality at 3 months, but the other outcomes could not differentiate between treatment options.

Due to the shortage of evidence concerning the most effective treatments for people with renal impairment, the committee made consensus recommendations based on their experience and clinical expertise and the summary of product characteristics documents (SPCs) of the options considered.

The committee agreed that traditionally, UFH has been used in people with severely impaired renal function (estimated creatinine clearance (CrCl) of less than 30 ml/min/) because UFH is cleared by the reticuloendothelial system and not renally and therefore does not present a risk of accumulation in this group of people. However, the committee noted that UFH is administered via a continuous intravenous infusion which is costly, involves 4 hourly blood tests, a high level of patient monitoring (which impacts on patient satisfaction) and is unsuitable for long-term use. In addition, based on experience the committee noted that UFH has higher rates of complications than other therapies, including heparin induced thrombocytopenia and additional cautions/side effects including heparin resistance, allergy and drug interactions.

In contrast, DOACs have variable levels of renal clearance and LMWH is cleared renally and may accumulate in people with renal impairment dependent on cause of renal failure. LMWH can be used in people with renal impairment but requires dose reduction and monitoring with LMWH anti- Xa levels to ensure it is working effectively. In addition, different brands of LMWH have different clearance rates (for example tinzaparin is cleared the best) and so use of LMWH requires specialist input or the use of locally developed protocols.

As the anticoagulant effect of VKA is unaffected by renal impairment and can be monitored the committee recommended LMWH+VKA for people with VTE and established renal failure (estimated CrCl <15). However, the committee noted that VKA can be involved in drug-drug interactions (and patients with CKD are often taking multiple drugs). It may also increase the risk of vascular calcification and VKA-related nephropathy, and INRs may be outside the target range for longer leading to supra-therapeutic anticoagulation (INR >4) and an increased bleeding risk. The committee noted that for people with VTE and severe renal impairment (estimated CrCl of 15 to 29) and with established renal failure (estimated CrCl <15) all methods of anticoagulation carry potential associated risks. The committee therefore agreed that any decision on therapy should be taken following a discussion with the patient about the relative clinical risks and benefits, and the associated care needs.

The committee noted that difficulties surrounding treatment for people with severe renal impairment or renal failure mean that treatment options are limited. Based on their clinical expertise and the relevant SPCs, the committee agreed that UFH with a VKA , LMWH with a VKA or a DOAC are suitable treatment options for people with estimated CrCl 30-50 ml/min

and more severe renal impairment (estimated CrCl 15-29 ml/min), but noted that in its summary of product characteristics documents (SPCs), dabigatran is not suitable for the latter group of people. However, only LMWH alone or with a VKA and UFH alone or with a VKA are recommended when estimated creatine clearance is < 15 ml/min based on the SPCs for the DOACs that advise that DOACs should not be used in these circumstances.

Taking into account the issues outlined above, the committee agreed that the available treatment options depend upon the level of renal impairment, but that it was not possible to specify a preferred option for each degree of impairment as this will depend upon the specific clinical situation.

The committee noted that dose adjustments need to be made for people with renal impairment and some of the treatment options, such as apixaban, need to be used with caution in people with an estimated CrCl of 15-29 ml/min. In addition, they also noted that monitoring using tests such as APTT (activated partial thromboplastin time) for UFH and anti-Xa for LMWH are very important to ensure that people with renal impairment have the best possible treatment and outcomes. They agreed that it is important to consult the SPCs and follow locally agreed protocols or advice from a specialist or multidisciplinary team, to ensure correct dosing and monitoring. The committee made a recommendation to reflect these points. They agreed that current practice has moved from the use of estimated glomerular filtrate rate (eGFR) to creatinine clearance as a measure of renal function and ensured that their recommendation accounted for this change in practice.

The committee were aware of the ongoing VERDICT (thromboembolism in renally impaired patients with direct-acting oral anticoagulants) RCT comparing apixaban and rivaroxaban to standard anticoagulation (ClinicalTrials.gov Identifier: NCT02664155).

People with VTE aged 65 years and older

The committee identified the elderly (at least 65 years old) as being particularly difficult to treat due to anticoagulants potentially having different effects in these groups compared to the general population of people with VTE leading to uncertainty about the most effective treatment options.

The committee did not make specific recommendations for people aged 65 years and over because data for this group was limited to the outcome of VTE-recurrence, and both the pairwise and NMA analyses could not differentiate between any of the treatment options. There was therefore no evidence to support a different treatment regimen for these people and the committee agreed that it was not necessary for them to make consensus recommendations.

Initial treatment of VTE in people with active cancer

The committee advised that people with cancer that is in remission would typically be treated the same as the general population of people with VTE and made a recommendation to reflect that this.

Please note that the following discussion refers specifically to people with active cancer.

The committee advised that it is established practice to give anticoagulation for 6 months in people with active cancer, based on the results of the CLOT (2003) trial which had a duration of 6 months. However, the committee agreed that for some people with VTE and active cancer, a shorter duration may be suitable. The committee therefore recommended that

treatment should be for a duration of 3 to 6 months to allow the treatment duration to be matched to individual needs. They also agreed that, similar to people without active cancer, a review should also take place after around 3 months of treatment. However, they noted that this may be too soon for some people with active cancer, depending on their treatment regimens for both cancer and VTE. They therefore made a recommendation for a review at 3-6 months to allow the review to be held at a suitable time for the individual.

The committee were concerned with the clinical evidence surrounding the use of DOACs in people with active cancer, in particular they noted that there are no trials published at the time of this review which have assessed apixaban and dabigatran specifically in cancer patients. There was also concern about the interactions that anticoagulants might have with chemotherapy and other cancer-related drugs. The committee highlighted a need for robust evidence on the effectiveness of the different treatments in people with cancer. Consequently, the committee were very cautious not to automatically generalise conclusions made for people with VTE to people with active cancer.

The committee considered evidence from pairwise analyses and NMAs and noted that there was evidence suggesting a reduction in VTE-recurrence in people given rivaroxaban, edoxaban or LMWH alone compared to LMWH + VKA. Apixaban and dabigatran could not be differentiated from any other treatment option for any of the outcomes assessed in the NMA or pairwise comparisons. However, the committee were concerned that the evidence available for apixaban and dabigatran, was limited to subgroup analyses as these trials were not designed specifically to address people with VTE in cancer patients and therefore do not adequately account for different types of cancer (such as those with cancers that have a high propensity to cause VTE).

The committee noted an increased risk of bleeding associated with edoxaban and rivaroxaban compared to LMWH alone. However, the committee also advised that people with GI cancer are prone to bleeding when taking oral anticoagulants and therefore these types of anticoagulants are typically not used in practice when treating these people. The edoxaban and rivaroxaban studies included people with gastrointestinal (GI) malignancies. When these studies excluded GI cancers in sub-group analyses the safety profiles of these DOACs improved compared to LMWH alone. Additionally, many of the increased bleeds associated with the DOACs were attributable specifically to GI and genitourinary (GU) bleeds.

The committee noted that the trends for effectiveness of the DOACs in people with cancer seem to be similar to those in the general population. The committee also took into account evidence about cost-effectiveness from the *de novo* economic model which demonstrated that apixaban had the highest probability of being the most cost-effective option followed by rivaroxaban (see the section on cost effectiveness and resource use for people with VTE and cancer for more details).

The committee noted that anticoagulants have the potential to interact with other drugs the person may be taking and that it is particularly important to take this into account when choosing an anticoagulant for people with cancer because they are particularly likely to be taking a range of drugs, including but not limited to those for chemotherapy, which have the potential for interactions with anticoagulants. They also agreed that the type of tumour/ tumour site may lead to an increased risk of bleeding and therefore need to be considered on an individual basis.

Taking these issues and the NMA evidence into account, the committee recommended that a DOAC be considered for the treatment of VTE in people with active cancer. Although the committee recognised that a DOAC would not be a suitable treatment for certain types of tumours, such as GI and GU malignancies, due an increased risk of bleeding they decided not to recommend against the use of DOACs with specific tumours because there is uncertainty about which other tumours might also have similar higher risks of bleeding, different stages of treatment might have a lower bleeding risk and because they wanted the assessment of bleeding risk to be made at the individual level rather than by following a list of excluded tumours that was likely to be incomplete.

The committee decided not to specify which DOAC should be used due to remaining uncertainty about the relative effectiveness of apixaban and dabigatran (due to the lack of cancer-specific trials for these drugs) and concerns about the bleeding risk for edoxaban and rivaroxaban.

The committee noted that in current practice LMWH is usually prescribed for 6 months or until the person is in remission from the underlying cancer because it has a favourable clinical profile. However, LMWH alone also showed improvements compared to edoxaban for major bleeding and to rivaroxaban for clinically relevant non major bleeding. The committee also took into account the results of the economic analysis which showed that LMWH alone is not cost effective due to its much higher cost (see the section below on cost effectiveness and resource use). Additional analyses highlighted that when compared just to LMWH+VKA, LMWH alone was not cost effective. However, the committee did not want to make a recommendation to not use LMWH based on the lack of cost-effectiveness because of its proven effectiveness in reducing VTE recurrence compared to LMWH+VKA and because they felt it was important to have a choice between parenteral (LMWH) and oral (VKA) treatment options depending on individual circumstances.

The committee acknowledged that LMWH+VKA may not be a practical option for some people due to possible drug interactions and difficulties associated with frequent INR monitoring which can lead to multiple competing appointments in people with cancer and VTE, making scheduling difficult and time consuming. In addition, several chemotherapy agents affect the liver making it difficult to keep the INR in therapeutic range. In addition, vomiting is a common side effect of chemotherapy and can result in non-absorption of oral anticoagulants (VKA and the DOACs). Other issues such as anorexia and mucositis may also mean that an oral anticoagulant is unsuitable. These issues may limit the practical usefulness of oral anticoagulants in people with cancer.

Taking these points into account, the committee agreed if a DOAC is unsuitable to consider either LMWH alone or LMWH+VKA, based on the individual's clinical situation and preferences.

The committee agreed that LMWH alone was an effective choice clinically and noted that it is licensed for the treatment of VTE in people with cancer whilst the DOACs are not. They agreed it was important to follow GMC guidance where possible, which states that licensed medicines should usually be recommended over non-licensed ones. However, they recognised that the cost of LMWH was prohibitive compared to the DOACs and LMWH +VKA and that if alternative treatment options were suitable and effective then it would be helpful to reduce the use of LMWH to conserve NHS resources.

The NMA demonstrated that UFH+VKA had a reduced rate of clinically relevant non-major bleeding compared with LMWH+VKA, rivaroxaban and dabigatran, and did not perform

significantly worse than any other drugs for the other outcomes of interest in this review. However, the committee were concerned that evidence for UFH+VKA comes from one study which is over 10 years old and were therefore uncomfortable changing recommendations regarding the use of UFH+VKA in people with cancer due to the ongoing uncertainty regarding its effectiveness.

The committee pointed out that there is a trial in progress comparing apixaban to LMWH alone in people with VTE and active cancer (CARAVAGGIO), which is expected to be published in early 2020. They therefore decided against making any specific research recommendations for a clinical trial test the effectiveness of apixaban in people with VTE and active cancer. They agreed that the recommendations concerning pharmacological treatment of VTE in people with cancer may need to be updated once this trial has been published. They were also aware of the ADAM trial (McBane 2019) which compared apixaban and dalteparin, but this study published after this evidence review was completed and is therefore not included in the analysis or the above discussions.

The committee noted that there was no data available for the extended therapy of VTE in people with cancer. However, the committee agreed that active cancer should be a subgroup analysis of their research recommendation to compare the DOACs with other treatments using individual patient data from already published trials (see appendix Q for more details) and that this analysis should look at initial and long term treatment.

Anticoagulant treatment for people with Antiphospholipid syndrome (APS)

For people with already diagnosed APS, anticoagulation has typically begun with VKA to a target INR of 2.5 (range 2.0-3.0) and there is an incentive for long term therapy due to an increased risk of VTE-recurrence in these individuals. However, the recent introduction of DOACs has led to an increased usage of these drugs to treat VTE.

Only one study has investigated the use of DOACs in people with VTE and APS. Cohen (2016) compared rivaroxaban to warfarin in people with VTE and positive tests for APS on two occasions, three months apart. Neither arm in this study experienced a major bleed or a recurrent event and the study could not differentiate any of the other outcomes of interest to this review. Additionally, Crowther (2003) compared standard intensity warfarin (INR 2.0-3.0) to high intensity warfarin (3.1 to 4.0) but could not differentiate VTE-recurrence between these treatments.

The committee was aware of a recent MHRA alert that identified an increased risk of recurrent thrombotic events in people with APS, and advised that DOACs are not recommended in people with APS, particularly those high-risk patients with triple positive APS. However, these recommendations were based on a study that did not meet the inclusion criteria for this review (Pengo, 2018). Pengo included 120 people with a history of thrombosis (arterial or venous) who were triple positive for APS. The study identified an increased risk of thrombotic events (specifically, arterial thrombotic events including ischemic stroke and myocardial infarction) in people given rivaroxaban compared to those given warfarin. However, this study did not distinguish between those people with an index VTE and those with an index arterial event and was therefore not included in the present review. Based on the findings for rivaroxaban, the efficacy of the other DOACs has been brought into question for these people and the MHRA alert covers all of the DOACs.

The section of the VTE guideline that covers thrombophilia testing is out of scope for this current update. The committee were therefore unable to make new recommendations in this

area. The 2012 VTE guideline recommended to not offer thrombophilia testing to patients who are continuing anticoagulation treatment. The committee agreed that in light of the MHRA alert and the potential for increased thrombotic events in people with APS when treated with a DOAC, this recommendation should be amended to allow for the potential testing for thrombophilia in people continuing treatment. It now says to not offer testing for hereditary thrombophilia and makes no mention of acquired thrombophilia. The committee noted that the rationale for not testing for heritable thrombophilia while people are taking anticoagulants remained valid because people with heritable thrombophilia are not at increased risk of recurrence while they remain on treatment. These people are not affected by the MHRA alert for APS which is an acquired form of thrombophilia.

The committee noted that the MHRA alert has raised several practical issues. Firstly, 2 sets of 3 tests (lupus anticoagulant, antiphospholipid antibodies and beta-2 glycoprotein antibodies) taken 3 months apart are needed to determine whether a person has APS and how many different types of antibodies they have (with triple antibodies being the most severe form). The first test is not taken until the person with VTE is in a stable condition and this is usually after 1 month of treatment. The second test is taken 3 months later. However, people with APS have an increased risk of thrombosis during this time if they receive DOACs because they are not taking an effective anticoagulant for their VTE. Secondly, a second test for APS is required to confirm an initial positive test and this second test is taken at least 12 weeks after the initial test. This means that testing for APS is less relevant in people with provoked VTE, who are usually only given a 3-month course of treatment. In contrast, people with an unprovoked VTE usually go on to receive treatment past 3 months and are therefore potential candidates for APS testing. Finally, it is currently necessary for the person to come off anticoagulation before testing for APS because tests for lupus anticoagulant are affected by the presence of anticoagulants. Therefore, testing is associated with an increased risk of VTE-recurrence due to this interruption in treatment. A new adsorbent test, DOAC-STOP, that does not require the person with VTE to stop taking DOACs exists, but there is a lack of evidence to support its widespread use, and there are only a limited number of laboratories with experience in performing this test.

The committee were unable to make any recommendations to address these issues, but they recognised the uncertainty concerning screening for APS that has been raised by the MHRA alert and the effect this is likely to be having on people with VTE who are taking DOACs. However, the committee were aware that the British Society for Haematology have recently updated their guideline on the investigation and management of APS in light of the MHRA alert and they hoped that the BSH document would prove useful guidance for clinicians and people with VTE.

Although thrombophilia testing was out of scope of this update, the committee were able make a recommendation in the anticoagulation treatment section of the guideline for people with triple positive APS to be offered LMWH+VKA, which reflects the MHRA alert.

Treatment failure

The committee agreed that in the event of treatment failure it is important to check whether the person has been adherent to their treatment regimen and to address any other sources of hypercoagulability. It may also be necessary to increase the dose of anticoagulant or change to an anticoagulant with a different mode of action to try to prevent further VTE recurrences. They made a recommendation to reflect these points and agreed that these were relevant during both the initial and extended phases of treatment.

Extended therapy of VTE

The committee agreed that after 3 months of initial treatment for a VTE it is important that the benefits and harms of keeping someone on anticoagulant therapy are assessed and that this is discussed in depth with the individual with VTE, even if it is already expected that the person will receive treatment beyond 3 months. At this point the decision-making moves from treatment to secondary prevention. Any decision to extend therapy must be carefully balanced against the risk of major bleeding (for more information on this, please see the review on determining the optimum length of treatment in VTE). The committee recommended that treatment should be reviewed at 3 months and emphasised the importance that this review process involves a discussion with the individual with VTE and that their preferences regarding treatment be taken into account. They noted that the initial treatment of VTE with DOACs is licensed for 6 months based on their SPCs, but they agreed that a review at 3 months in people receiving a 6-month course of treatment would allow for an opportunity to review clinical progress, adapt treatment based on the outcome of any provocation assessment, thrombophilia investigations or malignancy screen, and plan for any changes in prescription or dosing that may need to be made at the 6-month point. The committee were also aware of NICE's guideline on medicines optimisation which specifically detail things to take into account when conducting a structured medicines review with the objective of reaching an agreement with the person about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste. In addition, NICE's medicines adherence guideline has a relevant section with general good practice points for reviewing medicines. The committee noted that there are also relevant recommendations on shared decision making in the NICE guideline on patient experience in adult NHS services. The committee agreed that these recommendations covered general good practice and also applied to people with VTE and included cross references to these guidelines.

The committee noted that people with an unprovoked VTE are at higher risk of recurrence compared to those with a provoking risk factor whose risk of recurrence subsides when the provoking factor is removed. The committee agreed that because of this lower risk of recurrence, people with provoked VTE could come off anticoagulation completely if they had a simple disease course and the provoking factor was no longer present. In contrast, people with unprovoked VTE have a higher risk of recurrence and are more likely to continue treatment, but this decision requires consideration of bleeding risk and individual preferences as well as the risk of recurrence (See evidence review F on determining the optimum duration of treatment for VTE for the evidence behind these recommendations and a more detailed discussion that also covers the use of prognostic tools to aid the decision-making process.).

The committee discussed in length the evidence behind the different drugs available for the extended therapy of VTE. The committee noted that compared with placebo, the NMA demonstrated that all active drugs produced significantly fewer recurrent VTEs. The committee also noted that aspirin demonstrated higher rates of VTE-recurrence when compared to other active anticoagulants. The committee advised that this is due to mechanism of action of the drug not purely being one of anticoagulation, also having various cardiovascular effects.

The committee were concerned with the low quality evidence of the NMA for major bleeding during extended therapy and advised that clinically, it was not feasible that placebo would produce more major bleeds than apixaban due to the mechanism of action of the drug being the main driver of major bleeds. The committee felt that this limited the interpretability of this particular NMA as, due to apixaban having fewer number of absolute bleeds in the AMPLIFY-EXT trial, indirect evidence suggested significant improvements for apixaban compared to almost all other comparators.

Additionally, the committee discussed the prospect of changing treatment at the 3-month review to another form of treatment, why this may be beneficial in some scenarios and the difficulties associated with it. The committee noted the practical difficulties of changing drugs, including the differing monitoring and administrative requirements of different drugs, such as the frequent INR monitoring required for warfarin and the dosing differences between drugs, and the inconvenience of changing from a DOAC to warfarin due to the need to make regular clinic visits. Additionally, the committee agreed that a person with VTE who has not experienced an adverse event by the time of the first review may be reluctant to change drugs. Based on these concerns and their clinical experience, the committee agreed that if treatment is continued beyond 3 months, the first option should be to consider continuing the current treatment if it is already well tolerated.

The committee agreed that the evidence suggested that there is a continuity between how the anticoagulants perform in the initial treatment and how they perform in the extended phase of VTE, however the evidence for major bleeding has a large degree of uncertainty surrounding it. The network for clinically relevant non-major bleeds was of high quality and demonstrated a similar trend to that of initial treatment, with apixaban (2.5mg and 5mg) producing fewer bleeds than other active drugs compared in the review. The committee were concerned with this lack of precision for major bleeds as although there is some continuity between the rate at which a drug produces major bleeds and clinically relevant non-major bleeds, evidence from the initial treatment of VTE showed that different drugs were preferential when looking at major bleeds compared to clinically relevant non-major bleeds. The committee agreed that they could not make strong recommendations based solely on the data from clinically relevant non-major bleeds as this does not necessarily correspond to similar rates of major bleeds, which are of greater concern due to being potentially fatal.

The committee discussed the evidence from the economic model for switching treatment strategies. The cost-effectiveness analysis showed that for sequences that started with a DOAC, the most cost-effective strategy was to switch to apixaban (or in the case of apixaban as initial treatment, to remain on apixaban (see the cost effectiveness and resource use section below for more details of the model parameters associated with this result). The committee therefore agreed that for people already treated with a DOAC it would be most cost effective to consider switching to apixaban and made a recommendation to reflect this. However, the committee emphasised that this decision is very complex and should be made with considerations of the preferences of the person with VTE and the specific clinical presentation. The committee noted that after apixaban, VKA was the most cost-effective option. Although the committee agreed that it would typically not be clinically feasible to switch someone from a DOAC to VKA, due to this introducing a need for frequent INR monitoring, VKA remains an option in cases where there are clinical concerns regarding continuing treatment with a DOAC.

There was a lack of evidence about the relative effectiveness of the extended use of anticoagulation therapies in people at extremes of weight (<50kg or >120kg), and people

with active cancer, antiphospholipid syndrome or renal impairment. The committee agreed that, similar to people without these conditions, it was likely that the best course of action is to remain on the same treatment that had been taken during the initial treatment phase providing it is well tolerated. They made a consensus recommendation to reflect this. They noted that this decision should also take into account the individual's clinical situation and preferences, whether the VTE was provoked or unprovoked and the risk of VTE recurrence and major bleeding in the same way that these factors are taken into account for people who do not belong to one of these groups. They noted that in some cases, continued treatment may involve switching to another treatment option listed in the initial treatment recommendations if the person's preference or clinical situation has changed, or if the person has experienced adverse events or side effects during the initial treatment.

The committee discussed the potential of aspirin in the secondary prevention of VTE. Aspirin is not an anticoagulant and is therefore very different in its safety profile and in the side effects it produces compared to the other drugs in this review. The committee noted that aspirin is less effective than anticoagulants due to an increase in recurrent events and therefore advised that long-term treatment with aspirin is not ideal. However, aspirin reduced VTE recurrences compared to placebo and without the increase in bleeds seen with the anticoagulants. The committee therefore advised that aspirin is a possible option for those people requiring long-term treatment for VTE who decline to take an anticoagulant, following an informed discussion of the risks and benefits. The committee recommended that aspirin be considered in this group of people if a decision is made to continue therapy. However, they also noted that aspirin therapy can have potential significant side effects such as dyspepsia and peptic ulceration. The committee recommended a dose of 75 or 150mg as these are the doses currently used in UK practice.

Cost effectiveness and resource use

The committee was presented with economic evidence on the cost effectiveness of pharmacological treatments for confirmed venous thromboembolism, both from the *de novo* economic model developed for this guideline, and from the existing economic literature. The committee prioritised the evidence from the *de novo* model over evidence from the literature for a number of reasons. First, the majority of published economic analyses do not assess the entire decision space; only one evaluation includes all 4 DOACs. Second, the majority of published evaluations are funded by manufacturers of DOACs and, as such, are subject to a potential conflict of interest. Third, the one included study which assessed the entire decision space and was not funded by a DOAC manufacturer was subject to a number of methodological limitations, as noted in the economic evidence summaries.

Initial treatment and extended therapy for VTE

The committee considered the evidence from the *de novo* model and noted that, in the base-case analysis, when it was assumed that people remain on the same drug in the initial and extended phases of treatment, apixaban was highly cost effective both in people with a DVT and people with a PE. The finding that apixaban generated the most QALYs in the economic model was consistent with the results of the network meta-analyses, in which apixaban had a high probability of producing the lowest number of major and non-major clinically relevant bleeds and a favourable treatment effect on VTE recurrence (although this effect was not statistically significant at the 5% level compared to most other treatments). After apixaban, rivaroxaban had the next most favourable effect on the outcome major bleeding and generated the second highest total QALYs. Total costs for rivaroxaban were approximately

£70 higher than apixaban; the cost of the two drugs was similar and the difference in total costs was mainly due to differences in the number of bleeding events. The committee discussed concerns about the quality of the effectiveness evidence, which limited comparability between DOAC studies. As a result, the committee felt that uncertainty over the differences in bleeding rates reported in trials would also increase the uncertainty about the relative ranking of apixaban and rivaroxaban in the cost-effectiveness analysis.

When the model was expanded to consider the option of switching from any initial treatment to any extended therapy, the results were more uncertain. Sequences that started with apixaban as the initial treatment generated the most QALYs. The strategy of apixaban as initial treatment followed by either no further therapy or followed by a VKA as extended therapy were the least costly. However, the committee had noted that the latter strategy is unlikely to be adopted in clinical practice because switching from a DOAC to a VKA has additional monitoring requirements, which can be inconvenient and impact patients' quality of life. In the incremental analysis for people with a DVT, the only other strategy that was not dominated was apixaban as initial treatment followed by apixaban 5mg twice daily as extended therapy (ICER £26,161/QALY compared to apixaban followed by VKA). Probabilistic sensitivity analysis showed that there was considerable uncertainty in the results. At a threshold of £20,000/QALY, the strategy of apixaban as initial treatment followed by VKA standard as extended therapy had a 25% probability of being cost effective. For people with a PE, the ICER for apixaban as initial treatment followed by apixaban as extended therapy was £27,247/QALY compared to apixaban as initial treatment followed by a VKA as extended therapy. At a threshold of £20,000/QALY, the strategy of apixaban as initial treatment followed by VKA standard as extended therapy had a 40% probability of being cost effective. In both the DVT and PE analyses, the strategy of apixaban as initial treatment followed by apixaban 2.5mg twice daily as extended therapy was technically dominated because the total costs and QALYs for apixaban 2.5mg twice daily and apixaban 5mg twice daily as extended therapy were virtually the same and therefore in subsequent scenario analyses, the committee decided to retain only the licensed 2.5 mg twice daily dose to represent apixaban as extended therapy in the model.

The committee discussed the role of aspirin as an extended therapy option for secondary prevention of VTEs. In the extended therapy NMA, aspirin was not as effective as VKA or DOACs for the outcome VTE-recurrence but it also did not significantly increase the rate of major bleeding compared to placebo. Given its low acquisition cost compared to other treatment options, aspirin had a non-negligible probability of being cost effective. The committee agreed that aspirin would likely improve health outcomes compared to no treatment in the extended phase but did not consider either of these to be appropriate options for all patients, especially those at higher risk of VTE recurrence. When strategies with aspirin, no treatment and switching from a DOAC to a VKA were removed from the decision space, the sequence with the highest probability of being cost effective was to start on apixaban as initial treatment and remain on apixaban in the extended therapy phase (63% for people with a DVT and 61% for people with a PE). It was noted the difference in QALYs for all sequences beginning with the same initial treatment were generally very small. This is because there is greater uncertainty surrounding relative treatment effects in the extended phase and because the choice of treatment in the initial treatment phase (when the baseline risk of both VTE recurrence and bleeding are highest) has a much bigger impact on total QALYs.

The committee considered an additional set of incremental analyses in which a subset of all sequences with the same initial treatment were compared to each other but excluding

various extended therapy options that the committee felt were not clinically relevant for the majority of people with a VTE. For sequences that started with LMWH/VKA as initial treatment (excluding apixaban 5 mg twice daily, aspirin and no treatment from the extended phase), the most cost-effective strategy was to remain on VKA. For sequences that started with a DOAC (excluding VKA low, VKA standard, apixaban 5 mg twice daily, aspirin and no treatment from the extended phase), the most cost-effective strategy was to switch to apixaban (or in the case of apixaban as initial treatment, to remain on apixaban).

The committee recommended against the use of unfractionated heparin with VKA except in people with renal impairment, haemodynamic instability or an increased risk of bleeding. This is because in both the base case and the sequencing analyses, strategies with unfractionated heparin/VKA consistently generated the fewest QALYs, reflecting its unfavourable treatment effect on VTE recurrence in the NMA, and correspondingly these strategies were never cost effective compared to LMWH/VKA in the economic model.

The committee considered the potential resource impact of their recommendations. They felt that use of apixaban, rivaroxaban and other DOACs is likely to increase as a result, which may have a significant resource impact, given the higher acquisition cost of these drugs compared to VKAs. However, the committee were confident in this recommendation, given the clinical and economic evidence supporting it. Furthermore, the cost increase is likely to be at least partially offset by a reduced requirement for INR monitoring, and reduced numbers of bleeding events.

Initial treatment of VTE in people with active cancer

The committee were presented with results of the *de novo* economic model for the subgroup of patients with active cancer. For patients with DVT, results showed that apixaban generated the most QALYs, with an ICER of £12,727/QALY compared to rivaroxaban. Probabilistic results showed that, when one QALY is valued at £20,000, apixaban has a 49% probability of being the optimal choice, while rivaroxaban and unfractionated heparin/VKA have probabilities of 23% and 16% of being optimal respectively.

For patients with a PE, apixaban was also found to generate the most QALYs, with an ICER of £15,378/QALY compared to rivaroxaban. Probabilistic results showed that, when one QALY is valued at £20,000, apixaban had a 51% probability of being the optimal treatment option, while rivaroxaban and unfractionated heparin/VKA have probabilities of 26% and 13% respectively.

For both groups, LMWH alone had a 0% probability of being cost effective at a threshold value of £20,000/QALY, despite producing broadly similar health benefits to rivaroxaban. This is because the cost of LMWH treatment is higher compared to other regimens: LMWH costs close to £10 per day (including administration costs) whereas all other regimens cost below £3 per day. If compared to LMWH/VKA, LMWH alone generates more QALYs but produces an ICER of approximately £268,000/QALY for DVT and £189,000/QALY for PE.

The committee observed that rivaroxaban resulted in the lowest number of VTE recurrences in the cancer subgroup analysis but apixaban still produces the highest number of QALYs because it has the most favourable treatment effect on major bleeding. Overall, apixaban is less cost effective in the cancer subgroup than the main economic analysis for the overall DVT and PE populations. This is because treatment effects on bleeding are less pronounced, patients with cancer have a poorer survival than patients in the main cohort (preventing VTE-related deaths generate fewer QALYs), and cancer is expensive to manage.

Probabilistic sensitivity analysis also showed that there is considerably more uncertainty in results compared to the base case analysis, due to wider confidence intervals around treatment effects produced by the cancer subgroup NMAs.

The committee determined that, due to the greater level of uncertainty in the evidence for people with active cancer, they preferred not to specify one DOAC over another. They also acknowledged the results of the cost-effectiveness analysis, which showed that LMWH alone is not cost effective in patients with cancer due to its higher acquisition cost. It was noted that the 2012 guideline, which recommended LMWH alone, only considered economic evidence in cancer patients from 2 cost-effectiveness studies that were both conducted outside the UK (Aujesky 2005, Dranitsaris 2006), one of which suggested LMWH was not cost effective compared to VKA at US prices. Both of these published studies were excluded from this guideline update because of their limited relevance to the UK context. However, the committee also discussed that it would not be appropriate to recommend LMWH+VKA instead of LMWH alone based solely on the cost-effectiveness results. This is because VKA may not be a practical option for some people due to possible drug interactions and difficulties associated with frequent INR monitoring in people with cancer and VTE. The committee agreed on the need to take individual circumstances into account and recommended that if a DOAC is unsuitable, to consider either LMWH alone or LMWH+VKA.

The committee considered the resource impact of their recommendations in people with cancer. In current practice, LMWH alone is the most commonly used anticoagulant in people with VTE and active cancer. Increasing the use of either DOACs or VKA could produce cost savings due to the substantially lower cost of these regimens.

Other factors the committee took into account

The committee were interested in the effects of treatment options on quality of life, however they noted that only the EINSTEIN trial (rivaroxaban) reported this outcome. Participants reported on treatment benefits (such as improvements in general wellbeing and satisfaction with treatment) and burdens (such as treatment side effects) and the results showed greater treatment benefits and fewer treatment burdens for people offered rivaroxaban compared to LMWH + VKA. The committee agreed that rivaroxaban is likely to produce quality of life improvements for patients because it does not require frequent INR monitoring unlike VKA. However, the committee noted that there was a lack of blinding in the EINSTEIN trial and as a result there was a risk of bias for this subjective outcome, leading to the quality of evidence being graded as very low for this outcome. The committee noted that although there was no evidence available for the other DOACs, they would anticipate similar improvements in quality of life due to a reduction in risk of bleeding side effects and the removal of the need for INR monitoring.

The committee agreed that it was important to take patient preferences into account when deciding on treatment options, based on factors including mode of administration, frequency of dosing, monitoring requirements, animal derived versus synthetic treatments (see below), and previous experience with a particular drug. Treatment with warfarin or an alternative VKA requires frequent INR monitoring at either the physician's office, a warfarin clinic or at home using a home-INR testing device and people with VTE may prefer treatment options that require fewer check-ups (such as the DOACs). However, the committee noted that the reduced number of check-ups associated with DOACs could lead to reduced treatment adherence in some people and may lead to a fall in the number of incidental findings that are identified as a result of regular check-ups. The committee also noted that some patients

prefer VKA as the monitoring provides reassurance that they are appropriately anticoagulated.

The committee noted the importance of anticoagulant alert cards and information and agreed that these should not be limited to just VKA, but also cover other forms of anticoagulation such as the DOACs. The committee were aware of work by the BSH in collaboration with NHS Improvement to update the written information available for VKAs and DOACs and produce a common alert card for all oral anticoagulants (e.g. the yellow oral anticoagulant therapy alert card) for ease of recognition particularly by paramedics / in emergency situations. In addition, the committee noted that a Scottish DOAC card is now being implemented.

The committee also discussed the potential use of technology such as phone apps to store information about anticoagulant use or the potential to store this information on the main screen of a mobile phone, allowing paramedics to access this information in the case of an emergency. The committee agreed that storing information electronically on mobile phones could be useful, but they noted that older people, those who are less technologically able or who lack suitable devices may be unable to take advantage of this technology. They agreed that if this technology was to be used more widely in the future, possibly even replacing other forms of individual record keeping for the person with VTE, steps would need to be taken to prevent these people from being adversely affected.

The committee discussed equalities issues surrounding anticoagulation treatment for VTE including those concerning people who have a disability (learning disabilities, frailty or restricted movement); religious beliefs; age; people undergoing gender reassignment surgery; obesity; IV drug use; chronic kidney disease and people who are migrant workers, Gypsies, Roma or travellers.

They agreed that it was appropriate to make specific recommendations for people with VTE with obesity (referred to as >120kg in the guideline recommendations), and chronic kidney disease because these comorbidities can affect the choice of treatment either due to a lack of information about dosing restricting treatment options (for obesity and low body weight) or due to physical limitations linked to kidney disease. However, there was a shortage of evidence for people with restricted movement and therefore no recommendations were made. In contrast, IV drug users frequently have problems with adherence and may require different treatment regimens to overcome this issue. There was no evidence about which treatments would be most effective in IV drug users and the committee made a research recommendation to try to fill this gap.

The committee did not make any specific recommendations for people undergoing gender reassignment, migrant workers, Gypsies, Roma or travellers these groups due to a lack of evidence. However, they agreed that their recommendations did not need to be adapted for use in these groups because many of the issues concerning these groups were around access and monitoring/adherence to treatment which was not in the scope of this update. They agreed that the pharmacological treatment recommendations offer a range of treatment options in most cases and the clinician and person with VTE can select the most appropriate one for them given their clinical needs, preferences and circumstances.

There was also a lack of evidence for the effectiveness of anticoagulants treatment in people with learning disabilities or dementia. The committee noted that it is importance that patients have the mental capability to understand and follow instructions for their regimen or have carer to do it for them. The committee noted that people with learning disabilities or dementia

may need extra support to ensure that they are able to effectively take their medication and attend any monitoring. However, they agreed that this issue was not specific for VTE and that it was unnecessary to make any separate recommendations for these groups of people. The committee agreed that for those people with learning disabilities there is a need to ensure that treatment delivery is tailored to the individual and noted that there is NICE guideline on patient experience in adult NHS services, which addresses factors such as disabilities and effective communication, and information about supporting adherence in the NICE guideline on medicines adherence that is relevant here. In addition, the committee recommended that comorbidities, contraindications and the person's preferences are also taken into account during the decision-making process. The committee agreed that taken together these recommendations should enable the issue of adherence for those with learning disabilities to be taken into consideration to ensure that a suitable treatment regimen is chosen.

The committee also noted that heparin is porcine in origin and there is an existing recommendation in the 2012 guideline that draws attention to the animal origin of this product. They agreed that fondaparinux is often used in the initial treatment of VTE in people with objections to the use of animal-derived products, however following this initial period there is a lack of suitable animal-free products available. They noted that the DOACs apixaban and rivaroxaban contain lactose from cow's milk and that dabigatran and edoxaban are only licensed for use after treatment with LMWH. The committee were able to amend an existing recommendation to include the information about lactose.

Appendices

Appendix A – Review protocol

Review protocol: 1. What is the clinical and cost effectiveness of different pharmacological treatments for people with suspected DVT prior to confirmed diagnosis?

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of different pharmacological treatments for people with suspected DVT prior to confirmed diagnosis?
Type of review question	Intervention
Objective of the review	In CG144, parenteral anticoagulant was recommended for administration to people with suspected DVT, who had not had their DVT confirmed. Since the publication of CG144, newer, direct-acting oral anticoagulants are available, and are reportedly being used instead of parenteral anticoagulant for people with suspected DVT. Guidance is required on whether direct-acting oral anticoagulants are suitable for use in people with suspected DVT.
Eligibility criteria – population/disease	Adults (18+ years) with suspected DVT Suspected DVT is defined as DVT suspected on the basis of clinical symptoms and/or D-dimer test, but before confirmation by ultrasound imaging or equivalent.
Eligibility criteria – intervention(s)	• Apixaban • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) Note that intravenous LMWH will not be included. • Subcutaneous or intravenous unfractionated heparin (UFH)

	• Synthetic pentasacharides • Vitamin K antagonists • Aspirin (extended treatment only) Analysis will be stratified by treatment dose.
Eligibility criteria – comparator(s)	• To each other • Placebo/no treatment

Outcomes and prioritisation	• All-cause mortality
	• VTE-related mortality
	• Length of hospital stay
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury
	  ○ Heparin induced thrombocytopenia

Eligibility criteria – study design	RCT.
Other inclusion exclusion criteria	English language papers only.
Proposed sensitivity/sub-group analysis	• People with cancer. • Older people (defined as people over the age of 65)

	• People who have restricted movement (as defined by the study). • People with learning disabilities. • Intravenous drug users • People with chronic liver disease • People in a care home / nursing home • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease. • Differing treatment durations.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Appendix B
Information sources – databases and dates	• Sources to be searched ○ Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. MHRA Drug Alerts

	○ Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. • Supplementary search techniques ○ None identified • Limits ○ Studies reported in English ○ Study design RCT, SR and Observational filter will be applied (as agreed) ○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results ○ Date limit from August 2011
Identify if an update	This question is an update of a question in CG144. Original search date up to 01.08.2011. The current guideline CG144 does not have a separate section on interim anticoagulation therapy, but the recommendations on diagnosis (below) refer to interim treatment and may be updated by the addition of types of anticoagulants following this review. These recommendations are out of scope of the update apart from this potential addition. <u>Recommendations that may change as a result of this review:</u> 1.1.3Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score (see table 1) either: • a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test **or** • a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg

	vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan. **[2012]** 1.1.4Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score (see table 1) a D-dimer test and if the result is positive offer **either**: • a proximal leg vein ultrasound scan carried out within 4 hours of being requested **or** • an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. **[2012]**
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix c of the evidence review
Data collection process –	A standardised evidence table format will be used, and published as appendix E (clinical evidence

forms/duplicate	tables) or I (economic evidence tables) of the evidence review.
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of confidence in cumulative evidence	See appendix B
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by

of authors and guarantor	Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE
PROSPERO registration number	[If registered, add PROSPERO registration number]

Review protocol: 2. What is the clinical and cost effectiveness of different pharmacological treatments for people with suspected PE prior to confirmed diagnosis?

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of different pharmacological treatments for people with suspected PE prior to confirmed diagnosis?
Type of review question	Intervention
Objective of the review	In CG144, parenteral anticoagulant was recommended for administration to people with suspected PE, who had not had their PE confirmed. Since the publication of CG144, newer, direct-acting oral anticoagulants are available, and it is reported are being used instead of parenteral anticoagulant for people with suspected PE. Guidance is required on whether direct-acting oral anticoagulants are suitable for use in people with suspected PE.
Eligibility criteria – population/ disease	Adults (18+ years) with suspected PE Suspected PE is defined as PE suspected on the basis of clinical symptoms and/or D-dimer test, but before confirmation by CTPA or equivalent.
Eligibility criteria – interventio n(s)	• Apixaban • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) Note that intravenous LMWH will not be included. • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides • Vitamin K antagonists • Aspirin (extended treatment only)

	Analysis stratified by treatment dose.
Eligibility criteria – comparator(s)	• To each other • Placebo/no treatment

Outcomes and prioritisation	• All-cause mortality
	• VTE-related mortality
	• Length of hospital stay
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury
	  ○ Heparin induced thrombocytopenia

Eligibility criteria – study design	RCT
Other inclusion exclusion criteria	English language papers only

Proposed sensitivity/ sub-group analysis	• People with cancer. • Older people (defined as people over the age of 65) • People who have restricted movement (as defined by the study). • People with learning disabilities. • Intravenous drug users • Differing treatment durations. • People with chronic liver disease • People in a care home / nursing home • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease. Subgroups will be considered independently or as composite subgroups where data is available
Selection process – duplicate screening/ selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See appendix B
Information sources – databases and dates	• Sources to be searched ○ Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane

	CDSR, CENTRAL, DARE (legacy records) and HTA. MHRA Drug Alerts ○ Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. • Supplementary search techniques ○ None identified • Limits ○ Studies reported in English ○ Study design RCT, SR and Observational filter will be applied (as agreed) ○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results ○ Date limit from August 2011
Identify if an update	This question is an update of a question in CG144. Original search date up to 01.08.2011. The current guideline CG144 does not have a separate section on interim anticoagulation therapy, but the recommendations on diagnosis (below) refer to interim treatment and may be updated by the addition of types of anticoagulants following this review. These recommendations are out of scope of the update apart from this potential addition. <u>Recommendations that may be affected by the update:</u> 1.1.9Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score (see table 2) **either**: • an immediate computed tomography pulmonary angiogram (CTPA) **or** • immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. Consider a proximal leg vein ultrasound scan if

	the CTPA is negative and DVT is suspected. **[2012]** 1.1.10Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (see table 2) a D-dimer test and if the result is positive offer **either**: • an immediate CTPA **or** • immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. **[2012]** 1.1.11For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high: • Assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA. • If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy. **[2012]**
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review

Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of	See appendix B

confidence in cumulative evidence	
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	[If registered, add PROSPERO registration number]

Review protocol: 3. What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of DVT?

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of DVT?
Type of review question	Intervention
Objective of the review	This review should include the incorporation and sequencing of the following TAs alongside the other relevant pharmacological treatments: TA354, TA341, TA327, TA287, TA261
Eligibility criteria – population/disease	Adults (18+ years) with a confirmed diagnosis of DVT. (Studies will be excluded if >20% of population do not have confirmed DVT)
Eligibility criteria – intervention(s)	• Edoxaban • Apixaban • Dabigatran • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) - Note that intravenous LMWH will not be included as it is in not licensed in the UK • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides • Vitamin K antagonists • Aspirin (extended treatment only) Analysis will be stratified by dose and duration of treatment Combinations of treatments (simultaneous and sequential) will be considered.

Eligibility criteria – comparator(s)	• To each other • Placebo/no treatment

Outcomes and prioritisation	• All-cause mortality
	• VTE-related mortality
	• Recurrence of VTE
	  ○ Split by recurrent DVT and recurrent PE if data is available
	• Length of hospital stay
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• Post-thrombotic syndrome
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury
	  ○ Heparin induced thrombocytopenia

Eligibility criteria – study design	RCT.
Other inclusion exclusion criteria	English language papers only.
Proposed sensitivity/sub-group analysis	• People with cancer. • Older people (defined as people over the age of 65) • People who have restricted movement (as defined by the study). • People with learning disabilities. • Intravenous drug users

	• People in a care home / nursing home • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease. • People with chronic liver disease • First event vs. recurrent VTE • Provoked vs. unprovoked VTE • Differing treatment durations.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See appendix B

Information sources – databases and dates	• Sources to be searched
	  ○ Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. MHRA Drug Alerts
	  ○ Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied.
	• Supplementary search techniques
	  ○ None identified
	• Limits
	  ○ Studies reported in English
	  ○ Study design RCT, SR and Observational filter will be applied (as agreed)

	○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results ○ Date limit from August 2011
Identify if an update	This question is an update of a question in CG144. Original search date up to 01.08.2011. <u>Recommendations that may change as a result of this review:</u> 1.2.1 Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions: • For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay. • For patients with an increased risk of bleeding consider UFH. • For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism). Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal

	DVT or PE) is 2 or above for at least 24 hours, whichever is longer. **[2012]** 1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months [3]. At 6 months, assess the risks and benefits of continuing anticoagulation [4]. **[2012]** 1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 1.2.4 and 1.2.5). **[2012]** 1.2.5 Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. **[2012]**
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.

Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B A network meta-analysis is intended for this question
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of confidence in cumulative evidence	See appendix B
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.

Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
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Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	[If registered, add PROSPERO registration number]

Review protocol: 4. What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of PE?

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of different pharmacological treatments for people with a confirmed diagnosis of PE?
Type of review question	Intervention
Objective of the review	This review should include the incorporation and sequencing of the following TAs alongside the other relevant pharmacological treatments: TA354, TA341, TA327, TA287, TA261
Eligibility criteria – population/disease	Adults (18+ years) with a confirmed diagnosis of PE. (Studies will be excluded if >20% of population do not have confirmed PE)
Eligibility criteria – intervention(s)	• Edoxaban • Apixaban • Dabigatran • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) Note that intravenous LMWH will not be included. • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides • Vitamin K antagonists • Aspirin (extended treatment only) Analysis will be stratified by dose and duration of treatment

	Combinations of treatments (simultaneous and sequential) will be considered.
Eligibility criteria – comparator(s)	• To each other • Placebo/ No treatment

Outcomes and prioritisation	• All-cause mortality
	• VTE-related mortality
	• Recurrence of VTE
	  ○ Split by recurrent DVT and recurrent PE if data is available
	• Length of hospital stay
	• Quality of life
	  ○ Generic and disease-specific measures will be reported
	  ○ Overall score will be reported (data on subscales will not be reported)
	• Chronic thromboembolic pulmonary hypertension
	• Adverse events
	  ○ Total serious adverse events (as defined by the European medicines agency) will be reported if data is available.
	  ○ Major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis)
	  ○ Intracranial haemorrhage
	  ○ Liver injury
	  ○ Heparin induced thrombocytopenia

Eligibility criteria – study design	RCT.
Other inclusion exclusion criteria	English language papers only.

Proposed sensitivity/sub-group analysis	• People with cancer. • Older people (defined as people over the age of 65) • People who have restricted movement (as defined by the study). • People with learning disabilities. • Intravenous drug users • People in a care home / nursing home • People with obesity III (a BMI of 40 kg/m^2 or more). • People who have stage 3 to 5 chronic kidney disease. • People with chronic liver disease • First event vs. recurrent VTE • Provoked vs. unprovoked VTE • Differing treatment durations.
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See appendix B
Information sources –	• Sources to be searched ○ Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane

databases and dates	CDSR, CENTRAL, DARE (legacy records) and HTA. MHRA Drug Alerts ○ Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. • Supplementary search techniques ○ None identified • Limits ○ Studies reported in English ○ Study design RCT, SR and Observational filter will be applied (as agreed) ○ Animal studies will be excluded from the search results ○ Conference abstracts will be excluded from the search results ○ Date limit from August 2011
Identify if an update	This question is an update of a question in CG144. Original search date up to 01.08.2011. Recommendations that may change as a result of this review: 1.2.1 Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions: • For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay. • For patients with an increased risk of bleeding consider UFH. • For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see

	recommendations 1.2.7 and 1.2.8 on pharmacological systemic thrombolytic therapy in pulmonary embolism). Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 1.2.3 on VKA for patients with confirmed proximal DVT or PE) is 2 or above for at least 24 hours, whichever is longer. **[2012]** 1.2.2 Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months [3]. At 6 months, assess the risks and benefits of continuing anticoagulation [4]. **[2012]** 1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 1.2.4 and 1.2.5). **[2012]** 1.2.4 Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. **[2012]**
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10087
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C of the evidence review

Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or I (economic evidence tables) of the evidence review.
Methods for assessing bias at outcome/study level	See appendix B
Criteria for quantitative synthesis (where suitable)	See appendix B
Methods for analysis – combining studies and exploring (in)consistency	See appendix B A network meta-analysis is intended for this question
Meta-bias assessment – publication bias, selective reporting bias	See appendix B
Assessment of confidence in	See appendix B

cumulative evidence	
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NICE Guidelines Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guidelines Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods section of the evidence review.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
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Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies list of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.

- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 20. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 20: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.

Quality	Applicability	Use of systematic review
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Other study was quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the populations, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. No MIDs were identified through this process. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. The committee agreed that any difference in mortality would be clinically meaningful, and therefore the line of no effect was used as an MID. The committee chose not to specify any other MIDs by consensus.

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised

mean difference where no other MID was available, an MID of 0.5 was used. For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For hazard ratios where no other MID was available, no MIDs were set and the line of no effect was used to assess meaningful differences.

The 'Evidence to Recommendations' section of each review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 21

Table 21: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level.

GRADE criteria	Reasons for downgrading quality
	Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Publication bias

Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

For outcomes with a defined MID, evidence statements were divided into 4 groups as follows:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence showed there is an effect, but it is less than the defined MID.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

Methods for combining direct and indirect evidence (network meta-analysis) for interventions

Conventional 'pairwise' meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from two or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than two interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis overcomes these problems by combining all evidence into a single, internally coherent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions. Network meta-analyses were undertaken in all situations where the following three criteria were met:

- At least three treatment alternatives.
- A sufficiently connected network to enable valid estimates to be made.
- The aim of the review was to produce recommendations on the most effective option, rather than simply an unordered list of treatment alternatives.

Synthesis

Hierarchical Bayesian Network Meta-Analysis (NMA) was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

Results were reported summarising 50,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Unless otherwise specified, trial-specific baselines and treatment effects were assigned Normal (0,10000) priors, and the between-trial standard deviations used in random-effects models were given Uniform (0,5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed- and random-effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more parsimonious analysis, and was preferred.

Modified GRADE for network meta-analyses

A modified version of the standard GRADE approach for pairwise interventions was used to assess the quality of evidence across the network meta-analyses undertaken. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis. It is designed to provide a single overall quality rating for an NMA, which can then be combined with pairwise quality ratings for individual comparisons (if appropriate), to judge the overall strength of evidence for each comparison.

Table 22: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were at moderate or high risk of bias, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were at high risk of bias, the network was downgraded two levels.
Indirectness	Not serious: If fewer than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the overall network was not downgraded. Serious: If greater than 33.3% of the studies in the network meta-analysis were partially indirect or indirect, the network was downgraded one level. Very serious: If greater than 33.3% of the studies in the network meta-analysis were indirect, the network was downgraded two levels.
Inconsistency	N/A: Inconsistency was marked as not applicable if there were no links in the network where data from multiple studies (either direct or indirect) were synthesised. For network meta-analyses conducted under a Bayesian framework, the network was downgraded one level if the DIC for a random-effects model was lower than the DIC for a fixed-effects model. In addition, the direct and indirect treatment estimates were compared as a check on the consistency of the network.
Imprecision	The overall network was downgraded for imprecision if it was not possible to differentiate between any meaningfully distinct treatments options in the network (based on 95% confidence/credible intervals). Whether two options were meaningfully distinct was judged using the MIDs defined above for pairwise meta-analysis of the outcomes, if available; or statistical significance if MIDs were not available.

Evidence statements

In contrast to the pair-wise data, the NMA evidence statements for this review only described outcomes and drug comparisons where there was an effect (defined as the Credible intervals not crossing the line of no effect). For simplicity, where the NMA could not differentiate between the compared treatments no evidence statements were presented. However, to aid in the visualisation of results, the summary tables in appendix I include those comparisons for which the effect estimate did not cross the line of no effect, for each outcome as well as those for which an effect was detected. (Please see the pair-wise evidence statements

descriptions for an explanation of the different categories of evidence statement referred to here.)

Appendix C – Literature search strategies

Searches were run on 14th June 2018 in Medline, Medline in Process, Medline epub ahead of Print and Embase (all Wiley platform), the Cochrane Database of Systematic Reviews, CENTRAL and DARE (Wiley platform).and re run on 4th April 2019.The Medline strategy is presented below. Certain terms were date limited to post publication of the previous guideline. The NICE inhouse RCT filter has been used. The MHRA website was searched for drug safety alerts on 18th June 2018 and 18th April 2019.

1 Venous Thrombosis/
2 (phlegmasia adj2 dolens).tw.
3 (thrombo* adj2 (vein* or venous)).tw.
4 (venous adj stasis).tw.
5 (dvt or vte).tw.
6 Venous Thromboembolism/ or Embolism, paradoxical/
7 exp pulmonary embolism/
8 ((pulmonary or lung) adj4 (embol* or thromboembo* or microembol*)).tw.
9 (pulmonary adj infarction).tw
10 or/1-9
11 exp Antithrombins/
12 (antithrombin* or "factor x* inhibitor*" or " thrombin inhibitor*").tw.
13 (noac* or doac* or tsoac* or odi* or soda*).tw.
14 ((novel or non-vitamin k or direct or target-specific) adj2 (anticoagula* or anti coagula*)).tw.
15 (edoxaban or lixiana or roteas or savaysa or apixaban or eliqu?s or bms* or rivaroxaban or bay* or xarelto or dabigatran or bibr* or pradax* or rendix).tw.
16 or/11-15
17 anticoagulants/
18 (anticoagula* or anti coagula*).tw.
19 exp Heparin/
20 (heparin* or lmwh or ufh or ldh).tw.
21 (bemiparin or entervit or hepadren or hibor or ivor* or phivor or zibor).tw.
22 dalteparin/
23 (dalteparin or fragmin* or "kabi 2165" or k2165 or k 2165 or "low liquemin").tw.
24 enoxaparin/
25 (enoxaparin or clexan* or inhixa or klexane or lovenox or neoparin* or thorinane).tw.
26 (tinzaparin or innohep or logiparin).tw.
27 nadroparin/
28 (nadroparin or fraxiparin* or seledie or seleparin* or tedegliparin or arixta).tw.
29 (monoparin or multiparin or calciparin*).tw.
30 (fondaparin* or quixidar or pentasacharide* or idraparinux).tw.
31 ("vitamin k" adj2 antagonist*).tw
32 exp 4-hydroxycoumarins/
33 (4 hydroxycoumarin* or 4-hydrxycoumarin*).tw.
34 (warfarin* or adoisine or aldocumar or antrombin* or athrombin* or befarin or carfin or circuvit or coumadan or coumadin* or coumafene or coumaphene or dagonal or farin or

jantoven or kumatox or maforan or marevan or orfarin or panwarfarin or prothromadin or tintorane or uniwarfin or warfar or warfil or warnerin or sofarin).tw.
35 (acenocoumar* or acenokumarin or acitrom or ascumar or neo sintrom or neo-sintrom or neosintrom or neositron or nicoumalone or nicumalon or niffcoumar or nitrovarfarian or nitrowarfarin or sincoumar or sin?umar or sinthrom* or sintrom* or sintron or syncoumar or syncumar or syntrom or trombostop or zotil).tw.
36 Phenindione/
37 (phenindione or acluton or acoagine or arthrombon or athrombon or bindan or cronodione or dandilone or danilone or diadilan or dindevan or dineval or diophindane or emandione or eridione or eridone or fenhydren or fenilin or hedulin or hemolidione or indema or indon or phenidione or phenindion or phenyl indanedione or phenylin or phenylindandione or phenylindane dion or phenylindanedione or phenyllin or pindione or rectadione or thromasal or thrombantin or thrombasal or thrombosan or thrombusal or trompid).tw.
38 (Danaparoid or orgaran or Ziboror or antixarin or cy 222 or embolex or monoembolex or ardeparin or certoparin or parnaparin or reviparin or tedelparin or Dicoumarol or phenprocoumon or phepromaron or ethyl-biscoumacetate).tw.
39 or/17-38
40 10 and 16
41 10 and 39
42 limit 41 to ed=20110801-20180614
43 40 or 42
44 Randomized Controlled Trial.pt.
45 Controlled Clinical Trial.pt.
46 Clinical Trial.pt.
47 exp Clinical Trials as Topic/
48 Placebos/
49 Random Allocation/
50 Double-Blind Method/
51 Single-Blind Method/
52 Cross-Over Studies/
53 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
54 (random$ adj3 allocat$).tw.
55 placebo$.tw.
56 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
57 (crossover$ or (cross adj over$)).tw.
58 or/44-57
59 animals/ not humans/
60 58 not 59
61 43 and 60
62 limit 61 to english language

Additional searches were run in the same databases on 15th January 2019 to include terms for Aspirin. The Medline version is presented below

1. Aspirin/
2. (aspirin or danamep or "acetylsalicyclic acid").tw.

Searches to identify economic evidence were run on 21st June 2018 and 18th January 2019 in Medline, Medline in Process, Econlit and Embase (all va the Ovid platform), NHS EED and

the Health Technology Database (via the Wiley platform. NICE inhouse economic evaluation and Quality of Life filters were attached to the Medline and Embase strategies of lines 1-43 and 1-2 of the above searches. A single search to identify economic evidence across all questions was re run on 9th April 2019.The Medline version of the filters is displayed below

Economic evaluations

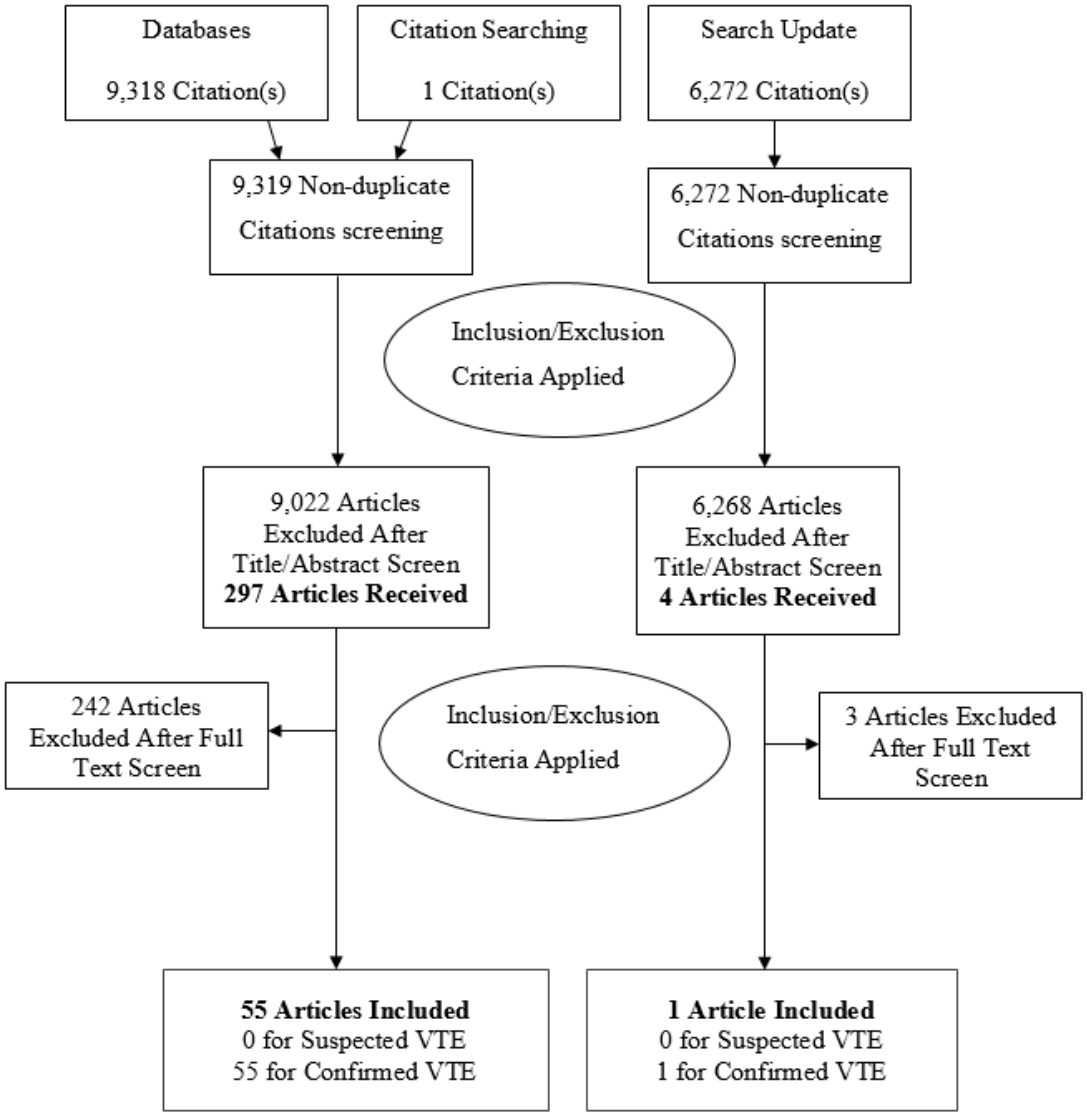
1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

Quality of Life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/ (22343)
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/ 1-30

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Studies were not downgraded for risk of bias due to a lack of blinding because the majority of outcomes of importance to this review (such as major bleeding and VTE-recurrence) were objectively assessed and therefore unlikely to be affected by the person with VTE having knowledge of which treatment they are receiving. Subjective outcomes relating to quality of life were marked down for risk of bias if the study was unblinded.

Although studies were not marked down for lack of blinding alone, a lack of blinding was noted as a cause for concern in studies that were marked down for risk of bias due for other reasons.

Initial treatment of VTE

Author (year)	Title	Study details	Quality assessment
Agnelli (2013) AMPLIFY trial	Oral apixaban for the treatment of acute venous thromboembolism.	**Study type** • Randomised controlled trial **Study details** • Study location *28 countries* • Study setting *358 centres in 28 countries* • Study dates *August 2008 - August 2012 (enrolment period)* • Duration of follow-up *Patients underwent assessment, either in the clinic or by telephone, at weeks 2, 4, 8, 12, 16, 20, and 24 (6 months) after randomization and 30 days after the end of the intended treatment period. Patients were instructed to report to the study centre if they had symptoms suggestive of recurrent venous thromboembolism or bleeding. Prespecified objective testing*	**Random sequence generation** • Low risk of bias *randomized using an interactive voice-response system and was stratified according to the qualifying diagnosis of either symptomatic proximal DVT or symptomatic PE* **Allocation concealment** • Unclear risk of bias **Blinding of participants and personnel** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		was required for patients in whom an outcome event was suspected. • Sources of funding *Funded by Pfizer and Bristol-Myers Squibb* • Associated studies *Agnelli 2013b: Cancer subgroup analysis Bleker 2016, Brekelsman 2017: Bleeding analysis Liu 2015: Hospital admission rates analysis* **Inclusion criteria** • ≥18 years • Objectively confirmed symptomatic DVT or PE *Proximal DVT** **Exclusion criteria** • Contraindication(s) for study drugs • Active bleeding *or high risk of bleeding* • Other *Received more than two doses of a once-daily LMWH regimen, fondaparinux, or a VKA; more than three doses of a twice-daily LMWH; or more than 36 hrs continuous IV heparin.*	*Study was double-blinded* **Blinding of outcome assessment** • Low risk of bias *events were rated by a blinded committee* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Active cancer with long-term LMWH treatment planned • Provoked DVT in absence of a persistent risk factor for recurrence • <6 month spanned anticoagulant treatment • Other indication requiring long-term anticoagulation *or dual antiplatelet therapy, treatment with aspirin (165mg daily or more) or treatment with potent inhibitors of cytochrome P-450 3A4* • Haemoglobin level <9mg/dL • Platelet count of <100,000 per cubic mm • Serum creatinine level > 2.5 mg/dL • Calculated creatinine clearance <25ml/min **Sample characteristics** • Sample size *5400 participants* • Split between study groups *2691 rivaroxaban; 2704 control* • Loss to follow-up *820 lost to follow-up- 30 did not receive intended treatment, 46 died, 332 had adverse event, 98 withdrew consent, 28 lost to follow-up, 286 had other reasons.* • %female *41% female* • Mean age (SD) *Apixaban group: 57.2 (SD 16.0) years Control group: 56.7 (SD 16.0) years*	

Author (year)	Title	Study details	Quality assessment
		• PE/DVT split (for VTE only studies) *Apixaban group: DVT only (65%), PE only (25.2%), DVT+PE (9.4%), could not be evaluated (0.4%) Control group: DVT only (65.9%), PE only (25.2%), DVT+PE (8.3%), could not be evaluated (0.6%)* • Provoked vs. unprovoked *89.8% unprovoked* • Previous VTE *Apixaban group: 17.2% previous VTE Control group: 15.1% previous VTE.* **Interventions** • LMWH + VKA *Enoxaparin at a dose of 1mg/kg body weight every 12 hours for 7at least 5 days and warfarin begun concomitantly and continued for 6 months. Enoxaparin or placebo was discontinued when a blinded INR of 2.0 or more was achieved.* • Apixaban *10mg twice daily for the first 7 days, followed by 5mg twice daily for 6 months.* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding *Clinically relevant nonmajor bleeding was defined as overt*	

Author (year)	Title	Study details	Quality assessment
		bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life. • Major bleeding *Bleeding was defined as major if it was overt and associated with a decrease in the haemoglobin level of 2 g per decilitre or more, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death.* • VTE-recurrence *composite measure of VTE recurrence of VTE-related death (including those in which PE could not be ruled out): Both these outcomes were taken to be indicative of a VTE.* • Serious adverse events	
Buller (2003)	Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism.	**Study type** • Randomised controlled trial **Study details** • Study location *Argentina, Austria, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Italy, Israel, Spain, Sweden, Switzerland, The Netherlands, United Kingdom and United States.* • Study setting *Hospitals* • Study dates	**Random sequence generation** • High risk of bias *"Interactive voice response system" does not describe a method of randomisation. For example, selection could be predicted on the basis of drug stocks or expiry dates. In addition, responses could be pre-recorded.* **Allocation concealment** • High risk of bias *"Interactive voice response system" does*

Author (year)	Title	Study details	Quality assessment
		May 2000 to March 2002 • Duration of follow-up *All the patients were contacted daily during the initial treatment period and at one and three months after the start of the study. At each contact, the patient was evaluated for symptoms and signs of recurrent venous thromboembolism and bleeding.* • Sources of funding *Supported by an unrestricted grant from NV Organon (Oss, the Netherlands) and Sanofi-Synthélabo (Paris).* **Inclusion criteria** • ≥18 years • PE *Diagnostic criteria were an intraluminal filling defect on spiral computed tomography (CT) or pulmonary angiography, a high-probability ventilation–perfusion lung scan, or a nondiagnostic lung scan with documentation of deep-vein thrombosis either by compression ultrasonography or by venography.* **Exclusion criteria** • Life expectancy <6 months • Thrombectomy or embolectomy • Vena cava filter fitted • Contraindication(s) for study drugs • Requiring thrombolysis • Pregnancy	*not describe a method of allocation concealment because responses can be pre-recorded.* **Blinding of participants and personnel** • High risk of bias *"Blinded adjudication" was mentioned in the introduction. However, no details of methodology were provided in the methods section.* **Blinding of outcome assessment** • High risk of bias *No methods for blinding mentioned.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• >24 hours of anticoagulants • Serum creatinine level >2.0 mg/dl • Uncontrolled hypertension **Sample characteristics** • Sample size *2213 people* • Split between study groups *Fondaparinux = 1103; Unfractionated heparin = 1110* • Loss to follow-up *Follow-up with respect to the primary efficacy outcome was incomplete for six of the patients assigned to the fondaparinux group (0.5 percent) and seven of those assigned to the unfractionated-heparin group (0.6 percent), either because of withdrawal of informed consent (six patients) or loss to follow-up (seven).* • %female *Fondaparinux = 54.5%; Unfractionated heparin = 57%* • Mean age (SD) *Fondaparinux = 63 years (16.2); Unfractionated heparin = 62 years (16.7)* **Interventions** • UFH + VKA *The patients assigned to unfractionated heparin received an initial intravenous bolus of at least 5000 IU, followed by at least*	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *No methods provided for randomisation, allocation concealment or blinding.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		1250 IU per hour, administered as a continuous intravenous infusion. The infusion dose was adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.5 times a control value. The activated partial-thromboplastin time was measured approximately six hours after the start of heparin treatment, about six hours after each measurement of the activated partial-thromboplastin time that was subtherapeutic or supratherapeutic, and otherwise daily. In both groups, treatment with a vitamin K antagonist was begun as soon as possible and within 72 hours after initiation of the study treatment. Initially, the prothrombin time was measured at least every other day, and the dose of vitamin K antagonist was adjusted to maintain the international normalised ratio (INR) at a value between 2.0 and 3.0. Administration of heparin or fondaparinux was continued for at least five days and until the INR had been greater than 2.0 for two consecutive days. Treatment with a vitamin K antagonist was continued for three months, and the INR was determined at least once per month. • Fondaparinux + VKA *The patients assigned to fondaparinux received a single daily subcutaneous injection of 5.0 mg (if their body weight was less than 50 kg), 7.5 mg (if their body weight was 50 to 100 kg), or 10.0 mg (if their body weight was greater than 100 kg). In both groups, treatment with a vitamin K antagonist was begun as soon as possible and within 72 hours after initiation of the study treatment. Initially, the prothrombin time was measured at least every other day, and the dose of vitamin K antagonist was adjusted to maintain the international normalised ratio (INR) at a*	

Author (year)	Title	Study details	Quality assessment
		value between 2.0 and 3.0. Administration of heparin or fondaparinux was continued for at least five days and until the INR had been greater than 2.0 for two consecutive days. Treatment with a vitamin K antagonist was continued for three months, and the INR was determined at least once per month. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding *Bleeding episodes that were clinically relevant but did not qualify as major (e.g., epistaxis that required intervention, formation of a large haematoma visible on the skin, or spontaneous macroscopic haematuria) were an additional safety outcome and were classified as clinically relevant nonmajor bleeding.* • Major bleeding *Bleeding was considered major if it was clinically overt and associated with a decrease of 2 g per decilitre or more in the haemoglobin level, led to the transfusion of 2 or more units of red cells or whole blood, was retroperitoneal or intracranial, occurred in a critical organ, or contributed to death.* • VTE-recurrence *Symptomatic recurrent venous thromboembolism was considered to have occurred if recurrent pulmonary embolism or deep-vein thrombosis was documented objectively or if there was a death in which pulmonary embolism was a contributing cause or could not be ruled out. In the absence of objective test*	

Author (year)	Title	Study details	Quality assessment
		results that adequately confirmed or ruled out recurrent venous thromboembolism, the diagnosis was accepted if the condition was managed with therapeutic dosages of low molecular-weight heparin for more than two days, thrombolysis, a vena cava filter, or thrombectomy. The objective criterion for the diagnosis of recurrent pulmonary embolism was a new intraluminal filling defect on spiral CT or pulmonary angiography; cut-off of contrast material in a vessel more than 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75 percent of a segment, with corresponding normal ventilation (i.e., a high-probability lung scan); a new nondiagnostic lung scan accompanied by documentation of deep-vein thrombosis by ultrasonography or venography; or confirmation of a new pulmonary embolism at autopsy. The objective criterion for the diagnosis of new deep-vein thrombosis was a new, non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.	
Buller (2004)	Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial.	**Study details** • Study location *The Netherlands, Sweden, USA, France, Australia, Canada, Italy* • Study setting *Hospitals* • Study dates	**Random sequence generation** • Low risk of bias *Randomisation was stratified by centre in balanced blocks of 4 patients.*

Author (year)	Title	Study details	Quality assessment
		April 2000 to July 2001 • Duration of follow-up *All patients were contacted daily during initial treatment and at 1 and 3 months. At each contact, patients were evaluated for symptomatic recurrence of deep venous thrombosis or pulmonary embolism and bleeding and were informed about the symptoms and signs of these conditions. They were instructed to report to the study centre on an emergency basis if any of these conditions occurred. If recurrent deep venous thrombosis or pulmonary embolism was suspected, the protocol required objective testing for confirmation.* • Sources of funding *Grant Support: By Sanofi-Synthelabo and NV Organon.* **Inclusion criteria** • ≥18 years • Acute-DVT inclusion/exclusion criteria *Acute symptomatic deep venous thrombosis involving the popliteal, femoral, or iliac veins or the trifurcation of the calf veins and who required antithrombotic therapy were eligible for the study. Diagnostic criteria for deep venous thrombosis were a noncompressible vein found on ultrasonography or an intraluminal filling defect found on venography.* **Exclusion criteria** • Symptoms of PE	**Allocation concealment** • Unclear risk of bias *Allocation concealment was not mentioned* **Blinding of participants and personnel** • High risk of bias *Methods of blinding are not provided.* **Blinding of outcome assessment** • High risk of bias *Methods of blinding are not provided.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Thrombectomy or embolectomy • Vena cava filter fitted • Contraindication(s) for study drugs • Pregnancy • Life expectancy <3 months • >24 hours of anticoagulants • Serum creatinine level >2.0 mg/dl • Uncontrolled hypertension **Sample characteristics** • Sample size *2205 people* • Split between study groups *Fondaparinux = 1098; Enoxaparin = 1107* • Loss to follow-up *12 patients were excluded in the fondaparinux group: 4 had incomplete follow-up, 5 were not treated with the study drug, 3 were switched to other treatment and not randomly assigned. 20 patients were excluded in the enoxaparin group: 11 had incomplete follow-up, 8 were not treated with the study drug, 1 was switched to the other drug and was therefore not randomly assigned.* • %female *Fondaparinux = 47%; Enoxaparin = 47.8%* • Mean age (SD) *Fondaparinux = 61.1 years (16.7); Enoxaparin = 61.5 years*	**Overall risk of bias** • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		(16.5) **Interventions** • LMWH + VKA *The patients allocated to enoxaparin received a twice-daily subcutaneous dose of 1 mg/kg of body weight and a once-daily subcutaneous injection of placebo that appeared identical to fondaparinux. In both groups, vitamin K antagonist therapy was started as soon as possible but within 72 hours of initiation of fondaparinux or enoxaparin therapy. The investigator chose the type of vitamin K antagonist therapy according to local hospital practice. The same type of vitamin K antagonist was recommended for all patients in a particular centre. During initial treatment, prothrombin times were measured at least every other day and the dose of vitamin K antagonist was adjusted to maintain the international normalised ratio between 2.0 and 3.0. Double-blind, initial treatment was continued for at least 5 days and until the international normalised ratio was greater than 2.0 for 2 consecutive days. Treatment with vitamin K antagonists was continued for 3 months, and the international normalised ratio was determined at least once per month.* • Fondaparinux + VKA *The patients allocated to fondaparinux received a once-daily subcutaneous injection of 5.0 mg if they weighed less than 50 kg, 7.5 mg if they weighed between 50 and 100 kg, or 10.0 mg if they weighed more than 100 kg. They also received twice-daily subcutaneous injections of placebo that appeared identical to*	

Author (year)	Title	Study details	Quality assessment
		enoxaparin. In both groups, vitamin K antagonist therapy was started as soon as possible but within 72 hours of initiation of fondaparinux or enoxaparin therapy. The investigator chose the type of vitamin K antagonist therapy according to local hospital practice. The same type of vitamin K antagonist was recommended for all patients in a particular centre. During initial treatment, prothrombin times were measured at least every other day and the dose of vitamin K antagonist was adjusted to maintain the international normalised ratio between 2.0 and 3.0. Double-blind, initial treatment was continued for at least 5 days and until the international normalised ratio was greater than 2.0 for 2 consecutive days. Treatment with vitamin K antagonists was continued for 3 months, and the international normalised ratio was determined at least once per month. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding *Bleeding episodes that were clinically relevant but not major (for example, epistaxis that required intervention or spontaneous macroscopic haematuria) were an additional safety outcome.* • Major bleeding *The main safety outcomes were major bleeding during the initial treatment period and 3-month mortality. Bleeding was defined as major if it was clinically overt and associated with a decrease in the haemoglobin level of 20 g/L or more, led to transfusion of*	

Author (year)	Title	Study details	Quality assessment
		2 or more units of red blood cells or whole blood cells, was retroperitoneal or intracranial, occurred in a critical organ, or contributed to death. • VTE-recurrence *The primary efficacy outcome was the incidence of symptomatic recurrent venous thromboembolism during the 3-month study period. Symptomatic recurrent venous thromboembolism was defined as objectively documented recurrent deep venous thrombosis or pulmonary embolism or death in which pulmonary embolism was a contributing cause or could not be excluded. Without objective test results to adequately confirm or exclude recurrent venous thromboembolism, this diagnosis was accepted if the physician managed the patient with therapeutic doses of LMWH for more than 2 days, thrombolysis, a vena cava filter, or thrombectomy. The criteria for the objective diagnosis of recurrent deep venous thrombosis were a new noncompressible venous segment or a substantial increase (>4 mm) in diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect found on venography. The criteria for the objective diagnosis of pulmonary embolism were an intraluminal filling defect on spiral computed tomography or pulmonary angiography, cut-off of a vessel of more than 2.5 mm in diameter on pulmonary angiography, perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan), nondiagnostic lung scan associated with new deep venous thrombosis documented by ultrasonography or venography, or pulmonary embolism*	

Author (year)	Title	Study details	Quality assessment
		confirmed by autopsy.	
Buller (2008)	Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study	**Study type** • Randomised controlled trial **Study details** • Study location *Australia, Austria, Czech Republic, France, Israel, Italy, Poland, South Africa, Sweden, The Netherlands* • Study setting *Hospitals* • Study dates *December 2005 to November 2006* • Duration of follow-up *Follow-up visits were scheduled at days 7, 14, 21, 49 and 84. At these visits, any symptoms of recurrent DVT or PE and bleeding were elicited. In addition, patients were instructed to report to the study site if any of these symptoms occurred between scheduled visits. Bilateral compression ultrasonography and perfusion lung scan were obtained at baseline and at the end of the intended study treatment period (days 84–91).* • Sources of funding *This study was sponsored by Bristol-Myers Squibb.* **Inclusion criteria** • Acute-DVT inclusion/exclusion criteria	**Random sequence generation** • High risk of bias *"Interactive voice response system" does not describe a method of randomisation. For example, selection could be predicted on the basis of drug stocks or expiry dates. In addition, responses could be pre-recorded.* **Allocation concealment** • High risk of bias *"Interactive voice response system" does not describe a method of allocation concealment because responses can be pre-recorded.* **Blinding of participants and personnel** • High risk of bias *Methods of blinding were not described.* **Blinding of outcome assessment** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		Acute symptomatic proximal DVT or extensive calf vein thrombosis, involving at least the upper third of the deep calf veins (trifurcation area) confirmed by compression ultrasonography (CUS) or venography, were potential candidates for the study. **Exclusion criteria** • Received VKA • Symptoms of PE • At risk of bleeding • Life expectancy <6 months • Thrombectomy or embolectomy • Vena cava filter fitted • Fibrinolytic agent administered for treatment of current episode • Contraindication(s) for study drugs • Creatine clearance <30ml/min • Alanine aminotransferase level >3x ULN • Bacterial endocarditis • Active bleeding • Pregnancy • >24 hours of anticoagulants • Uncontrolled hypertension • Childbearing potential without adequate contraception • Breast-feeding	*Methods of blinding were not described.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *No description of methodology for randomisation, allocation concealment or blinding.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size *520 people* • Split between study groups *Apixaban 5 mg twice-daily = 130; Apixaban 10 mg twice-daily = 134; Apixaban 20 mg once-daily = 128; LMWH & VKA = 128* • Loss to follow-up *Apixaban 5 mg twice-daily = 11 non-evaluable + 8 major protocol deviations; Apixaban 10 mg twice-daily = 8 non-evaluable + 6 major protocol deviations; Apixaban 20 mg once-daily = 8 non-evaluable + 12 major protocol deviations; LMWH & VKA = 8 non-evaluable + 6 major protocol deviations* • %female *Apixaban 5 mg twice-daily = 36%; Apixaban 10 mg twice-daily = 43%; Apixaban 20 mg once-daily = 35%; LMWH & VKA = 37%* • Mean age (SD) *Apixaban 5 mg twice-daily = 56 years (14); Apixaban 10 mg twice-daily = 59 years (17); Apixaban 20 mg once-daily = 60 years (15); LMWH & VKA = 59 years (16)* • Previous VTE *Apixaban 5 mg twice-daily = 28.5%; Apixaban 10 mg twice-daily = 20.9%; Apixaban 20 mg once-daily = 25.8%; LMWH & VKA = 24.2%* **Interventions** • LMWH + VKA *The intended treatment duration was 84–91 days. For the initial*	majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		treatment, tinzaparin 175 IU/kg, enoxaparin 1.5 mg/kg once-daily or 1.0 mg/kg twice-daily and fondaparinux were allowed. The minimum duration of heparin treatment was 5 days, inclusive of a period of up to 24 h before randomisation if a permitted LMWH was used. VKAs that could be used were warfarin, acenocoumarol, or phenprocoumon, which were started within 48 h after randomisation. VKA treatment was adjusted to maintain the International Normalized Ratio (INR) within the therapeutic range (target 2.5, range 2.0–3.0). LMWH treatment was continued until a stable INR > 2 was observed on two measurements at least 24 h apart. Initially, the INR had to be measured every 2–3 days, but thereafter at least once monthly. VKA treatment was continued until day 84 + 7. The choice of LMWH/VKA was made per centre. • Apixaban *Patients were assigned to apixaban 5 mg twice-daily, 10 mg twice-daily or 20 mg once-daily. The intended treatment duration was 84–91 days. For the initial treatment, tinzaparin 175 IU/kg, enoxaparin 1.5 mg/kg once-daily or 1.0 mg/kg twice-daily and fondaparinux were allowed.* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding *Clinically relevant, non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding, but*	

Author (year)	Title	Study details	Quality assessment
		associated with medical intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with any other discomfort for the patient, such as pain, or impairment of activities of daily life. • Major bleeding *Major bleeding was defined as clinically overt bleeding that was fatal, was into a critical organ (intracranial, retroperitoneal, or pericardial), or led to a fall in haemoglobin > 2 g/dL, or transfusion of two or more units of packed red blood cells or whole blood.* • VTE-recurrence	
Decousus (1998)	A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group.	**Study type** • Randomised controlled trial **Study details** • Study location *France* • Study setting *Hospitals* • Study dates *September 1991 to February 1995* • Duration of follow-up *Follow-up at 12 days, 2 years and 8 years* • Sources of funding *Bellon Rhone-Poulenc Rover Laboratories, cosponsors: Ministere Francais de la Sante, Caisse Nationale d'Assurance*	**Random sequence generation** • High risk of bias *A "central 24-hour computer telephone system" describes the method of communication, not the method of randomisation. For example, the patient split for the groups vena caval filter and no filter was 200 and 200. However, the split for the LMWH and the UFH group was 195 and 205. Therefore, the method of randomisation may not have been the same for the two sets of comparisons. In addition, voice activated responses can be pre-programed or can be influenced by the stocks of drugs available and their expiry dates. Therefore, it might be possible to*

Author (year)	Title	Study details	Quality assessment
		Maladie, Structure Regionale d'Evaluation Interhosptialiere Rhone-Alpes, Fondation de l'Avenir, Laboratoire B, Laboratoires Diagnostica Stago France. **Inclusion criteria** • DVT *Confirmed by venography* • High risk of PE *This was in the physician's opinion* **Exclusion criteria** • Vena cava filter fitted • Contraindication(s) for study drugs • Requiring thrombolysis • Pregnancy • Familial bleeding diathesis • >48 hours of anticoagulants • Short life expectancy • Severe renal failure • Severe hepatic failure • Likelihood of non-adherence to treatment **Sample characteristics** • Sample size *400 people*	*predict allocation, which is not the idea of randomisation.* **Allocation concealment** • High risk of bias *A "central 24-hour computer telephone system" describes the method of communication, not the method of allocation concealment. For example, voice activated responses can be pre-programed or can be influenced by the stocks of drugs available and their expiry dates. Therefore, it might be possible to predict allocation, which is not the idea of randomisation.* **Blinding of participants and personnel** • High risk of bias *There was no use of the word "blinding".* **Blinding of outcome assessment** • High risk of bias *Only the physician call at 2 years was blinded and it is reasonable to assume that the physician would have asked the patient what treatment they had received as part*

Author (year)	Title	Study details	Quality assessment
		• Split between study groups *Vena caval filter = 200; No vena caval filter = 200; LMWH = 195; UFH = 205* • Loss to follow-up *12 people* • %female *Vena caval filter = 54%; No vena caval filter = 51%; LMWH = 52%; UFH = 53%* • Mean age (SD) *Vena caval filter = 73 years (11); No vena caval filter = 72 years (11.5); LMWH = 73 years (10.5); UFH = 72 years (12)* • Previous VTE *Vena caval filter = 35%; No vena caval filter = 36%; LMWH = 36%; UFH = 35%* **Interventions** • Vena caval filter + LMWH/UFH + VKA + compression stockings *Vena caval filter: 4 types - Vena Tech LGM, titanium Greenfield, Cardial and Bird's Nest. These were inserted under fluoroscopic control through the femoral or jugular vein immediately after randomisation and cavography was performed. Patients assigned to unfractionated heparin (Fournier, Paris) received an intravenous bolus dose of 5000 IU, then a continuous intravenous infusion of 500 IU per kilogram of body weight per day for 8 to 12 days, adjusted according to the activated partial thromboplastin time so that the ratio of the patient's value to the*	*of history taking.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • High risk of bias *The study was powered for a total of 800 patients but after enrolment of 400 over four years the steering committee (unaware of the results) decided that the slow recruitment was not compatible with continuing the study.* **Overall risk of bias** • High

Author (year)	Title	Study details	Quality assessment
		control value remained between 1.5 and 2.5, according to the reagent used. Tests were performed four to six hours after the beginning of treatment or after a subtherapeutic activated partial thromboplastin time had been recorded, and then at least daily. Patients assigned to low-molecular-weight heparin were given a weight-adjusted dose (1 mg, or 100 International Factor Xa Inhibitory Units, per kilogram) of subcutaneous enoxaparin every 12 hours for 8 to 12 days. Warfarin or acenocoumarin therapy was started on day 4 and continued for at least three months. The dose was adjusted to achieve an international normalized ratio of 2 to 3. Treatment with either unfractionated heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2 or more for two consecutive days. If the use of an oral anticoagulant was not possible, subcutaneous unfractionated heparin was used (ratio of activated partial-thromboplastin time to control value, 1.5 to 2) for at least three months. Graded-compression stockings were prescribed for the same period. • LMWH/UFH + VKA + compression stockings *Patients assigned to unfractionated heparin (Fournier, Paris) received an intravenous bolus dose of 5000 IU, then a continuous intravenous infusion of 500 IU per kilogram of body weight per day for 8 to 12 days, adjusted according to the activated partial thromboplastin time so that the ratio of the patient's value to the control value remained between 1.5 and 2.5, according to the reagent used. Tests were performed four to six hours after the beginning of treatment or after a subtherapeutic activated partial thromboplastin time had been*	**Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		recorded, and then at least daily. Patients assigned to low-molecular-weight heparin were given a weight-adjusted dose (1 mg, or 100 International Factor Xa Inhibitory Units, per kilogram) of subcutaneous enoxaparin every 12 hours for 8 to 12 days. Warfarin or acenocoumarol therapy was started on day 4 and continued for at least three months. The dose was adjusted to achieve an international normalized ratio of 2 to 3. Treatment with either unfractionated heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2 or more for two consecutive days. If the use of an oral anticoagulant was not possible, subcutaneous unfractionated heparin was used (ratio of activated partial-thromboplastin time to control value, 1.5 to 2) for at least three months. Graded-compression stockings were prescribed for the same period. • Vena caval filter/no vena caval filter + LMWH + VKA + compression stockings *In this group, some patients received vena caval filters and some did not. Vena caval filter: 4 types - Vena Tech LGM, titanium Greenfield, Cardial and Bird's Nest. These were inserted under fluoroscopic control through the femoral or jugular vein immediately after randomisation and cavography was performed. Patients assigned to low-molecular-weight heparin were given a weight-adjusted dose (1 mg, or 100 International Factor Xa Inhibitory Units, per kilogram) of subcutaneous enoxaparin every 12 hours for 8 to 12 days. Warfarin or acenocoumarol therapy was started on day 4 and continued for at least three months. The dose was adjusted to achieve an international normalized ratio of 2 to 3. Treatment*	

Author (year)	Title	Study details	Quality assessment
		with either unfractionated heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2 or more for two consecutive days. If the use of an oral anticoagulant was not possible, subcutaneous unfractionated heparin was used (ratio of activated partial-thromboplastin time to control value, 1.5 to 2) for at least three months. Graded-compression stockings were prescribed for the same period. • Vena caval filter/no vena caval filter + UFH + VKA + compression stockings *In this group, some received vena caval filters and some did not. Vena caval filter: 4 types - Vena Tech LGM, titanium Greenfield, Cardial and Bird's Nest. These were inserted under fluoroscopic control through the femoral or jugular vein immediately after randomisation and cavography was performed. Patients assigned to unfractionated heparin (Fournier, Paris) received an intravenous bolus dose of 5000 IU, then a continuous intravenous infusion of 500 IU per kilogram of body weight per day for 8 to 12 days, adjusted according to the activated partial thromboplastin time so that the ratio of the patient's value to the control value remained between 1.5 and 2.5, according to the reagent used. Tests were performed four to six hours after the beginning of treatment or after a subtherapeutic activated partial thromboplastin time had been recorded, and then at least daily. Warfarin or acenocoumarol therapy was started on day 4 and continued for at least three months. The dose was adjusted to achieve an international normalized ratio of 2 to 3. Treatment with either unfractionated heparin or low-molecular-weight heparin was continued until the international normalized ratio*	

Author (year)	Title	Study details	Quality assessment
		was 2 or more for two consecutive days. If the use of an oral anticoagulant was not possible, subcutaneous unfractionated heparin was used (ratio of activated partial-thromboplastin time to control value, 1.5 to 2) for at least three months. Graded-compression stockings were prescribed for the same period. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events *Thrombocytopenia*	
Fiessinger (1996)	Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *Austria, France, Spain, Sweden* • Study setting *Hospitals* • Study dates • Duration of follow-up *Not mentioned*	**Random sequence generation** • Low risk of bias *Randomisation was conducted separately at each centre using a code generated by an SAS (Statistical Analysis System) program written for the purpose.* **Allocation concealment** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		• Sources of funding *Not mentioned* **Inclusion criteria** • DVT *Phlebographically proven DVT below the inguinal ligament with <8 days of symptoms.* **Exclusion criteria** • Symptoms of PE • Contraindication(s) for study drugs • Haemorrhagic stroke • Gastrointestinal bleeding • Uncontrolled hypertension • History of DVT within 1 year • Sequelae of previous DVT in the same leg • Previous anticoagulation before randomisation • Renal insufficiency • Hepatic insufficiency • Low platelet count • Recent surgery **Sample characteristics** • Sample size *268 patients*	*Open study - no blinding involved* **Blinding of participants and personnel** • High risk of bias *Open study - no blinding involved* **Blinding of outcome assessment** • High risk of bias *Open study - no blinding involved* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Split between study groups *LMWH = 130; UFH = 138* • Loss to follow-up *15 people* • %female *LMWH = 47.5%; UFH = 43.6%* • Mean age (SD) *LMWH (range) = 61.5 years (22-89); UFH = 60.5 years (18-88)* • Previous VTE *LMWH = 24.2%; UFH = 18%* **Interventions** • LMWH + VKA *Randomisation before phlebography: Immediate bolus dose of s.c 5000 IU. Full dose therapy could not be started until after phlebography , and not for 4 hr after initial injection* *Randomisation after phlebography: received full dose (10,000 IU?) straight away s.c. Oral anticoagulation was started on the same day or day after inclusion and continued for a period determined by the physician. Dalteparin and UFH stopped after 5-10 days, when INR 2-3 on 2 consecutive days.* • UFH + VKA *Randomisation before phlebography: i.v. 5000 IU* *Randomisation after phlebography: i.v infusion (20,000-40,000 IU/24 hr) adjusted to maintain APTT between 1.5-3.0 times the upper reference value at each centre. A bolus i.v. injection of UFH could at the discretion of the attending physician be given*	**Overall risk of bias** • Low Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		prior to the infusion of UFH. Oral anticoagulation was started on the same day or day after inclusion and continued for a period determined by the physician. Dalteparin and UFH stopped after 5-10 days, when INR 2-3 on 2 consecutive days. **Outcomes** • All-cause mortality • VTE-related mortality • Major bleeding *Any bleeding that led to death, interruption of treatment, blood transfusion or fall in the HB level of ≥30g/l* • VTE-recurrence	
Findik (2002)	Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism.	**Study type** • Randomised controlled trial **Study details** • Study location *Turkey* • Study setting *Hospital* • Study dates *August 1998 to January 2000* • Duration of follow-up *90 days* • Sources of funding	**Random sequence generation** • High risk of bias *Likely randomized however randomization method not given* **Allocation concealment** • High risk of bias *Likely randomized however randomization method not given* **Blinding of participants and personnel** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		Not mentioned **Inclusion criteria** • ≥18 years • PE *PTE objectively documented by ventilation/perfusion lung scanning showing a high probability of PTE or by scanning with indeterminate results that was accompanied by DVT confirmed by compression ultrasonography.* **Exclusion criteria** • Contraindication(s) for study drugs • Active bleeding • Pregnancy • Life expectancy <3 months • >24 hours of anticoagulants • Severe renal failure • Severe hepatic failure • Likelihood of non-adherence to treatment • Massive PE requiring thrombolytic therapy or pulmonary embolectomy **Sample characteristics** • Sample size *59 people*	*Blinding methodology was not given* **Blinding of outcome assessment** • High risk of bias *Blinding methodology was not given* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Randomization and blinding methodology not given.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the

Author (year)	Title	Study details	Quality assessment
		• Split between study groups *LMWH = 29; UFH = 30* • Loss to follow-up *None* • %female *LMWH = 52%; UFH = 50%* • Mean age (SD) *LMWH = 51 years (18); UFH = 49 years (15)* • Previous VTE *LMWH = 6%; UFH = 6%* **Interventions** • LMWH + VKA *Enoxaparin Duration: 10 days Dose, and frequency: 1mg/kg, 100 IU/kg twice daily Average daily dose, day 1 to end, IU: 27,744 Route: S/C Oral anticoagulant treatment was begun on the second day and continued for a total of 6 months. During treatment with the study drug, all patients were followed up in the hospital. Prothrombin times were measured every day, with the dose adjusted to achieve an INR between 2.0 and 3.0 for 2 consecutive days and the patient had received the study drug for at least 5 days. All patients were examined daily within 10 days of therapy and symptoms and signs of recurrent VTE or bleeding were sought. For all patients, compression ultrasonography of the lower limbs was planned at enrolment. Complete blood counts were obtained daily during the initial 8 days and whenever there was any bleeding. Perfusion lung*	majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		scans and compression ultrasonography were repeated in all patients on day 8 and day 90 • UFH + VKA *Duration: 10 days, mean ±Sd : 7.0 ±1.9 Dose, and frequency: initial bolus dose of 5000 IU followed by a dose of 1000 IU/hour given by continuous IV infusion. Dose adjusted so that the aPTT would be 1.5-2.5 times the control value Route: IV Oral anticoagulant treatment was begun on the second day and continued for a total of 6 months. During treatment with the study drug, all patients were followed up in the hospital. Prothrombin times were measured every day, with the dose adjusted to achieve an INR between 2.0 and 3.0 for 2 consecutive days and the patient had received the study drug for at least 5 days. All patients were examined daily within 10 days of therapy and symptoms and signs of recurrent VTE or bleeding were sought. For all patients, compression ultrasonography of the lower limbs was planned at enrolment. Complete blood counts were obtained daily during the initial 8 days and whenever there was any bleeding. Perfusion lung scans and compression ultrasonography were repeated in all patients on day 8 and day 90 (state any VTE related treatments here)*	
Hisatake (2017)	Short-Term Subcutaneous Fondaparinux and Oral Edoxaban for Acute Venous Thromboembolism	**Study type** • Randomised controlled trial	**Random sequence generation** • High risk of bias *The method of randomisation is not*

Author (year)	Title	Study details	Quality assessment
		Study details • Study location *Japan* • Study setting *Hospital* • Study dates *February 2015 to September 2016* • Duration of follow-up *7 days after treatment* • Sources of funding *This manuscript was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.* **Inclusion criteria** • Acute non-massive PE and/or acute DVT *These patients were symptomatic or asymptomatic, had elevated D-dimer on blood test during the perioperative periods or during hospitalization, and provided informed consent for study participation. PE was diagnosed on contrast-enhanced chest CT and DVT on lower-limb venous US.* **Exclusion criteria** • Vena cava filter fitted • Contraindication(s) for study drugs • Creatine clearance <30ml/min	*provided.* **Allocation concealment** • High risk of bias *This is an open-label study.* **Blinding of participants and personnel** • High risk of bias *This is an open-label study.* **Blinding of outcome assessment** • High risk of bias *This is an open-label study.* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Bacterial endocarditis • Active bleeding • Pregnancy • already receiving oral anticoagulation therapy • Haemorrhagic stroke • Gastrointestinal bleeding • Massive PE requiring thrombolytic therapy or pulmonary embolectomy • Hepatic disorders accompanied by coagulopathy **Sample characteristics** • Sample size *50 people* • Split between study groups *Fondaparinux = 25; Edoxaban = 25* • Loss to follow-up *2 patients: Fondaparinux = 1 (major bleeding on day 3); Edoxaban = 1 (PE exacerbation on day 4)* • %female *Fondaparinux = 56%; Edoxaban = 64%* • Mean age (SD) *Fondaparinux = 72 years (13); Edoxaban = 67 years (17)* • PE/DVT split (for VTE only studies) *% DVT, PE, PE with DVT: Fondaparinux = 56%, 4%, 40%; Edoxaban = 76%, 0%, 24%* • Previous VTE	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Method of randomization not provided and unclear whether allocation was concealed. Study was open label and therefore unblinded* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Fondaparinux = 0%; Edoxaban = 8% **Interventions** • Fondaparinux *Fondaparinux dose was determined in accordance with the package insert, according to body weight and estimated creatinine clearance (CrCl) calculated using the Cockcroft-Gault formula. The fondaparinux subjects received a once-daily SC dose depending on body weight (body weight <50 kg, 5 mg; 50–100 kg, 7.5 mg; >100 kg, 10 mg). After 7 days of treatment, the subjects underwent blood test, lower-limb venous US, and chest CT, and the results before and 7 days after treatment were compared.* • Edoxaban with parenteral AC *Edoxaban dose were determined in accordance with the package inserts, according to body weight and estimated creatinine clearance (CrCl) calculated using the Cockcroft-Gault formula. The edoxaban group received a once-daily oral dose, depending on estimated CrCl and body weight (estimated CrCl ≤50 mL/min, 30 mg; estimated CrCl >50 mL/min, body weight ≤60 kg, 30 mg; >60 kg, 60 mg). After 7 days of treatment, the subjects underwent blood test, lower-limb venous US, and chest CT, and the results before and 7 days after treatment were compared.*	

Author (year)	Title	Study details	Quality assessment
		Outcomes • Clinically relevant non-major bleeding *Minor bleeding was defined as all unusual clinically overt bleeding episodes reported by an investigator as an adverse event and not considered as major bleeding.* • Major bleeding *Major bleeding was defined as follows: (1) fatal bleeding; (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or i.m. bleeding with compartment syndrome; and (3) bleeding causing a fall in the haemoglobin requiring a transfusion of ≥2 units whole blood or red cells, in accordance with the International Society on Thrombosis and Haematosis.* • VTE-recurrence *Symptomatic VTE recurrence was evaluated on contrast-enhanced CT and/or lower-limb venous US when symptoms (i.e., appearance of dyspnoea, worsening leg edema, or leg pain) suspected to be associated with recurrent VTE were observed.*	
HOKUSAI-VTE investigators (2013)	Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism.[Erratum appears in N Engl J Med. 2014 Jan 23;370(4):390]	**Study type** • Randomised controlled trial **Study details** • Study location *37 countries*	**Random sequence generation** • Low risk of bias *Randomisation was performed with the use of an interactive web-based system*

Author (year)	Title	Study details	Quality assessment
		• Study setting *439 centres* • Study dates *January 2010- October 2012 (enrolment)* • Duration of follow-up *Participants were treated for a varying length of time Edoxaban arm: 11.8% received 3 months of treatment, 26.1% received between 3 and 6 months of treatment, 21.8% received >6months months treatment and 40.3% received 12 months treatment. Warfarin arm: 12.8% received 3 months of treatment, 26.3% received between 3 and 6 months of treatment, 20.7% received >6months months treatment and 40.2% received 12 months treatment. Follow-up was conducted in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug. Patients were instructed to report symptoms suggestive of recurrent venous thromboembolism or bleeding. Appropriate diagnostic testing, laboratory testing, or both were required in patients with suspected events.* • Sources of funding *Supported by Daiichi-Sankyo* • Associated studies *Raskob 2016 cancer subgroup analysis* **Inclusion criteria** • ≥18 years	**Allocation concealment** • Unclear risk of bias *Unclear whether randomization procedure allowed for allocation bias.* **Blinding of participants and personnel** • Low risk of bias *Administered in a double-blind, double dummy fashion.* **Blinding of outcome assessment** • Low risk of bias *A blinded committee rated all suspected outcome events* **Incomplete outcome data** • Low risk of bias **Selective reporting** • High risk of bias *Results are not stratified by treatment duration, limiting interpretability. Outcomes were reported at 12 months (even if intended treatment duration was 3 months*

Author (year)	Title	Study details	Quality assessment
		• Objectively confirmed symptomatic DVT or PE **Exclusion criteria** • Contraindication(s) for study drugs • Creatine clearance <30ml/min • Active cancer with long-term LMWH treatment planned • Other indication requiring long-term anticoagulation • received therapeutic doses of any heparin for >48 hours, prior randomization *or had one dose of VKA* • Continued to receive aspirin for >100mg daily or received dual platelet therapy **Sample characteristics** • Sample size *8292 randomized; 8240 analysed* • Split between study groups *4118 Edoxaban; 4122 Warfarin* • Loss to follow-up *52 participants did not receive intended drug and were excluded from analysis* • %female *42.8%* • Mean age (SD) *Edoxaban arm: 55.7 (SD 16.3) years Warfarin arm: 55.9 (SD 16.2) years*	*and the participants has been off treatment for 9 months). As outcomes in this review were reported in the format of hazard ratios or relative risks, there is a risk of bias due to uncertainty that the rate of events is proportionate after discontinuing treatment.* **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low *For recurrence and mortality outcomes reported as hazard ratios and at time points beyond 3 months, the study was marked down for risk of bias at the proportional hazard assumption is violated due to events being reported after treatment has been stopped.* *Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed.*

Author (year)	Title	Study details	Quality assessment
		• PE/DVT split (for VTE only studies) *4921 DVT only 3319 PE with or without DVT* • Provoked vs. unprovoked *65.7% unprovoked* • Previous VTE *18.4% previous VTE* **Interventions** • LMWH + VKA *Participants received at least 5 days parenteral heparin (LMWH or UFH). Warfarin was given concurrently for at least 3 months and for a maximum of 12 months, and was adjusted to maintain an INR between 2.0 and 3.0. Participants in this arm also received an Edoxaban-like placebo. Supplementary appendix shows that only 151 (3.7%) of participants received UFH with the rest receiving enoxaparin.* • Edoxaban plus parenteral AC *Participants received at least 5 days of heparin (LMWH or UFH). Following discontinuation of heparin, participants received 60mg Edoxaban orally, once daily, or 30mg (once daily) in those patients with creatinine clearance 30-50ml per minute, or a body weight of 60kg or less or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. Participants in this arm also received a warfarin-like placebo given concurrently with heparin, and a sham INR reading. Supplementary appendix shows that only 148 (3.6%) of*	*Only VTE-recurrence and mortality outcomes were marked down for risk of bias in GRADE.* **Directness** • Partially directly applicable *Outcomes were reported at 12 months, containing a mix of participants on treatment and participants that were intended to be treated for 3 months and discontinued accordingly. This was determined to be different to the review question as it covers the initial treatment and a period of discontinued treatment.* *Only VTE-recurrence and mortality outcomes were marked down for indirectness in GRADE. Bleeding outcomes were not downgraded as these were reported on treatment.*

Author (year)	Title	Study details	Quality assessment
		participants received UFH with the rest receiving enoxaparin. **Outcomes** • Clinically relevant non-major bleeding *Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life* *Data for this outcome was extracted for on-treatment up to 12 months* • Major bleeding *Bleeding was defined as major if it was overt and was associated with a decrease in haemoglobin of 2 g per decilitre or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death.* *Data for this outcome was extracted for on-treatment up to 12 months* • VTE-recurrence *For pairwise analysis, data for this outcome was extracted for at 3 months and at 12 months, with all events up until these time points being counted. For the NMA data were extracted for on-treatment events up to 12 months*	

Author (year)	Title	Study details	Quality assessment
		• Serious adverse events	
Investigators EINSTEIN-DVT (2010)	Oral rivaroxaban for symptomatic venous thromboembolism	**Study type** • Randomised controlled trial **Study details** • Study location *Acute-DVT study: 27 countries Continued treatment study: 27 countries* • Study setting *Acute-DVT study Australia (269 patients, 19 centres) Austria (94 patients, 5 centres) Brazil (48 patients, 8 centres) Canada (119 patients, 5 centres) China (211 patients, 14 centres) Czech Republic (234 patients, 7 centres) Denmark (35 patients, 3 centres) France (245 patients, 28 centres) Germany (250 patients, 22 centres) India (48 patients, 4 centres) Indonesia (76 patients, 5 centres) Italy (242 patients, 13 centres) Korea (10 patients, 2 centres) The Netherlands (379 patients, 7 centres) New Zealand (89 patients, 6 centres) Norway (43 patients, 4 centres) Philippines (26 patients, 2 centres) Poland (67 patients, 11 centres) Singapore (19 patients, 2 centres) South Africa (126 patients, 11 centres) Spain (32 patients, 4 centres) Sweden (37 patients, 4 centres) Switzerland (33 patients, 5 centres) Taiwan (8 patients, 3 centres) Thailand (13 patients, 2 centres) United Kingdom (30 patients, 4 centres) United States (207 patients, 19 centres) Continued treatment study Australia (129 patients, 18 centres) Austria (57 patients, 7 centres) Belgium (24 patients, 5*	**Random sequence generation** • Low risk of bias *randomly assigned using computerized voice-response system, stratified by country* **Allocation concealment** • High risk of bias *Intended treatment duration was determined by treating physician* **Blinding of participants and personnel** • High risk of bias *Acute DVT study was open-label. Continued treatment study was double-blind and therefore at high risk of bias.* **Blinding of outcome assessment** • Low risk of bias *Suspected outcome events were classified*

Author (year)	Title	Study details	Quality assessment
		centres) Brazil (14 patients, 6 centres) China (31 patients, 8 centres) Czech Republic (62 patients, 7 centres) Denmark (12 patients, 3 centres) France (135 patients, 18 centres) Germany (35 patients, 7 centres) Hungary (56 patients, 7 centres) India (19 patients, 4 centres) Indonesia (2 patients, 1 centre) Israel (46 patients, 7 centres) Italy (76 patients, 11 centres) Malaysia (5 patients, 1 centre) The Netherlands (96 patients, 5 centres) Norway (17 patients, 3 centres) Philippines (6 patients, 2 centres) Poland (43 patients, 7 centres) Singapore (19 patients, 2 centres) South Africa (42 patients, 10 centres) Spain (44 patients, 6 centres) Sweden (123 patients, 6 centres) Switzerland (5 patients, 2 centres) Thailand (9 patients, 2 centres) United Kingdom (7 patients, 3 centres) United States (29 patients, 9 centres) • Study dates *Acute-DVT study: May 2007 - September 2009 (enrolment)* *Continued treatment study: February 2007 - March 2009 (enrolment)* • Duration of follow-up *Up to 12 months for both studies* • Sources of funding *Both trials were sponsored by Bayer and Ortho-McNeil.* • Associated studies *Bamber 2013 quality of life study Prins 2014 cancer subgroup analysis study Prins 2015 quality of life study*	*by a blinded central adjudication committee* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • High risk of bias *Treatment length varied between participants with limited reporting for individual time-points, it is unclear whether event rates at the median length of treatment (6 months) was similar to overall event rate.* **Overall risk of bias** Acute DVT study: Moderate risk of bias: Study was unblinded and there is limited reporting on how treatment duration impacted on relative efficacy of regimens

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Acute-DVT inclusion/exclusion criteria *-Of legal age for consent -Acute, symptomatic, objectively confirmed proximal DVT -Without symptomatic PE -Not received therapeutic doses of LMWH, fondaparinux, or UFH for more than 48 hours or a single dose of VKA -Not received thrombectomy, a vena cava filter, or a fibrinolytic agent for current episode of thrombosis -No contraindications for treatments use in study. -No other indications for VKA -Creatine clearance >30 ml/min -No clinically significant liver disease -Alanine amino-transferase level <3xULN -No bacterial endocarditis -No active bleeding or high risk of bleeding -No contraindicating anticoagulant treatment -Systolic blood pressure <180mmHg AND diastolic blood pressure greater than 110 mmHg -Not pregnant or of childbearing potential (unless using proper contraceptive measures) -Not breast-feeding -No concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers -No participation in another experimental pharmacotherapeutic program within 30 days before screenings -Life expectancy over 3 months* • Continued treatment inclusion/exclusion criteria *-Objectively confirmed, symptomatic DVT or PE and had been treated for 6-12 months with acenocoumarol or warfarin or rivaroxaban -Need for continued treatment -No other indications for VKA -Creatine clearance >30 ml/min -No clinically significant liver disease -Alanine amino-transferase level <3xULN -No bacterial endocarditis -No active bleeding or high risk of bleeding -No contraindicating anticoagulant treatment -Systolic*	Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. However, the quality of life related outcomes were at high risk of bias due to this lack of blinding. Continued treatment study: Low risk of bias **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		blood pressure <180mmHg AND diastolic blood pressure greater than 110 mmHg -Not pregnant or of childbearing potential (unless using proper contraceptive measures) -Not breast-feeding -No concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers -No participation in another experimental pharmacotherapeutic program within 30 days before screenings -Life expectancy over 3 months **Sample characteristics** • Sample size *Acute DVT study: 3449 Continued treatment study: 1197* • Split between study groups *Acute DVT study: 1718 Rivaroxaban; 1711 LMWH+VKA Continued treatment study: 602 rivaroxaban; 594 placebo* • Loss to follow-up *Acute DVT study: 19 lost to follow-up Continued treatment study: 8 lost to follow-up* • %female *Acute DVT study: 43.2% female Continued treatment study: 42.1% female* • Mean age (SD) *Acute DVT study: 56.1 (SD 16.4) years Continued treatment study: 58.3 (SD 15.8) years* • PE/DVT split (for VTE only studies) *Continued treatment study: 38% PE; 62% DVT* • Provoked vs. unprovoked *Acute DVT study: 62% unprovoked Continued treatment study:*	

Author (year)	Title	Study details	Quality assessment
		74% unprovoked • Previous VTE *Acute DVT study: 19.3% previous VTE Continued treatment study: 16.1%* **Interventions** **Initial DVT study** • Rivaroxaban *Acute DVT study: Rivaroxaban 15mg twice daily for first 3 weeks followed by 20 mg once daily for intended 3, 6 or 12 months.* • LMWH + VKA *Acute DVT study: Subcutaneous enoxaparin (1.0 mg/kg body weight, twice daily; discontinued when INR was 2.0 or more for 2 consecutive days) + either warfarin or acenocoumarol (started within 48 hr after randomization. Enoxaparin was given for a median of 8 days with INR at end of 2.0 or higher in 80.8% of patients.* **Continued treatment study** • Rivaroxaban *20mg once daily for 6-12 months* • Placebo	

Author (year)	Title	Study details	Quality assessment
		6-12 months **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding *Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life.* • Major bleeding *Bleeding was defined as major if it was clinically overt and associated with a fall in the haemoglobin level of 20 g per litre or more, or if it led to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death.* • VTE-recurrence *The criteria for the diagnosis of deep-vein thrombosis were a new noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. The criteria for diagnosis of pulmonary embolism were a new intraluminal filling defect on spiral CT or pulmonary angiography, a cut-off of a vessel of more than 2.5 mm in*	

Author (year)	Title	Study details	Quality assessment
		diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non– high-probability perfusion defect associated with deep-vein thrombosis, as documented by ultrasonography or venography. Fatal pulmonary embolism was based on objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death). • Quality of life	
Investigators EINSTEIN-PE (2012)	Oral rivaroxaban for the treatment of symptomatic pulmonary embolism	**Study type** • Randomised controlled trial **Study details** • Study location *38 countries (see study setting)* • Study setting *Andorra (2 patients, 1 centre) Australia (499 patients, 23 centres) Austria (229 patients, 6 centres) Belgium (194 patients, 12 centres) Brazil (18 patients, 2 centres) Canada (137 patients, 4 centres) China (228 patients, 15 centres) Czech Republic (221 patients, 7 centres) Denmark (2 patients, 1 centre) Estonia (8 patients, 1 centre) Finland (10 patients, 2 centres) France (1171 patients, 34 centres) Germany (351 patients, 25 centres) Hong Kong (6 patients, 2 centres) Hungary (117 patients, 10 centres) India (2 patients, 1 centre) Indonesia (3 patients, 1 centre) Ireland (2 patients, 1 centre) Israel (155 patients, 10 centres)*	**Random sequence generation** • Low risk of bias *randomized using computerized voice-response system* **Allocation concealment** • High risk of bias *duration was determined by physician and therefore had potential for allocation bias* **Blinding of participants and personnel** • High risk of bias *Open-label*

Author (year)	Title	Study details	Quality assessment
		Italy (106 patients, 13 centres) Korea (11 patients, 4 centres) Latvia (4 patients, 1 centre) Lithuania (10 patients, 2 centres) Malaysia (2 patients, 1 centre) Netherlands (264 patients, 6 centres) New Zealand (114 patients, 5 centres) Norway (43 patients, 3 centres) Philippines (7 patients, 1 centre) Poland (58 patients, 7 centres) Singapore (2 patients, 1 centre) South Africa (239 patients, 10 centres) Spain (78 patients, 8 centres) Sweden (77 patients, 5 centres) Switzerland (75 patients, 6 centres) Taiwan (11 patients, 4 centres) Thailand (18 patients, 3 centres) United Kingdom (21 patients, 3 centres) United States (350 patients, 23 centres) • Study dates *March 2007 - March 2011 (enrolment)* • Duration of follow-up *1 year (1809 patients) 6 months (2774 patients) 3 months (239 patients) mean duration 266 days* • Sources of funding *Funded by Bayer and Janssen.* **Inclusion criteria** • Of legal age • PE *symptomatic PE with objective confirmation, with or without symptomatic DVT*	**Blinding of outcome assessment** • Low risk of bias *Blinded committee reviewed all outcome events* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • High risk of bias *Treatment length varied between participants with limited reporting for individual time-points, it is unclear whether event rates at the median length of treatment (6 months) was similar to overall event rate.* **Overall risk of bias** • Moderate *Treatment length varied between participants with limited reporting for*

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Received therapeutic dose of VKA or 48 hours of UFH, LMHW or fondaparinux • Thrombectomy or embolectomy • Vena cava filter fitted • Fibrinolytic agent administered for treatment of current episode • Contraindication(s) for study drugs • Other indication for VKA • Creatine clearance <30ml/min • Clinically significant liver disease • Alanine aminotransferase level >3x ULN • Bacterial endocarditis • Active bleeding *or high risk of bleeding contraindicating anticoagulant treatment* • Systolic blood pressure >180 mm Hg OR diastolic blood pressure >110 mm Hg • Other *Pregnancy, childbearing potential without proper use of contraceptive measures, breastfeeding, concomitant use of strong inhibitor of cytochrome P-450 3A4 or CYP3A4 inducer, or participating in another pharmacotherapy program within 30 days, or life expectancy <3 months* **Sample characteristics** • Sample size *4832 participants* • Split between study groups	*individual time-points, it is unclear whether event rates at the median length of treatment (6 months) was similar to overall event rate. Personnel and physicians were unblinded.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. However, the quality of evidence for quality of life specific outcomes were deemed at high risk of bias due to this lack of blinding. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		2419 rivaroxaban; 2413 LMWH+VKA • %female *47% female* • Mean age (SD) *Rivaroxaban arm: 57.9 (7.3) years Control arm: 57.5 (7.2) years* • Provoked vs. unprovoked *64.5% unprovoked* • Previous VTE *19.5% prior VTE* **Interventions** • Rivaroxaban *15 mg twice daily for first 3 weeks, followed by 20 mg once daily* • LMWH + VKA *Enoxaparin (1.0mg/kg body weight twice daily) and either warfarin or acenocoumarol, started within 48 hours after randomization. Enoxaparin was discontinued when the INR was 2.0 or more for 2 consecutive days and patient had received 5 days of enoxaparin treatment.* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence	

Author (year)	Title	Study details	Quality assessment
		• Quality of life	
Kakkar (2003)	Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *UK, Spain and Poland* • Study setting *Hospitals* • Study dates *Not provided* • Duration of follow-up *12 weeks, and 28±3 days after the last dose of the treatment* • Sources of funding *Laboratorios Farmaceuticos Rovi S.A., Madrid (manufacturer for LMWH)* **Inclusion criteria** • ≥18 years • Acute-DVT inclusion/exclusion criteria *Symptoms ≤14 days* **Exclusion criteria** • Symptoms of PE	**Random sequence generation** • High risk of bias *Randomisation methodology not provided* **Allocation concealment** • High risk of bias *No allocation concealment* **Blinding of participants and personnel** • High risk of bias *There was no blinding during treatment* **Blinding of outcome assessment** • High risk of bias *There was no blinding for the outcomes of interest in this review. However, given the nature of the outcomes, this is probably not possible.*

Author (year)	Title	Study details	Quality assessment
		• Fibrinolytic agent administered for treatment of current episode • Contraindication(s) for study drugs • Bacterial endocarditis • Platelet count of <100,000 per cubic mm • Duration of symptoms >14 days • Pregnancy • Gastrointestinal bleeding • Uncontrolled hypertension • >48 hours of anticoagulants • Severe renal failure • Severe hepatic failure • Likelihood of non-adherence to treatment • Previous anticoagulation before randomisation • Ischaemic CVA one month prior to enrolment • Known cerebral aneurysm • Spinal or epidural anaesthesia or lumbar puncture 3 days prior to enrolment • Body weight <35kg • Recreational use of drugs **Sample characteristics** • Sample size *297 people* • Split between study groups *UFH = 98; LMWH (once daily) = 105; LMWH (once daily followed by a maintenance dose) = 94* • Loss to follow-up	**Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Randomization and allocation concealment methodology now given. Study was unblinded however this is unlikely to have a major impact on key outcomes.* **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		None • %female *UFH = 46%; LMWH (once daily)= 42%; LMWH (once daily followed by a maintenance dose) = 38%* • Mean age (SD) *UFH = 61.2 years (49.9, 70.5); LMWH (once daily) = 61.2 years (44.4, 69.5); LMWH (once daily followed by a maintenance dose) = 63.2 (45.1, 70.8)* **Interventions** • LMWH + VKA *The group B patients received 115 anti-Xa IU per kg of bemiparin given as one injection every 24 h based on the patients weight (5,000 anti-Xa IU for a weight <50 kg, 7,500 anti-Xa IU for 50 to 70 kg and 10,000 anti-Xa IU for more than 70 kg).This group received a Vitamin K antagonist from day 3 in a dose of 10 mg per day for the first 3 days and then adjusted to achieve an international normalised ratio between 2 and 3 for 12 weeks.* • UFH + VKA *The group A patients received an initial intravenous bolus of 5,000 IU of UFH followed by a continuous intravenous infusion commenced at a dose of 40,000 IU per 24 h in patients at "low risk" of bleeding and 30,000 IU per 24 h in patients at "high risk" of bleeding. High risk of bleeding was defined by a patient presenting with any one of the following: a history of surgery or trauma within the previous 14 days, peptic ulcer disease, gastro-*	

Author (year)	Title	Study details	Quality assessment
		intestinal or Genito-urinary bleeding or patients with a platelet count of <150,000/mm3. Subsequent dose of heparin was adjusted according to daily measurement of activated partial thromboplastin time to achieve a value of 1.5 to 2.5 times the baseline level. This group received a Vitamin K antagonist from day 3 in a dose of 10 mg per day for the first 3 days and then adjusted to achieve an international normalised ratio between 2 and 3 for 12 weeks. • LMWH with a therapeutic dose and then a maintenance dose *These patients received 115 anti-Xa IU per kg of bemiparin given as one injection every 24 h based on the patients weight (5,000 anti-Xa IU for a weight <50 kg, 7,500 anti-Xa IU for 50 to 70 kg and 10,000 anti-Xa IU for more than 70 kg). These patients then received bemiparin in the same dosage regimen as group B for 10 days and this was followed by a fixed maintenance daily dose of 3,500 anti-Xa units until the end of the 90 days.* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	

Author (year)	Title	Study details	Quality assessment
Kearon (1999)	A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism.	**Study type** • Randomised controlled trial **Study details** • Study location *Canada* • Study dates *October 1994 - April 1997* • Duration of follow-up *24 months (on-treatment period). Follow-up stopped after initial recurrent event.* • Sources of funding *Supported by a grant from DuPont pharma and the Medical Research Council of Canada, the Heart and Stroke Foundation of Canada and Ministry of Health of Ontario.* **Inclusion criteria** • Already received anticoagulation therapy *for 3 uninterrupted months* • Idiopathic VTE **Exclusion criteria** • Other *allergic to contrast medium* • Other indication requiring long-term anticoagulation	**Random sequence generation** • Low risk of bias *likely randomized but using unclear methodology* **Allocation concealment** • Unclear risk of bias *Unclear whether allocation was concealed.* **Blinding of participants and personnel** • Low risk of bias *double-blind* **Blinding of outcome assessment** • Low risk of bias *outcomes adjudicated by a blinded central committee.* **Incomplete outcome data** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Pregnancy *or could become pregnant* • Life expectancy <2 years • Major psychiatric disorder • Unable to return for follow-up visits • require long-term NSAID treatment *or treatment of ticlopidine, sulfinpyrazone, dipyridamole or >160mg aspirin (daily)* • Familial bleeding diathesis **Sample characteristics** • Sample size *327 enrolled, 162 randomized.* • Split between study groups *79 Warfarin; 83 placebo* • Loss to follow-up *27 participants discontinued treatment prior to study completion* *All randomized participants were included in analysis* • %female *40% female* • Mean age (SD) *59 (SD16) years* • PE/DVT split (for VTE only studies) *75% DVT only, 25% PE only or PE with DVT* • Provoked vs. unprovoked *100% unprovoked* • Previous VTE	**Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		5% previous VTE **Interventions** • Placebo *for 24 months* • Warfarin alone *Warfarin adjusted to a target INR of 2.0-3.0, for 18 months* **Outcomes** • All-cause mortality • Major bleeding • VTE-recurrence	
Kearon (2006)	Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism.	**Study type** • Randomised controlled trial **Study details** • Study location *Canada and New Zealand* • Study setting *6 centres* • Study dates *September 1998 to February 2004* • Duration of follow-up	**Random sequence generation** • Low risk of bias *randomized using computer generated blocks of 2 or 4, stratified by clinical centre* **Allocation concealment** • Low risk of bias *clinical centres had to contact an automated centralized system.*

Author (year)	Title	Study details	Quality assessment
		3 months **Inclusion criteria** • ≥18 years • Objectively confirmed symptomatic DVT or PE **Exclusion criteria** • Contraindication(s) for study drugs *or to radiographic contrast* • Active bleeding • Pregnancy • Unable to return for follow-up visits • Life expectancy <3 months • contraindication to subcutaneous therapy *Such as shock or major surgery in past 48 hours* • >48 hours treatment with LMWH or UFH • were receiving long term anticoagulation • Serum creatinine level > 2.3 mg/dL • enrolled in competing study **Sample characteristics** • Sample size *708 participants* • Split between study groups *353 LMWH; 355 UFH*	**Blinding of participants and personnel** • High risk of bias *unblinded* **Blinding of outcome assessment** • Low risk of bias *outcome events and deaths were adjudicated by a blinded central committee* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up *8 randomized participants were not included in the final analysis (5 did not receive study drug, 3 did not have follow-up)* • %female *45% female* • Mean age (SD) *60 (SD 17) years* • PE/DVT split (for VTE only studies) *DVT alone 81%, PE 19%* • Previous VTE *10% previous VTE* **Interventions** • LMWH + VKA *subcutaneous; 100 IU/kg for all doses (10K IU/mL). Warfarin was adjusted to a target INR of 2.0 - 3.0, for at least 3 months* • UFH + VKA *subcutaneous; 333 U/kg followed by subsequent doses of 250 U/Kg. Warfarin was adjusted to a target INR of 2.0 - 3.0, for at least 3 months* **Outcomes** • All-cause mortality • Major bleeding • VTE-recurrence	Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Partially directly applicable *used subcutaneous UFH*

Author (year)	Title	Study details	Quality assessment
Koopman (1996)	Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low molecular-weight heparin administered at home	**Study type** • Randomised controlled trial **Study details** • Study location *Europe, Australia and New Zealand* • Study setting *Hospitals* • Study dates *Not mentioned* • Duration of follow-up *6 months* • Sources of funding *Sanofi Wintrop* **Inclusion criteria** • Acute-DVT inclusion/exclusion criteria *Acute symptomatic proximal DVT documented by venography and/or ultrasonography.* **Exclusion criteria** • Symptoms of PE • >24 hours of anticoagulants *Heparin* • Likelihood of non-adherence to treatment	**Random sequence generation** • Low risk of bias **Allocation concealment** • High risk of bias *Open label study* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *Open label study* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• VTE in the last 2 years • Post-thrombotic syndrome **Sample characteristics** • Sample size *400 people* • Split between study groups *UFH = 198; LMWH = 202* • Loss to follow-up *4 withdrew consent (2 in each group)* • %female *UFH = 52%; LMWH = 47%* • Mean age (SD) *UFH = 62 years (16); LMWH = 59 years (17)* • Previous VTE *UFH = 19%; LMWH = 20%* **Interventions** • LMWH + VKA *The patients randomly assigned to low-molecular-weight heparin received twice-daily injections of nadroparin-Ca with prefilled syringes, in doses adjusted for the patient's weight. Patients weighing less than 50 kg received a total daily dose of 8200 International Factor Xa Inhibitory Units per litre; those weighing between 50 and 70 kg, 12,300 International Factor Xa Inhibitory Units per litre; and those weighing over 70 kg, 18,400*	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Low risk Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		International Factor Xa Inhibitory Units per litre. There was no laboratory monitoring. Each patient was instructed by a nurse in the method of self-injection. If self-administration was impossible, the injections were given by a relative or a nurse. As soon as appropriate, patients were allowed to be treated at home. In each patient, oral anticoagulant treatment was initiated on the first day and continued for a total of three months, unless the persistence of risk factors required its continuation beyond that period. The dose was adjusted to achieve an international normalized ratio of 2.0 to 3.0. The intensity of anticoagulation in the first three months was expressed as the percentage of time during which a patient had a specific international normalized ratio (<2.0, 2.0 to 3.0, or >3.0), with this period calculated by linear interpolation. Treatment with either standard heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2.0 or above in two measurements 24 hours apart after at least five days of initial treatment. • UFH + VKA *Patients randomly assigned to standard heparin were admitted to the hospital and received heparin sodium in an intravenous loading dose of 5000 IU, followed by a continuous infusion of 1250 IU per hour. The dose was adjusted so that the activated partial-thromboplastin time would be from 1.5 to 2 times the mean value in normal subjects, as measured with a sensitive reagent (corresponding to 0.35 to 0.6 International Factor Xa Inhibitory Unit per litre). The tests were performed six hours after the start of treatment or if a subtherapeutic activated*	

Author (year)	Title	Study details	Quality assessment
		partial-thromboplastin time had been measured, and otherwise daily. In each patient, oral anticoagulant treatment was initiated on the first day and continued for a total of three months, unless the persistence of risk factors required its continuation beyond that period. The dose was adjusted to achieve an international normalized ratio of 2.0 to 3.0. The intensity of anticoagulation in the first three months was expressed as the percentage of time during which a patient had a specific international normalized ratio (<2.0, 2.0 to 3.0, or >3.0), with this period calculated by linear interpolation. Treatment with either standard heparin or low-molecular-weight heparin was continued until the international normalized ratio was 2.0 or above in two measurements 24 hours apart after at least five days of initial treatment. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Quality of life • Serious adverse events	

Author (year)	Title	Study details	Quality assessment
Levine (1996)	A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *Canada* • Study setting *Hospitals* • Study dates *May 1992 to January 1995* • Duration of follow-up *90 days* • Sources of funding *Not stated* **Inclusion criteria** • DVT *Consecutive patients in whom acute proximal deep-vein thrombosis (thrombosis involving the popliteal vein or a more proximal vein) had been confirmed by either venography or duplex ultrasonography.* **Exclusion criteria** • Symptoms of PE • At risk of bleeding	**Random sequence generation** • Low risk of bias *The randomisation was stratified according to centre, mode of diagnosis (venography or ultrasonography), and category of patient. The first category of patients included those who presented as outpatients. The second category included patients with deep-vein thrombosis who were admitted at night or on a weekend, who for logistic reasons could not be enrolled in the study immediately and thus were first treated with standard heparin. The third category included patients who were hospitalized for other reasons, such as surgery, and in whom deep-vein thrombosis was subsequently diagnosed.* **Allocation concealment** • High risk of bias *Open label study* **Blinding of participants and personnel** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		• Contraindication(s) for study drugs • Active bleeding • Pregnancy • >48 hours treatment with LMWH or UFH • Likelihood of non-adherence to treatment • 2 or more previous DVTs or PEs **Sample characteristics** • Sample size *500 people* • Split between study groups *LMWH = 247; UFH = 253* • Loss to follow-up *None* • %female *LMWH = 38%; UFH = 41.5%* • Mean age (SD) *LMWH = 57 years (17); UFH = 59 years (15)* • Previous VTE *LMWH = 30.8%; UFH = 32%* **Interventions** • LMWH + VKA *The patients assigned to therapy with low-molecular-weight heparin received 1 mg of enoxaparin per kilogram of body weight subcutaneously twice daily. The medication was supplied*	*Open label study* **Blinding of outcome assessment** • High risk of bias *Open label study* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low Note: this study was not downgraded to moderate risk of bias due to a lack of

Author (year)	Title	Study details	Quality assessment
		in 1-ml ampules, each containing 100 mg of enoxaparin (100 International Factor Xa Inhibitory Units per milligram). The patient (and a family member, if appropriate) was taught by the study nurse how to administer the study medication subcutaneously. The first dose was given by the patient under the supervision of the nurse. The medication was drawn up into 1-ml plastic syringes similar to those used for insulin injections and was injected through a 28.5-gauge needle. In some instances the study nurse loaded a series of syringes with the study medication and sent the patient home with enough syringes for several days of treatment. The patients began to receive warfarin sodium on the evening of the second day of treatment with the study medication. The first dose of warfarin was usually 10 mg. Thereafter, each patient's prothrombin time was measured daily, and warfarin was prescribed to achieve an international normalized ratio of 2.0 to 3.0. In the outpatients, the prothrombin time was measured daily either at the outpatient hospital laboratory or a community laboratory or at the patient's home, by a staff member of a community laboratory. The study medication was discontinued when the targeted therapeutic range for the international normalized ratio was reached and maintained for two consecutive days. However, each patient should have been treated for at least five days with either low-molecular-weight heparin or standard heparin. The study nurse contacted each outpatient daily by telephone to ensure that there were no problems and to adjust the dose of warfarin. Inpatients were seen daily by the study nurse. All the patients were scheduled to receive warfarin for at least three months. In	blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		the case of the patients admitted at night or on a weekend, the first dose of low-molecular-weight heparin was administered 30 to 60 minutes after the discontinuation of the heparin infusion. In this group, the period during which the patient had received standard heparin before randomization was considered part of the overall duration of heparin therapy. • UFH + VKA *The patients randomly assigned to therapy with standard heparin were admitted to the hospital. They received a bolus dose of 5000 units intravenously, followed by a continuous infusion of 20,000 units of standard heparin in 500 ml of a 5 percent dextrose solution, with 32 ml administered per hour. The activated partial-thromboplastin time was measured 6 hours after heparin therapy began, and the dose rate was adjusted to maintain this variable in the targeted therapeutic range of 60 to 85 seconds with use of a previously published nomogram. This range was equivalent to a heparin level of 0.2 to 0.4 unit per millilitre as measured by titration against protamine. The prothrombin time and activated partial-thromboplastin time of the patients in this group were measured at least once daily. The patients began to receive warfarin sodium on the evening of the second day of treatment with the study medication. The first dose of warfarin was usually 10 mg. Thereafter, each patient's prothrombin time was measured daily, and warfarin was prescribed to achieve an international normalized ratio of 2.0 to 3.0. In the outpatients, the prothrombin time was measured daily either at the outpatient hospital laboratory or a community laboratory or at the patient's home, by a staff member of a*	

Author (year)	Title	Study details	Quality assessment
		community laboratory. The study medication was discontinued when the targeted therapeutic range for the international normalized ratio was reached and maintained for two consecutive days. However, each patient should have been treated for at least five days with either low-molecular-weight heparin or standard heparin. The study nurse contacted each outpatient daily by telephone to ensure that there were no problems and to adjust the dose of warfarin. Inpatients were seen daily by the study nurse. All the patients were scheduled to receive warfarin for at least three months. In the case of the patients admitted at night or on a weekend, the first dose of low-molecular-weight heparin was administered 30 to 60 minutes after the discontinuation of the heparin infusion. In this group, the period during which the patient had received standard heparin before randomization was considered part of the overall duration of heparin therapy. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence	
Lindmarker (1994)	Comparison of once-daily subcutaneous Fragmin with continuous intravenous	**Study type** • Randomised controlled trial	**Random sequence generation** • High risk of bias *Randomisation was organised centrally*

Author (year)	Title	Study details	Quality assessment
	unfractionated heparin in the treatment of deep vein thrombosis.	**Study details** • Study location *Sweden* • Study setting *Hospitals* • Study dates *Not mentioned* • Duration of follow-up *6 months* • Sources of funding *Not stated. Assistance from employee of Pharmacia in acknowledgement.* **Inclusion criteria** • ≥18 years • DVT *Symptomatic distal and proximal DVT. Venographic confirmation of thrombosis of the leg below the inguinal ligament.* **Exclusion criteria** • Symptoms of PE • At risk of bleeding • Thrombectomy or embolectomy • Contraindication(s) for study drugs • Platelet count of <100,000 per cubic mm • Pregnancy • Uncontrolled hypertension	*using sealed envelopes. This method was abandoned because healthcare professionals could put the envelope up to a light and read the study arm through the envelope.* **Allocation concealment** • High risk of bias *No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *Open label study* **Incomplete outcome data** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Breast-feeding • Renal insufficiency • Hepatic insufficiency • >24 hours of heparin treatment • Surgery <5 days before • Previous DVT in the ipsilateral leg • DVT proximal of inguinal arch • Intracranial bleeding within previous 2 weeks **Sample characteristics** • Sample size *204 people* • Split between study groups *LMWH = 101; UFH = 103* • Loss to follow-up *None* • %female *LMWH = 47.5%; UFH = 38.8%* • Mean age (SD) *LMWH = 62.3 years (20-86); UFH = 59.5 years (20-87)* **Interventions** • LMWH + VKA *Once DVT was suspected an initial i. v. bolus injection of UFH 5000 IU, followed by a continuous i.v. infusion of UFH, 800-1700 IU/h, could be given to achieve adequate anticoagulation without delay and prevent PE. The decision to start UFH*	**Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Study was unblinded and allocation was not concealed from investigators. Randomization techniques used were out-dated.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		treatment before confirming the diagnosis was made by a responsible physician and is common in local practice. Diagnosis of DVT was confirmed venographically in all cases using the method of Rabinov and Paulin and employing a low osmolarity non-ionic contrast medium. UFH i.v. was continued for a maximum of 24 h before randomisation. In patients assigned to receive LMWH, infusion of UFH was stopped and simultaneously an injection of LMWH, 200 IU/kg, was given s.c. with a daily maximum single dose of 18,000 IU. Warfarin sodium was initiated with a dose of 10-15 mg on the day that venography was carried out. It was continued for a minimum of 3 months with the dose titrated against prothrombin time (PT) such that the International Normalised Ratio (INR) was maintained between 2.0 and 3.0. Treatment with LMWH was stopped when the PT was within the defined therapeutic range of 15-25% (INR 2.0-3.0) for 2 consecutive days. All patients received LMWH for at least 5 days, but for no longer than 9 days. • UFH + VKA *Once DVT was suspected an initial i. v. bolus injection of UFH 5000 IU, followed by a continuous i.v. infusion of UFH, 800-1700 IU/h, could be given to achieve adequate anticoagulation without delay and prevent PE. The decision to start UFH treatment before confirming the diagnosis was made by a responsible physician and is common in local practice. Diagnosis of DVT was confirmed venographically in all cases using the method of Rabinov and Paulin and employing a low osmolarity non-ionic contrast medium. UFH i.v. was continued*	

Author (year)	Title	Study details	Quality assessment
		for a maximum of 24 h before randomisation. All patients randomised to i.v. UFH treatment continued with infusion without interruption. The UFH dose was adjusted to maintain the activated partial thromboplastin time (APTT) between 1.5 and 3.0 times the upper limit of the reference value at each centre. Warfarin sodium was initiated with a dose of 10-15 mg on the day that venography was carried out. It was continued for a minimum of 3 months with the dose titrated against prothrombin time (PT) such that the International Normalised Ratio (INR) was maintained between 2.0 and 3.0. Treatment with UFH was stopped when the PT was within the defined therapeutic range of 15-25% (INR 2.0-3.0) for 2 consecutive days. All patients received UFH for at least 5 days, but for no longer than 9 days. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	
Lopaciuk (1992)	Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep	**Study type** • Randomised controlled trial	**Random sequence generation** • High risk of bias *Method of randomisation not provided*

Author (year)	Title	Study details	Quality assessment
	vein thrombosis: a Polish multicentre trial.	**Study details** • Study location *Poland* • Study setting *Hospital* • Study dates *February 1989 to December 1990* • Duration of follow-up *3 months* • Sources of funding *Not stated* **Inclusion criteria** • DVT *Phlebographically proven DVT (proximal or calf) duration of symptoms not longer than 10 days.* **Exclusion criteria** • Symptoms of PE • Contraindication(s) for study drugs • Pregnancy • Treatment with IV heparin • Phlegmasia cerulea dolens • Treatment with oral anticoagulants	**Allocation concealment** • High risk of bias *No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *No blinding* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Antithrombin III therapy **Sample characteristics** • Sample size *149 people* • Split between study groups *LMWH = 74; UFH = 72* • Loss to follow-up *3 people* • %female *LMWH = 47.3%; UFH = 41.6%* • Mean age (SD) *LMWH = 49.1 years (15.4); UFH = 47.8 years (15.4)* • Previous VTE *LMWH = 18.9%; UFH = 14.7%* **Interventions** • LMWH + VKA + compression stockings *Patients in the LMWH group were given subcutaneous injections of this drug in a fixed dose of 225 anti-Xa Institute Choay units/kg (92 anti-Xa IU/kg) every 12 h. The dose was not changed during the treatment period, regardless of possible changes observed in the activated partial thromboplastin time (APTT). The treatment with LMWH lasted 10 days. Oral anticoagulation with acenocoumarol was introduced on the 7th day of heparin administration and continued for at least 3*	**Overall risk of bias** • Moderate *The study was open label and therefore unblinded. The methodology for randomization was not given and it was unlikely that allocation was concealed from investigators.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		months in both groups. The dose of acenocoumarol was adjusted using the prothrombin time to maintain the international normalized ratio (INR) between 2.0 and 3.0. Whenever possible, patients were allowed to walk on the third day of heparin treatment, wearing elastic support. • UFH + VKA + compression stockings *In the UFH group the treatment was initiated by an intravenous bolus dose of 5,000 IU of UFH. The drug was then administered by subcutaneous injection every 12 h; for the first 2 or 3 injections the dose was calculated as 250 IU/kg each 12 h, the subsequent dosage was adjusted daily to maintain the APTT between 1.5 and 2.5 times the patient's basal value. The bolus injection appeared necessary in this group since two studies reported an inadequate early response (as measured by the APTT) in patients treated with subcutaneous UFH. The treatment with UFH lasted 10 days. Oral anticoagulation with acenocoumarol was introduced on the 7th day of heparin administration and continued for at least 3 months in both groups. The dose of acenocoumarol was adjusted using the prothrombin time to maintain the international normalized ratio (INR) between 2.0 and 3.0. Whenever possible, patients were allowed to walk on the third day of heparin treatment, wearing elastic support.* **Outcomes** • All-cause mortality • VTE-related mortality	

Author (year)	Title	Study details	Quality assessment
		• Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence	
Luomanmaki (1996)	A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *Sweden, Finland and USA* • Study setting *Hospitals* • Study dates *Not mentioned* • Duration of follow-up *6 months* • Sources of funding *Not reported. Pharmacia employee on author list.* **Inclusion criteria** • DVT *Suspected or confirmed DVT, with venography confirmed within 24 hours of randomisation or after randomisation.* • >20 years old	**Random sequence generation** • Low risk of bias *Randomisation was conducted separately at each participating centre using an SAS (Statistical Analysis System) program written for the purpose.* **Allocation concealment** • High risk of bias *No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *No blinding*

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Contraindication(s) for study drugs • Platelet count of <100,000 per cubic mm • Pregnancy • Haemorrhagic stroke *Within the last 2 months* • Gastrointestinal bleeding *Within the last 2 weeks* • Uncontrolled hypertension • Breast-feeding • Renal insufficiency • Hepatic insufficiency • Surgery <5 days before • Confirmed PE • Recent DVT • Sequelae of previous DVT in the same leg • Heparin treatment during the last 24 hours **Sample characteristics** • Sample size *330 people* • Split between study groups *LMWH = 163; UFH = 167* • Loss to follow-up *LMWH = 40/163 because DVT unconfirmed with venography, 6 withdrawn prior to therapy; UFH = 32/163 because DVT unconfirmed with venography, 4 withdrawn prior to therapy*	**Incomplete outcome data** • High risk of bias *High risk of attrition bias: DVT: 72/300 (24%) patients excluded after randomisation because DVT unconfirmed by venography – data about these patients not reported. Another 10/300 (3.3%) patients excluded after randomisation for other reasons.* **Selective reporting** • Low risk of bias **Other sources of bias** • High risk of bias *Details of oral anticoagulation therapy not specified, length determined by individual physicians.* **Overall risk of bias** • Moderate *Study was open label and therefore unblinded. It was also unlikely that allocation was concealed from*

Author (year)	Title	Study details	Quality assessment
		• %female *LMWH = 52.1% ; UFH = 47.3%* • Mean age (SD) *LMWH = 57.5 years (21-92); UFH = 60.5 years (22-93)* **Interventions** • LMWH + VKA *In patients randomized to LMWH before venography, treatment began with a single subcutaneous injection of 5000 IU LMWH. Patients in whom the diagnosis of DVT was subsequently confirmed by venography were eligible to continue in the study provided that the thrombus had not extended to the inguinal ligament. The first full dose of LMWH at a fixed subcutaneous dose of 200 IU/kg was administered at least 4 h after the initial bolus of 5000 IU. In patients randomised after venography, treatment with full-dose LMWH (200 U/kg) was started immediately. In all patients, oral anticoagulant (OAC) therapy was started on the same day as, or first day after, the initial venography. The length of OAC treatment was decided by the responsible physician. LMWH therapy continued for between 5 and 10 days, and was stopped when the result of the OAC test was within the therapeutic range.* • UFH + VKA *Patients randomized to UFH treatment prior to venography received an intravenous bolus injection of 5000 IU UFH. Continuous intravenous infusion of UFH (20000±40000 IU/24 hours, dose adjusted to maintain an activated partial*	*investigators. High risk of attrition bias* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		thromboplastin time (APTT) between 1.5 and 3 times the upper reference value at each centre) was started when the DVT diagnosis had been verified by venography or earlier if considered necessary. In patients randomized after venography, treatment with UFH (20000±40000 IU/24 hours), was started immediately. Patients randomized to UFH were permitted to receive an initial intravenous bolus dose of UFH of 5000 IU. In all patients, oral anticoagulant (OAC) therapy was started on the same day as, or first day after, the initial venography. The length of OAC treatment was decided by the responsible physician. UFH therapy continued for between 5 and 10 days, and was stopped when the result of the OAC test was within the therapeutic range. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	
Merli (2001)	Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease.	**Study type** • Randomised controlled trial	**Random sequence generation** • Low risk of bias *Randomisation was done without stratification in blocks of six, according to*

Author (year)	Title	Study details	Quality assessment
		Study details • Study location *Australia, Austria, Belgium, Denmark, France, Hungary, Ireland, Israel, Italy, The Netherlands, Norway, Poland, Spain, Sweden, United Kingdom and United States.* • Study setting *Hospitals* • Study dates *Not provided* • Duration of follow-up *3 months* • Sources of funding *Aventis Pharma* **Inclusion criteria** • ≥18 years • DVT *Symptomatic lower-extremity DVT confirmed by venography or ultrasonography (if venography was inconclusive)* • PE *Symptomatic PE confirmed by high-probability ventilation–perfusion scanning, or positive pulmonary angiography with confirmation of lower extremity DVT* **Exclusion criteria** • At risk of bleeding	*ascending randomisation number.* **Allocation concealment** • High risk of bias *The UFH group was not blinded* **Blinding of participants and personnel** • High risk of bias *The UFH group was not blinded* **Blinding of outcome assessment** • Low risk of bias *Observers who were aware of treatment assignment assessed patients daily and monthly during the 3-month follow-up for worsening or recurrence of deep venous thrombosis or pulmonary embolism, haemorrhage, adverse events, changes in concomitant medications and adequacy of warfarin use, and warfarin adherence.*

Author (year)	Title	Study details	Quality assessment
		• Vena cava filter fitted • Contraindication(s) for study drugs • Active bleeding • Pregnancy • Gastrointestinal bleeding • >24 hours of anticoagulants • Breast-feeding • Likelihood of non-adherence to treatment • Renal insufficiency • Hepatic insufficiency **Sample characteristics** • Sample size *900 people* • Split between study groups *UFH = 290; once-daily LMWH = 298; twice-daily LMWH = 312* • Loss to follow-up *UFH = 66; once-daily LMWH = 34; twice-daily LMWH = 36* • %female *UFH = 48%; once-daily LMWH = 46%; twice-daily LMWH = 42%* • Mean age (SD) *UFH = 60.9 years (18.0-91.0); once-daily LMWH = 60.7 years (19.0-91.0); twice-daily LMWH = 60.7 years (18.0-92.0)* • Previous VTE *UFH = 26.6%; once-daily LMWH = 22.1%; twice-daily LMWH =*	**Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		23.7% **Interventions** • UFH + VKA *Patients assigned to the nonblinded unfractionated heparin group received an intravenous bolus dose and infusion on the basis of an approved institution-specific nomogram. In most cases, administration was as follows: Six hours after the initial bolus, the activated partial thromboplastin time was measured and the dose was adjusted to maintain the specified value, which was between 55 and 80 seconds in most centres. Activated partial thromboplastin time was measured at least daily during unfractionated heparin treatment. Treatment was continued for at least 5 days, and warfarin was started within 72 hours of initial study drug administration. Some patients received phenprocoumon in place of warfarin sodium. Prothrombin time was measured daily, and patients could be discharged from the hospital after the international normalized ratio was found to be between 2.0 and 3.0 on 2 consecutive days. Oral anticoagulation was continued for at least 3 months.* • Once-daily LMWH + VKA *Patients assigned to LMWH received a weight-adjusted subcutaneous dose. This group had 1.5 mg/kg once daily. A total of three injections, study drug and placebo, were given each day to maintain blinding for volume of solutions and frequency of administration. Treatment was continued for at least 5 days, and warfarin was started within 72 hours of initial*	

Author (year)	Title	Study details	Quality assessment
		study drug administration. Some patients received phenprocoumon in place of warfarin sodium. Prothrombin time was measured daily, and patients could be discharged from the hospital after the international normalized ratio was found to be between 2.0 and 3.0 on 2 consecutive days. Oral anticoagulation was continued for at least 3 months. • Twice-daily LMWH + VKA *Patients assigned to LMWH received a weight-adjusted subcutaneous dose. This group had 1.0 mg/kg of body weight twice daily. A total of three injections, study drug and placebo, were given each day to maintain blinding for volume of solutions and frequency of administration. Treatment was continued for at least 5 days, and warfarin was started within 72 hours of initial study drug administration. Some patients received phenprocoumon in place of warfarin sodium. Prothrombin time was measured daily, and patients could be discharged from the hospital after the international normalized ratio was found to be between 2.0 and 3.0 on 2 consecutive days. Oral anticoagulation was continued for at least 3 months.* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence	

Author (year)	Title	Study details	Quality assessment
		• Serious adverse events	
Meyer (1995)	Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study.	**Study type** • Randomised controlled trial **Study details** • Study location *France* • Study setting *Hospital* • Study dates *Not provided* • Duration of follow-up *3 months* • Sources of funding *Pharmacia (manufacturer of LMWH)* **Inclusion criteria** • ≥18 years • PE *Onset of last symptoms suggestive of acute PE within the 5 preceding days. PE confirmed before randomisation, or within 24 hours of study treatment using pulmonary angiography.*	**Random sequence generation** • High risk of bias *Randomisation using sealed envelopes has a high risk of bias. This method is no longer used because healthcare professionals could hold the envelope up to a light and read the contents.* **Allocation concealment** • High risk of bias *No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *No blinding of the outcomes of interest*

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • <45 kg body weight • Contraindication(s) for study drugs • Other *Planned hospital stay <10 days. Pre-existing significant cardiorespiratory disease. Known proliferative diabetic retinopathy. Oral anticoagulant therapy within 5 days.* • Platelet count of <100,000 per cubic mm • High risk of bleeding • Pregnancy • Haemorrhagic stroke *Within the last 3 months* • Gastrointestinal bleeding • Familial bleeding diathesis • Breast-feeding • Renal insufficiency • Hepatic insufficiency • Ischaemic CVA one month prior to enrolment • Surgery <5 days before • Heparin treatment during the last 24 hours • >90 kg body weight • PE ruled out by angiography or Miller index >20/34 **Sample characteristics** • Sample size *60 people* • Split between study groups	**Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Open-label study and therefore unblinded. Randomization techniques are no longer used and it was unlikely that allocation was effectively concealed from investigators.* Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed.

Author (year)	Title	Study details	Quality assessment
		LMWH = 29; UFH = 31 • Loss to follow-up *5 people* • %female *LMWH = 69%; UFH = 45%* • Mean age (SD) *LMWH = 60 years (26-84); UFH = 61 years (20-88)* • Previous VTE *LMWH = 30%; UFH = 30%* **Interventions** • LMWH + VKA *The patients of the LMWH group were treated during 10 days with a fixed dosage of 120 anti-Xa IU/kg administered subcutaneously twice daily and without any laboratory adjustment during the treatment period. In both groups, oral anticoagulant therapy with Acenocoumarol was started on day 7 and heparin was maintained for at least 3 or 4 days until the INR. had stabilized between 2 to 3. Oral anticoagulant therapy was then continued for at least 3 months.* • UFH + VKA *The patients of the UFH group received heparin during 10 days as a continuous intravenous infusion, at an initial dosage of 500 IU/kg/24 h. Heparin dosage was subsequently adjusted daily to maintain APTT between 2-3 times the control value. In both groups, oral anticoagulant therapy with Acenocoumarol was started on day 7 and heparin was maintained for at least 3 or 4*	**Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		days until the INR. had stabilized between 2 to 3. Oral anticoagulant therapy was then continued for at least 3 months. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	
Nakamura (2015)	Apixaban for the Treatment of Japanese Subjects With Acute Venous Thromboembolism (AMPLIFY-J Study).[Erratum appears in Circ J. 2015;79(11):2520; PMID: 26497167]	**Study type** • Randomised controlled trial **Study details** • Study location *Japan* • Study setting *21 sites* • Duration of follow-up *5.5 months treatment period with a 30 day follow-up period* • Sources of funding *Study was funded by Pfizer and Bristol-Myers Squibb. Main author also received remuneration from Daiichi Sankyo and*	**Random sequence generation** • High risk of bias *Likely randomized however randomization method not given* **Allocation concealment** • Unclear risk of bias *unclear whether allocation was concealed from investigators* **Blinding of participants and personnel** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		Bayer, with research funds also received from the former. **Inclusion criteria** • Objectively confirmed symptomatic DVT or PE *Proximal DVT only, or PE* • >20 years old • Japanese **Exclusion criteria** • Thrombectomy or embolectomy • Fibrinolytic agent administered for treatment of current episode • Contraindication(s) for study drugs • Active bleeding *or at high risk of bleeding* • Other *>2 doses of fondaparinux, continuous UFH infusion of >36h, and >2 doses of oral vitamin K antagonist before first administration of the study drug; Haemoglobin <9g/dl; creatinine clearance <25ml/min* • Other indication requiring long-term anticoagulation *or dual antiplatelet therapy, or treatment with aspirin >165mg daily.* • Platelet count of <100,000 per cubic mm	*study was open label* **Blinding of outcome assessment** • Low risk of bias *All endpoints were adjudicated by a blinded committee* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Randomization methodology not given, unclear whether allocation was concealed. Physicians and personnel were unblinded*

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size *80 participants* • Split between study groups *40 apixaban (40 analysed); 40 UFH//warfarin (39 analysed)* • Loss to follow-up *1 participants did not receive treatment and was not analysed* *15 participants ended treatment early but were analysed* • %female *51.3% female* • Mean age (SD) *65.2 (SD 15.64) years* • PE/DVT split (for VTE only studies) *56.3% DVT; 43.8% PE* • Previous VTE *12.5% previous DVT* **Interventions** • Apixaban *10mg (twice daily) for 7 days, 5mg twice daily for 23 weeks* • UFH + VKA *continuous IV infusion of UFH as to maintain activated partial thromboplastin time in range 1.5-2.5-fold control value. Warfarin administered concomitantly, adjusted to maintain INR of 1.5-2.5.*	Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Outcomes • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	
Ninet (1991)	A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study.	**Study type** • Randomised controlled trial **Study details** • Study location *France* • Study setting *Hospitals* • Study dates *Not provided* • Duration of follow-up *12 weeks* • Sources of funding *Fraxiparine (LMWH) and UFH supplied by Sanofi* **Inclusion criteria** • DVT *Recent (< 5 days) proximal (above the origin of the popliteal*	**Random sequence generation** • Low risk of bias **Allocation concealment** • High risk of bias *No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label* **Blinding of outcome assessment** • High risk of bias *The outcomes of interest were not blinded*

Author (year)	Title	Study details	Quality assessment
		vein) DVT confirmed by bilateral venography **Exclusion criteria** • Other *Thrombosis affecting inferior vena cava* • Contraindication(s) for study drugs • Other *Pulmonary vascular obstruction 30% or more (lung scan). Thrombosis affecting inferior vena cava. Recent history (< 2 years) of cerebrovascular accident or thromboembolic episode.* • Platelet count of <100,000 per cubic mm • High risk of bleeding • Pregnancy • Recent surgery • >24 hours of heparin treatment • Treatment with oral anticoagulants **Sample characteristics** • Sample size *166 patients* • Split between study groups *LMWH = 85; UFH = 81* • Loss to follow-up *LMWH = 7; UFH = 6* • %female *Not mentioned*	**Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • High risk of bias *Use of VKA or heparin after the interventions was at the physicians' discretion. Reasons for no follow up in 13 patients not mentioned.* **Overall risk of bias** • Moderate *Study was unblinded and allocation concealment was unlikely. Additionally, reasons for lack of follow up in 13 patients was not mentioned.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) *Male/female: LMWH = 64.9 years (22)/61.9 years (3.1); UFH = 57.9 years (6)/64.9 years (3.1)* • Previous VTE *LMWH = 21.2%; UFH = 21%* **Interventions** • LMWH + VKA *In the LMWH group the dosage was 255 IC AXa u/kg 12 hourly. In practice, patients weighing less than 55 kg were given 0.5 ml (12,500 IC AXa u) per injection, patients weighing between 55 kg and 80 kg were given 0.6 ml (L5,000 IC AXa u), and patients weighing over 80 kg were given 0.7 ml (17,500 IC AXa u). The duration of the treatment was 10 days, and the doses of LMWH were not altered. After Day 10, each centre continued its usual anticoagulant regimen, either by subcutaneous heparin at adjusted doses or by oral anticoagulants.* • UFH + VKA *In the UFH group heparin was administered by continuous intravenous infusion at an initial dosage of.20 IU/kg/hour, and adjusted as required so as to keep the coagulation times, activated partial thromboplastin time (APTT) and/or calcium clotting time (CCT), between 1,.5 and 2.0 times the control time. After Day 10, each centre continued its usual anticoagulant regimen, either by subcutaneous heparin at adjusted doses or*	majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		by oral anticoagulants. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	
Piazza (2016)	Magnetic resonance venography to assess thrombus resolution with edoxaban monotherapy versus parenteral anticoagulation/warfarin for symptomatic deep vein thrombosis: A multicentre feasibility study	**Study type** • Randomised controlled trial **Study details** • Study location *USA* • Study setting *26 sites* • Study dates *September 2012 to January 2014* • Duration of follow-up *Followed up for days of treatment, with two MRV examinations (one at 36 hours following randomization and the other between 14 and 21 days following randomization).* • Sources of funding	**Random sequence generation** • High risk of bias *Unclear methodology for randomization* **Allocation concealment** • Unclear risk of bias *unclear whether allocation was concealed* **Blinding of participants and personnel** • High risk of bias *Open-label study* **Blinding of outcome assessment** • Low risk of bias *Suspected outcome events were assessed*

Author (year)	Title	Study details	Quality assessment
		Funded by Daiichi Sankyo	*by a blind review board*
		Inclusion criteria • DVT *DVT requiring one of following: Non-compressible vein on ultrasonography, intraluminal filling defect on contrast venography or intraluminal filling defect on contrast-enhanced CT*	**Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias
		Exclusion criteria • received therapeutic doses of any heparin for >48 hours, prior randomization *or received one dose of VKA* • PE	**Other sources of bias** • High risk of bias *Unclear how many participant in the Warfarin arm received UFH as opposed to LMWH, with the former being less commonly used in clinical practice.*
		Sample characteristics • Sample size *94 participants enrolled, 85 analysed* • Split between study groups *56 Edoxaban; 29 heparin + placebo* • Loss to follow-up *1 participants in heparin arm did not receive treatment. 12 participants (6 in each arm) did not complete treatment however were included in analysis.* • %female	**Overall risk of bias** • High *Physicians and participants were unblinded, unclear how many participant in the Warfarin arm received UFH as opposed to LMWH. Unclear methodology for randomization and allocation*

Author (year)	Title	Study details	Quality assessment
		Edoxaban arm: 26.8% female; VKA arm: 25% female • Mean age (SD) *Edoxaban arm: 55.6 (SD14.1) years; VKA arm: 53.1 (SD12.0) years* • Provoked vs. unprovoked *52% unprovoked in Edoxaban arm; 64% unprovoked VKA arm* **Interventions** • LMWH + VKA *Participants received heparin (UFH or LMWH) for at least 5 days and then received Warfarin maintained at an INR of 2.0 to 3.0 for 30 days* • Edoxaban without parenteral AC *Taken at a dose of 90mg (once daily) for 10 days (+/- 2 days) followed by 60 mg (on daily daily) Physicians had the option to give patients deemed to have insufficient creatinine clearance/ body weight the following dose: 45mg (once daily) for 10 days (+/- 2 days) followed by 30 mg (on daily daily)* **Outcomes** • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding	*concealment* **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
Prandoni (1992)	Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *Italy* • Study setting *Single site* • Study dates *May 1986 - April 1991* • Duration of follow-up *Clinical follow-up made at 1, 3 and 6 months using venograms* • Sources of funding *none reported* **Inclusion criteria** • DVT *Clinically suspected DVT to be confirmed as proximal DVT using contrast venography* **Exclusion criteria** • Contraindication(s) for study drugs *or allergy to contrast material* • Other *ongoing anticoagulant treatment at time of referral*	**Random sequence generation** • Low risk of bias *participants were randomized however randomization methodology not given.* **Allocation concealment** • Unclear risk of bias *randomization methodology not given, unclear whether allocation was concealed.* **Blinding of participants and personnel** • High risk of bias *Blinding methodology not given, unlikely to have been blinded.* **Blinding of outcome assessment** • Low risk of bias *outcomes reviewed by a blinded central committee* **Incomplete outcome data** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• Pregnancy • PE *Clinically suspected PE at referral.* • Previous VTE (prior to index VTE) *prior VTE in same leg within 2 previous years.* **Sample characteristics** • Sample size *175 participants; 170 received treatment* • Split between study groups *85 UFH; 85 LMWH* • %female *38.8% female* • Mean age (SD) *50.6% aged over 65 years. mean age not given.* • Previous VTE *14.7% previous VTE* **Interventions** • LMWH + VKA *Subcutaneous LMWH injections every 12 hours, consisting of 0.5ml for patients <55 kg, 0.6ml for those weighing 55-80kg, and 0.7ml for those >80kg. oral coumarin treatment (initial dose 5mg) started on day 7 of heparin treatment and adjusted to a target INR of 2.0-3.0.* • UFH + VKA	**Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Given intravenous bolus of 100 units/kg UFH followed by a continuous infusion of 35, 000 units per 24 hours. APTT was measures 6 hours after start of treatment and then once per day to maintain a target APTT of 1.5-2.0 times pre-treatment value. oral coumarin treatment (initial dose 5mg) started on day 7 of heparin treatment and adjusted to a target INR of 2.0-3.0. **Outcomes** • All-cause mortality • VTE-related mortality *Symptomatic DVT confirmed using venography or PE diagnosed by perfusion lung scan based on the presence of at least one segmental defect not seen on preceding scan.* • Clinically relevant non-major bleeding *minor bleeding: Defined as clinically overt but not meeting criteria for major bleeding.* • Major bleeding *severe bleeding: fall in haemoglobin concentration of at least 2 g/dl, if it was retroperitoneal or intracranial or if transfusion of 2 or more units of blood was needed.* • VTE-recurrence	
Prandoni (2004)	Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism.	**Study type** • Randomised controlled trial	**Random sequence generation** • Low risk of bias *Randomisation to UFH or LMWH treatment (stratified according to whether the patients presented with DVT only or with PE, and*

Author (year)	Title	Study details	Quality assessment
		Study details • Study location *Italy* • Study setting *Hospitals* • Study dates *October 1998 to April 2001* • Duration of follow-up *12 weeks* • Sources of funding *Grant from Gentium SpA, Como, Italy* **Inclusion criteria** • ≥18 years • DVT *Ascending phlebography, compression ultrasound of the proximal vein system, echo colour Doppler scan of the calf vein system in the case of clinical suspicion of DVT.* • PE *Ventilation-perfusion scanning, spiral computed tomographic scanning, and pulmonary angiography in the case of clinical suspicion of PE. In the presence of abnormal results of an ultrasound test of the lower extremities, the diagnosis of PE was also accepted if a perfusion lung scan was compatible with a high probability of PE when compared with the chest x-ray.*	*also stratified according to clinical centre) was performed with a computer algorithm and the use of a 24-hour telephone service that recorded patient information before disclosure of the treatment assigned.* **Allocation concealment** • High risk of bias *Open label study* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *No blinding* **Incomplete outcome data** • Unclear risk of bias *Deaths due to fatal bleeding not clearly reported.*

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Contraindication(s) for study drugs • Hemodynamic instability • Pregnancy • Previous VTE (prior to index VTE) *Less than 1 year earlier* • >24 hours of anticoagulants • Short life expectancy *<3 months* • Likelihood of non-adherence to treatment **Sample characteristics** • Sample size *720 people* • Split between study groups *LMWH = 360; UFH = 360* • Loss to follow-up *None* • %female *LMWH = 53.6%; UFH = 56.1%* • Mean age (SD) *LMWH = 67 years (14.8); UFH = 65.7 years (15.6)* • PE/DVT split (for VTE only studies) *DVT/PE: LMWH = 83.3%/16.7%; UFH = 83.6%/16.4%*	**Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Study was open label and therefore unblinded with allocation concealment unlikely. Deaths due to fatal bleeding were not clearly reported.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Interventions • LMWH + VKA *Patients randomized to LMWH received subcutaneous administration of LMWH, 85 U/kg twice daily. Oral anticoagulant treatment with warfarin sodium was started within the first 2 days and continued for a total of 12 weeks. During initial combined heparin and warfarin treatment, in both patient groups, prothrombin time was measured at least every other day, with the dose adjusted to achieve an international normalized ratio (INR) of 2.0 to 3.0, by adopting an identical approach. Heparin was discontinued when the INR was greater than 2.0 for 2 consecutive days and the patients had received the study drug for at least 5 days.* • UFH + VKA *Patients randomized to UFH were administered an intravenous bolus of heparin sodium and a subcutaneous injection of heparin calcium in doses adjusted to body weight (4000 U intravenously plus 12500 U subcutaneously in patients weighing less than 50 kg; 5000 U plus 15000 U, respectively, in those weighing 50 to 70 kg; and 6000 U plus 17500 U, respectively, in patients weighing more than 70 kg). The first APTT was measured after 6 hours, and subsequent dose adjustments during the first 48 hours were scheduled twice daily, with the APTT performed in the mid-interval. They were arranged in "steps" to be taken up or down according to APTT values, irrespective of body weight. The targeted APTT range (50-90 seconds) was calibrated to correspond to a plasma heparin level, as expressed by aXa activity, of 0.35 to 0.70 U/mL. After*	

Author (year)	Title	Study details	Quality assessment
		the first 48 hours, UFH administration was managed on the basis of daily APTT determinations. Oral anticoagulant treatment with warfarin sodium was started within the first 2 days and continued for a total of 12 weeks. During initial combined heparin and warfarin treatment, in both patient groups, prothrombin time was measured at least every other day, with the dose adjusted to achieve an international normalized ratio (INR) of 2.0 to 3.0, by adopting an identical approach. Heparin was discontinued when the INR was greater than 2.0 for 2 consecutive days and the patients had received the study drug for at least 5 days. **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Serious adverse events	
Ramacciotti (2004)	An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *Brazil*	**Random sequence generation** • High risk of bias *Method not provided* **Allocation concealment** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		• Study setting *Hospitals* • Study dates *Not mentioned* • Duration of follow-up *6 months* • Sources of funding *One of the authors is from Aventis Pharma, Bridgewater, USA* **Inclusion criteria** • ≥18 years • DVT *DVT symptoms ≤10 days. Proximal lower limb DVT.* **Exclusion criteria** • Symptoms of PE • Other *Weight <50 kg and >100 kg. Bilateral DVT. Surgery in the last 7 days* • Thrombectomy or embolectomy • Contraindication(s) for study drugs • Platelet count of <100,000 per cubic mm • Pregnancy • Familial bleeding diathesis • Uncontrolled hypertension • Short life expectancy	*No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label* **Blinding of outcome assessment** • High risk of bias *No blinding* **Incomplete outcome data** • High risk of bias *Mortality data not reported* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • High

Author (year)	Title	Study details	Quality assessment
		<6 months • Likelihood of non-adherence to treatment • Renal insufficiency • Hepatic insufficiency **Sample characteristics** • Sample size *201 people* • Split between study groups *LMWH = 104; UFH = 97* • Loss to follow-up *14.9% at 3 months* • %female *LMWH = 67%; UFH = 64%* • Mean age (SD) *LMWH = 46 years (19); UFH = 44 years (18)* **Interventions** • LMWH + VKA *LMWH (1.5 mg/kg OD s.c. for 5-10 days). All patients received warfarin (with a targeted INR 2-3) for at least 3 months, starting at day 1 or 2 of treatment.* • UFH + VKA *UFH (5000 IU i.v. bolus + i.v. 500 IU/kg/day adjusted to maintain an aPTT of 1.5--2.5 times the normal value for 5-10 days). All patients received warfarin (with a targeted INR 2-3) for at least 3*	*Open label study with methodology for randomization not provided and allocation unlikely to have been concealed from investigators. Mortality data was not reported.* **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		months, starting at day 1 or 2 of treatment. **Outcomes** • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence	
Schulman (2009) and (2014) RE-COVER I and II trials	Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis	**Study type** • Randomised controlled trial **Study details** • Study location *31 countries* • Study setting *RE-COVER: 208 sites across 31 countries RE-COVER II: 228 sites across 29 countries* • Study dates *RE-COVER I: April 2006 - November 2008 RE-COVER II: June 2008 - October 2010* • Duration of follow-up *Patients were assessed at 7 days and then monthly until 6 months and were told to contact their study site immediately if symptoms developed that were suggestive of venous thromboembolism or bleeding. An additional follow-up visit was scheduled for 30 days after completion of the study, unless the patient had discontinued the study drug before 6 months, had*	**Random sequence generation** • Low risk of bias *Randomized using an interactive voice-response system and a computer generate randomized scheme in blocks of 4* **Allocation concealment** • Unclear risk of bias *Unclear whether allocation was concealed* **Blinding of participants and personnel** • Low risk of bias *double-blinded* **Blinding of outcome assessment** • Low risk of bias *Suspected events were rated by a blinded*

Author (year)	Title	Study details	Quality assessment
		started open-label anticoagulant therapy, or had been enrolled in another trial. • Sources of funding *Both studies were funded and designed by Boehringer Ingelheim and the steering committee* • Associated studies *Schulman 2009: Data for RECOVER I Schulman 2015: Cancer subgroup analysis* **Inclusion criteria** • ≥18 years • Objectively confirmed symptomatic DVT or PE *diagnosis confirmed prior to randomisation* • 6 months of anticoagulation deemed appropriate **Exclusion criteria** • Life expectancy <6 months • Contraindication(s) for study drugs *or to radiographic contrast material* • Other indication for VKA • Creatine clearance <30ml/min • Baseline aminotransferase level >2x ULN *RE-COVER I study only* • Baseline aminotransferase levels >3x ULN *RE-COVER II study only* • Duration of symptoms >14 days	*committee* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Low *Low risk of bias although data is not segmentable by PE/DVT index event which limits interpretability of index event-specific effects* **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Hemodynamic instability *If presenting with PE* • Requiring thrombolysis *If presenting with PE* • Recent unstable CVD • High risk of bleeding • Pregnancy *or risk of becoming pregnant* • requirement for long term antiplatelet therapy **Sample characteristics** • Sample size *RE-COVER: 2564 RE-COVER II: 2589* • Split between study groups *RE-COVER: Dabigatran 1273; placebo 1266 RE-COVER II: Dabigatran 1280; placebo 1288* • %female *RE-COVER: 42% RE-COVER II: 39%* • Mean age (SD) *RE-COVER I: Dabigatran arm 55.0 (SD 15.8) years; placebo arm 54.4 (SD 16.2) years. RE-COVER II: Dabigatran 54.7 (SD16.2) years; placebo arm 55.1 (SD 16.3) years.* • PE/DVT split (for VTE only studies) *RE-COVER I: 69% DVT only, 21% PE only, 10% both, <1% neither. RE-COVER II: 68% DVT only, 23% PE only, 9% both, <1% neither.* • Previous VTE	

Author (year)	Title	Study details	Quality assessment
		RE-COVER I: 25.6% RE-COVER II: 17.5% **Interventions** • LMWH + VKA *Participants were given warfarin adjusted to achieve 2.0 - 3.0 INR and a Dabigatran-like placebo. Participants in this group received a parenteral anticoagulant (UFH or LMWH), typically beginning before randomization. On day of randomization Warfarin was given for at least 5 days and until the INR had been 2.0 or greater for at least 2 consecutive days, at which point parenteral AC was stopped Dabigatran-like placebo was administered. Study drugs were given for 6 months from randomization. RE-COVER I: only 11.3% of Dabigatran arm and 13.0% of warfarin arm received UFH RE-COVER II: only 15.5% of Dabigatran arm and 16.1% of warfarin arm received UFH* • Dabigatran plus parenteral AC *150mg (twice daily) with a warfarin-like placebo. Participants in this group received a parenteral anticoagulant that consisted of either UFH or LMWH, typically beginning before randomization. On day of randomization placebo was given along with a sham INR test. Dabigatran was administered at least 5 days following administration of placebo, at which point administration of parenteral AC was stopped. Study drugs were given for 6 months from randomization.*	

Author (year)	Title	Study details	Quality assessment
		Outcomes • All-cause mortality *Not extractable for PE and DVT patients separately* • VTE-related mortality *Not extractable for PE and DVT patients separately* • Clinically relevant non-major bleeding *Not extractable for PE and DVT patients separately* • Major bleeding *Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the haemoglobin level of at least 20 g per litre, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal.* • VTE-recurrence *Not extractable for PE and DVT patients separately* • Serious adverse events *Not extractable for PE and DVT patients separately*	
Simonneau (1993)	Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis.	**Study type** • Randomised controlled trial **Study details** • Study location *France and Belgium* • Study setting *Hospitals* • Study dates *October 1988 to March 1990*	**Random sequence generation** • High risk of bias *Randomisation involved sealed envelopes. This method is no longer used because healthcare professionals could put the envelopes up to a light and read the contents.* **Allocation concealment** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		• Duration of follow-up *3 months* • Sources of funding *Pharmuka lab (supplier of LMWH)* **Inclusion criteria** • ≥18 years • DVT *Proximal DVT (popliteal or more proximal veins). Symptoms less than 5 days.* **Exclusion criteria** • Symptoms of PE *Suspected acute pulmonary embolism which requires thrombolytic therapy or surgery (indicated in shock or left ventricular failure)* • Other *Received more than 25000IU heparin within the last 24 hours before referral. Surgery within the last 7 days. Treatment with sulfinpyrazone, ticlopidine or NSAID within the past 7 days.* • Contraindication(s) for study drugs • Active bleeding **Sample characteristics** • Sample size	*Randomisation involved sealed envelopes. This method is no longer used because healthcare professionals could put the envelopes up to a light and read the contents.* **Blinding of participants and personnel** • High risk of bias *Open label* **Blinding of outcome assessment** • High risk of bias *No blinding* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		134 people • Split between study groups *LMWH = 67; UFH = 67* • Loss to follow-up *None* • %female *LMWH = 43%; UFH = 48%* • Mean age (SD) *LMWH = 61 years (20); UFH = 64 years (17)* • Previous VTE *LMWH = 13%; UFH = 12%* **Interventions** • LMWH + VKA *LMWH Dose: 1.0mg/kg twice daily Route: subcutaneous injection Duration: 10 days Oral anticoagulation started on day 10 and continued for at least 3 months. INR adjusted to between 2.0-3.0* • UFH + VKA *unfractionated heparin sodium of porcine origin Dose: Initial dose of 500IU/kg/24 hours, adjusted to 1.5x to 2.5x APTT (measured 6 hours after start of treatment, then once daily) Route: continuous IV infusion Duration: 10 days Oral anticoagulation started on day 10 and continued for at least 3 months. INR adjusted to between 2.0-3.0*	**Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Study was unblinded and the randomization techniques used are outdated and no longer used due to the potential for the investigators to find out the allocation.* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Outcomes • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence	
Simonneau (1997)	A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire.	**Study type** • Randomised controlled trial **Study details** • Study location *France, Belgium and Switzerland* • Study setting *Hospitals* • Study dates *July 1995 to July 1996* • Duration of follow-up *3 months* • Sources of funding *Leo Pharma, France* **Inclusion criteria** • ≥18 years	**Random sequence generation** • High risk of bias *"Central randomisation was performed with the use of a 24-hour computer service." This does not describe the method of randomisation. For example, the computer might have been a voice-activated system that gave a pre-determined response or the response could have been "forced randomisation". Forced randomisation is when the response is determined by the drug stocks or drug expiry dates. Therefore, knowing this information it is possible to predict the 'randomisation' outcome.* **Allocation concealment** • High risk of bias

Author (year)	Title	Study details	Quality assessment
		• PE **Exclusion criteria** • Other *Received anticoagulant therapy >24h before entering study* • Thrombectomy or embolectomy • Contraindication(s) for study drugs • Active bleeding • Pregnancy • Life expectancy <3 months • Severe renal failure • Severe hepatic failure • Likelihood of non-adherence to treatment **Sample characteristics** • Sample size *612 people* • Split between study groups *LMWH = 304; UFH = 308* • Loss to follow-up *None* • %female *LMWH = 56%; UFH = 55%* • Mean age (SD) *LMWH = 67 years (16); UFH = 67 years (16)* • Previous VTE	*No allocation concealment* **Blinding of participants and personnel** • High risk of bias *Open label study* **Blinding of outcome assessment** • High risk of bias *No blinding* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Study was unblinded and the*

Author (year)	Title	Study details	Quality assessment
		LMWH = 26%; UFH = 28% **Interventions** • LMWH + VKA *LMWH Duration: minimum 5 days Dose, and frequency: 175 Iu/kg daily Route:sc VKA started day 1-3. (No details of drug/initial dose given) . Dose adjusted to achieve INR 2-3. Duration: 3 months Heparin continued until INR ≥2 on 2 consecutive days after minimum of 5 days treatment Use of antiplatelet or anti-inflammatory drugs prohibited during the study* • UFH + VKA *Duration: minimum 5 days Dose, and frequency: Initial bolus 50 IU/kg, then 500 IU/kg/day continuous infusion Route: iv Dose adjusted so aPTT 2-3x control VKA started day 1-3. (No details of drug/initial dose given) . Dose adjusted to achieve INR 2-3. Duration: 3 months Heparin continued until INR ≥2 on 2 consecutive days after minimum of 5 days treatment Use of antiplatelet or anti-inflammatory drugs prohibited during the study* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding	*randomization technique used meant that allocation was not effectively concealed from investigators* Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• VTE-recurrence • Serious adverse events	
Ucar (2015)	Comparison of LMWH versus UFH for haemorrhage and hospital mortality in the treatment of acute massive pulmonary thromboembolism after thrombolytic treatment : randomized controlled parallel group study	**Study type** • Randomised controlled trial **Study details** • Study location *Turkey* • Study setting *Hospital* • Study dates *Not provided* • Duration of follow-up *Not stated* • Sources of funding *Not stated* **Inclusion criteria** • ≥18 years • PE *Suspicion of acute PE. The study included the patients who had confirmed diagnosis of massive PE according to clinical findings and computerized thorax angiography.*	**Random sequence generation** • High risk of bias *The randomisation process involved the use of sealed envelopes. This method should no longer be used because healthcare professionals can put the envelopes up to a light and read the treatment allocation.* **Allocation concealment** • High risk of bias *The randomisation process involved the use of sealed envelopes. This method should no longer be used because healthcare professionals can put the envelopes up to a light and read the treatment allocation.* **Blinding of participants and personnel** • High risk of bias *Open label study*

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Other *Major surgery, CVA* • Contraindication(s) for study drugs • Previous anticoagulation before randomisation **Sample characteristics** • Sample size *121 people* • Split between study groups *LMWH = 60; UFH = 61* • Loss to follow-up *None* • %female *LMWH = 63%; UFH = 54%* • Mean age (SD) *LMWH = 64.2 years (16.1); UFH = 61.1 years (15.3)* • Previous VTE *LMWH = 5%; UFH = 7%* **Interventions** • LMWH + VKA *The patients assigned to therapy with LMWH were given the first dose of LMWH following thrombolytic therapy, and LMWH was administered every 12 hours according to the time of first administered dose of LMWH. Both groups overlapped with*	**Blinding of outcome assessment** • Low risk of bias **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • Moderate *Participants and personnel were unblinded and the randomization technique is no longer used as it does not effectively conceal allocation from the investigators* Note: this study was not downgraded to high risk of bias due to a lack of blinding as

Author (year)	Title	Study details	Quality assessment
		warfarin on the 1st day–5th day or the day target international normalised ratio (INR) level was achieved. When target INR was achieved, LMWH and UFH treatment was stopped. The patients were kept on warfarin, aiming for an INR between 2.0 and 3.0 for 3 months or more, depending on the presence of major risk factors. • UFH + VKA *The patients assigned to therapy with UFH were administered a constant heparin infusion (18 U/Kg per hour) and adjusted to maintain an activated partial thromboplastin time of 46–70 s. Both groups overlapped with warfarin on the 1st day–5th day or the day target international normalised ratio (INR) level was achieved. When target INR was achieved, LMWH and UFH treatment was stopped. The patients were kept on warfarin, aiming for an INR between 2.0 and 3.0 for 3 months or more, depending on the presence of major risk factors.* **Outcomes** • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding	the majority of outcomes are objectively assessed. **Directness** • Partially directly applicable *Only included participants that also underwent thrombolytic therapy*
Yamada (2015)	Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism - the J-EINSTEIN DVT and PE	**Study type** • Randomised controlled trial	**Random sequence generation** • Low risk of bias *performed centrally with a rivaroxaban to control ratio of 4:1 and further*

Author (year)	Title	Study details	Quality assessment
	program.[Erratum appears in Thromb J. 2016;14:11; PMID: 27222638]	**Study details** • Study location *Japan* • Study setting *39 sites* • Study dates *February 2012 - December 2013 (enrolment)* • Duration of follow-up *3,6 or 12 months. Only 22-day follow-up used for this study as segmentation of treatment times is not available for later time points.* • Sources of funding *Supported by Bayer* **Inclusion criteria** • Objectively confirmed symptomatic DVT or PE • >20 years old **Exclusion criteria** • Received therapeutic dose of VKA or 48 hours of UFH, LMHW or fondaparinux • Thrombectomy or embolectomy • Vena cava filter fitted • Fibrinolytic agent administered for treatment of current episode • Contraindication(s) for study drugs • Other indication for VKA	*randomisation in 1:1 manner to the two different rivaroxaban doses* **Allocation concealment** • Low risk of bias *performed centrally* **Blinding of participants and personnel** • High risk of bias *unblinded* **Blinding of outcome assessment** • Low risk of bias *adjudicated by a blinded, independent committee* **Incomplete outcome data** • Low risk of bias **Selective reporting** • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		or for UFH • Creatine clearance <30ml/min • Clinically significant liver disease • Alanine aminotransferase level >3x ULN • Bacterial endocarditis • Active bleeding *or high risk of bleeding contraindicating treatment with UFH or warfarin* • Systolic blood pressure >180 mm Hg OR diastolic blood pressure >110 mm Hg • Other *concomitant use of strong cytochrome P450 3A4 inhibitors* • Pregnancy *or child bearing potential without proper contraceptive measures, or breastfeeding.* • Life expectancy <3 months **Sample characteristics** • Sample size *94 participants* • Split between study groups *Rivaroxaban 15mg: 24 participants Rivaroxaban 10mg (Not retained for this review): 23 participants UFH+VKA: 12 participants* • %female *Rivaroxaban arm: 54.5% female UFH arm: 47.3% female* • Mean age (SD)	**Other sources of bias** • High risk of bias *Treatment duration ranged from 3 months to 12 months. It is unclear whether the outcome data for the entire study period referred to the total number of events at the end of the study (which would result in participants having gone differing lengths of time without any therapy) or at the end of treatment.* **Overall risk of bias** • Moderate *Personnel and participants were unblinded and treatment length differed between participants. As the study did not report "on-treatment" outcome data or hazard ratios, interpretability of outcomes is limited.* **Directness** • Directly applicable

Author (year)	Title	Study details	Quality assessment
		rivaroxaban arm: 68.8 (DF12.2) years UFH arm: 63.4 (SD18.3) years • PE/DVT split (for VTE only studies) *Rivaroxaban arm: 45.5% DVT only UFH arm: 63.2% DVT only* • Provoked vs. unprovoked *Rivaroxaban arm: 65.4% unprovoked UFH arm: 42.1% unprovoked* • Previous VTE *Rivaroxaban arm: 14.5% UFH arm: 5.3%* **Interventions** • Rivaroxaban *15 mg (twice daily for 3 weeks: at which point the outcome was assessed) then went on to receive 15mg once daily.* • UFH + VKA *UFH for at least 5 days followed by Warfarin adjusted to a target INR of 1.5-2.5* **Outcomes** • VTE-recurrence *at 22 days*	

1 **Initial treatment of VTE in people with cancer**

Author (year)	Title	Study details	Quality assessment
Agnelli (2013) *AMPLIFY subgroup analysis*	Oral apixaban for the treatment of acute venous thromboembolism	Study type • Randomised controlled trial Study details • Study location 28 countries • Study setting 358 centres in 28 countries • Study dates August 2008 - August 2012 (enrolment period) • Duration of follow-up Patients underwent assessment, either in the clinic or by telephone, at weeks 2, 4, 8, 12, 16, 20, and 24 (6 months) after randomization and 30 days after the end of the intended treatment period. Patients were instructed to report to the study centre if they had symptoms suggestive of recurrent venous thromboembolism or bleeding. Prespecified objective testing was required for patients in whom an outcome event was suspected. • Sources of funding Funded by Pfizer and Bristol-Myers Squibb • Associated studies Agnelli 2013b: Cancer subgroup analysis Bleker 2016, Brekelsman 2017: Bleeding analysis Liu 2015: Hospital admission rates analysis Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE	Random sequence generation • Low risk of bias randomized using an interactive voice-response system and was stratified according to the qualifying diagnosis of either symptomatic proximal DVT or symptomatic PE Allocation concealment • Unclear risk of bias Blinding of participants and personnel • Low risk of bias Study was double-blinded Blinding of outcome assessment • Low risk of bias Events were rated by a blinded committee Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Low risk however information for PE and DVT individually in not available. Other sources of bias • High risk of bias

Author (year)	Title	Study details	Quality assessment
		Proximal DVT* Exclusion criteria • Contraindication(s) for study drugs • Active bleeding or high risk of bleeding • Other Received more than two doses of a once-daily LMWH regimen, fondaparinux, or a VKA; more than three doses of a twice-daily LMWH; or more than 36 hrs continuous IV heparin. • Active cancer with long-term LMWH treatment planned • Provoked DVT in absence of a persistent risk factor for recurrence • <6 month planned anticoagulant treatment • Other indication requiring long-term anticoagulation or dual antiplatelet therapy, treatment with aspirin (165mg daily or more) or treatment with potent inhibitors of cytochrome P-450 3A4 • Haemoglobin level <9mg/dL • Platelet count of <100,000 per cubic mm • Serum creatinine level > 2.5 mg/dL • Calculated creatinine clearance <25ml/min Sample characteristics • Sample size 5400 participants (167 with cancer at baseline) • Split between study groups 2691 rivaroxaban (87 with cancer); 2704 control (80 with cancer) • Loss to follow-up 820 lost to follow-up- 30 did not receive intended treatment, 46 died, 332 had adverse event, 98 withdrew consent, 28 lost to follow-up, 286 had other reasons.	*This was a subgroup analysis of an RCT comparing treatments for VTE in general and therefore was not designed specifically for cancer patients* Overall risk of bias • Moderate Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• %female 41% female • Mean age (SD) Apixaban group: 57.2 (SD 16.0) years Control group: 56.7 (SD 16.0) years • PE/DVT split (for VTE only studies) Apixaban group: DVT only (65%), PE only (25.2%), DVT+PE (9.4%), could not be evaluated (0.4%) Control group: DVT only (65.9%), PE only (25.2%), DVT+PE (8.3%), could not be evaluated (0.6%) • Provoked vs. unprovoked 89.8% unprovoked • Previous VTE Apixaban group: 17.2% previous VTE Control group: 15.1% previous VTE. Interventions • LMWH + VKA Enoxaparin at a dose of 1mg/kg body weight every 12 hours for at least 5 days and warfarin begun concomitantly and continued for 6 months. Enoxaparin or placebo was discontinued when a blinded INR of 2.0 or more was achieved. • Apixaban 10mg twice daily for the first 7 days, followed by 5mg twice daily for 6 months. Outcomes • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding Clinically relevant nonmajor bleeding was defined as overt	

Author (year)	Title	Study details	Quality assessment
		bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life. • Major bleeding Bleeding was defined as major if it was overt and associated with a decrease in the haemoglobin level of 2 g per decilitre or more, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death. • VTE-recurrence composite measure of VTE recurrence of VTE-related death (including those in which PE could not be ruled out): Both these outcomes were taken to be indicative of a VTE. • Serious adverse events	
Deitcher (2006)	Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period.	Study type • Randomised controlled trial Study details • Study location USA • Study setting 27 centres • Study dates January 2001 - March 2002 • Duration of follow-up 180 days • Sources of funding Sponsored by Aventis Pharmaceuticals	Random sequence generation • High risk of bias methods of randomization were unclear Allocation concealment • High risk of bias Study was open label Blinding of participants and personnel • High risk of bias Study was open label Blinding of outcome assessment • High risk of bias Study was open label

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE catheter-associated VTE not eligible • active cancer must be an active, residual malignancy determined by the presence of measurable disease, persistently elevated tumour markers, metastatic disease after tumour debulking, or histologically or cytologically confirmed cancer. Participants must not be a candidate for curative intent surgery. Based on the investigator's judgements, participants must have an estimated survival length long enough to complete the study. Cancer must not be acute leukaemia or localized cutaneous malignancy. Exclusion criteria • Other baseline INR 2 or more, history of HIT, history of warfarin associated skin necrosis, baseline platelet count under 50,000/UL • Contraindication(s) for study drugs including severe liver disease, known nonirradiated intracerebral metastases, deep organ biopsy within 2 weeks, and major surgery within 1 week were excluded. • Creatine clearance <30ml/min • ECOG performance status 3 or 4 • >120kg body weight Sample characteristics • Sample size 102 participants • Split between study groups 32 LMWH alone (1.0mg), 36 LMWH alone (1.5mg), 34 warfarin.	Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Study was open label with an unclear methodology for randomization. Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up one participants in the 1.0mg LMWH alone group did not receive study drug. • %female not reported • Mean age (SD) 63.7 (SD12.0) years • PE/DVT split (for VTE only studies) PE: 43.6%, DVT 83.2%, PE and DVT 29.7% • Other 58.4% stage 4 cancer, 23.8% stage 3 cancer, 6.9% stage 2 cancer 4.0% stage 1 cancer Interventions • LMWH + VKA Subcutaneous twice daily enoxaparin (1.0mg/kg) for minimum of 5 days and until achievement of a stable INR between 2 and 3 on oral warfarin begun on day 2 of enoxaparin and continued for a total of 180 days of anticoagulation. • LMWH alone Group 1a: Subcutaneous twice daily enoxaparin (1.0mg/kg) for 5 days, followed by once daily enoxaparin (1.0mg/kg) for 175 days Group 1b: subcutaneous twice daily enoxaparin (1.0mg/kg) for 5 days, followed by once-daily enoxaparin (1.5mg/kg) for 175 days) Outcomes • All-cause mortality • Major bleeding considered major if it resulted in death, a serious life threatening clinical event requiring hospitalisation, transfusion of at least 2 units of packed red blood cells, a fall in haemoglobin of 2 grams or	

Author (year)	Title	Study details	Quality assessment
		more that was attributable to the bleeding event, a retroperitoneal, intracranial, or intraocular haemorrhage; the need for surgery or decompression of a closed space; or an ecchymosis or hematoma greater than 10cm in diameter. • VTE-recurrence event could be a not previously involved venous segment and symptomatic VTE extension within the same venous segment as index event	
Hokusai-VTE (2013) *Subgroup analysis*	Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism.[Erratum appears in N Engl J Med. 2014 Jan 23;370(4):390]	Study type • Randomised controlled trial Study details • Study location 37 countries • Study setting 439 centres • Study dates January 2010- October 2012 (enrolment) • Duration of follow-up Participants were treated for a varying length of time Edoxaban arm: 11.8% received 3 months of treatment, 26.1% received between 3 and 6 months of treatment, 21.8% received >6months months treatment and 40.3% received 12 months treatment. Warfarin arm: 12.8% received 3 months of treatment, 26.3% received between 3 and 6 months of treatment, 20.7% received >6months months treatment and 40.2% received 12 months treatment. Follow-up was conducted in the clinic or by telephone, on days 5 through 12, 30, and 60 after randomization and monthly thereafter while they were taking the study drug or every 3 months after discontinuing the study drug. Patients were instructed to	Random sequence generation • Low risk of bias Randomisation was performed with the use of an interactive web-based system Allocation concealment • Unclear risk of bias Unclear whether randomization procedure allowed for allocation bias. Blinding of participants and personnel • Low risk of bias Administered in a double-blind, double dummy fashion. Blinding of outcome assessment • Low risk of bias A blinded committee rated all suspected outcome events

Author (year)	Title	Study details	Quality assessment
		report symptoms suggestive of recurrent venous thromboembolism or bleeding. Appropriate diagnostic testing, laboratory testing, or both were required in patients with suspected events. • Sources of funding Supported by Daiichi-Sankyo • Associated studies Raskob 2016 cancer subgroup analysis Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE Exclusion criteria • Contraindication(s) for study drugs • Creatine clearance <30ml/min • Active cancer with long-term LMWH treatment planned • Other indication requiring long-term anticoagulation • received therapeutic doses of any heparin for >48 hours, prior randomization or had one dose of VKA • Continued to receive aspirin for >100mg daily or received dual platelet therapy Sample characteristics • Sample size 8292 randomized; 8240 analysed (208 with cancer) • Split between study groups 4118 Edoxaban (109 with cancer); 4122 Warfarin (99 with cancer) • Loss to follow-up 52 participants did not receive intended drug and were excluded	Incomplete outcome data • Low risk of bias Selective reporting • High risk of bias Results are not stratified by treatment duration, limiting interpretability. Intention to treat analysis not given for VTE recurrence. Other sources of bias •High risk of bias This was a subgroup analysis of an RCT comparing treatments for VTE in general and therefore was not designed specifically for cancer patients Overall risk of bias • High Subgroup analysis with limited interpretability regarding treatment length with outcomes typically reported at 12 months regardless of intended treatment duration and/or drug cessation. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		from analysis • %female 42.8% • Mean age (SD) Edoxaban arm: 55.7 (SD 16.3) years Warfarin arm: 55.9 (SD 16.2) years • PE/DVT split (for VTE only studies) 4921 DVT only 3319 PE with or without DVT • Provoked vs. unprovoked 65.7% unprovoked • Previous VTE 18.4% previous VTE Interventions • LMWH + VKA Participants received at least 5 days parenteral heparin (LMWH or UFH). Warfarin was given concurrently for at least 3 months and for a maximum of 12 months, and was adjusted to maintain an INR between 2.0 and 3.0. Participants in this arm also received an Edoxaban-like placebo. Supplementary appendix shows that only 151 (3.7%) of participants received UFH with the rest receiving enoxaparin. • Edoxaban plus parenteral AC Participants received at least 5 days of heparin (LMWH or UFH). Following discontinuation of heparin, participants received 60mg Edoxaban orally, once daily, or 30mg (once daily) in those patients with creatinine clearance 30-50ml per minute, or a body weight of 60kg or less or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. Participants in this arm also received a warfarin-like placebo given concurrently with heparin, and a sham INR reading.	

Author (year)	Title	Study details	Quality assessment
		Supplementary appendix shows that only 148 (3.6%) of participants received UFH with the rest receiving enoxaparin. Outcomes • Clinically relevant non-major bleeding Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life • Major bleeding Bleeding was defined as major if it was overt and was associated with a decrease in haemoglobin of 2 g per decilitre or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death. • VTE-recurrence • Serious adverse events	
Hull (2006)	Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer.	Study type • Randomised controlled trial Study details • Study location Canada • Study setting 23 centres • Study dates 1994-2003 • Duration of follow-up 3 months • Sources of funding	Random sequence generation • Low risk of bias computer-derived randomized treatment in blocks of 2 and 4. Allocation concealment • Unclear risk of bias Blinding of participants and personnel • High risk of bias study was open label

Author (year)	Title	Study details	Quality assessment
		Supported by a medical research council (Canadian institutes for health research) and an industry grant (Leo pharma). Inclusion criteria • ≥18 years • Active cancer • DVT acute proximal vein (popliteal, femoral or iliac-vein) thrombosis documented by venography or compression ultrasonography. Comorbid PE allowed. Exclusion criteria • Received therapeutic dose of VKA or 48 hours of UFH, LMHW or fondaparinux • Contraindication(s) for study drugs • Other indication for VKA if receiving VKA for condition • Active bleeding a bleeding diathesis or bleeding contraindication treatment. • Other History of HIT; malignant hypertension or blood pressure over 250 mm Hg systolic or 130 mm Hg diastolic; hepatic encephalopathy; renal failure necessitating dialysis; neurological or ophthalmic surgery within 14 days; PE requiring thrombolysis, thrombectomy or vena cava interruption. Lumbar puncture within 24 hours; eligible for home therapy with LMWH but could not be allocated to UFH; participating in other trial' unable to inject; geographic inaccessibility for follow-up; unable to give informed consent • Pregnancy or breast-feeding	Blinding of outcome assessment • Low risk of bias outcomes adjudicated by a central committee unaware of treatment allocation. Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Life expectancy <3 months Sample characteristics • Sample size 200 participants • Split between study groups 100 LMWH alone; 100 UFH + VKA • Loss to follow-up none • %female 49% female • Mean age (SD) 62% 60 years+ in LMWH alone arm 76% 60 years+ in the UFH+VKA arm • PE/DVT split (for VTE only studies) 93% had DVT at entry 21% had PE at entry • Previous VTE 19% had a prior VTE. • Other LMWH alone: 43 nonmetastatic cancer, 47 metastatic, 10 hematologic UFH+VKA: 51 nonmetastatic cancer, 36 metastatic, 13 hematologic Interventions • LMWH alone tinzaparin 175 IU/kg once daily • UFH + VKA 5000 units or 80 units/kg followed by continuous infusion. Warfarin was administered on day 1 at 5-10mg then adjusted to maintain the INR between 2.0-3.0 Heparin was discontinued at day 6 if INR	

Author (year)	Title	Study details	Quality assessment
		was therapeutic Outcomes • All-cause mortality • Clinically relevant non-major bleeding clinically overt, non major • Major bleeding fall in haemoglobin level of 2g/Dl or more, led to transfusion of 2 or more units of blood and if it was retroperitoneal, occurred in major joint, or was intracranial. • VTE-recurrence when a previously compressible proximal vein segment was not compressible on ultrasonography, or by the presence of a constant intraluminal filling defect in deep veins that was not present on the baseline venogram. PE confirmed using high probability lung scan findings, a nondiagnostic lung scan with documented new DVT; spiral CT showing thrombus in the central pulmonary arteries; PA revealing constant intraluminal filling defect or cut-off of a vessel greater than 2.5mm in diameter, or PE at autopsy.	
Investigators EINSTEIN-DVT (2010) and PE (2012) Subgroup analyses	Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT	Study type • Randomised controlled trial Study details • Study location 38 countries • Study setting 315 sites • Study dates March 2007-March 2011	Random sequence generation • Low risk of bias randomly assigned using computerized voice-response system, stratified by country Allocation concealment • High risk of bias Intended treatment duration was determined by treating physician

Author (year)	Title	Study details	Quality assessment
	and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials	• Duration of follow-up Up to 12 months • Sources of funding Both trials were sponsored by Bayer and Ortho-McNeil. • Associated studies Bamber 2013 quality of life study; Prins 2014 cancer subgroup analysis study; Prins 2015 quality of life study Inclusion criteria • Of legal age for consent; • Acute, symptomatic; • objectively confirmed proximal DVT; • Without symptomatic PE; • Not received therapeutic doses of LMWH, fondaparinux, or UFH for more than 48 hours or a single dose of VKA; • Not received thrombectomy, a vena cava filter, or a fibrinolytic agent for current episode of thrombosis; • No contraindications for treatments use in study; • No other indications for VKA -Creatine clearance >30 ml/min; • No clinically significant liver disease; • Alanine amino-transferase level <3xULN; • No bacterial endocarditis; • No active bleeding or high risk of bleeding; • No contraindicating anticoagulant treatment; • Systolic blood pressure <180mmHg AND diastolic blood pressure greater than 110 mmHg;	Blinding of participants and personnel • High risk of bias both studies were open label Blinding of outcome assessment • Low risk of bias Suspected outcome events were classified by a blinded central adjudication committee Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias Treatment length varied between participants with limited reporting for individual time-points, it is unclear whether event rates at the median length of treatment (6 months) was similar to overall event rate. Additionally, this was a subgroup analysis of an RCT comparing treatments for VTE in general and therefore was not designed specifically for cancer patients. Overall risk of bias • High Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Not pregnant or of childbearing potential (unless using proper contraceptive measures); • Not breast-feeding; • No concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers; • No participation in another experimental pharmacotherapeutic program within 30 days before screenings; • Life expectancy over 3 months Sample characteristics • Sample size 3449 (462 with cancer at baseline) 1718 Rivaroxaban (258 with cancer); 1711 LMWH+VKA (204 with cancer) • %female Rivaroxaban (cancer patients only): 41% female LMWH+VKA (cancer patients only): 47% female • Mean age (SD) Rivaroxaban (cancer patients only): 27% 75 years or older, 31% 65-75 years, 42% <65 years. LMWH+VKA (cancer patients only): 25% 75 years or older, 38% 65-75 years, 38% <65 years. • PE/DVT split (for VTE only studies) 3449 DVT study; 4832 PE study Interventions • Rivaroxaban 15mg twice daily for first 3 weeks followed by 20 mg once daily for intended 3, 6 or 12 months.	

Author (year)	Title	Study details	Quality assessment
		• LMWH + VKA Subcutaneous enoxaparin (1.0 mg/kg body weight, twice daily; discontinued when INR was 2.0 or more for 2 consecutive days) + either warfarin or acenocoumarol (started within 48 hr after randomization. Enoxaparin was given for a median of 8 days with INR at end of 2.0 or higher in 80.8% of patients. Outcomes • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life. • Major bleeding Bleeding was defined as major if it was clinically overt and associated with a fall in the haemoglobin level of 20 g per litre or more, or if it led to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death. • VTE-recurrence The criteria for the diagnosis of deep-vein thrombosis were a new noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. The criteria for diagnosis of pulmonary embolism were a new intraluminal filling defect on	

Author (year)	Title	Study details	Quality assessment
		spiral CT or pulmonary angiography, a cut-off of a vessel of more than 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non– high-probability perfusion defect associated with deep-vein thrombosis, as documented by ultrasonography or venography. Fatal pulmonary embolism was based on objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death). • Quality of life	
Lee (2003) CLOT trial	Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer.	Study type • Randomised controlled trial Study details • Study location Eight countries (Canada, Australia, New Zealand, US, Italy, The Netherlands, Spain, UK) • Study setting 48 clinical centres in eight countries • Study dates May 1999 - October 2001 (enrolment) • Duration of follow-up 6 months study period; contacted by telephone very two weeks and seen in clinic 1 week and 1,3 and 6 months after randomization. • Sources of funding Pharmacia provided funding	Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias Blinding of participants and personnel • High risk of bias Open-label Blinding of outcome assessment • Low risk of bias Suspected outcomes were assessed by a blinded committee Incomplete outcome data • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Objectively confirmed symptomatic DVT or PE newly diagnosed • active cancer other than basal-cell or squamous-cell carcinoma of the skin, within 6 months before enrolment, any treatment for cancer within previous 6 months, or recurrent or metastatic cancer. Exclusion criteria • Contraindication(s) for study drugs • Active bleeding within two weeks or had conditions associated with a high risk of serious bleeding • Pregnancy • <40kg or less body weight • ECOG performance status 3 or 4 • received therapeutic doses of any heparin for >48 hours, prior randomization • already receiving oral anticoagulation therapy • Platelet count <75,000 cubic millimetres • Creatinine level 3X ULN Sample characteristics • Sample size 676 participants • Split between study groups 338 LMWH + VKA, 338 LMWH alone • %female 51.5% female • Mean age (SD) LMWH+VKA: 62 (SD12) years LMWH: 63 (SD13) years	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• PE/DVT split (for VTE only studies) 69% DVT alone; 31% PE with or without DVT • Previous VTE 11.1% prior VTE Interventions • LMWH + VKA Dalteparin at a dose of 200 IU per/kg body weight subcutaneously once-daily for 5-7 days and a coumarin derivative for 6 months (target INR of 2.5) • LMWH alone Dalteparin alone for 6 months (200 IU per kg once-daily for one months followed by 150 IU per kg daily for five months) Outcomes • All-cause mortality • VTE-related mortality • Major bleeding • VTE-recurrence	
Lee (2015) CATCH trial	Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial.[Erratum appears in JAMA. 2017 Nov	Study type • Randomised controlled trial Study details • Study location 32 countries • Study setting 164 centres across 32 studies • Study dates August 2010 - November 2013 • Duration of follow-up	Random sequence generation • Low risk of bias randomized using computer generate sequence and stratified by tumour extent, geo-region and VTE history. Allocation concealment • Low risk of bias allocation was concealed until individual randomization using interactive voice-response

Author (year)	Title	Study details	Quality assessment
	28;318(20):2048; PMID: 29183049]	6 months • Sources of funding supported and funded by LEO pharma Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE proximal DVT or PE, or both • active cancer histological or cytological confirmation of malignancy (excluding basal cell carcinoma or nonmelanoma skin cancer) and any of following features: cancer diagnosis within previous 6m, recurrent regionally advanced or metastatic disease, treatment for cancer during previous 6 months, or not in complete remission from a haematological malignancy. Exclusion criteria • Life expectancy <6 months • Contraindication(s) for study drugs or known hypersensitivity to study drugs • Other creatinine clearance 20ml/min/1.73 m2 or lower; history of HIT; therapeutic anticoagulation at time of index event or for more than 72 hours prior to randomization; unlikely to comply with the protocol; participating in another interventional study; women of childbearing potential or fertile men not using effective contraception. Sample characteristics • Sample size 900 randomised	system. Blinding of participants and personnel • High risk of bias Study was open label Blinding of outcome assessment • Low risk of bias study was open label however all main outcomes were adjudicated by a central committee unaware of treatment allocation. Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Note: this study was not downgraded to moderate risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed.

Author (year)	Title	Study details	Quality assessment
		• Split between study groups 451 warfarin; 449 LMWH alone • Loss to follow-up 14 lost to follow up; however large number of people (n=242) were excluded from per-protocol analysis suggesting problems with discontinuation. • %female 59.4% female • Mean age (SD) Tinzaparin arm: 59.7 (SD12.7) years Warfarin arm: 58.8 (SD12.5) years • PE/DVT split (for VTE only studies) 57% DVT alone 30% PE and DVT 10% PE alone • Other 89.6% of patients had solid tumours (54.7% metastatic disease) 10.4% haematological malignancy 52.9% receiving anticancer therapy 6.3% had prior VTE. Interventions • LMWH + VKA Warfarin for 6 months, overlapping with tinzaparin (175 IU/kg) once daily for first 5-10 days and until INR >2.0 for 2 consecutive days thereafter continued on warfarin alone adjusted to maintain INR between 2.0 and 3.0, tested at least once every 2 weeks. • LMWH alone Participants received 175 IU/Kg tinzaparin once daily by subcutaneous injection for 6 months. Outcomes • All-cause mortality • VTE-related mortality	Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		PE or bleeding death. • Clinically relevant non-major bleeding required any medical or surgical intervention but not meeting criteria for major. • Major bleeding fatal bleeding or fall in haemoglobin of 2g/dL or more or that led to transfusion of 2+ units of whole blood or red cells • VTE-recurrence Symptomatic DVT, symptomatic nonfatal PE, fatal PE, incidental proximal DVT	
Meyer (2002)	Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study.	Study type • Randomised controlled trial Study details • Study location France • Study setting 25 centres • Study dates April 1995 - March 1999 • Duration of follow-up 3 months treatment period with some participants being given 6 months treatment • Sources of funding Supported by Aventis Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE • active cancer	Random sequence generation • Low risk of bias Randomization was performed using pre-sealed boxes with allocation balanced at each centre in blocks of 4. Allocation concealment • Low risk of bias Randomization was performed using pre-sealed boxes with allocation balanced at each centre in blocks of 4. Blinding of participants and personnel • High risk of bias Study was open label Blinding of outcome assessment • Low risk of bias all outcomes adjudicated by an independent

Author (year)	Title	Study details	Quality assessment
		of any type Exclusion criteria • Other History of HIT; allergy to iodine; fibrinolytic treatment within 3 days; VKA use for >5 days; treatment with full dose heparin for this episode of VTE, Major PE with shock • Contraindication(s) for study drugs active bleeding, diastolic blood pressure >120mm Hg, platelet count lower than 30 x 10^3/uL • Pregnancy • Life expectancy <3 months • Severe hepatic failure • severe renal failure • major surgery planned <3months Sample characteristics • Sample size 146 • Split between study groups 75 LMWH + warfarin; 71 LMWH alone • %female 50.7% female in LMWH+VKA arm 60.6% female in LMWH alone arm • Mean age (SD) LMWH+VKA arm: 66 (SD11) years LMWH alone: 65 (SD13) years • PE/DVT split (for VTE only studies) LMWH+VKA arm: DVT alone 33.3%, PE alone 14.7%, both 52% LMWH alone: DVT alone 26.8%, PE alone 11.3%, both 62% • Previous VTE 30.7% in LMWH+VKA arm 18.7% in LMWH alone arm	committee unaware of treatment allocation Incomplete outcome data • High risk of bias VTE-recurrence only reported as composite outcome combined with major bleeds (major bleeds reported separately). Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Unclear reporting for VTE recurrence however low risk of bias for outcomes reported Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Other 53% had metastatic cancer. Interventions • LMWH + VKA enoxaparin 1.5mg/kg of body weight subcutaneously once daily. 6-10mg warfarin adjusted to INR between 2-3 for 3 months. LMWH was stropped after INR was >2 for 2 consecutive days and for at least 4 days • LMWH alone enoxaparin 1.5mg/kg of body weight subcutaneously once daily for 3 months without dose adjustment. Outcomes • Clinically relevant non-major bleeding Overt but not meeting definition for major. • Major bleeding overt and associated with decrease in haemoglobin concentration >2.0 g/dL or with the need for transfusion of 2+ units of blood or if bleeding was retroperitoneal. • VTE-recurrence new or recurrent PE underwent VQ lung scan and/or angiography and was diagnosed if there was a new segmental or larger perfusion defect with normal ventilation on the lung scan or when a new intraluminal filling defect or a new sudden cut-off was observed in an arterial branch on angiography. Suspected new or recurrent DVT underwent CUS or venography, which ever test had been performed on inclusion and was defined as a lack of compressibility in a previously compressible venous segment on ultrasonography or as a new intraluminal filling defect on	

Author (year)	Title	Study details	Quality assessment
		venography.	
Raskob (2018) HOKUSAI -Cancer trial	Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism.	Study type • Randomised controlled trial Study details • Study location 13 countries • Study setting 114 centres • Study dates July 2015- December 2016 (enrolment) • Duration of follow-up minimum 9 months up to 12 months. • Sources of funding Daiichi Sankyo collaborated in the trial design, protocol, and oversight of the study as well as the collection and maintenance of the data. Inclusion criteria • Of legal age and able to write informed consent • Objectively confirmed symptomatic DVT or PE acute symptomatic or incidentally detected deep-vein thrombosis involving the popliteal, femoral, or iliac vein or the inferior vena cava; acute symptomatic pulmonary embolism that was confirmed by means of diagnostic imaging; or incidentally detected pulmonary embolism involving segmental or more proximal pulmonary arteries. • 6 months of anticoagulation deemed appropriate • active cancer	Random sequence generation • Low risk of bias Randomization was performed with the use of an interactive Web-based system, with stratification according to whether risk factors for bleeding were present and whether the patient met the criteria to receive a lower dose of edoxaban. Allocation concealment • Unclear risk of bias unclear whether randomization technique concealed allocation effectively. Blinding of participants and personnel • High risk of bias open-label trial Blinding of outcome assessment • Low risk of bias An independent clinical events committee, whose members were unaware of the treatment assignments, confirmed the qualifying diagnosis of venous thromboembolism. Incomplete outcome data • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		other than basal cell or squamous-cell skin cancer that was active or had been diagnosed within the previous 2 years and was objectively confirmed. Active cancer was defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months before randomization; or hematologic cancer that was not in complete remission. A single independent physician (the second author), who was unaware of the treatment assignments, reviewed the data for all the enrolled patients to confirm the diagnosis of cancer and to verify the status of cancer as active or inactive. Exclusion criteria • Other 1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE; 2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labelling), oral direct anticoagulants or VKA prior to randomization to treat the current (index) episode; 3. Treatment with therapeutic doses of an anticoagulant including dalteparin for an indication other than VTE prior to randomization; 4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban; 5. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization 6. Calculated CrCl < 30 mL/min; 7. History of heparin associated thrombocytopenia; 8. Acute hepatitis, chronic active hepatitis, liver cirrhosis; 9. Hepatocellular injury with concurrent transaminase (ALT/AST > 3 x ULN) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation; 10. Life expectancy < 3 months; 11. Platelet count < 50,000/mL; 12.	Selective reporting • Low risk of bias Other sources of bias • High risk of bias Limited interpretability regarding the differing treatment durations. Outcomes at 12 months are reported regardless of whether participant only received planned treatment for 6 months. Overall risk of bias • Moderate Limited interpretability regarding the differing treatment durations. Outcomes at 12 months are reported regardless of whether participant only received planned treatment for 6 months. Note: this study was not downgraded to high risk of bias due to a lack of blinding as the majority of outcomes are objectively assessed. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Uncontrolled hypertension as judged by the Investigator (e.g., systolic blood pressure (BP) > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment); 13. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding; Sample characteristics • Sample size 1046 • Split between study groups 522 edoxaban; 524 dalteparin • %female edoxaban arm: 46.9% female dalteparin arm: 49.8% female • Mean age (SD) edoxaban arm: 64.2 (SD11) years dalteparin arm: 63.7 (SD11.7) years • Previous VTE edoxaban arm: 9.4% dalteparin arm: 12.0% • Other 53% had metastatic disease. 72% had received cancer treatment within previous 4 weeks Interventions • LMWH alone Dalteparin was given subcutaneously at a dose of 200 IU per kilogram of body weight once daily for 30 days,4 with a maximum daily dose of 18,000 IU. Thereafter, dalteparin was given at a dose of 150 IU per kilogram once daily.4 If the platelet count declined to less than 100,000 per microliter during treatment, the dose of dalteparin was temporarily reduced. Given for 6-12 months determined by treating physician	

Author (year)	Title	Study details	Quality assessment
		• Edoxaban plus parenteral AC Edoxaban was started after a course of therapeutic- dose low-molecular-weight heparin was given subcutaneously for at least 5 days. This lead-in low-molecular-weight heparin was not required to be dalteparin; the choice of heparin and therapeutic regimen were at the discretion of the treating physician. Edoxaban was administered orally at a fixed dose of 60 mg once daily, with or without food. It was administered at a lower dose (30 mg once daily) in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors. given for 6-12 months determined by treating physician. Outcomes • All-cause mortality • VTE-related mortality VTE death: is defined as death due to a documented PE (either an objective test prior to death of the subject or PE detected during autopsy) or unexplained death i.e. death without a clear alternate cause and not a primary consequence of subject's underlying Cancer • Clinically relevant non-major bleeding A bleeding event will be classified as a clinically relevant non-major bleeding event if it is overt (i.e. is symptomatic or visualized by examination) not meeting the criteria for major bleeding, requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life. • Major bleeding A major bleeding event will be confirmed when it is a clinically overt bleeding event that meets at least one of the following: a) Fatal bleeding b) Bleeding in a critical area or organ such as:	

Author (year)	Title	Study details	Quality assessment
		Retroperitoneal □ Intracranial □ Intraocular □ Intraspinal □ Intra-articular □ Pericardial □ Intramuscular with compartment syndrome c) A clinically overt bleeding event □ that is associated with a fall in haemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or □ leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood. • VTE-recurrence Recurrent VTE is either: • symptomatic confirmed (recurrent) DVT or (recurrent) PE; • unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries: o Unsuspected DVT or PE are thrombi that are detected during imaging testing performed for other reasons (e.g., computed tomography (CT) for cancer staging) and not for suspicion of DVT or PE. • fatal PE. • Serious adverse events	
Romera (2009)	A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis.	Study type • Randomised controlled trial Study details • Study location Spain • Study setting 2 centres • Study dates January 2002 to January 2005 • Duration of follow-up 6 months (treatment duration) and 12 months total duration (not extracted) • Sources of funding Received grants from LEO pharma for the study and statistical	Random sequence generation • High risk of bias randomization methodology not given. Allocation concealment • High risk of bias open-label with randomization methodology not given. Blinding of participants and personnel • High risk of bias open-label Blinding of outcome assessment • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		analysis but did not have role in design, conduct or analysis of study itself Inclusion criteria • ≥18 years • DVT referred to the Vascular Surgery Department of the hospital with a first episode of acute proximal-vein thrombosis of the lower limbs (onset of symptoms less than 2 weeks) documented by compression ultrasonography Exclusion criteria • Other Severe blood pressure; haemoglobin concentration <7g/Dl-1; history of HIT; surgery in previous 14 days; lumbar puncture in previous 24h; receiving oral anticoagulant treatment or antiplatelet treatment for other conditions unable to discontinue this medication during the treatment interval. • Received therapeutic dose of VKA or 48 hours of UFH, LMHW or fondaparinux • Contraindication(s) for study drugs • Active bleeding • Platelet count of <100,000 per cubic mm • PE requiring thrombolytic therapy, surgical thrombectomy or vena cava interruption. Sample characteristics • Sample size 241 total. 69 with cancer (only those with cancer were extracted as study drugs were not applicable for general population).	ultrasonographic evaluation was performed blindly. Incomplete outcome data • High risk of bias only VTE recurrence was clearly reported for the cancer subgroup. Selective reporting • Low risk of bias Other sources of bias •High risk of bias This was a subgroup analysis of an RCT comparing treatments for VTE in general and therefore was not designed specifically for cancer patients. Overall risk of bias • High Subgroup analysis with randomization methodology not given and the study was open label. Additionally, only VTE-recurrence was reported for the cancer subgroup. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Split between study groups 36 LMWH therapy alone; 33 LMWH+VKA • %female LMWH alone: 50% female LMWH+VKA: 39.4% female • Mean age (SD) LMWH alone: 59.8 (SD15.5) years LMWH+VKA: 64.7 (SD15.2) years Interventions • LMWH + VKA Tinzaparin SC 175 AXa IU/kg body weight once daily until INR was >2 for at least 2 consecutive measurements and then received 3mg acenocoumarol orally adjusted to INR 2.0-3.0 for 6 months. • LMWH alone Tinzaparin SC 175 AXa IU/kg body weight once daily for 6 months Outcomes • Major bleeding overt and had fall in haemoglobin level of 2mg/dl or more and results in transfusion of 2+ units of blood, and was retroperitoneal, occurred into a major joint or was intracranial • VTE-recurrence Recurrent DVT or new episode of PE. Recurrent venous thrombosis was diagnosed when a previously compressible proximal-vein segment or segments were no longer compressible on ultrasonography. In patients with clinically suspected pulmonary embolism, the diagnosis was confirmed by a high-probability lung scan finding, an abnormal perfusion scan with documented new DVT or a spiral CT scan showing thrombus in	

Author (year)	Title	Study details	Quality assessment
		the pulmonary arteries.	
Schulman (2013) and (2013) *RE-COVER I and II subgroup analyses*	Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis	Study type • Randomised controlled trial Study details • Study location RE-COVER: 31 countries RE-COVER II: 29 countries • Study setting RE-COVER: 208 sites across 31 countries RE-COVER II: 228 sites across 29 countries • Study dates RE-COVER I: April 2006 - November 2008 RE-COVER II: June 2008 - October 2010 • Duration of follow-up Patients were assessed at 7 days and then monthly until 6 months and were told to contact their study site immediately if symptoms developed that were suggestive of venous thromboembolism or bleeding. An additional follow-up visit was scheduled for 30 days after completion of the study, unless the patient had discontinued the study drug before 6 months, had started open-label anticoagulant therapy, or had been enrolled in another trial. • Sources of funding Both studies were funded and designed by Boehringer Ingelheim and the steering committee • Associated studies Schulman 2009: Data for RECOVER I Schulman 2015: Cancer subgroup analysis Inclusion criteria • ≥18 years	Random sequence generation • Low risk of bias Randomized using an interactive voice-response system and a computer generate randomized scheme in blocks of 4 Allocation concealment • Unclear risk of bias Unclear whether allocation was concealed Blinding of participants and personnel • Low risk of bias double-blinded Blinding of outcome assessment • Low risk of bias Suspected events were rated by a blinded committee Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias •High risk of bias

Author (year)	Title	Study details	Quality assessment
		• Objectively confirmed symptomatic DVT or PE diagnosis confirmed prior to randomisation • 6 months of anticoagulation deemed appropriate Exclusion criteria • Life expectancy <6 months • Contraindication(s) for study drugs or to radiographic contrast material • Other indication for VKA • Creatine clearance <30ml/min • Baseline aminotransferase level >2x ULN RE-COVER I study only • Baseline aminotransferase levels >3x ULN RE-COVER II study only • Duration of symptoms >14 days • Hemodynamic instability If presenting with PE • Requiring thrombolysis If presenting with PE • Recent unstable CVD • High risk of bleeding • Pregnancy or risk of becoming pregnant • requirement for long term antiplatelet therapy Sample characteristics • Sample size RE-COVER: 2564 RE-COVER II: 2589 (221 with cancer before randomization, both studies combined) • Split between study groups RE-COVER: Dabigatran 1273; placebo 1266 RE-COVER II:	This was a subgroup analysis of an RCT comparing treatments for VTE in general and therefore was not designed specifically for cancer patients Overall risk of bias • Moderate Subgroup analysis and the data is not segmentable by PE/DVT index event which limits interpretability of index event-specific effects Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Dabigatran 1280 (114 with cancer); placebo 1288 (107 with cancer) • %female RE-COVER: 42% RE-COVER II: 39% (47% female among those with cancer, for both studies combined) • Mean age (SD) RE-COVER I: Dabigatran arm 55.0 (SD 15.8) years; placebo arm 54.4 (SD 16.2) years. RE-COVER II: Dabigatran 54.7 (SD16.2) years; placebo arm 55.1 (SD 16.3) years. (mean age among those with cancer was 63.4 [SD 12.1) years for both studies combined) • PE/DVT split (for VTE only studies) RE-COVER I: 69% DVT only, 21% PE only, 10% both, <1% neither. RE-COVER II: 68% DVT only, 23% PE only, 9% both, <1% neither. (among those with cancer, 75% had DVT only, 21% PE only, 6% both, for both studies combined) • Previous VTE RE-COVER I: 25.6% RE-COVER II: 17.5% (among those with cancer, 20% had a previous VTE) Interventions • LMWH + VKA Participants were given warfarin adjusted to achieve 2.0 - 3.0 INR and a Dabigatran-like placebo. Participants in this group received a parenteral anticoagulant (UFH or LMWH), typically beginning before randomization. On day of randomization Warfarin was given for at least 5 days and until the INR had been 2.0 or greater for at least 2 consecutive days, at which point parenteral AC was stopped Dabigatran-like placebo was administered. Study drugs were given for 6 months from randomization. RE-COVER I: only	

Author (year)	Title	Study details	Quality assessment
		11.3% of Dabigatran arm and 13.0% of warfarin arm received UFH RE-COVER II: only 15.5% of Dabigatran arm and 16.1% of warfarin arm received UFH • Dabigatran plus parenteral AC 150mg (twice daily) with a warfarin-like placebo. Participants in this group received a parenteral anticoagulant that consisted of either UFH or LMWH, typically beginning before randomization. On day of randomization placebo was given along with a sham INR test. Dabigatran was administered at least 5 days following administration of placebo, at which point administration of parenteral AC was stopped. Study drugs were given for 6 months from randomization. Outcomes • All-cause mortality Not extractable for PE and DVT patients separately • VTE-related mortality Not extractable for PE and DVT patients separately • Clinically relevant non-major bleeding Not extractable for PE and DVT patients separately • Major bleeding Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the haemoglobin level of at least 20 g per litre, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal. • VTE-recurrence Not extractable for PE and DVT patients separately • Serious adverse events Not extractable for PE and DVT patients separately	

Author (year)	Title	Study details	Quality assessment
Young (2018) SELECT-D trial	Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)	Study type • Randomised controlled trial Study details • Study location UK • Study setting 58 sites • Duration of follow-up Assessed at 3 months intervals until month 12 and then at 6 months intervals until month 24. those with index DVT underwent CUS of lower limbs at 5 months. Those with residual DVT or new PE were eligible for random assignment to 6 months of rivaroxaban or placebo. participants had to be without a VTE recurrence Inclusion criteria • ≥18 years • active cancer solid and hematologic malignancies, other than basal-cell or squamous-cell skin carcinoma, in the previous 6 months, any treatment for cancer in previous 6 months, recurrent or metastatic cancer, or cancer not in complete remission. Exclusion criteria • Other Under 40kg body weight; ECOG status greater than 2; inadequate hematologic, renal or hepatic function; any previous treatment dose of AC or >75mg aspirin per day (planned start time of study therapy was >96 hours after starting AC for this VTE); clinically significant liver disease; inadequate contraceptive measures if of	Random sequence generation • Low risk of bias randomly assigned centrally by telephoning Warwick clinical trials unit, assigned at 1:1 ratio using computer based minimization algorithm with stratification by stage of disease, baseline platelet count, type of VTE, risk of clotting by tumour type. Allocation concealment • Low risk of bias randomly assigned centrally by telephoning Warwick clinical trials unit, assigned at 1:1 ratio using computer based minimization algorithm with stratification by stage of disease, baseline platelet count, type of VTE, risk of clotting by tumour type. Blinding of participants and personnel • High risk of bias Trial staggered and participants were not blinded to treatment allocation. Blinding of outcome assessment • Low risk of bias main outcomes were adjudicated by a blind committee however it is unclear whether other outcomes were Incomplete outcome data • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		childbearing potential; uncontrolled hypertension; concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers or P-glycoprotein inhibitors or inducers. • Bacterial endocarditis • High risk of bleeding or active bleeding • Previous VTE (prior to index VTE) Sample characteristics • Sample size 670 enrolled, 406 randomized • Split between study groups 203 each arm • Loss to follow-up 11 found to be ineligible following randomization, 99 participants reported missing doses • %female Dalteparin arm: 52% Rivaroxaban arm: 43% • Mean age (SD) median 67 years • PE/DVT split (for VTE only studies) 52% incidental PE, 48% symptomatic DVT/PE • Other 83% currently receiving chemotherapy 58% metastatic cancer 40% early/locally advanced 2%hematologic malignancy All comparable between arms Interventions • Rivaroxaban 15mg tablet twice daily for first 3 weeks followed by 20mg tablets once daily for total of 6 months.	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• LMWH alone Dalteparin 200 IU/kg subcutaneously once daily for 30 days followed by 150 IU/kg once daily for 5 months. Outcomes • All-cause mortality • Clinically relevant non-major bleeding Clinically relevant non-major bleeding includes acute, clinically overt episodes such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that does not meet the criteria for major bleeding. Bleeding is categorised as minor if it is clinically overt but not adjudicated as major or clinically relevant non-major bleeding. • Major bleeding The definition of major bleeding is acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the haemoglobin level of 20 grams per litre or more over a 24-hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intra-spinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding • VTE-recurrence Symptomatic DVT is confirmed using venous ultrasound for a new non-compressible venous segment or a substantial increase (4mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography. When thrombosis of vessels proximal to the inguinal ligament is suspected, contrast-enhanced CT should be	

Author (year)	Title	Study details	Quality assessment
		considered. Non-fatal or fatal symptomatic or 'incidental' PE are confirmed as a new intraluminal filling defect on spiral CT or pulmonary angiography, a cut-off of a vessel of more than 2.5mm in diameter on Confidential Protocol Version 6.0 21-Sep-2016 Page 24 of 64 pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non-high probability perfusion defect associated with deep vein thrombosis as documented by ultrasonography or venography. Fatal pulmonary embolism is based on objective diagnostic testing, autopsy or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death).	

1 **Extended therapy for VTE**

Author (year)	Title	Study details	Quality assessment
Agnelli (2001) WODIT-DVT trial	Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators.	Study type • Randomised controlled trial Study details • Study location Italy • Study dates January 1995 - June 1998 • Duration of follow-up followed-up until the last enrolled participant received 2-years follow-up. follow-up visits at 3, 6, and 12 months after randomization and every 6 months thereafter until the completion of the study. • Sources of funding	Random sequence generation • Low risk of bias unclear randomization method, but likely conducted Allocation concealment • Unclear risk of bias Unclear whether allocation was concealed Blinding of participants and personnel • High risk of bias Open trial Blinding of outcome assessment • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		none reported Inclusion criteria • DVT Idiopathic proximal DVT, as demonstrated on compression ultrasonography or venography. • Already received anticoagulation therapy at least 3 months without VTE recurrence or major bleed • 15-85 years Exclusion criteria • Other indication requiring long-term anticoagulation • Life expectancy <2 years • Major psychiatric disorder • Unable to return for follow-up visits Sample characteristics • Sample size 267 participants • Split between study groups 133 warfarin; 134 discontinued • %female Warfarin arm: 38.8% female Discontinue arm: 45.5% female • Mean age (SD) Warfarin arm: 66.8 (SD6.7) years Discontinue arm: 67.7 (SD 7.3) years Interventions • Warfarin alone adjusted to achieve a target INR of 2.0-3.0	outcome assessment was blinded (unclear methodology) Incomplete outcome data • High risk of bias For several outcomes (adverse events and mortality) it is unclear how many events occurred during the 9 month intended treatment phase. Selective reporting • Low risk of bias Other sources of bias • High risk of bias Unclear whether both groups received interim parenteral AC following randomization; no segmentation of results for LMWH versus UFH Overall risk of bias • High Participants and physicians were unblinded. Unclear reporting of allocation concealment and the use of parenteral anticoagulants. Several outcomes were only reported overall and not in the initial 9 months "on-treatment" phase. Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Discontinue therapy Outcomes • All-cause mortality not extracted as it is unclear how many occurred during the on-treatment phase. • Major bleeding reported at 9 months (on-treatment period) and overall (only those in the first 9 months were analysed in this review). • VTE-recurrence Reported at 9 months (treatment period) and overall (this was excluded from the analysis as some participants were off-treatment. • Serious adverse events not extracted as it is unclear how many occurred during the on-treatment phase.	
Agnelli (2003) WODIT-PE trial	Extended oral anticoagulant therapy after a first episode of pulmonary embolism.	**Study type** • Randomised controlled trial **Study details** • Study location *Italy* • Study setting *19 Italian hospitals* • Study dates *January 1997 - December 2000* • Duration of follow-up *3-9 months* • Sources of funding	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias *unclear allocation concealment* **Blinding of participants and personnel** • High risk of bias *open-trial; participants and physicians were*

Author (year)	Title	Study details	Quality assessment
		none reported **Inclusion criteria** • PE *First episode of symptomatic, objectively confirmed PE* • Already received anticoagulation therapy *Completed 3 months uninterrupted oral AC without bleeding or recurrence.* • 15-85 years **Exclusion criteria** • Other *If PE was associated with permanent risk factors* • requirement for long term antiplatelet therapy *due to non-VTE conditions* • Life expectancy <2 years • Major psychiatric disorder • Unable to return for follow-up visits **Sample characteristics** • Sample size *326 participants* • Split between study groups *165 continue; 161 discontinue therapy* • Loss to follow-up *two participants in continued therapy group* • %female *Discontinued group: 58.4% female Continued group: 60.6% female*	*unblinded* **Blinding of outcome assessment** • Low risk of bias *outcome assessors were blinded; unclear methodology* **Incomplete outcome data** • High risk of bias *Outcome data reported only for end of follow-up period. limited reporting for occurrences taking places during treatment period.* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias **Overall risk of bias** • High *Physicians and participants were unblinded, allocation concealment was unclear and limited reporting for occurrences whilst on-treatment*

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) *Discontinued group: 61.0 (SD 15.5) years Continued group: 62.9 (SD 16.3) years* • PE/DVT split (for VTE only studies) *All had PE 55.3% had concomitant DVT* • Provoked vs. unprovoked *Discontinued group: 56.5% idiopathic PE Continued group: 54.5% idiopathic PE* **Interventions** • Warfarin alone *adjusted to an INR of between 2.0-3.0. Participants with idiopathic PE received 9 months additional therapy. Those with transient risk factors received 3 months additional therapy.* • Discontinue therapy **Outcomes** • All-cause mortality • Major bleeding • VTE-recurrence	**Directness** • Directly applicable
Agnelli (2013) AMPLIFY-EXT trial	Apixaban for extended treatment of venous thromboembolism	Study type • Randomised controlled trial Study details • Study location 28 countries • Study setting 328 sites in 28 countries • Study dates	Random sequence generation • Low risk of bias performed using an interactive voice-response system and stratified by initial diagnosis and participation or no participation in the AMPLIFY trial.

Author (year)	Title	Study details	Quality assessment
		May 2008 - July 2011 (enrolment) • Duration of follow-up intended follow-up: 1 year Participants underwent monthly follow-up for study period and an additional 30 days (post-treatment period) • Sources of funding Funded by Bristol-Myers Squibb and Pfizer) Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE • Already received anticoagulation therapy Already received standard anticoagulation therapy for 6-12 months or completed treatment with apixaban or enoxaparin + VKA as participants in the AMPLIFY trial, and there was clinical equipoise about continuing or stopping anticoagulant therapy. Exclusion criteria • Other required ongoing AC therapy, dual antiplatelet therapy, or aspirin at a dose >165mg daily. • Haemoglobin level <9mg/dL • Platelet count of <100,000 per cubic mm • Serum creatinine level > 2.5 mg/dL • Calculated creatinine clearance <25ml/min • symptomatic recurrence during prior anticoagulation therapy • Baseline aminotransferase level >2x ULN • Bilirubin level >1.5x ULN	Allocation concealment • Unclear risk of bias Blinding of participants and personnel • Low risk of bias unblinded Blinding of outcome assessment • Low risk of bias suspected outcomes were rated by a blinded committee Incomplete outcome data • Low risk of bias Low although not segmentable by index diagnosis Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size 2482 participants • Split between study groups Apixaban (2.5mg, twice daily): 840 Apixaban (5mg, twice daily): 813 Placebo: 829 • Loss to follow-up 5 participants were not included in the analysis an additional 436 discontinued treatment early. • %female 42% female • Mean age (SD) Apixaban 2.5mg: 56.6 (SD 15.3) years Apixaban 5mg: 56.4 (SD 15.6) years Placebo: 57.1 (SD 15.2) years • PE/DVT split (for VTE only studies) 65% DVT, 35% PE • Provoked vs. unprovoked 92% unprovoked VTE at current diagnosis • Previous VTE 12.7% had prior VTE Interventions • Placebo twice daily for 1-year • Apixaban 2.5mg apixaban or 5mg apixaban (all twice daily and administered for an intended 12 months). Outcomes • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding	

Author (year)	Title	Study details	Quality assessment
		• Major bleeding • VTE-recurrence Other outcomes reported but were not segmented by PE or DVT index groups • Serious adverse events	
Becattini (2012) WARFASA trial	Aspirin for preventing the recurrence of venous thromboembolism: editorial comment	Study type • Randomised controlled trial Study details • Study location *Italy* • Study setting • Study dates *May 2004 - August 2010* • Duration of follow-up *Patients were re-examined every 3 months during the first year after randomization and every 6 months thereafter.* • Sources of funding *1 patient excluded from efficacy and safety analysis* Inclusion criteria • ≥18 years • Already received anticoagulation therapy *treated for 6 to 18 months with vitamin K antagonists (with a target international normalized ratio [INR] of 2.0 to 3.0)* • VTE *Treated for first-ever, objectively confirmed, symptomatic, unprovoked proximal deep-vein thrombosis, pulmonary embolism, or both. Venous thromboembolism was*	Random sequence generation • Unclear risk of bias *states that participants were randomly assigned however no methodology was given.* Allocation concealment • Unclear risk of bias *no information given* Blinding of participants and personnel • Low risk of bias *double-blind* Blinding of outcome assessment • Low risk of bias *independent adjudicators for outcomes.* Incomplete outcome data • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		considered to be unprovoked when it occurred in the absence of any known risk factor for this event. Exclusion criteria • Contraindication(s) for study drugs *"know allergy or intolerance to aspirin"* • Other indication for VKA • Active bleeding *or high risk of bleeding, or a bleeding episode which occurred during the 6-18 months of anticoagulation.* • Pregnancy *or breast feeding* • Known cancer • known thrombophilia • Life expectancy < 6 months • Women with VTE associated with use of estro-progestin therapy Sample characteristics • Sample size *403* • Split between study groups *205 aspirin; 198 placebo* • %female *64% female* • Mean age (SD) *Aspirin arm: 61.9 (SD 15.3) years Placebo arm: 62.1 (SD 15.1) years* • PE/DVT split (for VTE only studies) *Aspirin arm: 59.5% DVT, 40.5% PE Placebo arm: 65.9%*	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate *Unclear randomization procedures.* Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		DVT, 34.1% PE Interventions • Placebo *for up to 2 years* • Aspirin *100 mg once daily for up to 2 years* Outcomes • All-cause mortality • Clinically relevant non-major bleeding • Major bleeding *Patients were instructed to report to the study centre immediately if they had symptoms suggestive of bleeding complications* • VTE-recurrence *Patients were instructed to report to the study centre immediately if they had symptoms suggestive of recurrent VTE*	
Brighton (2012) ASPIRE trial	Low-dose aspirin for preventing recurrent venous thromboembolism	Study type • Randomised controlled trial Study details • Study location *5 countries* • Study setting *56 sites* • Study dates	Random sequence generation • Low risk of bias *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).*

Author (year)	Title	Study details	Quality assessment
		May 2003 - August 2011 • Duration of follow-up *Patients attended follow-up visits at 1 month and 6 months after randomization and every 6 months thereafter and were contacted by telephone or e-mail at the 3-month mark between visits. Study drug given for up to 4 years.* Inclusion criteria • ≥18 years • Already received anticoagulation therapy *completed initial anticoagulation therapy with heparin followed by warfarin (or an effective alternative anticoagulant). The duration of the initial anticoagulation therapy had to be between 6 weeks and 24 months; however, it was recommended that a target international normalized ratio of 2 to 3 be maintained with warfarin therapy for 6 to 12 months.* • VTE *first unprovoked episode of objectively diagnosed symptomatic deep-vein thrombosis involving the popliteal vein or more proximal leg veins or an acute pulmonary embolism. Venous thromboembolism was considered to be unprovoked if it occurred in the absence of the following transient risk factors during the preceding 2 months: confinement to bed for more than 1 week, major surgery, trauma requiring a cast, pregnancy or the puerperium, and the use of the oral contraceptive pill or hormone-replacement therapy. Patients were not eligible for inclusion if the first unprovoked episode of venous thromboembolism had occurred more than 2 years before*	Allocation concealment • Unclear risk of bias *no information* Blinding of participants and personnel • Low risk of bias *"double-blind"* Blinding of outcome assessment • Low risk of bias *All episodes of venous thromboembolism, myocardial infarction, and stroke and the causes of death were adjudicated by an independent outcome assessment committee whose members were unaware of the group assignments. However, no mention of bleeding outcomes being adjudicated.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		enrolment Exclusion criteria • Contraindication(s) for study drugs *indication or contraindication for the use of aspirin, other antiplatelet therapy, or a nonsteroidal anti-inflammatory drug* • Other indication for VKA • Other *other medical problems that would interfere with participation in the trial or limit life expectancy.* • index event over 2 years prior to enrolment *Patients were not eligible for inclusion if the first unprovoked episode of venous thromboembolism had occurred more than 2 years before enrolment* Sample characteristics • Sample size *822 participants* • Split between study groups *411 aspirin arm; 411 placebo arm* • %female *46% women* • Mean age (SD) *Median age is 54 years* • PE/DVT split (for VTE only studies) *57% DVT alone; 28% PE alone; 14% both* • Other *36% had a BMI of 30 or higher; 5% had a prior provoked VTE; 2% active cancer; 73% received AC for at least 6*	Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		months prior to randomization. 9% received 12 months or more. Interventions • Placebo • Aspirin *100 mg for up to 4 years* Outcomes • All-cause mortality • Clinically relevant non-major bleeding *Bleeding episodes that did not meet the definition of major bleeding were considered to be clinically relevant only if they led to discontinuation of the study drug for more than 14 days.* • Major bleeding *Major bleeding was defined as overt bleeding that was associated with a decrease in haemoglobin of at least 2 g per decilitre or that necessitated transfusion of 2 or more units of blood, involved a critical site (e.g., retroperitoneal or intracranial bleeding), was disabling, required surgical intervention, or contributed to death.* • VTE-recurrence *The primary outcome of the study was a recurrence of venous thromboembolism, defined as a composite of symptomatic, objectively confirmed deep-vein thrombosis, nonfatal pulmonary embolism, or fatal pulmonary embolism. All patients who stopped using the study drug continued to be followed and were included in the*	

Author (year)	Title	Study details	Quality assessment
		intention-to-treat analysis.	
Cohen (2016)	Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial	Study type • Randomised controlled trial Study details • Duration of follow-up *Trial follow-up continued for 210 days (treatment of 180 days plus 30 days follow-up)* Inclusion criteria • ≥18 years • 6 months of anticoagulation deemed appropriate *already received warfarin to target INR of 2.5 for at least 3 months since last VTE event* • Thrombotic antiphospholipid syndrome *The index VTE must have occurred when taking no or subtherapeutic anticoagulant therapy. Participants must have been taking at least 3 months standard intensity warfarin since index VTE event. The diagnosis of aPL is based on the Sapporo (Sydney) International Consensus Criteria, and International Society of Thrombosis and Haemostasis Scientific Subcommittee (ISTH SCC) and British Committee for Standards in Haematology (BCSH) guidance* Exclusion criteria • Other *Women not using adequate contraception (unless they*	Random sequence generation • Low risk of bias *Randomisation was performed by a web-based independent randomisation service (Sealed Envelope, London, UK) to ensure allocation concealment. The schedule was created using permuted blocks with a random block length, stratified by centre and patient type (with vs without systemic lupus erythematosus).* Allocation concealment • Low risk of bias *Randomisation was performed by a web-based independent randomisation service (Sealed Envelope, London, UK) to ensure allocation concealment.* Blinding of participants and personnel • High risk of bias *open label study* Blinding of outcome assessment • High risk of bias *open label study*

Author (year)	Title	Study details	Quality assessment
		were postmenopausal or had undergone sterilisation); previous arterial thrombotic events due to antiphospholipid syndrome or recurrent VTE when taking warfarin within therapeutic range; alanine aminotransferase > 2X ULN; Child-Pugh class B or C cirrhosis; thrombocytopenia (platelets <75 × 10⁹/L); non-adherence to warfarin regimen (based on clinical assessment); taking azole class antifungals, protease inhibitors (e.g., ritonavir) for HIV, strong CYP3A4 inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's wort), or dronedarone; refusal to give consent for the study site to inform a family doctor or health-care professional responsible for anticoagulation care about participation. • Creatine clearance <30ml/min • Pregnancy Sample characteristics • Sample size *116* • Split between study groups *57 received Rivaroxaban, 59 received Warfarin* • %female *Rivaroxaban group: 74% Warfarin group: 71%* • Mean age (SD) *Rivaroxaban group: 47 (17) years Warfarin group: 50 (14) years* • PE/DVT split (for VTE only studies) *DVT index event: 56% in rivaroxaban group and 63% in warfarin group. PE index event: 44% in rivaroxaban group and 37% in warfarin group.*	Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low *Low risk of bias for objective outcomes. However, as the study was open label there is a moderate risk of bias for the quality of life outcomes as these are likely to have been impacted by knowledge of which drug they are receiving.* Directness • Partially applicable intended duration of treatment was 180 days however outcomes (except for quality of life*) were reported at 210 days. Quality of life outcomes were directly applicable to the review question.

Author (year)	Title	Study details	Quality assessment
		• Antiphospholipid antibodies *aPL categories I (excluding triple positive aPL): 28% in rivaroxaban group, 32% in warfarin group. I (including triple positive aPL): 12% in rivaroxaban group, 20% n warfarin group. IIa: 53% in rivaroxaban group, 39% n warfarin group. IIB: 5% in rivaroxaban group, 2% n warfarin group. IIC: 2% in rivaroxaban group, 7% n warfarin group.* Interventions • Rivaroxaban *20 mg oral rivaroxaban once daily (or 15 mg once daily* depending on local clinical care and following the summary of product characteristics in patients with creatinine clearance 30–49 mL/min) for 180 days only 4% (participants) of the rivaroxaban arm received 15 mg once daily (the rest received 20mg once daily).* • Warfarin alone *remain on standard intensity warfarin with target INR 2·5 (range 2·0–3·0)* Outcomes • Clinically relevant non-major bleeding *at day 210* • Major bleeding *at day 210* • VTE-recurrence *at day 210* • Quality of life *Mean Ed-5Q-5L quality of life scores at day 180 with*	

Author (year)	Title	Study details	Quality assessment
		subgroup breakdown for health utility and health state: VAS components. • Serious adverse events *at day 210*	
Couturaud (2015) PADIS-PE trial	Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial.[Summary for patients in JAMA. 2015 Jul 7;314(1):98; PMID: 26151285]	Study type • Randomised controlled trial Study details • Study location France • Study setting 14 hospitals • Study dates July 2007 - March 2012 (enrolment) Last visit September 30, 2014 • Duration of follow-up 18 months on-treatment with a median post-treatment follow-up of 24-months. • Sources of funding Supported by grants from the programme hospitalier de recherche clinique Inclusion criteria • ≥18 years • PE symptomatic, first episode and unprovoked • Already received anticoagulation therapy received 6 months (range 5.5-7 months) uninterrupted VKA therapy	Random sequence generation • Low risk of bias Randomization was likely conducted however a large number of participants (42.4% of initial 649 participants considered) were excluded prior to randomization Allocation concealment • Unclear risk of bias unclear whether allocation was concealed from investigators Blinding of participants and personnel • Low risk of bias "double-blind" Blinding of outcome assessment • Low risk of bias outcomes were adjudicated blindly by an independent central committee Incomplete outcome data • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Other major surgery planned within 18 months from randomization • Other indication requiring long-term anticoagulation requiring VKA • Platelet count of <100,000 per cubic mm • High risk of bleeding • Previous VTE (prior to index VTE) • recurrent VTE in treatment prior to enrolment or bleeding during this time. • known major thrombophilia • life expectancy <18 months Sample characteristics • Sample size 374 randomized. • Split between study groups 184 warfarin therapy; 187 placebo • Loss to follow-up 7 lost to follow-up by 18 months visit. • %female warfarin group: 57.6% female Placebo group: 44.9% female • Mean age (SD) 58.7 (SD 17.9) years 57.3 (SD 17.4) years • PE/DVT split (for VTE only studies) 31.4% of participants had a concomitant proximal DVT at inclusion • Provoked vs. unprovoked 100% unprovoked • Other	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		warfarin group: 73.4% received prior warfarin, 26.6% received prior fluindione Placebo group: 61.5% received prior warfarin, 39.6% received prior fluindione Interventions • Placebo with sham INR, for 18 months • Warfarin alone Warfarin adjusted to target INR of 2.0-3.0, for 18 months Outcomes • All-cause mortality • VTE-related mortality • Major bleeding • VTE-recurrence	
Couturaud (2019) PADIS-DVT trial	Six months versus two years of oral anticoagulation after a first episode of unprovoked deep vein thrombosis. The PADIS-DVT randomized, clinical trial	Study type • Randomised controlled trial Study details • Study location France • Study setting 8 hospitals • Study dates July 2007 - October 2013 • Duration of follow-up 18 months on-treatment with a total follow-up of 42 months (not extracted for this review). • Sources of funding Supported by grants from the programme hospitalier de	Random sequence generation • Low risk of bias Based on a computer algorithm, the randomization list was generated by an independent statistician (ClinInfo SA, Lyon, France) in randomly permuted blocks of four or six, with stratification by center. Allocation concealment • Low risk of bias This list was forwarded to a central anticoagulation clinic not involved in patient care, before the first patient enrolment.

Author (year)	Title	Study details	Quality assessment
		recherche clinique Inclusion criteria • ≥18 years • First episode of unprovoked VTE received 6 months (range 5.5-7 months) uninterrupted VKA therapy Exclusion criteria • Other major surgery planned within 18 months from randomization • Other indication requiring long-term anticoagulation requiring VKA • Platelet count of <100,000 per cubic mm • High risk of bleeding • Previous VTE (prior to index VTE) • recurrent VTE in treatment prior to enrolment or bleeding during this time. • known major thrombophilia • life expectancy <18 months Sample characteristics • Sample size 104 randomized. • Split between study groups 50 warfarin therapy; 54 placebo • Loss to follow-up 0 lost to follow-up by 18 months visit. • %female warfarin group: 38.0% female Placebo group: 27.8% female	Blinding of participants and personnel • Low risk of bias double-blinded Blinding of outcome assessment • Low risk of bias outcomes were adjudicated blindly by an independent central committee Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Mean age (SD) 59.0 (SD 17.2) years 61.5 (SD 14.5) years • Provoked vs. unprovoked 100% unprovoked Interventions • Placebo with sham INR, for 18 months • Warfarin alone Warfarin adjusted to target INR of 2.0-3.0, for 18 months Outcomes • All-cause mortality • VTE-related mortality • Major bleeding • VTE-recurrence	
Crowther (2003)	A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome.	Study type • Randomised controlled trial Study details • Study location *Canada* • Study setting *13 tertiary care rheumatology and thromboembolism clinics* • Study dates *Recruited from between February 1998 and May 2001* • Duration of follow-up *telephone or clinic visit at 3 month intervals, with clinic*	Random sequence generation • Low risk of bias *"Patients were randomized by means of telephone calls to the study coordinating center. Patients were stratified according to the presence or absence of previous arterial thromboembolism and according to the clinical center. The randomization sequence was generated with the use of a random-number table and was performed in blocks of two, four, or six patients."* Allocation concealment • Unclear risk of bias

Author (year)	Title	Study details	Quality assessment
		visits required at least twice yearly. Average duration of follow-up was 2.7 years in moderate intensity group and 2.6 years in the high-intensity group. • Sources of funding *Supported by a grant from the Canadian Institutes for Health Research (MCT 14390).* Inclusion criteria • antiphospholipid syndrome *"positive test for antiphospholipid antibodies on two occasions at least three months apart. Acceptable candidates included those whose tests showed the presence of lupus anticoagulant, as defined by the International Society on Thrombosis and Haemostasis, a moderate or high tier of IgG anticardiolipin antibody, or both. Patients who had only IgM anticardiolipin antibodies were not eligible for the study."* • thrombosis *"objectively confirmed arterial or venous thrombosis".* Exclusion criteria • Other *a geographic location that would preclude follow-up.* • Pregnancy *or a planned pregnancy during the study period* • Clinically significant bleeding diathesis *(e.g., refractory thrombocytopenia with a platelet count of less than 50,000 per cubic millimetre)* • Contraindication to warfarin • History of recurrent thrombosis while receiving warfarin	*Unclear whether the randomization procedure would accurately conceal allocation.* Blinding of participants and personnel • Low risk of bias *"To minimize bias, we tried to ensure that patients, treating physicians, and other study personnel and adjudicators were unaware of the treatment assignments. Hence, INR results were forwarded to the central warfarin monitors."* Blinding of outcome assessment • Low risk of bias *"To minimize bias, we tried to ensure that patients, treating physicians, and other study personnel and adjudicators were unaware of the treatment assignments. Hence, INR results were forwarded to the central warfarin monitors."* Incomplete outcome data • High risk of bias *Not all outcome data was segmented by the type of thrombotic event presenting at enrolment. This sub-group analysis was not pre-specified.*

Author (year)	Title	Study details	Quality assessment
		targeted to an INR of 2.0 or greater Sample characteristics • Sample size *114; 87 of relevance to this review (participants with previous venous thrombosis)* • Split between study groups • %female *48% in the high warfarin group and 71% in the standard warfarin group* *values given for overall study population and were not available specifically for those enrolled with VTE* • Mean age (SD) *mean age 43 years in the high warfarin group and 41 years in the standard warfarin group* *values given for overall study population and were not available specifically for those enrolled with VTE* • Other *Aspirin at enrolment and throughout study: 14% in the high warfarin group and 10% in the standard warfarin group* Thromboembolism within: 14% in the high warfarin group and 10% in the standard warfarin group* *values given for overall study population and were not available specifically for those enrolled with VTE* • Antiphospholipid antibodies *IgG anticardiolipin antibody alone: 39% in the high warfarin group and 38% in the standard warfarin group* Lupus anticoagulant alone: 43% in the high warfarin group and 43% in the standard warfarin group* Both: 18% in the high warfarin group and 19% in the standard warfarin group* *values given for overall study population*	Selective reporting • Low risk of bias Other sources of bias • High risk of bias *Less than 50% of participants experienced their thrombotic event within 6 months of enrolment. This large variance in the timing of the index event will impact the outcome and no attempts are made to adjust for this. Additionally, this variance likely means that there is differences in anticoagulation use prior to the study, however no information on this is available.* Overall risk of bias • Moderate *There was large variance in the timing of the index thrombotic event (with most participants experiencing the event >6 months prior to the study). Additionally, only the outcome of VTE-recurrence presents a breakdown according to the type of index event (venous or arterial).* Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		and were not available specifically for those enrolled with VTE Interventions • Warfarin alone *standard intensity warfarin (INR 2.0-3.0) or high intensity warfarin (INR 3.0-4.0)* Outcomes • VTE-recurrence	
Cushman (2006)	Hormonal factors and risk of recurrent venous thrombosis: the prevention of recurrent venous thromboembolism trial.	Study type • Randomised controlled trial Study details • Study location US • Study setting 53 centres • Study dates July 1998 - December 2002 • Duration of follow-up Approximately every 2 months for a mean of 2.1 years and a maximum of 4.3 years • Sources of funding Received funding from National Heart, Lung and Blood institute. Drug and placebo supplied by Bristol-Myers Squibb. Authors also received grants from various pharmaceutical companies including AstraZeneca, Bristol-Myers Squibb and Roche	Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias Unclear whether allocation was concealed Blinding of participants and personnel • Low risk of bias Double-blinded. Blinding of outcome assessment • Low risk of bias All endpoints were reviewed by a blinded committee of physicians

Author (year)	Title	Study details	Quality assessment
		• Associated studies Ridker 2003 Inclusion criteria • Already received anticoagulation therapy already received at least 3 months warfarin with to an INR of 2.0 - 3.0 • Idiopathic VTE defined as VTE that did not occur with 90 days of surgery or trauma Exclusion criteria • <30 years old • Metastatic cancer • Life expectancy <3 years • antiphospholipid syndrome • Haemorrhagic stroke • Gastrointestinal bleeding Sample characteristics • Sample size 508 participants • Split between study groups 255 warfarin; 253 placebo • %female Warfarin group: 47.1% Placebo group: 47.4% • Mean age (SD) Warfarin group: Median age 53 (IQR 46-65) years Placebo group: Median age 53 (IQR 47-64) years • Previous VTE Warfarin group: 40% had 2 or more prior VTEs Placebo group:36.8% had 2 or more prior VTEs	Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias Wide range of treatment duration with a lack of subgroup analysis, limiting interpretability. There was a wide range of time between receiving last dose of treatment prior to randomization, although the median duration is comparable between groups. Similarly, the duration of prior treatment varied. Overall risk of bias • Moderate Variability in current-trial and prior treatment lengths and varying length of time from prior treatment to randomization. Directness • Partially applicable Study drug is given at a dose less that that which is currently used in clinical practice

Author (year)	Title	Study details	Quality assessment
		• Other Median warfarin duration prior to treatment was 6.7 months for Warfarin arm and 6.4 months for placebo arm. Median length of time from last treatment to randomization was 7 weeks (range 12 days - 2 years) All participants received a 24 day run-in phase of warfarin treatment prior to randomization Interventions • Placebo patients participated in a 28-day open-label run-in phase designed to ensure that all participants could have their dose of warfarin titrated to a stable level that achieved an INR between 1.5 and 2.0 without exceeding a dose of 10 mg per day. The run-in phase was also used to exclude patients with a level of compliance of less than 85 percent. Patients were then given placebo with sham dose adjustments • Warfarin alone patients participated in a 28-day open-label run-in phase designed to ensure that all participants could have their dose of warfarin titrated to a stable level that achieved an INR between 1.5 and 2.0 without exceeding a dose of 10 mg per day. The run-in phase was also used to exclude patients with a level of compliance of less than 85 percent. Participants were then given low-intensity warfarin (Coumadin, provided without charge by Bristol-Myers Squibb; target INR, 1.5 to 2.0). Outcomes • All-cause mortality • Major bleeding	

Author (year)	Title	Study details	Quality assessment
		Defined as bleeding episode that led to hospitalisation of transfusion. • VTE-recurrence The end point of recurrent deep venous thrombosis was considered to be confirmed if there was a positive venographic study, Doppler compression ultrasonography, or MRI. Events documented by clinical diagnosis alone were not considered to be confirmed. The end point of pulmonary embolism was considered to be confirmed if there was a positive angiogram, a ventilation–perfusion scan that showed at least two segmental defects without ventilation defects, or clear evidence of thrombosis documented by CT or MRI of the chest. In cases of deep venous thrombosis or pulmonary embolism in which the recurrent event occurred in the same leg or lung field as the index event, documentation demonstrating a clear difference between the two events was required.	
Investigators EINSTEIN-DVT (2010) EINSTEIN-EXT trial	Oral rivaroxaban for symptomatic venous thromboembolism	Study type • Randomised controlled trial Study details • Study location 27 countries • Study dates February 2007 - March 2009 (enrolment) • Duration of follow-up Up to 12 months for both studies • Sources of funding sponsored by Bayer and Ortho-McNeil. • Associated studies Bamber 2013 quality of life study Prins 2014 cancer	Random sequence generation • Low risk of bias randomly assigned using computerized voice-response system, stratified by country Allocation concealment • High risk of bias Intended treatment duration was determined by treating physician Blinding of participants and personnel • Low risk of bias double-blind

Author (year)	Title	Study details	Quality assessment
		subgroup analysis study Prins 2015 quality of life study Inclusion criteria -Objectively confirmed, symptomatic DVT or PE and had been treated for 6-12 months with acenocoumarol or warfarin or rivaroxaban -Need for continued treatment -No other indications for VKA -Creatine clearance >30 ml/min -No clinically significant liver disease -Alanine amino-transferase level <3xULN -No bacterial endocarditis -No active bleeding or high risk of bleeding -No contraindicating anticoagulant treatment -Systolic blood pressure <180mmHg AND diastolic blood pressure greater than 110 mmHg -Not pregnant or of childbearing potential (unless using proper contraceptive measures) -Not breast-feeding -No concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers -No participation in another experimental pharmacotherapeutic program within 30 days before screenings -Life expectancy over 3 months Sample characteristics • Sample size 1197 • Split between study groups 602 rivaroxaban; 594 placebo • Loss to follow-up 8 lost to follow-up • %female 42.1% female • Mean age (SD) 58.3 (SD 15.8) years • PE/DVT split (for VTE only studies) 38% PE; 62% DVT	Blinding of outcome assessment • Low risk of bias Suspected outcome events were classified by a blinded central adjudication committee Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias Treatment length varied between participants with limited reporting for individual time-points, it is unclear whether event rates at the median length of treatment (6 months) was similar to overall event rate. Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Provoked vs. unprovoked 74% unprovoked • Previous VTE 16.1% Interventions • Rivaroxaban 20mg once daily for 6-12 months • Placebo Outcomes • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life. • Major bleeding Bleeding was defined as major if it was clinically overt and associated with a fall in the haemoglobin level of 20 g per litre or more, or if it led to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death. • VTE-recurrence The criteria for the diagnosis of deep-vein thrombosis were a new noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on	

Author (year)	Title	Study details	Quality assessment
		venography. The criteria for diagnosis of pulmonary embolism were a new intraluminal filling defect on spiral CT or pulmonary angiography, a cut-off of a vessel of more than 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non– high-probability perfusion defect associated with deep-vein thrombosis, as documented by ultrasonography or venography. Fatal pulmonary embolism was based on objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death). • Quality of life	
Kearon (1999)	A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism.	Study type • Randomised controlled trial Study details • Study location Canada • Study dates October 1994 - April 1997 • Duration of follow-up 24 months (on-treatment period). Follow-up stopped after initial recurrent event. • Sources of funding Supported by a grant from DuPont pharma and the Medical Research Council of Canada, the Heart and Stroke Foundation of Canada and Ministry of Health of Ontario.	Random sequence generation • Low risk of bias likely randomized but using unclear methodology Allocation concealment • Unclear risk of bias Unclear whether allocation was concealed. Blinding of participants and personnel • Low risk of bias double-blind Blinding of outcome assessment • Low risk of bias outcomes adjudicated by a blinded central committee.

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Already received anticoagulation therapy for 3 uninterrupted months • Idiopathic VTE Exclusion criteria • Other allergic to contrast medium • Other indication requiring long-term anticoagulation • Pregnancy or could become pregnant • Life expectancy <2 years • Major psychiatric disorder • Unable to return for follow-up visits • require long-term NSAID treatment or treatment of ticlopidine, sulfinpyrazone, dipyridamole or >160mg aspirin (daily) • Familial bleeding diathesis Sample characteristics • Sample size 327 enrolled, 162 randomized. • Split between study groups 79 Warfarin; 83 placebo • Loss to follow-up 27 participants discontinued treatment prior to study completion All randomized participants were included in analysis • %female 40% female • Mean age (SD) 59 (SD16) years	Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• PE/DVT split (for VTE only studies) 75% DVT only, 25% PE only or PE with DVT • Provoked vs. unprovoked 100% unprovoked • Previous VTE 5% previous VTE • Other AC prior to enrolment: minimum of 3 months, mean 15 weeks (SD 2 weeks). Interventions • Placebo for 24 months • Warfarin alone Warfarin adjusted to a target INR of 2.0-3.0, for 24 months Outcomes • All-cause mortality • Major bleeding clinically overt and associated with either a fall in the haemoglobin level of at least 2.0 g per decilitre or a need for the transfusion of two or more units of red cells; if it was retroperitoneal or intracranial; or if it warranted the permanent discontinuation of the study drug. • VTE-recurrence Deep-vein thrombosis was diagnosed if the sonogram revealed that a common femoral or popliteal venous segment had become newly noncompressible, as compared with the base-line compression sonogram. 6 All other findings, including normal results on compression ultrasonography of the proximal veins, were considered nondiagnostic, and ipsilateral ascending venography was	

Author (year)	Title	Study details	Quality assessment
		performed, supplemented by the findings on serial impedance plethysmography or compression ultrasonography if venography was nondiagnostic (showing areas of non-filling without an intraluminal filling defect).	
Kearon (2003) ELATE trial	Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism.	Study type • Randomised controlled trial Study details • Study location *Canada & USA* • Study setting *16 centres across Canada.* • Study dates *December 1, 1998 to May 30, 2001; follow-up stopped on June 30, 2002.* • Duration of follow-up *"The mean duration of follow-up was 2.4 years in both groups; the mean period during which patients received double-blind treatment was 2.1 years in the low-intensity–therapy group and 2.2 years in the conventional-intensity–therapy group. "* • Sources of funding *Supported by the Canadian Institutes of Health Research.* Inclusion criteria • Already received anticoagulation therapy *of 3 or more months conventional intensity warfarin*	Random sequence generation • Low risk of bias *"After patients provided written informed consent, randomization was performed with stratification according to clinical centre and according to whether the patient had completed three to four months or more than four months of initial anticoagulant therapy. A computer algorithm, with a randomly determined block size of two or four within each stratum, generated lists in which patients were assigned to either long-term, low-intensity warfarin therapy (target INR, 1.5 to 1.9) or conventional-intensity warfarin therapy (target INR, 2.0 to 3.0)."* Allocation concealment • Low risk of bias *"Allocation lists were sent to an "anticoagulation monitor" at each clinical centre who was not involved in the patients' care."* Blinding of participants and personnel • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		therapy. • VTE *unprovoked VTE, defined as objectively confirmed, symptomatic, proximal deep venous thrombosis or pulmonary embolism that occurred in the absence of a major risk factor for thrombosis.* Exclusion criteria • Contraindication(s) for study drugs *including a high risk of bleeding or allergy to contrast medium.* • Other indication for VKA • antiphospholipid syndrome • Life expectancy <2 years Sample characteristics • Sample size *738* • Split between study groups *369 in each arm* • Loss to follow-up *Double-blind treatment was permanently discontinued in 84 patients assigned to low-intensity therapy (because of bleeding in 6, another contraindication to anticoagulant therapy in 4, confirmed venous thromboembolism in 10, another indication for conventional-intensity anticoagulant therapy in 14, the preference of the patient in 29, and other reasons in 21) and in 58 patients assigned to conventional-intensity therapy (because of bleeding in 7, confirmed venous thromboembolism in 2,*	*double-blind* Blinding of outcome assessment • Low risk of bias *outcomes were adjudicated by a blinded committee.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		another indication for conventional-intensity anticoagulant therapy in 5, the preference of the patient in 21, and other reasons in 23). • %female *45% female* • Mean age (SD) *57 (SD 16) years* • PE/DVT split (for VTE only studies) *DVT only 65%, PE + DVT 35%* • Provoked vs. unprovoked *100% unprovoked* • Previous VTE *31% had 2 or more prior episodes of VTE* • Other *47% had an abnormal CUS of proximal deep veins at enrolment (same for both arms)* Interventions • Warfarin alone *standard intensity (INR 2.0-3.0 warfarin)* • low-intensity warfarin *INR 1.5-1.9* Outcomes • All-cause mortality • Major bleeding *Bleeding was defined as major if it was clinically overt and associated with a decrease in the haemoglobin level of at least 2.0 g per decilitre or a need for transfusion of two or more units of red cells or if it involved a critical site (e.g.,	

Author (year)	Title	Study details	Quality assessment
		retroperitoneal or intracranial bleeding). • VTE-recurrence *Patients were assessed every six months and were told to report to the centre immediately if symptoms developed that were suggestive of venous thromboembolism or if they had bleeding. Suspected recurrent venous thromboembolism was evaluated by means of objective diagnostic testing*	
Schulman (2013) RE-MEDY and RE-SONATE trials	Extended use of dabigatran, warfarin, or placebo in venous thromboembolism	Study type • Randomised controlled trial Study details • Study location RE-MEDY: 33 countries RE-SONATE: 21 countries. • Study setting RE-MEDY: 265 sites in 33 countries RE-SONATE: 147 sites in 21 countries. • Study dates RE-MEDY: July 2006 - July 2010 RE-SONATE: November 2007 - September 2010 • Duration of follow-up RE-MEDY: Initially designed as 18-month treatment study but extended to be 36 months with duration spanning from 6-36 months. Patients were assessed at 15 and 30 days and then monthly until day 180, and then every 90 days until end of treatment. RE-SONATE: 6 months study period plus 12 months follow-up to study long term effects. • Sources of funding Funded by Boehringer Ingelheim	Random sequence generation • Low risk of bias Participants were randomized using a voice-response system Allocation concealment • Unclear risk of bias Unclear whether randomization procedure prevented allocation bias Blinding of participants and personnel • Low risk of bias study was double-blinded Blinding of outcome assessment • Low risk of bias Suspected outcome events were assessed by a blinded committee Incomplete outcome data • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • ≥18 years • Objectively confirmed symptomatic DVT or PE • Already received anticoagulation therapy or took part in RE-COVER or RE-COVER II trials as part of the Dabigatran arms. RE-MEDY- already received 3-12 months treatment RE-SONATE: already received 6-18 months treatment Exclusion criteria • RE-MEDY exclusion criteria -Symptomatic DVT or PE at screening - Patients with primary PE with suspected origin other that leg limbs (e.g. upper limbs, right heart). - Actual or anticipated use of vena cava filter - Interruption of anticoagulant therapy for 2 or more weeks during the 3-6 months of treatment for the prior venous thromboembolism (VTE). - Patients who in the investigator's opinion should not be treated with warfarin - Allergy to warfarin or dabigatran, or to one of the excipients included in these medications -Patients who in the investigator's judgement are perceived as having an excessive risk of bleeding, for example because of: o Haemorrhagic disorder or bleeding diathesis o Trauma or major surgery within the last month or as long as an excessive risk of bleeding persists after these events, or planned major surgery o Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm o History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding o Gastrointestinal haemorrhage within the past 3 months. o Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days o	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Treatment with thrombolytic agents within 14 days before enrolment o Anticipated need of restricted medication during the treatment period o Known thrombocytopenia (platelet count <100·109 /L) - Known anaemia (haemoglobin <100 g/L) -Need of anticoagulant treatment for disorders other than VTE -Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis or history of myocardial infarction within the last 3 months - Elevated aspartate-amino transferase (AST) or alanine-amino transferase (ALT) >2x upper limit of normal (ULN) based on the local lab results obtained at screening and prior to randomization (or central screening lab if available on time). - Liver disease expected to have any potential impact on survival (e.g. acute hepatitis, or possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery) -Patients who have developed transaminase elevations upon exposure to ximelagatran - Severe renal impairment (estimated creatinine clearance ≤30 ml/min) - Women who are pregnant, nursing or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study. • RE-SONATE exclusion criteria -Younger than 18 years of age - Indication for vitamin K antagonist other than DVT and/or PE - Patients in whom anticoagulant treatment for their index PE or DVT should be continued - Active liver disease or liver disease decreasing survival (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 x ULN -Creatinine clearance <30 ml/min - Acute bacterial endocarditis - Active bleeding or high risk for bleeding. - Uncontrolled hypertension (investigators judgement) - Intake of another experimental	

Author (year)	Title	Study details	Quality assessment
		drug within the 30 days prior to randomization into the study - Life expectancy <6 months -Childbearing potential without proper contraceptive measures, pregnancy or breast feeding - Patients with known hypersensitivity to dabigatran or any other component of the investigational product or the placebo capsules - Patients deemed unsuitable for inclusion by the investigator, because considered unreliable to comply with the requirements of the study and/or compliance with study drug administration, or because having any condition or disease which in the opinion of the investigator would not allow safe participation in the study. Sample characteristics • Sample size RE-MEDY: 2866 participants RE-SONATE: 1353 participants • Split between study groups RE-MEDY: 1430 Dabigatran arm, 1426 warfarin arm RE-SONATE: 681 Dabigatran arm, 662 Placebo arm • %female RE-MEDY: 39.0% female RE-SONATE: 44.6% female • Mean age (SD) RE-MEDY: Dabigatran arm 55.4 (SD15.0) years; warfarin arm 53.9 (SD15.3) years RE-SONATE: Dabigatran arm 56.1 (SD 15.3) years; placebo arm 55.5 (SD 15.1) years • PE/DVT split (for VTE only studies) RE-MEDY: 65.1% DVT only, 23.1% PE only, 11.8% both, 0.1% neither RE-SONATE: 65.0% DVT only, 26.9% PE only, 6.1% both, 2.0% neither	

Author (year)	Title	Study details	Quality assessment
		Interventions • RE-MEDY Dabigatran arm: 150mg twice daily for 6-36 months and a warfarin-like placebo and sham INR Warfarin arm: To maintain an INR of 2.0 to 3.0, treated for 6-36 months, and Dabigatran-like placebo • RE-SONATE Dabigatran arm: 150mg twice daily for 6 months Placebo arm: 6 months Outcomes • All-cause mortality • VTE-related mortality • Clinically relevant non-major bleeding • Major bleeding • VTE-recurrence • Quality of life • Serious adverse events	
Sterne (2017)	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	**Study type** • Network Meta- Analysis (NMA) **Study details** • Dates searched *2008 to September 2014* • Databases searched *MEDLINE and PREMEDLINE In-Process & Other Non-Indexed Citations, EMBASE and The Cochrane Library. NHS Economic Evaluation Database (NHS EED) and NICE Technology Appraisals were also searched.* • Sources of funding	**Rationale for review included?** • Yes *The limitations of previous synthesis research was discussed as a reason to undertake the review.* **Study inclusion/exclusion criteria specified clearly?** • Yes *Inclusion/exclusion criteria were about the type of RCTs, participants, interventions and comparators.*

Author (year)	Title	Study details	Quality assessment
		The Health Technology Assessment programme of the National Institute for Health Research. **Study inclusion criteria** • Phase II or Phase III RCTs using either a superiority or a non-inferiority design **Study exclusion criteria** • Trials in participants who were eligible for only parenteral (injected) anticoagulation • Studies evaluating fixed-dose administration of warfarin **Participant inclusion criteria** • Adults *≥ 18 years* • Eligible for oral anticoagulation or (antithrombotic) treatment • Secondary prevention of VTE Adults who have completed a minimum of 3 months of anticoagulant treatment for objectively confirmed first VTE without recurrence (secondary prevention) **Participant exclusion criteria** • None stated	**Description of network and potential biases related to it?** • Yes *From Chapter 3 Review methods: 'The intervention categories (or network nodes) are labelled throughout the report using drug, frequency and dose, or INR range, as appropriate.' '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.'* **Summary measures stated?** • Yes *Odds ratios were reported: 'The primary NMAs treat the data as binomial, modelling the number of events out of the total number of participants using a logistic model.'* **Methodology for data handling described?** • Yes *All analyses were based on fixed-effects models because there was insufficient replication of intervention comparisons to allow estimation of the heterogeneity variance. All meta-analyses were done within a Bayesian framework.* **Statistical methods to compare direct and indirect data described?**

Author (year)	Title	Study details	Quality assessment
		Interventions • Dabigatran • Apixaban • Edoxaban • Betrixaban • Rivaroxaban **Comparators** • Therapeutic doses of warfarin • Other VKA (with optimal INR range 2–4) • Placebo • No treatment **Outcomes** • Symptomatic VTE • Symptomatic DVT • Symptomatic PE • Major bleeding • CRB *Clinically relevant bleeding defined as clinically relevant non-major (CRNM) bleeding or major bleeding.* • Myocardial infarction • All-cause mortality **Analysis** • NMA methodology *All meta-analyses were performed within a Bayesian framework, using freely available WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK)*	• Yes *Inconsistency was checked at the network level visually and with model of fit and selection statistics.* **Description of subgroup, sensitivity and meta-regression analyses where applicable?** • Yes *There was a list of characteristics and factors as well as summary assessment of risk of bias for each outcome that were prespecified for subgroup and meta-regression analyses.* **Network diagram available?** • Yes *A network diagram was reported for each outcome.* **Characteristics of the treatment network described?** • Yes *Treatment networks were described for each outcome.* **Results of each meta-analysis presented?** • Yes *Results of NMAs were reported as ORs and 95% credible intervals. 'Rankograms' were not possible to derive for this network because many*

Author (year)	Title	Study details	Quality assessment
		and code. **Measures** • Odds Ratios (ORs)	*comparisons were imprecisely estimated. Forest plots were also reported for all contributing data with ORs and 95% confidence intervals.* **Investigations of inconsistency carried out?** • Yes *Inconsistency was carried out but model fit and selection statistics were not reported in results tables.* **Results presented for additional analyses?** • Incomplete presentation *Subgroup and meta-regression analyses were planned to examine the extent to which patient- and study-level prespecified characteristics explain between-study heterogeneity but these analyses were not reported. Supplementary analyses were reported as hazard ratios for symptomatic recurrent VTE and for bleeding events (CRB or major bleeding).* **Discussion of study limitations?** • Incomplete discussion *Limitations were discussed about the evidence base informing data analyses but no limitations were discussed about the NMAs.*

Author (year)	Title	Study details	Quality assessment
			Overall quality • Moderate *Additional analyses were incompletely reported. NMA limitations were not discussed.* **Applicability as a source of data** • Partially applicable *The NMA did not cover all outcomes of interest.*
Weitz (2017) EINSTEIN-CHOICE trial	Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism	Study type • Randomised controlled trial Study details • Study location *31 countries* • Study setting *244 sites across 31 countries* • Study dates *March 2014 - March 2016* • Duration of follow-up *up to 12 months* • Sources of funding *Supported by Bayer* Inclusion criteria • ≥18 years • Already received anticoagulation therapy *received 6-12 months of VKA or DOAC that was not interrupted for more than 7 days before randomization*	Random sequence generation • Low risk of bias *Randomization with a block size of six was performed with the use of an interactive voice-response system and was stratified according to the index diagnosis (deep-vein thrombosis or pulmonary embolism) and country.* Allocation concealment • Unclear risk of bias *Randomization with a block size of six was performed with the use of an interactive voice-response system and - unclear whether allocation was concealed until after randomization was completed.* Blinding of participants and personnel • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		• VTE *objectively confirmed proximal DVT or PE.* Exclusion criteria • Creatine clearance <30ml/min • Other *hepatic disease associated with a coagulopathy.* Sample characteristics • Sample size *3,365* • Loss to follow-up *31 participants did not take study medication and were not included in ITT; 218 participants were not included in the per protocol analysis.* • %female *55.4%* • Mean age (SD) *Rivaroxaban 20mg arm: 57.9±14.7 Rivaroxaban 10mg arm: 58.8±14.7 Aspirin 100mg arm: 58.8±14.7* • PE/DVT split (for VTE only studies) *Isolated DVT 51%; PE only 34%; both 15%* • Provoked vs. unprovoked *41.3% unprovoked* • Other *2.7% active cancer; Intended treatment duration (balanced between arms): 60.4% 12 months; 21% 9 to <12 months; 18.6% 6 months*	*Study was double blinded* Blinding of outcome assessment • Low risk of bias *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 that occurred during the study. An independent data and safety monitoring committee periodically reviewed the study outcomes.* Incomplete outcome data • Low risk of bias *Low risk overall however outcome data was not segmented by intended treatment duration* Selective reporting • Low risk of bias Other sources of bias • Low risk of bias

Author (year)	Title	Study details	Quality assessment
		Interventions • Rivaroxaban *20mg / 10mg once daily* • Aspirin *100 mg once daily* Outcomes • All-cause mortality • Clinically relevant non-major bleeding *Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, unscheduled contact with a physician, interruption or discontinuation of the study drug, or discomfort or impairment of activities of daily living.* • Major bleeding *defined as overt bleeding that was associated with a decrease in the haemoglobin level of 2 g per decilitre or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death.* • VTE-recurrence *either (1) or (2) 1) Symptoms of PE with one of the following findings: A (new) intraluminal filling defect in (sub)segmental or more proximal branches on spiral computed tomography (CT) scan A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (V/Q scan) Inconclusive spiral CT,*	Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		pulmonary angiography or lung scintigraphy with demonstration of deep vein thrombosis (DVT) in the lower extremities by compression ultrasound or venography □ Fatal PE based on autopsy or objective diagnostic testing prior to death □ Death that could not be attributed to a documented cause and for which PE/DVT could not be ruled out (unexplained death), 2) Symptoms of DVT with one of the following findings: Abnormal compression ultrasound where compression had been normal or, if non-compressible at screening or baseline, a substantial increase (≥4 mm) in diameter of the thrombus during full compression □ An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography. The accepted tests for venous thrombosis at other sites were ultrasound, venography, CT or magnetic resonance imaging (MRI). The criteria for venous thrombosis at other locations documented by US were incompressibility of a new vein or extension of the area involved in a previously partly incompressible vein, or presence of echogenic material combined with absence of flow in an area that could not be compressed in a new vein or extension of the area involved in a previously affected vein. For venography, CT or MRI, the criterion for VTE was an intraluminal filling defect in a vein or vein segment.	

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1 **Published NMAs**

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Author (year)	Title	Study details	Quality assessment
Sterne (2017)	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	**Study type** • Network Meta- Analysis (NMA) **Study details** • Dates searched *2008 to September 2014* • Databases searched *MEDLINE and PREMEDLINE In-Process & Other Non-Indexed Citations, EMBASE and The Cochrane Library. NHS Economic Evaluation Database (NHS EED) and NICE Technology Appraisals were also searched.* • Sources of funding *The Health Technology Assessment programme of the National Institute for Health Research.* **Study inclusion criteria** • Phase II or Phase III RCTs using either a superiority or a non-inferiority design **Study exclusion criteria** • Trials in participants who were eligible for only parenteral (injected) anticoagulation • Studies evaluating fixed-dose administration of warfarin	**Rationale for review included?** • Yes *The limitations of previous synthesis research was discussed as a reason to undertake the review.* **Study inclusion/exclusion criteria specified clearly?** • Yes *Inclusion/exclusion criteria were about the type of RCTs, participants, interventions and comparators.* **Description of network and potential biases related to it?** • Yes *From Chapter 3 Review methods: 'The intervention categories (or network nodes) are labelled throughout the report using drug, frequency and dose, or INR range, as appropriate.' '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.'* **Summary measures stated?** • Yes *Odds ratios were reported: 'The primary NMAs*

		Participant inclusion criteria • Adults ≥ *18 years* • Eligible for oral anticoagulation or (antithrombotic) treatment • Acute treatment of VTE Adults who have received a new or recurrent objectively confirmed diagnosis of acute symptomatic VTE **Participant exclusion criteria** • None stated **Interventions** • Dabigatran • Apixaban • Edoxaban • Betrixaban • Rivaroxaban **Comparators** • Therapeutic doses of warfarin • Other VKA (with optimal INR range 2–4) **Outcomes** • Symptomatic VTE • Symptomatic DVT • Symptomatic PE • Major bleeding • CRB	*treat the data as binomial, modelling the number of events out of the total number of participants using a logistic model.'* **Methodology for data handling described?** • Yes *All analyses were based on fixed-effects models because there was insufficient replication of intervention comparisons to allow estimation of the heterogeneity variance. All meta-analyses were done within a Bayesian framework.* **Statistical methods to compare direct and indirect data described?** • Yes *Inconsistency was checked at the network level visually and with model of fit and selection statistics.* **Description of subgroup, sensitivity and meta-regression analyses where applicable?** • Yes *There was a list of characteristics and factors as well as summary assessment of risk of bias for each outcome that were prespecified for subgroup and meta-regression analyses.* **Network diagram available?** • Yes

		Clinically relevant bleeding defined as clinically relevant non-major (CRNM) bleeding or major bleeding. • Myocardial infarction • All-cause mortality **Analysis** • NMA methodology *All meta-analyses were performed within a Bayesian framework, using freely available WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and code.* **Measures** • Odds Ratios (ORs)	*A network diagram was reported for each outcome.* **Characteristics of the treatment network described?** • Yes *Treatment networks were described for each outcome.* **Results of each meta-analysis presented?** • Yes *Results of NMAs were reported as ORs and 95% credible intervals. A summary of results across outcomes was reported as a 'rankogram' illustrating the probability that each treatment is best, second best, and so on, for each outcome. Forest plots were also reported for all contributing data with ORs and 95% confidence intervals.* **Investigations of inconsistency carried out?** • Yes *Inconsistency was carried out but model fit and selection statistics were not reported in results tables.* **Results presented for additional analyses?** • No *Subgroup and meta-regression analyses were planned to examine the extent to which patient- and study-level prespecified characteristics explain*

			between-study heterogeneity but these analyses were not reported. **Discussion of study limitations?** • Incomplete discussion *Limitations were discussed about the evidence base informing data analyses but no limitations were discussed about the NMAs.* **Overall quality** • Moderate *Additional analyses were planned but results on these were not reported. NMA limitations were not discussed.* **Applicability as a source of data** • Partially applicable *The NMA did not cover all outcomes of interest.*
Wang (2018)	Extended treatment of venous thromboembolism: a systematic review and network meta-analysis	**Study type** • Network Meta- Analysis (NMA) **Study details** • Dates searched *Medline (1950 to April 2017), Embase (1980 to April 2017), and CENTRAL databases from January 2013 to April 2017. Conference proceedings of the American Society of Haematology and the International Society on Thrombosis and Haemostasis were searched from 2013*	**Rationale for review included?** • Yes *The aim of the review was to help physicians and patients decide on the optimal management strategy for secondary prevention of VTE.* **Study inclusion/exclusion criteria specified clearly?**

		to 2017. • Databases searched *Medline, Embase, CENTRAL, conference proceedings of the American Society of Haematology and the International Society on Thrombosis and Haemostasis.* • Sources of funding *'The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.'* **Study inclusion criteria** • RCTs *Comparing any oral anticoagulant regimen or aspirin with one another, placebo or observation for extended treatment for secondary prevention of VTE.* • Report at least one of the outcomes of interest • Definition of extended treatment *Management beyond the first 3 months of acute VTE treatment.* **Study exclusion criteria** • Data on ximelagatran *This is because ximelagatran is not available for clinical practice.* **Participant inclusion criteria** • None stated	• Yes **Description of network and potential biases related to it?** • Yes *The evidence network for recurrent VTE and major bleeding was presented as a network diagram.* **Summary measures stated?** • Yes *'Median ORs or HRs and 95% credible intervals (CrIs) were reported as appropriate. The probability of the estimating rank and the surface under the cumulative ranking curve for a given regimen were calculated.'* **Methodology for data handling described?** • Yes *Bayesian network meta-analysis was used. Recurrent VTE, major bleeding and all-cause mortality were based on the binomial likelihood model. The Poisson likelihood model was used for analyses on fatal recurrent VTE and fatal bleeding as those events were rare and most studies contained at least one zero cell. All analyses were conducted in random-effects models with vague priors using WinBUGS V.1.4.3.*

		Participant exclusion criteria • None stated **Interventions** • Aspirin *100 mg once daily* • Low-intensity VKAs *Targeting an international normalised ratio between 1.5 and 2.0.* • Standard-intensity VKAs *Targeting an international normalised ratio between 2.0 and 3.0.* • Low-dose factor Xa inhibitors *Apixaban 2.5 mg twice daily and rivaroxaban 10 mg once daily* • Standard-dose factor Xa inhibitors *Apixaban 5 mg twice daily, edoxaban 60 mg (dose reduced to 30 mg by study criteria) once daily, and rivaroxaban 20 mg once daily.* • Direct thrombin inhibitor *Dabigatran 150 mg twice daily.* **Comparators** • Placebo • Observation **Outcomes** • Major bleeding • All-cause mortality • Recurrent VTE	**Statistical methods to compare direct and indirect data described?** • Yes *'Inconsistency in the network was assessed by comparing statistics for deviance and the deviance information criterion in fitted consistency and inconsistency models. The goodness of model fit was assessed based on residual deviance and the deviance information criterion. Trace plots and the Brooks-Gelman-Rubin statistic were checked to ensure convergence. No corrections for studies with no events were used.'* **Description of subgroup, sensitivity and meta-regression analyses where applicable?** • Yes *Subgroup analyses were performed on patients at potentially higher risk of recurrent VTE, including male patients, patients with index PE and patients with unprovoked VTE. Meta-regression was conducted to examine potential effects of baseline patient characteristics. Sensitivity analyses on recurrent VTE and major bleeding were performed.* **Network diagram available?** • Yes **Characteristics of the treatment network described?** • Yes

		• Fatal recurrent VTE **Analysis** • NMA methodology *All analyses were conducted in random-effects models with vague priors using WinBUGS V.1.4.3 (MRC Biostatistics Unit, Cambridge, UK).* **Measures** • Hazard ratios (HRs) *Median HRs and 95% credible intervals were reported as appropriate.* • Odds Ratios (ORs) *Median ORs and 95% credible intervals were reported as appropriate.*	*Characteristics of studies and estimated event rates were reported in tables.* **Results of each meta-analysis presented?** • Incomplete presentation *Direct estimates were not reported. Effect estimates of all pairwise comparisons in the evidence network were reported. Forest plots show oral anticoagulants or aspirin compared with placebo or observation. Surface under the cumulative ranking curve was reported for each outcome in the main text and in the supplementary material.* **Investigations of inconsistency carried out?** • Yes *Inconsistency investigations were reported as posterior mean deviance distributions, total residual deviance, and deviance information criterion in the supplementary material.* **Results presented for additional analyses?** • Yes *Subgroup analyses, meta-regression and sensitivity analyses were reported in the supplementary material.* **Discussion of study limitations?** • Yes

			Limitations were discussed about external validity (some patients were under-represented) and differences in included studies (this was investigated doing subgroup, meta-regression, and sensitivity analyses which showed no changes in conclusions). **Overall quality** • Moderate *Direct estimates were not reported.* **Applicability as a source of data** • Partially applicable *The NMA did not cover all outcomes of interest and some interventions were merged.*

1

Appendix F – Forest plots

Initial treatment analyses

LMWH + VKA versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

VTE recurrence

Figure 20: VTE-recurrence 14 days: Any VTE event

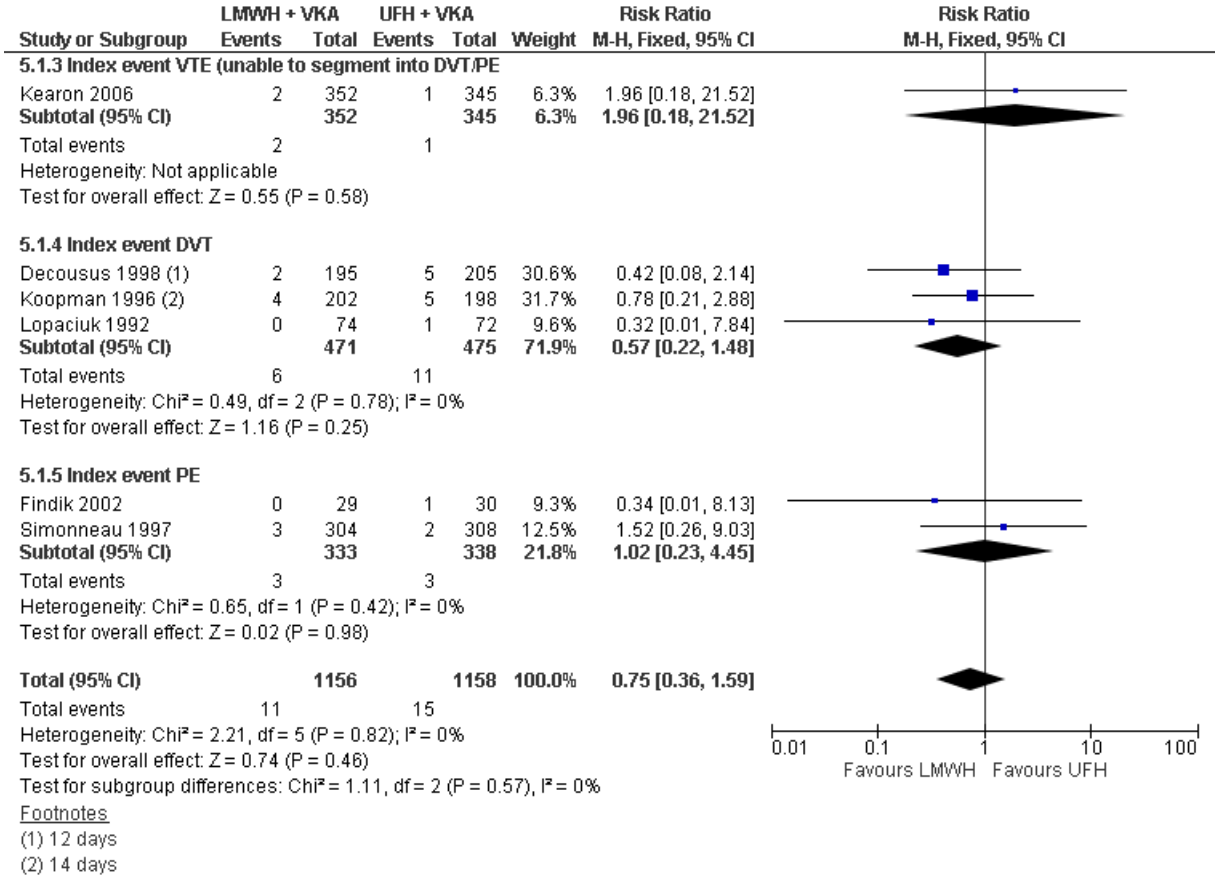


Figure 21: VTE recurrence 14 days: PE only

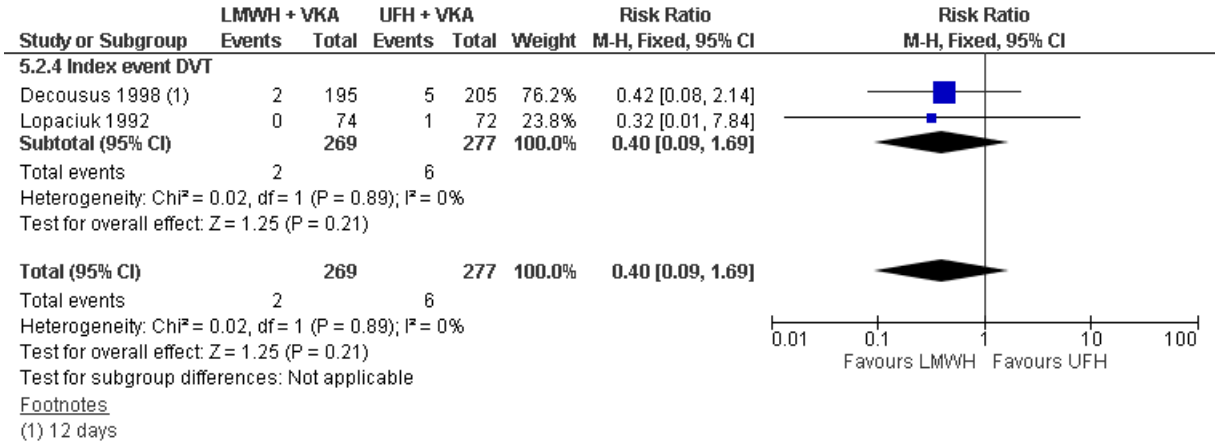
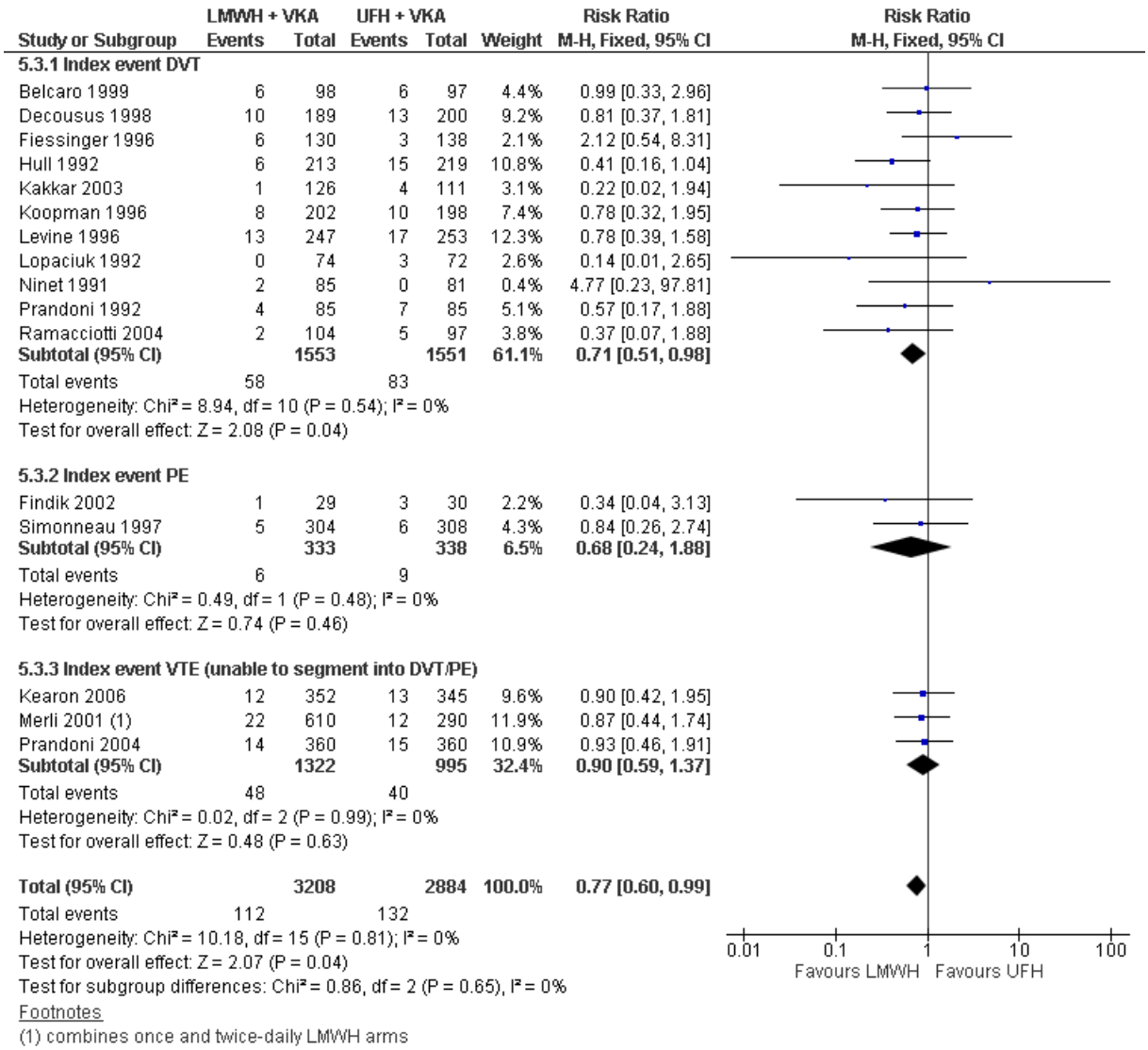


Figure 22: VTE recurrence 3 months: Any VTE event



Footnotes

(1) combines once and twice-daily LMWH arms

Figure 23 Funnel plot for VTE recurrence 3 months: Any VTE event

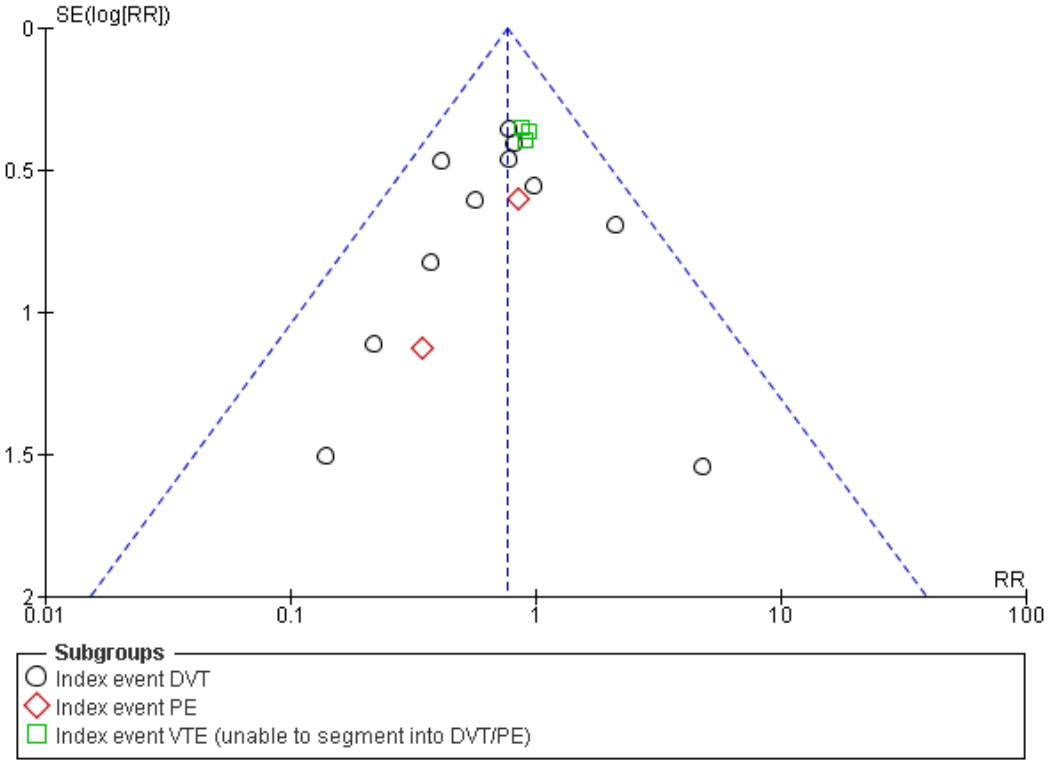


Figure 24: VTE recurrence 3 months: DVT only

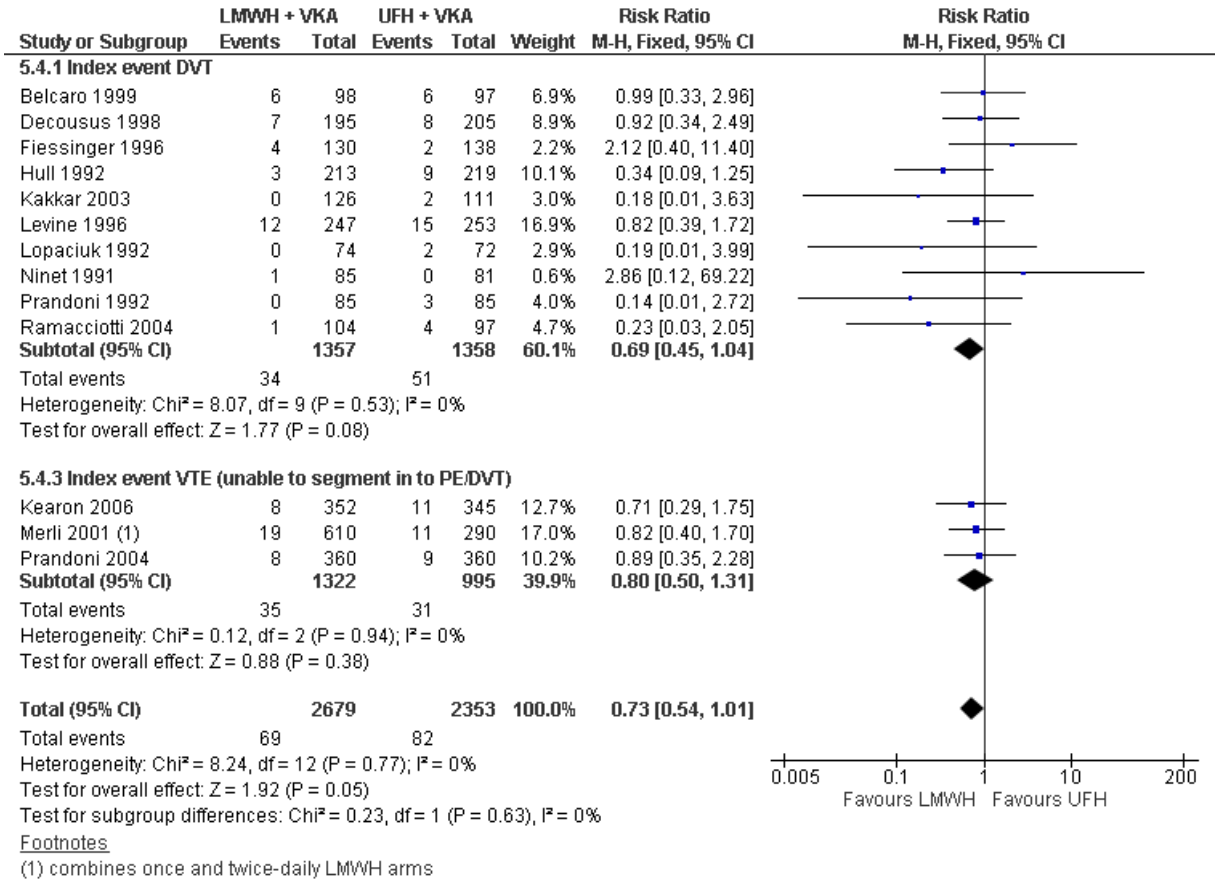


Figure 25: Funnel plot for VTE recurrence 3 months: DVT only

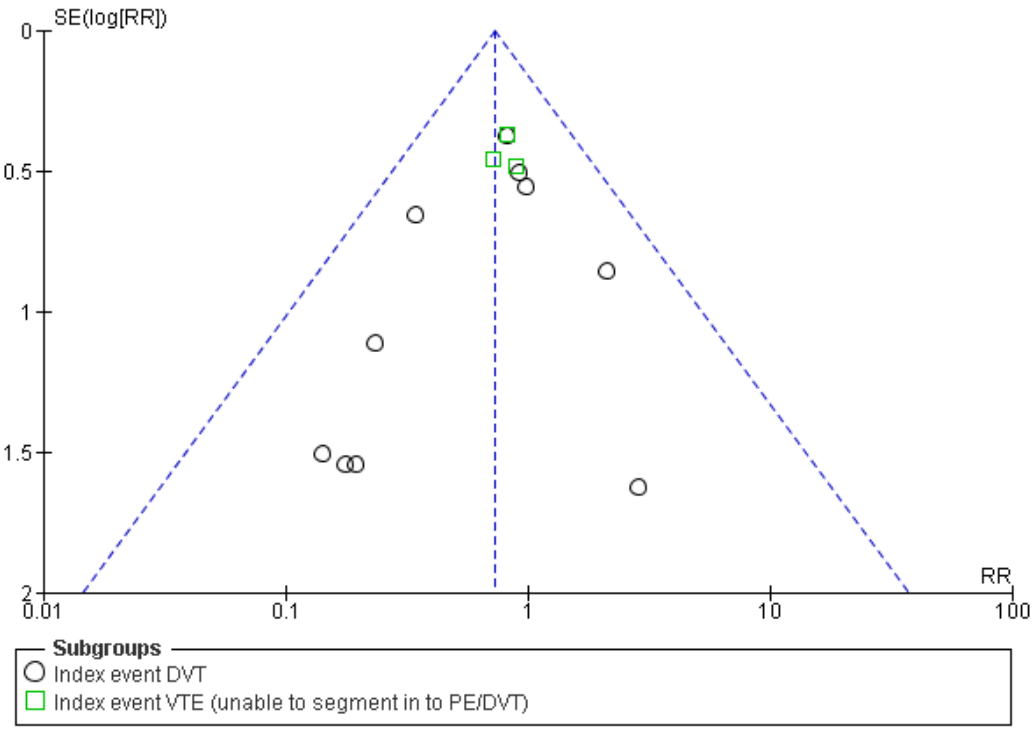
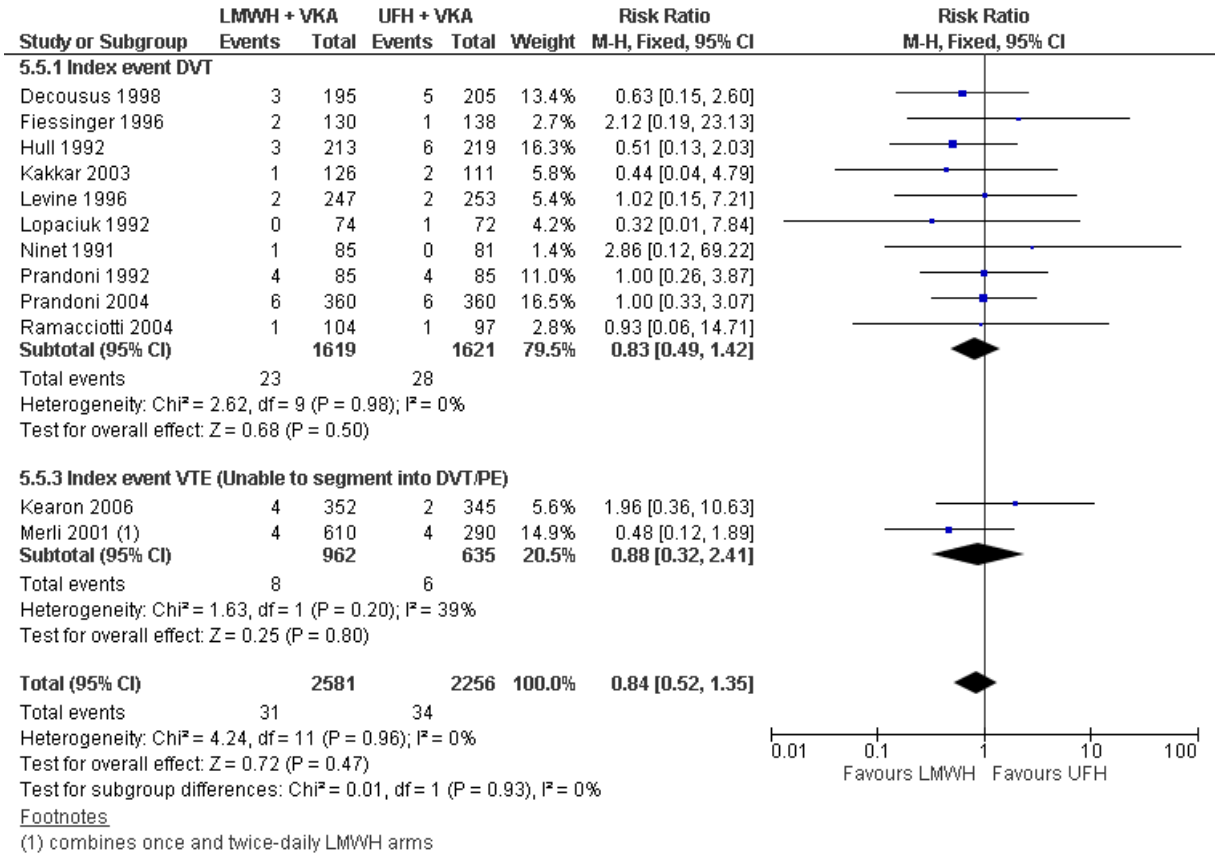


Figure 26: VTE recurrence 3 months: PE only



Footnotes

(1) combines once and twice-daily LMWH arms

Major bleeding

Figure 27: Major bleeding 14 days: all major bleeds

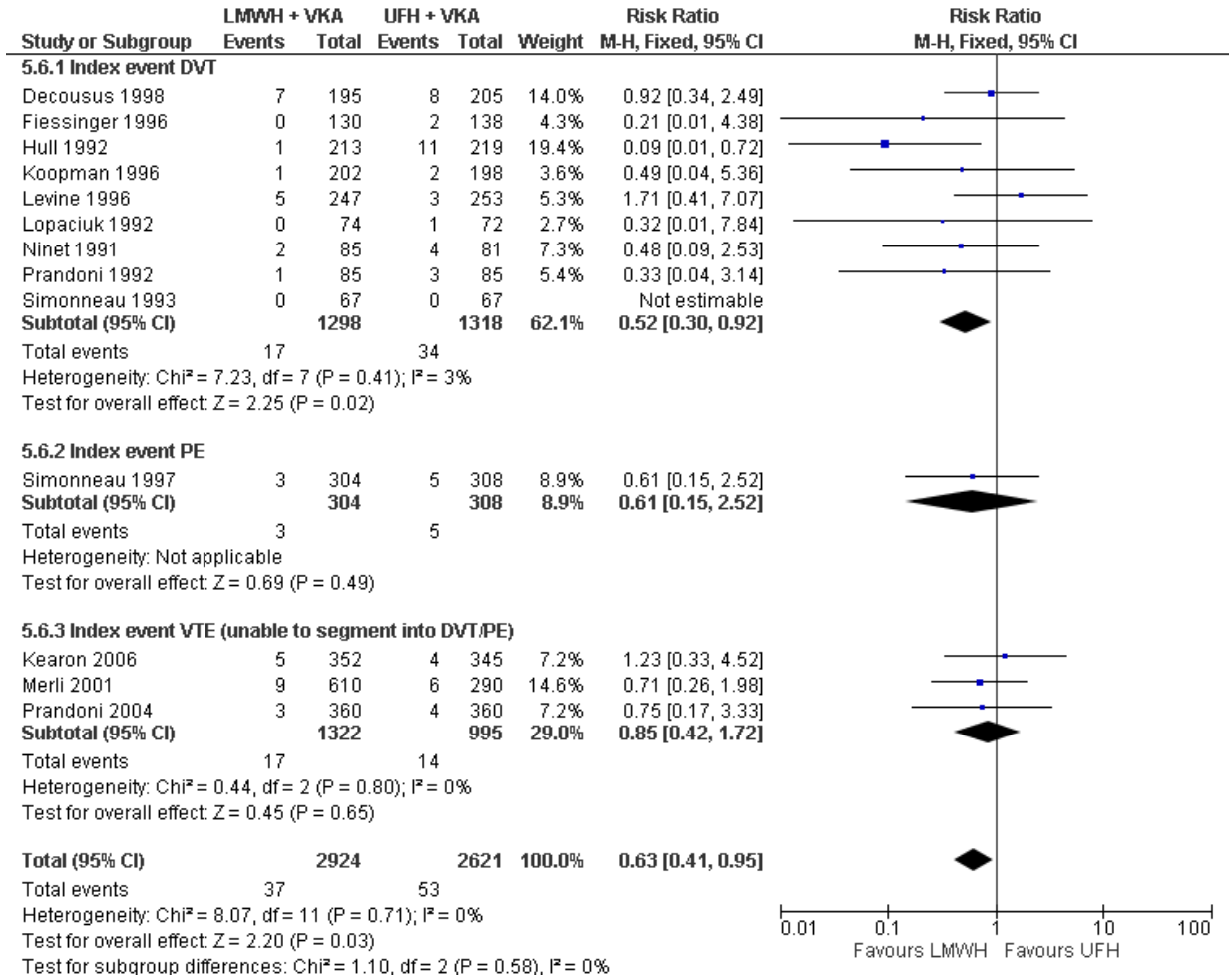


Figure 28: Funnel plot for major bleeding 14 days: all major bleeds

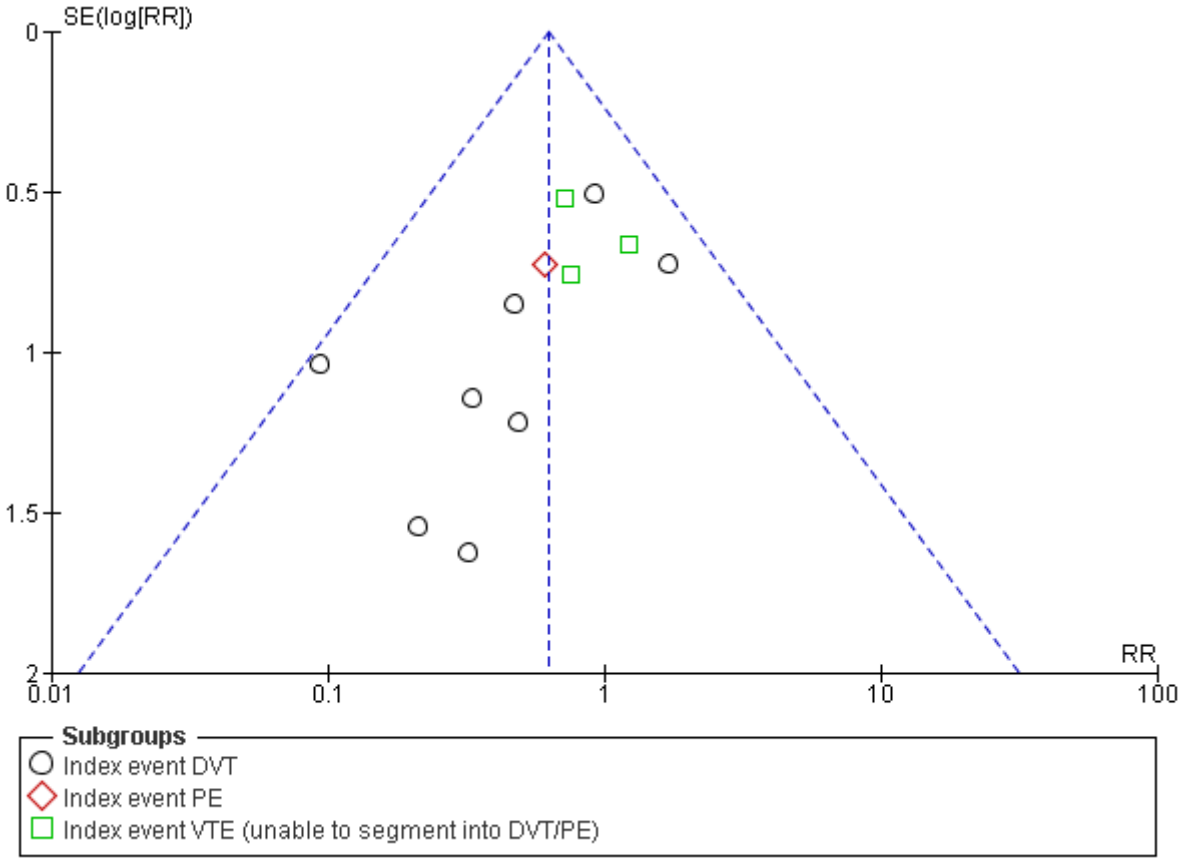
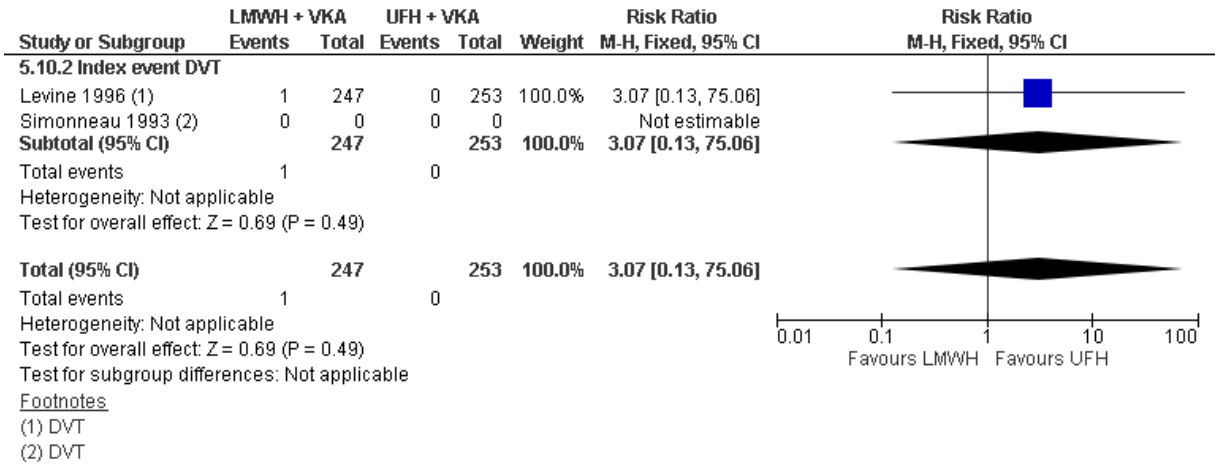


Figure 29: Major bleeding 14 days: intracranial bleeds only



Study or Subgroup	LMWH + VKA Events	Total	UFH + VKA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.10.2 Index event DVT						
Levine 1996 (1)	1	247	0	253	100.0%	3.07 [0.13, 75.06]
Simonneau 1993 (2)	0	0	0	0		Not estimable
Subtotal (95% CI)		**247**		**253**	**100.0%**	**3.07 [0.13, 75.06]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**247**		**253**	**100.0%**	**3.07 [0.13, 75.06]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						

Footnotes
(1) DVT
(2) DVT

Figure 30: Major bleeding 14 days: fatal bleeds only

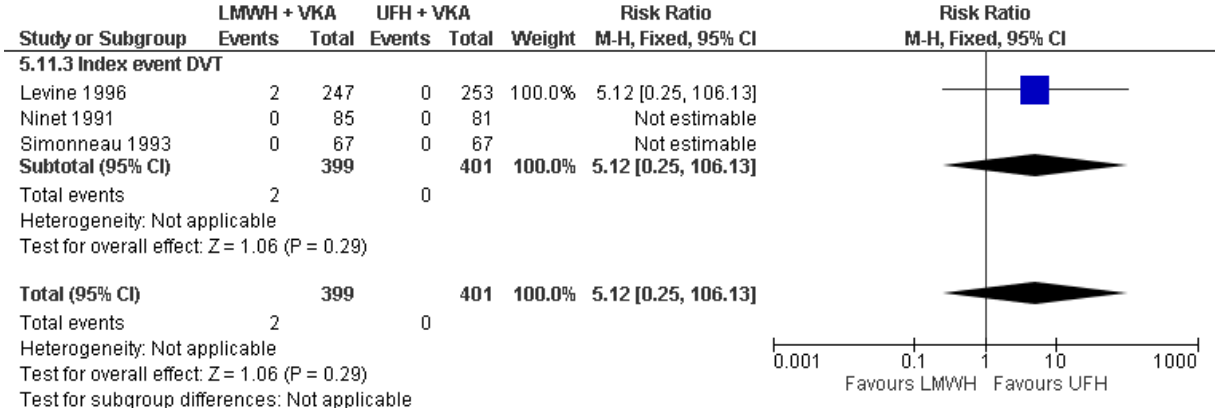
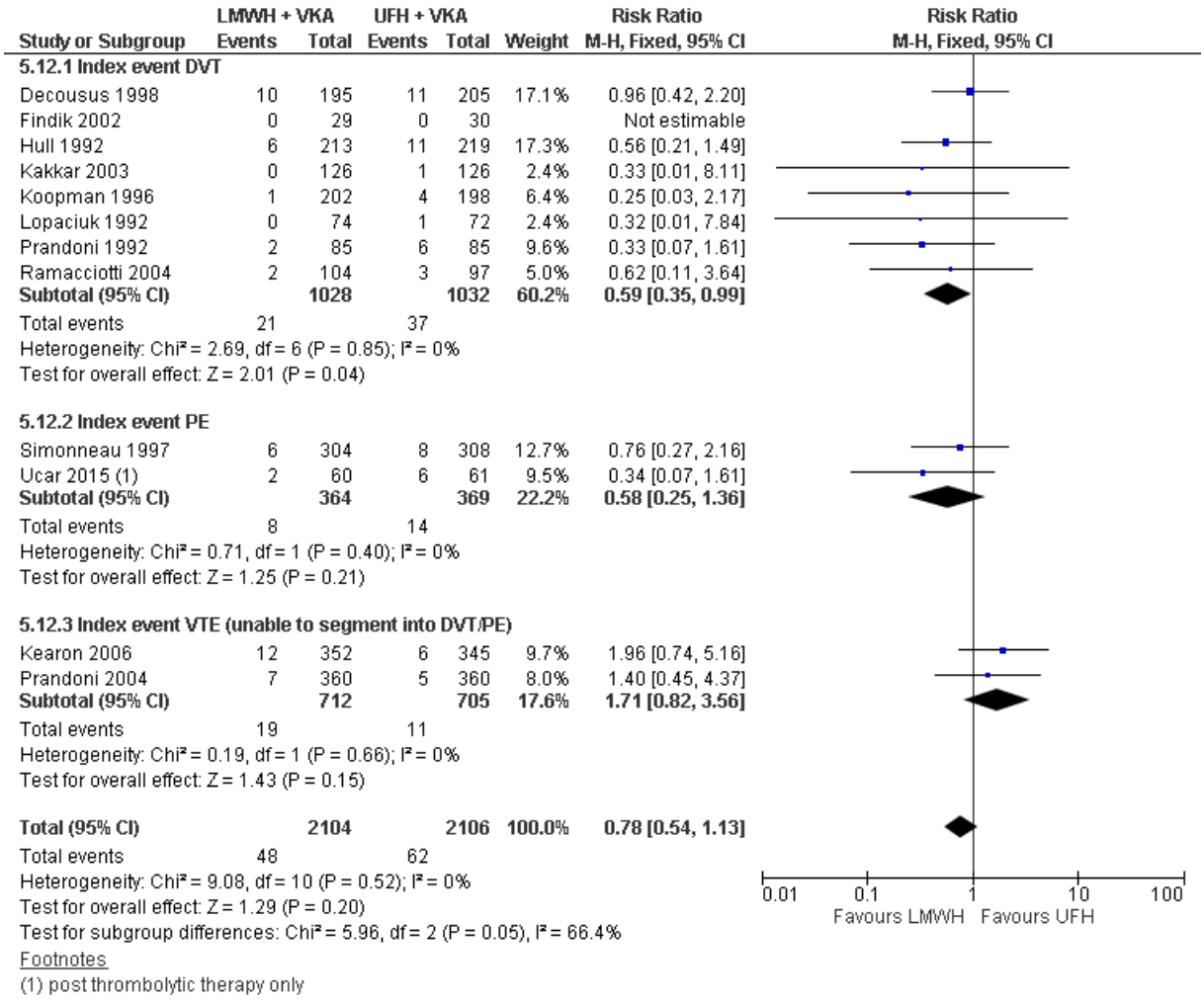


Figure 31: Major bleeding 3 months: all major bleeds



Footnotes

(1) post thrombolytic therapy only

Figure 32: Funnel plot for major bleeding 3 months: all major bleeds

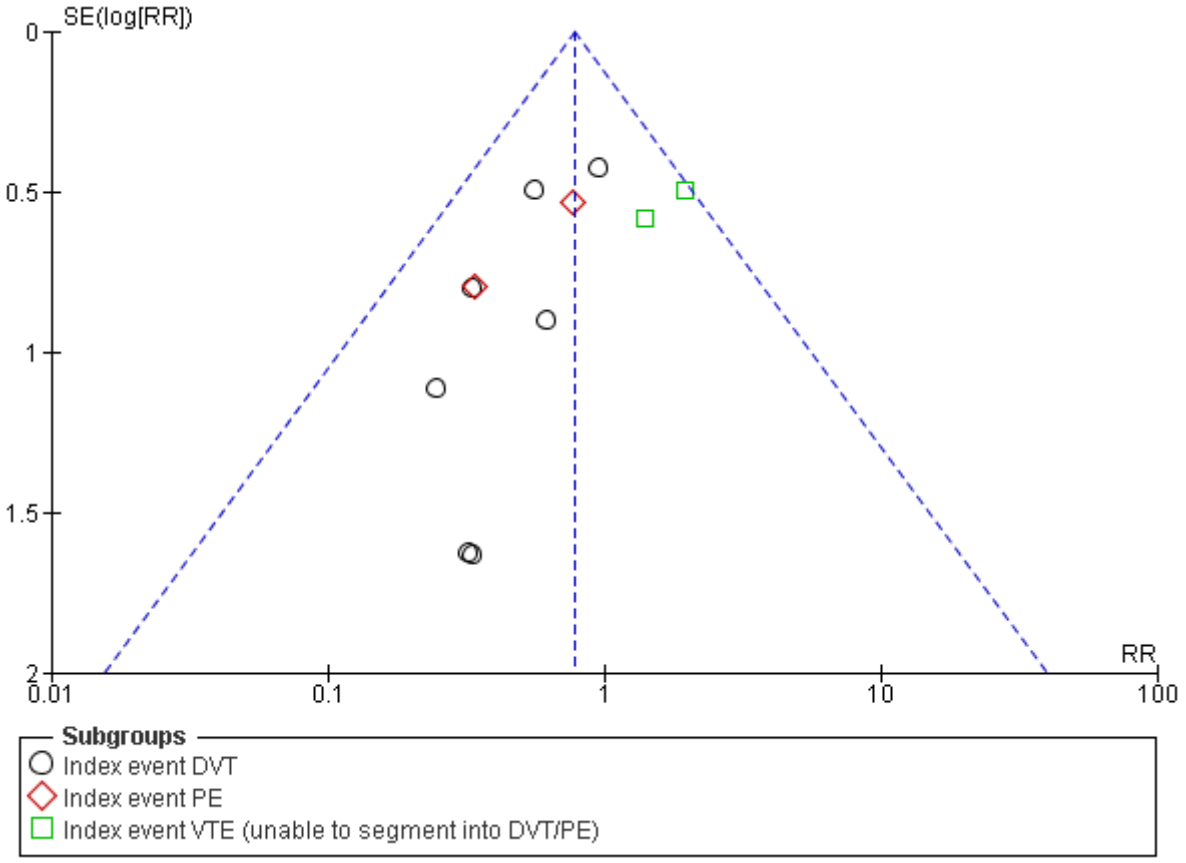


Figure 33: Major bleeding 3 months: intracranial bleeds only

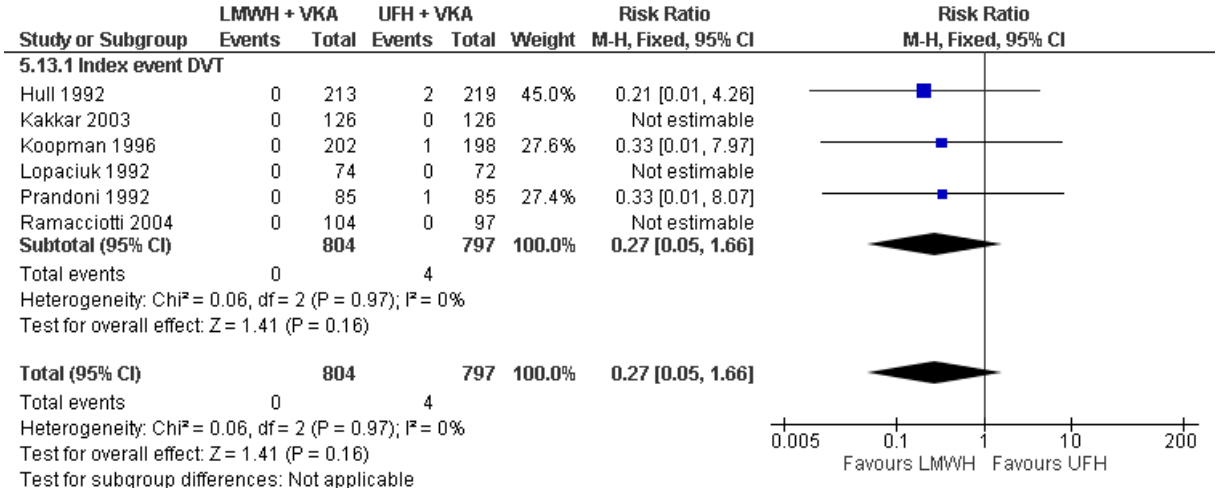
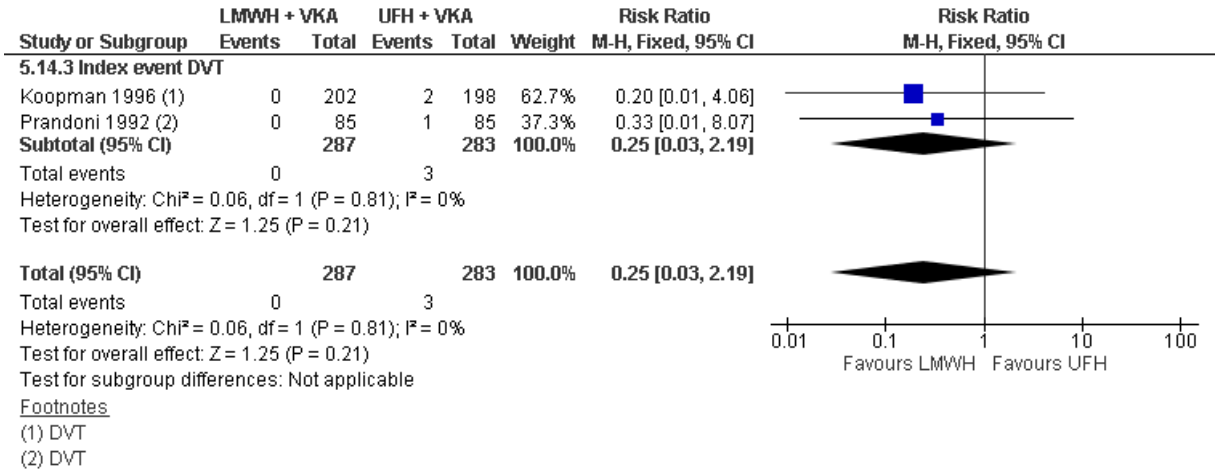


Figure 34: Major bleeding 3 months: fatal bleeds only



Clinically relevant non-major bleeding

Figure 35: Clinically relevant non-major bleeding during heparin treatment up to 14 days

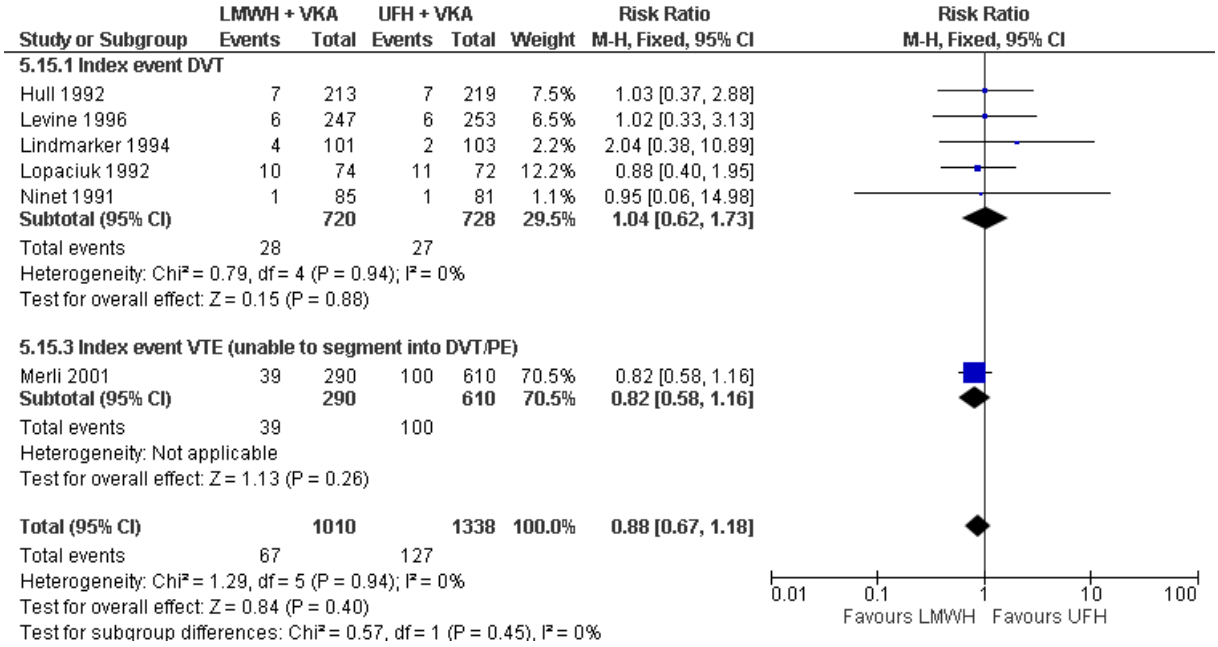
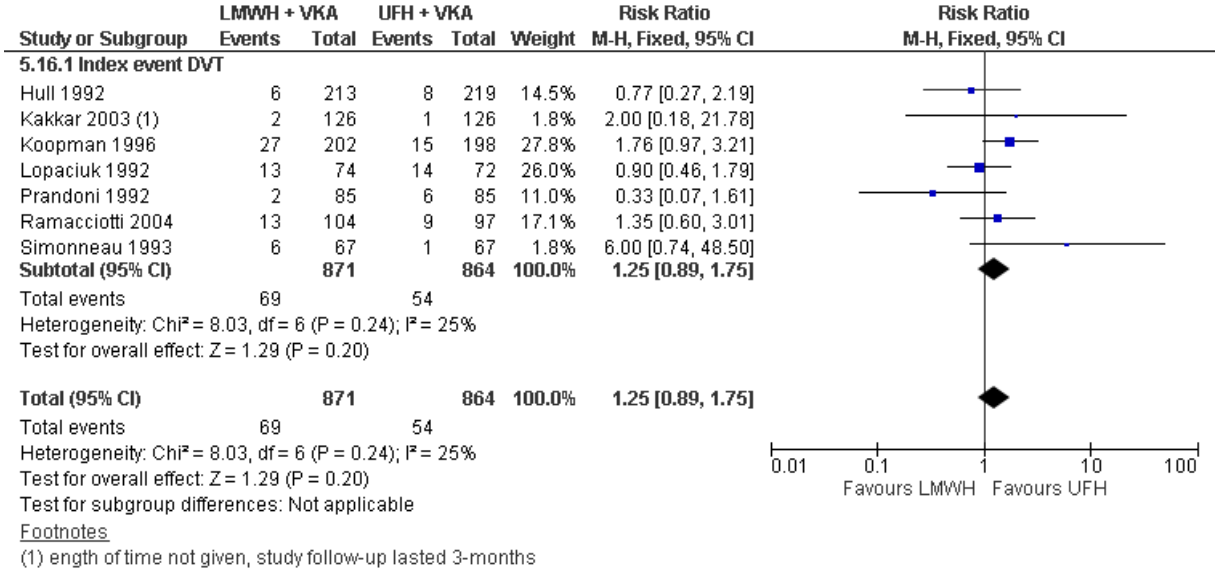


Figure 36: Clinically relevant non-major bleeding 3 months



All-cause mortality

Figure 37: All-cause mortality 14 days

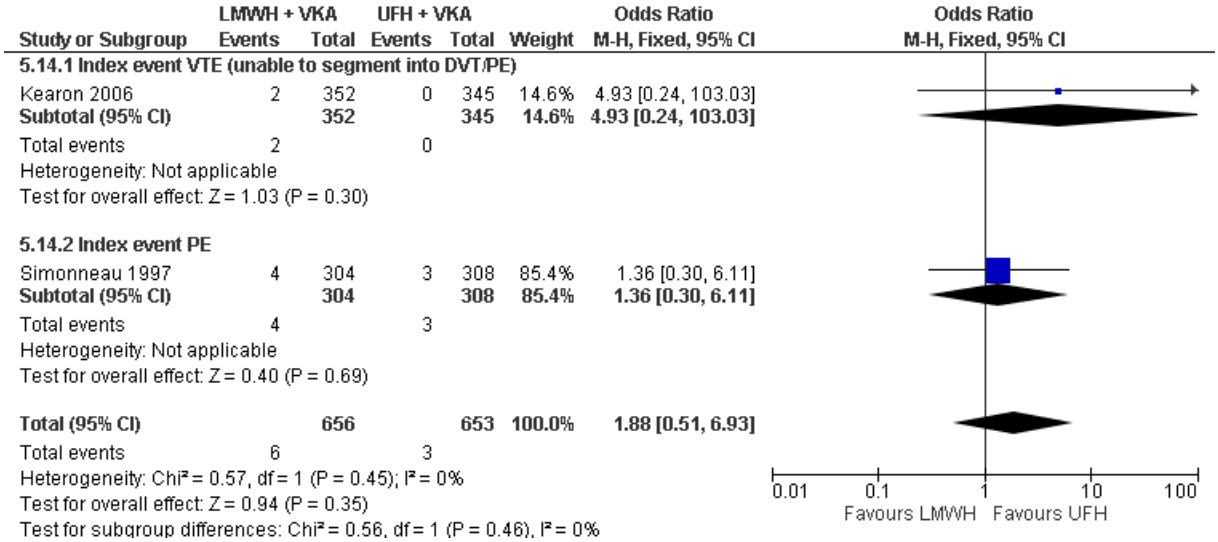


Figure 38: All cause mortality 3 months

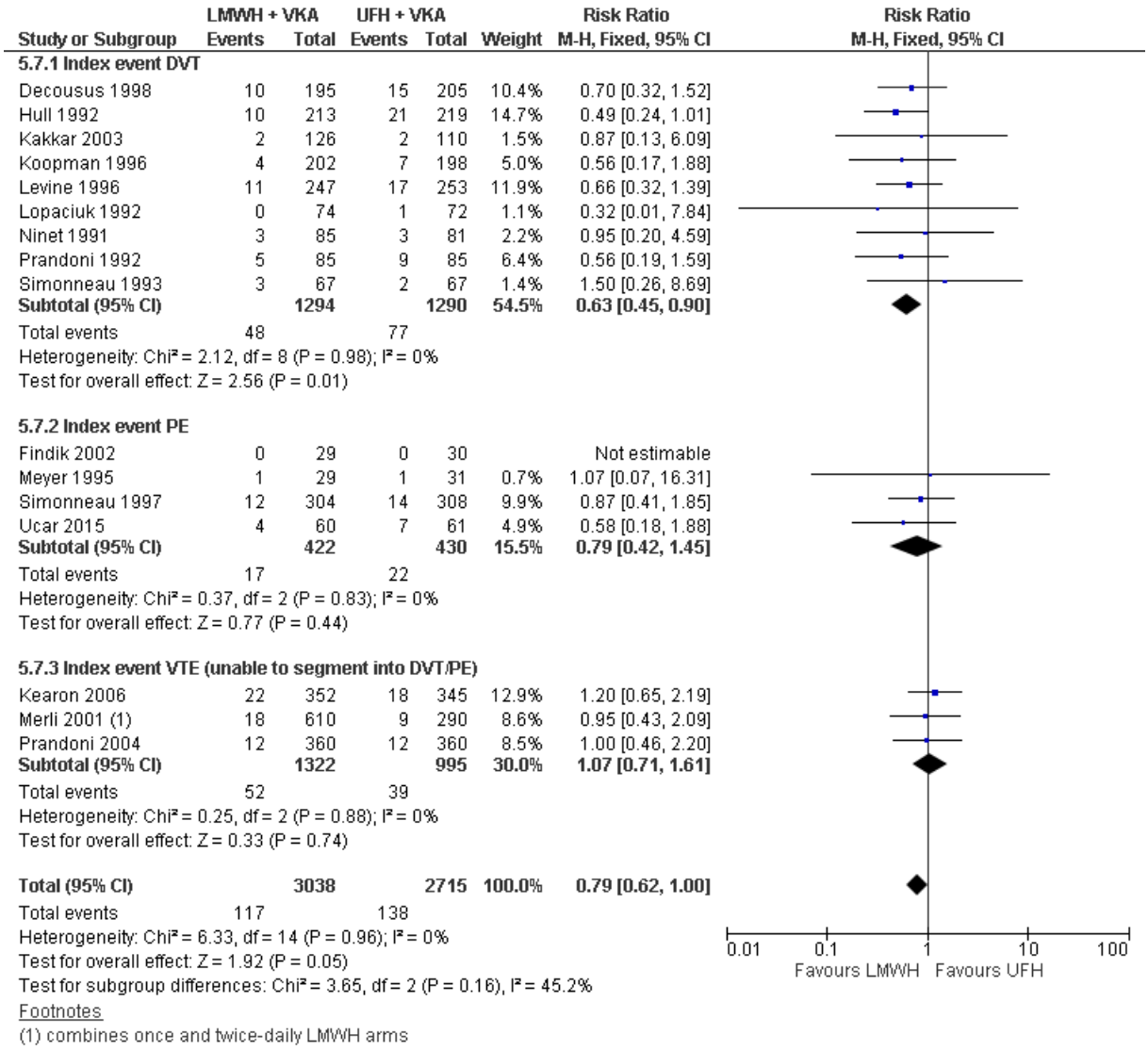
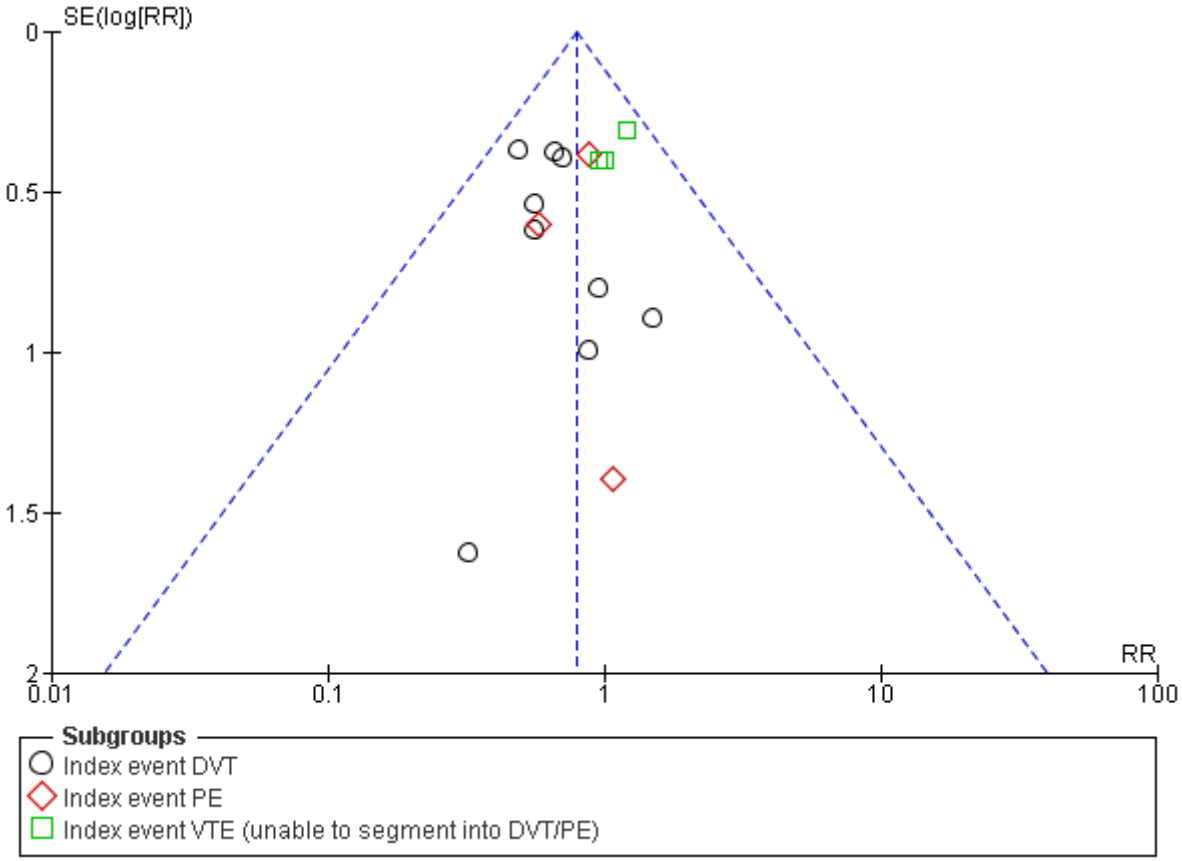
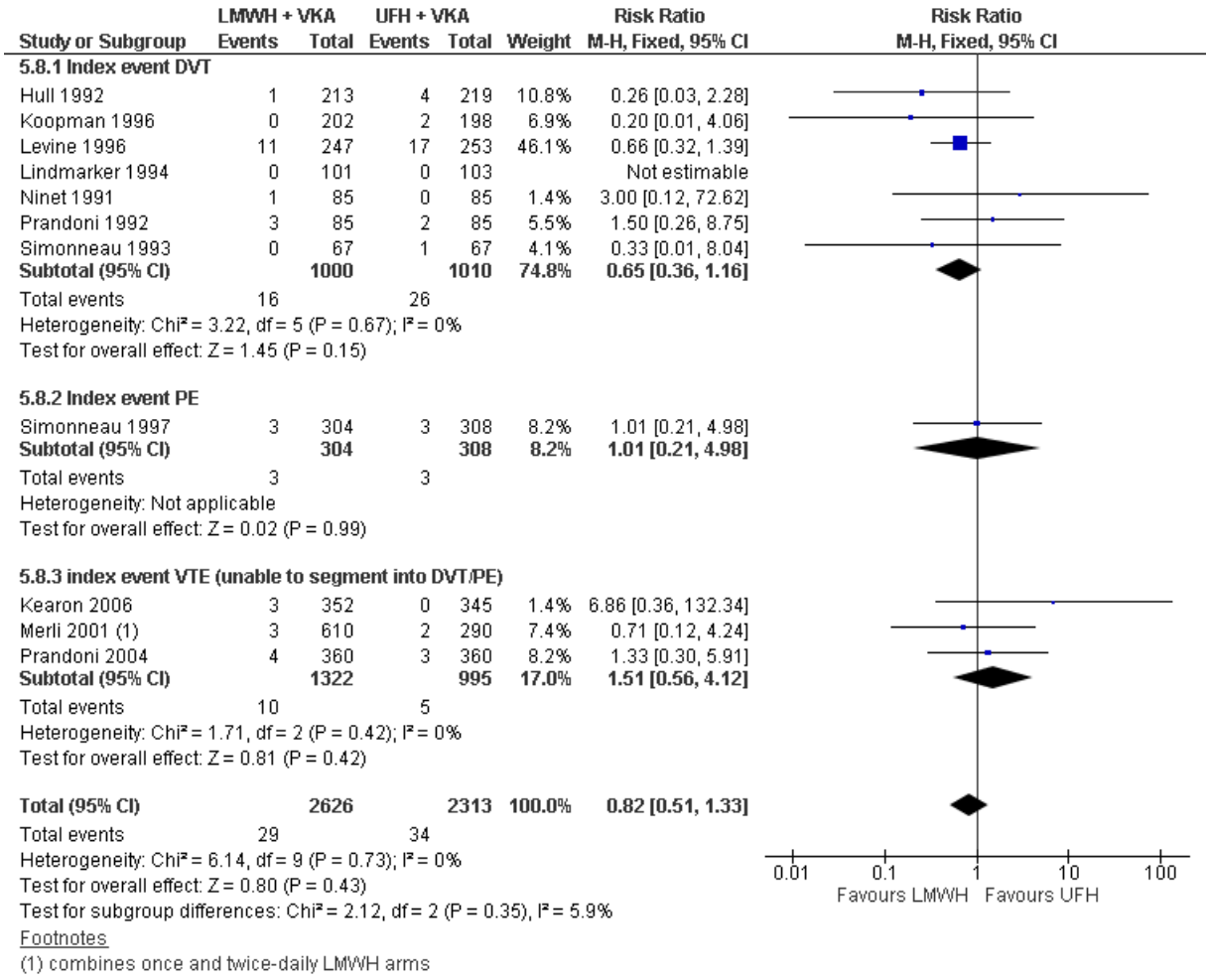


Figure 39: Funnel plot for all-cause mortality 3 months



VTE-related mortality

Figure 40: VTE-related mortality 3 months

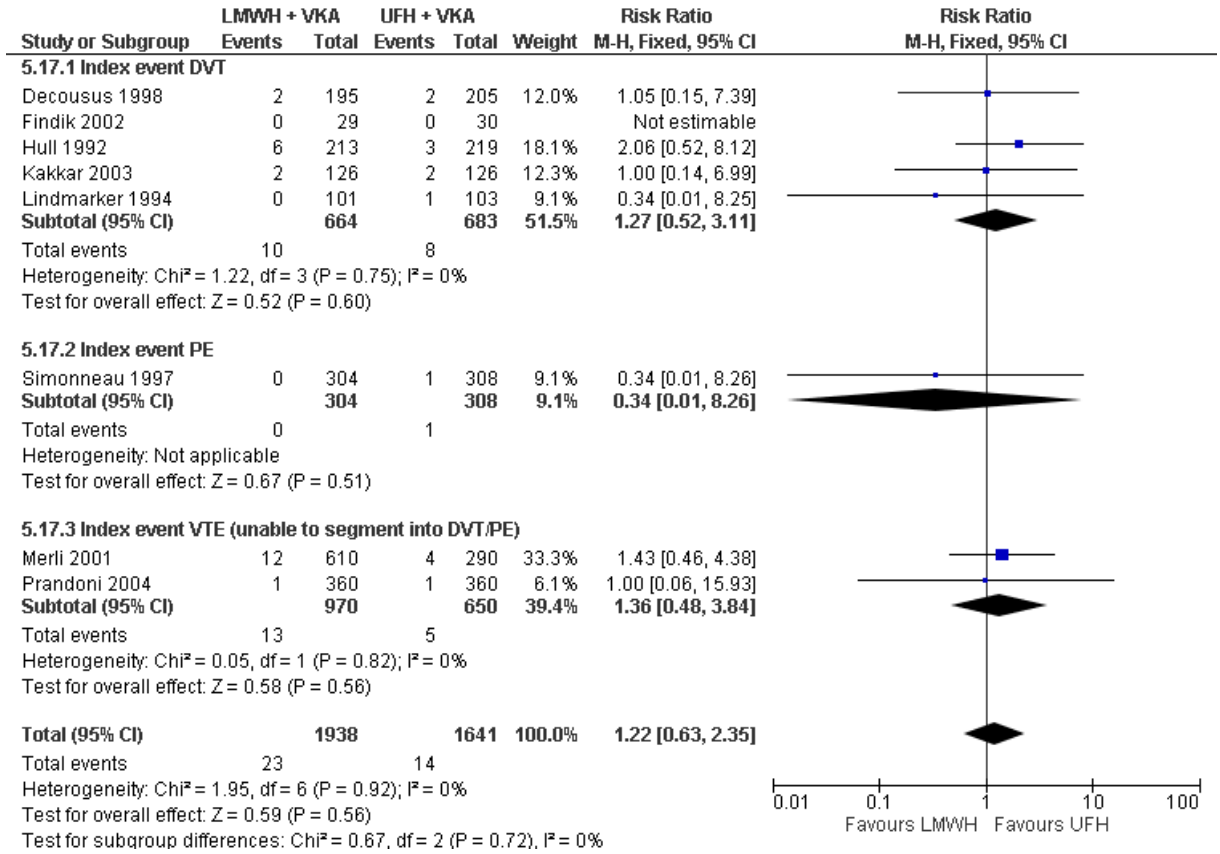


Footnotes

(1) combines once and twice-daily LMWH arms

Heparin-induced thrombocytopenia

Figure 41: HIT during heparin therapy period



Sensitivity analyses

VTE recurrence

Figure 42: VTE-recurrence 3 months: Any VTE event sensitvity analysis (high risk of bias studies removed)

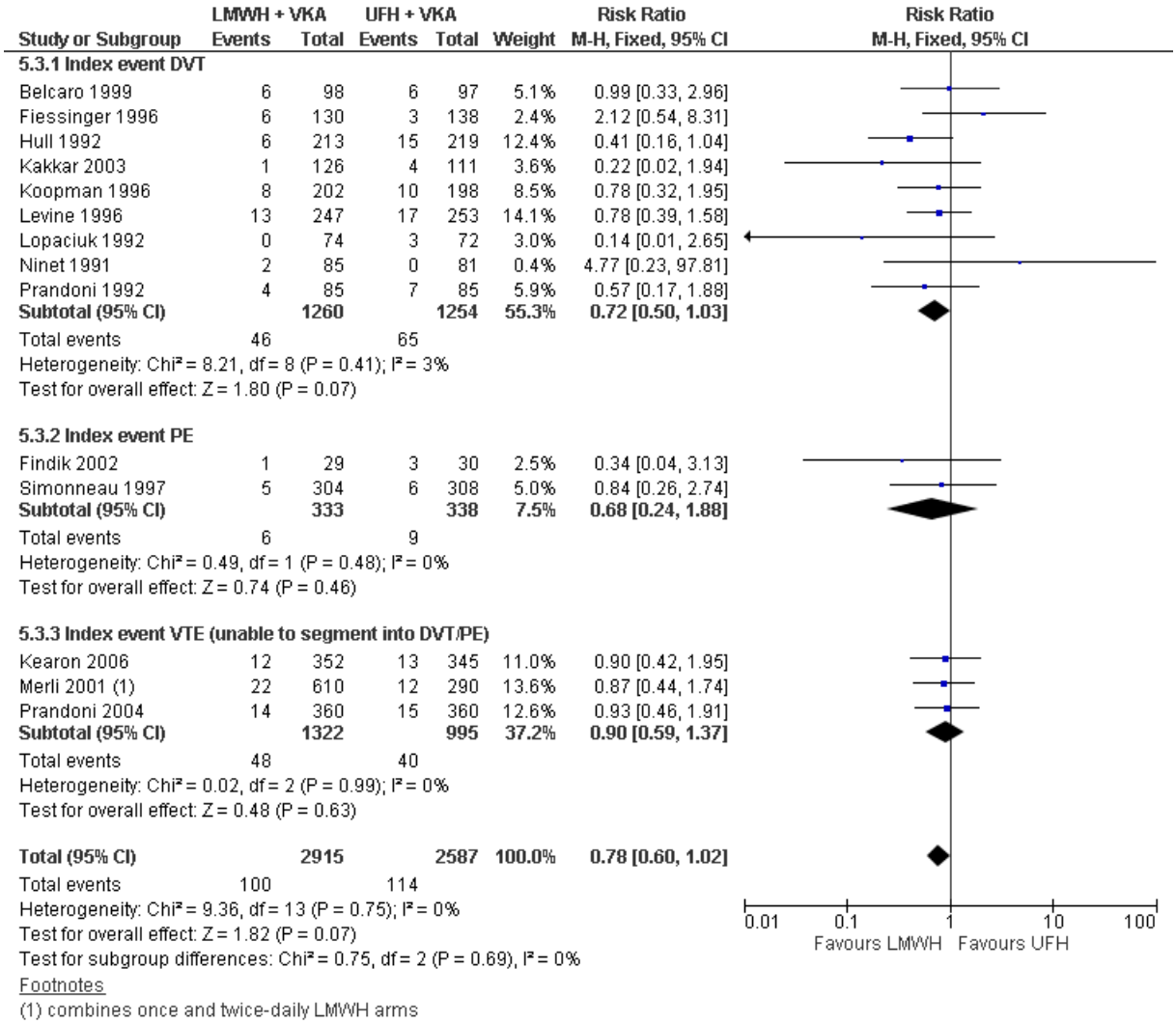
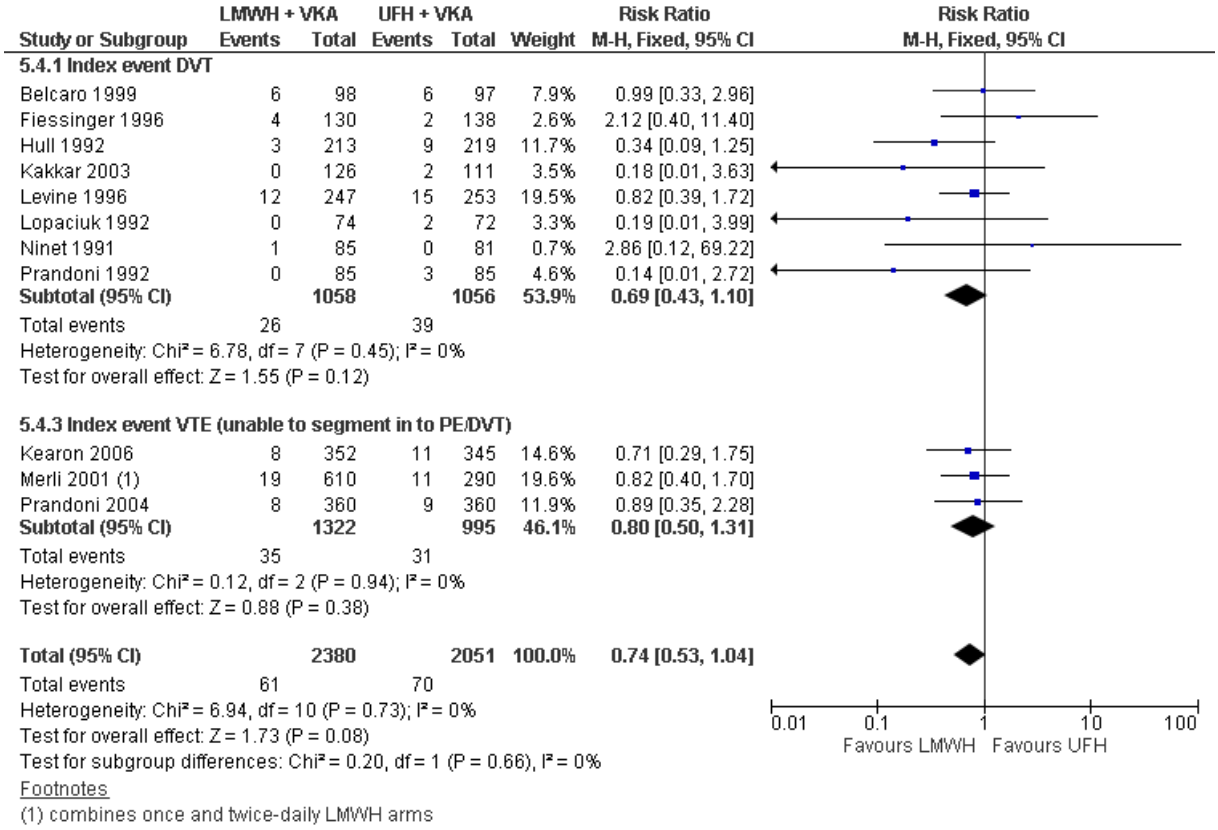


Figure 43: DVT-occurrence 3 months: sensitivity analysis (high risk of bias studies removed)



Major bleeding

Figure 44: Major bleeding 14 days: all major bleeds sensitivity analysis (high risk of bias studies excluded)

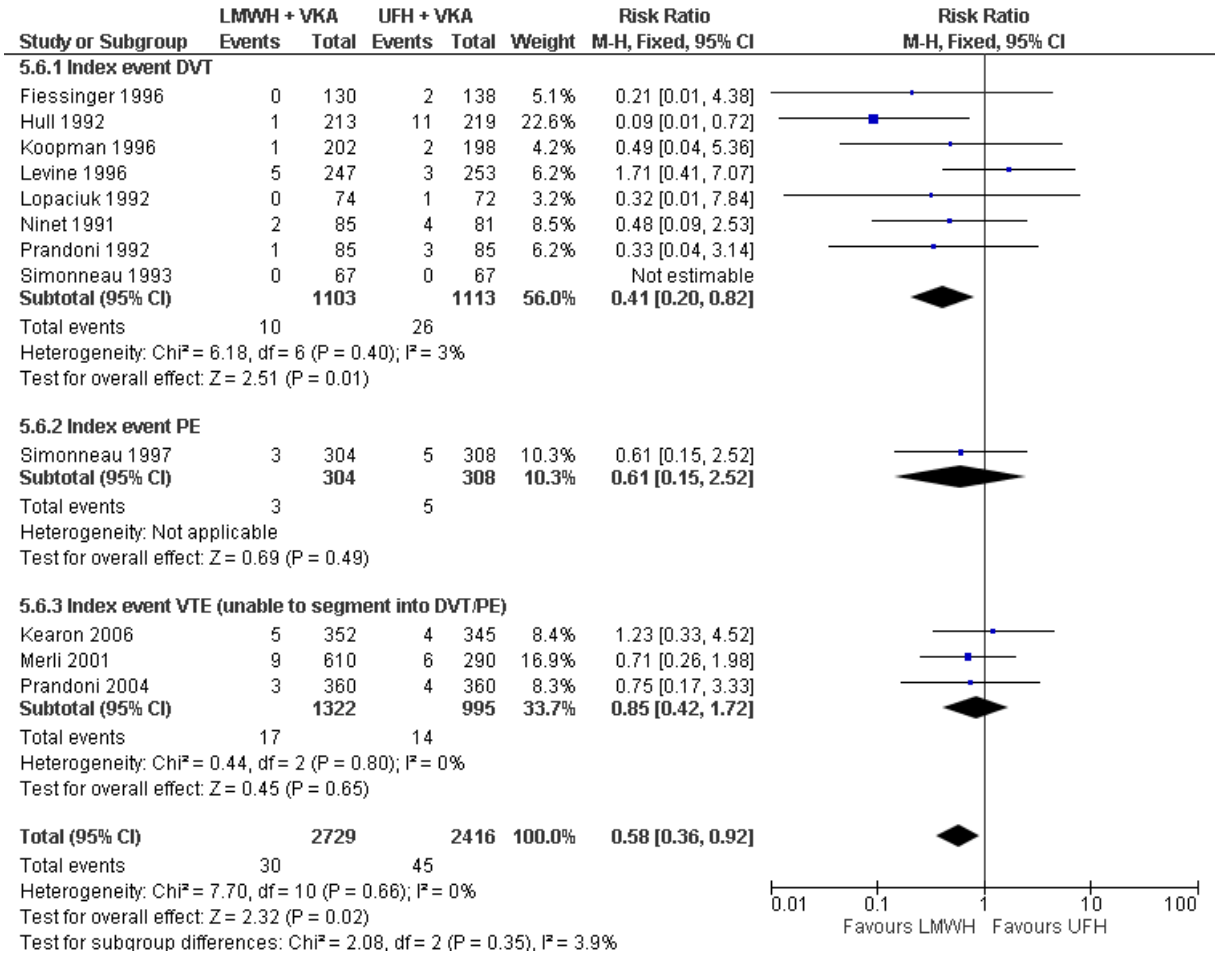


Figure 45: Major bleeding 3 months: all major bleeds sensitivity analysis (high risk of bias studies excluded)

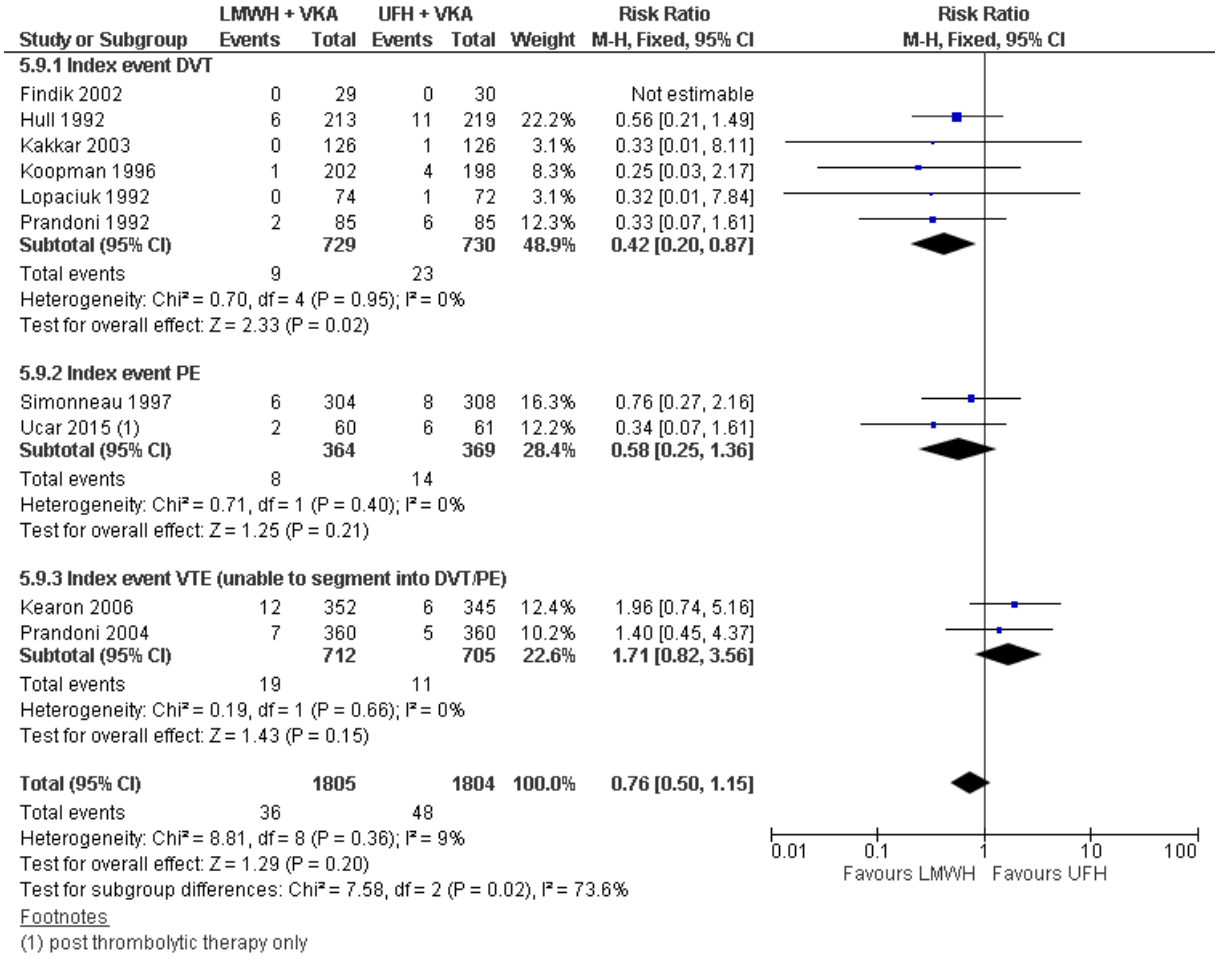
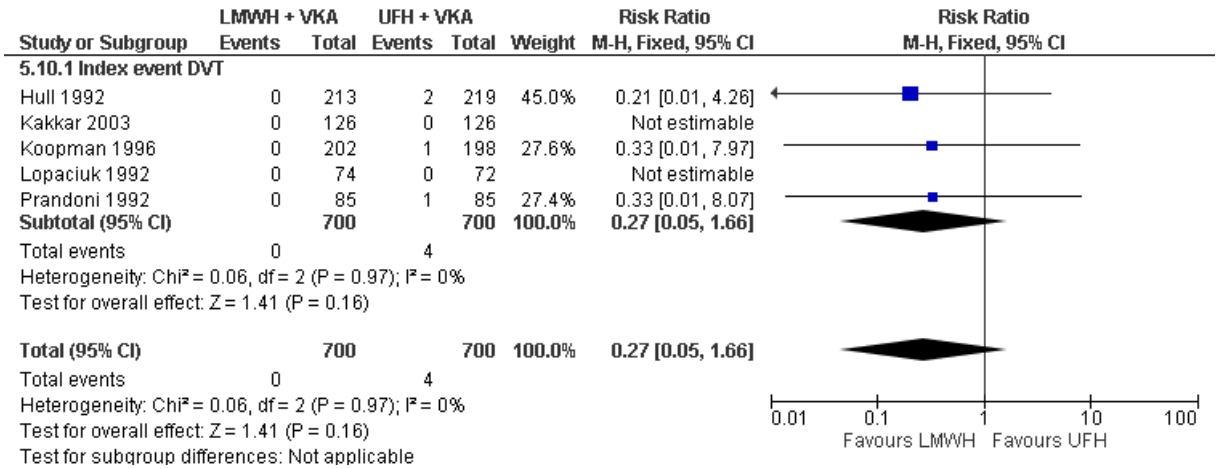
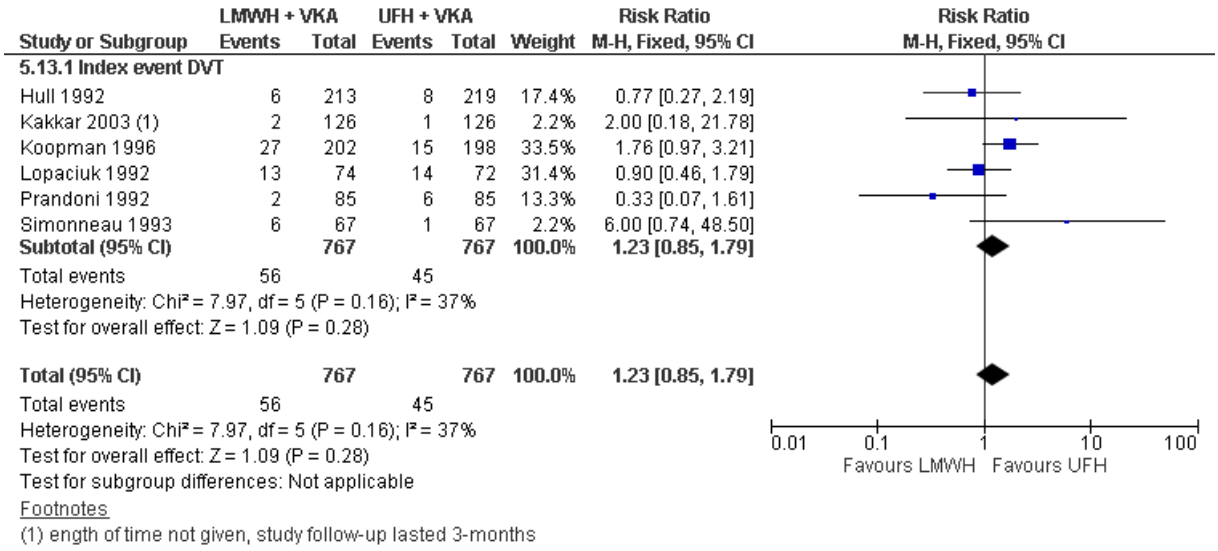


Figure 46: Major bleeding 3 months: intracranial bleeds sensitivity analysis (high risk of bias studies excluded)



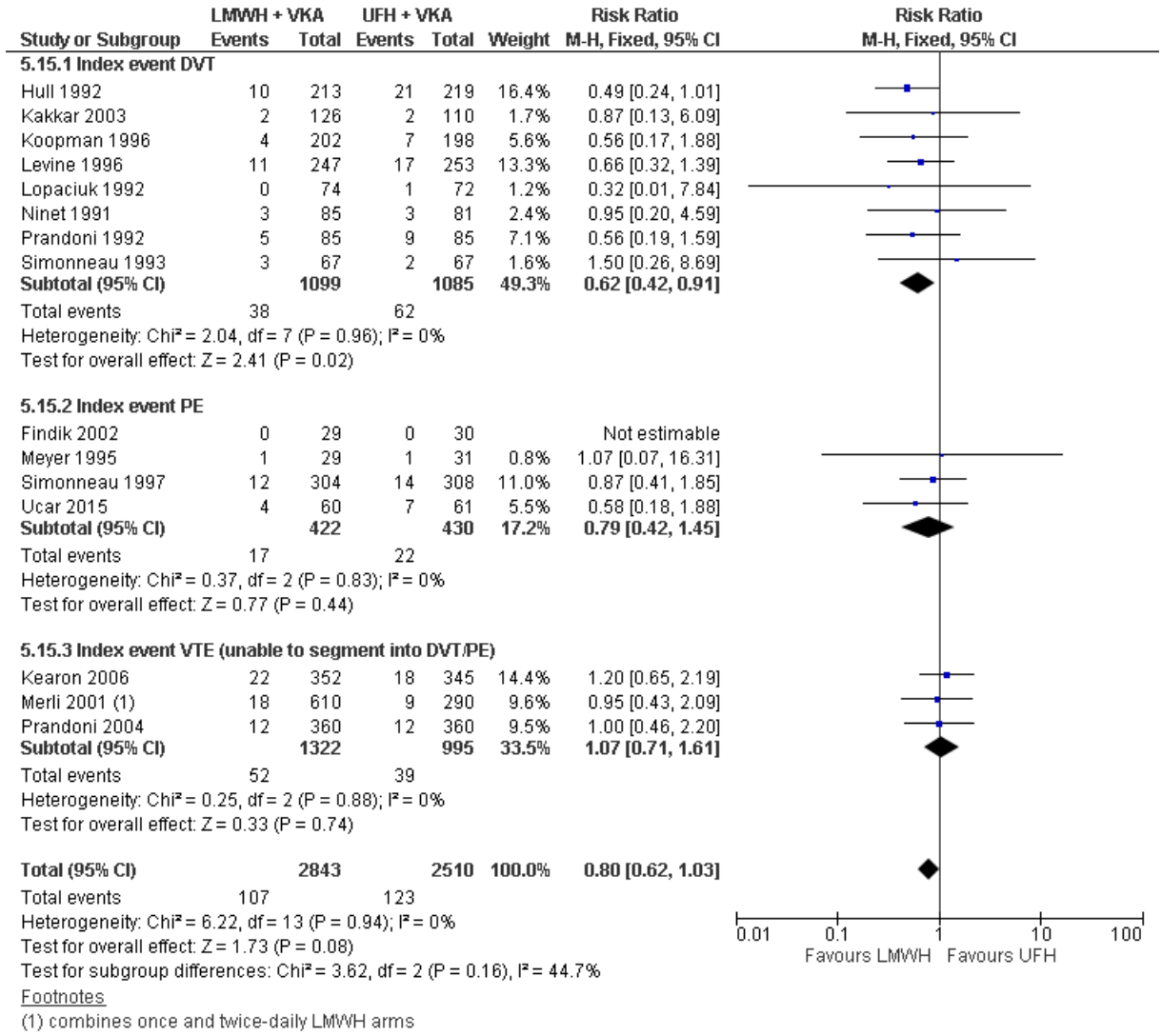
Clinically relevant non-major bleeding

Figure 47: Clinically relevant non-major bleeding 3 months sensitivity analysis (high risk of bias studies excluded)



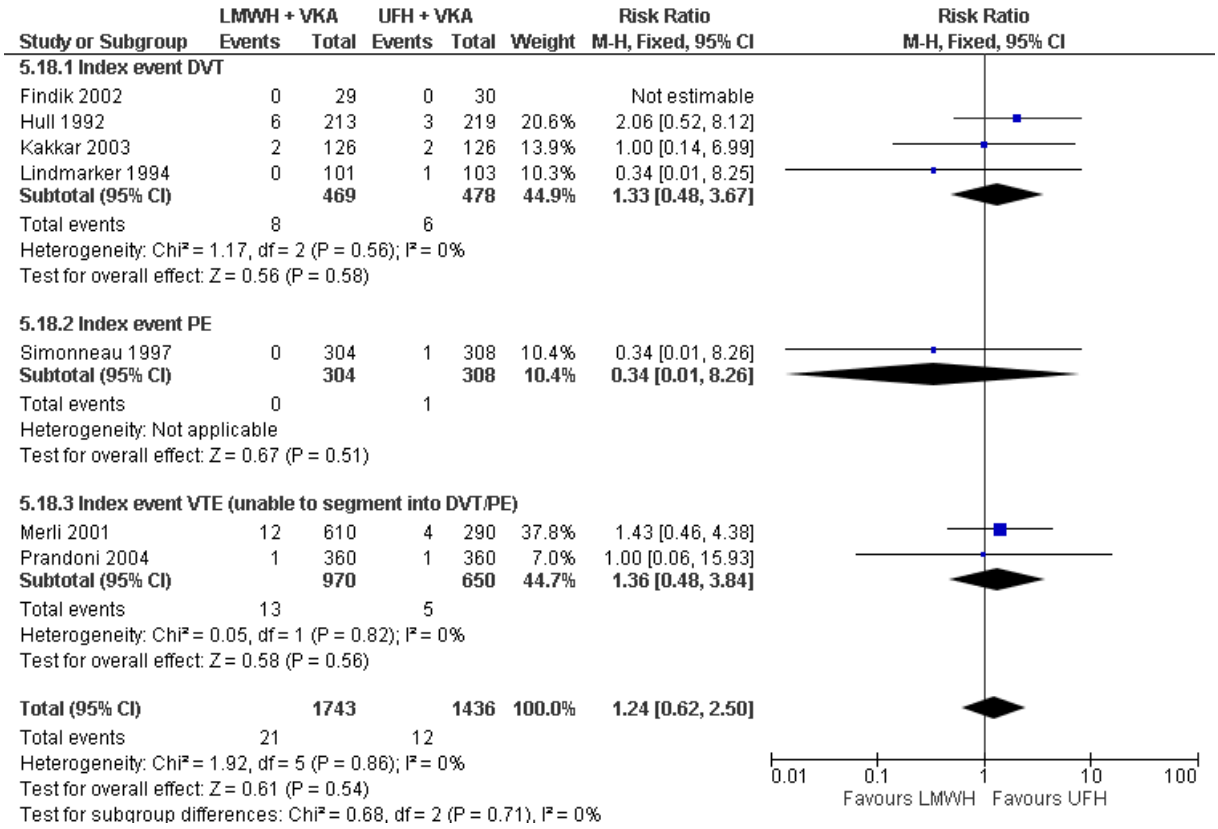
All-cause mortality

Figure 48: All-cause mortality 3 months sensitivity analysis (high risk of bias studies excluded)



1 *Heparin-induced thrombocytopenia*

2 **Figure 49: HIT during heparin therapy period sensitivity analysis (high risk of bias**
3 **studies excluded)**

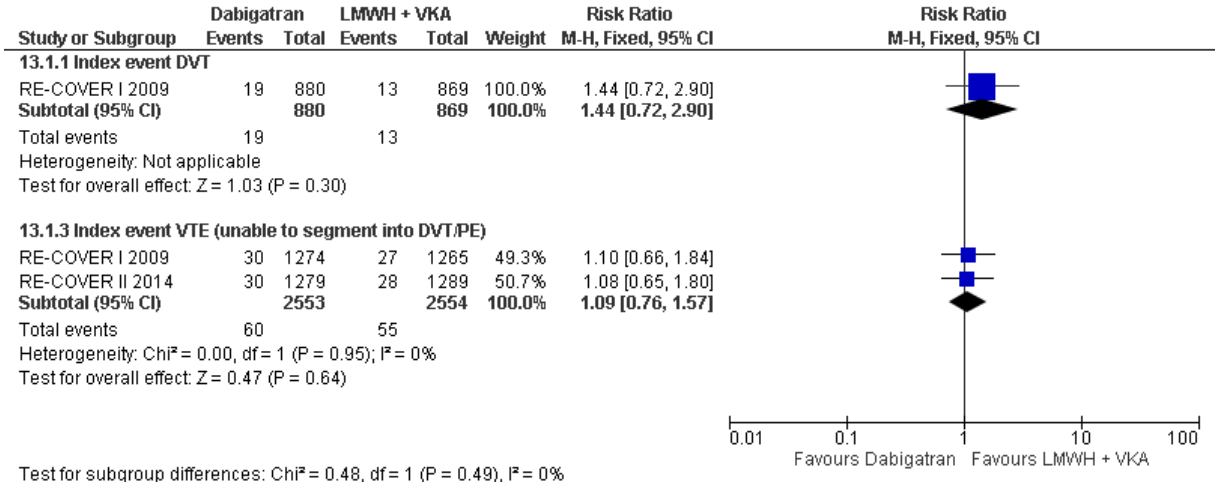


4

Dabigatran (150mg twice daily) versus LMWH + VKA for VTE

VTE-recurrence

Figure 50: VTE recurrence 6 months



Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%

Figure 51: VTE recurrence 6 months

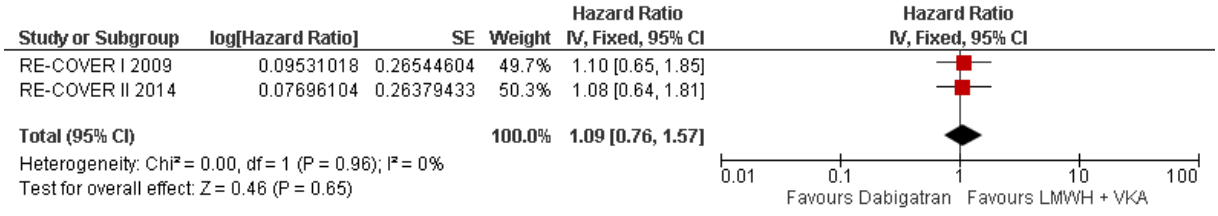


Figure 52: DVT-occurrence 6 months

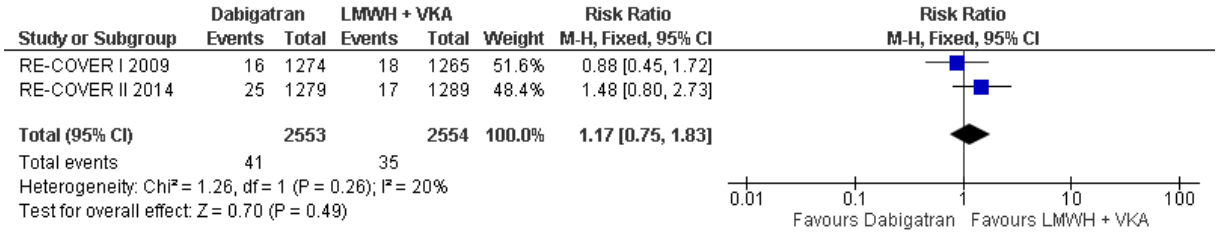
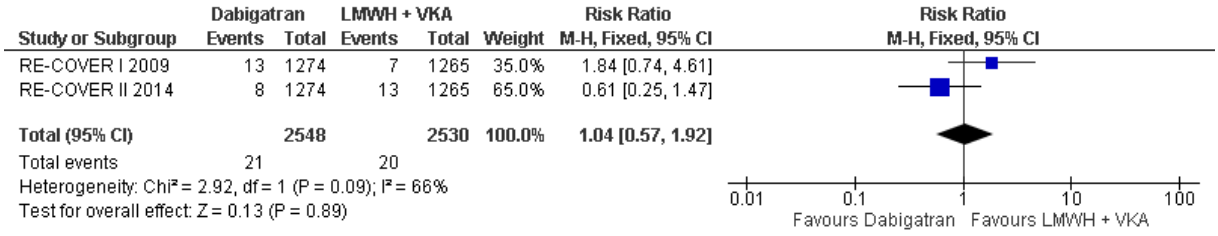
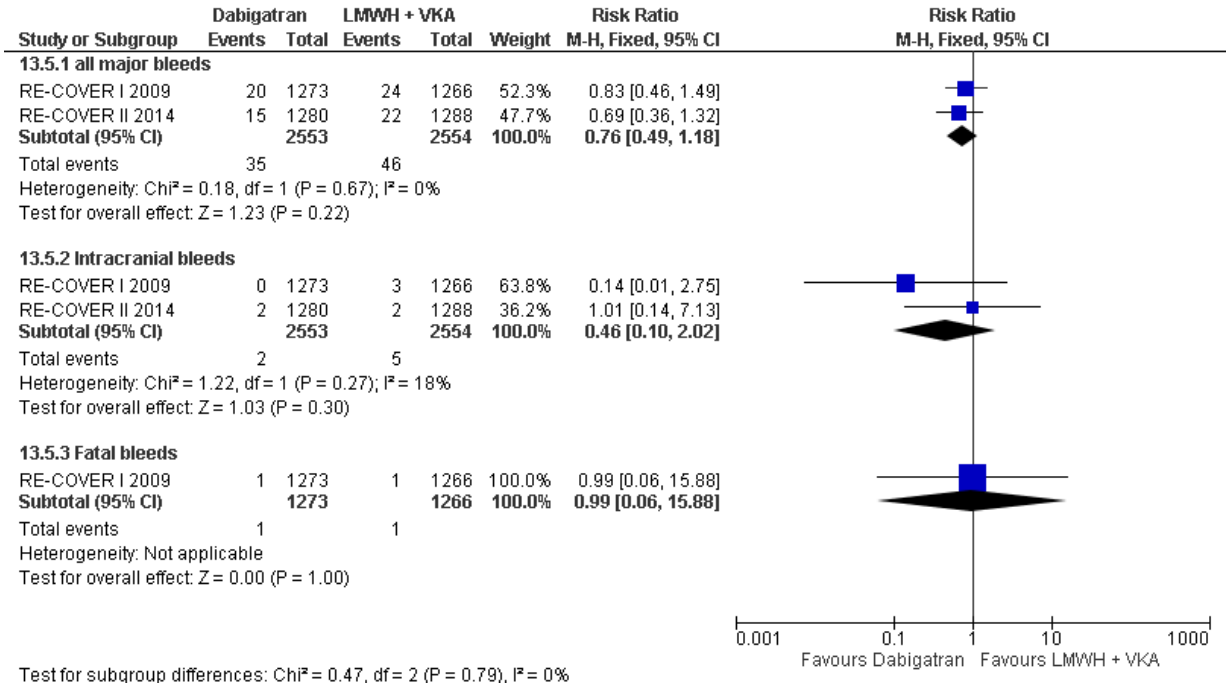


Figure 53: PE-occurrence 6 months



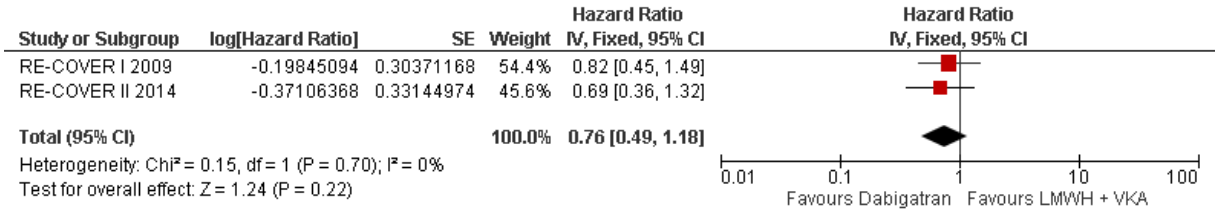
Major bleeding

Figure 54: Major bleeding 6 months



Test for subgroup differences: Chi² = 0.47, df = 2 (P = 0.79), I² = 0%

Figure 55: Major bleeding event 6 months

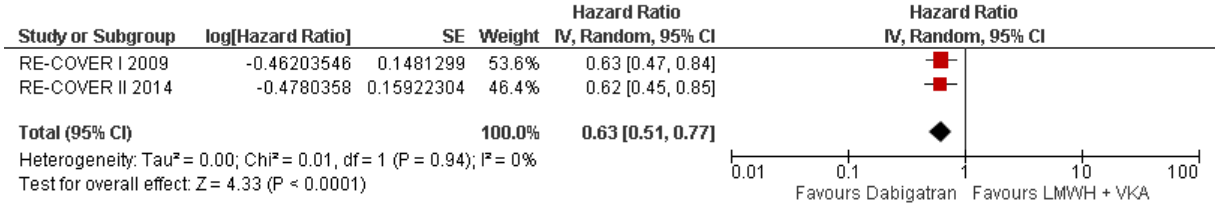


Clinically-relevant non-major bleeding

Figure 56: Clinically relevant non major bleeding 6 months

Footnotes
(1) Calculated as total bleeds - major bleeds
(2) Calculated as total bleeds - major bleeds

Figure 57: Major bleeding or CRNMB event 6 months



All-cause mortality

Figure 58: All-cause mortality 6 months

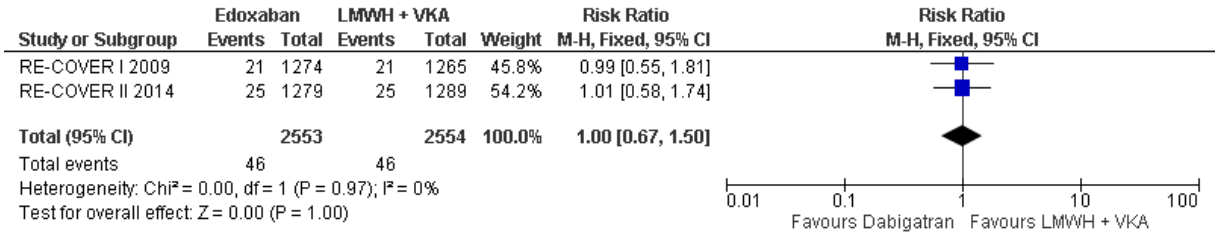
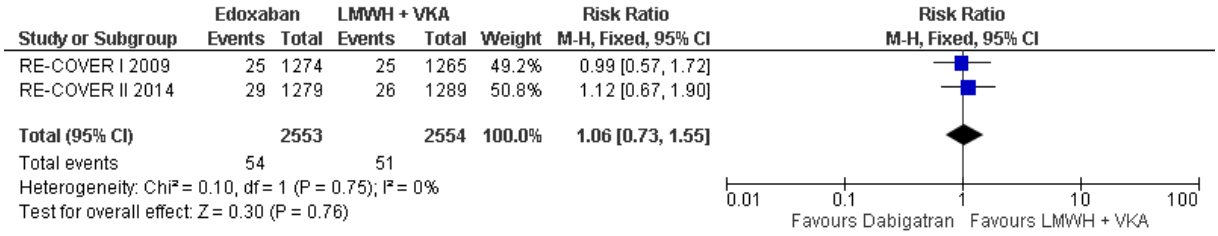


Figure 59: All-cause mortality 7 months



VTE-related mortality

Figure 60: VTE-related mortality 6 months

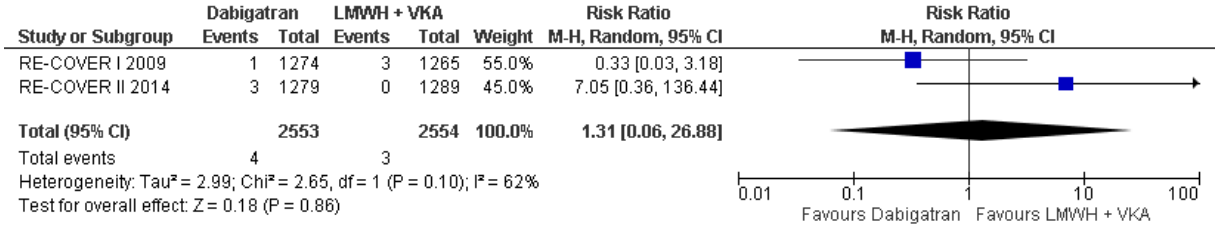
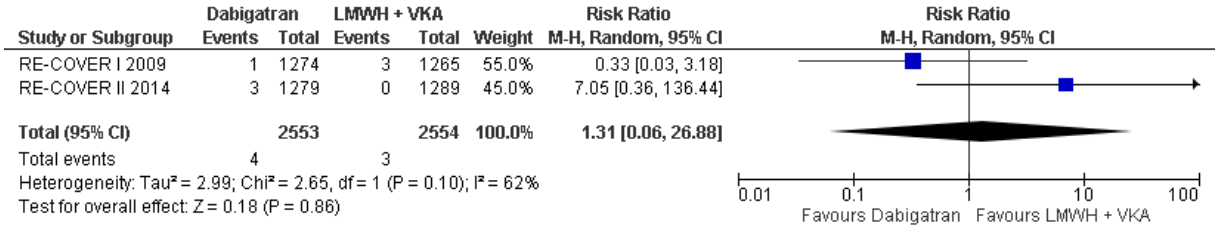


Figure 61: VTE-related mortality 7 months

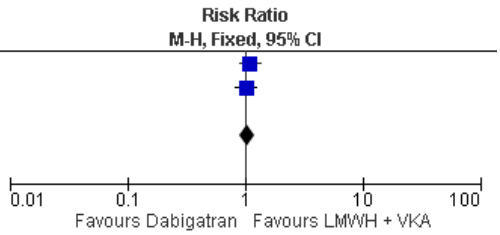


Serious adverse events

Figure 62: Serious adverse events 6 months

Study or Subgroup	Dabigatran Events	Total	LMWH + VKA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-COVER I 2009	165	1273	150	1266	49.7%	1.09 [0.89, 1.35]
RE-COVER II 2014	156	1280	153	1288	50.3%	1.03 [0.83, 1.26]
Total (95% CI)		**2553**		**2554**	**100.0%**	**1.06 [0.91, 1.23]**
Total events	321		303			

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)



Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

VTE-recurrence

Figure 63: VTE-recurrence up to 12 months

Study or Subgroup	Rivaroxaban Events	Total	LMWH + VKA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.1.1 Index event DVT						
EINSTEIN-DVT 2010 (1)	36	1731	51	1718	49.1%	0.70 [0.46, 1.07]
Subtotal (95% CI)		**1731**		**1718**	**49.1%**	**0.70 [0.46, 1.07]**
Total events	36		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
20.1.2 Index event PE						
EINSTEIN-PE	50	2419	44	2413	50.9%	1.13 [0.76, 1.69]
Subtotal (95% CI)		**2419**		**2413**	**50.9%**	**1.13 [0.76, 1.69]**
Total events	50		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**4150**		**4131**	**100.0%**	**0.90 [0.56, 1.43]**
Total events	86		95			

Heterogeneity: Tau² = 0.07; Chi² = 2.63, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Chi² = 2.63, df = 1 (P = 0.11), I² = 61.9%

Footnotes
(1) taken from "VTE-recurrence" in EINSTEIN-DVT paper

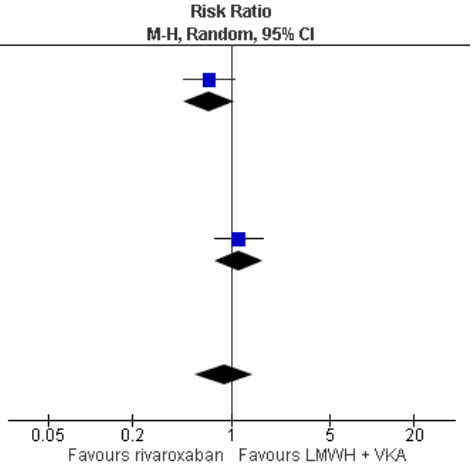
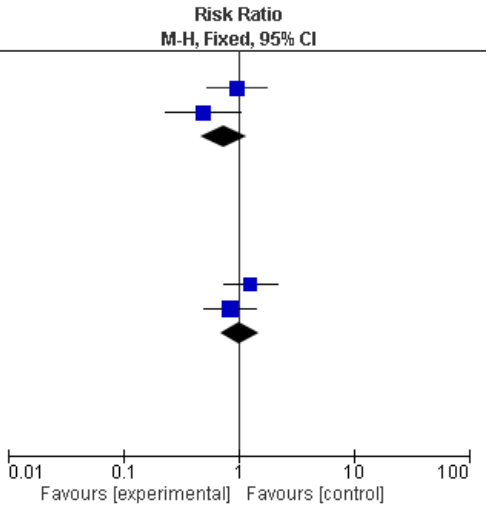


Figure 64: VTE-recurrence up to 12 months (subgroup analysis by age)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.3 age at least 65 years						
EINSTEIN PE	21	958	21	934	50.8%	0.97 [0.54, 1.77]
EINSTEIN-DVT	10	586	21	607	49.2%	0.49 [0.23, 1.04]
Subtotal (95% CI)		**1544**		**1541**	**100.0%**	**0.74 [0.47, 1.17]**
Total events	31		42			
Heterogeneity: Chi² = 1.96, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 1.30 (P = 0.20)						
1.1.4 age <65 years						
EINSTEIN PE	29	1461	23	1479	42.9%	1.28 [0.74, 2.20]
EINSTEIN-DVT	26	1145	30	1111	57.1%	0.84 [0.50, 1.41]
Subtotal (95% CI)		**2606**		**2590**	**100.0%**	**1.03 [0.71, 1.49]**
Total events	55		53			
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.14 (P = 0.89)						



Test for subgroup differences: Chi² = 1.20, df = 1 (P = 0.27), I² = 16.9%

Figure 65: VTE recurrence

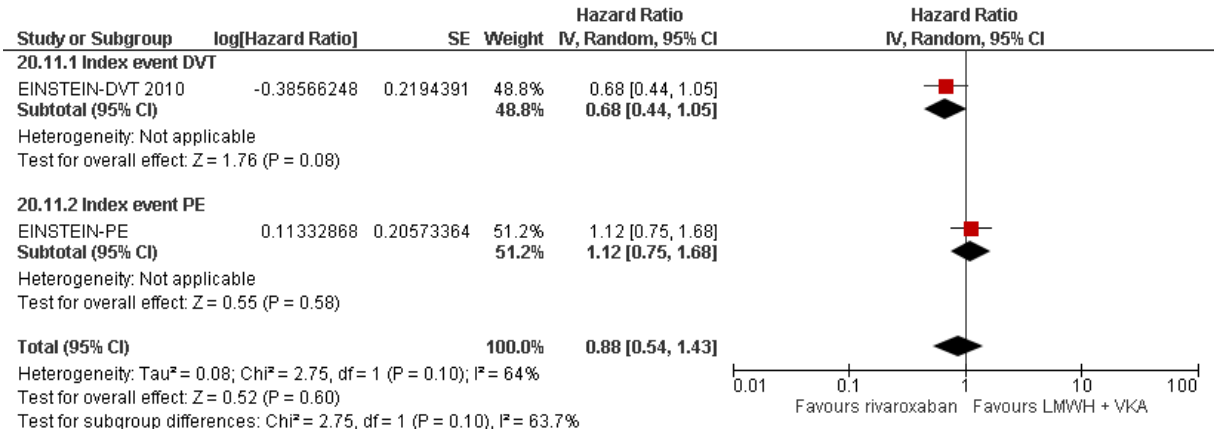


Figure 66: DVT-occurrence up to 12 months

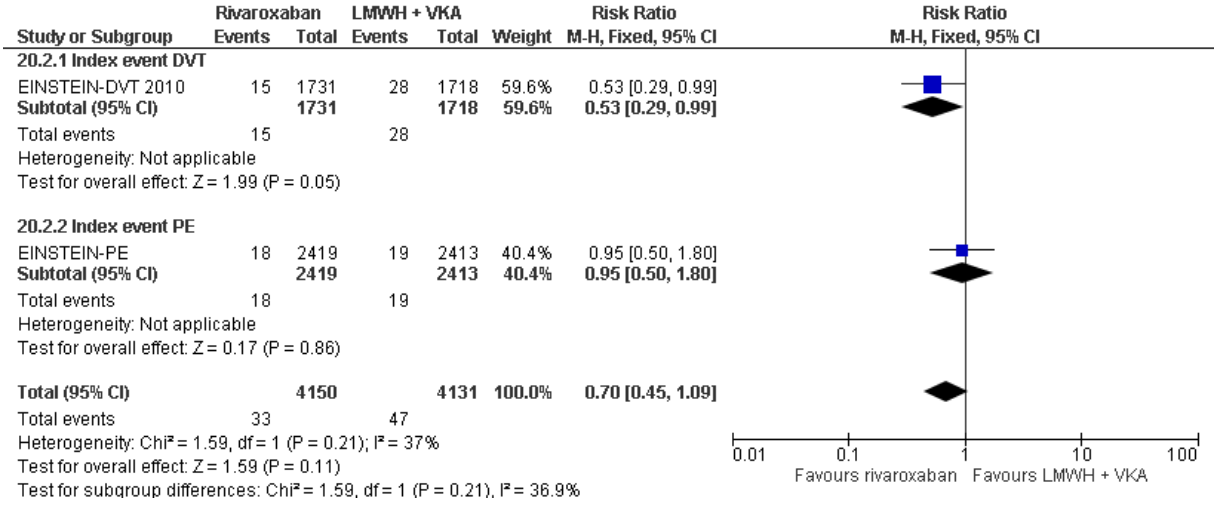
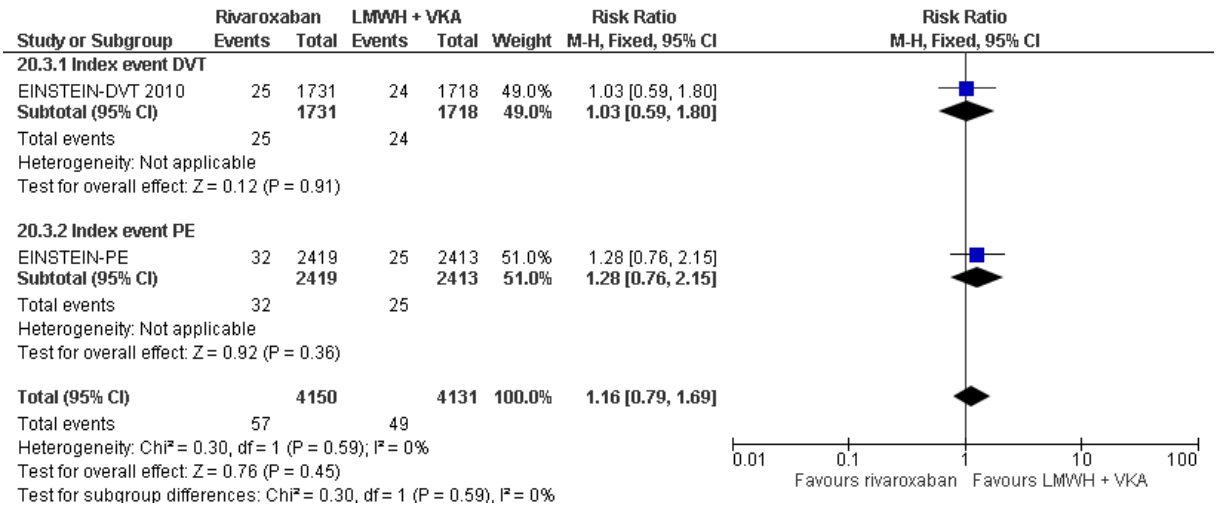
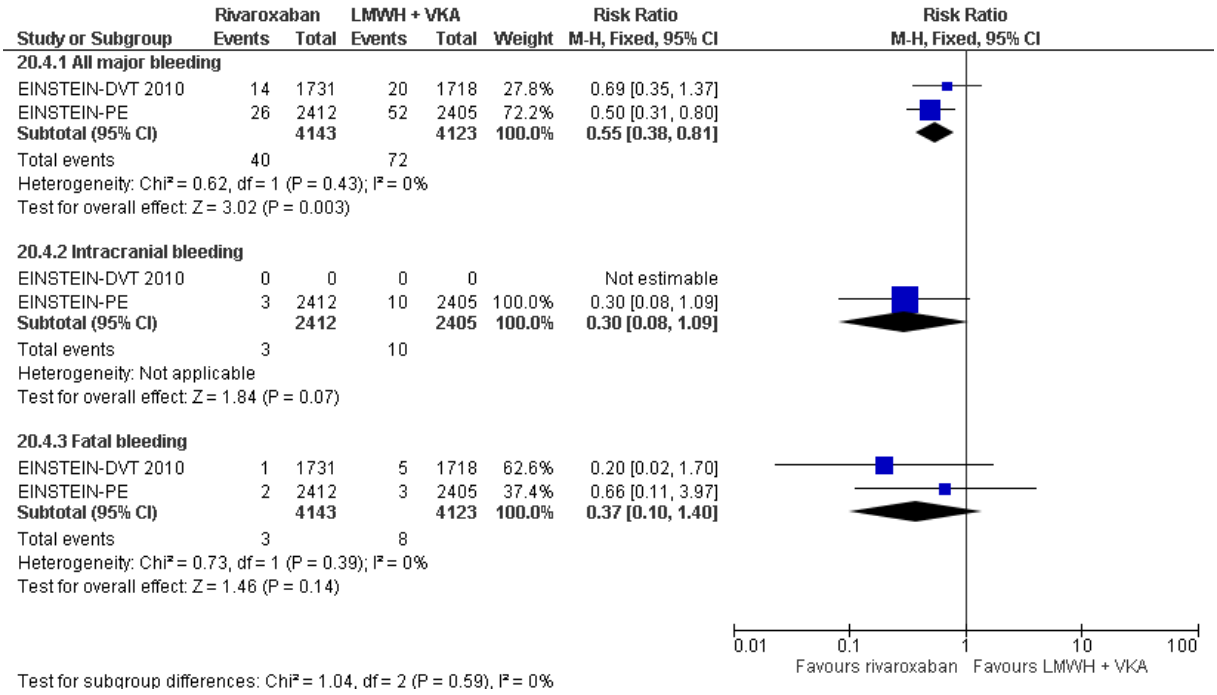


Figure 67: PE-occurrence up to 12 months



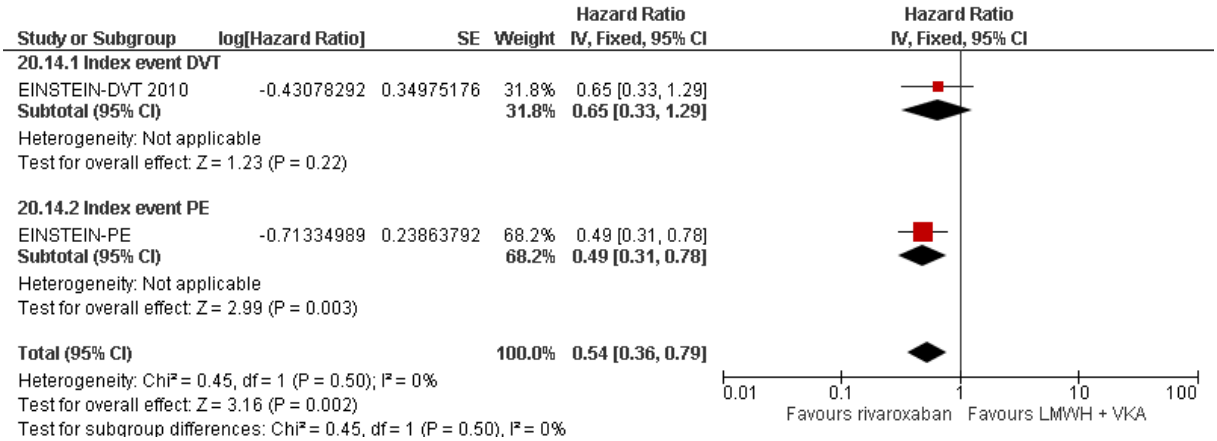
Major bleeding

Figure 68: Major-bleeding on treatment up to 12 months



Test for subgroup differences: Chi² = 1.04, df = 2 (P = 0.59), I² = 0%

Figure 69: Major bleeding event



Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%

Clinically relevant non-major bleeding

Figure 70: Clinically relevant non-major bleeding on treatment up to 12 months

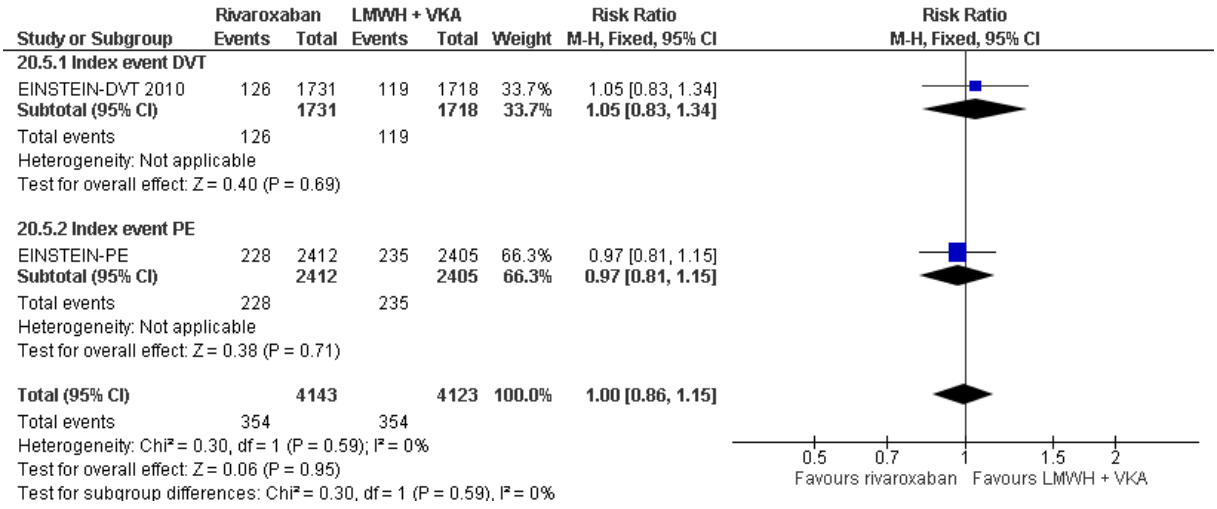
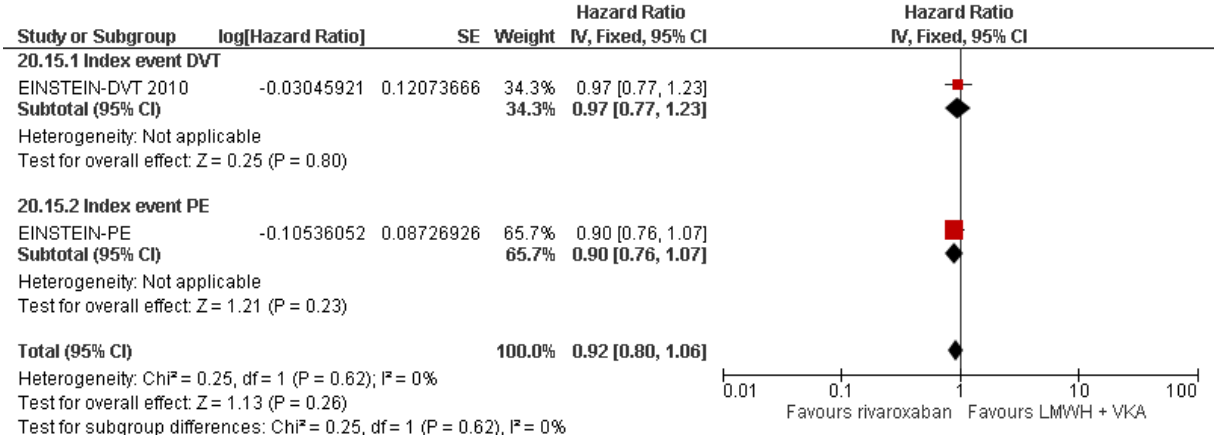


Figure 71: Major bleeding or CRNMB event



All-cause mortality

Figure 72: All-cause mortality on treatment up to 12 months

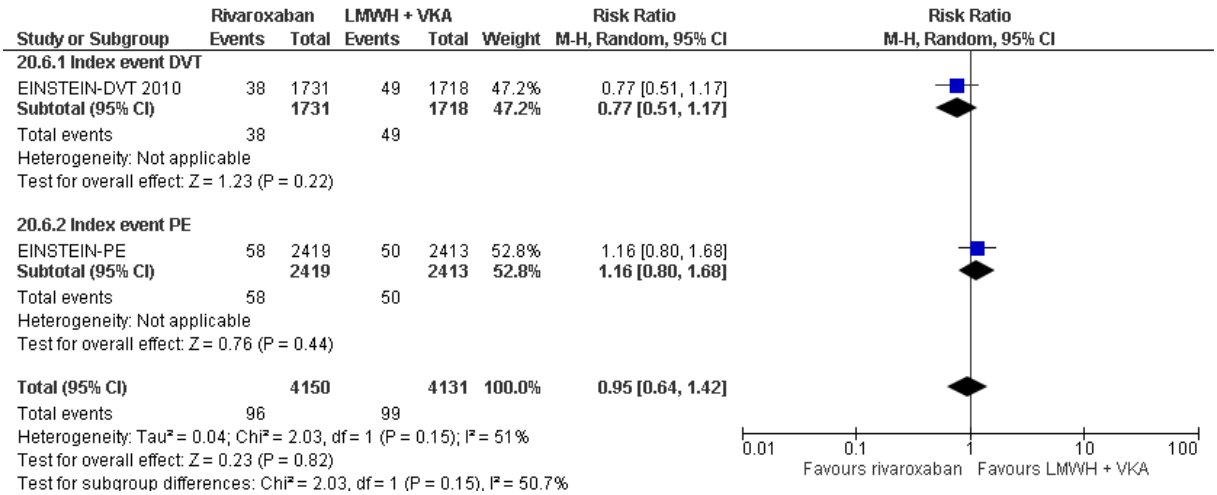
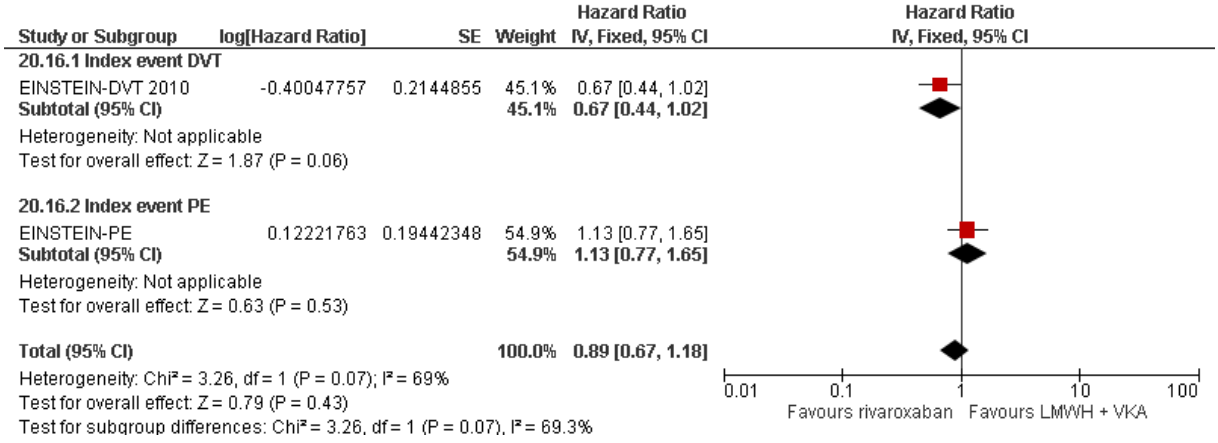
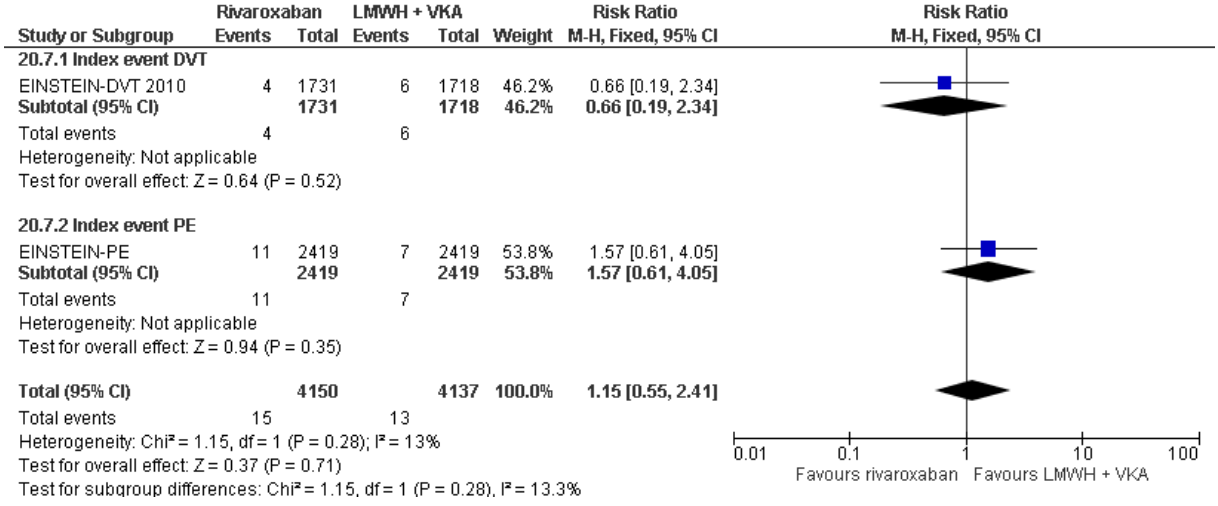


Figure 73: All-cause mortality



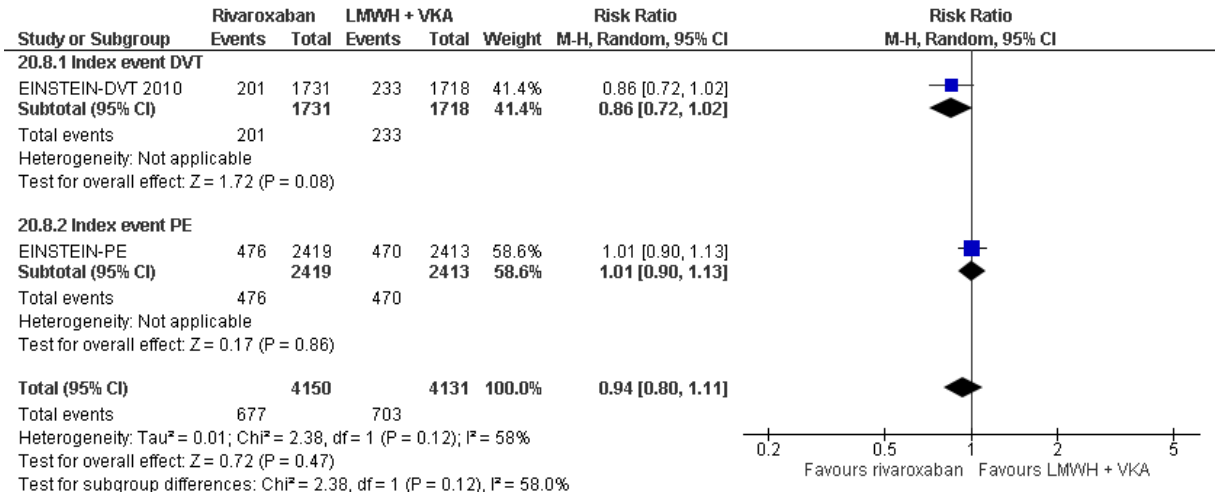
VTE-related mortality

Figure 74: VTE related mortality on treatment up to 12 months



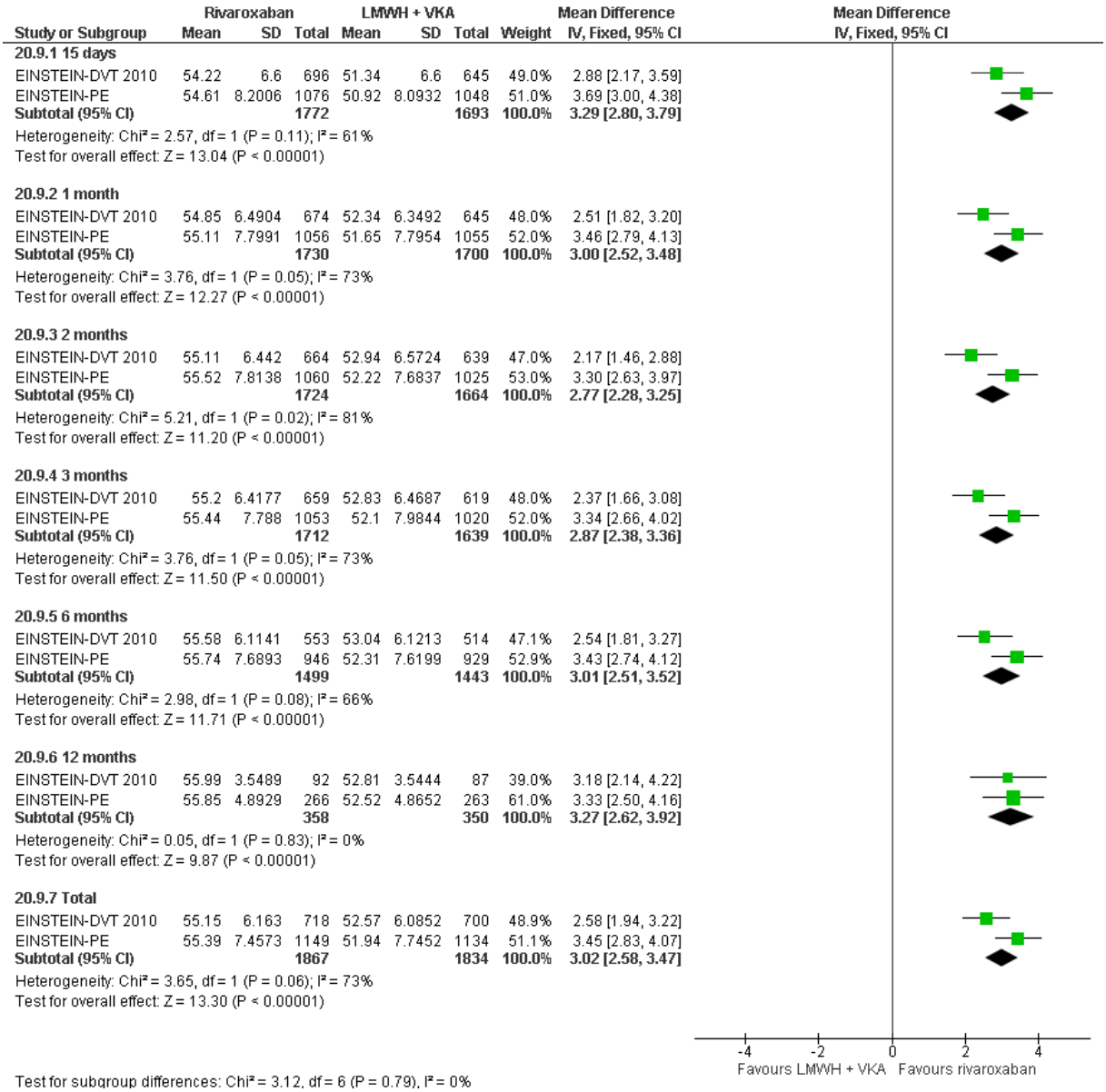
Serious adverse events

Figure 75: Serious adverse events on treatment up to 12 months



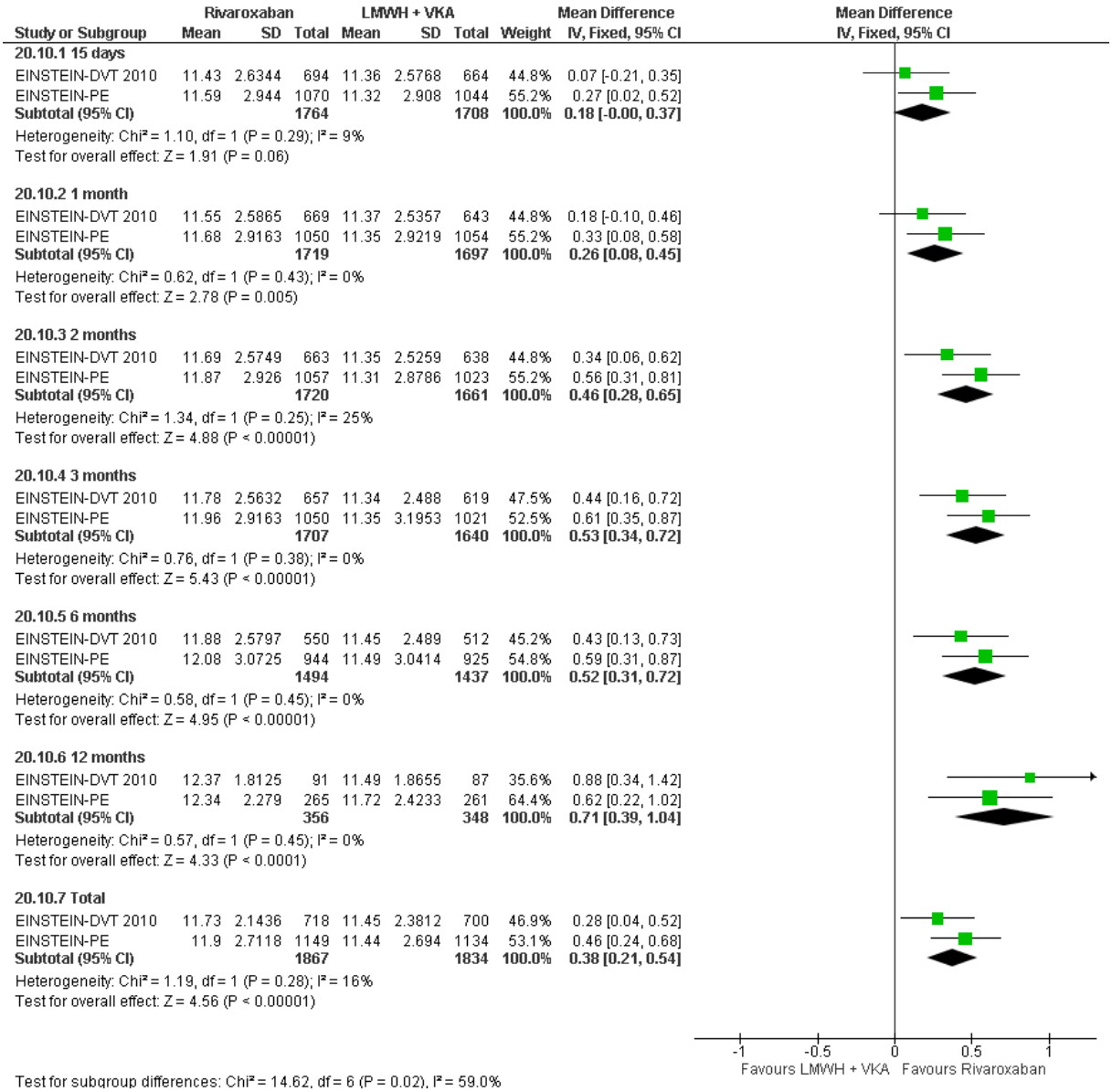
Quality of life

Figure 76: Quality of life: Anti-clot treatment scale burdens



Test for subgroup differences: Chi² = 3.12, df = 6 (P = 0.79), I² = 0%

Figure 77: Quality of life: Anti-clot treatment scale benefits



Test for subgroup differences: Chi² = 14.62, df = 6 (P = 0.02), I² = 59.0%

Initial treatment in cancer analyses

LMWH + VKA versus LMWH alone for the initial treatment of VTE in people with cancer (DVT and/or PE)

VTE-recurrence

Figure 78: VTE-recurrence 6 months (with subgroup analyses for renal insufficiency)

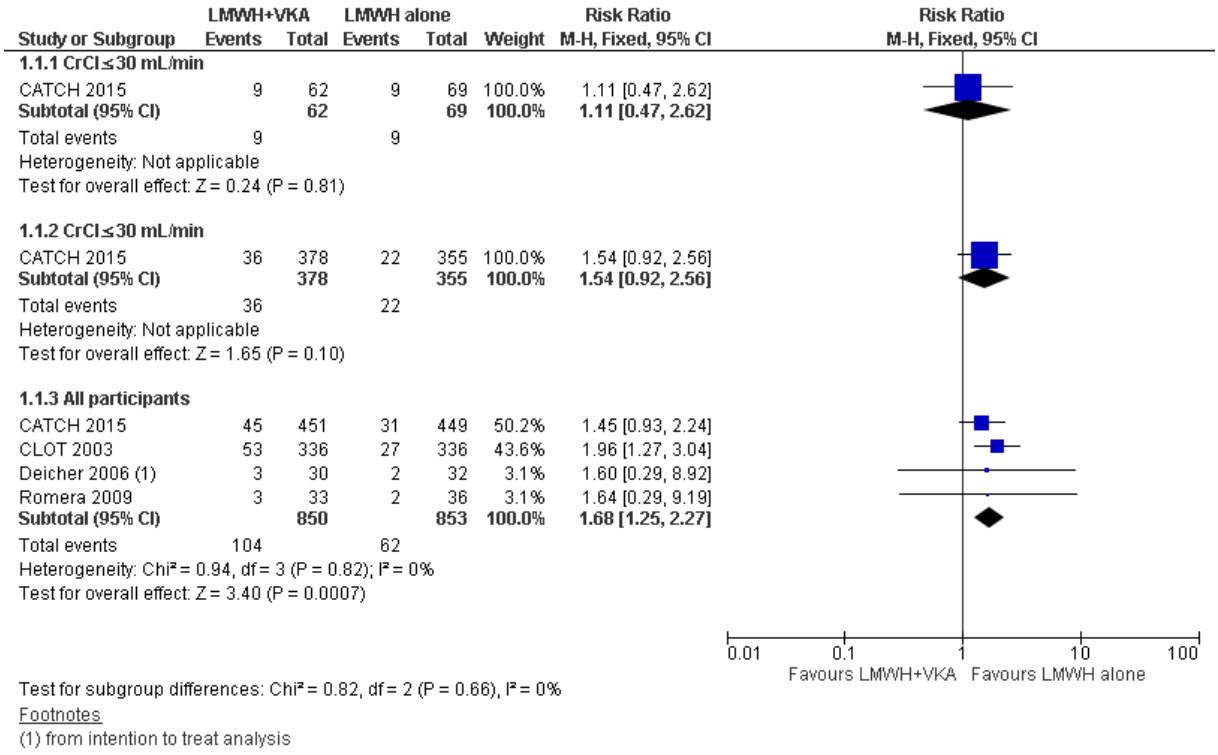


Figure 79: VTE-recurrence

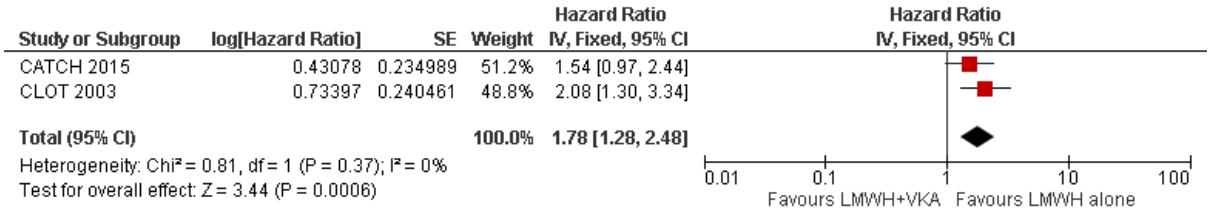
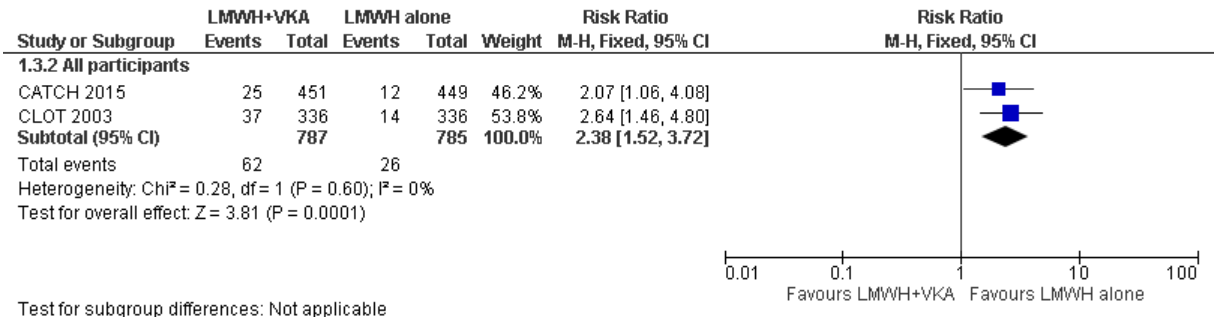
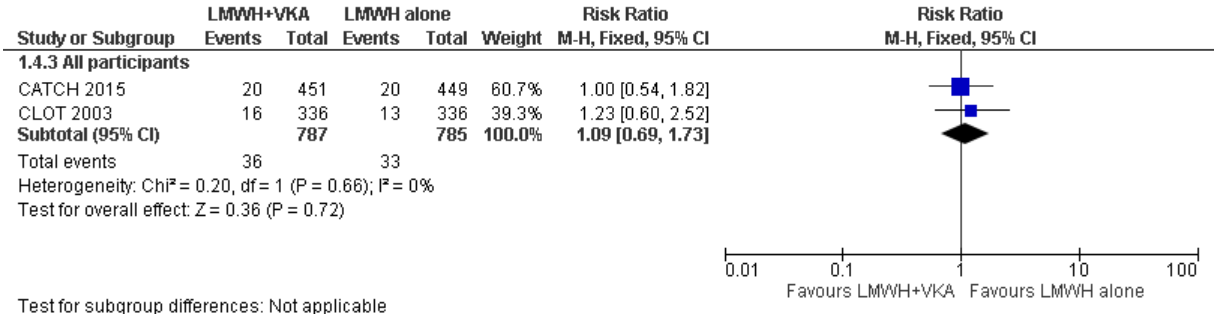


Figure 80: DVT-occurrence 6 months



Test for subgroup differences: Not applicable

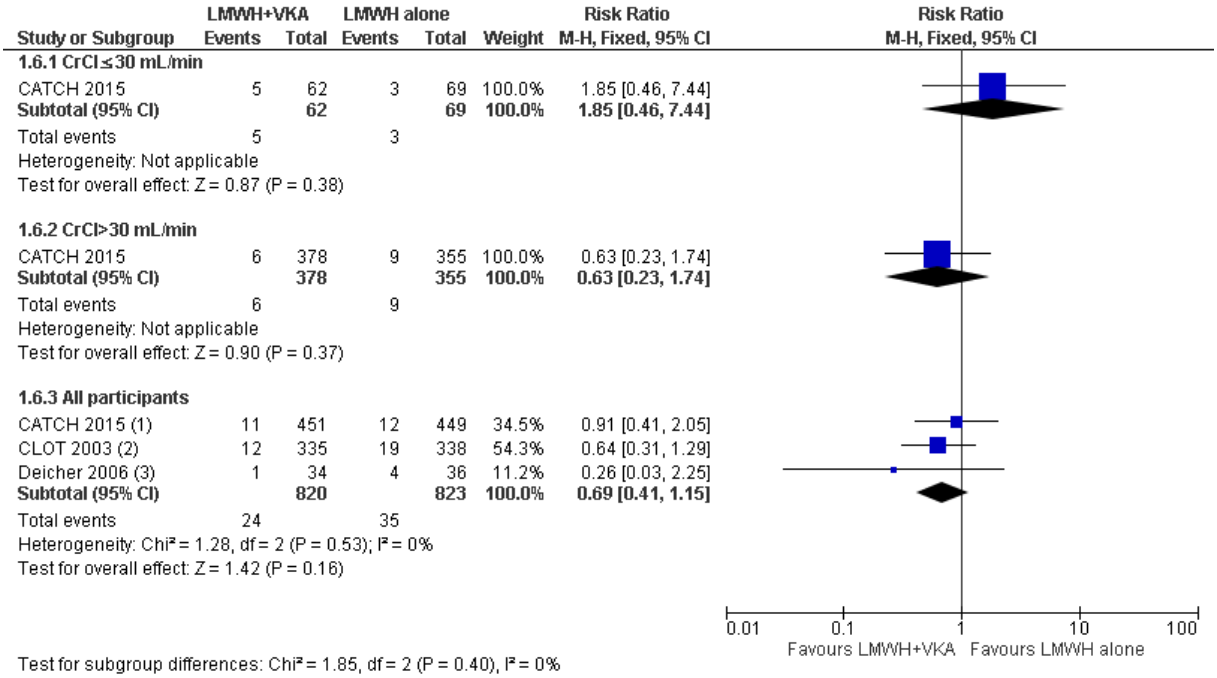
Figure 81: PE-occurrence 6 months



Test for subgroup differences: Not applicable

Major bleeding

Figure 82: Major bleeding 6 months (with subgroup analyses for renal insufficiency)



Test for subgroup differences: Chi² = 1.85, df = 2 (P = 0.40), I² = 0%

Footnotes

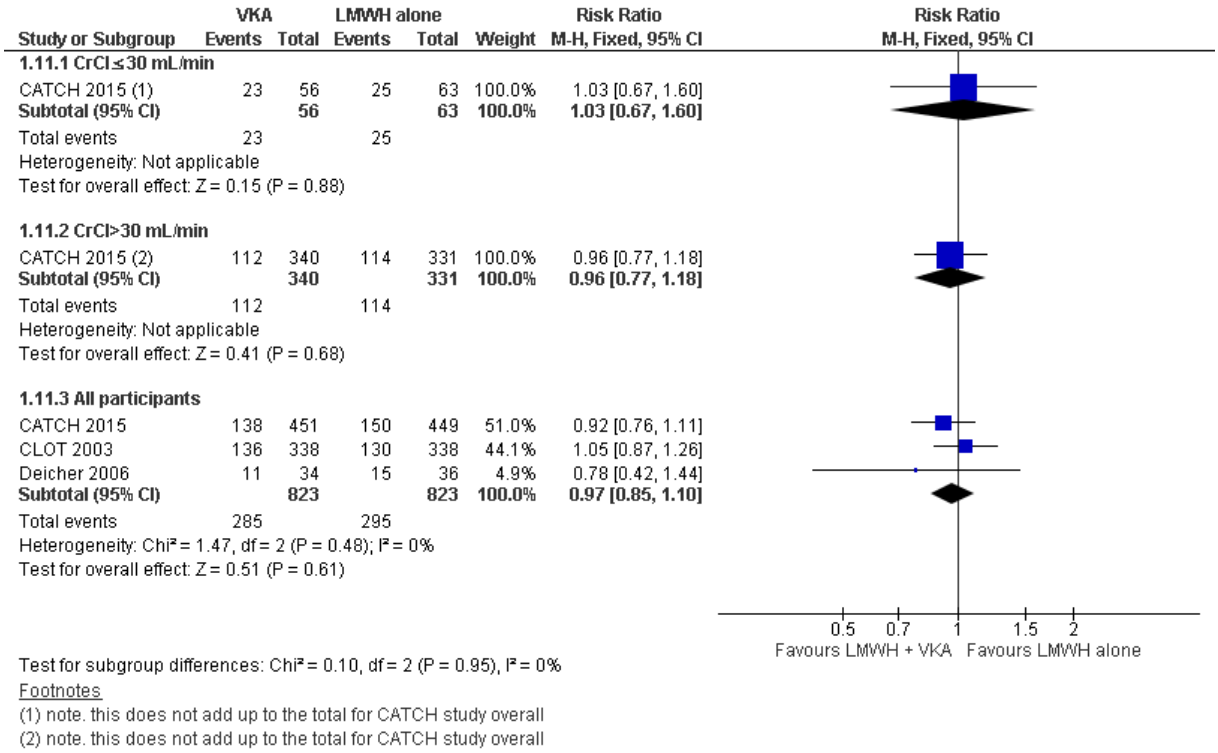
(1) from safety analysis however unclear if all on-treatment

(2) from safety analysis however unclear if all on-treatment

(3) from ITT analysis

All-cause mortality

Figure 83: All-cause mortality 6 months (with subgroup analyses for renal insufficiency)

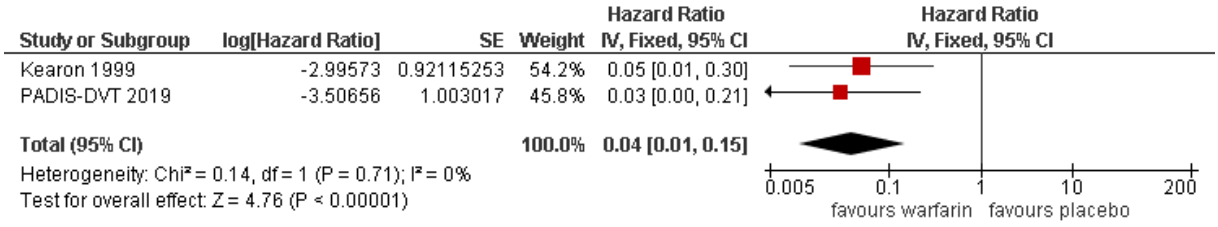


Extended therapy analyses

Warfarin (to a target INR of 2.0-3.0) versus placebo for the extended therapy of DVT-only

VTE-recurrence

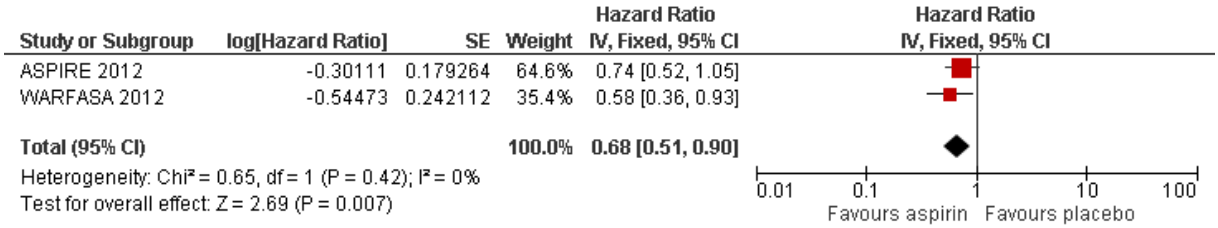
Figure 84: VTE-recurrence up to 12 months



1 **Aspirin versus placebo for the extended therapy of VTE (DVT and/or PE)**

2 ***VTE-recurrence***

3 **Figure 85: VTE-recurrence**



4

Appendix G – GRADE profiles

Initial treatment of VTE

Pairwise meta-analyses

Fondaparinux + VKA versus LMWH + VKA for the initial treatment of DVT

Table 23 Fondaparinux + VKA versus LMWH + VKA for the initial treatment of DVT

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (fondaparinux+VKA)	
VTE recurrence up to 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Very serious[1]	43/1098	45/1107	RR 0.96 (0.64 to 1.45)	4.07 per 100	3.90 per 100 (2.60 to 5.89)	Low
DVT-occurrence up to 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Serious[2]	18/1098	28/1107	RR 0.65 (0.36 to 1.16)	2.53 per 100	1.64 per 100 (0.91 to 2.93)	Moderate
PE-occurrence up to 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Serious[2]	25/1098	17/1107	RR 1.48	1.54 per 100	2.27 per 100 (1.24 to 4.19)	Moderate

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (fondaparinux+VKA)	
								(0.81 to 2.73)			
Major bleeding 14 days (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Very serious[1]	12/1098	13/1107	RR 0.93 (0.43 to 2.03)	1.17 per 100	1.09 per 100 (0.50 to 2.38)	Low
Major bleeding 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Very serious[1]	28/1098	26/1107	RR 1.09 (0.63 to 1.87)	2.35 per 100	2.56 per 100 (1.48 to 4.39)	Low
Clinically relevant non-major bleeding 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Very serious[1]	60/1098	63/1107	RR 0.96 (0.68 to 1.35)	5.69 per 100	5.46 per 100 (3.87 to 7.68)	Low
VTE-related mortality 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Serious[3]	5/1098	5/1107	RR 1.01 (0.29 to 3.47)	0.45 per 100	0.46 per 100 (0.13 to 0.61)	Moderate
All-cause mortality 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2004)	RCT	Not serious	N/A	Not serious	Serious[3]	41/1098	33/1107	RR 1.25	2.98 per 100	3.73 per 100 (2.38 to 5.87)	Moderate

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (fondaparinux+VKA)	Quality
								(0.80 to 1.97)			

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect

Fondaparinux + VKA versus UFH + VKA for the initial treatment of PE

Table 24 Fondaparinux + VKA versus UFH + VKA for the initial treatment of PE

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Fondaparinux+VKA)	Quality
VTE recurrence up to 3 months (RR <1 favours Fondaparinux)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Fondaparinux+VKA)	
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Serious[2]	42/1103	56/1110	RR 0.75 (0.51 to 1.12)	5.05 per 100	3.78 per 100 (2.57 to 5.65)	Low
DVT-occurrence up to 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Very serious[3]	12/1103	17/1110	RR 0.71 (0.34 to 1.48)	1.53 per 100	1.09 (0.52 to 2.27)	Very low
PE-occurrence up to 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Serious[2]	30/1103	39/1110	RR 0.77 (0.48 to 1.24)	3.51 per 100	2.71 per 100 (1.69 to 4.36)	Low
Major bleeding 14 days (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Very serious[3]	14/1103	12/1110	RR 1.17 (0.55 to 2.53)	1.08 per 100	1.26 per 100 (0.59 to 2.74)	Very low
Major bleeding 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Very serious[3]	22/1103	26/1110	RR 0.85 (0.49 to 1.49)	2.34 per 100	1.99 per 100 (1.15 to 3.49)	Very low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Fondaparinux+VKA)	
Clinically relevant non-major bleeding 14 days (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Serious[2]	35/1103	57/1110	RR 0.62 (0.41 to 0.93)	5.14 per 100	3.18 per 100 (2.11 to 4.78)	Low
Clinically relevant non-major bleeding 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Serious[2]	62/1103	92/1110	RR 0.68 (0.50 to 0.93)	8.29 per 100	5.64 per 100 (4.14 to 7.71)	Low
VTE-related mortality 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Serious[4]	16/1103	15/1110	RR 1.07 (0.53 to 2.16)	1.35 per 100	1.45 per 100 (0.72 to 2.92)	Low
All-cause mortality 3 months (RR <1 favours Fondaparinux)											
1 (Buller 2003)	RCT	Serious[1]	N/A	Not serious	Serious[4]	57/1103	48/1110	RR 1.20 (0.82 to 1.74)	4.32 per 100	5.19 per 100 (3.55 to 7.52)	Low

1. >33.3% of studies by weight in meta-analysis were at moderate or high risk of bias
2. 95% confidence interval crosses one end of a defined MID interval

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Fondaparinux	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Fondaparinux+VKA)	Quality
3. 95% confidence interval crosses both ends of a defined MID interval 4. 95% CI crosses line of no effect											

LMWH + VKA versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 25 LMWH + VKA versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
VTE recurrence 14 days (RR <1 favours LMWH) (Figure 20)											
6 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	11/1156	15/1158	RR 0.75 (0.36 to 1.59)	1.30 per 100	0.97 per 100 (0.47 to 2.06)	Very Low
Subgroup analysis (VTE index event only): VTE recurrence up to 14 days (RR <1 favours LMWH) (Figure 20)											
1 (Kearon 2006)	RCT	Not serious	N/A	Not serious	Very serious[2]	2/352	1/345	RR 1.96	0.29 per 100	0.57 per 100 (0.05 to 6.24)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
								(0.18 to 21.52)			
Subgroup analysis (DVT index event only): VTE recurrence up to 14 days (RR <1 favours LMWH) (Figure 20)											
3 studies	RCT	Very serious[3]	Not serious	Serious4	Very serious[2]	6/471	11/475	RR 0.57 (0.22 to 1.48)	2.32 per 100	1.32 per 100 (0.51 to 3.43)	Very low
Subgroup analysis (PE index event only): VTE recurrence up to 14 days (RR <1 favours LMWH) (Figure 20)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	3/333	3/338	RR 1.02 (0.23 to 4.45)	0.89 per 100	0.91 per 100 (0.20 to 3.95)	Very low
VTE recurrence up to 14 days: PE only: index event DVT (RR <1 favours LMWH) (Figure 21)											
2 studies	RCT	Very serious[3]	Not serious	Serious[4]	Very serious[2]	2/269	6/277	RR 0.40 (0.09 to 1.69)	2.17 per 100	0.87 per 100 (0.19 to 3.66)	Very low
VTE recurrence 3 months (RR <1 favours LMWH) (Figure 22**)**											
16 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	112/3208	132/2884	RR 0.77 (0.60 to 0.99)	4.58 per 100	3.52 per 100 (2.75 to 4.53)	Low
Subgroup analysis (VTE index event only): VTE recurrence 3 months (RR <1 favours LMWH) (Figure 22**)**											
3 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	48/1322	40/995	RR 0.90 (0.59 to 1.37)	4.02 per 100	3.62 per 100 (2.37 to 5.51)	Very low
Subgroup analysis (DVT index event only): VTE recurrence 3 months (RR <1 favours LMWH) (Figure 22**)**											
11 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	58/1553	83/1551	RR 0.71 (0.51 to 0.98)	5.35 per 100	3.80 per 100 (2.73 to 5.24)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
Subgroup analysis (PE index event only): VTE recurrence 3 months (RR <1 favours LMWH) (Figure 22)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	6/333	9/338	RR 0.68 (0.24 to 1.88)	2.66 per 100	1.81 per 100 (0.64 to 5.01)	Very low
VTE recurrence 3 months: DVT only (Figure 24)											
13 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	69/2679	82/2353	RR 0.73 (0.54 to 1.01)	3.48 per 100	2.54 per 100 (1.88 to 3.52)	Low
Subgroup analysis (VTE index event only): VTE recurrence 3 months: DVT only (Figure 24)											
3 studies	RCT	Not serious	Not serious	Not serious	Very serious[2]	35/1322	31/995	RR 0.80 (0.50 to 1.31)	3.12 per 100	2.49 per 100 (1.56 to 4.08)	Low
Subgroup analysis (DVT index event only): VTE recurrence 3 months: DVT only (Figure 24)											
10 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	34/1357	51/1358	RR 0.69 (0.45 to 1.04)	3.76 per 100	2.59 per 100 (1.69 to 3.91)	Low
VTE recurrence 3 months: PE only (Figure 26)											
12 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	31/2581	34/2256	RR 0.84 (0.52 to 1.35)	1.51 per 100	1.27 per 100 (0.78 to 2.03)	Very low
Subgroup analysis (VTE index event only): VTE recurrence 3 months: PE only (Figure 26)											
2 studies	RCT	Not serious	Serious6	Not serious	Very serious[2]	8/962	6/635	RR 0.88 (0.32 to 2.41)	0.94 per 100	0.83 per 100 (0.30 to 2.28)	Very low
Subgroup analysis (DVT index event only): VTE recurrence 3 months: PE only (Figure 26)											
10 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	23/1619	28/1621	RR 0.83	1.73 per 100	1.43 per 100 (0.85 to 2.45)	Very low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
								(0.49 to 1.42)			
Major bleeding 14 days: all major bleeds (Figure 27)											
13 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	37/2924	53/2621	RR 0.63 (0.41 to 0.95)	2.02 per 100	1.27 per 100 (0.83 to 1.92)	Low
Subgroup analysis (VTE index event only): Major bleeding 14 days: all major bleeds (Figure 27)											
3 studies	RCT	Not serious	Not serious	Not serious	Very serious[2]	17/1322	14/995	RR 0.85 (0.42 to 1.72)	1.41 per 100	1.20 per 100 (0.59 to 2.42)	Low
Subgroup analysis (DVT index only): Major bleeding 14 days: all major bleeds (Figure 27)											
9 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	17/1298	34/1318	RR 0.52 (0.30 to 0.92)	2.58 per 100	1.34 per 100 (0.77 to 2.37)	Low
Subgroup analysis (PE index only): Major bleeding 14 days: all major bleeds (Figure 27)											
1 study (Simonneau 1997)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	3/304	5/308	RR 0.61 (0.15 to 2.52)	1.62 per 100	0.99 per 100 (0.24 to 4.09)	Very low
Major bleeding 14 days: Intracranial bleeds only (only DVT-only index event data were available) (Figure 27)											
2 studies	RCT	Serious[1]	N/A	Not serious	Very serious[2]	1/247	0/253	RR 3.07 (0.13 to 75.06)	Not calculable[8]	Not calculable[8]	Very low
Major bleeding 14 days: Fatal bleeds only (Figure 30)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	
3 studies	RCT	Serious[1]	N/A	Not serious	Very serious[2]	2/399	0/401	RR 5.12 (0.25 to 106.13)	Not calculable[8]	Not calculable[8]	Very low
Major bleeding 3 months all major bleeds (Figure 31)											
12 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	48/2104	62/2106	RR 0.78 (0.54 to 1.13)	2.94 per 100	2.30 per 100 (1.59 to 3.33)	Low
Subgroup analysis (VTE index event only): Major bleeding 3 months all major bleeds (Figure 31)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	19/712	11/705	RR 1.71 (0.82 to 3.56)	1.56 per 100	2.67 per 100 (1.28 to 5.55)	Low
Subgroup analysis (DVT index only): Major bleeding 3 months all major bleeds (Figure 31)											
8 studies	RCT	Very serious[3]	Not serious	Not serious	Serious[5]	21/1028	37/1032	RR 0.59 (0.35 to 0.99)	3.59 per 100	2.12 per 100 (1.25 to 3.55)	Very low
Subgroup analysis (PE index only): Major bleeding 3 months all major bleeds (Figure 31)											
2 studies	RCT	Serious[1]	Not serious	Serious[4]	Very serious[2]	8/364	14/369	RR 0.58 (0.25 to 1.36)	3.79 per 100	2.20 per 100 (0.95 to 5.16)	Very low
Major bleeding 3 months: Intracranial bleeds only (Figure 33)											
6 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	0/804	4/797	RR 0.27 (0.05 to 1.66)	Not calculable[8]	Not calculable[8]	Very low
Major bleeding 3 months: Fatal bleeds only (Figure 34)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	0/287	3/283	RR 0.25 (0.03 to 2.19)	Not calculable[8]	Not calculable[8]	Very low
Clinically relevant non-major bleeding up to 14 days following initiation of treatment administration (Figure 35)											
6 studies	RCT	Not serious	Not serious	Not serious	Serious[5]	67/1010	127/1338	RR 0.88 (0.67 to 1.18)	9.49 per 100	8.35 per 100 (6.36 to 11.20)	Medium
Subgroup analysis (VTE index event only) Clinically relevant non-major bleeding up to 14 days following initiation of treatment administration (Figure 35)											
1 study (Merli 2001)	RCT	Not serious	N/A	Not serious	Serious[5]	39/290	100/610	RR 0.82 (0.58 to 1.16)	16.39 per 100	13.44 per 100 (9.51 to 19.02)	Medium
Subgroup analysis (DVT index only): Clinically relevant non-major bleeding up to 14 days following initiation of treatment administration (Figure 35)											
5 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	28/720	27/728	RR 1.04 (0.62 to 1.73)	3.71 per 100	3.86 per 100 (2.30 to 6.42)	Very low
Clinically relevant non-major bleeding 3 months (Figure 36)											
7 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	69/871	54/864	RR 1.25 (0.89 to 1.75)	7.92 per 100	9.90 per 100 (7.05 to 13.86)	Low
All-cause mortality up to 14 days following initiation of treatment administration (Figure 37)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	6/656	3/653	RR 1.87 (0.51 to 6.82)	0.46 per 100	0.86 per 100 (0.23 to 3.13)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
Subgroup analysis (VTE index only): All-cause mortality up to 14 days following initiation of treatment administration (Figure 37)											
1 study (Kearon 2006)	RCT	Not serious	N/A	Not serious	Serious[7]	2/352	0/345	RR 4.90 (0.24 to 101.71)	Not calculable[8]	Not calculable[8]	Medium
Subgroup analysis (PE index only): All-cause mortality up to 14 days following initiation of treatment administration (Figure 37)											
1 study (Simonneau 1997)	RCT	Serious[1]	N/A	Not serious	Serious[7]	4/304	3/308	RR 1.35 (0.30 to 5.99)	0.97 per 100	1.31 per 100 (0.29 to 5.83)	Low
All-cause mortality 3 months (Figure 38)											
16 studies	RCT	Serious[1]	Not serious	Not serious	Not serious	117/3038	138/2715	RR 0.79 (0.62 to 1.00)	5.08 per 100	4.02 per 100 (3.15 to 5.08)	Medium
Subgroup analysis (VTE index only): All-cause mortality 3 months (Figure 38)											
3 studies	RCT	Not serious	Not serious	Not serious	Serious[7]	52/1322	39/995	RR 1.07 (0.71 to 1.61)	3.92 per 100	4.19 per 100 (2.78 to 6.31)	Medium
Subgroup analysis (DVT index only): All-cause mortality 3 months (Figure 38)											
9 studies	RCT	Serious[1]	Not serious	Not serious	Not serious	48/1294	77/1290	RR 0.63 (0.45 to 0.90)	5.97 per 100	3.76 per 100 (2.69 to 5.37)	Medium
Subgroup analysis (PE index only): All-cause mortality 3 months (Figure 38)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	
4 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	17/422	22/430	RR 0.79 (0.42 to 1.45)	5.12 per 100	4.04 per 100 (2.15 to 7.42)	Low
VTE related mortality 3 months (Figure 40)											
11 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	29/2626	34/2313	RR 0.82 (0.51 to 1.33)	1.47 per 100	1.21 per 100 (0.75 to 1.96)	Low
Subgroup analysis (VTE index only): VTE related mortality 3 months (Figure 40)											
3 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	10/1322	5/995	RR 1.51 (0.56 to 4.12)	0.50 per 100	0.76 per 100 (0.28 to 2.07)	Low
Subgroup analysis (DVT index only): VTE related mortality 3 months (Figure 40)											
7 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	16/1000	26/1010	RR 0.65 (0.36 to 1.16)	2.57 per 100	1.67 per 100 (0.93 to 2.99)	Low
Subgroup analysis (PE index only): VTE related mortality 3 months (Figure 40)											
1 study (Simonneau 1997)	RCT	Serious[1]	N/A	Not serious	Serious[7]	3/304	3/308	RR 1.01 (0.21 to 4.98)	0.97 per 100	0.98 per 100 (0.20 to 2.85)	Low
Heparin inducted thrombocytopenia during heparin therapy period (Figure 41)											
8 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	23/1938	14/1641	RR 1.22 (0.63 to 2.35)	0.85 per 100	1.04 per 100 (0.54 to 2.00)	Very low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
Subgroup analysis (VTE index only): Heparin inducted thrombocytopenia up to 14 days following initiation of treatment administration (Figure 41)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[2]	13/970	5/650	RR 1.36 (0.48 to 3.84)	0.77 per 100	1.05 per 100 (0.37 to 2.95)	Low
Subgroup analysis (DVT index only): Heparin inducted thrombocytopenia up to 14 days following initiation of treatment administration (Figure 41)											
5 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	10/664	8/683	RR 1.27 (0.52 to 3.11)	1.17 per 100	1.49 per 100 (0.61 to 3.64)	Very low
Subgroup analysis (PE index only): Heparin inducted thrombocytopenia up to 14 days following initiation of treatment administration (Figure 41)											
1 study	RCT	Serious[1]	N/A	Not serious	Very serious[2]	0/304	1/308	RR 0.34 (0.01 to 8.26)	Not calculable[8]	Not calculable[8]	Very low

1. >33.3% of studies were at high or moderate risk of bias.
2. 95% CI crosses both boundary of the MIDs (0.8, 1.25)
3. >33.3% of studies were at high risk of bias
4. >33.3% of studies were partially direct or indirect studies
5. 95% CI crosses one boundary of the MIDs (0.8, 1.25).
6. I2 >33.3%
7. 95% CI crosses line of no effect
8. Absolute effect could not be calculated due to 0 events being recorded in at least one group.

Sensitivity analyses for LMWH + VKA versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 26 Sensitivity analyses removing studies at high risk of bias for LMWH + VKA versus UFH + VKA for the initial treatment of VTE (DVT and/or PE).

Results are reported for the pooled analysis and the subgroup where the study/ studies at high risk of bias have been removed. Other subgroup results are unaltered from Table 25.

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH)	Absolute: intervention (LMWH)	Quality
Sensitivity analysis (high risk of bias studies removed from index event DVT) VTE recurrence at 3 months (RR <1 favours LMWH) (Figure 42)											
14 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	100/2915	114/2587	RR 0.78 (0.60 to 1.02)	4.41 per 100	3.04 per 100 (2.12 to 4.32)	Low
Sensitivity analysis (high risk of bias studies removed) VTE recurrence at 3 months: index event DVT only (RR <1 favours LMWH) (Figure 42)											
9 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	46/1260	65/1254	RR 0.72 (0.50 to 1.03)	5.18 per 100	4.04 per 100 (3.11 to 5.29)	Low
Sensitivity analysis (high risk of bias studies removed from index event DVT) DVT-occurrence at 3 months (RR <1 favours LMWH) (Figure 43)											
11 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	61/2380	70/2051	RR 0.74 (0.53 to 1.04)	3.41 per 100	2.53 per 100 (1.81 to 3.55)	Low
Sensitivity analysis (high risk of bias studies removed from DVT-occurrence at 3 months: index event DVT only (RR <1 favours LMWH) (Figure 43)											
8 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	26/1058	39/1056	RR 0.69 (0.43 to 1.10)	3.69 per 100	2.55 per 100 (1.59 to 4.06)	Low
Sensitivity analysis (high risk of bias studies removed from index event DVT) Major bleeding at 14 days: all major bleeds (RR <1 favours LMWH) (Figure 44)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH)	Absolute: intervention (LMWH)	
12 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	30/2729	45/2416	RR 0.58 (0.36 to 0.92)	1.86 per 100	1.08 per 100 (0.67 to 1.71)	Low
Sensitivity analysis (high risk of bias studies removed) Major bleeding at 14 days: index event DVT only (RR <1 favours LMWH) (Figure 44)											
8 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	10/1103	26/1113	RR 0.41 (0.20 to 0.82)	2.34 per 100	0.96 per 100 (0.47 to 1.92)	Low
Sensitivity analysis (high risk of bias studies removed from index event DVT) Major bleeding at 3 months: all major bleeds (RR <1 favours LMWH) (Figure 45)											
10 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	36/1805	48/1804	RR 0.76 (0.50 to 1.15)	3.15 per 100	2.39 per 100 (1.58 to 3.62)	Low
Sensitivity analysis (high risk of bias studies removed) Major bleeding at 3 months: all major bleeds: index event DVT only (RR <1 favours LMWH) (Figure 45)											
6 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	9/729	23/730	RR 0.42 (0.20 to 0.87)	2.66 per 100	1.12 per 100 (0.53 to 2.31)	Low
Sensitivity analysis (high risk of bias studies removed) Major bleeding at 3 months: intracranial bleeds only (RR <1 favours LMWH) (Figure 46)											
5 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	0/700	4/700	RR 0.27 (0.05 to 1.66)	Not calculable[8]	Not calculable[8]	Very low
Sensitivity analysis (high risk of bias studies removed) clinically relevant non-major bleeding at 3 months (RR <1 favours LMWH) (Figure 47)											
6 studies	RCT	Serious[1]	Serious6	Not serious	Very serious[2]	56/767	45/767	RR 1.23 (0.85 to 1.79)	5.87 per 100	7.22 per 100 (4.99 to 10.50)	Very low
Sensitivity analysis (high risk of bias studies removed from index event DVT) all-cause mortality (RR <1 favours LMWH) (Figure 48)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH)	Absolute: intervention (LMWH)	Quality
15 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	107/2843	123/2510	RR 0.80 (0.62 to 1.03)	4.90 per 100	3.92 per 100 (3.04 to 5.05)	Low
Sensitivity analysis (high risk of bias studies removed) all-cause mortality: index event DVT only (RR <1 favours LMWH) (Figure 48)											
8 studies	RCT	Serious[1]	Not serious	Not serious	Serious[7]	38/1099	62/1085	RR 0.62 (0.42 to 0.91)	5.71 per 100	3.54 per 100 (2.40 to 5.20)	Low
Sensitivity analysis (high risk of bias studies removed from index event DVT) heparin induced thrombocytopenia during heparin treatment (RR <1 favours LMWH) (Figure 49)											
7 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	21/1743	12/1436	RR 1.24 (0.62 to 2.50)	0.84 per 100	1.04 per 100 (0.52,2.09)	Very low
Sensitivity analysis (high risk of bias studies removed) heparin induced thrombocytopenia during heparin treatment: index event DVT only (RR <1 favours LMWH) (Figure 49)											
7 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	8/469	6/478	RR 1.33 (0.48 to 3.67)	1.26 per 100	1.67 per 100 (0.60 to 4.61)	Very low

1. >33.3% of studies were at high or moderate risk of bias.
2. 95% CI crosses both boundary of the MIDs (0.8, 1.25)
3. >33.3% of studies were at high risk of bias
4. >33.3% of studies were partially direct or indirect studies
5. 95% CI crosses one boundary of the MIDs (0.8, 1.25).
6. I2 >33.3%
7. 95% CI crosses line of no effect

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH)	Absolute: intervention (LMWH)	Quality
8. Absolute effect could not be calculated due to 0 events being recorded in at least one group.											

LMWH + VKA versus UFH + VKA for the initial treatment of DVT in elderly people with impaired renal function (CrCl≤30 mL/min)

Table 27 LMWH + VKA versus UFH + VKA for the initial treatment of DVT in elderly people with impaired renal function (CrCl≤30 mL/min)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
VTE recurrence 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Very serious[2]	7/269	3/270	RR 2.15 (0.61 to 7.59)	1.11 per 100	2.39 per 100 (0.68, 18.16)	Low
Subgroup analysis (CrCl≤30 mL/min): VTE recurrence 3 months (RR <1 favours LMWH)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Very serious[2]	2/70	0/68	RR 4.86 (0.24 to 99.39)	Not calculable[3]	Not calculable[3]	Low
Subgroup analysis (CrCl>30 mL/min): VTE recurrence 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Very serious[2]	5/199	3/202	RR 1.69 (0.41 to 6.98)	1.49 per 100	2.51 per 100 (0.61, 17.55)	Low
Major bleeding 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Very serious[2]	12/269	10/270	RR 1.20 (0.53 to 2.72)	3.7 per 100	4.43 per 100 (1.95, 12.04)	Low
Subgroup analysis (CrCl≤30 mL/min): Major bleeding 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Very serious[2]	5/70	4/68	RR 1.21 (0.34 to 4.33)	5.88 per 100	7.14 per 100 (2, 30.94)	Low
Subgroup analysis (CrCl>30 mL/min): Major bleeding 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Very serious[2]	7/199	6/202	RR 1.18 (0.41 to 3.46)	2.97 per 100	3.52 per 100 (1.2, 12.18)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH + VKA	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (LMWH+VKA)	Quality
All-cause mortality 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Not serious	31/269	17/270	RR 1.83 (1.04 to 3.23)	6.3 per 100	11.52 per 100 (6.54, 37.18)	High
Serious adverse events 3 months (RR <1 favours LMWH)											
1 study (Leizorovicz 2011)	RCT	Not serious	N/A	Not serious	Serious[1]	63/269	52/270	RR 1.22 (0.88 to 1.68)	19.26 per 100	23.42 per 100 (16.9, 39.46)	Moderate

1. 95% CI crosses one boundary of the MIDs (0.8, 1.25).
2. 95% CI crosses both boundary of the MIDs (0.8, 1.25)
3. Absolute effect could not be calculated due to 0 events being recorded in at least one group.

Apixaban (5/10mg twice daily for 7 days followed by 5mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 28 Apixaban (5/10mg twice daily for 7 days followed by 5mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control LMWH+VKA)	Absolute: intervention (apixaban)	
VTE recurrence up to 3 months (RR <1 favours Apixaban)											
1 (Buller 2008)	RCT	Serious1	N/A	Not serious	Very serious[2]	3/117	3/118	RR 1.01 (0.21 to 4.90)	2.54 per 100	2.57 per 100 (0.53 to 12.46)	Very low
DVT-occurrence up to 3 months (RR <1 favours Apixaban)											
1 (Buller 2008)	RCT	Serious1	N/A	Not serious	Very serious[2]	3/117	2/118	RR 1.51 (0.26 to 8.89)	1.69 per 100	2.56 per 100 (0.44 to 15.07)	Very low
PE-occurrence up to 3 months (RR <1 favours Apixaban)											
1 (Buller 2008)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	0/117	1/118	RR 0.34 (0.01 to 8.17)	Not calculable[5]	Not calculable[5]	Very low
VTE recurrence up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Serious3	59/2598	70/2622	RR 0.85 (0.60 to 1.20)	2.67 per 100	2.27 per 100 (1.60 to 3.20)	Moderate
Subgroup analysis (BMI<30 kg/m^2): VTE recurrence up to 6 months (RR <1 favours Apixaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control LMWH+VKA)	Absolute: intervention (apixaban)	
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	43/1678	42/1708	RR 1.04 (0.68, 1.59)	2.46 per 100	2.56 per 100 (1.68, 3.90)	Low
Subgroup analysis (BMI≥30 kg/m^2): VTE recurrence up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Serious3	16/917	28/910	RR 0.57 (0.31, 1.04)	3.08 per 100	1.74 per 100 (0.95, 3.20)	Moderate
Subgroup analysis (<65 years old): VTE recurrence up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	39/1678	47/1714	RR 0.85 (0.56, 1.29)	2.74 per 100	2.32 per 100 (1.53, 3.53)	Low
Subgroup analysis (≥65 years old): VTE recurrence up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	20/931	24/921	RR 0.82 (0.46, 1.48)	2.61 per 100	2.15 per 100 (1.20, 3.86)	Low
Subgroup analysis (DVT index event only): VTE recurrence up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	38/1698	47/1736	RR 0.83 (0.54 to 1.26)	2.71 per 100	2.25 per 100 (1.46 to 3.41)	Low
Subgroup analysis (PE index event only): VTE recurrence up to 6 months (RR <1 favours Apixaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control LMWH+VKA)	Absolute: intervention (apixaban)	
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	21/900	23/886	RR 0.90 (0.50 to 1.61)	2.60 per 100	2.34 per 100 (1.30 to 4.18)	Low
Major bleeding 3 months (RR <1 favours Apixaban)											
1 (Buller 2008)	RCT	Not serious	N/A	Not serious	Very serious[2]	1/128	0/126	RR 2.95 (0.12 to 71.82)	Not calculable[5]	Not calculable[5]	Very low
Major bleeding 6 months: All major bleeding (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Not serious	15/2676	49/2689	RR 0.31 (0.17 to 0.55)	1.82 per 100	0.56 per 100 (0.31 to 1.00)	High
Subgroup analysis (BMI<30 kg/m^2):Major bleeding up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Serious[4]	12/1724	29/1740	RR 0.41 (0.21, 0.81)	1.67 per 100	0.69 per 100 (0.35, 1.36)	Moderate
Subgroup analysis (BMI≥30 kg/m^2): Major bleeding up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Not serious	3/937	20/920	RR 0.14 (0.04, 0.49)	2.17 per 100	0.31 per 100 (0.09, 1.06)	High
Subgroup analysis (<65 years old): Major bleeding up to 6 months (RR <1 favours Apixaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control LMWH+VKA)	Absolute: intervention (apixaban)	
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Not serious	7/1725	20/1753	RR 0.35 (0.15, 0.84)	1.14 per 100	0.40 per 100 (0.17, 0.96)	High
Subgroup analysis (≥65 years old): Major bleeding up to 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Serious[4]	8/951	29/936	RR 0.27 (0.12, 0.58)	3.10 per 100	0.82 per 100 (0.37, 1.81)	Moderate
Intracranial bleeding 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	3/2676	6/2689	RR 0.50 (0.13 to 2.01)	0.22 per 100	0.11 per 100 (0.03 to 0.45)	Low
Fatal bleeding 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	2/2676	3/2689	RR 0.67 (0.11 to 4.01)	0.11 per 100	0.07 per 100 (0.01 to 0.45)	Low
Clinically relevant non-major bleeding 3 months (RR <1 favours Apixaban)											
1 (Buller 2008)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	10/128	10/126	RR 0.98 (0.42 to 2.28)	7.94 per 100	7.78 per 100 (3.33 to 18.10)	Very low
Clinically relevant non-major bleeding 6 months (RR <1 favours Apixaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control LMWH+VKA)	Absolute: intervention (apixaban)	
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Not serious	103/2691	215/2704	RR 0.48 (0.38 to 0.61)	7.95 per 100	3.82 per 100 (3.02 to 4.85)	High
All cause mortality 3 months (RR <1 favours Apixaban)											
1 (Buller 2008)	RCT	Serious[1]	N/A	Not serious	Serious[4]	3/128	0/126	RR 6.89 (0.36 to 132.07)	Not calculable[5]	Not calculable[5]	Low
All cause mortality 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Serious[4]	41/2676	52/2689	RR 0.79 (0.53 to 1.19)	1.93 per 100	1.53 (1.02 to 2.30)	Moderate
VTE-related mortality 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Serious[4]	12/2691	16/2704	RR 0.75 (0.36 to 1.59)	0.59 per 100	0.44 per 100 (0.21 to 0.94)	Moderate
Serious adverse events 6 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY trial*	RCT	Not serious	N/A	Not serious	Not serious	417/2676	410/2689	RR 1.02 (0.90 to 1.16)	15.25 per 100	15.55 per 100 (13.72 to 17.69)	High

1. >33.3% of studies were at high or moderate risk of bias.
2. 95% CI crosses both lines of the MIDs (0.8, 1.25).
3. 95% CI crosses one line of the MIDs (0.8, 1.25).

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control LMWH+VKA)	Absolute: intervention (apixaban)	Quality
4. 95% CI crosses line of no effect 5. Absolute effect could not be calculated due to 0 events being recorded in at least one group. Absolute effect could not be calculated due to 0 events being recorded in at least one group.											

Apixaban (10mg twice daily for 7 days followed by 5mg twice daily) versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 29 Apixaban (10mg twice daily for 7 days followed by 5mg twice daily) versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (apixaban)	Quality
PE-occurrence 5.5 months (RR <1 favours Apixaban)											
1 (Nakamura 2015) *J-AMPLIFY trial*	RCT	Serious[1]	N/A	Not serious	Very serious[2]	0/40	1/39	RR 0.33 (0.01 to 7.75)	2.56 per 100	0.85 per 100 (0.03 to 19.87)	Very low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (apixaban)	Quality
Major bleeding 5.5 months (RR <1 favours Apixaban)											
1 (Nakamura 2015) *J-AMPLIFY trial*	RCT	Serious[1]	N/A	Not serious	Very serious[2]	0/40	2/39	RR 0.20 (0.01 to 3.94)	Not calculable[4]	Not calculable[4]	Very low
Non-major clinically relevant bleeding 5.5 months (RR <1 favours Apixaban)											
1 (Nakamura 2015) *J-AMPLIFY trial*	RCT	Serious[1]	N/A	Not serious	Serious3	3/40	9/39	RR 0.36 (0.11 to 1.13)	23.08 per 100	8.31 per 100 (2.54 to 26.08)	Low
Subgroup analysis (DVT index event only): Non-major clinically relevant bleeding 5.5 months (RR <1 favours Apixaban)											
1 (Nakamura 2015) *J-AMPLIFY trial*	RCT	Serious[1]	N/A	Not serious	Very serious[2]	0/22	5/22	RR 0.09 (0.01 to 1.55)	Not calculable[4]	Not calculable[4]	Very low
Subgroup analysis (PE index event only): Non-major clinically relevant bleeding 5.5 months (RR <1 favours Apixaban)											
1 (Nakamura 2015) *J-AMPLIFY trial*	RCT	Serious[1]	N/A	Not serious	Very serious[2]	3/18	4/17	RR 0.71 (0.19 to 2.71)	23.53 per 100	16.71 per 100 (4.47 to 63.76)	Very low
Serious adverse events 5.5 months (RR <1 favours Apixaban)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Apixaban	UFH + VKA	Relative (95% CI)	Absolute: control (UFH+VKA)	Absolute: intervention (apixaban)	Quality
1 (Nakamura 2015) *J-AMPLIFY trial*	RCT	Serious[1]	N/A	Not serious	Very serious[2]	3/40	7/39	RR 0.42 (0.12 to 1.50)	17.95 per 100	7.54 per 100 (2.15 to 26.92)	Very low

1. >33.3% of studies were at high or moderate risk of bias.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. 95% CI crosses one line of the MID (0.8).
4. Absolute effect could not be calculated due to 0 events being recorded in at least one group. Absolute effect could not be calculated due to 0 events being recorded in at least one group.

Edoxaban (30/60mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 30 Edoxaban (30/60mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Edoxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (edoxaban)	Quality
VTE-recurrence 3 months: any VTE event (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	57/4118	72/4122	RR 0.79 (0.56 to 1.12)	1.24 per 100	1.06 per 100 (0.72 to 1.60)	Low
VTE-recurrence up to 12 months: any VTE event (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious[8]	Very serious[1]	66/4118	80/4122	RR 0.82 (0.60 to 1.14)	1.94 per 100	1.59 per 100 (1.16 to 2.21)	Very low
Subgroup analysis (fragile patients only): VTE recurrence up to 12 months (RR <1 favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	Not serious	Not serious	Serious[2]	18/715	34/706	RR 0.52 (0.30, 0.92)	4.82 per 100	2.52 per 100	Moderate

										(1.44, 4.42)	
Subgroup analysis (non-fragile patients only): VTE recurrence up to 12 months (RR <1 favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	Not serious	Not serious	Very serious[1]	112/3403	112/3416	RR 1.00 (0.78, 1.30)	3.28 per 100	3.29 per 100 (2.54, 4.26)	Low
Subgroup analysis (DVT index event only): VTE recurrence up to 12 months any VTE event (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious[8]	Very serious[1]	48/2468	50/2453	RR 0.95 (0.64 to 1.41)	2.04 per 100	1.94 per 100 (1.30 to 2.87)	Very low
Subgroup analysis (PE index event only): VTE recurrence up to 12 months any VTE event (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Serious[7]	N/A	Serious[8]	Serious2	18/1650	30/1669	RR 0.61 (0.34 to 1.08)	1.80 per 100	1.10 per 100 (0.61 to 1.94)	Very low
Major bleeding 3 months: All major bleeding (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Not serious	Serious[2]	38/4118	29/4122	RR 1.31 (0.81 to 2.12)	0.70 per 100	0.92 per 100 (0.57 to 1.49)	Moderate
Intracranial bleeding 3 months (RR <1 Favours edoxaban)											
1 (HOKUSA	RCT	Not serious	N/A	Not serious	Very serious[1]	2/4118	6/4122	RR 0.33 (0.07 to 1.65)	0.15 per 100	0.05 per 100	Low

I-VTE 2013)										(0.01 to 0.24)	
Fatal bleeding 3 months (RR <1 Favours edoxaban)											
1 (HOKUSA I-VTE 2013)	RCT	Not seriou s	N/A	Not serious	Very serious[1]	2/4118	5/4122	RR 0.40 (0.08 to 2.06)	0.12 per 100	0.05 per 100 (0.01 to 0.25)	Low
Major bleeding 12 months: All major bleeding (RR <1 Favours edoxaban)											
1 (HOKUSA I-VTE 2013)	RCT	Not seriou s	N/A	Not serious	Serious[2]	56/4118	66/4122	RR 0.85 (0.60 to 1.21)	1.60 per 100	1.36 per 100 (0.96 to 1.94)	Moder ate
Intracranial bleeding 12 months (RR <1 Favours edoxaban)											
1 (HOKUSA I-VTE 2013)	RCT	Not seriou s	N/A	Not serious	Very serious[1]	5/4118	6/4122	RR 0.83 (0.25 to 2.73)	0.15 per 100	0.12 per 100 (0.04 to 0.40)	Low
Fatal bleeding 12 months (RR <1 Favours edoxaban)											
1 (HOKUSA I-VTE 2013)	RCT	Not seriou s	N/A	Not serious	Serious2	2/4118	10/4122	RR 0.20 (0.04 to 0.91)	0.24 per 100	0.05 per 100 (0.01 to 0.22)	Moder ate
Clinically relevant non-major bleeding 3 months (RR <1 Favours edoxaban)											

1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Not serious	Serious2	177/4118	251/4122	RR 0.71 (0.59 to 0.85)	6.09 per 100	4.32 per 100 (3.59 to 5.18)	Moderate
Clinically relevant non-major bleeding 12 months (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Not serious	Serious2	298/4118	368/4122	RR 0.81 (0.70 to 0.94)	8.93 per 100	7.23 per 100 (6.25 to 8.39)	Moderate
All-cause mortality up to 12 months (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious8	Serious3	132/4118	126/4122	RR 1.05 (0.82 to 1.33)	3.06 per 100	3.21 per 100 (2.51 to 4.07)	Low
VTE-related mortality up to 12 months (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious[8]	Serious[2]	26/4118	26/4122	RR 1.00 (0.58 to 1.72)	0.63 per 100	0.63 per 100 (0.37 to 1.08)	Low
Serious adverse events up to 12 months (RR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious[8]	Not serious	503/4118	504/4122	RR 1.00 (0.89 to 1.12)	12.23 per 100	12.23 per 100 (10.88 to 13.69)	Moderate

Subgroup analysis (90mg Edoxaban dose given instead of parenteral anticoagulation): Clinically relevant non-major bleeding 3 months (RR <1 Favours edoxaban)											
1 (Piazza 2016)	RCT	Very serious[4]	N/A	Not serious	Very serious[2]	3/56	2/28	RR 0.75 (0.13, 4.23)	7.14 per 100	5.36 per 100 (0.93 to 30.21)	Very low
Subgroup analysis (90mg Edoxaban dose given instead of parenteral anticoagulation): VTE-recurrence 3 months (RR <1 Favours edoxaban)											
1 (Piazza 2016)	RCT	Very serious4	N/A	Not serious	Very serious[2]	2/56	1/28	RR 1.00 (0.09, 10.56)	3.57 per 100	3.57 per 100 (0.32 to 37.71	Very low
VTE recurrence (HR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013) *taken from Raskob 2016 subgroup analysis at 3 months*	RCT	Not serious	N/A	Serious[8]	Serious[3]	N/A	N/A	HR 0.79 (0.56, 1.12)	N/A	N/A	Low
Subgroup analysis (index event DVT only): VTE recurrence (HR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Serious[7]	N/A	Serious[8]	Serious[3]	N/A	N/A	HR 0.60 (0.34, 1.07)	N/A	N/A	Very low
Subgroup analysis (index event PE): VTE recurrence (HR <1 Favours edoxaban)											

1 (HOKUSAI-VTE 2013)	RCT	Serious[7]	N/A	Serious[8]	Serious[3]	N/A	N/A	HR 0.96 (0.64, 1.43)	N/A	N/A	Very low
Major bleeding (HR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious[8]	Serious[3]	N/A	N/A	HR 0.84 (0.59, 1.20)	N/A	N/A	Low
Clinically relevant non-major bleeding (HR <1 Favours edoxaban)											
1 (HOKUSAI-VTE 2013)	RCT	Not serious	N/A	Serious[8]	Serious[3]	N/A	N/A	HR 0.80 (0.68, 0.94)	N/A	N/A	Low

1. >33.3% of studies were at high or moderate risk of bias.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. 95% CI crosses line of no effect
4. Study was at high risk of bias
5. Outcome was reported as 12-months “on-treatment”, excluding those participants that discontinued the drug.
6. Unclear whether this outcome was reported “on-treatment” or purely based on occurrences up to 12 months (regardless of intended or actual treatment duration).
7. Study was at moderate risk of bias
8. Study was only partially applicable to the review question.

Edoxaban (30/60mg once daily) versus Fondaparinux for the initial treatment of VTE (DVT and/or PE)

Table 31 Edoxaban (30/60mg once daily) versus Fondaparinux for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Edoxaban	Fondaparinux	Relative (95% CI)	Absolute: control (Fondaparinux)	Absolute: intervention (edoxaban)	Quality
Major bleeding 7 days (RR <1 Favours Edoxaban)											
1 (Hisatake 2017)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	0/25	1/25	RR 0.33 (0.01 to 7.81)	Not calculable[2]	Not calculable[2]	Very low
VTE recurrence (RR <1 Favours Edoxaban)											
1 (Hisatake 2017)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	1/25	0/25	RR 3.00 (0.13 to 70.30)	N/A	N/A	Very low
PE-occurrence (RR <1 Favours Edoxaban)											
1 (Hisatake 2017)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	1/25	0/25	RR 3.00 (0.13 to 70.30)	N/A	N/A	Very low

1. 95% CI crosses both lines of the MIDs (0.8, 1.25).
2. Absolute effect could not be calculated due to 0 events being recorded in at least one group. Absolute effect could not be calculated due to 0 events being recorded in at least one group.

Dabigatran (150mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 32 Dabigatran (150mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Dabigatran)	Quality
VTE recurrence up to 6 months Index event DVT (RR <1 favours Dabigatran) (Figure 50)											
1 (Schulman 2009) *RE-COVER trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	19/880	13/869	RR 1.44 (0.72 to 2.90)	1.50 per 100	2.15 per 100 (1.08 to 4.34)	Low
VTE recurrence up to 6 months Index event VTE (RR <1 favours Dabigatran) (Figure 50)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[1]	60/2553	55/2554	RR 1.09 (0.76 to 1.57)	2.15 per 100	2.35 per 100 (1.64 to 3.38)	Low
VTE recurrence (HR <1 favours Dabigatran) (Figure 51)											
2 studies	RCT	Not serious	Not serious	Not serious	Serious[4]	N/A	N/A	HR 1.09 (0.76 to 1.57)	N/A	N/A	Moderate
Subgroup analysis (BMI <30kg/m^2): VTE recurrence up to 6 months (RR <1 favours Dabigatran)											
1 (Schulman 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	34/1700	34/1747	RR 1.03 (0.64, 1.65)	1.95 per 100	2.00 per 100 (1.25, 3.20)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Dabigatran)	Quality
RE-COVER I and II trials combined											
Subgroup analysis (BMI ≥30kg/m^2): VTE recurrence up to 6 months (RR <1 favours Dabigatran)											
1 (Schulman 2013) *RE-COVER I and II trials combined*	RCT	Not serious	N/A	Not serious	Very serious[1]	26/846	21/804	RR 1.18 (0.67, 2.07)	2.61 per 100	3.07 per 100 (1.74, 5.42)	Low
Subgroup analysis (<65 years old): VTE recurrence up to 6 months (RR <1 favours Dabigatran)											
1 (Schulman 2013) *RE-COVER I and II trials combined*	RCT	Not serious	N/A	Not serious	Very serious[1]	46/1769	40/1748	RR 1.14 (0.75, 1.73)	2.29 per 100	2.60 per 100 (1.71, 3.95)	Low
Subgroup analysis (≥65 years old): VTE recurrence up to 6 months (RR <1 favours Dabigatran)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Dabigatran)	Quality
1 (Schulman 2013) *RE-COVER I and II trials combined*	RCT	Not serious	N/A	Not serious	Very serious[1]	14/784	15/806	RR 0.96 (0.47, 1.97)	1.86 per 100	1.79 per 100 (0.87, 3.67)	Low
DVT-occurrence up to 6 months (RR <1 favours Dabigatran) (Figure 52)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[1]	41/2553	35/2554	RR 1.17 (0.75 to 1.83)	1.37 per 100	1.60 per 100 (1.03 to 2.51)	Low
DVT-occurrence (HR <1 favours Dabigatran)											
1 (Schulman 2009) *RE-COVER I*	RCT	N/A	Not serious	Not serious	Serious[4]	N/A	N/A	HR 0.87 (0.44 to 1.72)	N/A	N/A	Moderate
PE-occurrence up to 6 months (RR <1 favours Dabigatran) (Figure 53)											
2 studies	RCT	Not serious	Serious[2]	Not serious	Very serious[1]	21/2548	20/2530	RR 1.04 (0.57 to 1.92)	0.79 per 100	0.81 per 100 (0.45 to 1.52)	Low
Major bleeding 6 months (RR <1 favours Dabigatran) (Figure 54)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Dabigatran)	Quality
2 studies	RCT	Not serious	Not serious	Not serious	Serious[3]	35/2553	46/2554	RR 0.76 (0.49 to 1.18)	1.80 per 100	1.37 per 100 (0.88 to 2.13)	Moderate
Intracranial bleeding 6 months (RR <1 favours Dabigatran) (Figure 54)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[1]	2/2553	5/2554	RR 0.46 (0.10 to 2.02)	0.20 per 100	0.09 per 100 (0.02 to 0.40	Low
Fatal bleeding 6 months (RR <1 favours Dabigatran) (Figure 54)											
1 (Schulman 2009) *RE-COVER I*	RCT	N/A	Not serious	Not serious	Very serious[1]	1/1273	1/1266	RR 0.99 (0.06 to 15.88)	0.08 per 100	0.08 per 100 (0 to 1.25)	Low
Major bleeding (HR <1 favours Dabigatran) (Figure 55)											
2 studies	RCT	Not serious	Not serious	Not serious	Serious[4]	N/A	N/A	HR 0.76 (0.49 to 1.18)	N/A	N/A	Moderate
Clinically relevant non-major bleeding 6 months (RR <1 favours Dabigatran) (Figure 56)											
2 studies	RCT	Not serious	Not serious	Not serious	Not serious	100/2553	167/2554	RR 0.60 (0.47 to 0.76)	6.54 per 100	3.92 per 100 (3.07 to 4.97)	High

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Dabigatran)	Quality
Major or clinically relevant non-major bleeding event (HR <1 favours Dabigatran) (Figure 57)											
2 studies	RCT	Not serious	Not serious	Not serious	Not serious	N/A	N/A	HR 0.63 (0.51 to 0.77)	N/A	N/A	High
All-cause mortality 6 months (RR <1 favours Dabigatran) (Figure 58)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[1]	46/2553	46/2554	RR 1.00 (0.67 to 1.50)	1.80 per 100	1.80 per 100 (1.21 to 2.70)	Low
All-cause mortality 7 months (RR <1 favours Dabigatran) (Figure 59)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[1]	54/2553	51/2554	RR 1.06 (0.73 to 1.55)	2 per 100	2.12 per 100 (1.46 to 3.10)	Low
All-cause mortality (HR <1 favours Dabigatran)											
1 (Schulman 2009) *RE-COVER I*	RCT	N/A	Not serious	Not serious	Serious[4]	N/A	N/A	HR 0.98 (0.53 to 1.80)	N/A	N/A	Moderate
VTE-related mortality 6 months (RR <1 favours Dabigatran) (Figure 60)											
2 studies	RCT	Not serious	Serious[2]	Not serious	Very serious[1]	4/2553	3/2554	RR 1.31 (0.06 to 26.88)	0.12 per 100	0.15 per 100	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (Dabigatran)	Quality
										(0.01 to 3.16)	
VTE-related mortality 7 months (RR <1 favours Dabigatran) (Figure 61)											
2 studies	RCT	Not serious	Serious[2]	Not serious	Very serious[1]	4/2553	3/2554	RR 1.31 (0.06 to 26.88)	0.12 per 100	0.15 per 100 (0.01 to 3.16)	Low
VTE-related mortality (HR <1 favours Dabigatran)											
1 (Schulman 2009) *RE-COVER I*	RCT	N/A	Not serious	Not serious	Serious[4]	N/A	N/A	HR 0.33 (0.03 to 3.38)	N/A	N/A	Moderate
Serious adverse events (RR <1 favours Dabigatran) (Figure 62)											
2 studies	RCT	Not serious	Not serious	Not serious	Not serious	321/2553	303/2554	RR 1.06 (0.91 to 1.23)	11.86 per 100	12.58 per 100 (10.80 to 14.59)	High

1. 95% confidence interval crosses both ends of a defined MID interval.
2. I2 of between 33.3% and 66.7%
3. 95% confidence interval crosses one end of a defined MID interval.
4. 95% CI crosses line of no effect

Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 33 Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	Quality
VTE recurrence up to 12-months (RR <1 favours Rivaroxaban) (Figure 63)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	86/4150	95/4131	RR 0.90 (0.56 to 1.43)	2.30 per 100	2.07 per 100 (1.29 to 3.29)	Very low
Subgroup analysis (DVT index event only): VTE recurrence up to 12-months (RR <1 favours Rivaroxaban) (Figure 63)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Serious4	36/1731	51/1718	RR 0.70 (0.46 to 1.07)	2.97 per 100	2.08 per 100 (1.37 to 3.18)	Very low
Subgroup analysis (PE index event only): VTE recurrence up to 12 months (RR <1 favours Rivaroxaban) (Figure 63)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	50/2419	44/2413	RR 1.13 (0.76 to 1.69)	1.82 per 100	2.06 per 100 (1.39 to 3.08)	Very low
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban) (Figure 64)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Serious4	31/1544	42/1541	RR 0.74 (0.47, 1.17)	2.73 per 100	1.99 per 100 (1.25, 3.19)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	Quality
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban) (Figure 64)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	55/2606	53/2590	RR 1.03 (0.71. 1.49)	2.05 per 100	2.11 per 100 (1.43, 3.09)	Very low
VTE recurrence (up to 12 months) (Figure 65)											
2 studies	RCT	Not serious	Serious[6]	Not serious	Serious[5]	4150	4131	HR 0.88 (0.54 to 1.43)	N/A	N/A	Low
Subgroup analysis (Index event DVT-only): VTE recurrence (up to 12 months)											
1 (EINSTEIN-DVT 2010)	RCT	Not serious	N/A	Not serious	Serious5	1731	1718	HR 0.68 (0.44 to 1.05)	N/A	N/A	Moderate
Subgroup analysis (Index event PE-only): VTE recurrence (up to 12 months)											
1 (EINSTEIN-PE 2012)	RCT	Not serious	N/A	Not serious	Serious5	2419	2413	HR 1.12 (0.75 to 1.68)	N/A	N/A	Moderate
Subgroup analysis (PE index event only, BMI <30 kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	39/1668	32/1643	RR 1.20 (0.76, 1.91)	1.95 per 100	2.34 per 100 (1.47, 3.71)	Very low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	Quality
Subgroup analysis (PE index event only, BMI ≥30 kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	11/741	11/755	RR 1.02 (0.44, 2.34)	1.46 per 100	1.48 per 100 (0.65, 3.40)	Very low
DVT-occurrence up to 12 months (RR <1 favours Rivaroxaban) (Figure 66)											
2 studies	RCT	Serious[1]	Serious6	Not serious	Serious4	33/4150	47/4131	RR 0.70 (0.45 to 1.09)	1.14 per 100	0.80 per 100 (0.51 to 1.24)	Very low
Subgroup analysis (DVT index event only): DVT-occurrence up to 12 month (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Serious4	15/1731	28/1718	RR 0.53 (0.29 to 0.99)	1.63 per 100	0.86 per 100 (0.47 to 1.61)	Low
Subgroup analysis (PE index event only): DVT-occurrence up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	18/2419	19/2413	RR 0.95 (0.50 to 1.80)	0.79 per 100	0.75 per 100 (0.39 to 1.42)	Very low
PE-occurrence up to 12 months RR <1 favours Rivaroxaban) (Figure 67)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	57/4150	49/4131	RR 1.16 (0.79 to 1.69)	1.19 per 100	1.38 per 100 (0.94 to 2.00)	Very low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
Subgroup analysis (DVT index event only): PE-occurrence up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	25/1731	24/1718	RR 1.03 (0.59 to 1.80)	1.40 per 100	1.44 per 100 (0.82 to 2.51)	Very low
Subgroup analysis (PE index event only): PE-occurrence up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	32/2419	25/2413	RR 1.28 (0.76 to 2.15)	1.04 per 100	1.33 per (0.79 to 2.23)	Very low
Subgroup analysis (Index event PE-only): DVT-occurrence (up to 12 months)											
1 (EINSTEIN-PE 2012)	RCT	Not serious	N/A	Not serious	Serious[5]	2419	2413	HR 0.94 (0.49 to 1.80)	N/A	N/A	Moderate
Subgroup analysis (Index event PE-only): PE-occurrence (up to 12 months)											
1 (EINSTEIN-PE 2012)	RCT	Not serious	N/A	Not serious	Serious[5]	2419	2413	HR 1.16 (0.70 to 1.93)	N/A	N/A	Moderate
Major bleeding 12 months (RR <1 favours Rivaroxaban) (Figure 68)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
2 studies	RCT	Serious[1]	Not serious	Not serious	Serious[4]	40/4143	72/4123	RR 0.55 (0.38 to 0.81)	1.75 per 100	0.96 per 100 (0.66 to 1.41)	Low
Intracranial bleeding only 12 months (RR <1 favours Rivaroxaban) (Figure 68)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Serious[4]	3/2412	10/2405	RR 0.30 (0.08 to 1.09)	0.42 per 100	0.12 per 100 (0.03 to 0.45)	Low
Fatal bleeding only 12 months (RR <1 favours Rivaroxaban) (Figure 68)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Very serious[2]	3/4143	8/4123	RR 0.37 (0.10 to 1.40)	0.19 per 100	0.07 per 100 (0.02 to 0.27)	Very low
Major bleeding event (up to 12 months) (Figure 69)											
2 studies	RCT	Not serious	Not serious	Not serious	Not serious	4150	4131	HR 0.54 (0.36 to 0.79)	N/A	N/A	High
Subgroup analysis (Index event DVT-only): Major bleeding (up to 12 months) (Figure 69)											
1 (EINSTEIN-DVT 2010)	RCT	Not serious	N/A	Not serious	Serious[5]	1731	1718	HR 0.65 (0.33 to 1.29)	N/A	N/A	Moderate
Subgroup analysis (Index event PE-only): Major bleeding (up to 12 months) (Figure 69)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
1 (EINSTEIN-PE 2012)	RCT	Not serious	N/A	Not serious	Serious[5]	2419	2413	HR 0.49 (0.31 to 0.79)	N/A	N/A	Moderate
Clinically relevant non-major bleeding 12 months (RR <1 favours Rivaroxaban) (Figure 70)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Not serious	354/4143	354/4123	RR 1.00 (0.86 to 1.15)	8.59 per 100	8.59 per 100 (7.38 to 9.87)	Moderate
Subgroup analysis (DVT index event only): Clinically relevant non-major bleeding 12 months (RR <1 favours Rivaroxaban) (Figure 70)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Serious[4]	126/1731	119/1718	RR 1.05 (0.83 to 1.34)	6.93 per 100	7.27 per 100 (5.75 to 9.28)	Low
Subgroup analysis (PE index event only): Clinically relevant non-major bleeding 12 months (RR <1 favours Rivaroxaban) (Figure 70)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Not serious	228/2412	235/2405	RR 0.97 (0.81 to 1.15)	9.77 per 100	9.48 per 100 (7.91 to 11.24)	Moderate
Major bleeding or CRNMB event (up to 12 months) (Figure 71)											
2 studies	RCT	Not serious	Not serious	Not serious	Serious[5]	4150	4131	HR 0.92 (0.80 to 1.06)	N/A	N/A	Moderate
Subgroup analysis (Index event DVT-only): Major or clinically relevant non-major bleeding (up to 12 months) (Figure 71)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
1 (EINSTEIN-DVT 2010)	RCT	Not serious	N/A	Not serious	Serious[5]	1731	1718	HR 0.97 (0.77 to 1.23)	N/A	N/A	Moderate
Subgroup analysis (Index event PE-only): Major or clinically relevant non-major bleeding (up to 12 months) (Figure 71)											
1 (EINSTEIN-PE 2012)	RCT	Not serious	N/A	Not serious	Serious[5]	2419	2413	HR 0.90 (0.76 to 1.07)	N/A	N/A	Moderate
All-cause mortality 12 months (RR <1 favours Rivaroxaban) (Figure 72)											
2 studies	RCT	Serious[1]	Serious6	Not serious	Serious[5]	96/4150	99/4131	RR 0.95 (0.64 to 1.42)	2.40 per 100	2.28 per 100 (1.53 to 3.40)	Very low
Subgroup analysis (DVT index event only): All cause mortality 12 months (RR <1 favours Rivaroxaban) (Figure 72)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Serious[5]	38/1731	49/1718	RR 0.77 (0.51 to 1.17)	2.85 per 100	2.20 per 100 (1.45 to 3.34)	Low
Subgroup analysis (PE index event only): All-cause mortality 12 months (RR <1 favours Rivaroxaban) (Figure 72)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Serious[5]	58/2419	50/2413	RR 1.16 (0.80 to 1.68)	2.07 per 100	2.40 per 100 (1.66 to 3.48)	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
All-cause mortality (Figure 73)											
2 studies	RCT	Not serious	Serious6	Not serious	Serious[5]	4150	4131	HR 0.89 (0.67 to 1.18)	N/A	N/A	Low
Subgroup analysis (Index event DVT-only): all-cause mortality (Figure 73)											
1 (EINSTEIN-DVT 2010)	RCT	Not serious	N/A	Not serious	Serious[5]	1731	1718	HR 0.67 (0.44 to 1.02)	N/A	N/A	Moderate
Subgroup analysis (Index event PE-only): all-cause mortality (Figure 73)											
1 (EINSTEIN-PE 2012)	RCT	Not serious	N/A	Not serious	Serious[5]	2419	2413	HR 1.13 (0.77 to 1.65)	N/A	N/A	Moderate
VTE-related mortality 12 months (RR <1 favours Rivaroxaban) (Figure 74)											
2 studies	RCT	Serious[1]	Not serious	Not serious	Serious[5]	15/4150	13/4137	RR 1.15 (0.55 to 2.41)	0.31 per 100	0.36 per 100 (0.17 to 0.76)	Low
Subgroup analysis (DVT event only): VTE related mortality 12 months (RR <1 favours Rivaroxaban) (Figure 74)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Serious[5]	4/1731	6/1718	RR 0.66 (0.19 to 2.34)	0.35 per 100	0.23 per 100 (0.07 to 0.82)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	Quality
Subgroup analysis (PE event only): VTE related mortality 12 months (RR <1 favours Rivaroxaban) (Figure 74)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Serious[5]	11/2419	7/2413	RR 1.57 (0.61 to 4.05)	0.29 per 100	0.45 per 100 (0.18 to 1.17)	Low
Serious adverse events (RR <1 favours Rivaroxaban) (Figure 75)											
2 studies	RCT	Serious[1]	Serious6	Not serious	Not serious	677/4150	703/4131	RR 0.94 (0.80 to 1.11)	17.02 per 100	16 per 100 (13.61 to 18.89)	Low
Subgroup analysis (DVT index event only): Serious adverse events (RR <1 favours Rivaroxaban) (Figure 75)											
1 (EINSTEIN-DVT 2010)	RCT	Serious[1]	N/A	Not serious	Serious[4]	201/1731	233/1718	RR 0.86 (0.72 to 1.02)	13.56 per 100	11.66 per 100 (9.76 to 13.83)	Low
Subgroup analysis (PE index event only): Serious adverse events (RR <1 favours Rivaroxaban) (Figure 75)											
1 (EINSTEIN-PE 2012)	RCT	Serious[1]	N/A	Not serious	Not serious	476/2419	470/2413	RR 1.01 (0.90 to 1.13)	19.48 per 100	18.31 per 100 (15.58 to 21.62)	Moderate
Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											
2 studies	RCT	Very serious[8]	Very Serious[7]	Not serious	Not serious	1867	1834	MD 3.02 (2.58 to 3.47)	N/A	N/A	Very low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
Subgroup analysis: 15 days: Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											
2 studies	RCT	Very serious [8]	Serious[6]	Not serious	Not serious	1772	1693	MD 3.29 (2.80 to 3.79)	N/A	N/A	Very low
Subgroup analysis: 1 month: Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											
2 studies	RCT	Very serious [8]	Serious[6]	Not serious	Not serious	1730	1700	MD 3.00 (2.52 to 3.48)	N/A	N/A	Very low
Subgroup analysis: 2 months: Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											
2 studies	RCT	Very serious [8]	N/A	Not serious	Not serious	1724	1664	MD 2.77 (2.28 to 3.25)	N/A	N/A	Very low
Subgroup analysis: 3 months: Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											
2 studies	RCT	Very serious [8]	Very serious[7]	Not serious	Not serious	1712	1639	MD 2.87 (2.38 to 3.36)	N/A	N/A	Very low
Subgroup analysis: 6 months: Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											
2 studies	RCT	Very serious [8]	Serious[6]	Not serious	Not serious	1499	1443	MD 3.01 (2.51 to 3.52)	N/A	N/A	Very low
Subgroup analysis: 12 months: Quality of life: anti-clot treatment scale burdens (MD <0 favours Rivaroxaban) (Figure 76)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	358	350	MD 3.27 (2.62 to 3.92)	N/A	N/A	Very low
Quality of life: anti-clot scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	1867	1834	MD 0.38 (0.21 to 0.54)	N/A	N/A	Very low
Subgroup analysis: 15 days: Quality of life: anti-clot treatment scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	1764	1708	MD 0.18 (0 to 0.37)	N/A	N/A	Very low
Subgroup analysis: 1 month: Quality of life: anti-clot treatment scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	1719	1697	MD 0.26 (0.08 to 0.45)	N/A	N/A	Very low
Subgroup analysis: 2 months: Quality of life: anti-clot treatment scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	1720	1661	MD 0.46 (0.28 to 0.65)	N/A	N/A	Very low
Subgroup analysis: 3 months: Quality of life: anti-clot treatment scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	1707	1640	MD 0.53 (0.34 to 0.72)	N/A	N/A	Very low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
Subgroup analysis: 6 months: Quality of life: anti-clot treatment scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Not serious	1494	1437	MD 0.52 (0.31 to 0.72)	N/A	N/A	Very low
Subgroup analysis: 12 months: Quality of life: anti-clot treatment scale benefits (MD <0 favours Rivaroxaban) (Figure 77)											
2 studies	RCT	Very serious [8]	Not serious	Not serious	Serious5	356	348	MD 0.71 (0.39 to 1.04)	N/A	N/A	Very low

1. >33.3% of studies were at high or moderate risk of bias and this was deemed as being important to this outcome.
2. 95% CI crosses both lines of the MIDs (0.8, 1.25).
3. Study was at a moderate risk of bias.
4. 95% CI crosses one line of the MIDs (0.8, 1.25).
5. 95% CI crosses line of no effect.
6. I2 of between 33.3% and 66.7%
7. I2 greater than 66.6%
8. >33.3% of studies were at high risk of bias.

Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Table 34 Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus UFH + VKA for the initial treatment of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	UFH + VKA	Relative (95% CI)	Absolute: control (UFH)	Absolute: intervention (rivaroxaban)	Quality
Recurrent VTE at 22 days (RR <1 favours Rivaroxaban)											
1 (Yamada 2015) *J-EINSTEIN trial*	RCT	Serious[1]	Serious[2]	Not serious	Very serious[3]	1/52	1/19	RR 0.41 (0.07 to 2.39)	5.26 per 100	2.16 per 100	Very low
Subgroup analysis (DVT index event only): Recurrent VTE at 22 days (RR <1 favours Rivaroxaban)											
1 (Yamada 2015) *J-EINSTEIN trial*	RCT	Serious[1]	N/A	Not serious	Very serious[3]	1/24	0/12	RR 1.56 (0.07 to 35.67)	Not calculable[4]	Not calculable[4]	Very low
Subgroup analysis (PE index event only): Recurrent VTE at 22 days (RR <1 favours Rivaroxaban)											
1 (Yamada 2015) *J-EINSTEIN trial*	RCT	Serious[1]	N/A	Not serious	Very serious[3]	0/28	1/7	RR 0.09 (0.00 to 2.05)	Not calculable[4]	Not calculable[4]	Very low

1. >33.3% of studies were at high or moderate risk of bias.
2. I2 of between 33.3% and 66.7%

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	UFH + VKA	Relative (95% CI)	Absolute: control (UFH)	Absolute: intervention (rivaroxaban)	Quality

3. 95% confidence interval crosses both ends of a defined MID interval.

4. Absolute effect could not be calculated due to 0 events being recorded in at least one group.

1 **Network meta-analyses**

2 **Table 35 Network meta-analysis results for initial treatment of VTE**

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
26	RCT	37,857	See appendix H	Serious[1]	Not serious	Serious[2]	Not serious	Low
Major-bleeding (on-treatment period plus wash-out period of up to 7 days following treatment cessation)								
21	RCT	35,880	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate
Clinically relevant non-major bleeding (on-treatment period plus wash-out period of up to 7 days following treatment cessation)								
17	RCT	33,489	See appendix H	Serious[1]	Not serious	Serious[2]	Not serious	Low
All-cause mortality (on-treatment)								
24	RCT	37,359	See appendix H	Serious[1]	Not serious	Not serious[3]	Not serious	Moderate
VTE-related mortality (on-treatment)								
24	RCT	33,969	See appendix H	Serious[1]	Not serious	Not serious	Serious[4]	Low

1. >33.3% of studies in the NMA were at moderate or high risk of bias.
2. Visual inspection of the relative effectiveness charts identified at least one major difference between pairwise and NMA results.
3. This model was not marked down for inconsistency between a disparity between the pairwise and NMA estimates for apixaban relative to low-molecular weight heparin. The pairwise estimate was derived from a random effects model (due to the I^2 for the pooled analysis being >50%, resulting in a small study deriving a much larger weighted contribution to the overall analysis) whereas the NMA used a fixed effect model. However, the estimate of the NMA (HR 0.85, 95% CIs 0.56, 1.27) is very similar to the pairwise data when a fixed effects model is used (HR 0.82, 95% CIs 0.55, 1.24).
4. All of the NMA comparisons cross the line of no effect.

4

Table 36 Network meta-analysis results for initial treatment of DVT

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
17	RCT	19,107	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate
Major-bleeding (on-treatment period plus wash-out period of up to 7 days following treatment cessation)								
9	RCT	11,682	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate
Clinically relevant non-major bleeding (on-treatment period plus wash-out period of up to 7 days following treatment cessation)								
11	RCT	7,667	See appendix H	Serious[1]	Not serious	Very serious[2]	Serious[3]	Very low
All-cause mortality (on-treatment)								
11	RCT	8,492	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate

1. >33.3% of studies in the NMA were at moderate or high risk of bias.
2. The DIC is lower in the random effects model than the selected fixed effects one (although not by 3.00) and visual inspection of the relative effectiveness charts identified at least one major difference between pairwise analysis and NMA.
3. All of the NMA comparisons cross the line of no effect.

Table 37 Network meta-analysis results for initial treatment of PE

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
17	RCT	12,821	See appendix H	Serious[1]	Not serious	Not serious	Serious[3]	Low
Major-bleeding (on-treatment period plus wash-out period of up to 7 days following treatment cessation)								
6	RCT	9,628	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate

* Studies with zero events in both arms removed from analysis.

1. >33.3% of studies in the NMA were at moderate or high risk of bias.
2. All of the NMA comparisons cross the line of no effect.

Table 38 Network meta-analysis results for initial treatment of VTE in people aged 65 years or older

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
4	RCT	6,527	See appendix H	Serious[1]	Not serious	Not serious	Serious[3]	Low

* Studies with zero events in both arms removed from analysis.

1. >33.3% of studies in the NMA were at moderate or high risk of bias.
2. All of the NMA comparisons cross the line of no effect.

Table 39 Network meta-analysis results for initial treatment of VTE in people with obesity

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
3	RCT	4,973	See appendix H	Serious[1]	Not serious	Not serious	Serious[3]	Low

* Studies with zero events in both arms removed from analysis.

1. >33.3% of studies in the NMA were at moderate or high risk of bias.
2. All of the NMA comparisons cross the line of no effect.

Initial treatment of VTE in people with cancer

Pairwise meta-analyses

LMWH + VKA versus LMWH alone for the initial treatment of VTE in people with cancer

Table 40 LMWH + VKA versus LMWH alone for the initial treatment of VTE in people with cancer

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH+VKA	LMWH	Relative (95% CI)	Absolute: control (LMWH)	Absolute: intervention (LMWH+VKA)	Quality
VTE recurrence up to 6 months (RR <1 favours LMWH+VKA) (Figure 78)											
4 studies	RCT	Not serious	Not serious	Not serious	Not serious	104/850	62/853	RR 1.68 (1.25, 2.27)	7.27 per 100	12.22 per 100 (9.06, 16.49)	High
Subgroup analysis (CrCl≤30 mL/min): VTE recurrence up to 6 months (RR <1 favours LMWH+VKA) (Figure 78)											
1 study (Lee 2015) *CATCH trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	9/62	9/69	RR 1.11 (0.47, 2.62)	13.04 per 100	14.52 per 100 (6.16, 34.23)	Low
Subgroup analysis (CrCl>30 mL/min): VTE recurrence up to 6 months (RR <1 favours LMWH+VKA) (Figure 78)											
1 study (Lee 2015) *CATCH trial*	RCT	Not serious	N/A	Not serious	Serious[2]	36/378	22/355	RR 1.54 (0.92, 2.56)	6.2 per 100	9.52 per 100 (5.72, 15.86)	Moderate
VTE-recurrence (HR <1 favours LMWH+VKA) (Figure 79)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH+VKA	LMWH	Relative (95% CI)	Absolute: control (LMWH)	Absolute: intervention (LMWH+VKA)	
2 studies	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 1.78 (1.28, 2.48)	N/A	N/A	High
DVT-occurrence up to 6 months (RR <1 favours LMWH+VKA) (Figure 80)											
2 studies	RCT	Not serious	Not serious	Not serious	Not serious	62/787	26/785	RR 2.38 (1.52, 3.72)	3.31 per 100	7.88 per 100 (5.05, 12.32)	High
DVT-occurrence (HR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 2.08 (1.04, 4.17)	N/A	N/A	High
PE-occurrence up to 6 months (RR <1 favours LMWH+VKA) (Figure 81)											
2 studies	RCT	Not serious	Not serious	Not serious	Very serious[1]	36/787	33/785	RR 1.09 (0.69, 1.73)	4.2 per 100	4.57 per 100 (2.88, 7.26)	Low
Major bleeding up to 3 months (RR <1 favours LMWH+VKA)											
1 study (Meyer 2002)	RCT	Not serious	N/A	Not serious	Serious[2]	12/75	5/71	RR 2.27 (0.84, 6.12)	7.04 per 100	16 per 100 (5.94, 43.12)	Moderate
Major bleeding up to 6 months (RR <1 favours LMWH+VKA) (Figure 82)											
3 studies	RCT	Not serious	Not serious	Not serious	Serious[2]	24/820	35/823	RR 0.69 (0.41, 1.15)	4.25 per 100	2.94 per 100 (1.76, 4.89)	Moderate
Subgroup analysis (CrCl≤30 mL/min): major bleeding up to 6 months (RR <1 favours LMWH+VKA) (Figure 82)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH+VKA	LMWH	Relative (95% CI)	Absolute: control (LMWH)	Absolute: intervention (LMWH+VKA)	
1 study (CATCH 2015)	RCT	Not serious	Not serious	Not serious	Very serious[1]	5/62	3/69	RR 1.85 (0.46, 7.44)	4.35 per 100	8.06 per 100 (2.01, 32.37)	Low
Subgroup analysis (CrCl>30 mL/min): major bleeding up to 6 months (RR <1 favours LMWH+VKA) (Figure 82)											
1 study (CATCH 2015)	RCT	Not serious	Not serious	Not serious	Very serious[1]	6/378	9/355	RR 0.63 (0.23, 1.74)	2.54 per 100	1.59 per 100 (0.57, 4.41)	Low
Major bleeding (HR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.12 (0.50, 2.51)	N/A	N/A	Moderate
Intracranial bleeds up to 6 months (RR <1 favours LMWH+VKA)											
1 study (CLOT 2003)	RCT	Not serious	N/A	Not serious	Very serious[1]	2/335	1/338	RR 2.02 (0.18, 22.15)	0.3 per 100	0.6 per 100 (0.05, 6.55)	Low
Clinically relevant non-major bleeding up to 6 months (RR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Serious[2]	69/451	49/449	RR 1.40 (1.00, 1.97)	10.91 per 100	15.3 per 100 (10.87, 21.54)	Moderate
Clinically relevant non-major bleeding (HR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 1.72 (1.19, 2.50)	N/A	N/A	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH+VKA	LMWH	Relative (95% CI)	Absolute: control (LMWH)	Absolute: intervention (LMWH+VKA)	
Subgroup analysis (CrCl≤30 mL/min): clinically relevant non-major bleeding up to 6 months (RR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Very serious[1]	10/62	7/69	RR 1.59 (0.64, 3.92)	10.14 per 100	16.13 per 100 (6.54, 39.79)	Low
Subgroup analysis (CrCl>30 mL/min): clinically relevant non-major bleeding up to 6 months (RR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Not serious	54/378	36/733	RR 1.41 (0.95, 2.01)	4.91 per 100	14.29 per 100 (9.61, 21.23)	Low
All-cause mortality up to 3 months (RR <1 favours LMWH+VKA)											
1 study (Meyer 2002)	RCT	Not serious	N/A	Not serious	Serious[2]	17/75	8/71	RR 2.01 (0.93, 4.37)	11.27 per 100	22.67 per 100 (10.44, 49.21)	Moderate
All-cause mortality up to 6 months (RR <1 favours LMWH+VKA) (Figure 83)											
2 studies	RCT	Not serious	Not serious	Not serious	Serious[3]	285/823	295/823	RR 0.97 (0.85, 1.1)	35.84 per 100	34.64 per 100 (30.4, 39.48)	Moderate
Subgroup analysis (CrCl≤30 mL/min): All-cause mortality up to 6 months (RR <1 favours LMWH+VKA) (Figure 83)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Serious[3]	23/53	25/63	RR 1.04 (0.67, 1.6)	39.68 per 100	41.07 per 100 (26.53, 63.59)	Moderate
Subgroup analysis (CrCl>30 mL/min): All-cause mortality up to 6 months (RR <1 favours LMWH+VKA) (Figure 83)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Serious[3]	112/340	114/331	RR 0.96 (0.77, 1.18)	34.44 per 100	32.94 per 100 (26.64, 40.73)	Moderate

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	LMWH+VKA	LMWH	Relative (95% CI)	Absolute: control (LMWH)	Absolute: intervention (LMWH+VKA)	Quality
All-cause mortality (HR <1 favours LMWH+VKA)											
1 study (CATCH, 2015)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 0.93 (0.73, 1.17)	N/A	N/A	Moderate
VTE-related mortality up to 6 months (RR <1 favours LMWH+VKA)											
1 study (CATCH 2015)	RCT	Not serious	N/A	Not serious	Serious[3]	22/451	20/449	RR 1.10 (0.61, 1.98)	4.45 per 100	4.88 per 100 (2.70, 8.81)	Moderate
Serious adverse events (RR <1 favours LMWH+VKA)											
1 study (Deicher 2006)	RCT	Serious [4]	N/A	Not serious	Serious[2]	17/34	23/36	RR 0.78 (0.52, 1.19)	63.89 per 100	50 per 100 (32.97, 75.82)	Low

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect.
4. Study was at moderate risk of bias.

UFH+VKA versus LMWH alone for the initial treatment of VTE in people with cancer

Table 41 UFH+VKA versus LMWH alone for the initial treatment of VTE in people with cancer

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	UFH+VKA	LMWH	Relative (95% CI)	Absolute: control (LMWH)	Absolute: intervention (UFH+VKA)	
VTE recurrence up to 3 months (RR <1 favours UFH+VKA)											
1 study (Hull 2006)	RCT	Not serious	N/A	Not serious	Very serious[1]	10/100	6/100	RR 1.67 (0.63, 4.41)	6 per 100	10 per 100 (3.78, 26.47)	Low
Major bleeding up to 3 months (RR <1 favours UFH+VKA)											
1 study (Hull 2006)	RCT	Not serious	N/A	Not serious	Very serious[1]	7/100	7/100	RR 1 (0.36, 2.75)	7 per 100	7 per 100 (2.55, 19.23)	Low
Clinically relevant non-major bleeding up to 3 months (RR <1 favours UFH+VKA)											
1 study (Hull 2006)	RCT	Not serious	N/A	Not serious	Very serious[1]	17/100	20/100	RR 0.85 (0.47, 1.52)	20 per 100	17 per 100 (9.48, 30.49)	Low
All-cause mortality up to 3 months (RR <1 favours UFH+VKA)											
1 study (Hull 2006)	RCT	Not serious	N/A	Not serious	Very serious[1]	19/100	20/100	RR 0.95 (0.54, 1.67)	20 per 100	19 per 100 (10.82, 33.38)	Low

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect

Apixaban versus LMWH + VKA for the initial treatment of VTE in people with cancer

Table 42 Apixaban versus LMWH + VKA for the initial treatment of VTE in people with cancer

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (apixaban)	
VTE recurrence up to 6 months (RR <1 favours apixaban)											
1 study (Agnelli 2013) *AMPLIFY subgroup analysis*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	3/81	5/78	RR 0.58 (0.14, 2.34)	6.41 per 100	3.70 per 100 (0.92, 14.98)	Very low
Major bleeding up to 6 months (RR <1 favours apixaban)											
1 study (Agnelli 2013) *AMPLIFY subgroup analysis*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	2/87	4/80	RR 0.46 (0.09, 2.44)	5 per 100	2.30 per 100 (0.43, 12.21)	Very low
Clinically relevant non-major bleeding up to 6 months (RR <1 favours apixaban)											
1 study (Agnelli 2013) *AMPLIFY subgroup analysis*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	9/87	14/80	RR 0.59 (0.27, 1.29)	17.5 per 100	10.34 per 100 (4.74, 22.58)	Very low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	apixaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (apixaban)	Quality
1. Study was only partially applicable to the review question: Subgroup analysis. 2. 95% confidence interval crosses both ends of a defined MID interval.											

Rivaroxaban versus LMWH + VKA for the initial treatment of VTE in people with cancer

Table 43 Rivaroxaban versus LMWH + VKA for the initial treatment of VTE in people with cancer

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	Quality
VTE recurrence up to 12 months (RR <1 favours apixaban)											
1 study (EINSTEIN-DVT 2010 and PE 2012) *Subgroup analyses*	RCT	Serious[1]	N/A	Serious[2]	Very serious[3]	6/258	8/204	RR 0.59 (0.21, 1.68)	3.92 per 100	2.33 per 100 (0.82, 6.60)	Very low
Major bleeding up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
1 study (EINSTEIN-DVT 2010 and PE 2012) *Subgroup analyses*	RCT	Serious[1]	N/A	Serious[2]	Very serious[3]	5/257	8/202	RR 0.49 (0.16, 1.48)	3.96 per 100	1.95 per 100 (0.65, 5.86)	Very low
Clinically relevant non-major bleeds up to 12 months (RR <1 favours rivaroxaban)											
1 study (EINSTEIN-DVT 2010 and PE 2012) *Subgroup analyses*	RCT	Serious[1]	N/A	Serious[2]	Very serious[3]	25/257	19/202	RR 1.04 (0.59, 1.84)	9.31 per 100	9.73 per 100 (5.51, 17.16)	Very low
All-cause mortality up to 12 months (RR <1 favours rivaroxaban)											
1 study (EINSTEIN-DVT 2010 and PE 2012) *Subgroup analyses*	RCT	Serious[1]	N/A	Serious[2]	Serious[4]	38/258	36/204	RR 0.83 (0.55, 1.27)	17.65 per 100	14.73 per 100 (9.70, 22.35)	Very low
VTE-recurrence (HR <1 favours rivaroxaban)											
1 study (EINSTEIN-DVT	RCT	Serious[1]	N/A	Serious[2]	Serious[4]	N/A	N/A	HR 0.62 (0.21, 1.81)	N/A	N/A	Very low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	Quality
2010 and PE 2012) *Subgroup analyses*											
Major bleed (HR <1 favours rivaroxaban)											
1 study (EINSTEIN-DVT 2010 and PE 2012) *Subgroup analyses*	RCT	Serious[1]	N/A	Serious[2]	Serious[4]	N/A	N/A	HR 0.47 (0.15, 1.46)	N/A	N/A	Very low
All-cause mortality (HR <1 favours rivaroxaban)											
1 study (EINSTEIN-DVT 2010 and PE 2012) *Subgroup analyses*	RCT	Serious[1]	N/A	Serious[2]	Serious[4]	N/A	N/A	HR 0.82 (0.52, 1.30)	N/A	N/A	Very low
Any clinically relevant bleed (RR <1 favours rivaroxaban)											
1 study (EINSTEIN-DVT 2010 and PE 2012)	RCT	Serious[1]	N/A	Serious[2]	Serious[4]	N/A	N/A	HR 0.82 (0.48, 1.39)	N/A	N/A	Very low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (rivaroxaban)	
Subgroup analyses											

1. Study was at moderate risk of bias
2. Study was only partially applicable to the review question: Subgroup analysis.
3. 95% confidence interval crosses both ends of a defined MID interval.
4. 95% CI crosses line of no effect

Rivaroxaban versus LMWH alone for the initial treatment of DVT

Table 44 Rivaroxaban versus LMWH alone for the initial treatment of DVT

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH alone	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (rivaroxaban)	
VTE recurrence up to 6 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH alone	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (rivaroxaban)	
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Serious[2]	8/203	18/203	RR 0.44 (0.2, 1.00)	8.87 per 100	3.94 per 100 (1.75, 8.86)	Moderate
DVT-occurrence up to 6 months (RR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	3/203	7/203	RR 0.43 (0.11, 1.63)	3.45 per 100	1.48 per 100 (0.39, 5.64)	Low
PE-occurrence up to 6 months (RR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	4/203	9/203	RR 0.44 (0.14, 1.42)	4.43 per 100	1.97 per 100 (0.62, 6.30)	Low
Major bleeding up to 6 months (RR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D*	RCT	Not serious	N/A	Not serious	Very serious[1]	11/203	6/203	RR 1.83 (0.69, 4.86)	2.96 per 100	5.42 per 100 (2.04, 14.37)	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH alone	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (rivaroxaban)	
trial											
Clinically relevant non-major bleeding up to 6 months (RR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Not serious	25/203	7/203	RR 3.57 (1.58, 8.07)	3.45 per 100	12.32 per 100 (5.45, 27.83)	High
All-cause mortality up to 6 months (RR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Serious[2]	48/203	56/203	RR 0.86 (0.61, 1.2)	27.59 per 100	23.65 per 100 (16.95, 32.98)	Moderate
VTE-recurrence (HR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.43 (0.19, 0.98)	N/A	N/A	High
Major bleed (HR <1 favours rivaroxaban)											
1 study (Young 2018)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.83 (0.68, 4.94)	N/A	N/A	Moderate

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	LMWH alone	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (rivaroxaban)	Quality
SELECT-D trial											
Clinically relevant major bleed (HR <1 favours rivaroxaban)											
1 study (Young 2018) *SELECT-D trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 3.76 (1.63, 8.68)	N/A	N/A	Moderate

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect

Dabigatran versus LMWH + VKA for the initial treatment of VTE in people with cancer

Table 45 Dabigatran versus LMWH + VKA for the initial treatment of VTE in people with cancer

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (dabigatran)	
VTE recurrence up to 6 months (RR <1 favours dabigatran)											
1 study (Schulman 2015) *analysis of RE-COVER trials*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	4/114	5/107	RR 0.75 (0.21, 2.72)	4.67 per 100	3.51 per 100 (0.97, 12.72)	Very low
Major bleeding up to 6 months (RR <1 favours dabigatran)											
1 study (Schulman 2015) *analysis of RE-COVER trials*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	4/105	3/100	RR 1.27 (0.29, 5.53)	3 per 100	3.81 per 100 (0.87, 16.60)	Very low
Clinically relevant non-major bleeding up to 6 months (RR <1 favours dabigatran)											
1 study (Schulman 2015) *analysis of RE-*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	10/105	6/100	RR 1.59 (0.6, 4.21)	6 per 100	9.52 per 100 (3.59, 25.23)	Very low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (dabigatran)	
COVER trials											
All-cause mortality up to 6 months (RR <1 favours dabigatran)											
1 study (Schulman 2015) *analysis of RE-COVER trials*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	16/114	16/107	RR 0.94 (0.49, 1.78)	14.95 per 100	14.04 per 100 (7.39, 25.23)	Very low
VTE-related mortality up to 6 months (RR <1 favours dabigatran)											
1 study (Schulman 2015) *analysis of RE-COVER trials*	RCT	Not serious	N/A	Serious[1]	Very serious[2]	1/114	2/107	RR 0.47 (0.04, 5.1)	1.87 per 100	0.88 per 100 (0.08, 9.53)	Very low
VTE recurrence (HR <1 favours dabigatran)											
1 study (Schulman 2015) *analysis of RE-COVER trials*	RCT	Not serious	N/A	Serious[1]	Serious[2]	N/A	N/A	HR 0.74 (0.20, 2.72)	N/A	N/A	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH+VKA)	Absolute: intervention (dabigatran)	Quality

1. Study was only partially applicable to the review question: Subgroup analysis.
2. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect

Edoxaban versus LMWH alone for the initial treatment of VTE in people with cancer

Table 46 Edoxaban versus LMWH alone for the initial treatment of VTE in people with cancer

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	edoxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (edoxaban)	Quality
VTE recurrence up to 6 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	34/522	46/524	RR 0.74 (0.48, 1.14)	8.78 per 100	6.51 per 100 (4.25, 9.98)	Low
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours edoxaban)											
1 study (Raskob 2018)	RCT	Serious[1]	N/A	Not serious	Serious[2]	22/246	33/261	RR 0.71 (0.42, 1.18)	12.64 per 100	8.94 per 100 (5.37, 14.90)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	edoxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (edoxaban)	Quality
SELECT-D trial											
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	19/276	26/263	RR 0.70 (0.40, 1.23)	9.89 per 100	6.88 per 100 (3.91, 12.14)	Low
DVT recurrence up to 6 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	15/522	25/524	RR 0.60 (0.32, 1.13)	4.77 per 100	2.87 per 100 (1.53, 5.39)	Low
PE recurrence up to 6 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Very Serious[3]	23/522	24/524	RR 0.96 (0.55, 1.68)	4.58 per 100	4.41 per 100 (2.52, 7.71)	Very low
Major bleeding up to 12 months (RR <1 favours edoxaban)											
1 study (Raskob 2018)	RCT	Serious[1]	N/A	Not serious	Serious[2]	32/522	16/524	RR 2.01 (1.12, 3.61)	3.05 per 100	6.13 per 100 (3.41, 11.03)	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	edoxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (edoxaban)	
SELECT-D trial											
Subgroup analysis (<65 years old): Major bleeding up to 12 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Very Serious[3]	12/246	8/261	RR 1.62 (0.65, 4.04)	3.07 per 100	4.97 per 100 (2.00, 12.38)	Very low
Subgroup analysis (≥65 years old): major bleeding up to 12 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Very Serious[3]	20/276	8/263	RR 2.49 (1.08, 5.76)	3.04 per 100	7.57 per 100 (3.28, 17.51)	Very low
Clinically relevant non major bleeding up to 12 months (RR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	70/522	48/524	RR 1.46 (1.03, 2.07)	9.16 per 100	13.41 per 100 (9.48, 18.97)	Low
All-cause mortality up to 6 months (RR <1 favours edoxaban)											
1 study (Raskob 2018)	RCT	Serious[1]	N/A	Not serious	Serious[2]	140/522	127/524	RR 1.11 (0.9, 1.36)	24.24 per 100	26.82 per 100 (21.80, 33.00)	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	edoxaban	LMWH + VKA	Relative (95% CI)	Absolute: control (LMWH alone)	Absolute: intervention (edoxaban)	Quality
SELECT-D trial											
Time to VTE-recurrence (HR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	N/A	N/A	HR 0.75 (0.48, 1.17)	N/A	N/A	Low
Time to any-cause mortality (HR <1 favours edoxaban)											
1 study (Raskob 2018) *SELECT-D trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	N/A	N/A	HR 1.14 (0.90, 1.45)	N/A	N/A	Low

Network meta-analyses

Table 47 Network meta-analysis results for the initial treatment of VTE in people with cancer NMAs

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (intention to treat)								
10	RCT	4,197	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate
Major bleeding (on-treatment period)								

10	RCT	4,291	See appendix H	Serious[1]	Not serious	Very serious[2,4]	Serious[3]	Very low
Clinically relevant non-major bleeding (on-treatment period)								
7	RCT	3,385	See appendix H	Serious[1]	Not serious	Serious[4]	Not serious	Low
All-cause mortality (intention to treat)								
9	RCT	4,127	See appendix H	Serious[1]	Not serious	Not serious	Serious[3]	Low

1. >33.3% of studies in the NMA were at moderate or high risk of bias.
2. The DIC is lower in the random effects model than the selected fixed effects one
3. All of the NMA comparisons cross the line of no effect.
4. Visual inspection of the relative effectiveness charts identified at least one major difference between pairwise and NMA results.

Extended therapy for VTE

Pairwise meta-analyses

Apixaban 2.5mg versus placebo for the extended therapy of VTE

Table 48 Apixaban 2.5mg versus placebo for the extended therapy of VTE

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	
VTE recurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	14/840	73/829	RR 0.19 (0.11 to 0.33)	8.81 per 100	1.66 per 100 (0.97, 2.91)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	2/565	40/548	RR 0.05 (0.01, 0.20)	7.30 per 100	0.35 per 100 (0.09, 1.46)	High
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	12/275	33/281	RR 0.37 (0.20, 0.70)	11.74 per 100	4.36 per 100 (2.30, 8.27)	High
Subgroup analysis (Index event DVT): VTE recurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	6/544	52/551	RR 0.12 (0.05 to 0.27)	9.44 per 100	1.11 per 100 (0.48, 2.55)	High
Subgroup analysis (Index event PE): VTE recurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	8/296	21/278	RR 0.36 (0.16 to 0.79)	7.55 per 100	2.72 per 100 (1.22, 5.97)	High
Major-bleeds up to 12 months (RR <1 favours apixaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	2/840	4/829	RR 0.49 (0.09 to 2.69)	0.48 per 100	0.24 per 100 (0.04, 1.30)	Low
Clinically relevant non major-bleeds up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	25/840	19/829	RR 1.30 (0.72 to 2.34)	2.29 per 100	2.98 per 100 (1.65, 5.36)	Low
All-cause mortality up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[3]	7/840	14/829	RR 0.49 (0.20 to 1.22)	1.69 per 100	0.83 per 100 (0.34, 2.05)	Moderate
VTE-related mortality up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[3]	2/840	7/829	RR 0.28 (0.06 to 1.35)	0.84 per 100	0.24 per 100 (0.05, 1.14)	Moderate
Serious adverse events (RR <1 favours apixaban)											
1 (Agnelli 2013)	RCT	Not serious	N/A	Not serious	Serious[2]	112/840	158/829	RR 0.70 (0.56 to 0.87)	19.06 per 100	13.33 per 100	Moderate

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	
AMPLIFY-EXT trial										(10.68, 16.65)	
PE-occurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[2]	10/840	22/829	RR 0.45 (0.21 to 0.94)	2.65 per 100	1.19 per 100 (0.57, 2.50)	Moderate
DVT-occurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	6/840	53/829	RR 0.11 (0.05 to 0.26)	6.39 per 100	0.71 per 100 (0.31, 1.65)	High

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect

Apixaban 5mg versus placebo for the extended therapy of VTE

Table 49 Apixaban 5mg versus placebo for the extended therapy of VTE

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	
VTE recurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	14/813	73/829	RR 0.20 (0.11 to 0.34)	8.81 per 100	1.73 per 100 (0.98, 3.04)	High
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	11/550	40/548	RR 0.27 (0.14, 0.53)	7.30 per 100	2.00 per 100 (1.04, 3.86)	High
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours Apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	3/263	33/281	RR 0.10 (0.03, 0.31)	11.74 per 100	1.14 per 100 (0.35, 3.67)	High
Subgroup analysis (Index event DVT): VTE recurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	10/527	52/551	RR 0.20 (0.10 to 0.39)	9.44 per 100	1.9 per 100 (0.97, 3.69)	High
Subgroup analysis (Index event PE): VTE recurrence up to 12 months (RR <1 favours apixaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	4/286	21/278	RR 0.19 (0.06 to 0.53)	7.55 per 100	1.4 per 100 (0.49, 4.02)	High
Major-bleeds up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	1/813	4/829	RR 0.25 (0.03 to 2.28)	0.48 per 100	0.12 per 100 (0.01, 1.10)	Low
Clinically relevant non major-bleeds up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[2]	34/813	19/829	RR 1.82 (1.05 to 3.17)	2.29 per 100	4.18 per 100 (2.41, 7.27)	Moderate
All-cause mortality up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	4/813	14/829	RR 0.29 (0.10 to 0.88)	1.69 per 100	0.49 per 100 (0.16, 1.49)	High
VTE-related mortality up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[3]	3/813	7/829	RR 0.44 (0.11 to 1.68)	0.84 per 100	0.37 per 100 (0.10, 1.42)	Moderate

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	imprecision	apixaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (apixaban)	Quality
Serious adverse events (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[2]	107/813	158/829	RR 0.69 (0.55 to 0.87)	19.06 per 100	13.16 per 100 (10.50, 16.49)	Moderate
PE-occurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	7/813	22/829	RR 0.32 (0.14 to 0.76)	2.65 per 100	0.86 per 100 (0.37, 2.00)	High
DVT-occurrence up to 12 months (RR <1 favours apixaban)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	8/813	53/829	RR 0.15 (0.07 to 0.32)	6.39 per 100	0.98 per 100 (0.47, 2.06)	High
1. 95% confidence interval crosses both ends of a defined MID interval. 2. 95% confidence interval crosses one end of a defined MID interval 3. 95% CI crosses line of no effect											

Apixaban 2.5mg versus apixaban 5mg for the extended therapy of VTE

Table 50 Apixaban 2.5mg versus apixaban 5mg for the extended therapy of VTE

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2.5mg	5mg	Relative (95% CI)	Absolute: control (5mg)	Absolute: intervention (2.5mg)	
VTE recurrence up to 12 months (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	14/840	14/813	RR 0.97 (0.46 to 2.02)	1.73 per 100	1.66 per 100 (0.8, 3.47)	Low
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours Apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	2/565	11/550	RR 0.18 (0.04, 0.79)	2.00 per 100	0.35 per 100 (0.08, 1.59)	High
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours Apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Not serious	12/275	3/263	RR 3.83 (1.09, 13.40)	1.14 per 100	4.36 per 100 (1.25, 15.29)	High
Subgroup analysis (Index event DVT): VTE recurrence up to 12 months (RR <1 favours apixaban 2.5mg)											
1	RCT	Not serious	N/A	Not serious	Very serious[1]	6/544	10/813	RR 0.58	1.9 per 100	1.1 per 100 (0.4, 3.01)	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2.5mg	5mg	Relative (95% CI)	Absolute: control (5mg)	Absolute: intervention (2.5mg)	
(Agnelli 2013) *AMPLIFY-EXT trial*								(0.21 to 1.59)			
Subgroup analysis (Index event PE): VTE recurrence up to 12 months (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	8/296	4/286	RR 1.93 (0.59 to 6.35)	1.4 per 100	2.72 per 100 (0.82, 8.88)	Low
Major-bleeds up to 12 months (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	2/840	1/813	RR 1.94 (0.18 to 21.31)	0.12 per 100	0.24 per 100 (0.02, 2.62)	Low
Clinically relevant non major-bleeds up to 12 months (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[2]	25/840	34/813	RR 0.71 (0.43 to 1.18)	4.18 per 100	2.98 per 100 (1.79, 4.94)	Moderate
All-cause mortality up to 12 months (RR <1 favours apixaban 2.5mg)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2.5mg	5mg	Relative (95% CI)	Absolute: control (5mg)	Absolute: intervention (2.5mg)	
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[3]	7/840	4/813	RR 1.69 (0.50 to 5.76)	0.49 per 100	0.83 per 100 (0.24, 2.84)	Moderate
VTE-related mortality up to 12 months (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Serious[3]	2/840	3/813	RR 0.65 (0.11 to 3.85)	0.37 per 100	0.24 per 100 (0.04, 1.42)	Moderate
Serious adverse events (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	112/840	107/813	RR 1.01 (0.79 to 1.30)	13.16 per 100	13.33 per 100 (10.42, 17.07)	Low
PE-occurrence up to 12 months (RR <1 favours apixaban 2.5mg)											
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	10/840	7/813	RR 1.38 (0.53 to 3.61)	0.86 per 100	1.19 per 100 (0.46, 3.11)	Low
DVT-occurrence up to 12 months (RR <1 favours apixaban 2.5mg)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	2.5mg	5mg	Relative (95% CI)	Absolute: control (5mg)	Absolute: intervention (2.5mg)	
1 (Agnelli 2013) *AMPLIFY-EXT trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	6/840	8/813	RR 0.73 (0.25 to 2.08)	0.98 per 100	0.71 per 100 (0.25, 2.05)	Low
1. 95% confidence interval crosses both ends of a defined MID interval. 2. 95% confidence interval crosses one end of a defined MID interval 3. 95% CI crosses line of no effect											

Rivaroxaban 20mg versus placebo for the extended therapy of VTE (DVT and/or PE)

Table 51 Rivaroxaban 20mg versus placebo for the extended therapy of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (rivaroxaban)	
VTE recurrence up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEI	RCT	Not serious	N/A	Not serious	Not serious	8/602	42/594	RR 0.19 (0.09 to 0.40)	7.07 per 100	1.33 per 100	High

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (rivaroxaban)	Quality
N-EXT 2015)										(0.63, 2.81)	
Subgroup analysis (<65 years old): Recurrent VTE up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEI N-EXT 2015)	RCT	Not serious	N/A	Not serious	Not serious	4/360	23/374	RR 0.18 (0.06, 0.52)	6.15 per 100	1.11 per 100 (0.37, 3.5)	High
Subgroup analysis (>65 years old): Recurrent VTE up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEI N-EXT 2015)	RCT	Not serious	N/A	Not serious	Not serious	4/242	19/220	RR 0.19 (0.07, 0.55)	8.64 per 100	1.64 per 100 (0.60, 4.75)	High
VTE-recurrence (HR <1 favours Rivaroxaban)											
1 (EINSTEI N-EXT 2015)	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.18 (0.09 to 0.37)	N/A	N/A	High
Recurrent DVT up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEI N-EXT 2015)	RCT	Not serious	N/A	Not serious	Not serious	5/602	31/594	RR 0.16 (0.06 to 0.41)	5.22 per 100	0.83 per 100 (0.33, 2.12)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (rivaroxaban)	
Recurrent PE up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-EXT 2015)	RCT	Not serious	N/A	Not serious	Not serious	3/602	14/594	RR 0.21 (0.06 to 0.73)	2.36 per 100	0.50 per 100 (0.14, 1.73)	High
Major bleeding up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-EXT 2015)	RCT	Not serious	N/A	Not serious	Very serious[1]	4/598	0/590	RR 8.88 (0.48 to 164.57)	Not calculable[3]	Not calculable[3]	Low
Clinically relevant non major bleeding up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-EXT 2015)	RCT	Not serious	N/A	Not serious	Not serious	32/598	7/590	RR 4.51 (2.01 to 10.14)	1.19 per 100	5.35 per 100 (2.38, 12.03)	High
All-cause mortality up to 12 months (RR <1 favours Rivaroxaban)											
1 (EINSTEIN-EXT 2015)	RCT	Not serious	N/A	Not serious	Serious[2]	1/602	2/594	RR 0.49 (0.04 to 5.43)	0.34 per 100	0.17 per 100 (0.02, 1.83)	Moderate
VTE-related mortality up to 12 months (RR <1 favours Rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Rivaroxaban	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (rivaroxaban)	
1 (EINSTEI N-EXT 2015)	RCT	Not serious	N/A	Not serious	Serious[2]	1/602	1/594	RR 0.99 (0.06 to 15.74)	0.17 per 100	0.17 per 100 (0.01, 2.65)	Moderat e
1. 95% confidence interval crosses both ends of a defined MID interval. 2. 95% CI crosses line of no effect. 3. Absolute effect could not be calculated due to 0 events being recorded in at least one group..											

Dabigatran versus warfarin for the extended therapy of VTE (DVT and/or PE)

Table 52 Dabigatran versus warfarin for the extended therapy of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (dabigatran)	
VTE recurrence up to 36 months (RR <1 favours dabigatran)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (dabigatran)	
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[1]	26/1430	18/1426	RR 1.45 (0.80 to 2.62)	1.26 per 100	1.83 per 100 (1.01, 4.8)	Moderate
VTE recurrence (HR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.44 (0.78 to 2.65)	N/A	N/A	Moderate
Subgroup analysis (<65 years old): VTE recurrence up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	21/987	16/1025	RR 1.36 (0.72, 2.60)	1.56 per 100	2.13 per 100 (1.12, 4.05)	Low
Subgroup analysis (≥65 years old): VTE recurrence up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	5/443	2/407	RR 2.30 (0.45, 11.77)	0.49 per 100	1.13 per 100 (0.22, 5.79)	Low
Subgroup analysis (index event DVT): Recurrent VTE up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Very serious[1]	12/939	11/923	RR 1.07 (0.48 to 2.42)	1.19 per 100	1.28 per 100 (0.57, 2.88)	Low
Subgroup analysis (index event PE): Recurrent VTE up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[1]	14/491	7/503	RR 2.05 (0.83 to 5.03)	1.39 per 100	2.85 per 100 (1.16, 7.00)	Moderate

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (dabigatran)	
DVT-occurrence up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Very serious[2]	17/1430	13/1426	RR 1.30 (0.64 to 2.67)	0.91 per 100	1.19 per 100 (0.58, 2.44)	Low
DVT-occurrence (HR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.32 (0.64 to 2.72)	N/A	N/A	Moderate
PE-occurrence up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Very serious[2]	10/1430	5/1426	RR 1.99 (0.68 to 5.82)	0.35 per 100	0.70 per 100 (0.24, 2.04)	Low
Non-fatal PE (HR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 2.04 (0.70 to 5.96)	N/A	N/A	Moderate
Major bleeding up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[1]	13/1430	25/1426	RR 0.52 (0.27 to 1.01)	1.75 per 100	0.91 per 100 (0.47, 1.77)	Moderate
Major bleeding (HR <1 favours dabigatran)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (dabigatran)	Quality
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 0.52 (0.27 to 1.01)	N/A	N/A	Moderate
Clinically relevant non major bleeding up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Serious[4]	N/A	Not serious	Not serious	67/1430	120/1426	RR 0.56 (0.42 to 0.74)	8.42 per 100	4.69 per 100 (3.51, 6.26)	Moderate
All-cause mortality up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	17/1430	19/1426	RR 0.89 (0.47 to 1.71)	1.33 per 100	1.19 per 100 (0.62, 2.28)	Moderate
All-cause mortality (HR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 0.90 (0.47 to 1.72)	N/A	N/A	Moderate
VTE-related mortality (HR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.01 (0.06 to 16.60)	N/A	N/A	Moderate
VTE-related mortality up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Serious[3]	1/1430	1/1426	RR 1.00 (0.06 to 15.93)	0.07 per 100	0.07 per 100	Moderate

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	dabigatran	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (dabigatran)	
										(0.00, 1.12)	
Serious adverse events at end of treatment up to 36 months (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Not serious	227/1430	224/1426	RR 1.01 (0.85 to 1.20)	15.71 per 100	15.87 per 100 (13.4, 18.80)	High
Serious adverse events in the 30 days following end of treatment (RR <1 favours dabigatran)											
1 (Re-MEDY 2013)	RCT	Not serious	N/A	Not serious	Very serious[2]	33/1430	41/1426	RR 0.80 (0.51 to 1.26)	2.88 per 100	2.31 per 100 (1.47, 3.63)	Low

1. 95% confidence interval crosses one end of a defined MID interval.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. 95% CI crosses line of no effect.
4. Study did not report CRNMB as a separate outcome; this was determined by subtracting major bleeding from major bleeds/clinically relevant non-major bleeds composite outcome.

Dabigatran versus placebo for the extended therapy of VTE (DVT and/or PE)

Table 53 Dabigatran versus placebo for the extended therapy of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (dabigatran)	
VTE recurrence up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	3/681	37/662	RR 0.09 (0.03 to 0.27)	5.59 per 100	0.51 per 100 (0.17, 1.51)	High
Subgroup analysis (<65 years old): VTE recurrence up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	2/444	18/447	RR 0.11 (0.03, 0.48)	4.03 per 100	0.45 per 100 (0.11, 1.93)	High
Subgroup analysis (≥65 years old): VTE recurrence up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	1/237	19/215	RR 0.05 (0.01, 0.35)	8.84 per 100	0.44 per 100 (0.09, 3.09)	High
Subgroup analysis (index event DVT): Recurrent VTE up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	3/451	23/449	RR 0.13 (0.04 to 0.43)	5.12 per 100	0.67 per 100 (0.2, 2.20)	High
Subgroup analysis (index event PE): Recurrent VTE up to 6 months (RR <1 favours dabigatran)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (dabigatran)	
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	0/230	14/213	RR 0.03 (0.00 to 0.53)	Not calculable[4]	Not calculable[4]	High
VTE-recurrence (HR <1 favours dabigatran)											
1 (RE-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.08 (0.02 to 0.28)	N/A	N/A	High
DVT-occurrence up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	2/681	22/662	RR 0.09 (0.02 to 0.37)	3.32 per 100	0.29 per 100 (0.07, 1.24)	High
PE-occurrence up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Not serious	1/681	14/662	RR 0.07 (0.01 to 0.53)	2.11 per 100	0.15 per 100 (0.02, 1.11)	High
Major bleeding up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Very serious[2]	2/681	0/662	RR 4.86 (0.23 to 101.05)	Not calculable[4]	Not calculable[4]	Low
Clinically relevant non major bleeding up to 6 months (RR <1 favours dabigatran)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Dabigatran	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (dabigatran)	Quality
1 (Re-SONATE 2013)	RCT	Serious[3]	N/A	Not serious	Not serious	34/681	12/662	RR 2.75 (1.44 to 5.27)	1.81 per 100	4.99 per 100 (2.61, 9.56)	Moderate
Serious adverse events at end of treatment up to 6 months (RR <1 favours dabigatran)											
1 (Re-SONATE 2013)	RCT	Not serious	N/A	Not serious	Serious[1]	47/681	60/662	RR 0.76 (0.53 to 1.10)	9.06 per 100	6.9 per 100 (4.78, 9.96)	Moderate

1. 95% confidence interval crosses one end of a defined MID interval.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. Study did not CRNMB report as a separate outcome; this was determined by subtracting major bleeding from major bleeds/clinically relevant non-major bleeds composite outcome.
4. Absolute effect could not be calculated due to 0 events being recorded in at least one group..

Warfarin (INR 2.0-3.0) versus discontinued treatment for the extended therapy of VTE (DVT and/or PE)

Table 54 Warfarin (INR 2.0-3.0) versus discontinued treatment for the extended therapy of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	Discontinued treatment	Relative (95% CI)	Absolute: control (discontinued)	Absolute: intervention (warfarin)	
VTE-recurrence up to 18 months (RR <1 favours warfarin)											
1 (WODIT-DVT 2001)	RCT	Very serious[3]	N/A	Not serious	Serious[1]	4/134	11/133	RR 0.36 (0.12 to 1.11)	8.27 per 100	2.99 per 100 (0.97, 9.14)	Very low
Major bleeds up to 9 months (RR <1 favours warfarin)											
1 (WODIT-DVT 2001)	RCT	Very serious[3]	N/A	Not serious	Very serious[2]	4/134	1/133	RR 3.97 (0.45 to 35.06)	0.75 per 100	2.99 per 100 (0.34, 26.36)	Very low
Major bleeds up to 9 months (RR <1 favours warfarin)											
1 (WODIT-PE 2001)	RCT	Very serious[3]	N/A	Not serious	Very serious[2]	3/165	1/161	RR 2.93 (0.31 to 27.85)	0.62 per 100	1.82 per 100 (0.19, 17.30)	Very low
Fatal bleeds up to 9 months (RR <1 favours warfarin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	Discontinued treatment	Relative (95% CI)	Absolute: control (discontinued)	Absolute: intervention (warfarin)	
1 (WODIT-DVT 2001)	RCT	Very serious[3]	N/A	Not serious	Very serious[2]	0/134	1/133	RR 0.33 (0.01 to 8.05)	Not calculable[4]	Not calculable[4]	Very low

1. 95% confidence interval crosses one end of a defined MID interval.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. Study was at high risk of bias.
4. Absolute effect could not be calculated due to 0 events being recorded in at least one group..

Low-intensity warfarin (INR 1.5-2.0) versus placebo for the extended therapy of VTE (DVT and/or PE)

Table 55 Low-intensity warfarin (INR 1.5-2.0) versus placebo for the extended therapy of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
VTE-recurrence up to 4.3 years (RR <1 favours warfarin)											
1 (Cushman 2006)	RCT	Serious[3]	N/A	Serious[1]	Not serious	14/255	38/253	RR 0.37 (0.20 to 0.66)	15.02 per 100	5.49 per 100	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
										(3.05, 9.88)	
VTE-recurrence (HR <1 favours warfarin)											
1 (Cushman 2006)	RCT	Serious[3]	N/A	Serious[1]	Not serious	N/A	N/A	HR 0.36 (0.19 to 0.68)	N/A	N/A	Low
Major bleeding up to 4.3 years (RR <1 favours warfarin)											
1 (Cushman 2006)	RCT	Serious[3]	N/A	Serious[1]	Very serious[2]	5/255	2/253	RR 2.48 (0.49 to 12.67)	0.79 per 100	1.96 per 100 (0.38, 10.01)	Very low
Major bleeding (HR <1 favours warfarin)											
1 (Cushman 2006)	RCT	Serious[3]	N/A	Serious[1]	Serious[4]	N/A	N/A	HR 2.53 (0.49 to 13.05)	N/A	N/A	Very low
All-cause mortality up to 4.3 years (RR <1 favours warfarin)											
1 (Cushman 2006)	RCT	Serious[3]	N/A	Serious[1]	Serious[4]	4/255	8/253	RR 0.50 (0.15 to 1.63)	3.16 per 100	1.57 per 100 (0.48, 5.14)	Very low
All-cause mortality (HR <1 favours warfarin)											

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	Quality
1 (Cushman 2006)	RCT	Serious[3]	N/A	Serious[1]	Serious[4]	N/A	N/A	HR 0.50 (0.15 to 1.67)	N/A	N/A	Very low

1. Study was only partially applicable.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. Study was at moderate risk of bias.
4. 95% CI crosses line of no effect.

Warfarin (INR 2.0-3.0) versus low-intensity warfarin (INR 1.5-1.9) for the extended therapy of VTE (DVT and/or PE)

Table 56 Warfarin (INR 2.0-3.0) versus low-intensity warfarin (INR 1.5-1.9) for the extended therapy of VTE (DVT and/or PE)

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Standard intensity	Low intensity	Relative (95% CI)	Absolute: control (warfarin low intensity)	Absolute: intervention (warfarin standard)	Quality
VTE-recurrence up to 51.6 years (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Serious[1]	6/369	16/369	RR 0.37 (0.15 to 0.93)	5.95 per 100	2.20 per 100 (0.89 to 5.53)	Moderate
Subgroup analysis (age <65 years old): VTE-recurrence up to 51.6 months (RR <1 favours standard intensity warfarin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Standard intensity	Low intensity	Relative (95% CI)	Absolute: control (warfarin low intensity)	Absolute: intervention (warfarin standard)	
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	3/242	8/236	RR 0.37 (0.10, 1.37)	3.39 per 100 (0.91, 12.62)	1.24 per 100	Low
Subgroup analysis (age ≥65 years old): VTE-recurrence up to 51.6 months (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	3/127	8/133	RR 0.39 (0.11, 1.45)	6.02 per 100 (1.63, 22.17)	2.36 per 100	Low
Subgroup analysis (Index event DVT): VTE-recurrence up to 51.6 months (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	4/227	9/252	RR 0.49 (0.15 to 1.58)	3.57 per 100	1.75 per 100 (0.54, 5.64)	Low
Subgroup analysis (Index event PE): VTE-recurrence up to 51.6 months (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	2/142	7/117	RR 0.24 (0.05 to 1.11)	5.98 per 100	1.44 per 100 (0.30, 6.64)	Low
VTE-recurrence (HR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.36 (0.14 to 0.90)	N/A	N/A	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Standard intensity	Low intensity	Relative (95% CI)	Absolute: control (warfarin low intensity)	Absolute: intervention (warfarin standard)	
Major bleeding up to 51.6 years (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	8/369	9/369	RR 0.89 (0.35 to 2.28)	2.28 per 100	2.44 per 100 (0.85, 5.56)	Low
Subgroup analysis (age <65 years old): major bleeding up to 51.6 months (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	3/236	4/242	RR 0.77 (0.17, 3.46)	1.65 per 100	1.27 per 100 (0.28, 5.72)	Low
Subgroup analysis (age ≥65 years old): major bleeding up to 51.6 months (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	6/133	4/127	RR 1.45 (0.40, 5.27)	3.15 per 100	4.58 per 100 (1.26, 16.61)	Low
Major bleeding (HR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 0.83 (0.30 to 2.28)	N/A	N/A	Moderate
All-cause mortality up to 51.6 months (RR <1 favours standard intensity warfarin)											
1 (Kearon 2003)	RCT	Not serious	N/A	Not serious	Serious[3]	8/369	16/369	RR 0.50 (0.22 to 1.15)	4.34 per 100	2.17 per 100	Moderate

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Standard intensity	Low intensity	Relative (95% CI)	Absolute: control (warfarin low intensity)	Absolute: intervention (warfarin standard)	
ELATE trial										(0.95, 4.99)	
All-cause mortality (HR <1 favours standard intensity warfarin)											
1 (Kearon 2003) *ELATE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 0.48 (0.21 to 1.10)	N/A	N/A	Moderate

1. 95% confidence interval crosses one end of a defined MID interval.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. 95% CI crosses line of no effect

Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of DVT-only

Table 57 Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of DVT-only

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
VTE-recurrence up to 18 months (RR <1 favours warfarin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Not serious	0/50	16/54	RR 0.03 (0.00 to 0.53)	Not calculable[5]	Not calculable[5]	High
subgroup analysis (BMI <30 kg/m^2): VTE-recurrence up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Not serious	0/39	15/48	RR 0.04 (0.00 to 0.64)	Not calculable[5]	Not calculable[5]	High
subgroup analysis (BMI ≥30kg/m^2): VTE-recurrence up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	0/11	1/6	RR 0.19 (0.01 to 4.15)	Not calculable[5]	Not calculable[5]	Low
VTE-recurrence up to 24 months (RR <1 favours warfarin)											
1 (Kearon 1999)	RCT	Not serious	N/A	Not serious	Not serious	1/79	17/83	RR 0.06 (0.01 to 0.45)	20.48 per 100	1.27 per 100 (0.17, 9.29)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
VTE-recurrence (HR <1 favours warfarin) (Figure 84)											
2 studies	RCTs	Not serious	Not serious	Not serious	Not serious	N/A	N/A	HR 0.04 (0.01 to 0.15)	N/A	N/A	High
DVT-occurrence up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Not serious	0/50	13/54	RR 0.04 (0.00 to 0.65)	Not estimable	Not estimable	High
DVT-occurrence up to 24 months (RR <1 favours warfarin)											
1 (Kearon 1999)	RCT	Not serious	N/A	Not serious	Not serious	0/79	11/83	RR 0.05 (0.00 to 0.76)	Not calculable[5]	Not calculable[5]	High
PE-occurrence up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	0/50	3/54	RR 0.15 (0.01 to 2.91)	Not estimable	Not estimable	Low
PE-occurrence up to 24 months (RR <1 favours warfarin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
1 (Kearon 1999)	RCT	Not serious	N/A	Not serious	Very serious[2]	1/79	6/83	RR 0.18 (0.02 to 1.42)	7.23 per 100	1.27 per 100 (0.16, 10.28)	Low
Major bleeds up to 24 months (RR <1 favours warfarin)											
1 (Kearon 1999)	RCT	Not serious	N/A	Not serious	Very serious[2]	3/79	0/83	RR 7.35 (0.39 to 140.05)	Not calculable[5]	Not calculable[5]	Low
All-cause mortality up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	0/50	2/54	RR 0.22 (0.01 to 4.39)	3.61 per 100	1.27 per 100 (0.13, 11.92)	Low
All-cause mortality up to 24 months (RR <1 favours warfarin)											
1 (Kearon 1999)	RCT	Not serious	N/A	Not serious	Serious[4]	1/79	3/83	RR 0.35 (0.04 to 3.30)	3.61 per 100	1.27 per 100 (0.13, 11.92)	High
All-cause mortality (HR <1 favours warfarin)											
1 (Kearon 1999)	RCT	Not serious	N/A	Not serious	Serious[4]	N/A	N/A	HR 0.25 (0.03 to 2.28)	N/A	N/A	Moderate

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	Quality
VTE-related mortality up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2019) *PADIS-DVT trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	0/50	1/54	RR 0.35 (0.01 to 8.87)	Not estimable	Not estimable	Low

1. 95% confidence interval crosses one end of a defined MID interval.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. Study was at high risk of bias
4. 95% CI crosses line of no effect.
5. Absolute effect could not be calculated due to 0 events being recorded in at least one group.

1 ***Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of PE***

2 **Table 58 Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of PE**

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	Quality
VTE-recurrence up to 9 months (RR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Not serious	3/184	25/187	RR 0.12 (0.04 to 0.40)	13.37 per 100	1.63 per 100 (0.5, 5.31)	High
(subgroup analysis: BMI <30 kg/m^2): VTE-recurrence up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Not serious	4/131	19/146	RR 0.23 (0.08, 0.67)	13.01 per 100	3.05 per 100 (1.07, 8.74)	High
(subgroup analysis: BMI ≥30kg/m^2): VTE-recurrence up to 18 months (RR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	2/52	6/39	RR 0.25 (0.05, 1.17)	15.38 per 100	3.85 per 100 (0.82, 18.04)	Moderate

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
VTE-recurrence (HR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.15 (0.05 to 0.44)	N/A	N/A	High
DVT-occurrence up to 9 months (RR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Not serious	2/184	21/187	RR 0.10 (0.02 to 0.41)	11.23 per 100	1.09 per 100 (0.26, 4.57)	High
PE-occurrence up to 9 months (RR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Very serious[2]	1/184	4/187	RR 0.25 (0.03 to 2.25)	2.14 per 100	0.54 per 100 (0.06, 4.82)	High
Major bleeds up to 9 months (RR <1 favours warfarin)											
1 (Couturaud 2015)	RCT	Not serious	N/A	Not serious	Very serious[2]	3/184	0/187	RR 7.11 (0.37 to 136.76)	Not calculable[5]	Not calculable[5]	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Warfarin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (warfarin)	
PADIS-PE trial											
Major bleed (HR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Serious[4]	N/A	N/A	HR 3.96 (0.44 to 35.76)	N/A	N/A	Moderate
All-cause mortality up to 9 months (RR <1 favours warfarin)											
1 (Couturaud 2015) *PADIS-PE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	2/184	2/187	RR 1.02 (0.14 to 7.14)	1.07 per 100	1.09 per 100 (0.15, 7.64)	Moderate

1. 95% confidence interval crosses one end of a defined MID interval.
2. 95% confidence interval crosses both ends of a defined MID interval.
3. Study was at high risk of bias
4. 95% CI crosses line of no effect.
5. Absolute effect could not be calculated due to 0 events being recorded in at least one group..

1 ***Rivaroxaban 10mg versus aspirin for the extended therapy of VTE***

2 **Table 59 Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of PE**

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	13/1125	50/1124	RR 0.26 (0.14 to 0.48)	4.45 per 100	1.16 per 100 (0.62 to 2.14)	High
Subgroup analysis (fragile patients only): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	4/164	7/178	RR 0.62 (0.18, 2.08)	3.93 per 100	2.44 per 100 (0.73, 8.18)	Low
Subgroup analysis (non-fragile patients only): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017)	RCT	Not serious	N/A	Not serious	Not serious	9/963	43/953	RR 0.21 (0.10, 0.42)	4.51 per 100	0.93 per 100 (0.46, 1.91)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
EINSTEIN-CHOICE trial											
Subgroup analysis (BMI <30kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	7/751	36/756	RR 0.20 (0.09, 0.44)	4.76 per 100	0.93 per 100 (0.42, 2.08)	High
Subgroup analysis (BMI ≥30kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[4]	6/376	14/375	RR 0.43 (0.17, 1.10)	3.73 per 100	1.60 per 100 (0.62, 4.11)	Moderate
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017)	RCT	Not serious	N/A	Not serious	Not serious	6/678	30/684	RR 0.20 (0.08, 0.48)	4.39 per 100	0.88 per 100 (0.37, 2.11)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
EINSTEIN-CHOICE trial											
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[4]	7/449	20/447	RR 0.35 (0.15, 0.82)	4.47 per 100	1.56 per 100 (0.67, 3.65)	Moderate
Subgroup analysis (Index event DVT): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	5/565	27/577	RR 0.19 (0.07 to 0.49)	4.68 per 100	0.89 per 100 (0.33 to 2.29)	High
Subgroup analysis (Index event PE): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017)	RCT	Not serious	N/A	Not serious	Not serious	8/536	23/547	RR 0.34 (0.15 to 0.75)	4.20 per 100	1.43 per 100 (0.63 to 3.15)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
EINSTEIN-CHOICE trial											
VTE-recurrence (HR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.26 (0.14 to 0.48)	N/A	N/A	High
DVT-occurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	8/1127	29/1131	RR 0.28 (0.13 to 0.60)	2.56 per 100	0.72 per 100 (0.33 to 1.54)	High
PE-occurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017)	RCT	Not serious	N/A	Not serious	Not serious	6/1107	21/1131	RR 0.29 (0.12 to 0.71)	1.86 per 100	0.54 per 100 (0.22 to 1.32)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
EINSTEIN-CHOICE trial											
Major bleeding up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	5/1127	3/1131	RR 1.67 (0.40 to 6.98)	0.27 per 100	0.44 per 100 (0.11 to 1.85)	Low
Major bleeding (HR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.64 (0.39 to 6.87)	N/A	N/A	Moderate
Clinically relevant non-major bleeding up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017)	RCT	Not serious	N/A	Not serious	Very serious[1]	22/1127	20/1131	RR 1.10 (0.61 to 2.01)	1.77 per 100	1.95 per 100 (1.08 to 3.55)	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
EINSTEIN-CHOICE trial											
All-cause mortality up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	2/1127	7/1131	RR 0.29 (0.06 to 1.38)	0.62 per 100	0.18 per 100 (0.04 to 0.85)	Low
VTE-related mortality up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	0/1127	2/1131	RR 0.20 (0.01 to 4.18)	Not calculable [4]	Not calculable[4]	Low

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect
4. Absolute effect could not be calculated due to 0 events being recorded in at least one group..

1 ***Rivaroxaban 20mg versus aspirin for the extended therapy of VTE***

2 **Table 60 Rivaroxaban 20mg versus aspirin for the extended therapy of VTE**

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	17/1101	50/1124	RR 0.35 (0.20 to 0.60)	4.45 per 100	1.56 per 100 (0.89 to 2.67)	High
Subgroup analysis (fragile patients only): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	1/149	7/178	RR 0.17 (0.02 to 1.37)	3.93 per 100	0.67 per 100 (0.08, 5.39)	Low
Subgroup analysis (non-fragile patients only): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	16/958	43/953	RR 0.37 (0.21 to 0.65)	4.51 per 100	1.67 per 100 (0.95, 2.93)	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
Subgroup analysis (BMI <30kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	12/712	36/756	RR 0.35 (0.19 to 0.67)	4.76 per 100	1.67 per 100 (0.90, 3.19)	High
Subgroup analysis (BMI ≥30kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	5/394	14/375	RR 0.34 (0.12 to 0.93)	3.73 per 100	1.27 (0.45, 3.47)	High
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	10/691	30/684	RR 0.33 (0.16 to 0.67)	4.39 per 100	1.45 per 100 (0.70, 2.94)	High
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	7/416	20/447	RR 0.38 (0.16 to 0.88)	4.47 per 100	1.70 per 100 (0.72, 3.94)	High
Subgroup analysis (Index event DVT): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	5/565	27/577	RR 0.19 (0.07 to 0.49)	4.68 per 100	0.89 per 100 (0.33 to 2.29)	High
Subgroup analysis (Index event PE): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	12/536	23/547	RR 0.53 (0.27 to 1.06)	4.20 per 100	2.23 per 100 (1.14 to 4.46)	Moderate
VTE-recurrence (HR <1 favours rivaroxaban)											
1 (Weitz 2017)	RCT	Not serious	N/A	Not serious	Not serious	N/A	N/A	HR 0.34 (0.20 to 0.58)	N/A	N/A	High

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
EINSTEIN-CHOICE trial											
DVT-occurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Not serious	9/1107	29/1131	RR 0.32 (0.15 to 0.67)	2.56 per 100	0.82 per 100 (0.38 to 1.72)	High
PE-occurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	8/1107	21/1131	RR 0.39 (0.17 to 0.87)	1.86 per 100	0.72 per 100 (0.32 to 1.62)	Moderate
Major bleeding up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	6/1107	3/1131	RR 2.04 (0.51 to 8.15)	0.27 per 100	0.54 per 100 (0.14 to 2.16)	Low

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
Major bleeding (HR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 2.01 (0.50 to 8.06)	N/A	N/A	Moderate
Clinically relevant non-major bleeding up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	30/1107	20/1131	RR 1.53 (0.88 to 2.68)	1.77 per 100	2.71 per 100 (1.56 to 4.74)	Moderate
All-cause mortality up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	8/1107	7/1131	RR 1.17 (0.42 to 3.21)	0.62 per 100	0.72 per 100 (0.26 to 1.99)	Low
VTE-related mortality up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	aspirin	Relative (95% CI)	Absolute: control (aspirin)	Absolute: intervention (rivaroxaban)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	2/1107	2/1131	RR 1.02 (0.14 to 7.24)	0.18 per 100	0.18 per 100 (0.02 to 1.28)	Low
1. 95% confidence interval crosses both ends of a defined MID interval. 2. 95% confidence interval crosses one end of a defined MID interval 3. 95% CI crosses line of no effect											

1 ***Rivaroxaban 20mg versus 10mg for the extended therapy of VTE***

2 **Table 61 Rivaroxaban 20mg versus 10mg for the extended therapy of VTE**

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	17/1101	13/1125	RR 1.35 (0.66 to 2.75)	1.16 per 100	1.56 per 100 (0.76 to 3.18)	Low
Subgroup analysis (fragile patients only): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	1/149	4/164	RR 0.28 (0.03, 2.44)	2.44 per 100	0.67 per 100	Low
Subgroup analysis (non-fragile patients only): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	16/958	9/963	RR 1.79 (0.79, 4.00)	0.93 per 100	1.67 per 100	Low
Subgroup analysis (BMI <30kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	12/712	7/751	RR 1.82 (0.71, 4.55)	0.93 per 100	1.69 per 100	Low
Subgroup analysis (BMI ≥30kg/m^2): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	5/394	6/376	RR 0.79 (0.24, 2.56)	1.60 per 100	1.27 per 100	Low
Subgroup analysis (<65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	10/691	6/678	RR 1.64 (0.60, 4.55)	0.88 per 100	1.45 per 100	Low
Subgroup analysis (≥65 years old): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	7/416	7/449	RR 1.08 (0.38, 3.03)	1.56 per 100	1.68 per 100	Low
Subgroup analysis (Index event DVT): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	5/565	5/565	RR 1.00 (0.29 to 3.44)	0.88 per 100	0.88 per 100 (0.26 to 3.04)	Low
Subgroup analysis (Index event PE): VTE recurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	12/536	8/560	RR 1.57 (0.65 to 3.80)	1.43 per 100	2.24 per 100 (0.93 to 5.43)	Low
VTE-recurrence (HR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.34 (0.65 to 2.76)	N/A	N/A	Moderate
DVT-occurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	9/1107	7/1127	RR 1.31 (0.49 to 3.50)	0.62 per 100	0.81 per 100 (0.30 to 2.17)	Low
PE-occurrence up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	8/1107	6/1127	RR 1.36 (0.47 to 3.90)	0.53 per 100	0.72 per 100 (0.25 to 2.08)	Low
Major bleeding up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	6/1107	5/1127	RR 1.22 (0.37 to 3.99)	0.44 per 100	0.54 per 100 (0.16 to 1.77)	Low
Major-bleed (HR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[3]	N/A	N/A	HR 1.23 (0.37 to 4.06)	N/A	N/A	Moderate
Clinically relevant non-major bleeding up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	30/1107	22/1127	RR 1.39 (0.81 to 2.39)	1.95 per 100	2.71 per 100 (1.58 to 4.67)	Moderate
All-cause mortality up to 12 months (RR <1 favours rivaroxaban)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	20mg	10mg	Relative (95% CI)	Absolute: control (10mg)	Absolute: intervention (20mg)	
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	8/1107	2/1127	RR 4.07 (0.87 to 19.13)	0.18 per 100	0.72 per 100 (0.15 to 3.39)	Moderate
VTE-related mortality up to 12 months (RR <1 favours rivaroxaban)											
1 (Weitz 2017) *EINSTEIN-CHOICE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	2/1107	0/1127	RR 5.09 (0.24 to 105.91)	Not calculable [4]	Not calculable[4]	Low

1. 95% confidence interval crosses both ends of a defined MID interval.
2. 95% confidence interval crosses one end of a defined MID interval
3. 95% CI crosses line of no effect
4. Not calculable as zero events in control arm.

1 ***Aspirin versus placebo for the extended therapy of VTE (DVT and/or PE)***

2 **Table 62 Aspirin versus placebo for the extended therapy of VTE (DVT and/or PE)**

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	aspirin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (aspirin)	
VTE-recurrence up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	28/205	43/197	RR 0.62 (0.40 to 0.96)	21.83 per 100	13.75 per 100 (8.95 to 21.17)	Low
Subgroup analysis (Index event DVT): VTE-recurrence up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	17/122	27/130	RR 0.67 (0.39 to 1.17)	20.77 per 100	13.92 per 100 (8.10 to 24.30)	Low
Subgroup analysis (Index event PE): VTE-recurrence up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	11/83	16/67	RR 0.55 (0.26 to 1.11)	23.88 per 100	13.13 per 100 (6.21 to 26.51)	Low
VTE-recurrence up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	57/411	73/411	RR 0.78 (0.57 to 1.07)	17.94 per 100	13.99 per 100 (10.22 to 19.19)	Moderate
Subgroup analysis (Index event DVT): VTE-recurrence up to 48 months (RR <1 favours aspirin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	aspirin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (aspirin)	
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	39/236	43/232	RR 0.89 (0.60 to 1.32)	18.53 per 100	16.50 per 100 (11.12 to 24.47)	Low
Subgroup analysis (Index event PE): VTE-recurrence up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	18/171	30/175	RR 0.61 (0.36 to 1.06)	17.14 per 100	10.46 per 100 (6.17 to 18.17)	Moderate
Subgroup analysis (BMI<30 kg/m^2): VTE-recurrence up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	32/249	43/271	RR 0.81 (0.53, 1.24)	15.87 per 100	12.85 per 100 (8.41, 19.64)	Moderate
Subgroup analysis (BMI≥30 kg/m^2): VTE-recurrence up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	25/160	30/140	RR 0.73 (0.45, 1.18)	21.43 per 100	15.63 per 100 (9.67, 25.25)	Moderate
Subgroup analysis (<65 years old): VTE-recurrence up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	31/145	45/125	RR 0.59 (0.40, 0.88)	36.00 per 100	21.24 per 100 (14.40, 31.68)	Moderate
Subgroup analysis (≥65 years old): VTE-recurrence up to 48 months (RR <1 favours aspirin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	aspirin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (aspirin)	
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	26/266	28/286	1.00 (0.60, 1.66)	9.79 per 100	9.79 (5.87, 16.25)	Low
VTE-recurrence (RR <1 favours aspirin) (Figure 85)											
2 studies	RCT	Serious[5]	Not serious	Not serious	Not serious	N/A	N/A	RR 0.68 (0.51 to 0.90)	N/A	N/A	Moderate
DVT-occurrence up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	16/205	28/197	RR 0.55 (0.31 to 0.98)	14.21 per 100	7.82 per 100 (4.41 to 13.93)	Low
PE-occurrence up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	12/205	15/197	RR 0.77 (0.37 to 1.60)	7.61 per 100	5.86 per 100 (2.82 to 12.18)	Low
Major bleeding up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Very serious[1]	1/205	1/197	RR 0.96 (0.06 to 15.26)	0.51 per 100	0.49 per 100 (0.03 to 7.75)	Very low
Major bleeding up to 48 months (RR <1 favours aspirin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	aspirin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (aspirin)	
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	8/411	6/411	RR 1.33 (0.47 to 3.81)	1.46 per 100	1.94 per 100 (0.69 to 5.56)	Low
Clinically relevant non major bleeding up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Very serious[1]	3/205	3/197	RR 0.96 (0.20 to 4.70)	1.52 per 100	1.46 per 100 (0.30 to 7.16)	Very Low
Clinically relevant non major bleeding up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Very serious[1]	6/411	2/411	RR 3.00 (0.61 to 14.78)	0.49 per 100	1.46 per 100 (0.30 to 7.19)	Low
All-cause mortality up to 24 months (RR <1 favours aspirin)											
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[2]	3/205	3/197	RR 0.96 (0.20 to 4.70)	1.52 per 100	1.46 per 100 (0.30 to 7.16)	Low
All-cause mortality up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	16/411	18/411	RR 0.89 (0.46 to 1.72)	4.38 per 100	3.90 per 100 (2.01 to 7.53)	Low
All-cause mortality 24 months (RR <1 favours aspirin)											

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	aspirin	placebo	Relative (95% CI)	Absolute: control (placebo)	Absolute: intervention (aspirin)	
1 (Becattini 2012) *WARFASA trial*	RCT	Serious[1]	N/A	Not serious	Serious[4]	N/A	N/A	RR 1.04 (0.32 to 3.40)	N/A	N/A	Low
VTE-related mortality up to 48 months (RR <1 favours aspirin)											
1 (Brighton 2012) *ASPIRE trial*	RCT	Not serious	N/A	Not serious	Serious[2]	1/411	3/411	RR 0.33 (0.03 to 3.19)	0.73 per 100	0.24 per 100 (0.02 to 2.33)	Low

1. Study was at moderate risk of bias
2. 95% confidence interval crosses one end of a defined MID interval.
3. 95% confidence interval crosses both ends of a defined MID interval.
4. 95% CI crosses line of no effect
5. >33.3% of studies were at moderate/high risk of bias

1 ***Rivaroxaban versus warfarin (INR 2.0-3.0) for the extended therapy of VTE (DVT and/or PE) associated with antiphospholipid syndrome***

2 **Table 63 Rivaroxaban versus warfarin (INR 2.0-3.0) for the extended therapy of VTE (DVT and/or PE) associated with antiphospholipid**
3 **syndrome**

Quality assessment						No of patients		Effect			Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (rivaroxaban)	
VTE-recurrence up to day 210 (RR <1 favours rivaroxaban)											
1 (Cohen 2016)	RCT	Not serious	N/A	Serious[5]	Serious[2]	0/57	0/58	Not estimable[2]	Not estimable[2]	Not estimable[2]	Low
Quality of life: Health utility component of ED-5Q-5L score, at day 180 (RR <1 favours rivaroxaban)											
1 (Cohen 2016)	RCT	Serious[3]	N/A	Not serious	Serious[4]	Mean (SD) score 0.82 (0.15)	Mean (SD) score 0.78 (0.15)	Mean difference 0.04 (-0.02, 0.09)	N/A	N/A	Low
Quality of life: Health state (visual analogue score) component of ED-5Q-5L score, at day 180 (RR <1 favours rivaroxaban)											
1 (Cohen 2016)	RCT	Serious[3]	N/A	Not serious	Serious[4]	Mean (SD) score 80 (13.6)	Mean (SD) score 73 (13.3)	Mean difference 6.50 (1.40, 11.50)	N/A	N/A	Low
Major bleeding at day 210 (RR <1 favours rivaroxaban)											
1 (Cohen 2016)	RCT	Not serious	N/A	Not estimable	Serious[2]	0/57	0/58	Not estimable[2]	Not estimable[2]	Not estimable[2]	Low

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	rivaroxaban	warfarin	Relative (95% CI)	Absolute: control (warfarin)	Absolute: intervention (rivaroxaban)	Quality
Clinically relevant non-major bleeding at day 210 (RR <1 favours rivaroxaban)											
1 (Cohen 2016)	RCT	Not serious	N/A	Not estimable	Very serious[1]	3/57	2/55	1.45 (0.25, 8.33)	3.64 per 100	5.27 per 100 (0.91, 30.29)	Very low
Serious adverse events at day 210 (RR <1 favours rivaroxaban)											
1 (Cohen 2016)	RCT	Not serious	N/A	Not estimable	Very serious[1]	4/57	3/55	1.29 (0.30, 5.49)	5.45 per 100	7.04 per 100 (1.64, 29.95)	Very low

1. 95% confidence interval crosses both ends of a defined MID interval.
2. Effect estimate was not possible as both groups had 0 events.
3. Study was at moderate risk of bias.
4. 95% confidence interval crosses one end of a defined MID interval.
5. Study was only partially applicable to the review question for this outcome.

1 ***High intensity warfarin (INR 3.1-4.0) versus standard intensity warfarin (INR 2.0-3.0) for the extended therapy of VTE (DVT and/or PE)***
2 ***associated with antiphospholipid syndrome***

3 **Table 64 High intensity warfarin (INR 3.1-4.0) versus standard intensity warfarin (INR 2.0-3.0) for the extended therapy of VTE (DVT**
4 **and/or PE) associated with antiphospholipid syndrome**

Quality assessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	High intensity	Standard intensity	Relative (95% CI)	Absolute: control (low intensity)	Absolute: intervention (high intensity)	Quality
VTE-recurrence during long-term follow-up (HR <1 favours rivaroxaban)											
1 (Crowther 2003)	RCT	Serious[1]	N/A	Not serious	Very serious[2]	N/A	N/A	HR 2.90 (0.30 – 28.00)	N/A	N/A	Very low
1. Study was at moderate risk of bias 2. 95% confidence interval crosses the line of no effect.											

5 **Network meta-analyses**

6 **Table 65 Network meta-analysis results for the extended therapy of VTE**

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (intention to treat)								
12	RCT	14,637	See appendix H	Serious[3]	Not serious	Not serious	Not serious	Moderate
Major bleeding (on-treatment period)								
13	RCT	14,840	See appendix H	Serious[3]	Not serious	Serious[2]	Not serious	Low
Clinically relevant non-major bleeding (on-treatment period)								
7	RCT	12,458	See appendix H	Not serious	Not serious	Not serious	Not serious	High
All-cause mortality (intention to treat)								

10	RCT	12,913	See appendix H	Not serious	Not serious	Not serious	Not serious	High
VTE-related mortality (intention to treat)								
4	RCT	7,865	See appendix H	Not serious	Not serious	Serious[2]	Serious[1]	Low

1. All of the NMA comparisons cross the line of no effect.
2. Visual inspection of the relative effectiveness charts identified at least one major difference between pairwise analysis and NMA.
3. >33.3% of studies were at moderate/high risk of bias.

5

6 **Table 66 Network meta-analysis results for the extended therapy of DVT**

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (intention to treat)								
9	RCT	7,719	See appendix H	Serious[2]	Not serious	Serious[1]	Not serious	Moderate

1. The DIC is lower in the random effects model than the selected fixed effects one (although not by 3.00).
2. >33.3% of studies were at moderate/high risk of bias.

12 **Table 67 Network meta-analysis results for the extended therapy of PE**

13

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (intention to treat)								
4	RCT	4,697	See appendix H	Not serious	Not serious	Serious[1]	Not serious	Moderate

1. The DIC is lower in the random effects model than the selected fixed effects one (although not by 3.00).

Table 68 Network meta-analysis results for extended therapy of VTE in people aged 65 years or older

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
7	RCT	4,707	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate

* Studies with zero events in both arms removed from analysis.

3. >33.3% of studies in the NMA were at moderate or high risk of bias.
4. All of the NMA comparisons cross the line of no effect.

Table 69 Network meta-analysis results for extended therapy of VTE in people with obesity

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
VTE-recurrence (on-treatment period)								
4	RCT	1,553	See appendix H	Serious[1]	Not serious	Not serious	Not serious	Moderate

* Studies with zero events in both arms removed from analysis.

3. >33.3% of studies in the NMA were at moderate or high risk of bias.
4. All of the NMA comparisons cross the line of no effect.

Appendix H – Network meta-analysis results

Initial treatment of VTE

The following tables and figures are based on NMA models using evidence from RCTs comparing anticoagulants for the treatment of VTE (DVT and/or PE). The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 70.

Table 70: Venous thromboembolism: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
26	VTE-recurrence	FE	219.42	45.83	47	-	FE
		RE	221.19	45.56		0.11 (0.01, 0.39)	
21**	Major bleeding	FE	157.49	38.2	37	-	FE
		RE	158.32	37.8		0.19 (0.00, 0.74)	
17	Clinically relevant non-major bleeding	FE	208.74	35.62	33	-	FE
		RE	210.47	35.06		0.11 (0.01, 0.54)	
24**	All-cause mortality	FE	232.56	42.7	45	-	FE
		RE	233.97	41.3		0.15 (0.01, 0.45)	
17**	VTE-related mortality	FE	161.05	42.12	34	-	FE
		RE	161.84	38.62		0.68 (0.03, 2.81)	

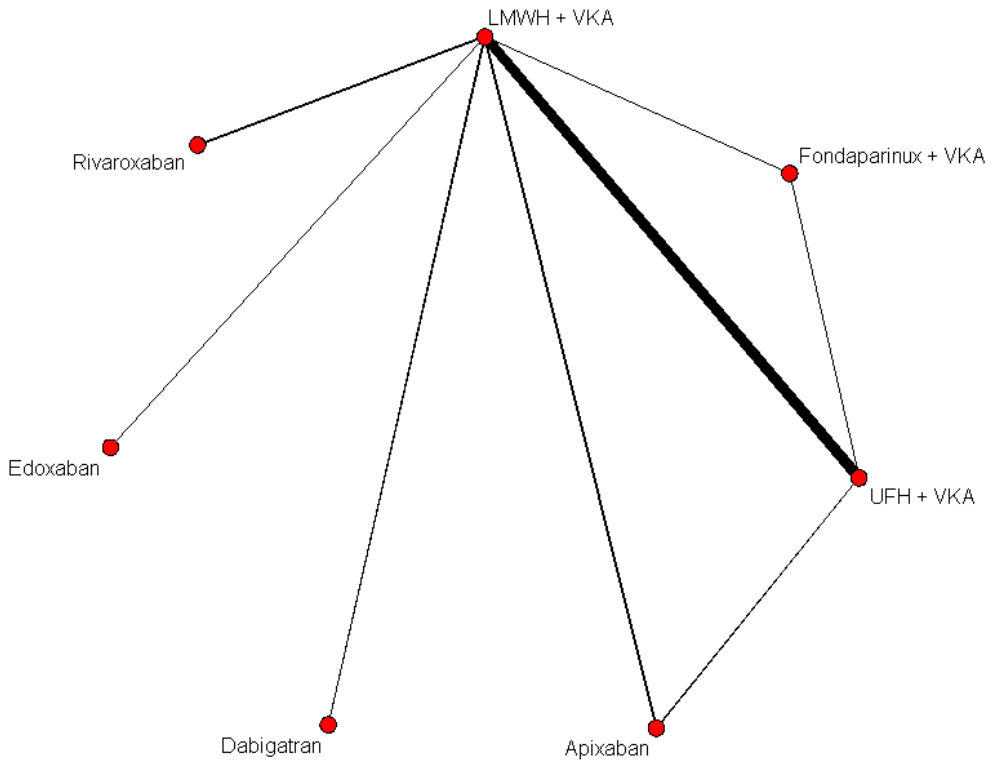
*Studies with zero events in both arms were removed as they do not contribute data to the NMA.

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
**Studies with zero events in either arm had 0.5 added to the event rate for both arms and 1 added to the total population for both arms, this was only done in instances when the model was unable to run (or was uninterpretable in its output).							

VTE-recurrence (during treatment period)

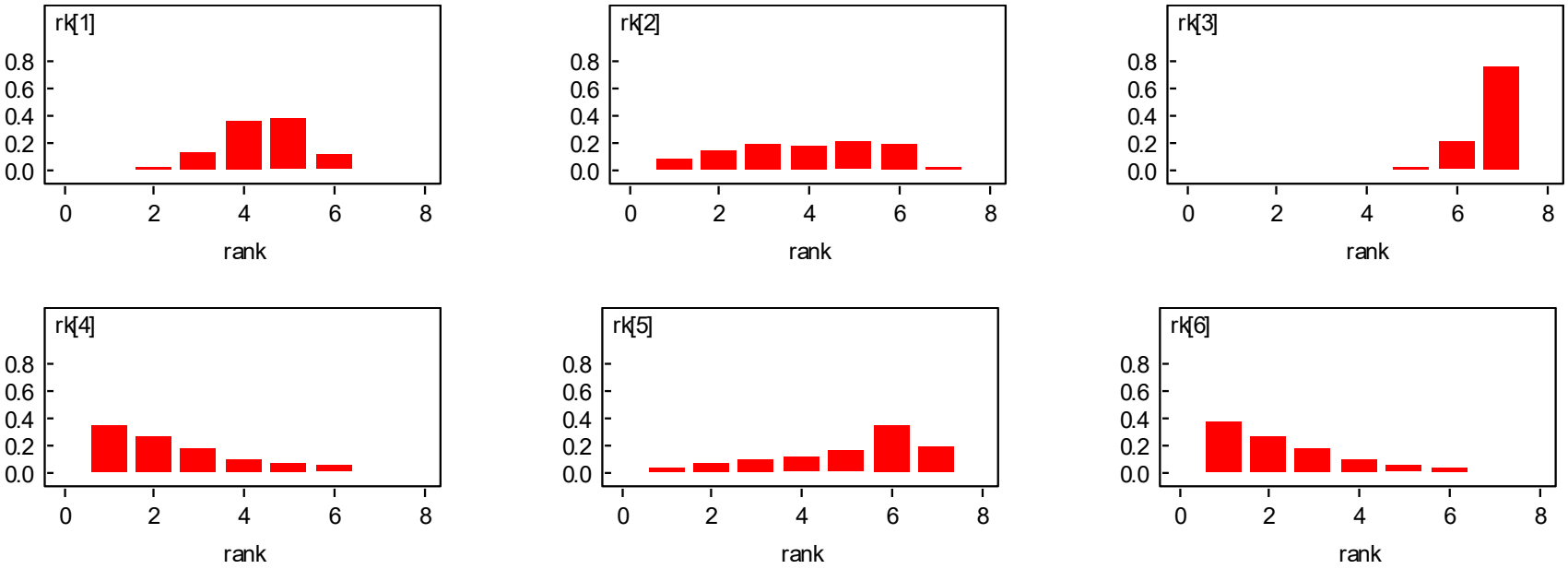
Network diagram

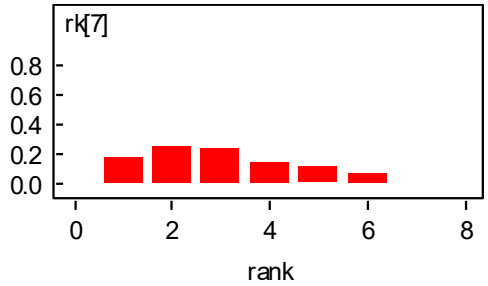
Figure 86 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

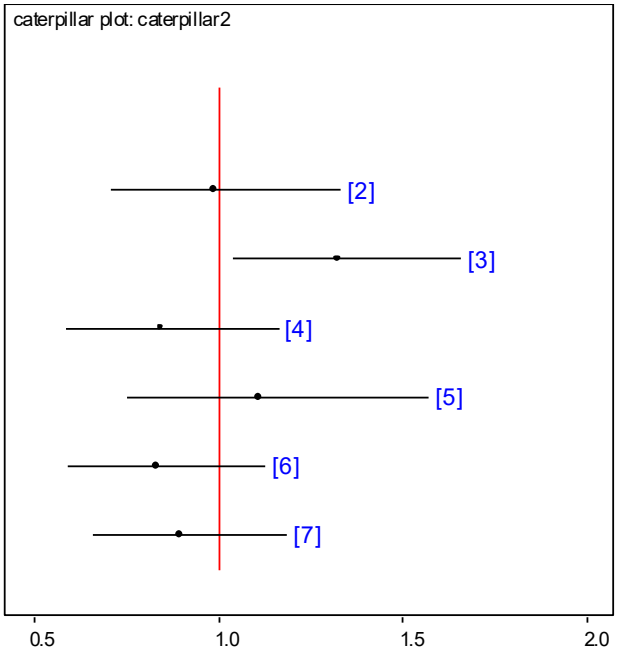
Figure 87 Probability of the treatment assuming each treatment rank. (Group 1= low-molecular weight heparin + vitamin K antagonist, group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Rank 1 is best.)




rk[7]
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
rank

Caterpillar plot

Figure 88 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

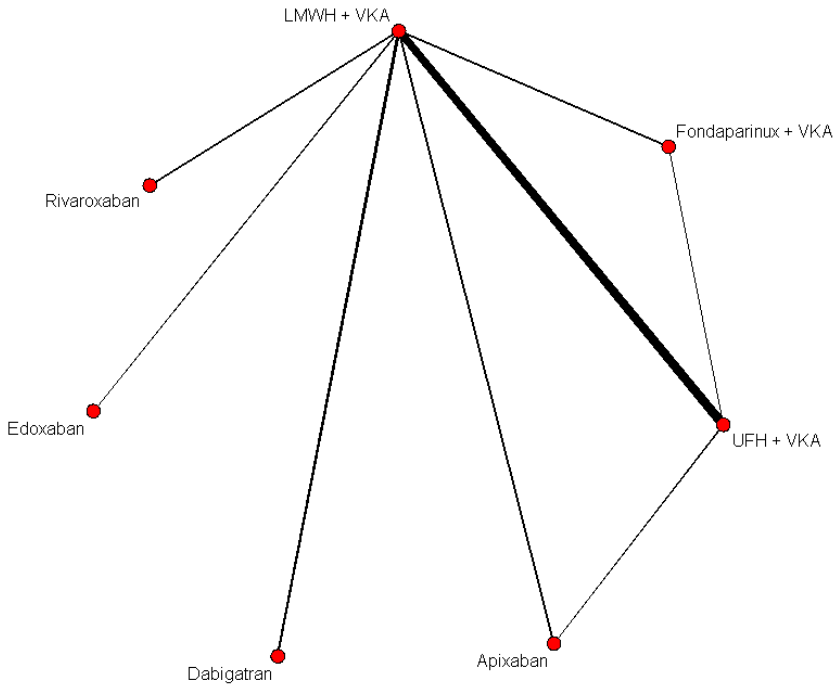
Table 71 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	**Fondaparinux + VKA**	**UFH + VKA**	**Apixaban**	**Dabigatran**	**Edoxaban**	**Rivaroxaban**
LMWH + VKA		0.96 (0.63, 1.46)	1.28 (0.99, 1.67)	0.84 (0.60, 1.18)	1.09 (0.76, 1.57)	0.82 (0.59,1.13)	0.88 (0.54, 1.43)
Fondaparinux + VKA	0.97 (0.71, 1.33)		1.33 (0.89, 2.00)	-	-	-	-
UFH + VKA	1.31 (1.04, 1.66)	1.35 (0.99, 1.84)		0.33 (0.01, 7.75)	-	-	-
Apixaban	0.83 (0.59, 1.17)	0.86 (0.54, 1.35)	0.63 (0.42, 0.95)		-	-	-
Dabigatran	1.09 (0.76, 1.57)	1.12 (0.69, 1.82)	0.83 (0.54, 1.28)	1.31 (0.80, 2.16)		-	-
Edoxaban	0.82 (0.60, 1.13)	0.84 (0.54, 1.32)	0.62 (0.42, 0.93)	0.99 (0.62, 1.57)	0.75 (0.46, 1.22)		-
Rivaroxaban	0.89 (0.66, 1.19)	0.91 (0.59, 1.40)	0.68 (0.46, 0.98)	1.07 (0.68, 1.68)	0.81 (0.51, 1.30)	1.08 (0.70,1.67)	

Major-bleeding (during treatment period and during wash-out period of up to 7 days post treatment cessation)

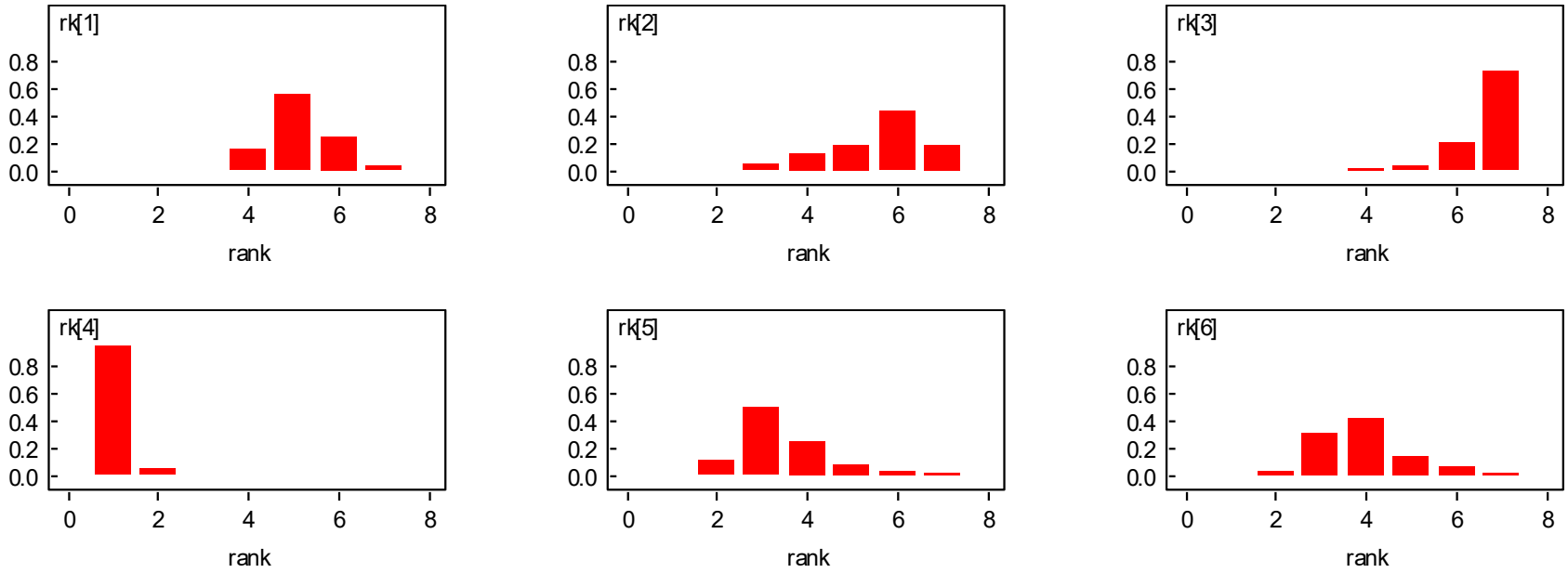
Network diagram

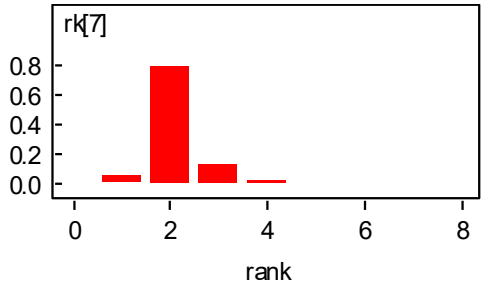
Figure 89 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

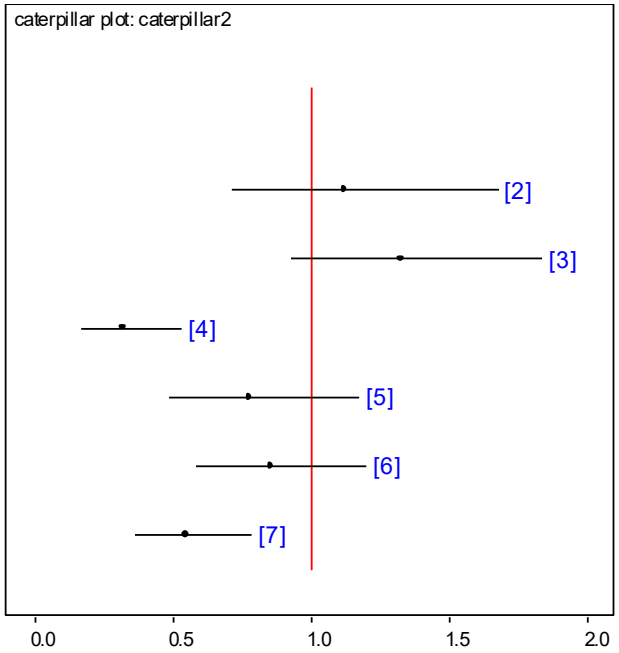
Figure 90 Probability of the treatment assuming each treatment rank. (Group 1= low-molecular weight heparin + vitamin K antagonist, group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5= dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Rank 1 is best.)




rk[7]
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
rank

Caterpillar plot

Figure 91 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

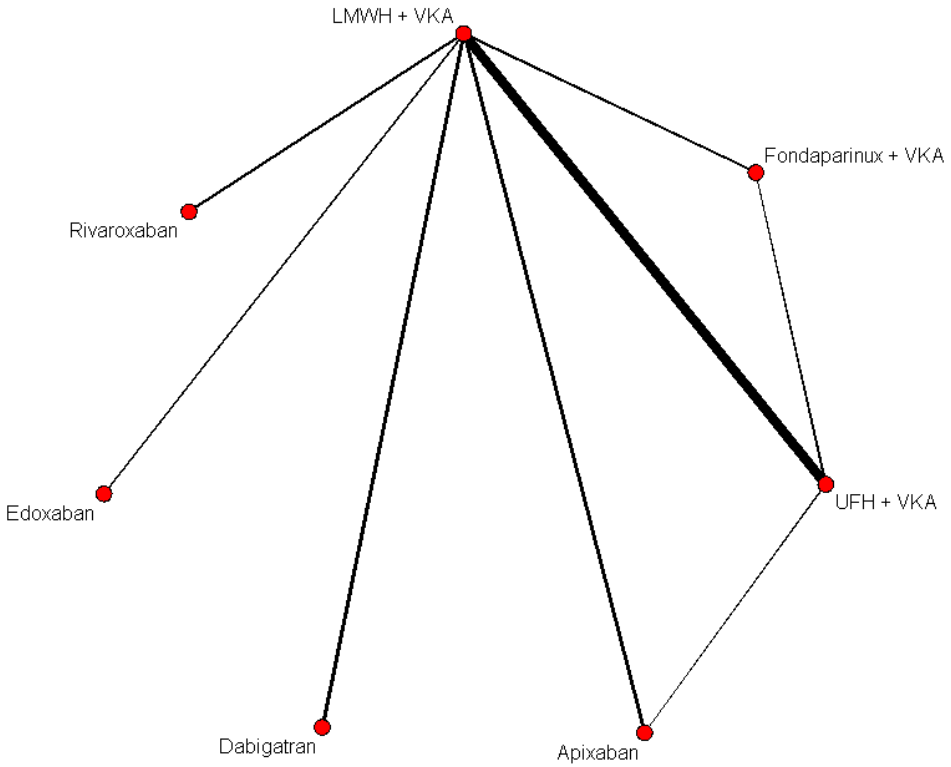
Table 72 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
LMWH + VKA		1.09 (0.64, 1.85)	1.25 (0.85,1.85)	0.33 (0.19,0.58)	0.76 (0.49, 1.18)	0.84 (0.59, 1.20)	0.54 (0.36, 0.79)
Fondaparinux + VKA	1.10 (0.72, 1.68)		1.18 (0.67, 2.04)	-	-	-	-
UFH + VKA	1.30 (0.93, 1.83)	1.19 (0.77, 1.83)		0.20 (0.01 to 3.94	-	-	-
Apixaban	0.31 (0.17, 0.54)	0.28 (0.14, 0.57)	0.24 (0.12, 0.45)		-	-	-
Dabigatran	0.76 (0.49, 1.17)	0.69 (0.38, 1.27)	0.58 (0.33, 1.01)	2.44 (1.21, 5.10)		-	-
Edoxaban	0.84 (0.59, 1.20)	0.77 (0.44, 1.34)	0.64 (0.39, 1.06)	2.70 (1.41, 5.40)	1.11 (0.63, 1.95)		-
Rivaroxaban	0.54 (0.36, 0.79)	0.49 (0.28, 0.87)	0.41 (0.25, 0.69)	1.72 (0.89, 3.51)	0.71 (0.39, 1.27)	0.64 (0.38, 1.08)	

Clinically relevant non-major bleeding (during treatment period and during wash-out period of up to 7 days post treatment cessation)

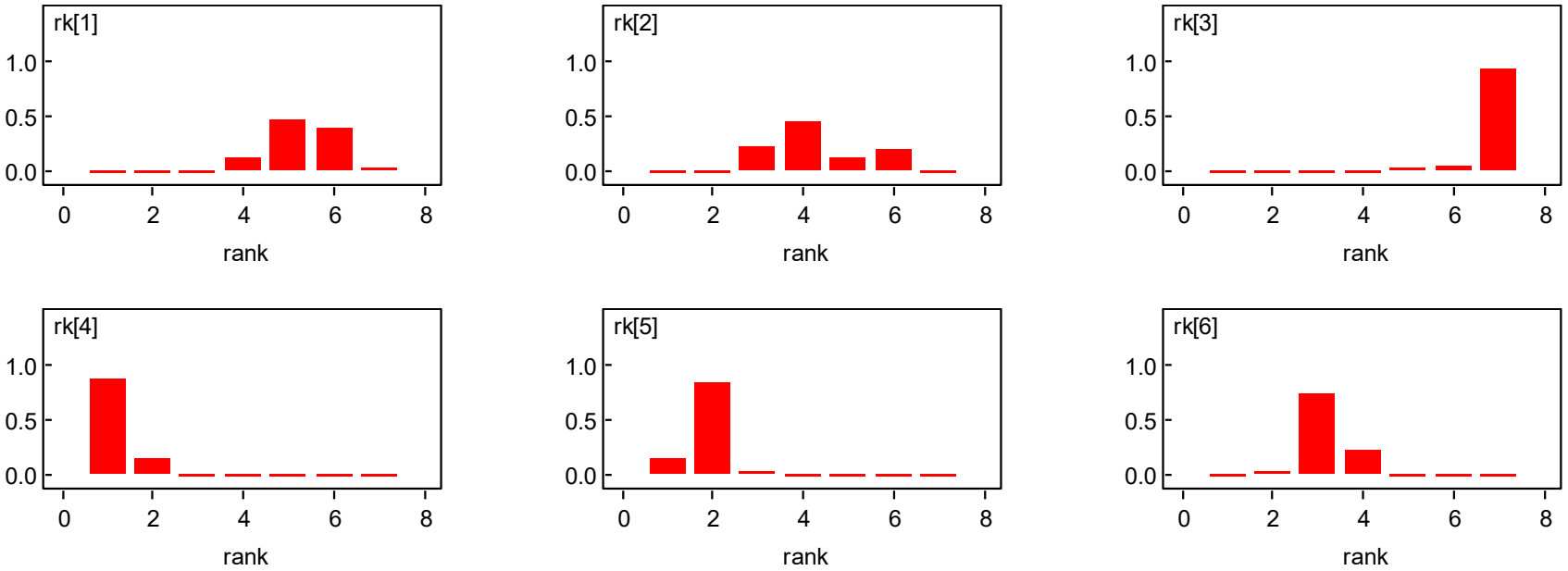
Network diagram

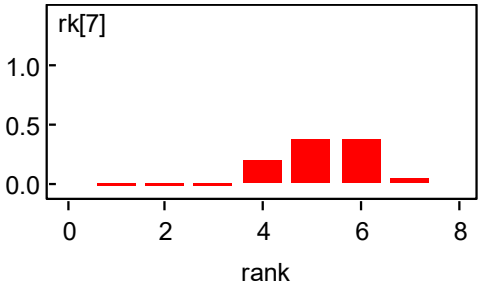
Figure 92 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

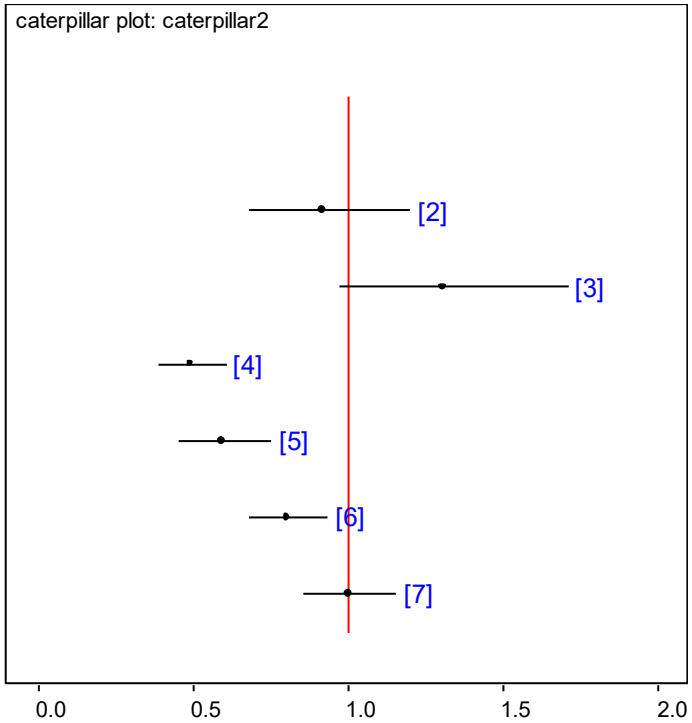
Figure 93 Probability of the treatment assuming each treatment rank. (Group 1= low-molecular weight heparin + vitamin K antagonist, group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5= dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Rank 1 is best.)




rk[7]
1.0
0.5
0.0
0
2
4
6
8
rank

Caterpillar plot

Figure 94 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

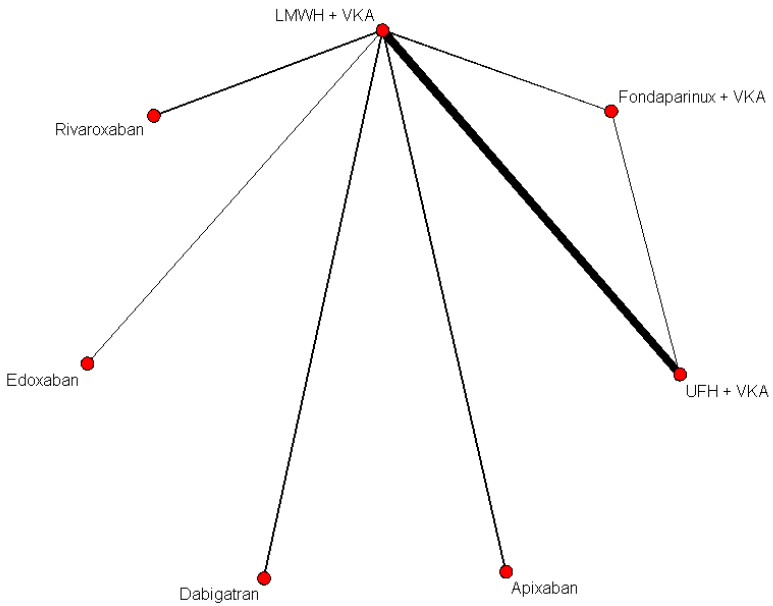
Table 73 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
LMWH + VKA		0.96 (0.67, 1.37)	1.19 (0.85, 1.67)	0.60 (0.30, 1.18)	0.59 (0.46, 0.76)	0.80 (0.68, 0.94)	1.00 (0.86, 1.15)
Fondaparinux + VKA	0.90 (0.68, 1.20)		1.49 (1.09, 2.08)	-	-	-	-
UFH + VKA	1.29 (0.98, 1.71)	1.43 (1.09, 1.87)		0.30 (0.08, 1.10)	-	-	-
Apixaban	0.49 (0.39, 0.61)	0.54 (0.38, 0.77)	0.38 (0.27, 0.53)		-	-	-
Dabigatran	0.59 (0.46, 0.75)	0.65 (0.44, 0.95)	0.46 (0.31, 0.66)	1.21 (0.86, 1.69)		-	-
Edoxaban	0.80 (0.68, 0.94)	0.88 (0.64, 1.22)	0.62 (0.45, 0.85)	1.64 (1.25, 2.15)	1.36 (1.01, 1.82)		-
Rivaroxaban	1.00 (0.86, 1.16)	1.10 (0.80, 1.52)	0.77 (0.56, 1.06)	2.04 (1.56, 2.67)	1.69 (1.27, 2.26)	1.25 (1.00, 1.55)	

All-cause mortality (during treatment period)

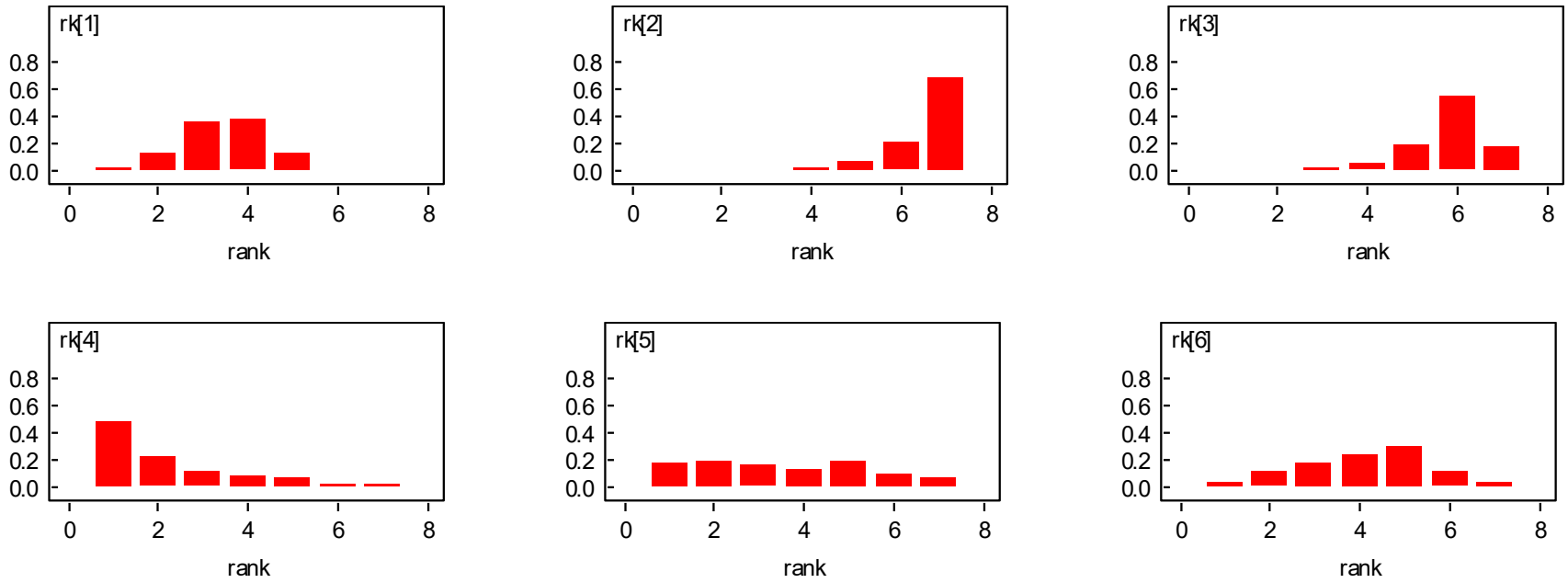
Network diagram

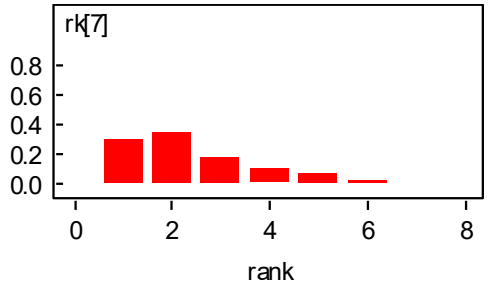
Figure 95 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

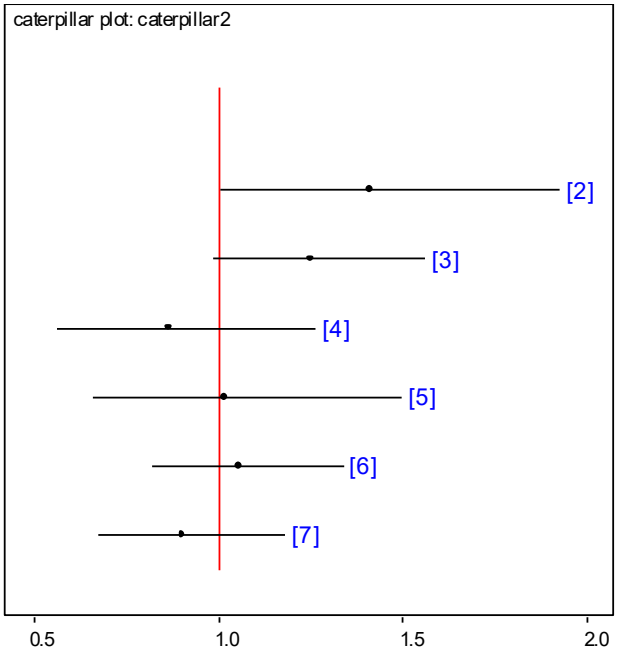
Figure 96 Probability of the treatment assuming each treatment rank. (Group 1= low-molecular weight heparin + vitamin K antagonist, group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Rank 1 is best.)




rk[7]
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
rank

Caterpillar plot

Figure 97 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = fondaparinux + vitamin K antagonist, group 3 = unfractionated heparin + vitamin K antagonist, group 4 = apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

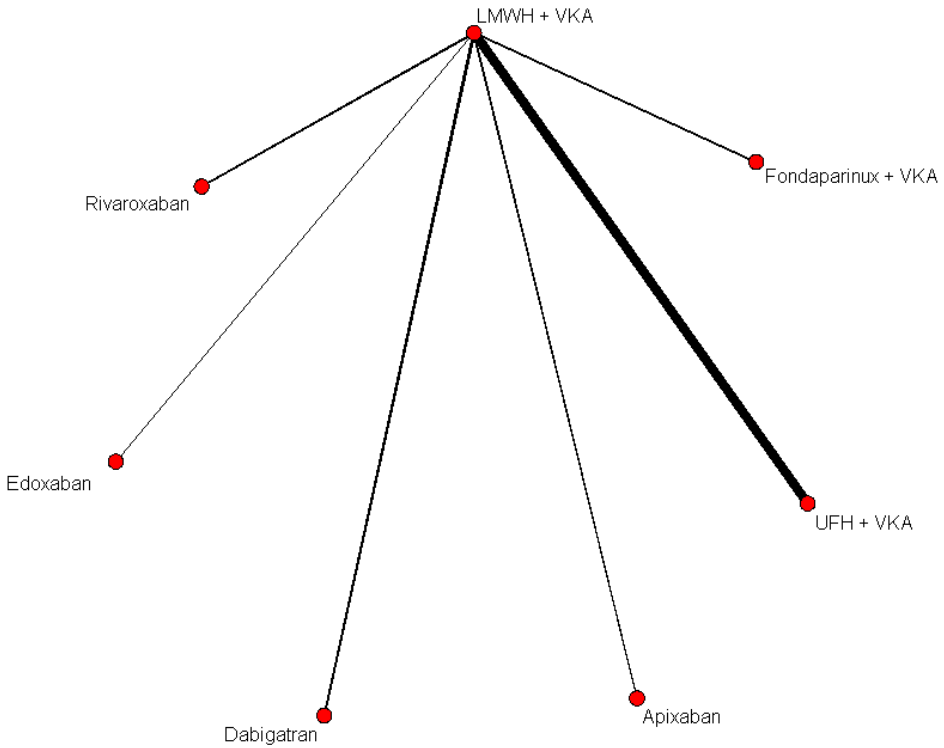
Table 74 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	**Fondaparinux + VKA**	**UFH + VKA**	**Apixaban**	**Dabigatran**	**Edoxaban**	**Rivaroxaban**
LMWH + VKA		1.26 (0.80, 1.99)	1.32 (0.99,1.64)	1.40 (0.36,134.99)	1.00 (0.66,1.50)	1.05 (0.82, 1.34)	0.88 (0.53, 1.46)
Fondaparinux + VKA	1.39 (1.01,1.93)		0.83 (0.57, 1.22)	-	-	-	-
UFH + VKA	1.24 (0.99,1.56)	0.89 (0.65, 1.21)		-	-	-	-
Apixaban	0.85 (0.56,1.27)	0.61 (0.36, 1.02)	0.68 (0.43, 1.09)		-	-	-
Dabigatran	1.00 (0.66,1.50)	0.71 (0.42, 1.21)	0.80 (0.50, 1.28)	1.18 (0.66, 2.09)		-	-
Edoxaban	1.05 (0.82,1.34)	0.75 (0.50, 1.13)	0.85 (0.60, 1.18)	1.24 (0.77, 1.99)	1.06 (0.65,1.70)		-
Rivaroxaban	0.89 (0.67,1.18)	0.64 (0.42, 0.98)	0.72 (0.50, 1.03)	1.05 (0.65, 1.72)	0.90 (0.55,1.48)	0.85 (0.59, 1.24)	

VTE-related mortality (during treatment period)

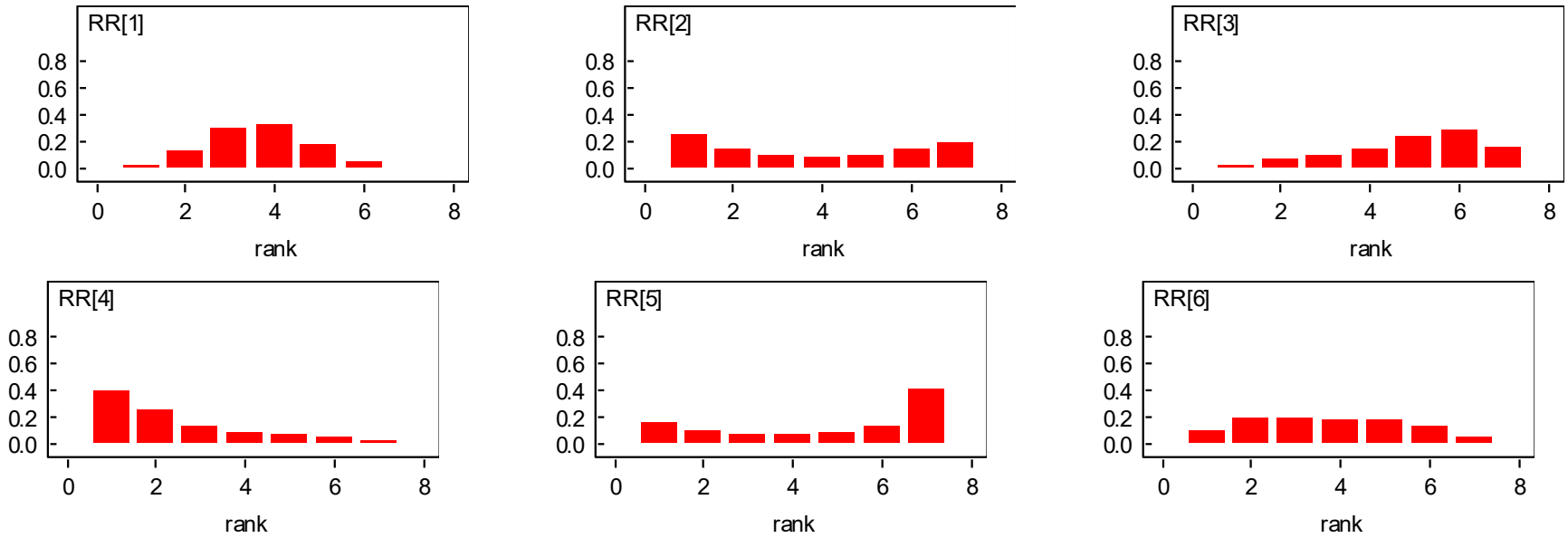
Network diagram

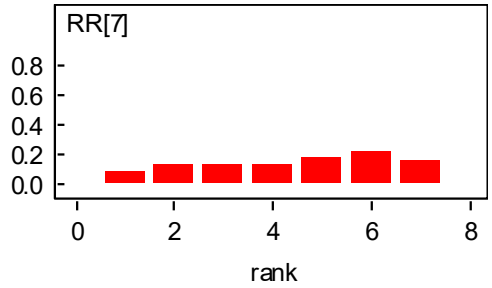
Figure 98 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

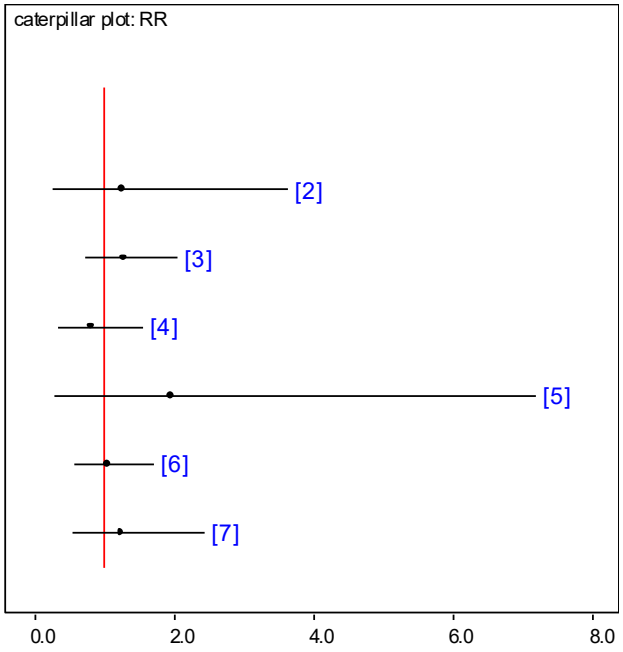
Figure 99 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = fondaparinux+VKA, group 3 = UFH+VKA, group 4= apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Rank 1 is best.)




RR[7]
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
rank

Caterpillar plot

Figure 100 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = fondaparinux+VKA, group 3 = UFH+VKA, group 4= apixaban, group 5 = dabigatran, group 6 = edoxaban, group 7 = rivaroxaban. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 75 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
LMWH + VKA		1.01 (0.29, 3.47)	1.22 (0.75, 1.96)	0.75 (0.36, 1.59)	1.31 (0.06, 26.88)	1.00 (0.58, 1.72)	1.15 (0.55, 2.41)
Fondaparinux + VKA	1.01 (0.27, 3.63)		0.93 (0.46, 1.89)	-	-	-	-
UFH + VKA	1.23 (0.75, 2.05)	1.23 (0.31, 5.04)		-	-	-	-
Apixaban	0.75 (0.35, 1.58)	0.74 (0.17, 3.37)	0.61 (0.24, 1.49)		-	-	-
Dabigatran	1.37 (0.29, 7.20)	1.37 (0.18, 11.23)	1.12 (0.21, 6.27)	1.84 (0.32, 11.30)		-	-
Edoxaban	1.00 (0.60, 1.73)	0.99 (0.25, 4.12)	0.81 (0.38, 1.71)	1.34 (0.53, 3.46)	0.73 (0.13, 3.83)		-
Rivaroxaban	1.15 (0.55, 2.46)	1.15 (0.26, 5.23)	0.94 (0.38, 2.31)	1.54 (0.54, 4.53)	0.84 (0.14, 4.79)	1.15 (0.46, 2.92)	

Initial treatment of DVT

The following tables and figures are based on the NMA models using evidence from RCTs comparing anticoagulants for the treatment of DVT. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 76.

Table 76: Deep vein thrombosis: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
17	VTE-recurrence	FE	161.72	34.38	32	-	FE
		RE	163.48	33.95		0.22 (0.01, 0.95)	
11* and **	Major-bleeding	FE	96.03	17.97	21	-	FE
		RE	97.49	17.83		0.38 (0.02,1.47)	
11	Clinically relevant non-major bleeding	FE	133.71	30.47	22	-	RE
		RE	130.61	23.48		0.94 (0.11, 2.95	
11**	All-cause mortality	FE	98.94	14.77	21	-	FE
		RE	100.85	15.47		0.19 (0.01, 0.80)	

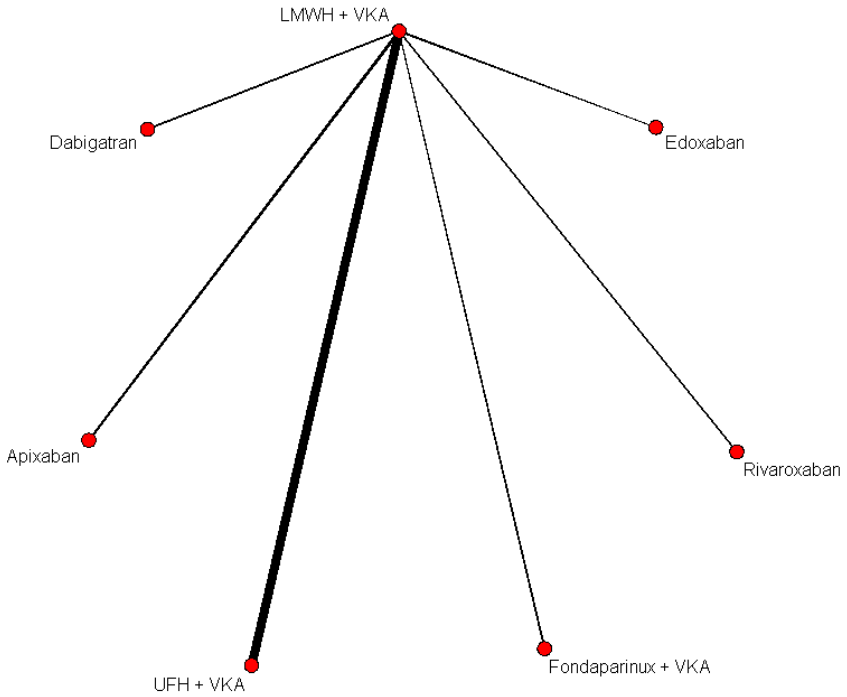
* Studies with zero events in both arms were removed as they do not contribute data to the NMA.

**Studies with zero events in either arm had 0.5 added to the event rate for both arms and 1 added to the total population for both arms, this was only done in instances when the model was unable to run (or was uninterpretable in its output).

VTE-recurrence (during treatment period)

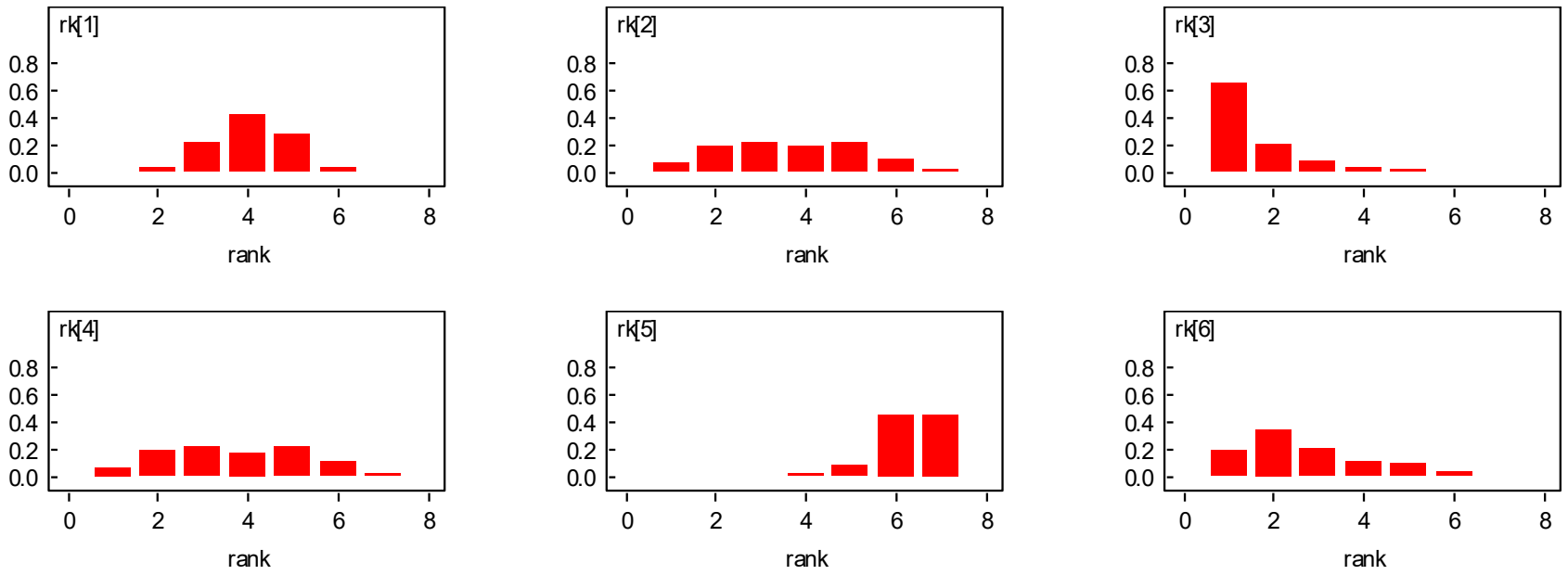
Network diagram

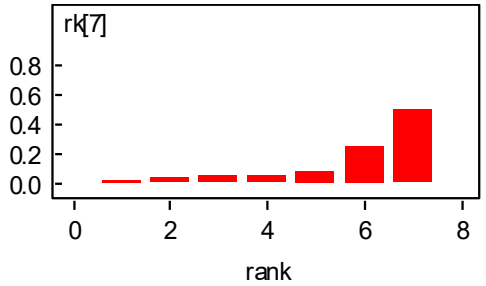
Figure 101 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

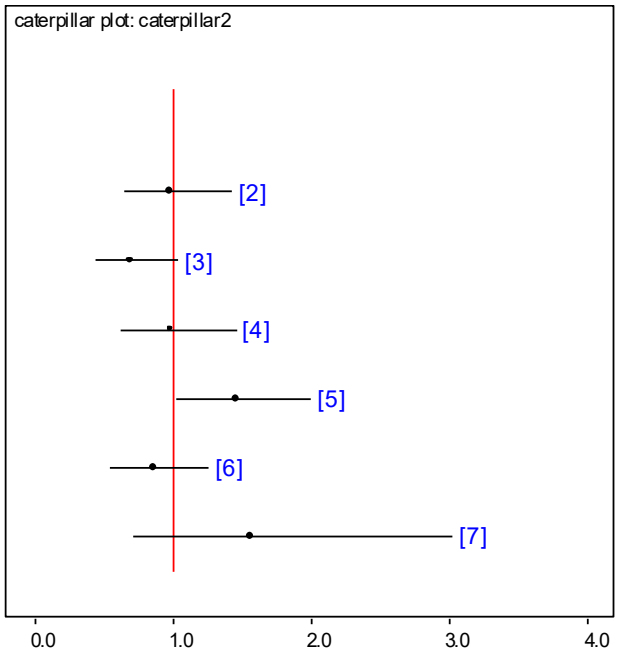
Figure 102 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = edoxaban, group 3 = rivaroxaban, group 4 = fondaparinux + VKA, group 5 = UFH+VKA, group 6 = Apixaban, group 7 = Dabigatran. Rank 1 is best.)




rk[7]
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
rank

Caterpillar plot

Figure 103 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = edoxaban, group 3 = rivaroxaban, group 4 = fondaparinux + VKA, group 5 = UFH+VKA, group 6 = Apixaban, group 7 = Dabigatran. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

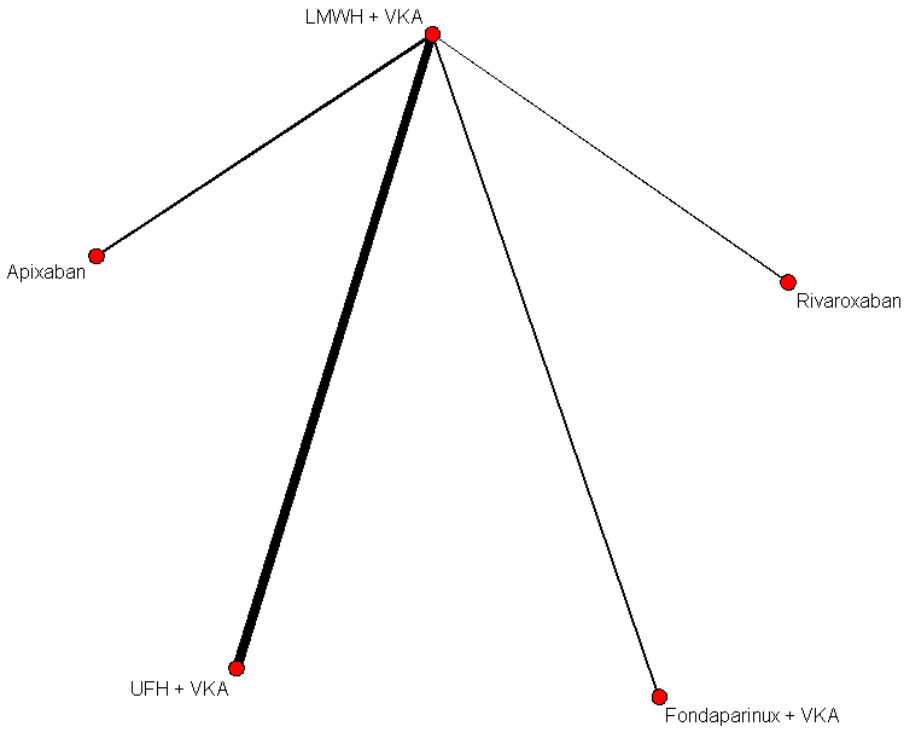
Table 77 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Edoxaban	Rivaroxaban	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran
LMWH + VKA		0.96 (0.64, 1.43)	0.68 (0.44, 1.05)	0.96 (0.63, 1.46)	1.41 (0.99, 1.96)	0.84 (0.56, 1.27)	1.45 (0.72, 2.93)
Edoxaban	0.96 (0.65, 1.43)		-	-	-	-	-
Rivaroxaban	0.68 (0.44, 1.05)	0.71 (0.39, 1.27)		-	-	-	-
Fondaparinux + VKA	0.96 (0.63, 1.47)	1.00 (0.56, 1.79)	1.42 (0.77, 2.58)		-	-	-
UFH + VKA	1.43 (1.03, 2.01)	1.49 (0.89, 2.51)	2.11 (1.22, 3.65)	1.49 (0.87, 2.56)		-	-
Apixaban	0.84 (0.55, 1.27)	0.88 (0.49, 1.56)	1.24 (0.68, 2.24)	0.87 (0.48, 1.58)	0.59 (0.34, 1.00)		-
Dabigatran	1.46 (0.72, 3.05)	1.52 (0.68, 3.51)	2.15 (0.94, 5.05)	1.52 (0.67, 3.54)	1.02 (0.47, 2.29)	1.74 (0.77, 4.04)	

Major-bleeding (during treatment period plus wash-out period of up to 7 days post-treatment cessation)

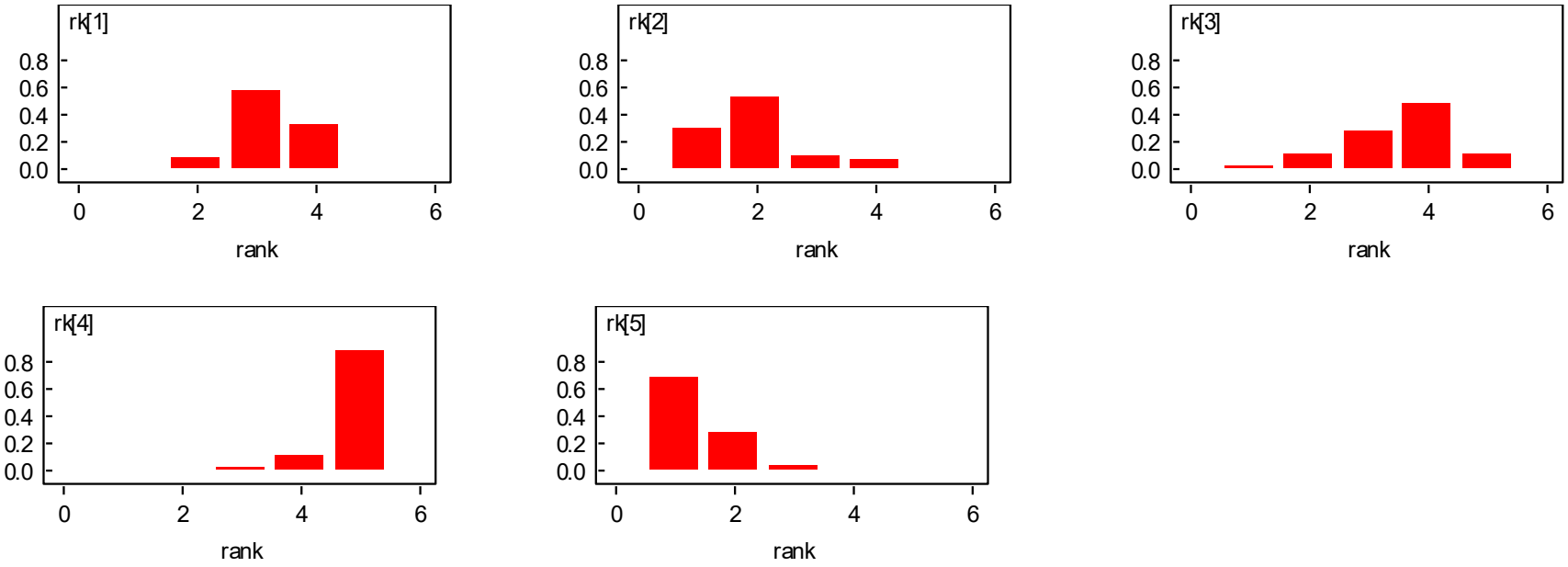
Network diagram

Figure 104 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



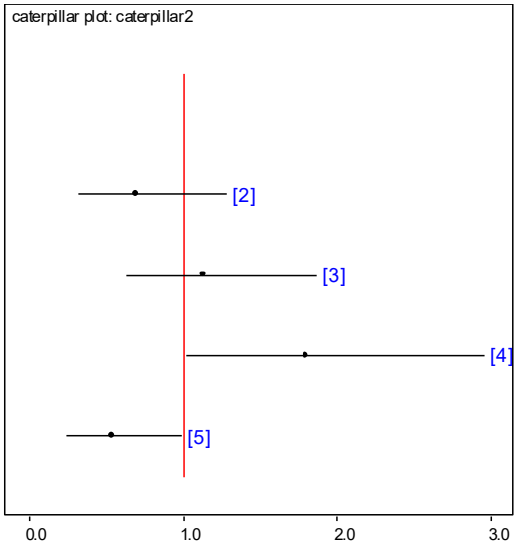
Rank probability histograms

Figure 105 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = Rivaroxaban, group 3 = fondaparinux+VKA, group 4 = UFH+VKA, 5 = Apixaban. Rank 1 is best.)



Caterpillar plot

Figure 106 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = Rivaroxaban, group 3 = fondaparinux+VKA, group 4 = UFH+VKA, group 5 = Apixaban. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

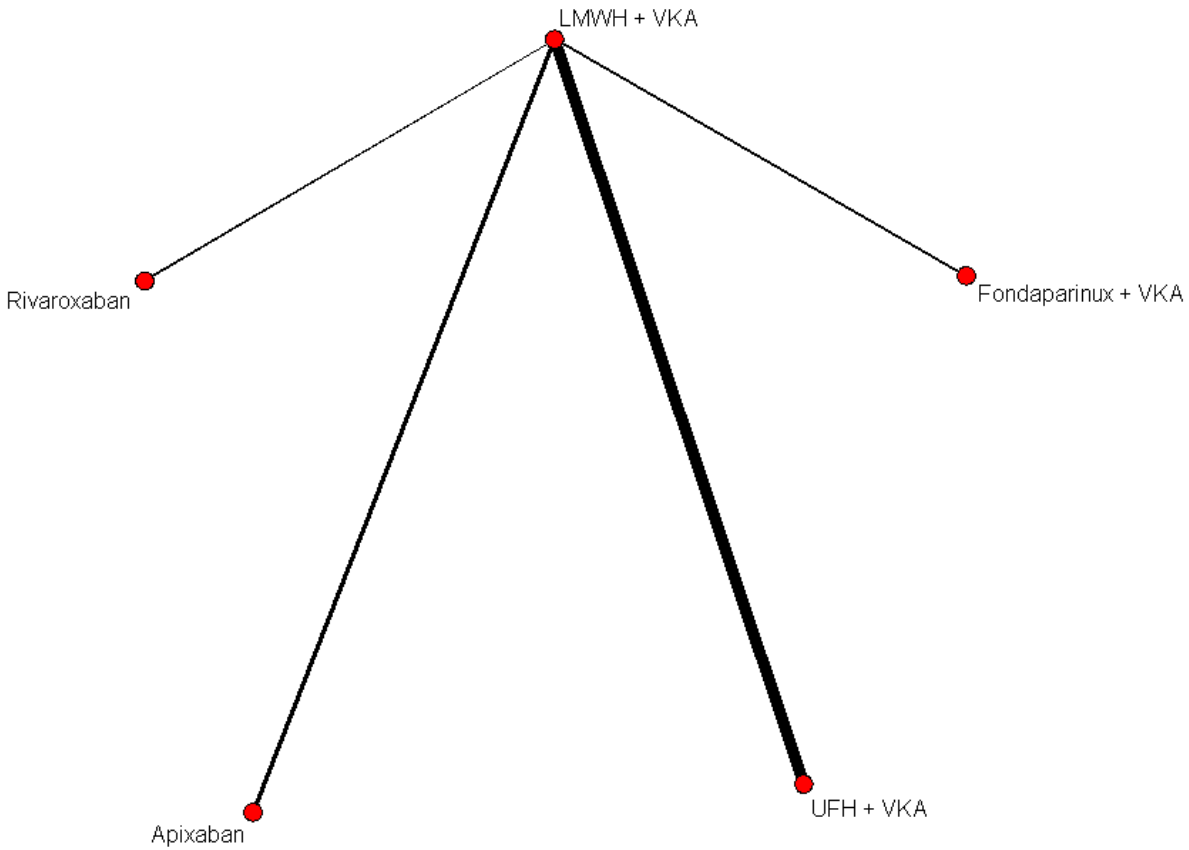
Table 78 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Rivaroxaban	Fondaparinux+VKA	UFH+VKA	Apixaban
LMWH + VKA		0.65 (0.33, 1.29)	1.09 (0.64,1.85)	1.67 (0.97, 2.86)	0.51 (0.25, 1.02)
Rivaroxaban	0.65 (0.33, 1.29)		-	-	-
Fondaparinux + VKA	1.09 (0.63, 1.87)	1.67 (0.70, 4.00)		-	-
UFH+VKA	1.72 (1.02, 2.97)	2.66 (1.12, 6.35)	1.59 (0.75, 3.41)		-
Apixaban	0.51 (0.25, 0.99)	0.78 (0.29, 2.04)	0.47 (0.19, 1.10)	0.29 (0.12, 0.69)	

Clinically relevant non major-bleeding (during treatment period plus wash-out period of up to 7 days post-treatment cessation)

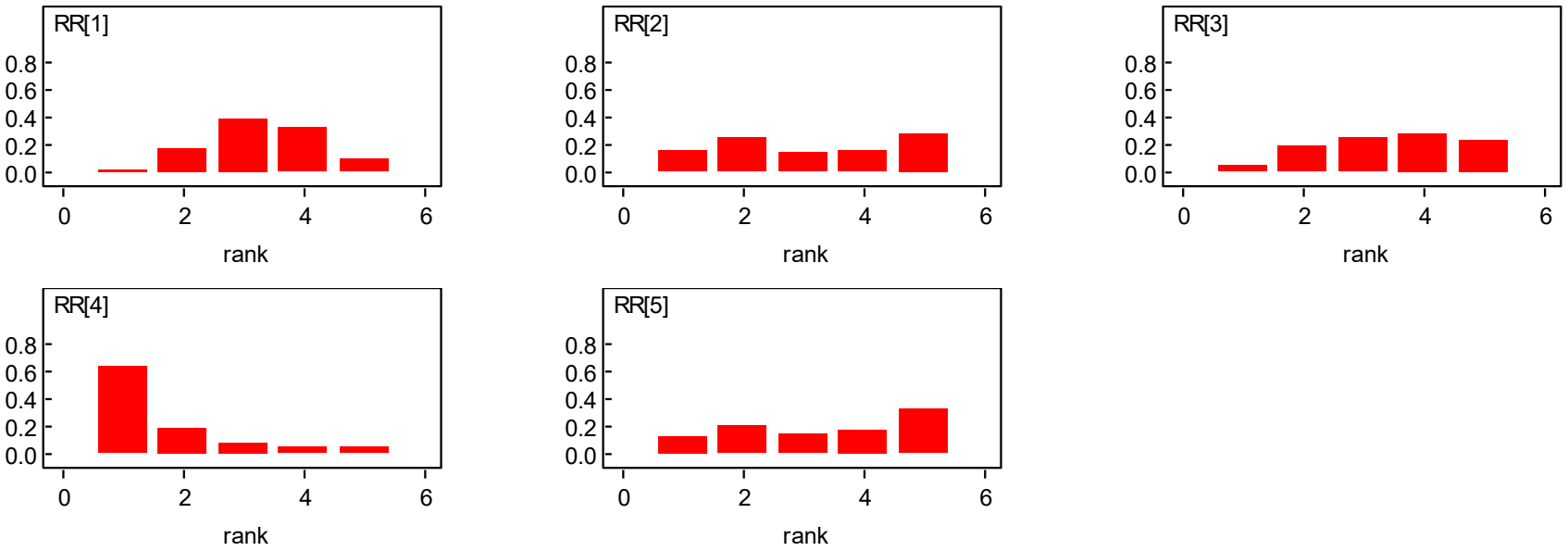
Network diagram

Figure 107 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



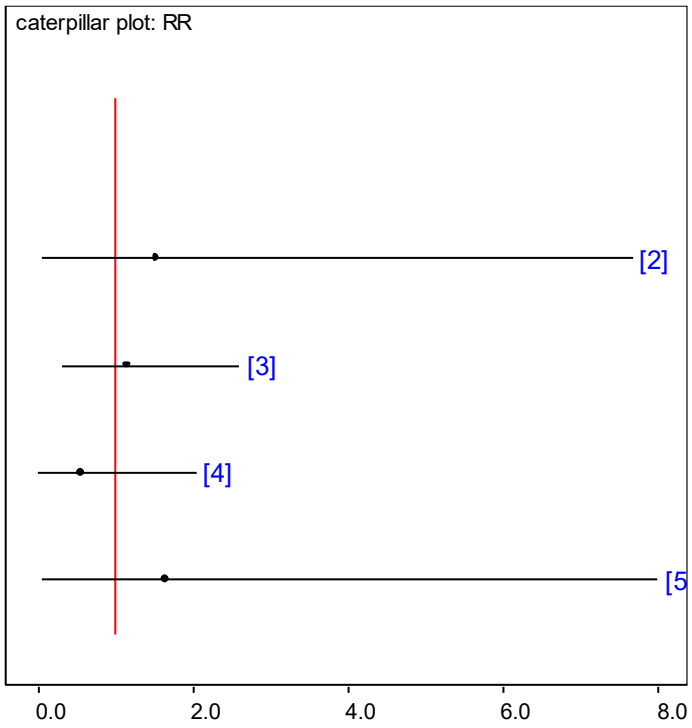
Rank probability histograms

Figure 108 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = fondaparinux+VKA, group 3 = UFH+VKA, 4 = Apixaban, 5= rivaroxaban. Rank 1 is best.)



Caterpillar plot

Figure 109 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = fondaparinux+VKA, group 3 = UFH+VKA, 4 = Apixaban, 5= rivaroxaban. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

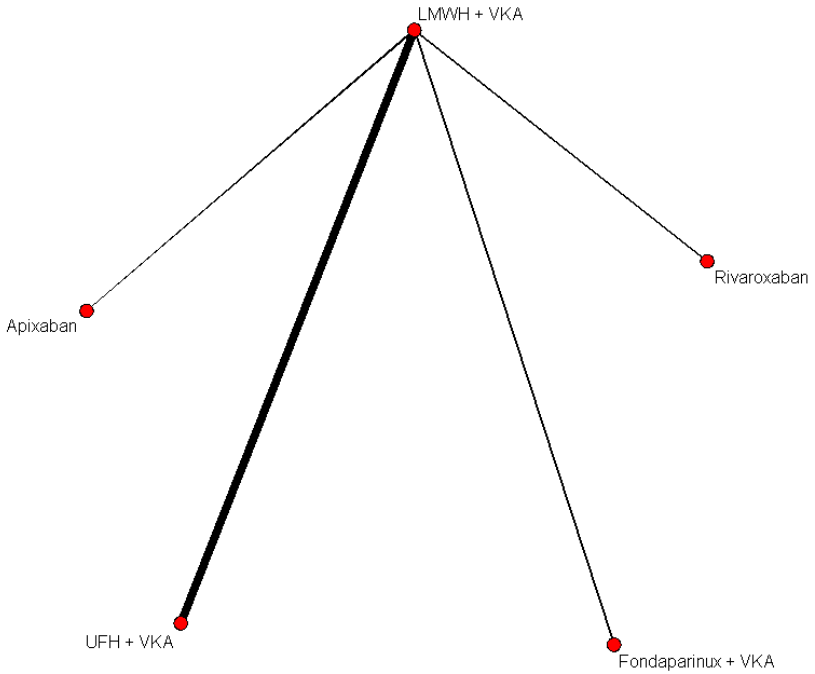
Table 79 Relative effectiveness of all pairwise combinations. (Upper diagonal: risk ratios (RRs) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Fondaparinux+VKA	UFH+VKA	Apixaban	Rivaroxaban
LMWH + VKA		0.96 (0.68, 1.35)	1.19 (0.85, 1.67)	0.98 (0.42, 2.28)	1.05 (0.83, 1.34)
Fondaparinux + VKA	0.96 (0.63, 7.67)		-	-	-
UFH+VKA	1.05 (0.32, 2.61)	1.10 (0.10, 17.71)		0.09 (0.01, 1.55)	-
Apixaban	0.40 (0.02, 2.05)	0.43 (0.01, 6.91)	0.39 (0.02, 2.65)		-
Rivaroxaban	1.05 (0.07, 8.01)	1.09 (0.04, 30.82)	0.99 (0.06, 10.67)	2.52 (0.16, 120.80)	

All-cause mortality (during treatment period)

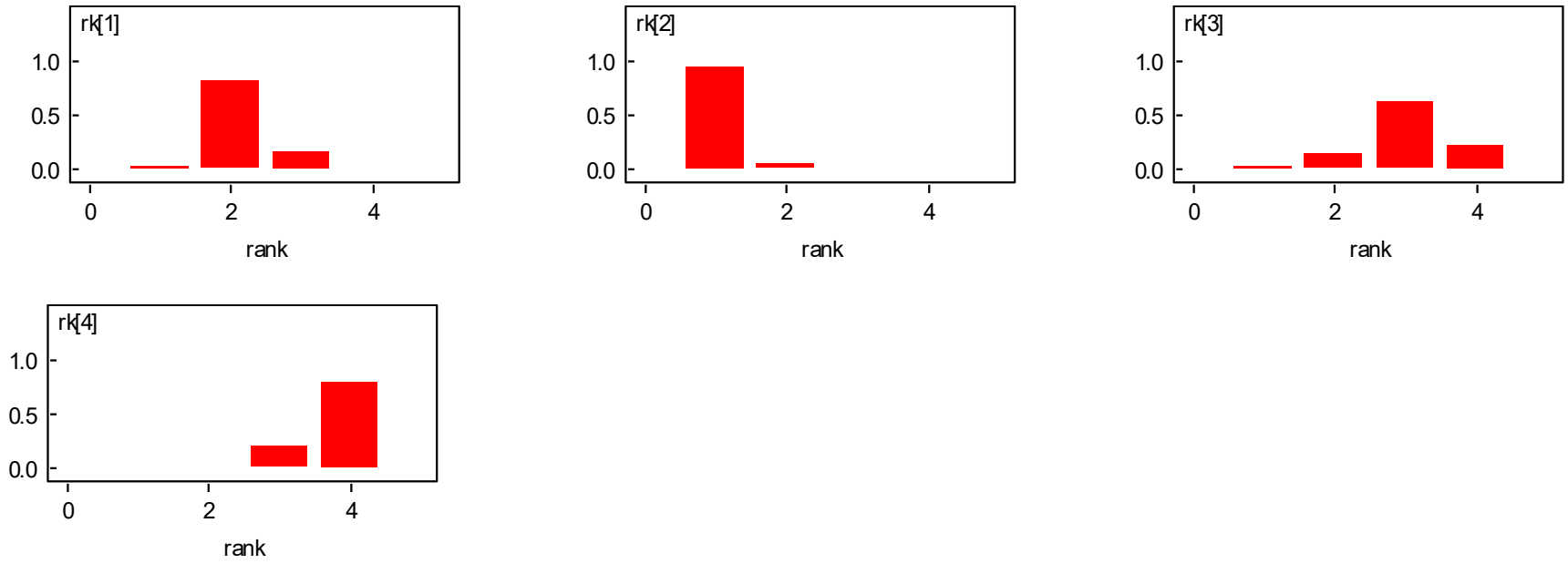
Network diagram

Figure 110 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



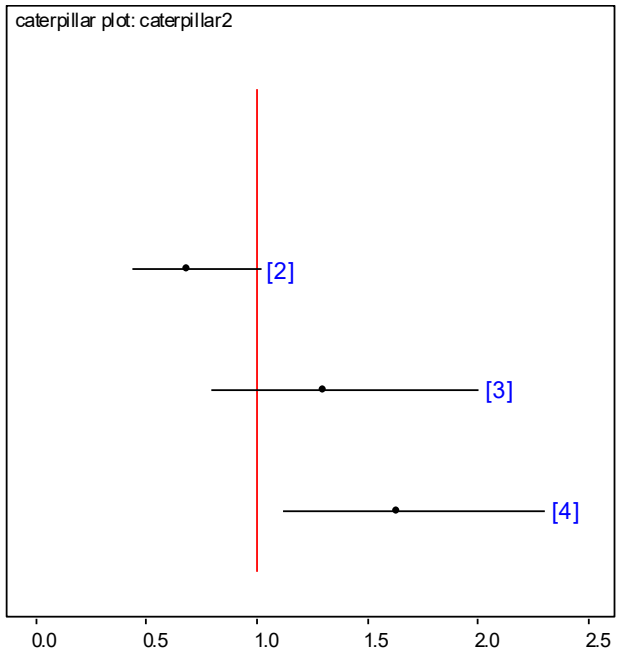
Rank probability histograms

Figure 111 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = Rivaroxaban, group 3 = fondaparinux+VKA, group 4 = UFH+VKA. Rank 1 is best.)



Caterpillar plot

Figure 112 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = Rivaroxaban, group 3 = fondaparinux+VKA, group 4 = UFH+VKA. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 80 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Rivaroxaban	Fondaparinux+VKA	UFH+VKA
LMWH + VKA		0.67 (0.44, 1.02)	1.26 (0.80,1.99)	1.59 (1.11, 2.27)
Rivaroxaban	0.67 (0.44, 1.02)			-
Fondaparinux + VKA	1.26 (0.80, 2.01)	1.89 (1.01, 3.52)		-
UFH+VKA	1.60 (1.12, 2.31)	2.39 (1.38, 4.18)	1.27 (0.71, 2.29)	

Initial treatment of PE

The following tables and figures are based on the NMA model data developed by NICE using evidence from RCTs comparing anticoagulants for the treatment of PE. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 81.

Table 81: Pulmonary embolism: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

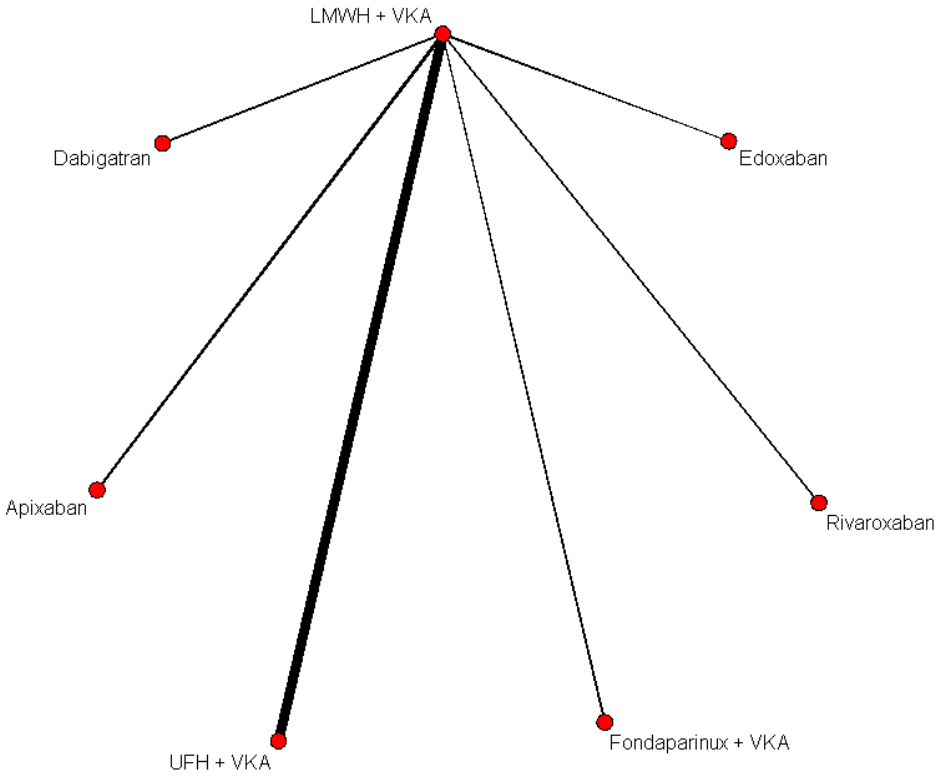
Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
7	VTE-recurrence	FE	62.43	11.04	12	-	FE
		RE	62.96	11.14		0.85 (0.04, 1.93)	
6*	Major-bleeding	FE	52.59	9.65	11	-	FE
		RE	53.34	9.71		0.77 (0.03, 1.93)	

* Studies with zero events in either arm had 0.5 added to the event rate for both arms and 1 added to the total population for both arms, this was only done in instances when the model was unable to run (or was uninterpretable in its output).

VTE-recurrence (during treatment period)

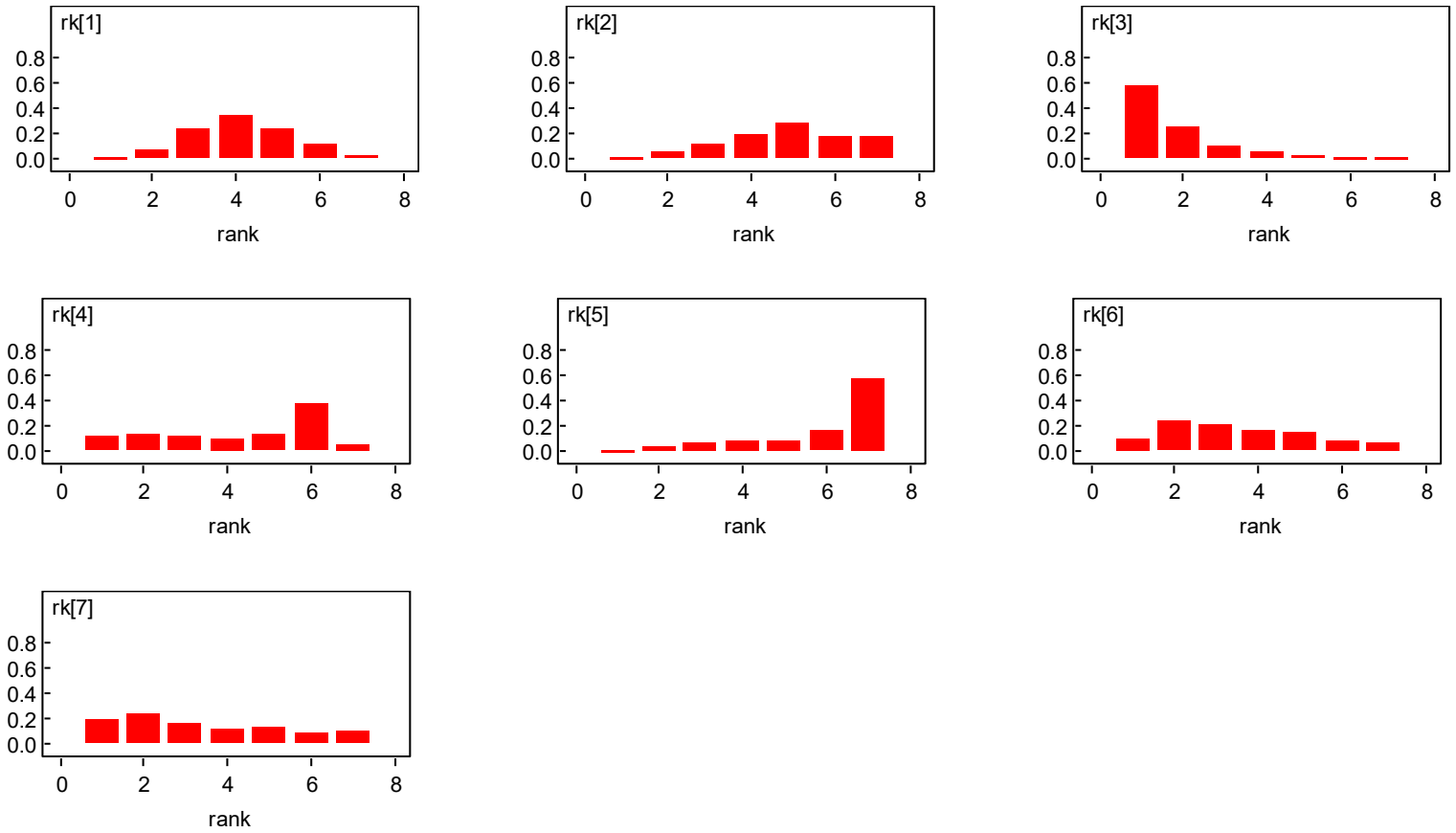
Network diagram

Figure 113 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



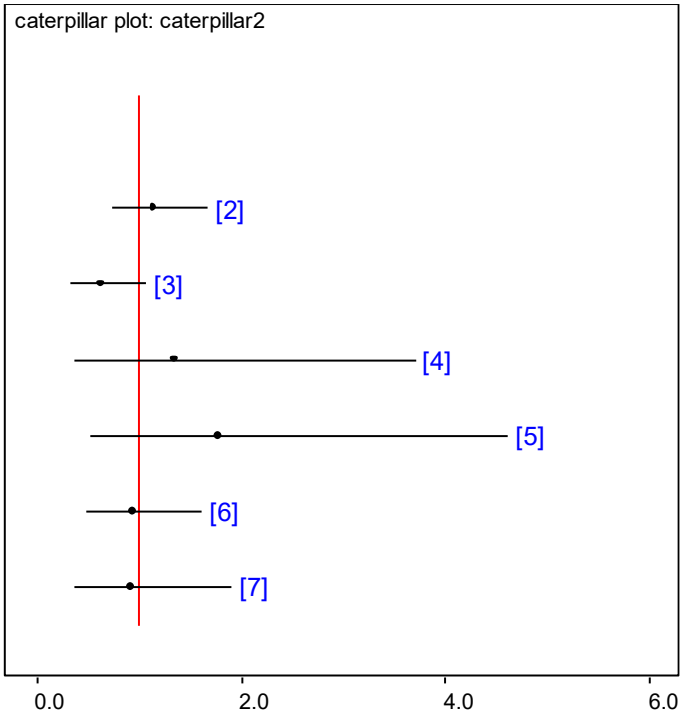
Rank probability histograms

Figure 114 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 =rivaroxaban, group 3 = edoxaban, group 4 = fondaparinux + VKA, group 5 = UFH+VKA, group 6 = Apixaban. Rank 1 is best.)



Caterpillar plot

Figure 115 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 =rivaroxaban, group 3 = edoxaban, group 4 = fondaparinux + VKA, group 5 = UFH+VKA, group 6 = Apixaban. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

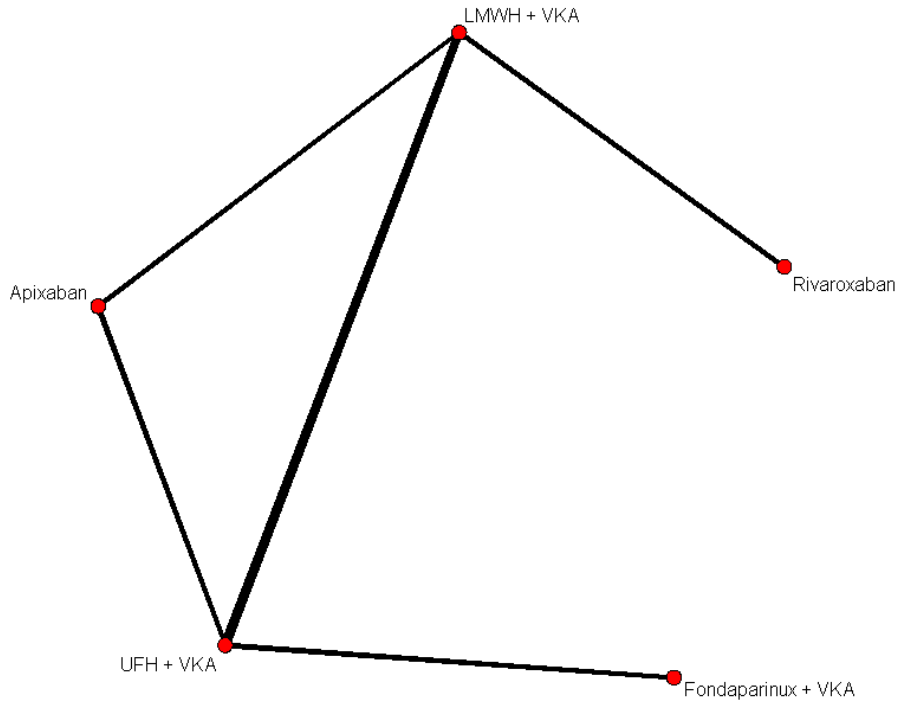
Table 82 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Rivaroxaban	Edoxaban	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran
LMWH + VKA		1.12 (0.75, 1.68)	0.60 (0.34, 1.07)	-	1.45 (0.51, 4.17)	0.90 (0.50, 1.62)	0.85 (0.83, 1.90)
Rivaroxaban	1.12 (0.75, 1.68)		-	-	-	-	-
Edoxaban	0.60 (0.33, 1.07)	0.54 (0.26, 1.09)		-	-	-	-
Fondaparinux + VKA	1.13 (0.37, 3.77)	1.01 (0.31, 3.60)	1.89 (0.53, 7.13)		-	-	-
UFH + VKA	1.51 (0.53, 4.67)	1.36 (0.44, 4.48)	2.53 (0.76, 8.93)	1.34 (0.90, 2.01)		-	-
Apixaban	0.90 (0.49, 1.63)	0.80 (0.39, 1.65)	1.50 (0.65, 3.44)	0.79 (0.21, 2.82)	0.59 (0.17, 1.97)		-
Dabigatran	0.84 (0.37, 1.90)	0.75 (0.30, 1.87)	1.41 (0.51, 3.83)	0.74 (0.17, 2.99)	0.56 (0.14, 2.11)	0.94 (0.34, 2.59)	

Major-bleeding (during treatment period plus wash-out period of up to 7 days post-treatment cessation)

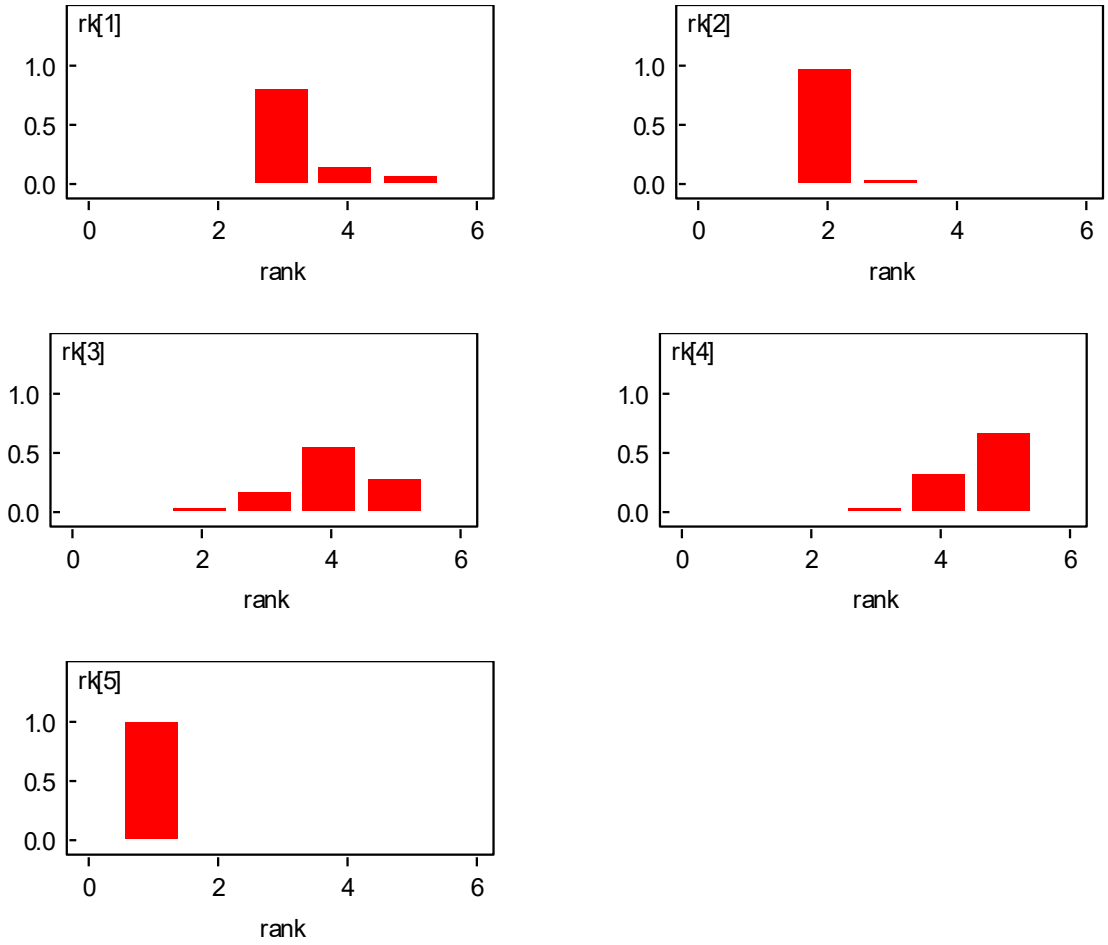
Network diagram

Figure 116 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



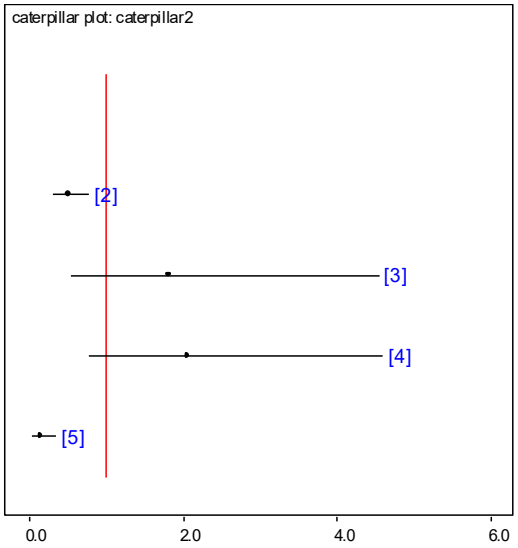
Rank probability histograms

Figure 117 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = Rivaroxaban, group 3 = fondaparinux+VKA, group 4 = UFH+VKA. Rank 1 is best.)



Caterpillar plot

Figure 118 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = Rivaroxaban, group 3 = fondaparinux+VKA, group 4 = UFH+VKA. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 83 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	Rivaroxaban	Fondaparinux+VKA	UFH+VKA	Apixaban
LMWH + VKA		0.49 (0.31, 0.78)	-	1.69 (0.70, 4.17)	0.15 (0.05, 0.44)
Rivaroxaban	0.49 (0.31, 0.78)		-	-	-
Fondaparinux + VKA	1.56 (0.55, 4.55)	3.18 (1.02, 10.29)		1.18 (0.67, 2.08)	-
UFH+VKA	1.84 (0.78, 4.60)	3.76 (1.41, 10.56)	1.18 (0.67, 2.11)		0.18 (0.01, 3.72)
Apixaban	0.13 (0.04, 0.35)	0.27 (0.07, 0.81)	0.08 (0.02, 0.35)	0.07 (0.02, 0.27)	

Initial treatment of VTE in people aged 65 years or older

The following tables and figures are based on the NMA model data developed by NICE using evidence from RCTs comparing anticoagulants for the treatment of VTE. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 84.

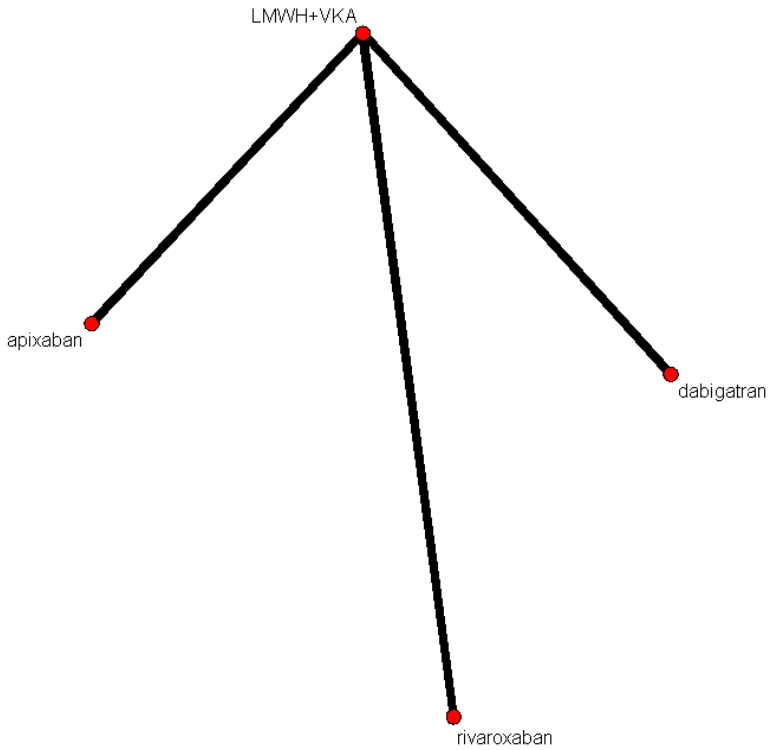
Table 84: Venous thromboembolism: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
4	VTE-recurrence	FE	53.58	11.04	8	-	FE
		RE	53.58	7.46		1.30 (0.06, 4.69)	

VTE-recurrence (during treatment period)

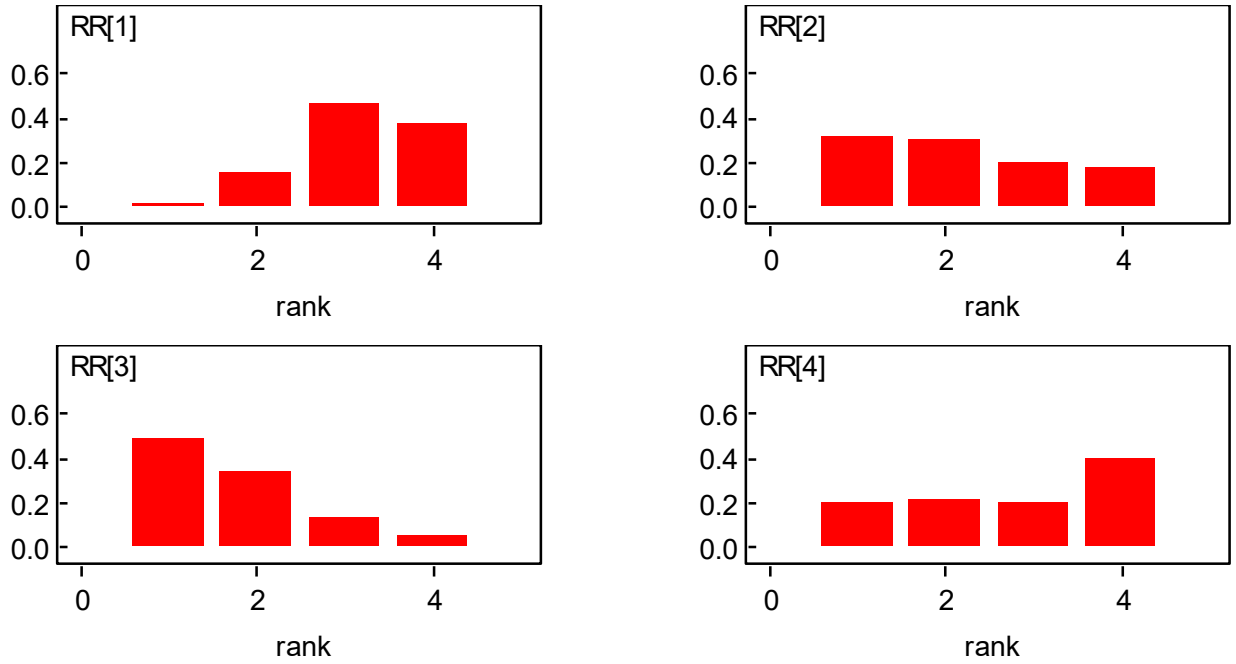
Network diagram

Figure 119 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



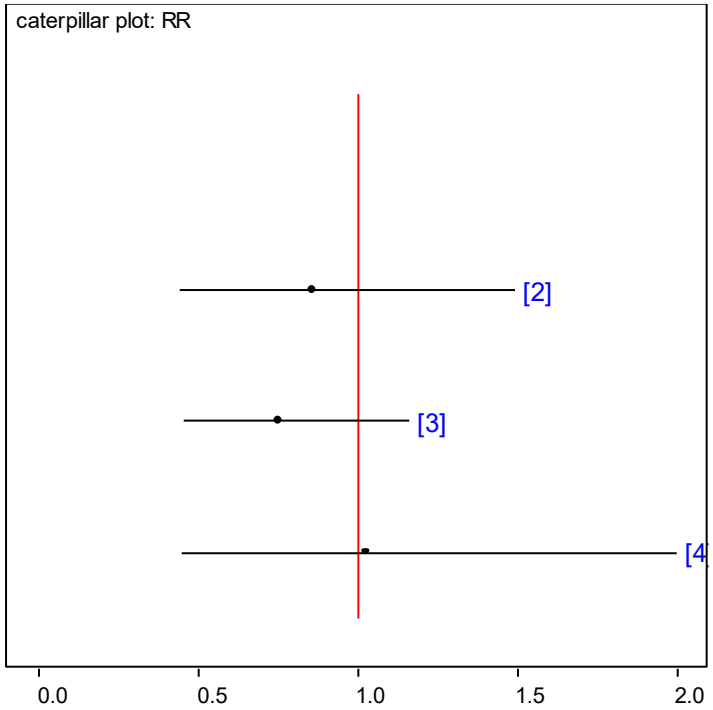
Rank probability histograms

Figure 120 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 =apixaban, group 3 = rivaroxaban, group 4 = dabigatran. Rank 1 is best.)



Caterpillar plot

Figure 121 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 = apixaban, group 3 = rivaroxaban, group 4 = dabigatran. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 85 Relative effectiveness of all pairwise combinations. (Upper diagonal: risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	**Apixaban**	**Rivaroxaban**	**Dabigatran**
LMWH + VKA		0.82 (0.46, 1.48)	0.73 (0.46, 1.17)	0.96 (0.47, 1.97)
Apixaban	0.83 (0.46, 1.44)		-	-
Rivaroxaban	0.75 (0.48, 1.15)	0.89 (0.44, 1.85)		-
Dabigatran	0.96 (0.47, 1.86)	1.15 (0.47, 2.78)	1.28 (0.56, 2.86)	

Initial treatment of VTE in people with obesity

The following tables and figures are based on the NMA model data developed by NICE using evidence from RCTs comparing anticoagulants for the treatment of VTE in people with obesity (BMI ≥30 kg/m^2). The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 86Table 81.

Table 86: Venous thromboembolism: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

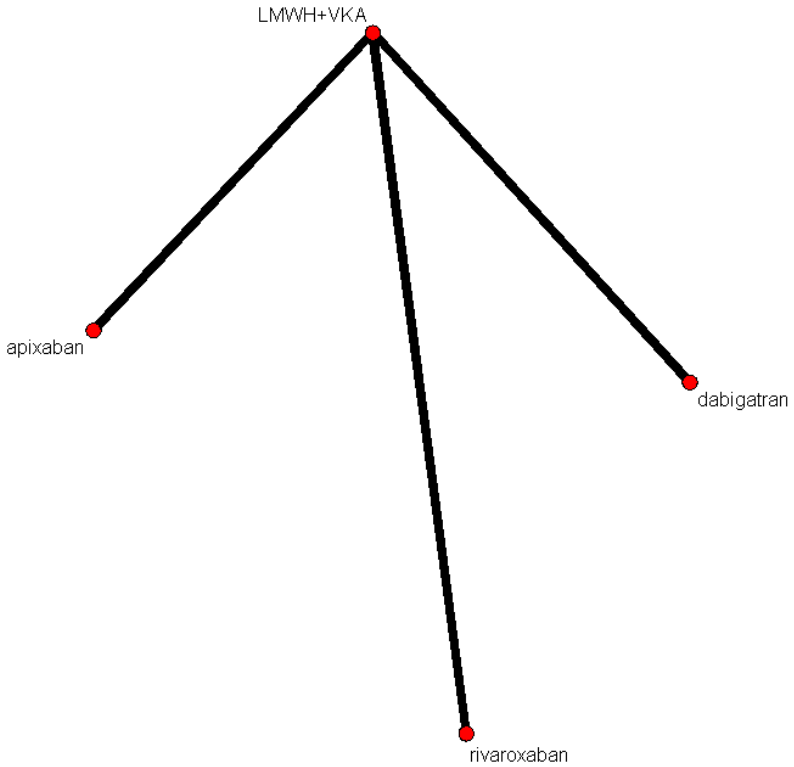
Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
3	VTE-recurrence	FE	40.23	5.43	6	-	FE
		RE	40.18	5.39		2.49 (0.13, 4.88)	

* Studies with zero events in either arm had 0.5 added to the event rate for both arms and 1 added to the total population for both arms, this was only done in instances when the model was unable to run (or was uninterpretable in its output).

VTE-recurrence (during treatment period)

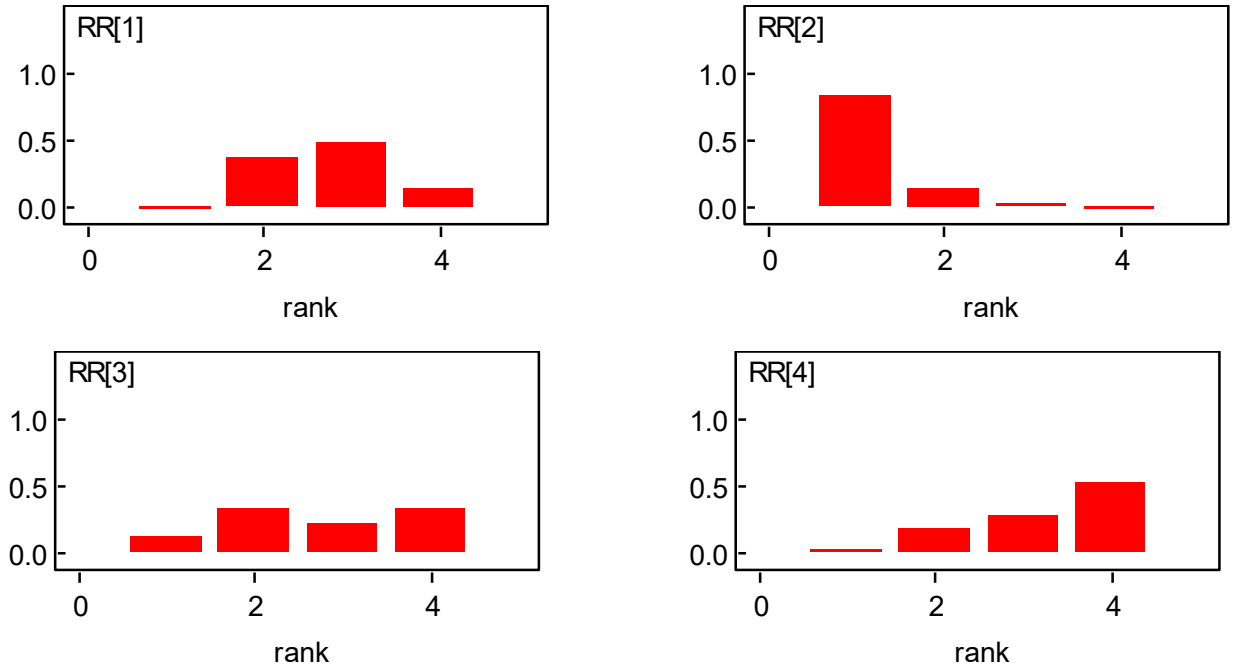
Network diagram

Figure 122 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



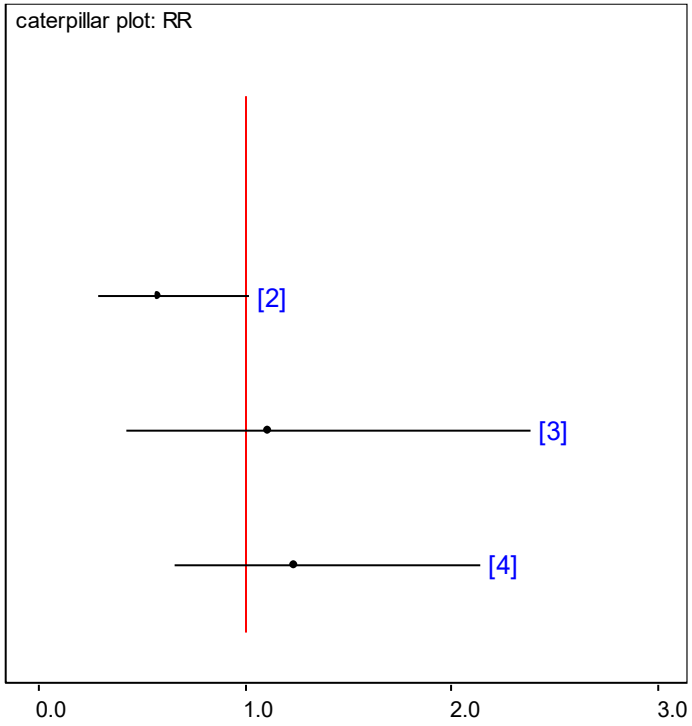
Rank probability histograms

Figure 123 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 =apixaban group 3 = rivaroxaban, group 4 = dabigatran. Rank 1 is best.)



Caterpillar plot

Figure 124 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (Group 1= LMWH+VKA, group 2 =apixaban group 3= rivaroxaban, group 4 = dabigatran. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 87 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	LMWH + VKA	**Apixaban**	**Rivaroxaban**	**Dabigatran**
LMWH + VKA		0.57 (0.31, 1.04)	1.02 (0.44, 2.34)	1.18 (0.67, 2.07)
Apixaban	0.56 (0.30, 1.02)		-	-
Rivaroxaban	1.01 (0.43, 2.31)	1.81 (0.64, 5.08)		-
Dabigatran	1.18 (0.67, 2.08)	2.10 (0.92, 4.92)	1.17 (0.43, 3.23)	

Initial treatment of VTE in people with cancer

The following tables and figures are based on the NMA models using evidence from RCTs comparing anticoagulants for the initial treatment of VTE (DVT and/or PE) in people with cancer. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 88.

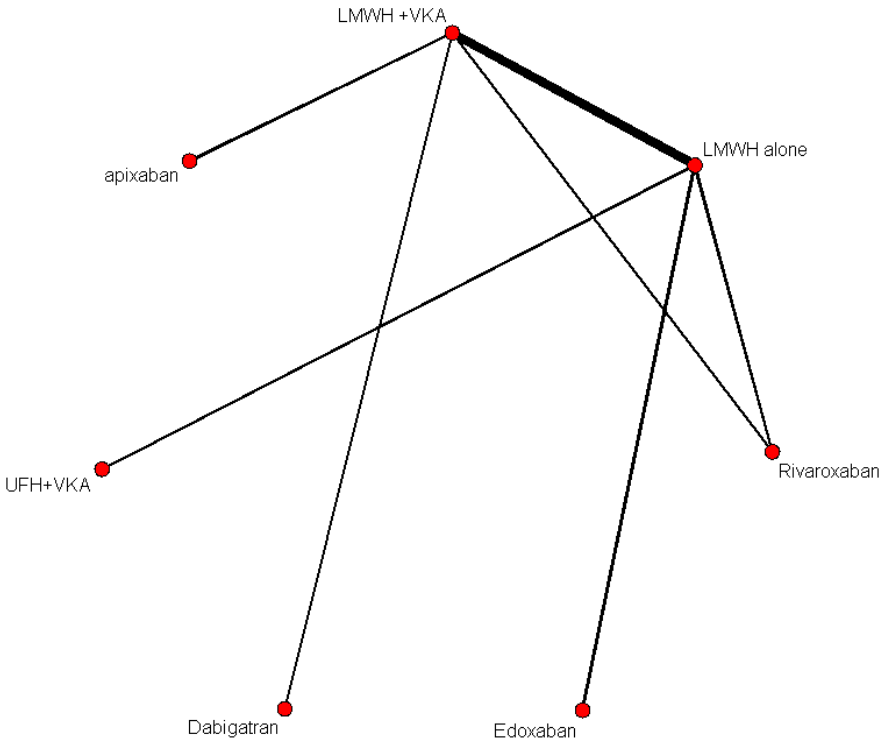
Table 88: Venous thromboembolism with cancer: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
10	VTE-recurrence	FE	46.15	12.12	14	-	FE
		RE	47.52	11.98		0.31 (0.02, 1.41)	
10	Major bleeding	FE	80.99	21.09	16	-	FE
		RE	79.58	16.42		0.75 (0.07, 1.84)	
7	CRNMB	FE	68.67	12.18	12	-	FE
		RE	68.84	11.50		0.70 (0.03, 1.91)	
9	All-cause mortality	FE	67.41	14.08	14	-	FE
		RE	69.01	13.75		0.17 (0.01, 1.04)	

VTE-recurrence (during study period)

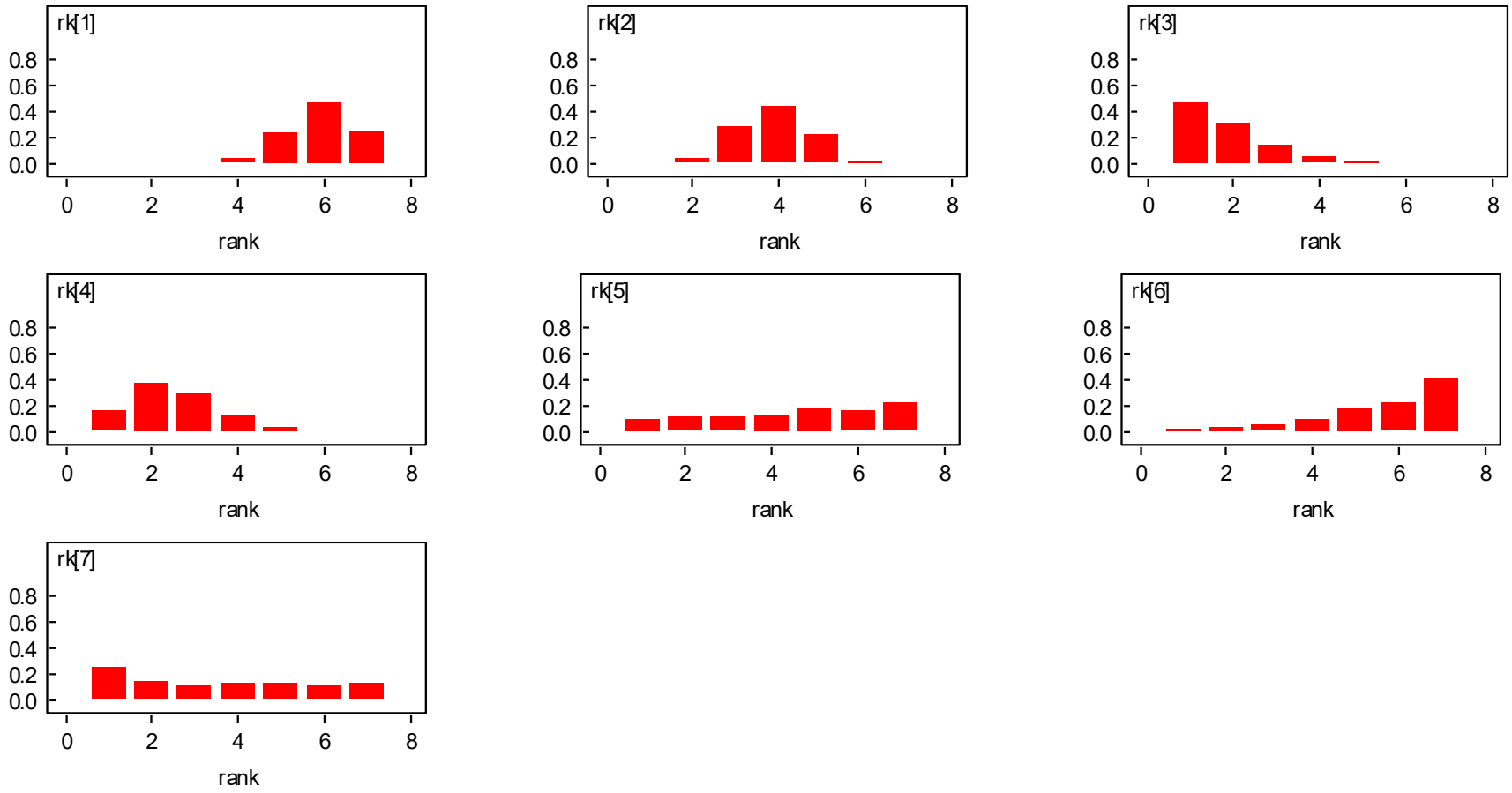
Network diagram

Figure 125 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



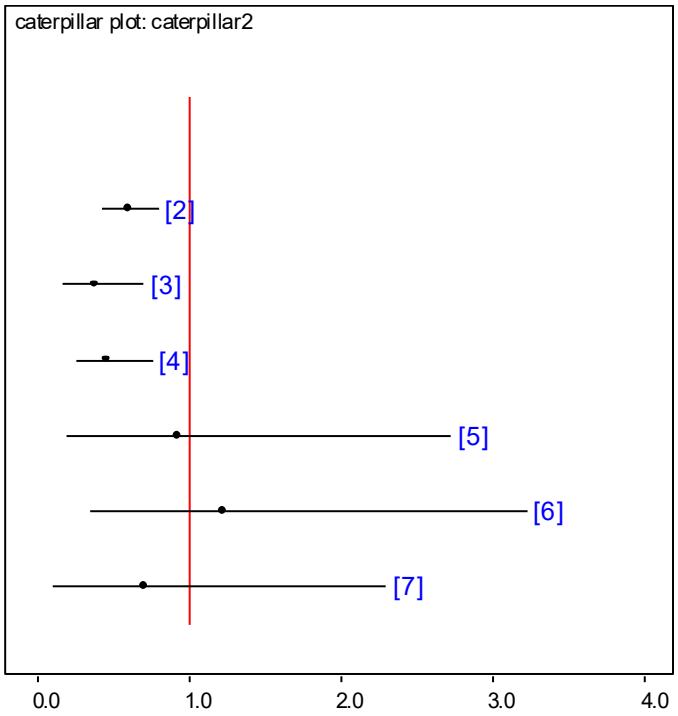
Rank probability histograms

Figure 126 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = LMWH alone, group 3 = rivaroxaban, group 4= edoxaban, group 5= dabigatran, group 6 = UFH+VKA, group 7= apixaban. Rank 1 is best.)



Caterpillar plot

Figure 127 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = LMWH alone, group 3 = rivaroxaban, group 4= edoxaban, group 5= dabigatran, group 6 = UFH+VKA, group 7= apixaban. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

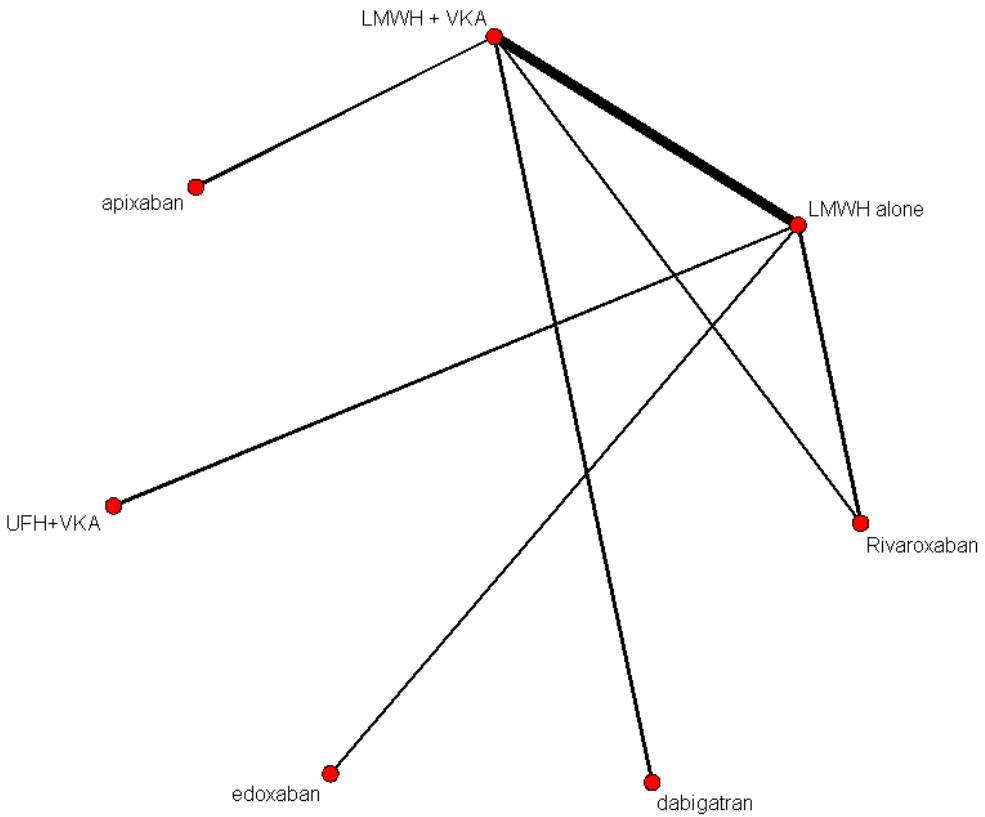
Table 89 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH+VKA	LMWH alone	rivaroxaban	edoxaban	dabigatran	UFH+VKA	apixaban
LMWH+VKA		0.56 (0.41, 0.78)	0.62 (0.21, 1.81)	-	0.74 (0.20, 2.72)	-	0.57 (0.14, 2.38)
LMWH alone	0.59 (0.43, 0.80)		0.43 (0.19, 0.98)	0.75 (0.48, 1.17)	-	1.70 (0.62, 4.69)	-
rivaroxaban	0.35 (0.18, 0.70)	0.60 (0.31, 1.16)			-	-	-
edoxaban	0.44 (0.26, 0.76)	0.75 (0.48, 1.17)	1.25 (0.56, 2.79)		-	-	-
dabigatran	0.74 (0.20, 2.73)	1.25 (0.33, 4.77)	2.08 (0.48, 9.09)	1.66 (0.40, 6.84)		-	-
UFH+VKA	1.03 (0.36, 3.23)	1.74 (0.63, 5.24)	2.92 (0.86, 10.53)	2.33 (0.77, 7.63)	1.41 (0.26, 7.83)		-
apixaban	0.54 (0.10, 2.30)	0.91 (0.17, 4.04)	1.53 (0.26, 7.62)	1.22 (0.22, 5.78)	0.73 (0.09, 5.13)	0.52 (0.07, 3.19)	

Major bleeding (during on-treatment period)

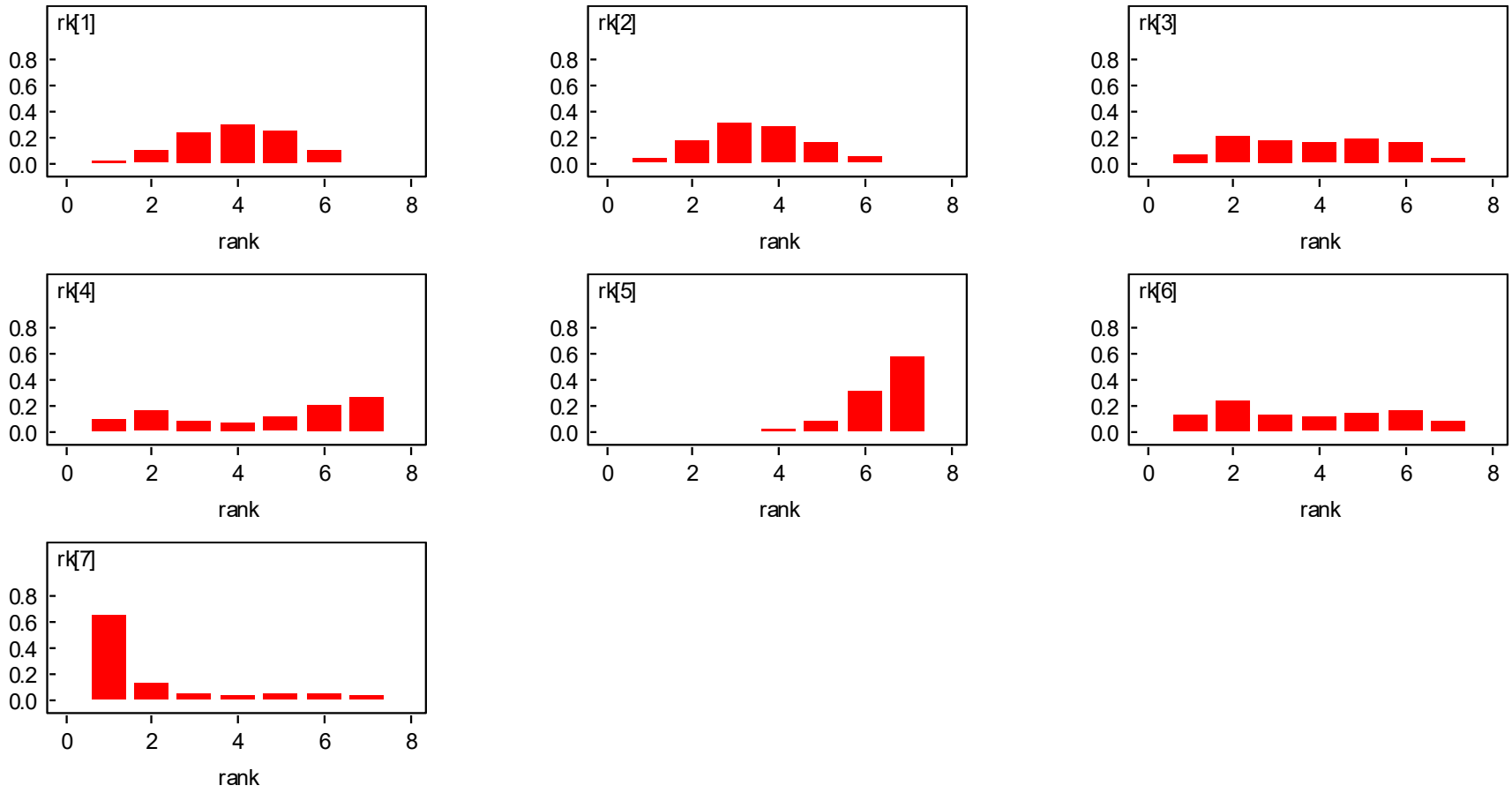
Network diagram

Figure 128 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



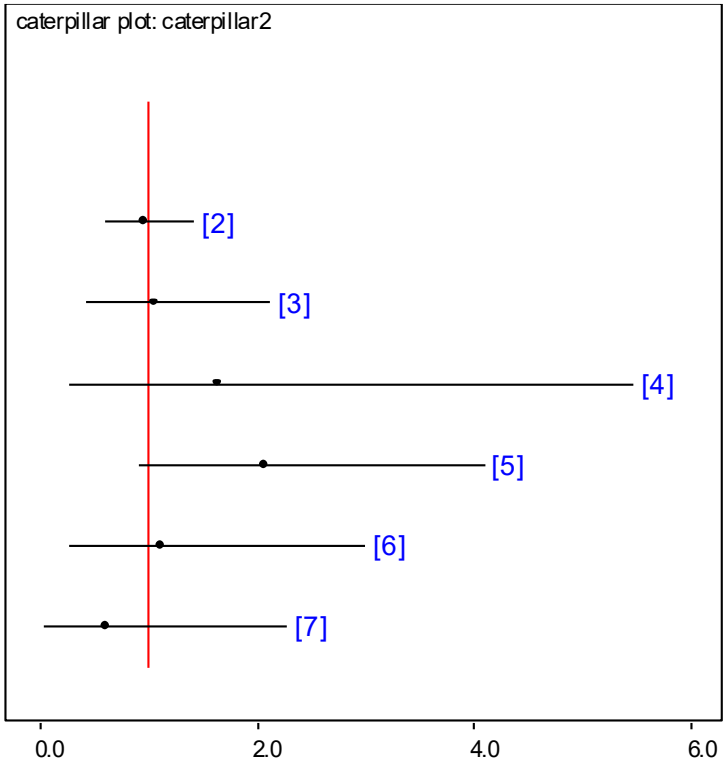
Rank probability histograms

Figure 129 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = LMWH alone, group 3 = rivaroxaban, group 4= dabigatran, group 5 = edoxaban, group 6= UFH+VKA, group 7=apixaban. Rank 1 is best.)



Caterpillar plot

Figure 130 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = LMWH alone, group 3 = rivaroxaban, group 4= dabigatran, group 5 = edoxaban, group 6= UFH+VKA, group 7=apixaban. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

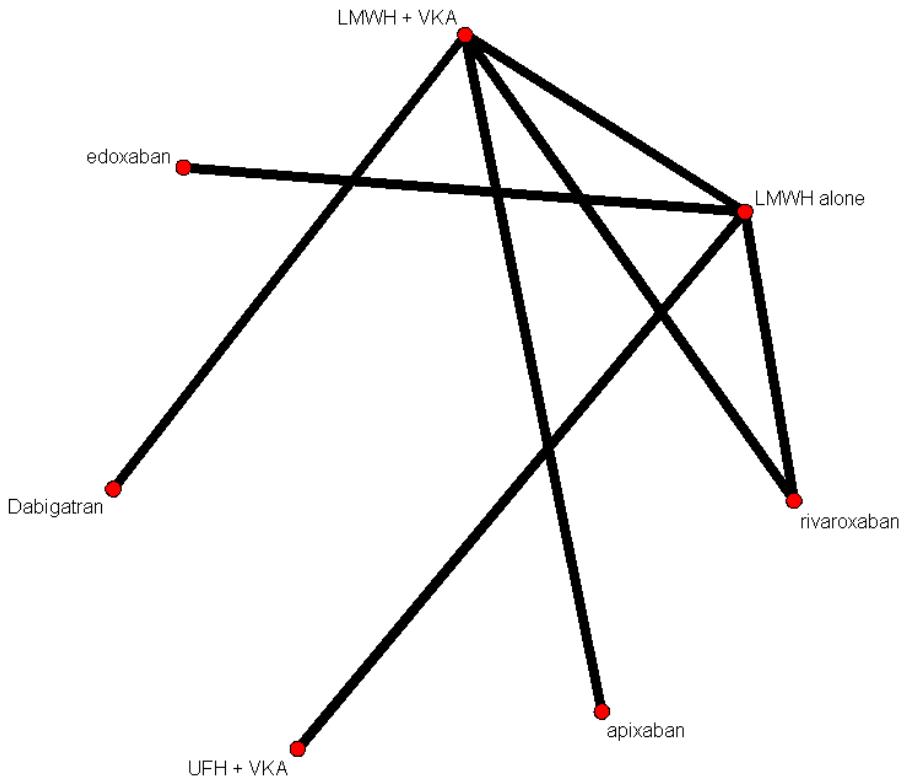
Table 90 Relative effectiveness of all pairwise combinations. (Upper diagonal: Hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH+VKA	LMWH alone	rivaroxaban	dabigatran	edoxaban	UFH+VKA	apixaban
LMWH+VKA		1.04 (0.65, 1.67)	0.47 (0.15, 1.46)	1.23 (0.28, 5.45)	-	-	0.45 (0.08, 2.48)
LMWH alone	0.93 (0.61, 1.43)		1.83 (0.68, 4.94)	-	2.04 (1.12, 3.72)	1.00 (0.35, 2.85)	-
rivaroxaban	0.97 (0.45, 2.14)	1.05 (0.49, 2.27)		-	-	-	-
dabigatran	1.23 (0.28, 5.44)	1.32 (0.28, 6.20)	1.27 (0.24, 6.83)		-	-	-
edoxaban	1.92 (0.93, 4.11)	2.07 (1.15, 3.87)	1.98 (0.74, 5.33)	1.57 (0.30, 8.24)		-	-
UFH+VKA	0.93 (0.29, 3.00)	1.00 (0.34, 2.98)	0.95 (0.25, 3.60)	0.75 (0.11, 5.01)	0.48 (0.14, 1.66)		-
apixaban	0.41 (0.05, 2.30)	0.45 (0.05, 2.59)	0.42 (0.05, 2.82)	0.33 (0.03, 3.28)	0.21 (0.02, 1.39)	0.44 (0.04, 3.58)	

Clinically relevant non-major bleeding (during on-treatment period)

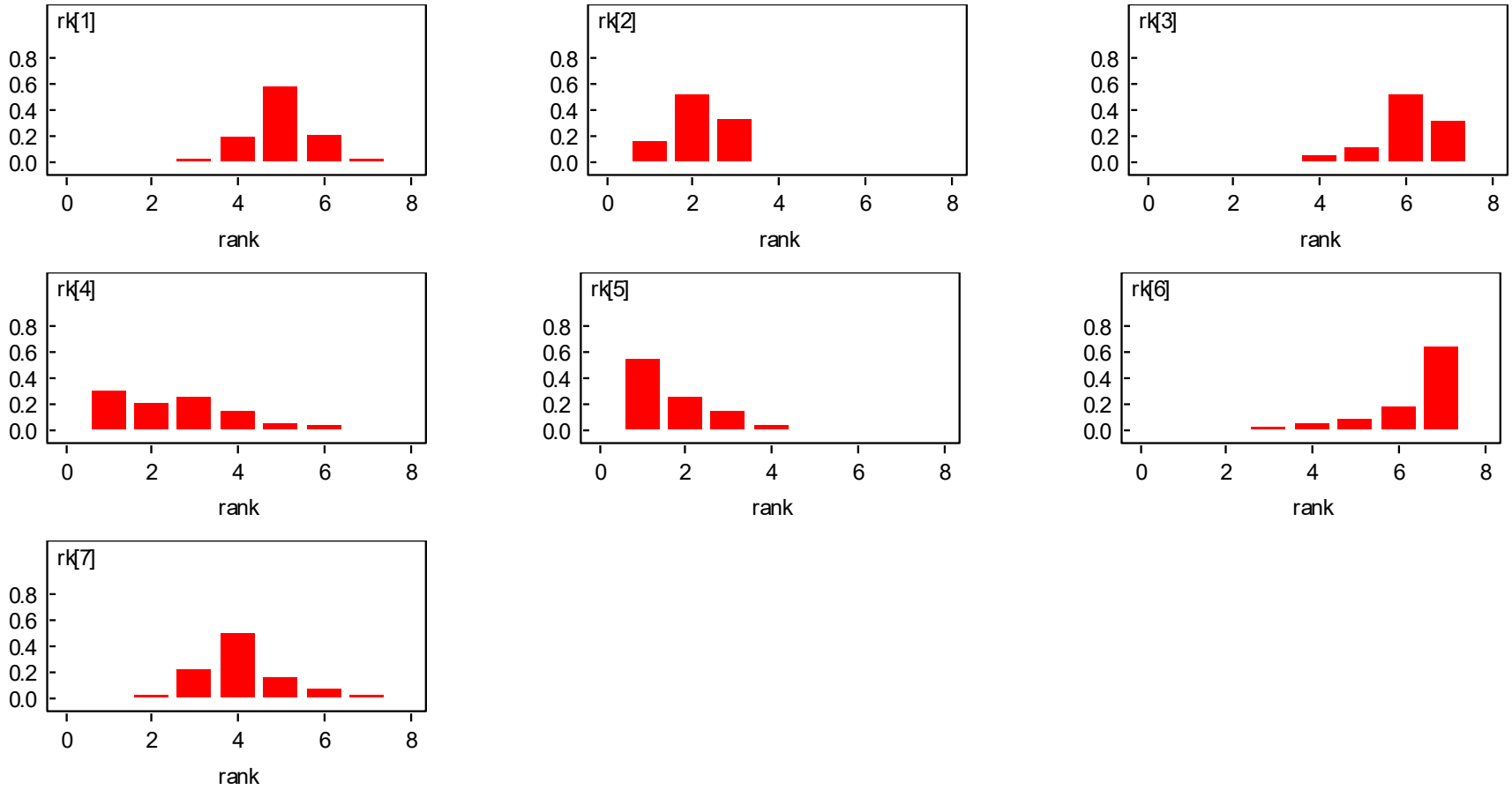
Network diagram

Figure 131 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



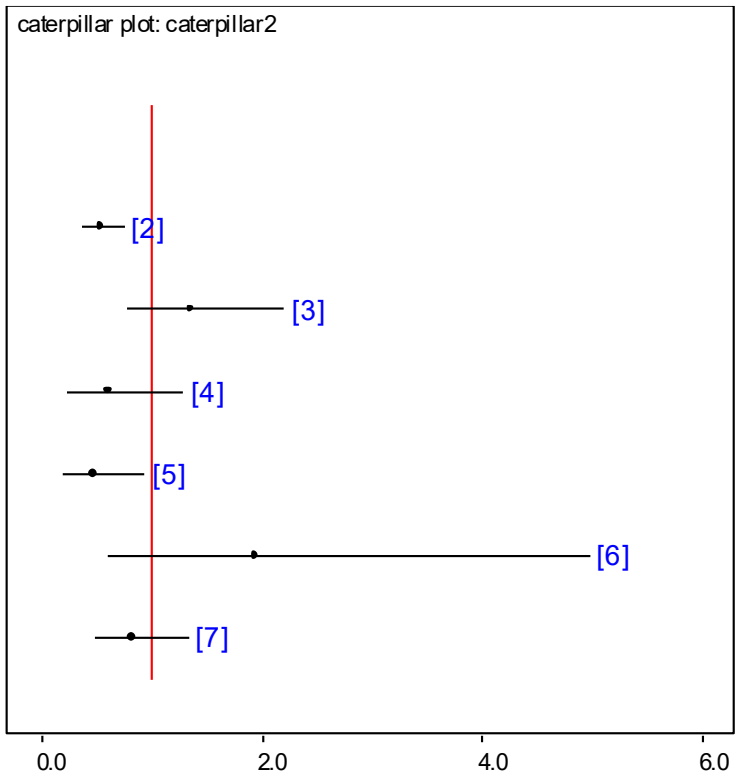
Rank probability histograms

Figure 132 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = LMWH alone, group 3 = rivaroxaban, group 4 = apixaban, group 5 = UFH+VKA, group 6= dabigatran, group 7=edoxaban. Rank 1 is best.)



Caterpillar plot

Figure 133 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. group 2 = LMWH alone, group 3 = rivaroxaban, group 4 = apixaban, group 5 = UFH+VKA, group 6= dabigatran, group 7=edoxaban. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

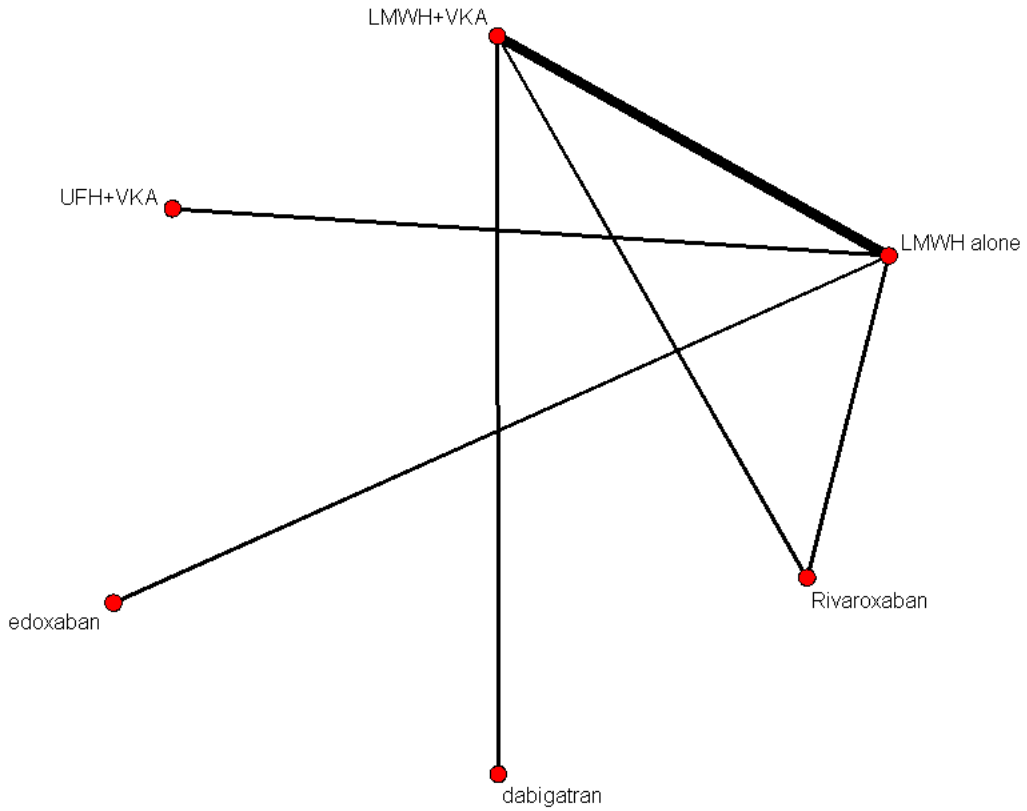
Table 91 Relative effectiveness of all pairwise combinations. (Upper diagonal: Hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH+VKA	**LMWH alone**	**rivaroxaban**	**apixaban**	**UFH+VKA**	**dabigatran**	**edoxaban**
LMWH+VKA		0.58 (0.40, 0.84)	1.05 (0.58, 1.90)	0.57 (0.25, 1.31)	-	1.62 (0.59, 4.45)	-
LMWH alone	0.53 (0.38, 0.76)		3.76 (1.63, 8.68)	-	0.84 (0.44, 1.60)	-	1.50 (1.04, 2.16)
rivaroxaban	1.31 (0.79, 2.21)	2.46 (1.43, 4.26)		-	-	-	-
apixaban	0.56 (0.23, 1.29)	1.05 (0.40, 2.60)	0.43 (0.15, 1.13)		-	-	-
UFH+VKA	0.44 (0.21, 0.94)	0.84 (0.43, 1.60)	0.34 (0.14, 0.79)	0.80 (0.26, 2.52)		-	-
dabigatran	1.66 (0.61, 4.98)	3.11 (1.07, 9.82)	1.27 (0.41, 4.23)	2.99 (0.80, 11.94)	3.73 (1.06, 14.07)		-
edoxaban	0.80 (0.48, 1.34)	1.50 (1.05, 2.18)	0.61 (0.32, 1.18)	1.44 (0.54, 4.00)	1.80 (0.85, 3.84)	0.48 (0.14, 1.50)	

All-cause mortality (during study period)

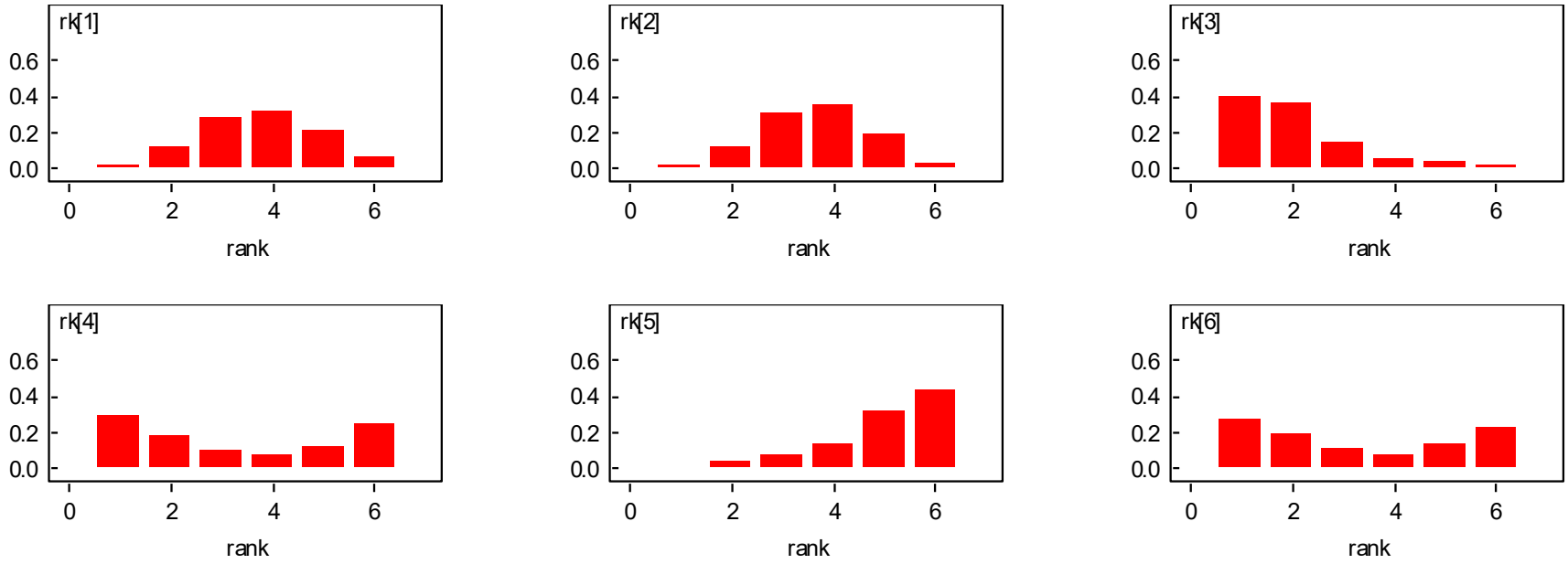
Network diagram

Figure 134 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



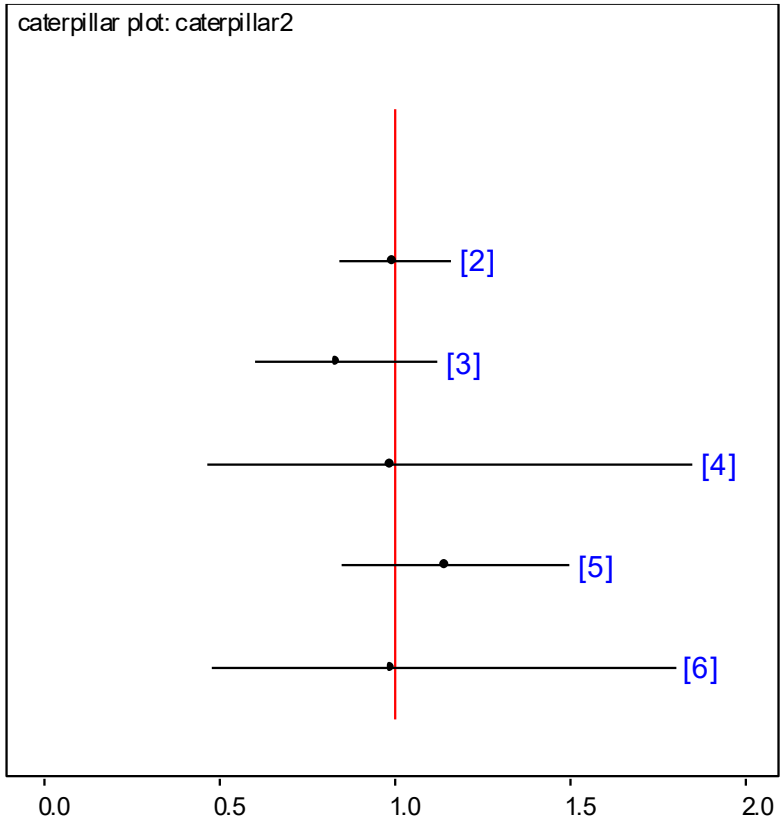
Rank probability histograms

Figure 135 Probability of the treatment assuming each treatment rank. (Group 1= LMWH+VKA, group 2 = LMWH alone, group 3 = rivaroxaban, group 4= dabigatran, group 5= edoxaban, group 6 = UFH+VKA. Rank 1 is best.)



Caterpillar plot

Figure 136 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = LMWH alone, group 3 = rivaroxaban, group 4= dabigatran, group 5= edoxaban, group 6 = UFH+VKA. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

Table 92 Relative effectiveness of all pairwise combinations. (Upper diagonal: Hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

	LMWH+VKA	LMWH alone	rivaroxaban	dabigatran	edoxaban	UFH+VKA
LMWH+VKA		1.00 (0.85, 1.18)	0.82 (0.52, 1.30)	0.93 (0.47, 1.85)	-	-
LMWH alone	0.99 (0.85, 1.16)		0.84 (0.57, 1.23)	-	1.14 (0.90, 1.45)	0.94 (0.50, 1.77)
Rivaroxaban	0.82 (0.60, 1.12)	0.83 (0.61, 1.13)		-	-	-
Dabigatran	0.93 (0.47, 1.85)	0.94 (0.46, 1.90)	1.13 (0.53, 2.40)		-	-
edoxaban	1.13 (0.85, 1.50)	1.14 (0.90, 1.45)	1.37 (0.93, 2.02)	1.22 (0.58, 2.57)		-
UFH+VKA	0.94 (0.48, 1.80)	0.94 (0.50, 1.79)	1.14 (0.56, 2.30)	1.01 (0.39, 2.60)	0.83 (0.42, 1.63)	

Extended therapy for VTE

The following tables and figures are based on the NMA models using evidence from RCTs comparing anticoagulants for the extended therapy of VTE (DVT and/or PE) in people who have already received at least 3 months of anticoagulation therapy. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 93.

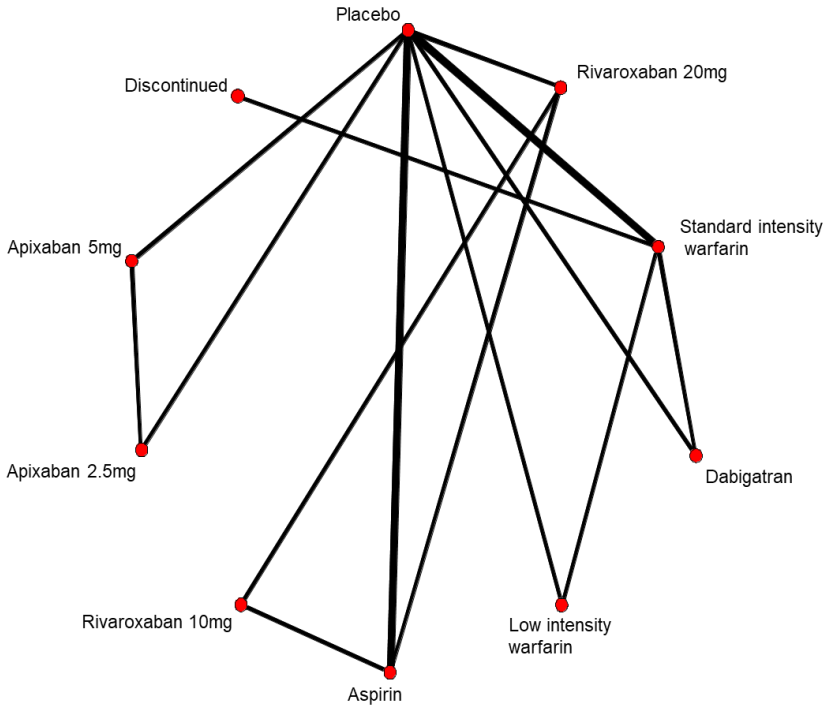
Table 93: Venous thromboembolism (extended therapy): model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
13	VTE-recurrence	FE	49.14	14.63	18	-	FE
		RE	51.08	14.87		0.20 (0.01, 0.94)	
13	Major bleeding	FE	87.15	24.29	24	-	FE
		RE	87.26	22.66		0.94 (0.05, 1.94)	
7	CRNMB	FE	103.06	14.98	16	-	FE
		RE	104.46	15.16		0.80 (0.04, 4.23)	
11	All-cause mortality	FE	78.11	16.63	19	-	FE
		RE	79.73	17.11		0.37 (0.02, 1.62)	
5	VTE-related mortality	FE	51.62	11.74	12	-	FE
		RE	52.56	12.20		1.71 (0.07, 4.76)	

VTE-recurrence (during study period)

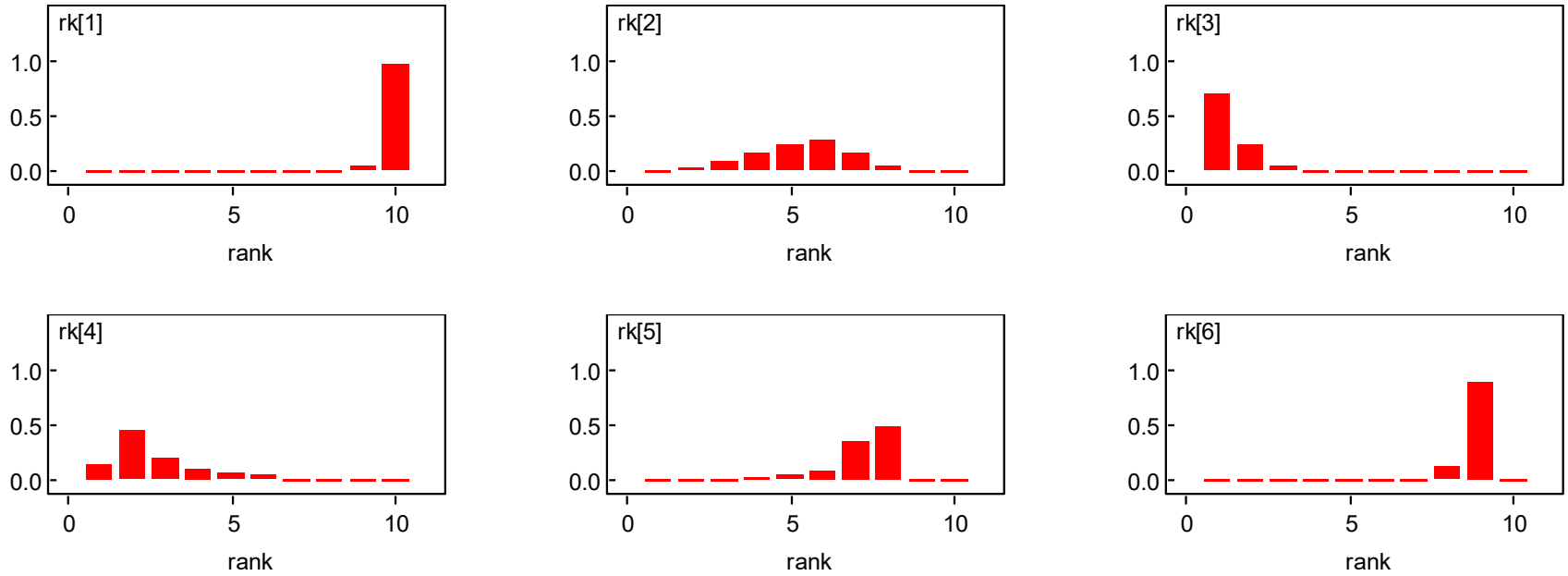
Network diagram

Figure 137 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

Figure 138 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = rivaroxaban 20mg, group 3 = warfarin INR 2.0-3.0, group 4= dabigatran, group 5= Warfarin INR 1.5-2.0, group 6 = aspirin 100mg, group 7 = rivaroxaban 10mg, group 8 = apixaban 2.5mg, group 9 = apixaban 5mg, group 10 = discontinuation of anticoagulation. Rank 1 is best.)



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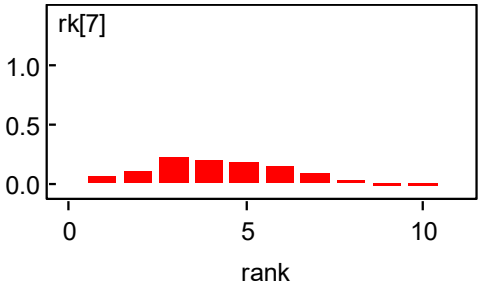
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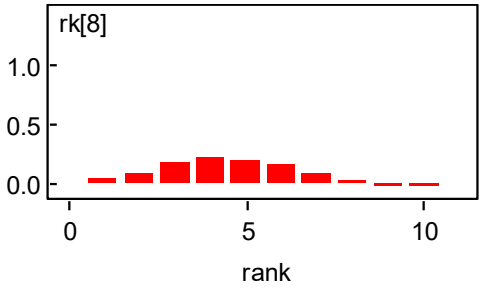
rank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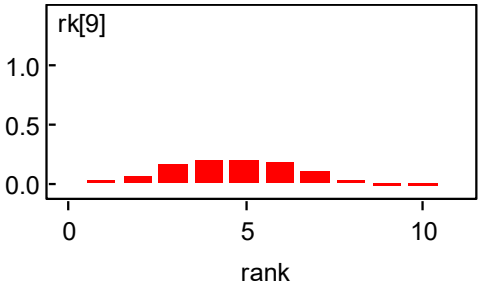
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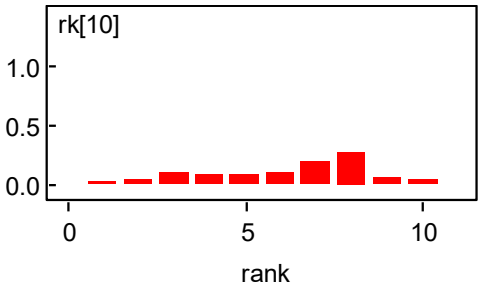
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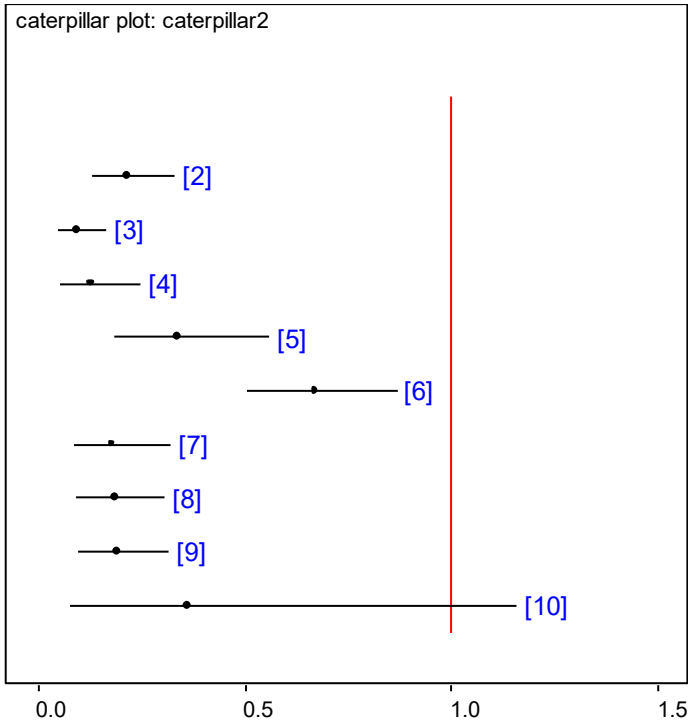
rank

Caterpillar plot

Figure 139 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. Group 2 = rivaroxaban 20mg, group 3 = warfarin INR 2.0-3.0, group 4= dabigatran, group 5= Warfarin INR 1.5-2.0, group 6 = aspirin 100mg, group 7 = rivaroxaban 10mg, group 8 = apixaban 2.5mg, group 9 = apixaban 5mg, group 10 = discontinuation of anticoagulation. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

Table 94 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

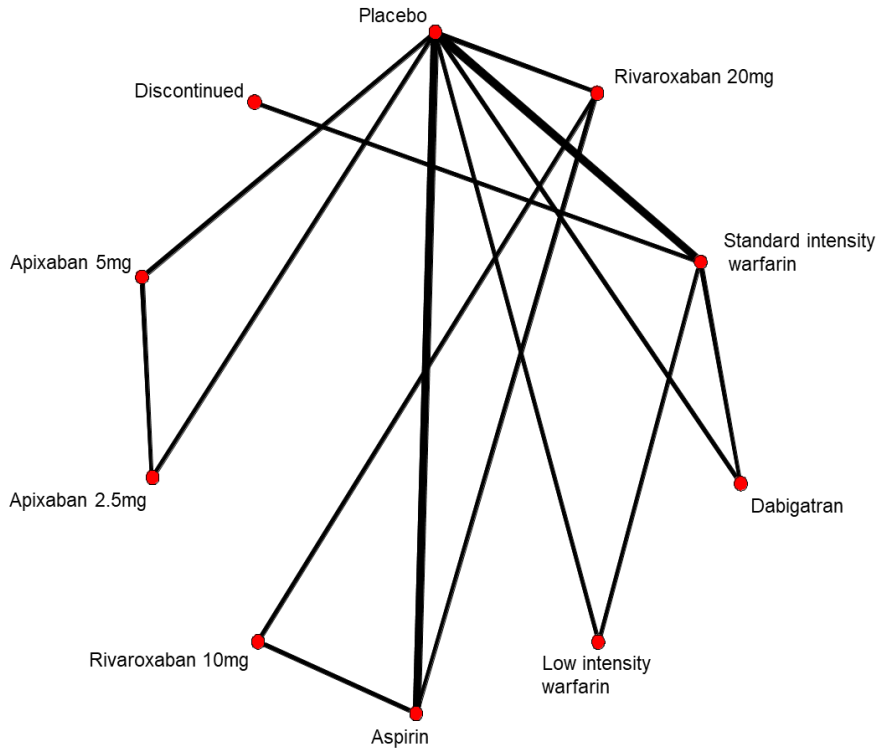
	Placebo	rivaroxaban 20mg	warfarin standard	dabigatran	warfarin low-intensity	Aspirin 100mg	Rivaroxaban 10 mg	Apixaban 2.5mg	Apixaban 5mg	Discontinued
Placebo		0.18 (0.09, 0.37)	0.09 (0.04, 0.20)	0.08 (0.02, 0.28)	0.36 (0.19, 0.68)	0.68 (0.51, 0.90)	-	0.18 (0.10, 0.32)	0.19 (0.11, 0.33)	-
Rivaroxaban 20mg	0.21 (0.13, 0.33)		-	-	-	2.94 (1.72, 5.00)	0.75 (0.36, 1.54)	-	-	-
warfarin standard	0.09 (0.05, 0.17)	0.43 (0.20, 0.93)		1.44 (0.78, 2.65)	2.78 (1.11, 7.14)	-	-	-	-	2.86 (0.91, 9.09)
dabigatran	0.12 (0.06, 0.25)	0.57 (0.24, 1.36)	1.31 (0.75, 2.30)		-	-	-	-	-	-
warfarin low-intensity	0.32 (0.18, 0.56)	1.55 (0.75, 3.20)	3.56 (1.84, 6.92)	2.72 (1.20, 6.10)		-	-	-	-	-
Aspirin 100mg	0.66 (0.51, 0.87)	3.18 (2.04, 4.98)	7.34 (3.79, 14.25)	5.59 (2.55, 12.19)	2.06 (1.11, 3.82)		0.26 (0.14, 0.48)	-	-	-
Rivaroxaban 10mg	0.17 (0.09, 0.32)	0.81 (0.41, 1.61)	1.88 (0.77, 4.52)	1.43 (0.53, 3.78)	0.53 (0.22, 1.24)	0.26 (0.14, 0.46)		-	-	-
apixaban 2.5mg	0.18 (0.10, 0.31)	0.85 (0.40, 1.76)	1.97 (0.83, 4.45)	1.49 (0.58, 3.75)	0.55 (0.24, 1.21)	0.27 (0.14, 0.49)	1.05 (0.43, 2.46)		1.03 (0.49, 2.17)	-
apixaban 5mg	0.18 (0.10, 0.32)	0.88 (0.41, 1.82)	2.03 (0.86, 4.60)	1.54 (0.60, 3.86)	0.57 (0.25, 1.24)	0.28 (0.14, 0.51)	1.08 (0.45, 2.54)	1.03 (0.49, 2.20)		

Discontinued	0.27 (0.08, 1.16)	1.32 (0.34, 6.00)	3.01 (1.01, 11.37)	2.31 (0.67, 9.63)	0.85 (0.23, 3.70)	0.41 (0.11, 1.79)	1.62 (0.39, 7.88)	1.55 (0.39, 7.34)	1.50 (0.38, 7.13)	

Major bleeding (during on-treatment period)

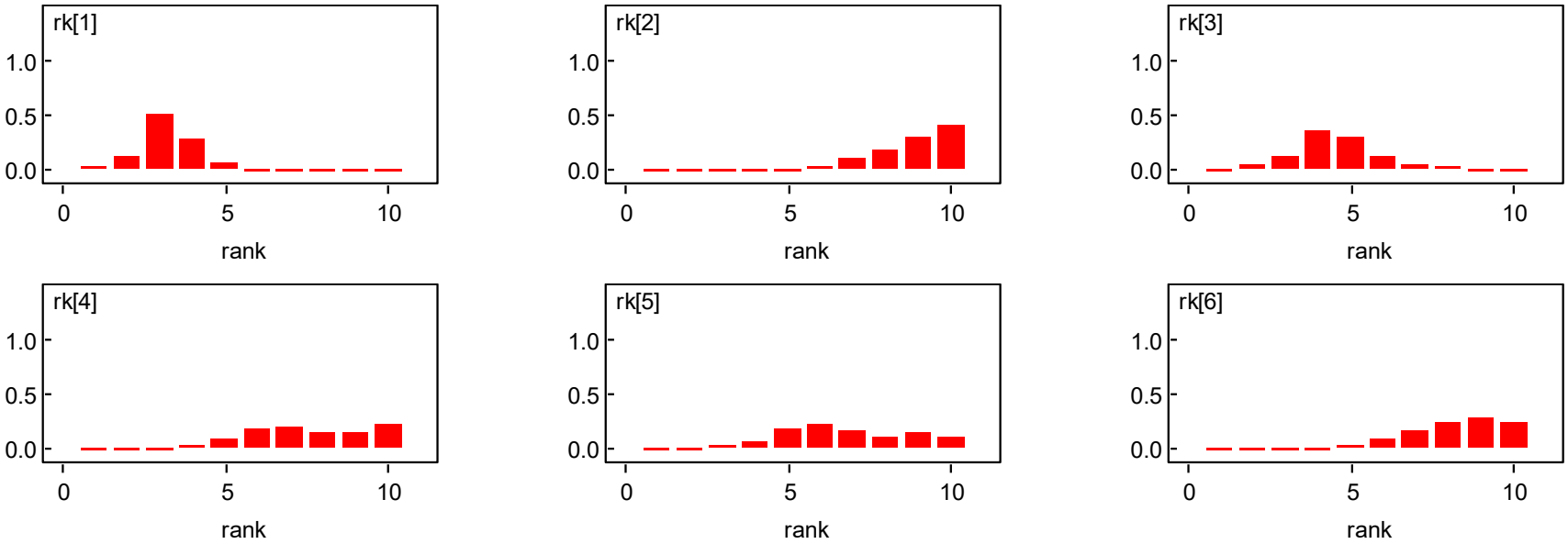
Network diagram

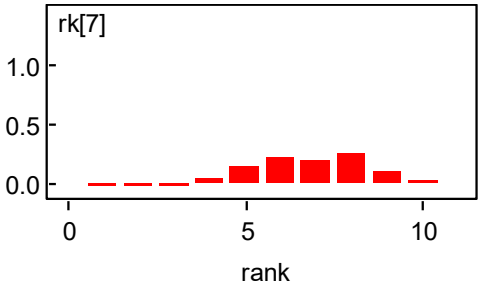
Figure 140 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



Rank probability histograms

Figure 141 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = warfarin INR 2.0-3.0, group 3 = aspirin 100mg, group 4 = rivaroxaban 20mg, group 5 = rivaroxaban 10mg, group 6= warfarin INR 1.5-2.0, group 7= dabigatran, group 8 = apixaban 2.5mg, group 9 = apixaban 5mg, group 10 = discontinuation of anticoagulation. Rank 1 is best.)

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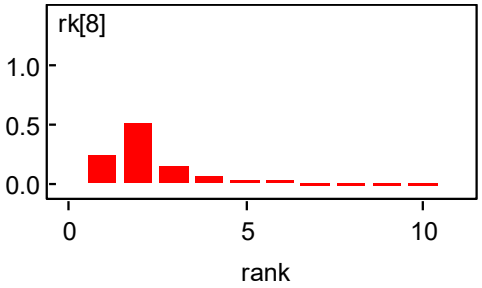
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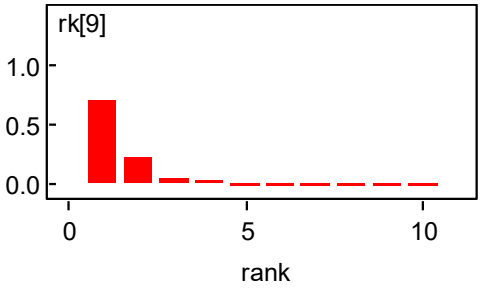
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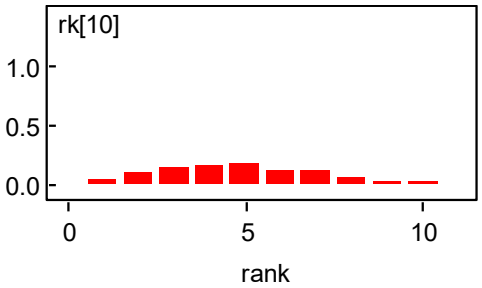
rank


rk[10]
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0.5
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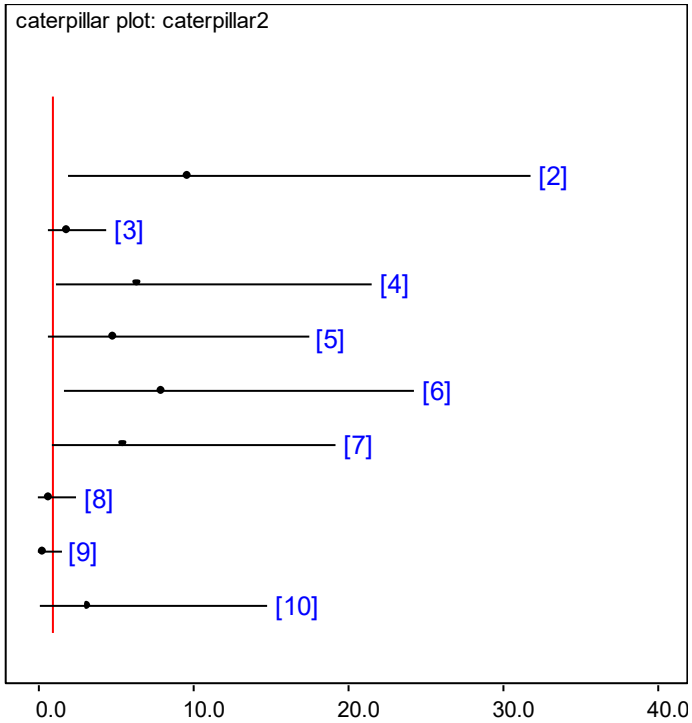
0
5
10
rank

Caterpillar plot

Figure 142 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = warfarin INR 2.0-3.0, group 3 = aspirin 100mg, group 4 = rivaroxaban 20mg, group 5 = rivaroxaban 10mg, group 6= warfarin INR 1.5-2.0, group 7= dabigatran, group 8 = apixaban 2.5mg, group 9 = apixaban 5mg, group 10 = discontinuation of anticoagulation. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

Table 95 Relative effectiveness of all pairwise combinations. (Upper diagonal: hazard ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. HRs greater than 1 favour the row defining treatment, HRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, HR less than 1 favour the row defining treatment. HRs greater than 1 favour the column defining treatment.)

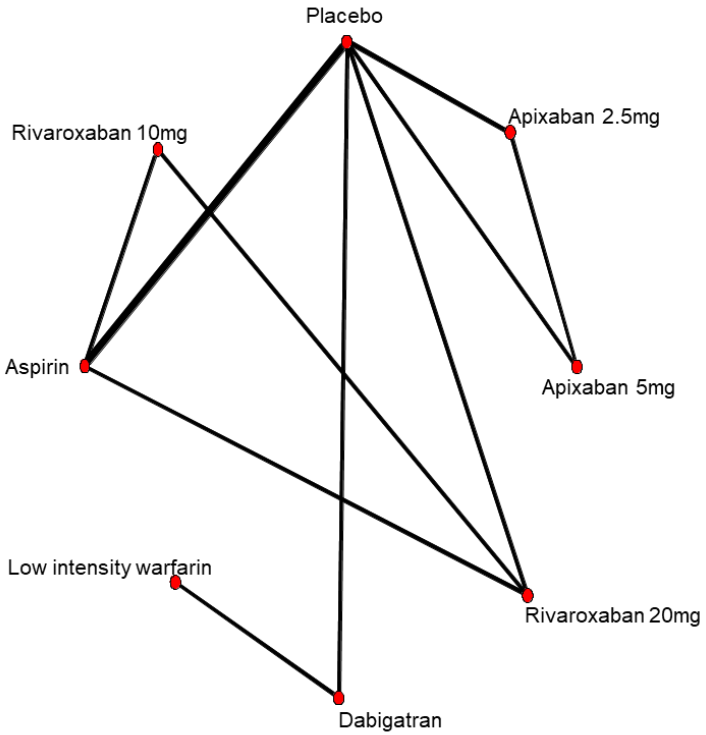
	Placebo	**warfarin standard**	**Aspirin 100mg**	**rivaroxaban 20mg**	**Rivaroxaban 10 mg**	**warfarin low-intensity**	**dabigatran**	**Apixaban 2.5mg**	**Apixaban 5mg**	**Discontinued**
Placebo		7.33 (0.90, 59.50)	-	8.91 (0.48, 165.48)	-	2.53 (0.49, 13.05)	4.87 (0.23, 101.39)	0.49 (0.09, 2.69)	0.25 (0.03, 2.28)	-
warfarin standard	7.17 (1.96, 31.85)		-	-	-	1.20 (0.44. 4.80)	0.52 (0.27, 1.01)	-	-	0.29 (0.06, 1.39)
Aspirin 100mg	1.60 (0.62, 4.43)	0.22 (0.04, 1.17)		2.01 (0.50, 8.06)	1.64 (0.39, 6.87)	-	-	-	-	-
Rivaroxaban 20mg	4.70 (1.19, 21.54)	0.65 (0.09, 4.80)	2.95 (0.87, 10.49)		0.81 (0.25, 2.70)	-	-	-	-	-
Rivaroxaban 10mg	3.39 (0.71, 17.51)	0.47 (0.05, 3.83)	2.11 (0.55, 8.42)	0.72 (0.22, 2.31)		-	-	-	-	-
warfarin low-intensity	6.21 (1.71, 24.31)	0.85 (0.33, 2.17)	3.87 (0.76, 20.30)	1.32 (0.18, 9.23)	1.83 (0.23, 14.53)		-	-	-	-

dabigatran	3.92 (0.96, 19.27)	0.55 (0.28, 1.05)	2.46 (0.43, 15.60)	0.84 (0.11, 6.90)	1.17 (0.13, 10.72)	0.64 (0.21, 2.01)		-	-	-
apixaban 2.5mg	0.45 (0.05, 2.51)	0.06 (0.00, 0.55)	0.28 (0.03, 1.99)	0.09 (0.01, 0.88)	0.13 (0.01, 1.37)	0.07 (0.01, 0.63)	0.11 (0.01, 1.08)		0.52 (0.05, 5.69)	-
apixaban 5mg	0.19 (0.01, 1.54)	0.03 (0.00, 0.32)	0.12 (0.00, 1.20)	0.04 (0.00, 0.51)	0.05 (0.00, 0.78)	0.03 (0.00, 0.37)	0.05 (0.00, 0.63)	0.43 (0.01, 5.49)		
Discontinued	1.79 (0.17, 14.84)	0.25 (0.03, 1.12)	1.11 (0.08, 11.51)	0.37 (0.02, 4.81)	0.52 (0.03, 7.33)	0.29 (0.03, 1.73)	0.46 (0.06, 2.36)	4.06 (0.22, 75.74)	9.80 (0.39, 474.20)	

Clinically relevant non-major bleeding (during on-treatment period)

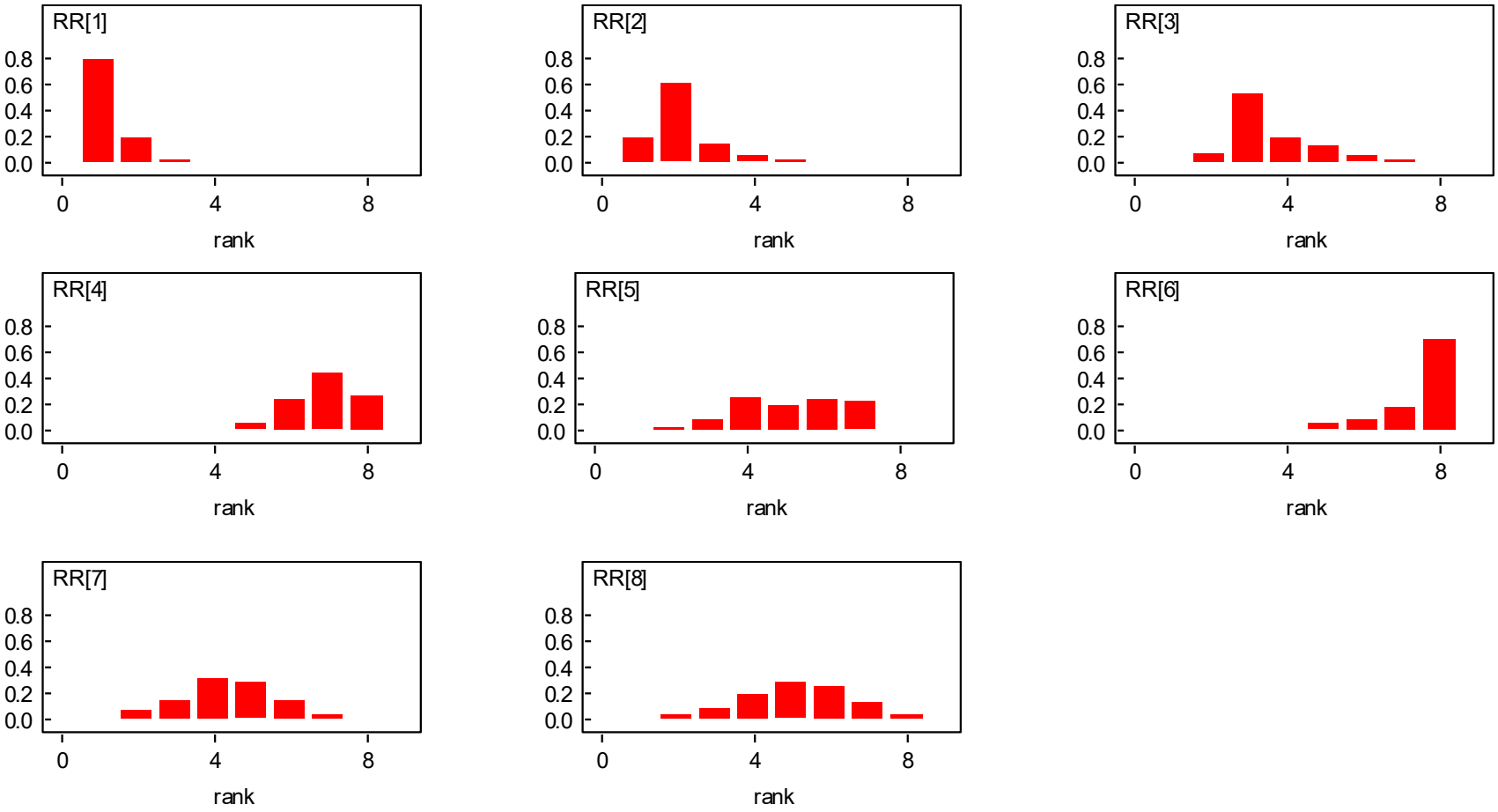
Network diagram

Figure 143 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



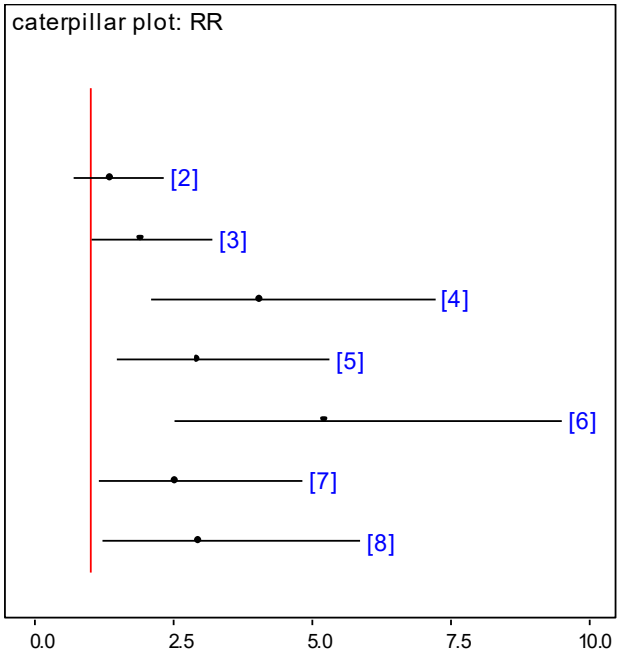
Rank probability histograms

Figure 144 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = apixaban 2.5mg, group 3= apixaban 5mg, group 4 = rivaroxaban 20mg, group 5= dabigatran, group 6= Warfarin INR 2.0-3.0, group 7=aspirin 100mg, group 8= rivaroxaban 10mg. Rank 1 is best.)



Caterpillar plot

Figure 145 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. group 2 = apixaban 2.5mg, group 3= apixaban 5mg, group 4 = rivaroxaban 20mg, group 5= dabigatran, group 6= Warfarin INR 2.0-3.0, group 7=aspirin 100mg, group 8= rivaroxaban 10mg. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

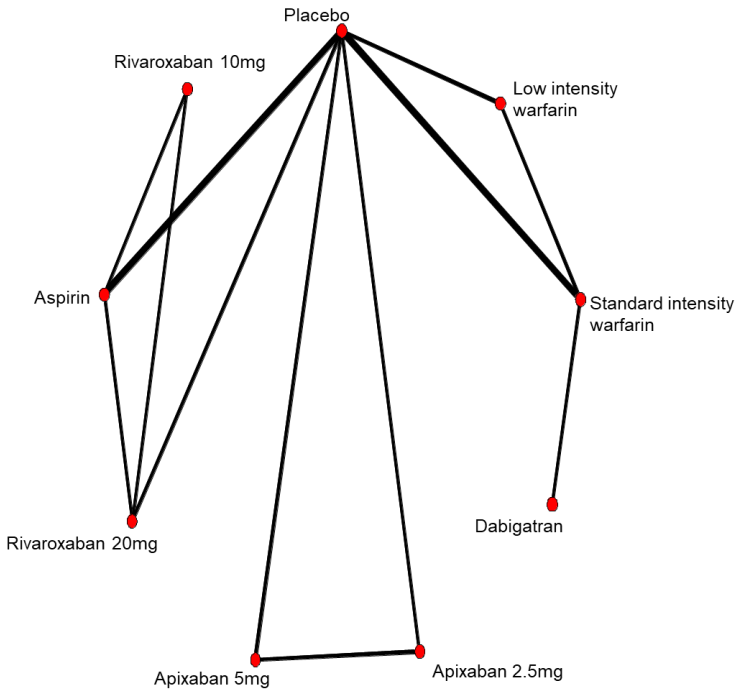
Table 96 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	placebo	apixaban 2.5mg	apixaban 5mg	Rivaroxaban 20mg	dabigatran	warfarin standard	aspirin 100mg	rivaroxaban 10mg
placebo		1.30 (0.72, 2.34)	1.82 (1.05, 3.17)	4.51 (2.01, 10.14)	2.75 (1.44, 5.27)	-	1.77 (0.60, 5.23)	-
apixaban 2.5mg	1.30 (0.72, 2.36)		1.41 (0.85, 2.33)	-	-	-	-	-
apixaban 5mg	1.83 (1.06, 3.21)	1.41 (0.86, 2.37)		-	-	-	-	-
rivaroxaban 20mg	3.84 (2.11, 7.23)	2.96 (1.27, 7.05)	2.09 (0.92, 4.84)		-	-	0.65 (0.37, 1.14)	0.72 (0.42, 1.23)
dabigatran	2.78 (1.50, 5.33)	2.14 (0.91, 5.16)	1.52 (0.66, 3.54)	0.73 (0.30, 1.75)		1.78 (1.35, 2.38)	-	-
warfarin standard	4.94 (2.55, 9.51)	3.80 (1.57, 9.20)	2.69 (1.14, 6.34)	1.29 (0.51, 3.12)	1.77 (1.34, 2.33)		-	-
aspirin 100mg	2.36 (1.18, 4.85)	1.82 (0.73, 4.63)	1.29 (0.53, 3.18)	0.62 (0.37, 1.01)	0.85 (0.33, 2.22)	0.48 (0.18, 1.28)		1.10 (0.61. 2.01)
rivaroxaban 10mg	2.73 (1.25, 5.89)	2.10 (0.78, 5.57)	1.49 (0.57, 3.84)	0.71 (0.42, 1.17)	0.98 (0.36, 2.67)	0.55 (0.20, 1.55)	1.15 (0.65, 2.03)	

All-cause mortality (during study period)

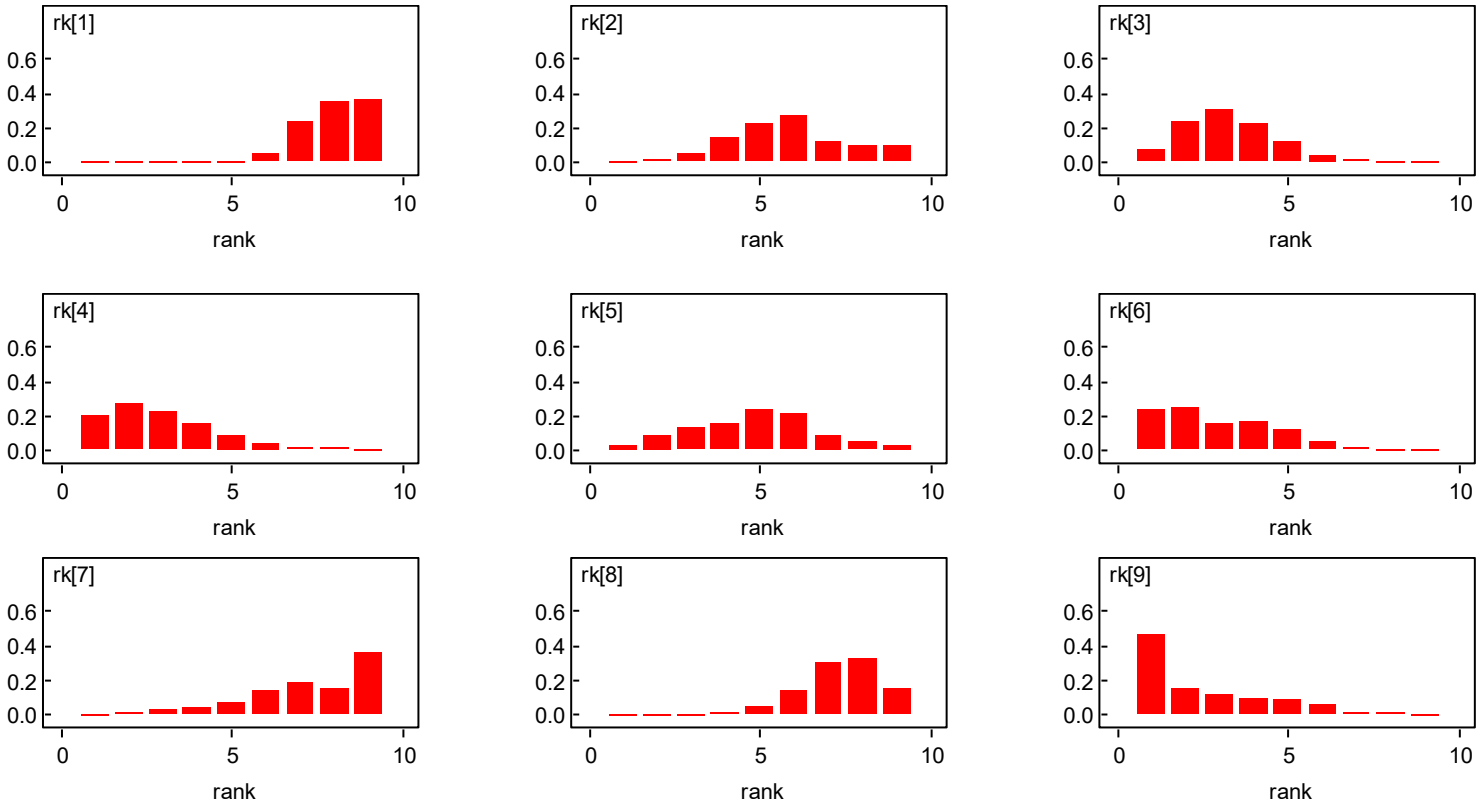
Network diagram

Figure 146 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



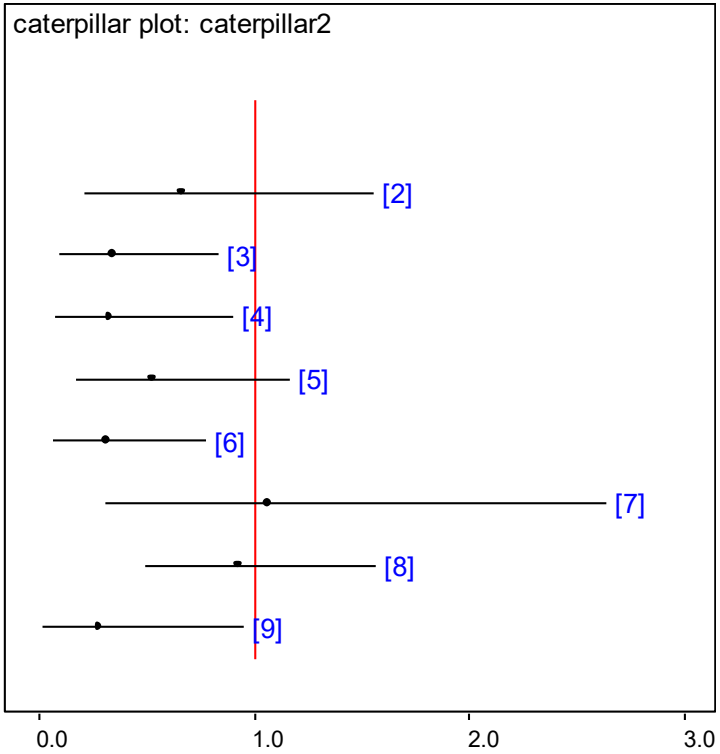
Rank probability histograms

Figure 147 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2= Warfarin INR 1.5-2.0, group 3 = warfarin INR 2.0-3.0, group 4= dabigatran, group 5 = apixaban 2.5mg, group 6 = apixaban 5mg, group 7 = rivaroxaban 20mg, group 8 = aspirin 100mg, group 9 = rivaroxaban 10mg. Rank 1 is best.)



Caterpillar plot

Figure 148 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. Group 2= Warfarin INR 1.5-2.0, group 3 = warfarin INR 2.0-3.0, group 4= dabigatran, group 5 = apixaban 2.5mg, group 6 = apixaban 5mg, group 7 = rivaroxaban 20mg, group 8 = aspirin 100mg, group 9 = rivaroxaban 10mg. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

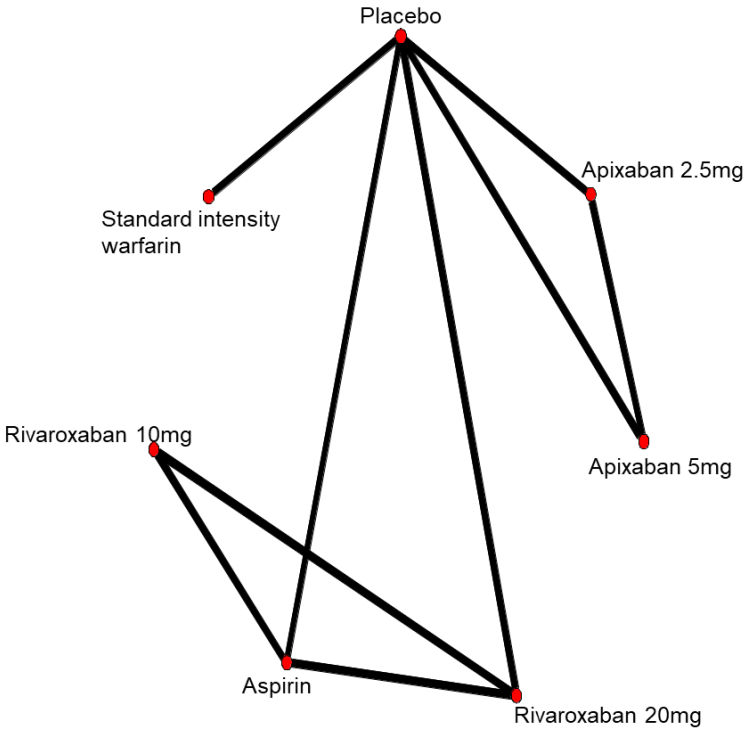
Table 97 Relative effectiveness of all pairwise combinations. (Upper diagonal: Ratio ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	Placebo	Warfarin low-intensity	Warfarin standard	dabigatran	apixaban 2.5mg	Apixaban 5mg	Rivaroxaban 20mg	Aspirin 100mg	Rivaroxaban 10mg
Placebo		0.50 (0.15, 1.63)	0.46 (0.12, 1.72)	-	0.49 (0.20, 1.22)	0.29 (0.10, 0.88)	0.49 (0.04, 5.44)	0.92 (0.51, 1.66)	-
Warfarin low-intensity	0.59 (0.22, 1.56)		0.48 (0.21, 1.10)	-	-	-	-	-	-
Warfarin standard	0.30 (0.10, 0.84)	0.51 (0.24, 1.11)		0.90 (0.47, 1.72)	-	-	-	-	-
dabigatran	0.27 (0.08, 0.91)	0.46 (0.17, 1.26)	0.90 (0.47, 1.72)		-	-	-	-	-
apixaban 2.5mg	0.48 (0.18, 1.17)	0.81 (0.20, 3.11)	1.58 (0.38, 6.30)	1.76 (0.37, 8.12)		0.59 (0.17, 2.01)	-	-	-
Apixaban 5mg	0.27 (0.07, 0.78)	0.46 (0.09, 1.99)	0.89 (0.17, 4.02)	0.99 (0.17, 5.09)	0.57 (0.14, 1.93)		-	-	-
Rivaroxaban 20mg	0.92 (0.31, 2.64)	1.56 (0.37, 6.66)	3.03 (0.69, 13.55)	3.36 (0.67, 17.16)	1.92 (0.48, 8.07)	3.41 (0.75, 17.78)		0.86 (0.31, 2.36)	0.24 (0.05, 1.15)
Aspirin 100mg	0.89 (0.50, 1.57)	1.51 (0.49, 4.75)	2.92 (0.91, 9.77)	3.24 (0.86, 12.77)	1.85 (0.64, 5.75)	3.27 (0.98, 13.32)	0.96 (0.37, 2.52)		0.29 (0.06, 1.38)
Rivaroxaban 10mg	0.21 (0.03, 0.96)	0.35 (0.04, 2.22)	0.67 (0.07, 4.51)	0.75 (0.07, 5.58)	0.43 (0.05, 2.69)	0.76 (0.07, 5.73)	0.23 (0.03, 0.96)	0.24 (0.03, 0.99)	

VTE-related mortality (during study period)

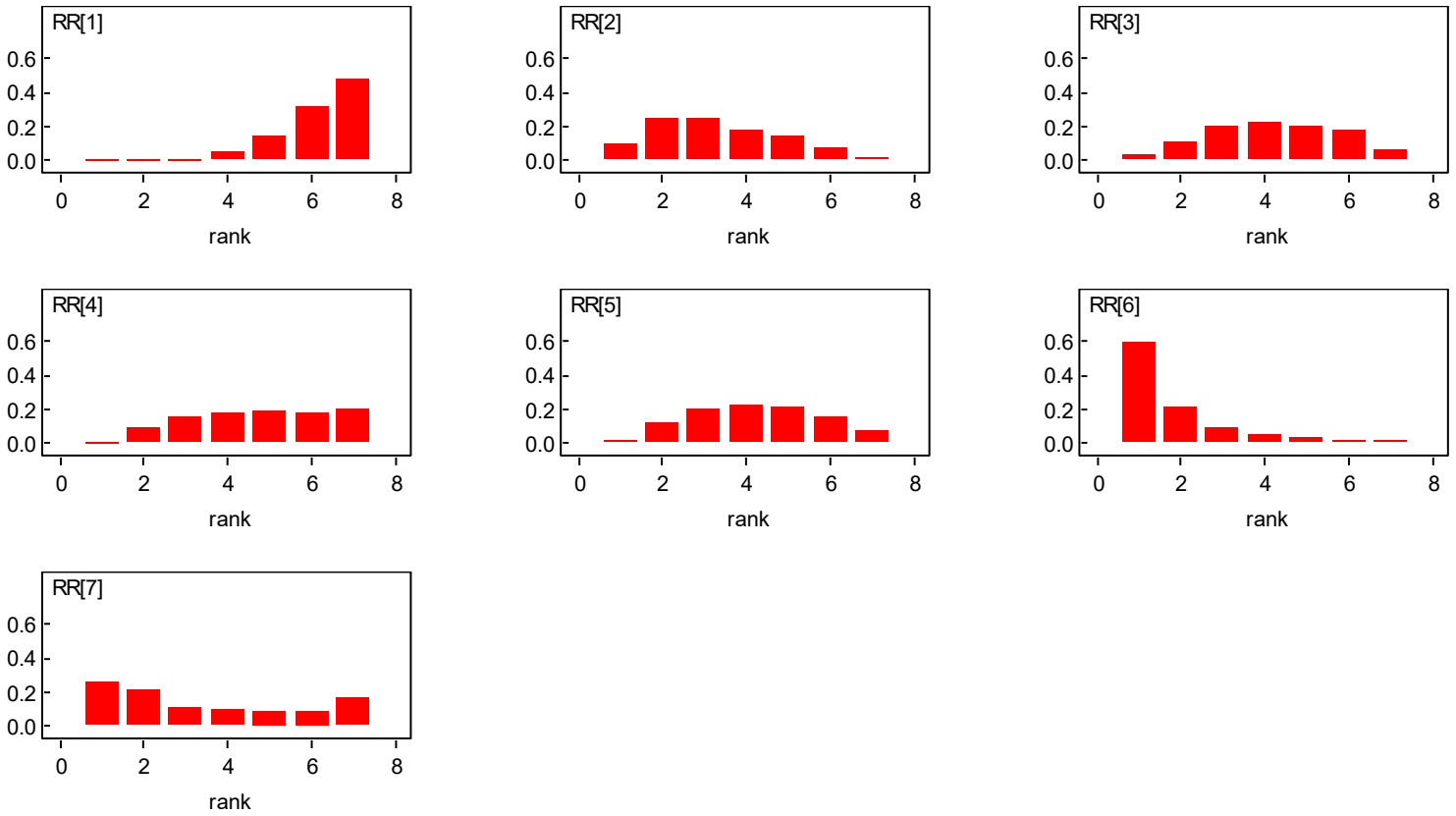
Network diagram

Figure 149 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



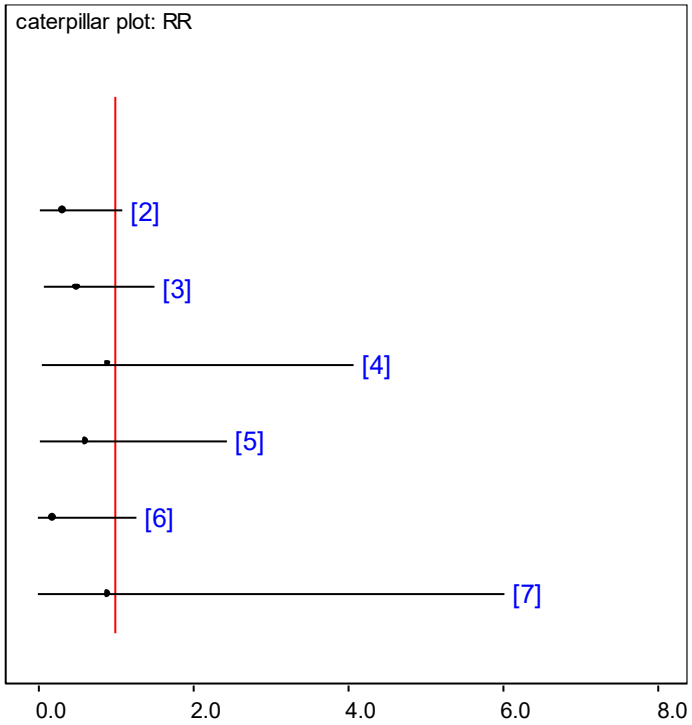
Rank probability histograms

Figure 150 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = apixaban 2.5mg, group 3= apixaban 5mg, group 4 = rivaroxaban 20mg, group 5 = aspirin 100mg, group 6 = rivaroxaban 10mg, group 7 = warfarin standard. Rank 1 is best.)



Caterpillar plot

Figure 151 Relative effectiveness of all options versus placebo. (Hazard ratios with 95% credible intervals and line of no effect in red. group 2 = apixaban 2.5mg, group 3= apixaban 5mg, group 4 = rivaroxaban 20mg, group 5 = aspirin 100mg, group 6 = rivaroxaban 10mg, group 7 = warfarin standard. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

Table 98 Relative effectiveness of all pairwise combinations. (Upper diagonal: Ratio ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	Placebo	apixaban 2.5mg	Apixaban 5mg	rivaroxaban 20mg	Aspirin 100mg	Rivaroxaban 10mg	Warfarin standard
Placebo		0.28 (0.06, 1.35)	0.44 (0.11, 1.68)	0.99 (0.06, 15.74)	0.33 (0.03, 3.19)	-	0.35 (0.01, 8.87)
apixaban 2.5mg	0.25 (0.03, 1.10)		1.54 (0.26, 9.09)	-	-	-	-
apixaban 5mg	0.41 (0.08, 1.53)	1.64 (0.25, 14.22)		-	-	-	-
rivaroxaban 20mg	0.52 (0.05, 4.08)	2.13 (0.13, 37.54)	1.28 (0.08, 17.03)		0.98 (0.14, 7.14)	0.20 (0.01, 4.17)	-
aspirin 100mg	0.40 (0.04, 2.45)	1.65 (0.11, 24.17)	0.99 (0.08, 10.86)	0.78 (0.14, 4.26)		0.20 (0.01, 4.18)	-
rivaroxaban 10mg	0.04 (0.00, 1.28)	0.17 (0.00, 9.18)	0.10 (0.00, 4.60)	0.09 (0.00, 1.53)	0.12 (0.00, 2.17)		-

Warfarin standard	0.20 (0.00, 6.03)	0.82 (0.00, 42.66)	0.49 (0.00, 21.43)	0.38 (0.00, 25.02)	0.49 (0.00, 28.77)	4.72 (0.00, 5642.00)	

Extended therapy for DVT

The following tables and figures are based on the NMA models using evidence from RCTs comparing anticoagulants for the extended therapy of VTE (DVT and/or PE) in people who have already received at least 3 months of anticoagulation therapy. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 99.

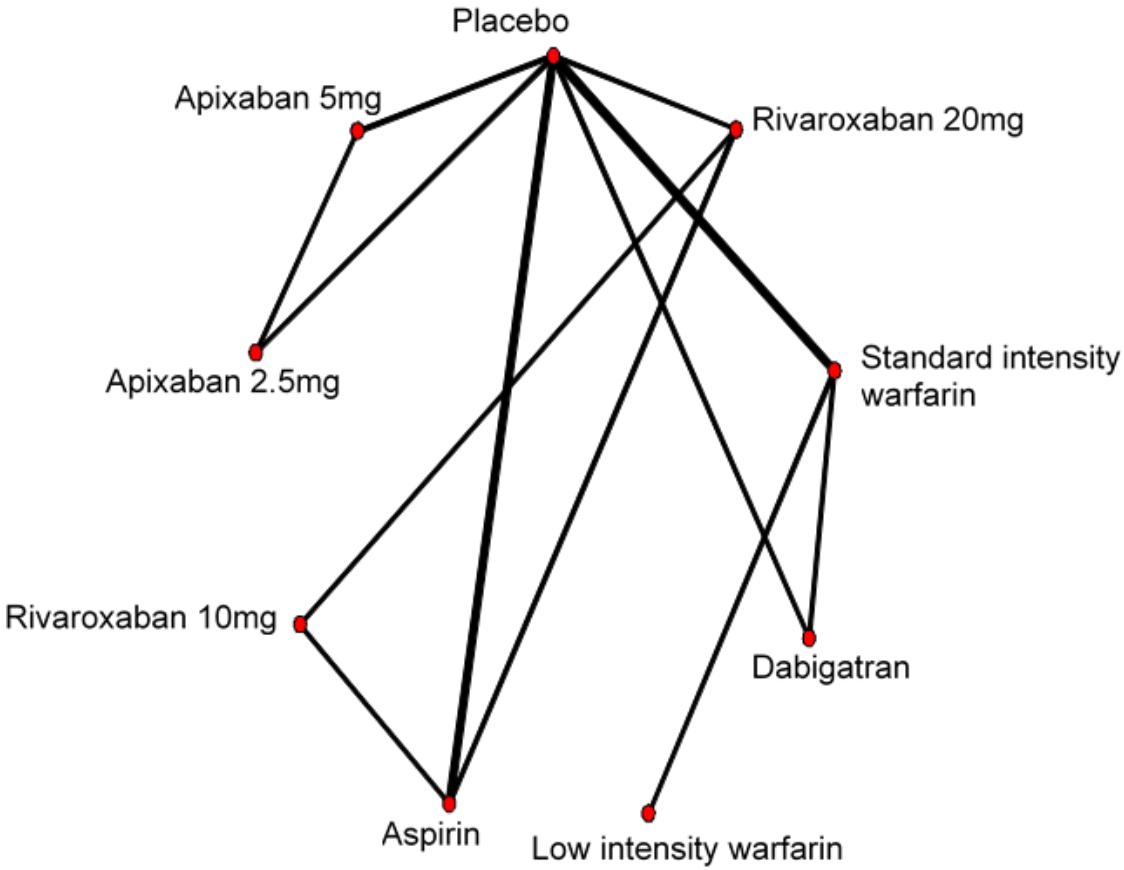
Table 99: Deep vein thrombosis (extended therapy): model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
10	VTE-recurrence	FE	115.54	17.96	21	-	FE
		RE	117.18	18.50		0.35 (0.01, 1.65)	

VTE-recurrence (during study period)

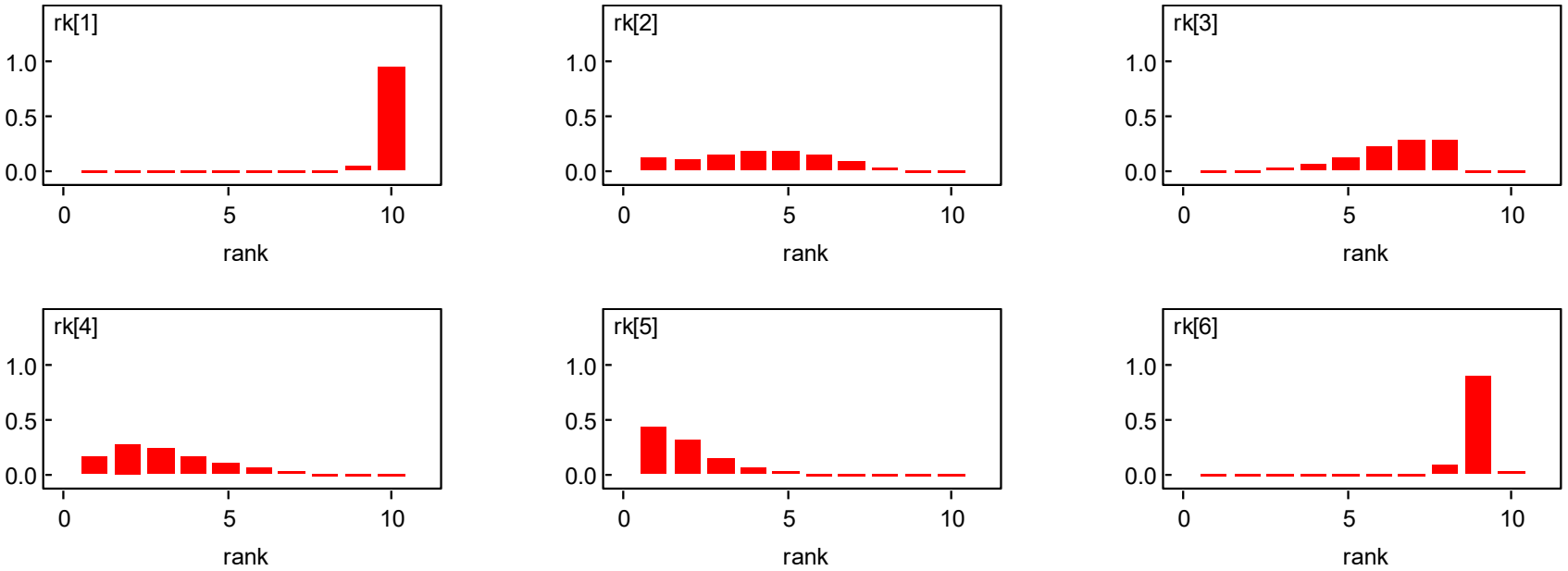
Network diagram

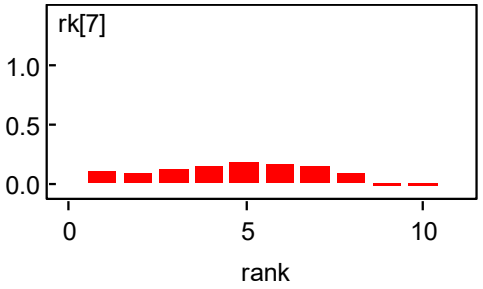
Figure 152 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.

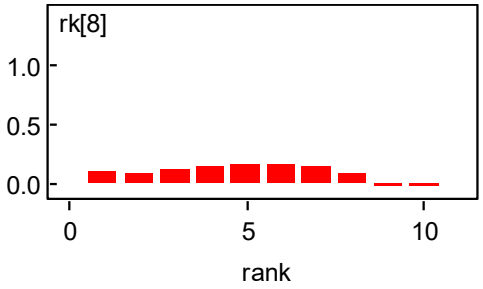

Placebo
Apixaban 5mg
Rivaroxaban 20mg
Apixaban 2.5mg
Standard intensity warfarin
Rivaroxaban 10mg
Dabigatran
Aspirin
Low intensity warfarin

Rank probability histograms

Figure 153 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = apixaban 2.5mg, group 3 = apixaban 5mg, group 4 = dabigatran, group 5 = warfarin INR 2.0-3.0, group 6 = aspirin 100mg, group 7 = rivaroxaban 20mg, group 8 = rivaroxaban 10mg, group 9 = discontinuation, group 10 = low-intensity warfarin INR 1.5-2.0. Rank 1 is best.)




rk[7]
1.0
0.5
0.0
0
5
10
rank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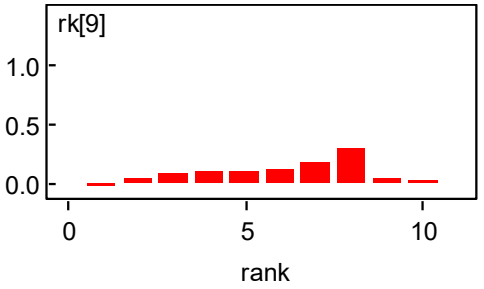
0.5
0.0
0
5
10
rank


rk[9]
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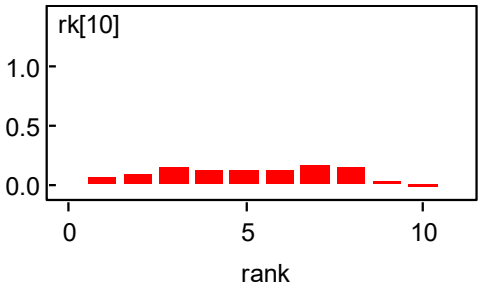
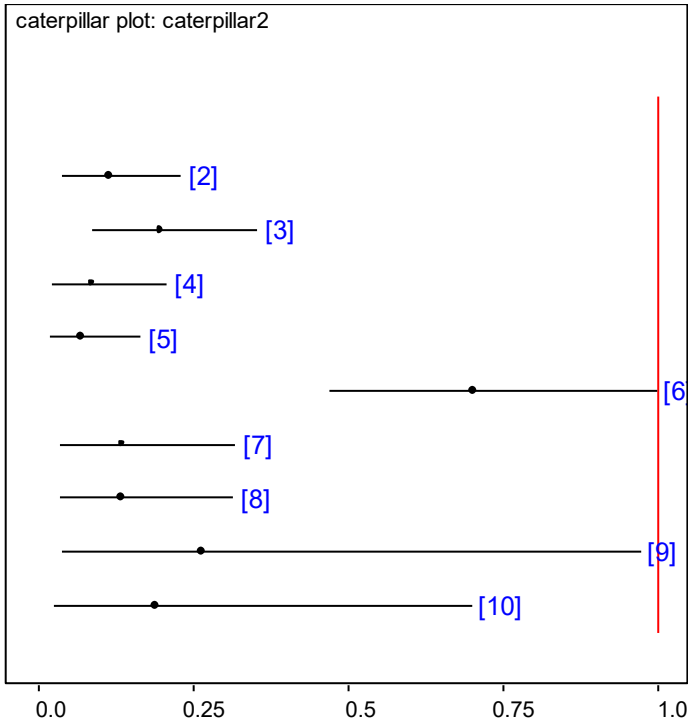
0.5
0.0
0
5
10
rank


rk[10]
1.0
0.5
0.0
0
5
10
rank

Caterpillar plot

Figure 154 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. group 2 = apixaban 2.5mg, group 3 = apixaban 5mg, group 4 = dabigatran, group 5 = warfarin INR 2.0-3.0, group 6 = aspirin 100mg, group 7 = rivaroxaban 20mg, group 8 = rivaroxaban 10mg, group 9 = discontinuation, group 10 = low-intensity warfarin INR 1.5-2.0. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

Table 100 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	Placebo	Apixaban 2.5mg	Apixaban 5mg	dabigatran	warfarin standard	aspirin 100mg	rivaroxaban 20mg	rivaroxaban 10mg	Discontinuation	Low intensity warfarin
Placebo		0.12 (0.05 to 0.27)	0.15 (0.07, 0.32)	0.13 (0.04 to 0.43)	0.04 (0.01, 0.15)	0.71 (0.50, 1.00)-	-	-	-	-
Apixaban 2.5mg	0.11 (0.04, 0.23)		1.72 (0.63, 4.76)	-	-	-	-	-	-	-
Apixaban 5mg	0.19 (0.09, 0.35)	1.77 (0.65, 5.30)		-	-	-	-	-	-	-
dabigatran	0.08 (0.02, 0.21)	0.73 (0.18, 2.91)	0.41 (0.11, 1.43)		0.93 (0.41 to 2.08)	-	-	-	-	-
warfarin standard	0.06 (0.02, 0.17)	0.57 (0.15, 2.31)	0.32 (0.09, 1.13)	0.79 (0.36, 1.71)			-	-	2.78 (0.90, 8.33)	2.04 (0.63, 6.67)
aspirin 100mg	0.69 (0.47, 1.00)	6.48 (2.72, 18.37)	3.67 (1.74, 8.40)	8.95 (3.07, 29.88)	11.47 (3.87, 35.96)		0.19 (0.07, 0.49)	0.19 (0.07, 0.49)	-	-
rivaroxaban 20mg	0.12 (0.04, 0.32)	1.14 (0.28, 4.45)	0.64 (0.17, 2.18)	1.56 (0.34, 7.08)	1.99 (0.43, 8.61)	0.18 (0.06, 0.43)		1.00 (0.29, 3.44)	-	-

rivaroxaban 10mg	0.12 (0.04, 0.32)	1.14 (0.28, 4.47)	0.64 (0.17, 2.18)	1.56 (0.34, 7.06)	1.99 (0.43, 8.56)	0.18 (0.06, 0.43)	1.00 (0.27, 3.75)			-
Discontinuation	0.18 (0.04, 0.97)	1.76 (0.30, 11.74)	0.99 (0.18, 6.05)	2.40 (0.61, 10.94)	3.02 (1.00, 11.42)	0.27 (0.05, 1.46)	1.55 (0.24, 11.40)	1.55 (0.24, 11.28)		-
Low intensity warfarin	0.13 (0.03, 0.70)	1.24 (0.21, 8.53)	0.70 (0.12, 4.33)	1.71 (0.42, 7.99)	2.15 (0.68, 8.23)	0.19 (0.04, 1.06)	1.10 (0.16, 8.26)	1.10 (0.17, 8.31)	0.71 (0.12, 4.06)	

1

Extended therapy for PE

The following tables and figures are based on the NMA models using evidence from RCTs comparing anticoagulants for the extended therapy of VTE (DVT and/or PE) in people who have already received at least 3 months of anticoagulation therapy. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 101.

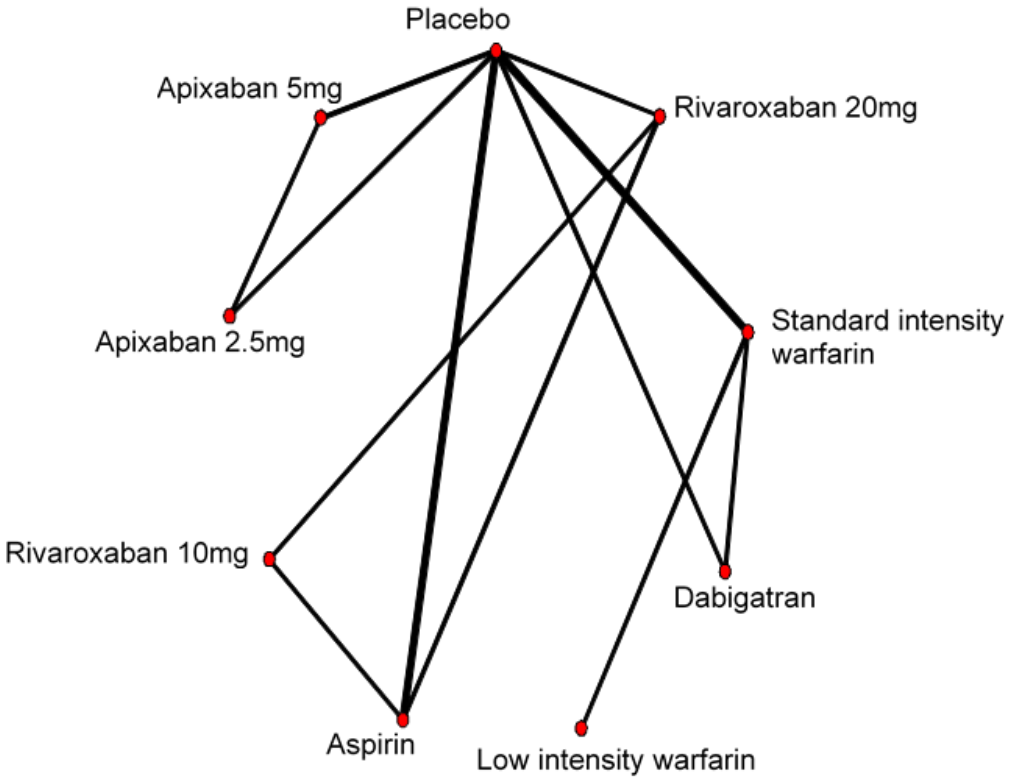
Table 101: Pulmonary embolism (extended therapy): model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
8	VTE-recurrence	FE	98.93	18.60	17	-	FE
		RE	98.70	16.81		0.83 (0.04, 1.91)	

VTE-recurrence (during study period)

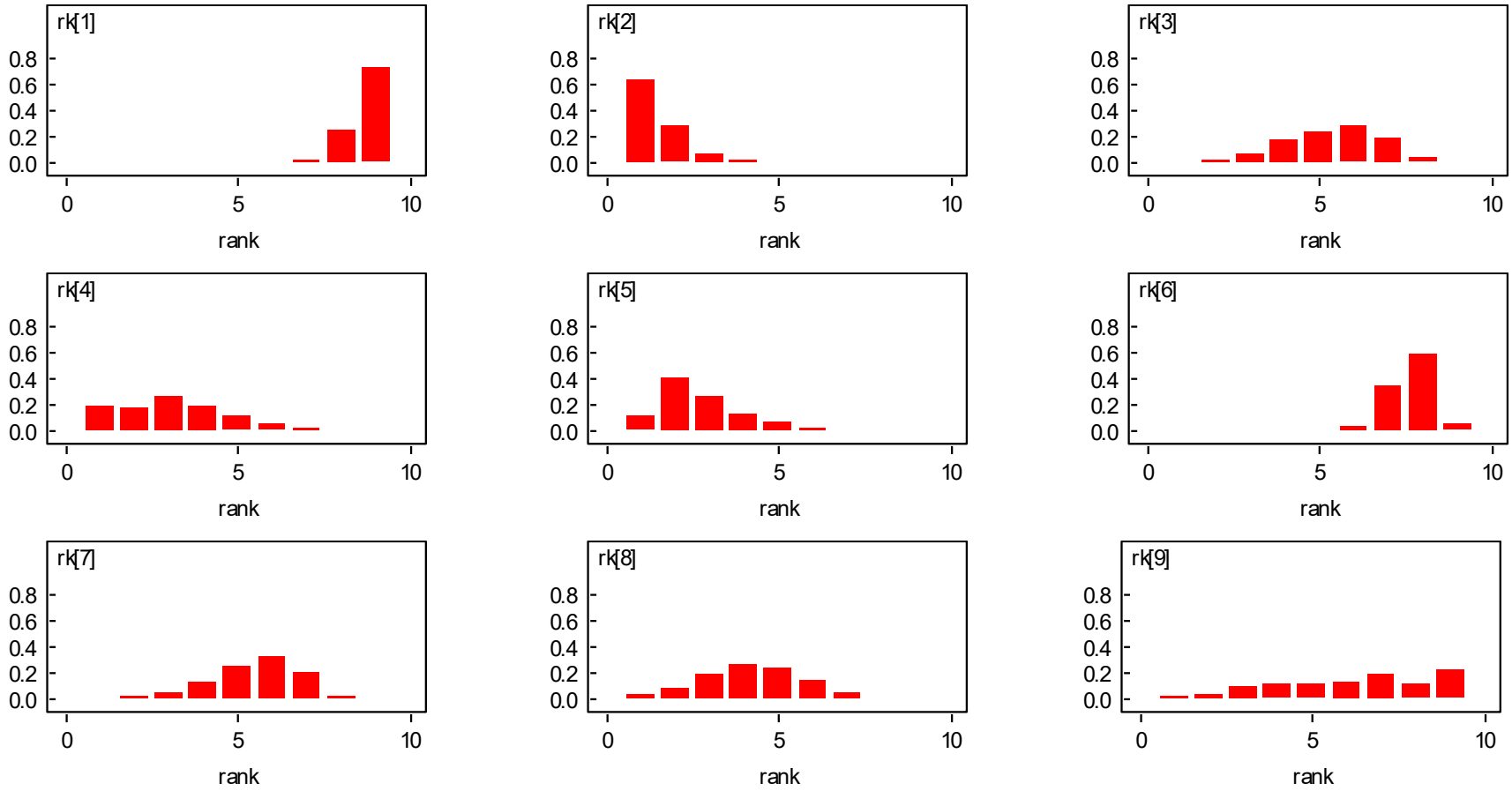
Network diagram

Figure 155 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.


Placebo
Apixaban 5mg
Rivaroxaban 20mg
Apixaban 2.5mg
Standard intensity warfarin
Rivaroxaban 10mg
Dabigatran
Aspirin
Low intensity warfarin

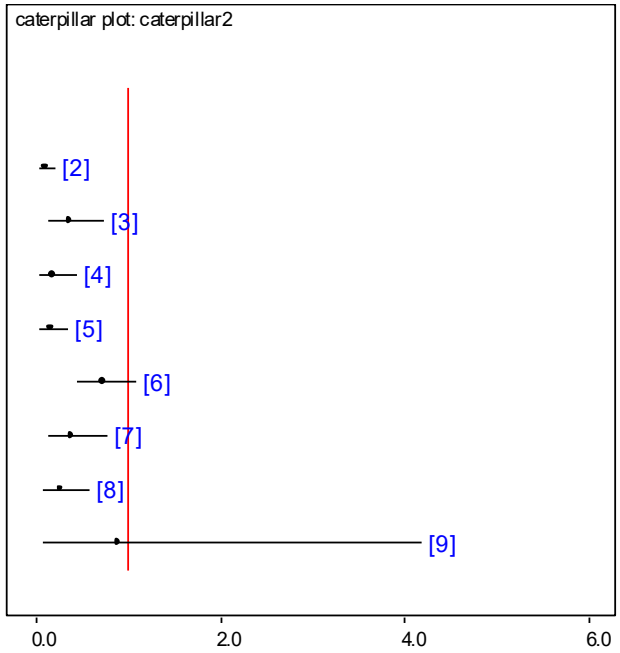
Rank probability histograms

Figure 156 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 = Warfarin INR 2.0-3.0, group 3 = apixaban 2.5mg, group 4 = apixaban 5mg, group 5 = dabigatran, group 6 = aspirin 100mg, group 7 = rivaroxaban 20mg, group 8 = rivaroxaban 10mg, group 9 = low-intensity warfarin INR 1.5-2.0. Rank 1 is best.)



Caterpillar plot

Figure 157 Relative effectiveness of all options versus placebo. (Risk ratios with 95% credible intervals and line of no effect in red. group 2 = Warfarin INR 2.0-3.0, group 3 = apixaban 2.5mg, group 4 = apixaban 5mg, group 5 = dabigatran, group 6 = aspirin 100mg, group 7 = rivaroxaban 20mg, group 8 = rivaroxaban 10mg, group 9 = low-intensity warfarin INR 1.5-2.0. Values greater than 1 favour placebo, values less than 1 favour the comparators)



Relative effectiveness chart

Table 102 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (HR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median HRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	placebo	warfarin standard	apixaban 2.5mg	apixaban 5mg	dabigatran	aspirin 100mg	rivaroxaban 20mg	rivaroxaban 10mg	Low-intensity warfarin
placebo		-	0.35 (0.15, 0.79)	0.18 (0.06, 0.52)	0.03 (0.00, 0.52)	0.47 (0.26, 0.85)	-	-	-
warfarin standard	0.09 (0.04, 0.23)		-	-	2.06 (0.83, 5.11)	-	-	-	4.17 (0.90, 20.00)
apixaban 2.5mg	0.34 (0.14, 0.74)	3.70 (1.05, 12.51)		0.51 (0.15, 1.69)	-	-	-	-	-
apixaban 5mg	0.17 (0.05, 0.45)	1.80 (0.39, 7.15)	0.49 (0.13, 1.61)			-	-	-	-
dabigatran	0.14 (0.05, 0.36)	1.49 (0.68, 3.34)	0.41 (0.11, 1.50)	0.83 (0.19, 4.04)		-	-	-	-
aspirin 100mg	0.71 (0.46, 1.09)	7.77 (2.88, 21.68)	2.10 (0.86, 5.63)	4.28 (1.45, 16.19)	5.16 (1.79, 16.35)		0.50 (0.25, 1.01)	0.35 (0.16, 0.78)	-

rivaroxaban 20mg	0.35 (0.15, 0.79)	3.86 (1.13, 13.28)	1.05 (0.33, 3.46)	2.14 (0.57, 9.43)	2.56 (0.70, 9.74)	0.50 (0.24, 0.98)		0.69 (0.28, 1.70)	-
rivaroxaban 10mg	0.24 (0.09, 0.59)	2.63 (0.71, 9.59)	0.71 (0.20, 2.49)	1.46 (0.36, 6.75)	1.75 (0.45, 7.03)	0.34 (0.14, 0.74)	0.68 (0.27, 1.67)		-
Low-intensity warfarin	0.46 (0.08, 4.19)	5.00 (1.13, 38.63)	1.39 (0.19, 14.53)	2.89 (0.36, 34.26)	3.39 (0.61, 29.10)	0.65 (0.10, 6.14)	1.33 (0.18, 13.94)	1.96 (0.26, 21.06)	

Extended therapy for VTE in people age 65 years or older

The following tables and figures are based on the NMA model data developed by NICE using evidence from RCTs comparing anticoagulants for the treatment of VTE in people aged 65 years or older. The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 103.

Table 103: Venous thromboembolism: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

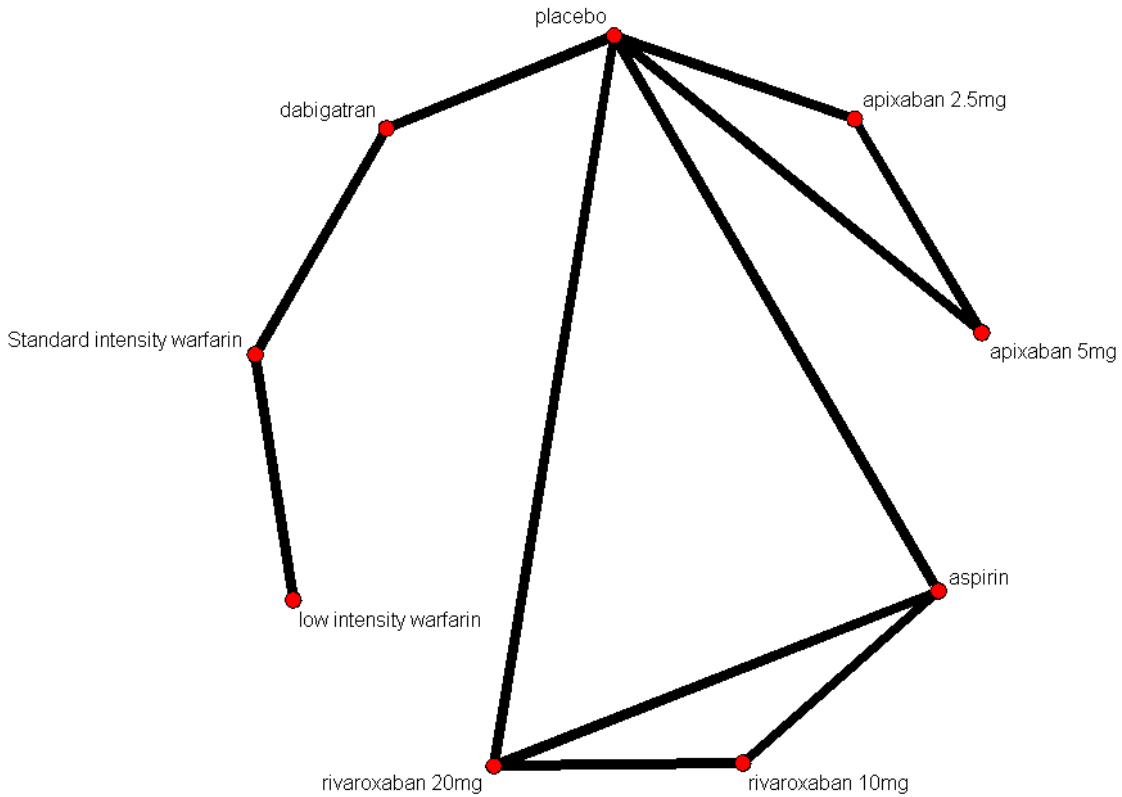
Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
7	VTE-recurrence	FE	62.43	11.04	14	-	FE
		RE	62.96	11.14		0.85 (0.04, 1.93)	

* Studies with zero events in either arm had 0.5 added to the event rate for both arms and 1 added to the total population for both arms, this was only done in instances when the model was unable to run (or was uninterpretable in its output).

VTE-recurrence (during treatment period)

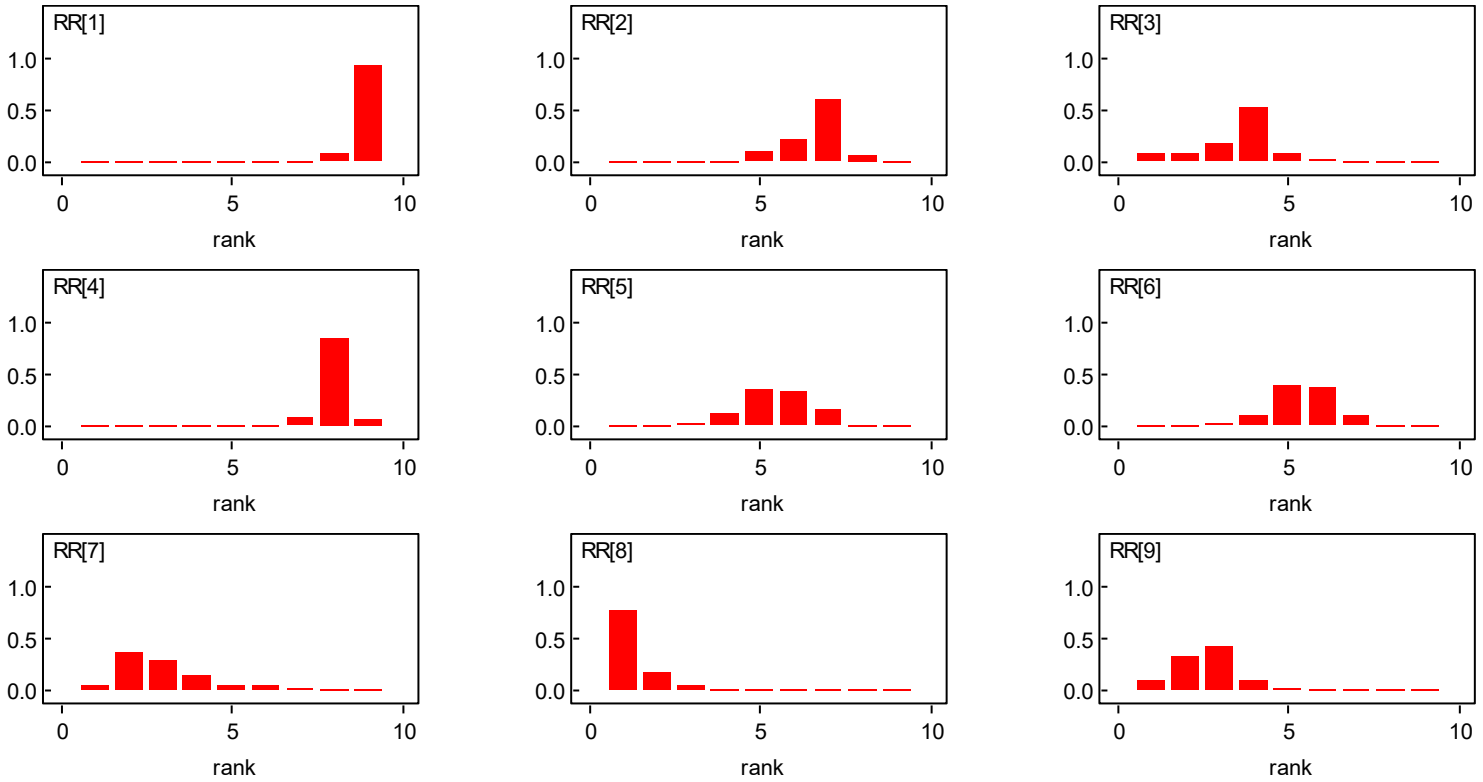
Network diagram

Figure 158 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



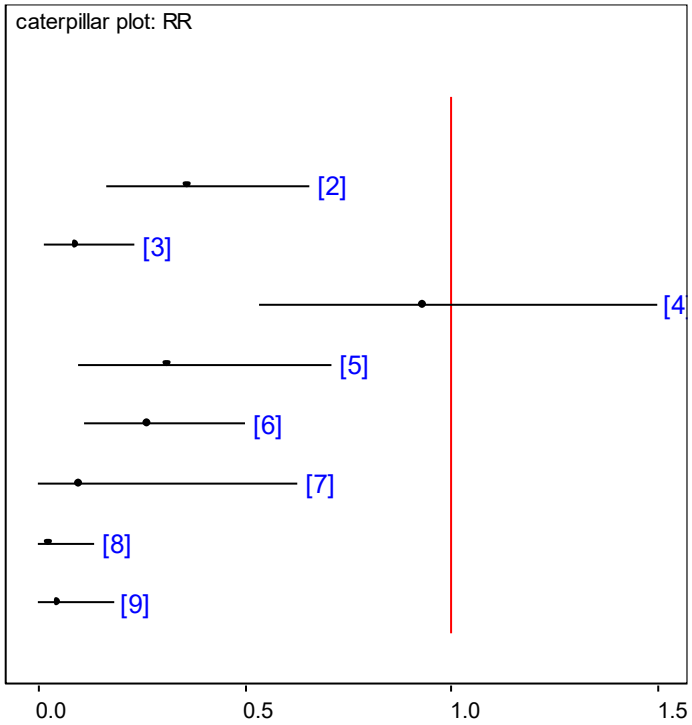
Rank probability histograms

Figure 159 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 =apixaban 2.5mg, group 3 = apixaban 5mg, group 4 = aspirin, group 5 = rivaroxaban 10mg, group 6 = rivaroxaban 20mg, group 7 = low-intensity warfarin, group 8 = standard intensity warfarin, group 9 = dabigatran. Rank 1 is best.)



Caterpillar plot

Figure 160 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (group 2 =apixaban 2.5mg, group 3 = apixaban 5mg, group 4 = aspirin, group 5 = rivaroxaban 10mg, group 6 = rivaroxaban 20mg, group 7 = low-intensity warfarin, group 8 = standard intensity warfarin, group 9 = dabigatran). Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 104 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	Placebo	Apixaban 2.5mg	Apixaban 5mg	Aspirin	Rivaroxaban 10mg	Rivaroxaban 20mg	Low intensity warfarin	Standard intensity warfarin	Dabigatran
Placebo		0.37 (0.20, 0.70)	0.10 (0.03, 0.31)	1.00 (0.60, 1.66)	-	0.19 (0.07, 0.55)	-	-	0.05 (0.01, 0.35)
Apixaban 2.5mg	0.37 (0.18, 0.68)		0.26 (0.07, 0.92)	-	-	-	-	-	-
Apixaban 5mg	0.09 (0.02, 0.25)	0.24 (0.05, 0.77)		-	-	-	-	-	-
Aspirin	0.91 (0.56, 1.43)	2.49 (1.13, 5.77)	10.39 (3.20, 49.51)		0.35 (0.15, 0.82)	0.38 (0.16, 0.88)	-	-	-
Rivaroxaban 10mg	0.30 (0.11, 0.73)	0.82 (0.25, 2.57)	3.45 (0.78, 19.38)	0.33 (0.13, 0.72)		1.08 (0.38, 3.03)	-	-	-
Rivaroxaban 20mg	0.27 (0.13, 0.53)	0.74 (0.28, 1.96)	3.09 (0.83, 15.64)	0.30 (0.14, 0.57)	0.89 (0.34, 2.53)		-	-	-
Low intensity warfarin	0.03 (0.00, 0.65)	0.10 (0.00, 1.95)	0.41 (0.01, 10.60)	0.04 (0.00, 0.75)	0.12 (0.00, 2.63)	0.13 (0.00, 2.69)		0.39 (0.11, 1.45)	-
Standard intensity warfarin	0.01 (0.00, 0.15)	0.03 (0.00, 0.46)	0.14 (0.00, 2.64)	0.01 (0.00, 0.18)	0.04 (0.00, 0.64)	0.05 (0.00, 0.64)	0.35 (0.07, 1.29)		2.30 (0.45, 11.77)
Dabigatran	0.03 (0.00, 0.20)	0.10 (0.00, 0.64)	0.40 (0.01, 4.02)	0.04 (0.00, 0.24)	0.11 (0.00, 0.91)	0.13 (0.01, 0.88)	0.90 (0.10, 10.48)	2.58 (0.52, 20.57)	

Extended therapy for VTE in people with obesity

The following tables and figures are based on the NMA model data developed by NICE using evidence from RCTs comparing anticoagulants for the treatment of VTE in people with obesity (BMI≥30 kg/m^2). The choice of fixed effect or random effects model is made according to the methods in appendix B and is summarised in Table 81.

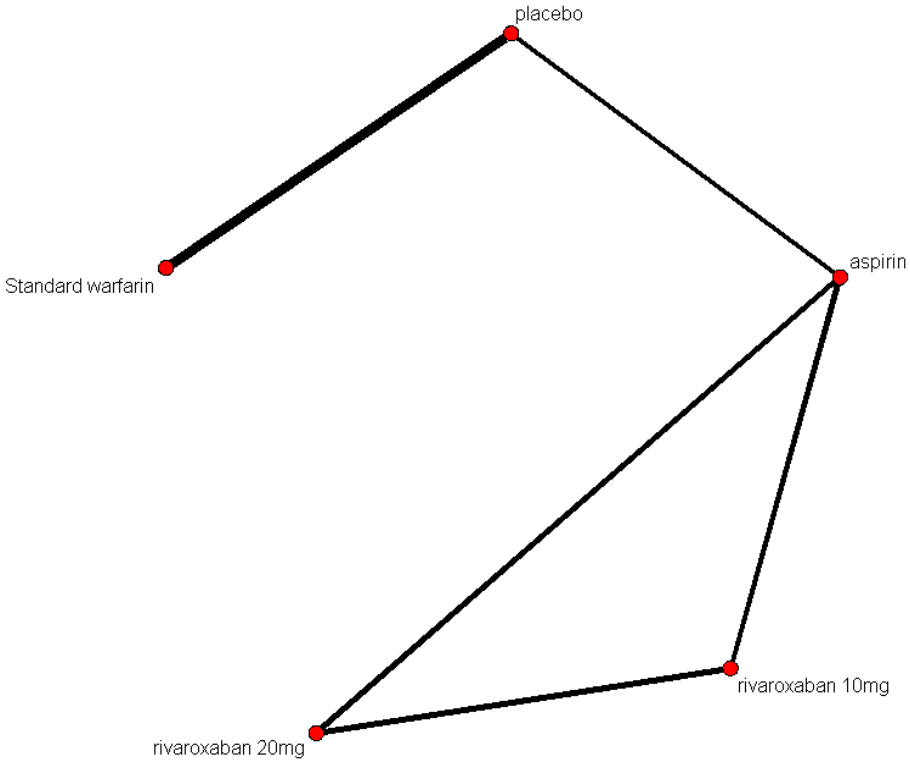
Table 105: Venous thromboembolism: model fit statistics used to select fixed or random effect models for all comparisons and outcomes

Number of Studies	Outcome	Model	Total model DIC	Total residual deviance	No. of data-points	Between-study SD (95% CrI)	Preferred model
4	VTE-recurrence	FE	46.23	8.37	16	-	FE
		RE	46.39	8.26		2.37 (0.11, 4.86)	

VTE-recurrence (during treatment period)

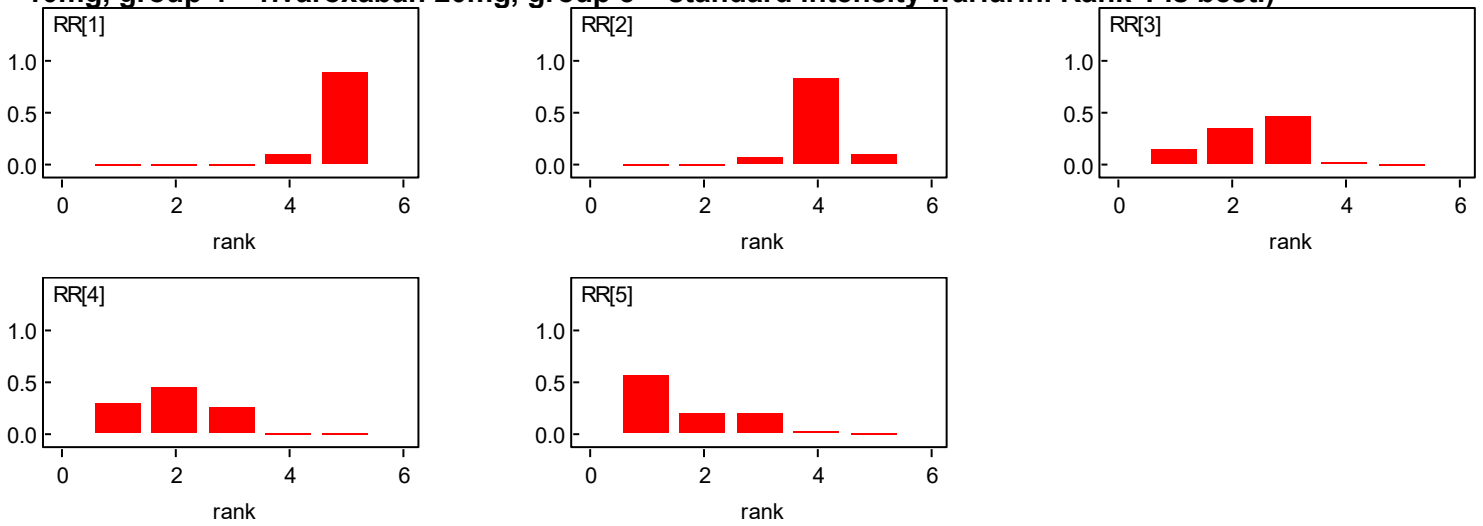
Network diagram

Figure 161 Diagram of the network of studies underlying the NMA. The thickness of the line represents the number of studies.



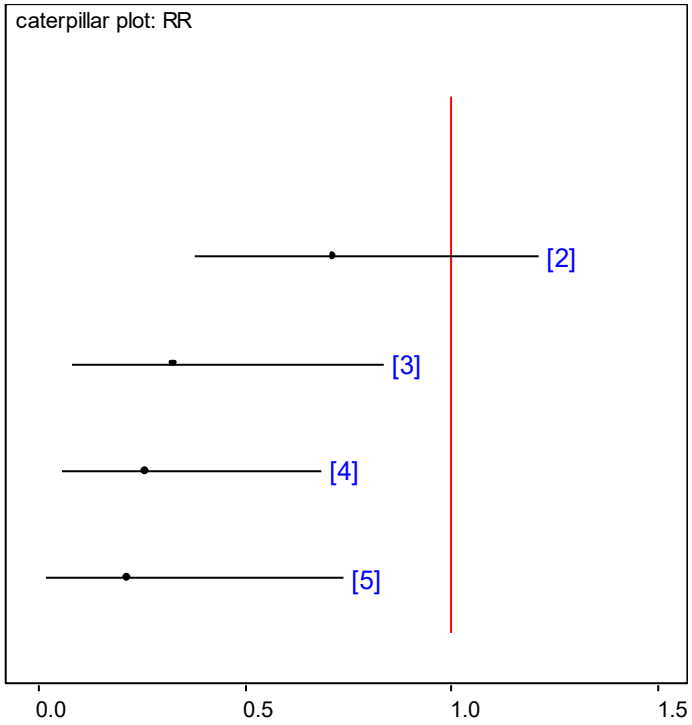
Rank probability histograms

Figure 162 Probability of the treatment assuming each treatment rank. (Group 1= placebo, group 2 =, aspirin, group 3 = rivaroxaban 10mg, group 4 = rivaroxaban 20mg, group 5 = standard intensity warfarin. Rank 1 is best.)



Caterpillar plot

Figure 163 Relative effectiveness of all options versus low-molecular weight heparin + vitamin K antagonist. (group 2 =, aspirin, group 3 = rivaroxaban 10mg, group 4 = rivaroxaban 20mg, group 5 = standard intensity warfarin. Rank 1 is best. Values greater than 1 favour LMWH+VKA, values less than 1 favour the comparators)



Relative effectiveness chart

Table 106 Relative effectiveness of all pairwise combinations. (Upper diagonal: Risk ratios (RR) with 95% confidence intervals from the pair-wise meta-analysis. RRs greater than 1 favour the row defining treatment, RRs less than 1 favour the column defining treatment. Lower diagonal: posterior median RRs with 95% credible intervals from NMA results, RR less than 1 favour the row defining treatment. RRs greater than 1 favour the column defining treatment.)

	Placebo	**Aspirin**	**Rivaroxaban 10mg**	**Rivaroxaban 20mg**	**Standard intensity warfarin**
Placebo		0.73 (0.31, 1.04)	-	-	0.24 (0.06, 0.94)
Aspirin	0.73 (0.43, 1.17)		0.43 (0.17, 1.10)	0.34 (0.12, 0.93)	-
Rivaroxaban 10mg	0.33 (0.10, 0.87)	0.45 (0.16, 1.04)		0.79 (0.24, 2.56)	-
Rivaroxaban 20mg	0.26 (0.07, 0.74)	0.36 (0.12, 0.88)	0.80 (0.24, 2.51)		-
Standard intensity warfarin	0.19 (0.02, 0.78)	0.26 (0.03, 1.18)	0.58 (0.06, 3.69)	0.73 (0.08, 4.88)	

Appendix I – Network meta-analysis summary tables

Initial treatment of VTE

Table 107 Summary of NMA results for the initial treatment of VTE.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. Abbreviations are as follows: Fondaparinux + VKA (Fond + VKA).

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
				Improvements compared to:			
VTE-recurrence	• UFH + VKA	-	-	• UFH + VKA	-	• UFH + VKA	• UFH + VKA
Major bleeding	-	-	-	• UFH + VKA • LMWH + VKA • Fond + VKA • Dabigatran • Edoxaban	-	-	• UFH + VKA • LMWH + VKA • Fond + VKA
Clinically relevant non-major bleeding	-	-	-	• UFH + VKA • LMWH + VKA • Fond + VKA • Edoxaban • Rivaroxaban	• UFH + VKA • LMWH + VKA • Fond + VKA • Edoxaban • Rivaroxaban	• LMWH + VKA	-
All-cause mortality	• Fond + VKA	-	-	-	-	-	• Fond + VKA

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Improvements compared to:							
VTE-related mortality	-	-	-	-	-	-	-

Initial treatment of DVT

Table 108 Summary of NMA results for the initial treatment of DVT.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. “Not available” indicates where outcome data for a specific drug was not available. Abbreviations are as follows: Fondaparinux + VKA (Fond + VKA)

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Improvements compared to:							
VTE-recurrence	• UFH + VKA	-	-	• UFH + VKA	-	-	• UFH + VKA
Major bleeding	• UFH+VKAUFH + VKA	-	-	• UFH + VKA • LMWH+VKA	Not available	Not available	• UFH + VKA
Clinically relevant non-major bleeding	-	-	-	-	-	-	-
All-cause mortality	• UFH + VKA	-	-	Not available	Not available	Not available	• UFH + VKA • Fond+VKA

Initial treatment of PE

Table 109 Summary of NMA results for the initial treatment of PE.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. “Not available” indicates where outcome data for a specific drug was not available. Abbreviations are as follows: Fondaparinux + VKA (Fond + VKA).

Outcome	LMWH + VKA	Fondaparinux + VKA	UFH + VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Improvements compared to:							
VTE-recurrence	-	-	-	-	-	-	-
Major bleeding	-	-	-	• UFH + VKA • Rivaroxaban • LMWH+VKA • Fond + VKA	Not available	Not available	• UFH + VKA • LMWH+VKA • Fond + VKA

Table 110 Summary of NMA results for the initial treatment of VTE in people aged 65 years or older.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. “Not available” indicates where outcome data for a specific drug was not available.

Outcome	LMWH + VKA	Apixaban	Rivaroxaban	Dabigatran
Improvements compared to:				
VTE-recurrence	-	-	-	-

Table 111 Summary of NMA results for the initial treatment of VTE in people with obesity.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. “Not available” indicates where outcome data for a specific drug was not available.

Outcome	LMWH + VKA	Apixaban	Rivaroxaban	Dabigatran
Improvements compared to:				
VTE-recurrence	-	-	-	-

Initial treatment of VTE in people with cancer

Table 112 Summary of NMA results for the initial treatment of VTE in people with cancer.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments.

Outcome	LMWH+ VKA	LMWH alone	rivaroxaban	edoxaban	dabigatran	UFH+VKA	apixaban
Improvements compared to:							
VTE-recurrence	-	• LMWH+VKA	• LMWH+VKA	LMWH+VKA	-	-	-
Major-bleeding	-	• Edoxaban	-	-	-	-	-
CRNMB	-	• LMWH+VKA • Rivaroxaban • Edoxaban • Dabigatran	-	-	-	• LMWH+VKA • Rivaroxaban • Dabigatran	-
All-cause mortality	-	-	-	-	-	-	-

Extended therapy for VTE

Table 113 Summary of NMA results for extended therapy for VTE.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. Abbreviations are as follows: Apixaban 5mg (Apix 5), Dabigatran (Dabig), Rivaroxaban 20mg (Riv 20), Rivaroxaban 10mg (Riv 10), Warfarin low-intensity (Warf L), Warfarin standard (Warf S), Discontinued (Disc), Aspirin 100mg (Asp), Placebo (plac), not available (NAv).

Outcome	placebo	rivaroxaban 20mg	rivaroxaban 10mg	dabigatran	warfarin low-intensity	apixaban 2.5mg	apixaban 5mg	discontinuation	aspirin 100mg	warfarin standard
Improvements compared to:										
VTE-recurrence	-	• Plac • Asp	• Plac • Asp	• Plac • Warf L • Asp	• Plac • Asp	• Plac • Asp	• Plac • Asp	-	• Plac	• Plac • Warf L • Asp • Disc
Major bleeding	• Warf (S and L) • Riv 20	-	-	-	-	• Warf (S and L) • Riv 20	• Warf (S and L) • Riv (20 and 10) • Dabig	-	-	-

CRNMB	• Warf S • Riv (20and 10) • Apix 5 • Dabig • Asp	-	-	• Warf S	NAv	• Warf S • Riv 20	• Warf S • Riv 20	NAv	-	-
All-cause mortality	-	-	• Plac • Riv 20 • Asp	-	-	-	• Plac	NAv	-	• Plac
VTE-related mortality	-	-	-	NAv	NAv	-	-	NAv	-	-

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Extended therapy for DVT

Table 114 Summary of NMA results for extended therapy of DVT

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. Abbreviations are as follows: Aspirin 100mg (Aspirin).

Outcome	placebo	rivaroxaban 20mg	rivaroxaban 10mg	dabigatran	warfarin low-intensity	apixaban 2.5mg	apixaban 5mg	discontinuation	aspirin 100mg	warfarin standard
	Improvements compared to:									
VTE-recurrence	-	• Placebo • Aspirin	• Placebo • Aspirin	• Placebo • Aspirin	Placebo	• Placebo • Aspirin	• Placebo • Aspirin	-	• Placebo	• Placebo • Aspirin

Extended therapy for PE

Table 115 Summary of NMA results for extended therapy of PE

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. Abbreviations are as follows: Aspirin 100mg (Aspirin).

Outcome	placebo	rivaroxaban 20mg	rivaroxaban 10mg	dabigatran	warfarin low-intensity	apixaban 2.5mg	apixaban 5mg	discontinuation	aspirin 100mg	warfarin standard
Improvements compared to:										
VTE-recurrence	-	• Placebo • Aspirin	• Placebo • Aspirin	• Placebo • Aspirin		• Placebo	• Placebo • Aspirin	Not available	-	• Placebo • Aspirin

Extended therapy for VTE in people aged 65 years or older.

Table 116 Summary of NMA results for the extended therapy of VTE in people aged 65 years or older.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. "Not available" indicates where outcome data for a specific drug was not available. Abbreviations are as follows: Aspirin 100mg (Aspirin).

Outcome	placebo	Apixaban 2.5mg	Apixaban 5mg	Aspirin	Rivaroxaban 10mg	Rivaroxaban 20mg	Low intensity warfarin	Standard intensity warfarin	Dabigatran
Improvements compared to:									
VTE-recurrence	-	• Placebo	• Placebo • Apixaban 2.5mg • Aspirin	• Placebo	• Placebo • Aspirin	• Placebo • Aspirin	• Placebo • Aspirin	• Placebo • Aspirin • Apixaban 2.5mg • Rivaroxaban 10mg • Rivaroxaban 20mg	• Placebo • Aspirin • Apixaban 2.5mg • Rivaroxaban 10mg • Rivaroxaban 20mg

Extended therapy in people with obesity

Table 117 Summary of NMA results for the extended therapy of VTE in people with obesity.

The columns list the drugs (or drug combinations) and the rows list the outcomes. Within each box, the drug combinations listed represent results where there was an improvement in that outcome. Results have been reversed where necessary to ensure that they are presented as improvements. Boxes with dashes represent cases where the NMA could not differentiate between treatments. “Not available” indicates where outcome data for a specific drug was not available.

Outcome	placebo	Aspirin	rivaroxaban 10mg	Rivaroxaban 20mg	Standard intensity warfarin
Improvements compared to:					
VTE-recurrence	-		• Placebo	• Placebo • Aspirin 100mg	• Placebo

Appendix J – Event data to hazard ratio conversions

Raw data

The included studies presented results as a mixture of hazard ratio (HR) data and event data. In cases where only event data was presented for a particular outcome of interest the meta- analysis and NMA models used this data and present the results as risk ratios (RRs). However, where HRs were available these were extracted preferentially as this form of data helps to overcome the differing lengths of follow-up between studies. This led to the situation where, for some outcomes, there was a mix of HR and event data. To allow for the difference in data types, the NMAs for these outcomes used clog-log models and presented results as HRs.

To allow pairwise, direct comparison results to be presented in relative effectiveness charts for comparison to the NMA results, all event data was converted into hazard ratio data. All conversions were carried out post-hoc by the Guideline Updates Team. The assumptions underlying this analysis are covered in the committee discussions of the evidence and methods section. The conversion from event rate data to HR data is based on the methods presented in Watkins, C. and Bennett, I., (2018).

The raw data used for these conversions and the converted hazard ratios can be found below in the following tables: Table 118 to Table 121 for the initial treatment of VTE; Table 122 to Table 124 for the initial treatment of DVT and Table 125 to Table 126 for the initial treatment of PE.

For the extended therapy analyses the converted hazard ratios can be found in Table 127 to Table 130.

The converted hazard ratios for the initial treatment of cancer analyses are reported in Table 131 to Table 134.

Conversions for initial treatment of VTE network

Table 118 VTE recurrence

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	43	1098	45	1107	0.96 (0.63, 1.46)
Buller 2003	42	1103	56	1110	0.75 (0.50, 1.12)
Belcaro 1999	6	98	6	97	0.99 (0.32, 3.07)
Decousus 1998	10	189	13	200	0.81 (0.35, 1.84)
Fiessinger 1996	6	130	3	138	2.15 (0.54, 8.60)
Findik 2002	1	29	3	30	0.33 (0.03, 3.20)
Hull 1992	6	213	15	219	0.40 (0.16, 1.04)
Kakkar 2003	1	126	4	111	0.22 (0.02, 1.94)
Kearon 2006	12	352	13	345	0.90 (0.41, 1.98)
Koopman 1996	8	202	10	198	0.78 (0.31, 1.98)
Levine 1996	13	247	17	253	0.78 (0.38, 1.60)
Lopaciuk 1992	0	74	3	72	0.14 (0.01, 2.64)
Merli 2001	22	610	12	290	0.87 (0.43, 1.76)

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Ninet 1991	2	85	0	81	4.82 (0.23, 100.47)
Prandoni 1992	4	85	7	85	0.56 (0.16, 1.92)
Prandoni 2004	14	360	15	360	0.93 (0.45, 1.93)
Ramacciotti 2004	2	104	5	97	0.37 (0.07, 1.89)
Simonneau 1997	5	304	6	308	0.84 (0.26, 2.76)
AMPLIFY 2013	59	2691	71	2704	0.83 (0.59, 1.18)
Buller 2008	3	117	3	128	1.10 (0.22, 5.43)
J-Amplify 2015	0	40	1	39	0.32 (0.01, 7.88)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the pairwise conversions only.

Table 119 Major-bleeding

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	28	1098	26	1107	1.09 (0.64, 1.85)
Buller 2003	22	1103	26	1110	0.85 (0.48, 1.50)
Decousus 1998	10	195	11	205	0.95 (0.41, 2.25)
Hull 1992	6	213	11	219	0.55 (0.21, 1.50)
Kakkar 2003 *	0	126	1	126	0.33 (0.01, 8.15)
Kearon 2006	12	352	6	345	1.98 (0.74, 5.27)
Koopman 1996	1	202	4	198	0.24 (0.03, 2.18)
Lopaciuk 1992 *	0	74	1	72	0.32 (0.01, 7.91)
Prandoni 1992	2	85	6	85	0.33 (0.07, 1.61)
Prandoni 2004	7	360	5	360	1.40 (0.45, 4.42)
Ramacciotti 2004	2	104	3	97	0.62 (0.10, 3.70)
Simonneau 1997	6	304	8	308	0.76 (0.26, 2.18)
AMPLIFY (Agnelli 2013)	15	2676	49	2689	0.31 (0.17, 0.55)
Buller 2008*	1	128	0	126	2.96 (0.12, 72.78)
J-AMPLIFY*	0	40	2	39	0.19 (0.01, 3.96)
Ucar 2015	2	60	6	61	0.33 (0.07, 1.62)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the pairwise conversions only.

Table 120 Clinically relevant non-major bleeding

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	60	1098	63	1107	0.96 (0.67, 1.37)
Buller 2003	62	1103	92	1110	0.67 (0.48, 0.92)
Hull 1992	6	213	8	219	0.77 (0.27, 2.21)
Kakkar 2003	2	126	1	126	2.01 (0.18, 22.15)
Koopman 1996	27	202	15	198	1.82 (0.97, 3.42)
Lopaciuk 1992	13	74	14	72	0.89 (0.42, 1.90)

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Prandoni 1992	2	85	6	85	0.33 (0.07, 1.61)
Ramacciotti 2004	13	104	9	97	1.37 (0.59, 3.21)
Simonneau 1993	6	67	1	67	6.24 (0.75, 51.83)
AMPLIFY 2013	103	2691	215	2704	0.47 (0.37, 0.60)
Buller 2008	10	128	10	126	0.98 (0.41, 2.36)
RE-COVER I 2009	51	1273	87	1266	0.57 (0.41, 0.81)
RE-COVER II 2014	49	1280	80	1288	0.61 (0.43, 0.87)
J-AMPLIFY	3	40	9	39	0.30 (0.08, 1.10)
EINSTEIN-DVT	126	1718	119	1711	1.06 (0.82, 1.36)
EINSTEIN-PE	228	2419	235	2413	0.97 (0.81, 1.16)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the pairwise conversions only.

Table 121 All-cause mortality

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	41	1098	33	1107	1.26 (0.80, 1.99)
Buller 2003	57	1103	48	1110	1.20 (0.82, 1.76)
Decousus 1998	10	195	15	205	0.69 (0.31, 1.54)
Hull 1992	10	213	21	219	0.48 (0.22, 1.01)
Kakkar 2003	2	126	2	110	0.87 (0.12, 6.19)
Koopman 1996	4	202	7	198	0.56 (0.16, 1.90)
Levine 1996	11	247	17	253	0.65 (0.31, 1.40)
Lopaciuk 1992*	0.5	75	1.5	73	0.32 (0.01, 7.91)
Ninet 1991	3	85	3	81	0.95 (0.19, 4.72)
Prandoni 1992	5	85	9	85	0.54 (0.18, 1.62)
Simonneau 1993	3	67	2	67	1.51 (0.25, 9.05)
Meyer 1995	1	29	1	31	1.07 (0.07, 17.11)
Simonneau 1997	12	304	14	308	0.87 (0.40, 1.87)
Ucar 2015	4	60	7	61	0.57 (0.17, 1.93)
Kearon 2006	22	352	18	345	1.20 (0.65, 2.25)
Merli 2001	18	610	9	290	0.95 (0.43, 2.11)
Prandoni 2004	12	360	12	360	1.00 (0.45, 2.23)
AMPLIFY 2013	41	2676	52	2689	0.79 (0.53, 1.19)
Buller 2008*	3.5	129	0.5	127	6.97 (0.36, 134.99)
HOKUSAI-VTE 2013	132	4118	126	4122	1.05 (0.82, 1.34)
RE-COVER II 2014	25	1279	25	1289	1.01 (0.58, 1.75)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. For this network, the conversion was done for the pairwise conversions only.

Conversions for initial treatment of DVT network

Table 122 VTE-recurrence

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	43	1098	45	1107	0.96 (0.63, 1.46)
Belcaro 1999	6	98	6	97	0.99 (0.32, 3.07)
Decousus 1998	10	189	13	200	0.81 (0.35, 1.84)
Fiessinger 1996	6	130	3	138	2.15 (0.54, 8.60)
Hull 1992	6	213	15	219	0.40 (0.16, 1.04)
Kakkar 2003	1	126	4	111	0.22 (0.02, 1.94)
Koopman 1996	8	202	10	198	0.78 (0.31, 1.98)
Levine 1996	13	247	17	253	0.78 (0.38, 1.60)
Lopaciuk 1992	0	74	3	72	0.14 (0.01, 2.64)
Ninet 1991	2	85	0	81	4.82 (0.23, 100.47)
Prandoni 1992	4	85	7	85	0.56 (0.16, 1.92)
Ramacciotti 2004	2	104	5	97	0.37 (0.07, 1.89)
AMPLIFY 2013	38	1698	47	1736	0.82(0.54, 1.26)
Buller 2008	3	117	3	128	1.09 (0.22, 5.43)
RE-COVER 2009	19	880	13	869	1.45 (0.23, 0.95)

Table 123 Major-bleeding

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	28	1098	26	1107	0.85 (0.48, 1.50)
Decousus 1998	10	195	11	205	0.95 (0.41, 2.25)
Hull 1992	6	213	11	219	0.55 (0.21, 1.50)
Kakkar 2003 *	0.5	127	1.5	127	0.33 (0.01, 8.15)
Koopman 1996	1	202	4	198	0.24 (0.03, 2.18)
Lopaciuk 1992 *	0.5	75	1.5	72	0.32 (0.01, 7.91)
Prandoni 1992	2	85	6	85	0.33 (0.07, 1.61)
Ramacciotti 2004	2	104	3	97	0.10, 3.70)
Buller 2008*	1.5	129	0.5	127	2.96 (0.12, 72.78)
AMPLIFY 2013	11	1738	24	1773	0.47 (0.23, 0.95)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the NMA model and the pairwise conversions.

Table 124 All-cause mortality

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2004	41	1098	33	1107	1.20 (0.82, 1.76)
Decousus 1998	10	195	15	205	0.69 (0.31, 1.54)
Hull 1992	10	213	21	219	0.48 (0.22, 1.01)
Kakkar 2003	2	126	2	110	0.87 (0.12, 6.19)
Koopman 1996	4	202	7	198	0.56 (0.16, 1.90)
Levine 1996	11	247	17	253	0.65 (0.31, 1.40)
Lopaciuk 1992*	0.5	75	1.5	73	0.32 (0.01, 7.91)
Ninet 1991	3	85	3	81	0.95 (0.19, 4.72)
Prandoni 1992	5	85	9	85	0.54 (0.18, 1.62)
Simonneau 1993	3	67	2	67	1.51 (0.25, 9.05)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the NMA model and the pairwise conversions.

Conversions for initial treatment of PE network

Table 125 VTE recurrence

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2003	42	1103	56	1110	0.75 (0.50, 1.12)
Findik 2002	1	29	3	30	0.33 (0.03, 3.20)
Simonneau 1997	5	304	6	308	0.84 (0.26, 2.76)
AMPLIFY 2013	21	900	23	886	0.90 (0.50, 1.62)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the pairwise conversions only.

Table 126 Major-bleeding

Study	Events arm 1	Total arm 1	Events arm 2	Total arm 2	Converted hazard ratio
Buller 2003	22	1103	26	1110	0.85 (0.48, 1.50)
Simonneau 1997	6	304	8	308	0.76 (0.26, 2.18)
AMPLIFY (Agnelli 2013)	4	928	25	902	0.15 (0.05, 0.44)
J-AMPLIFY*	0.5	19	2.5	18	0.18 (0.01, 3.72)
Ucar 2015	2	60	6	61	0.33 (0.07, 1.62)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the pairwise conversions only.

Conversions for extended therapy for VTE

Table 127 VTE recurrence

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY-EXT 2013 (apixaban 2.5mg versus placebo)	14	840	73	829	HR 0.18 (0.10, 0.32)
AMPLIFY-EXT 2013 (apixaban 5mg versus placebo)	14	813	73	829	HR 0.19 (0.11, 0.33)
AMPLIFY-EXT 2013 (apixaban 2.5mg versus apixaban 5mg)	14	840	14	813	HR 0.97 (0.46, 2.03)
Agnelli 2001	4	134	11	133	HR 0.35 (0.11, 1.10)

Table 128 Major bleeding

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY-EXT 2013 (placebo versus apixaban 2.5mg)	4	829	2	840	HR 2.03 (0.37, 11.08)
AMPLIFY-EXT 2013 (placebo versus apixaban 5mg)	4	829	1	813	HR 3.93 (0.44, 35.16)
AMPLIFY-EXT 2013 (apixaban 5mg versus apixaban 2.5mg)	1	813	2	840	HR 0.52 (0.05, 5.69)
EINSTEIN-EXT	4.5	599	0.5	591	HR 8.91 (0.48, 165.48)
Kearon 1999	3.5	80	0.5	84	HR 7.49 (0.39, 145.07)
RE-SONATE	2.5	682	0.5	663	HR 4.87 (0.23, 101.39)
WODIT-DVT 2001	4	134	1	133	HR 4.02 (0.45, 35.93)
PADIS-PE	3.5	185	0.5	188	HR 7.17 (0.37, 138.85)
ASPIRE 2012	6	411	8	411	HR 0.75 (0.26, 2.16)
WARFASA 2012	1	197	1	205	HR 1.04 (0.07, 16.64)
WODIT-PE 2003	3	165	1	161	HR 2.95 (0.31, 28.31)

*0.5 was added to the event rate and 1 to the total for each arm for any study that had 0 events in either arm. This was done for the pairwise conversions only.

Table 129 All-cause mortality

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY-EXT 2013 (apixaban 2.5mg versus placebo)	7	840	14	829	HR 0.49 (0.2, 1.22)
AMPLIFY-EXT 2013 (apixaban 5mg versus placebo)	4	813	14	829	HR 0.29 (0.1, 0.88)
AMPLIFY-EXT 2013 (apixaban 2.5mg versus apixaban 5mg)	7	840	4	813	HR 1.7 (0.5, 5.8)
EINSTEIN-EXT 2010	1	602	2	594	HR 0.49 (0.04, 5.44)
PADIS-PE 2015	2	184	2	187	HR 1.02 (0.14, 7.22)
PADIS-DVT 2019*	0.5	51	2.5	55	HR 0.21 (0.01, 4.41)
ASPIRE 2012	16	411	18	411	HR 0.89 (0.45, 1.74)
EINSTEIN CHOICE comparison 1 (aspirin versus rivaroxaban 20mg)	7	1131	8	1107	HR 0.86 (0.31, 2.36)
EINSTEIN CHOICE comparison 1 (rivaroxaban 10mg versus aspirin)	2	1127	7	1131	HR 0.29 (0.06, 1.38)
EINSTEIN CHOICE comparison 1 (rivaroxaban 10mg versus rivaroxaban 20mg)	2	1127	8	1107	HR 0.24 (0.05, 1.15)

Conversions for extended therapy for PE

Table 130 VTE recurrence

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY-EXT 2013 (apixaban 2.5mg versus placebo)	8	296	21	278	HR 0.35 (0.15, 0.79)
AMPLIFY-EXT 2013 (apixaban 5mg versus placebo)	4	286	21	278	HR 0.18 (0.06, 0.52)

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY-EXT 2013 (apixaban 2.5mg versus apixaban 5mg)	8	296	4	286	HR 1.95 (0.59, 6.46)
REMEDY 2012	14	491	7	503	HR 2.06 (0.83, 5.11)
RESONATE 2012	0.5	231	14.5	214	HR 0.03 (0, 0.52)
EINSTEIN-CHOICE (rivaroxaban 20 mg versus aspirin)	12	560	23	547	HR 0.5 (0.25, 1.01)
EINSTEIN-CHOICE (rivaroxaban 10 mg versus aspirin)	8	536	23	547	HR 0.35 (0.16, 0.78)
EINSTEIN-CHOICE (rivaroxaban 10 mg versus 20mg)	8	536	12	560	HR 0.69 (0.28, 1.7)
WARFASA 2012	11	83	16	67	HR 0.52 (0.24, 1.12)
ASPIRE 2012	27	171	33	175	HR 0.82 (0.49, 1.37)

Conversions for initial treatment of VTE in cancer network

Table 131 VTE recurrence

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
Romera 2009	3	33	2	36	HR 1.67 (0.28, 9.98)
Deicher 2006	3	30	2	32	HR 1.63 (0.27, 9.78)
Hull 2006	10	100	6	100	HR 1.7 (0.62, 4.69)
AMPLIFY 2013	3	81	5	78	HR 0.57 (0.14, 2.38)

Table 132 Major-bleeding

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
CLOT 2003	12	335	19	338	HR 0.63 (0.31, 1.3)
Deicher 2006	1	34	4	36	HR 0.25 (0.03, 2.27)
Meyer 2002	12	75	5	71	HR 2.39 (0.84, 6.78)
Hull 2006	7	100	7	100	HR 1 (0.35, 2.85)

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY 2013	2	87	4	80	HR 0.45 (0.08, 2.48)
HOKUSAI-Cancer 2018	36	522	21	524	HR 1.75 (1.02, 2.99)

Table 133 Clinically relevant non-major bleeding

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
AMPLIFY 2013	9	87	14	80	HR 0.57 (0.25, 1.31)
Hull 2006	17	100	20	100	HR 0.84 (0.44, 1.6)
EINSTEIN trials	25	257	19	204	HR 1.05 (0.58, 1.9)
RE-COVER trials	10	105	6	100	HR 1.62 (0.59, 4.45)
HOKUSAI-Cancer 2018	76	522	58	524	HR 1.50 (1.04, 2.16)

Table 134 All-cause mortality

Study	Events arm 1	total arm 1	Events arm 2	total arm 2	Converted hazard ratio
CLOT 2003	136	338	130	338	HR 1.06 (0.83, 1.35)
Deicher 2006	11	34	15	36	HR 0.73 (0.33, 1.59)
Meyer 2002	17	75	8	71	HR 2.15 (0.93, 4.99)
Hull 2006	19	100	20	100	HR 0.94 (0.5, 1.77)
SELECT-D 2018	48	203	56	203	HR 0.84 (0.57, 1.23)

Forest plots

For all NMA comparisons that used converted data (from event data to hazard data), pairwise analyses were carried out again using hazard ratio data to provide pooled results for the pairwise analysis part of the relative effectiveness charts. The forest plots for the converted pairwise analyses can be found below.

LMWH + VKA versus UFH+VKA for the initial treatment of VTE (DVT and/or PE)

Figure 164: VTE-recurrence: Any VTE event (converted from event data)

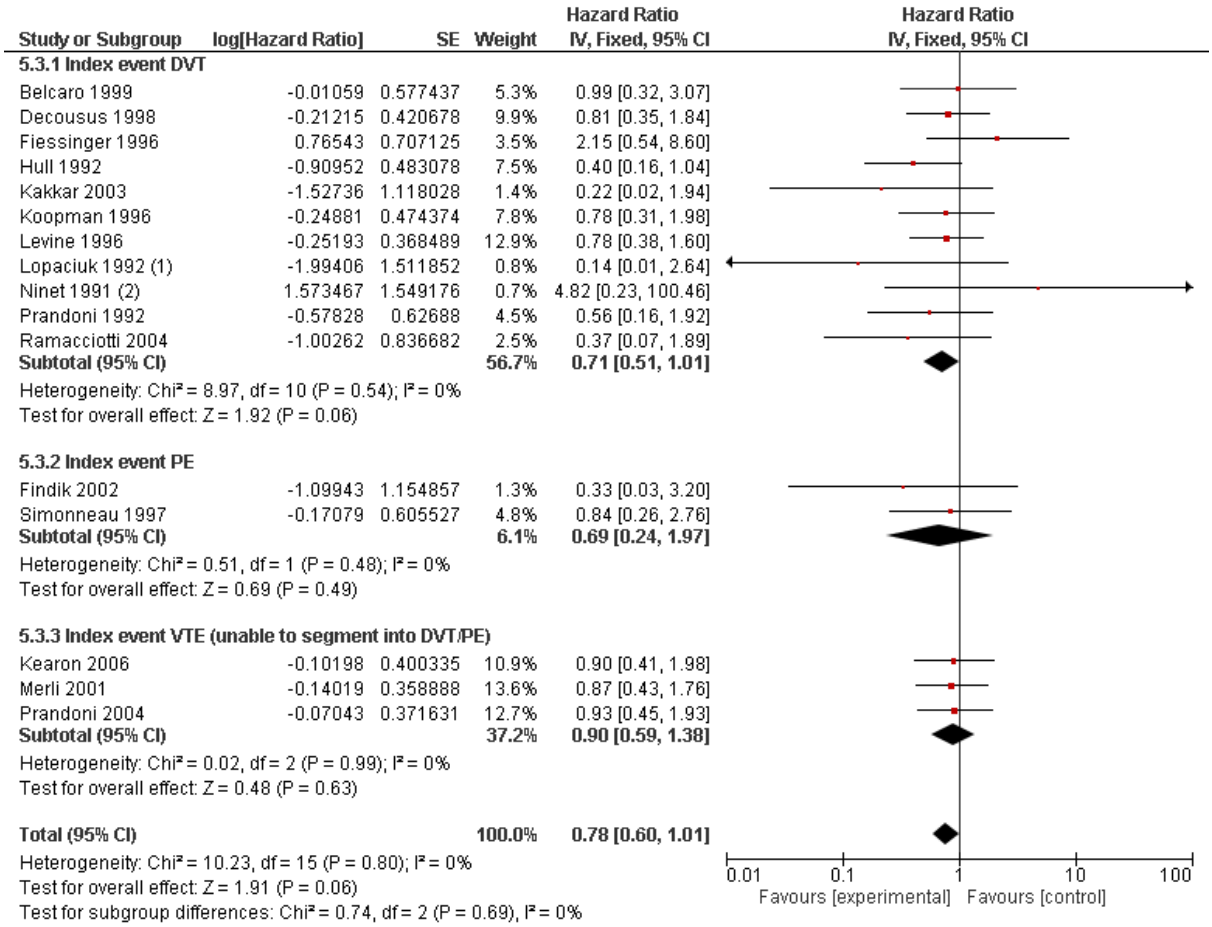


Figure 165: Major bleeding: all major bleeds (converted from event data)

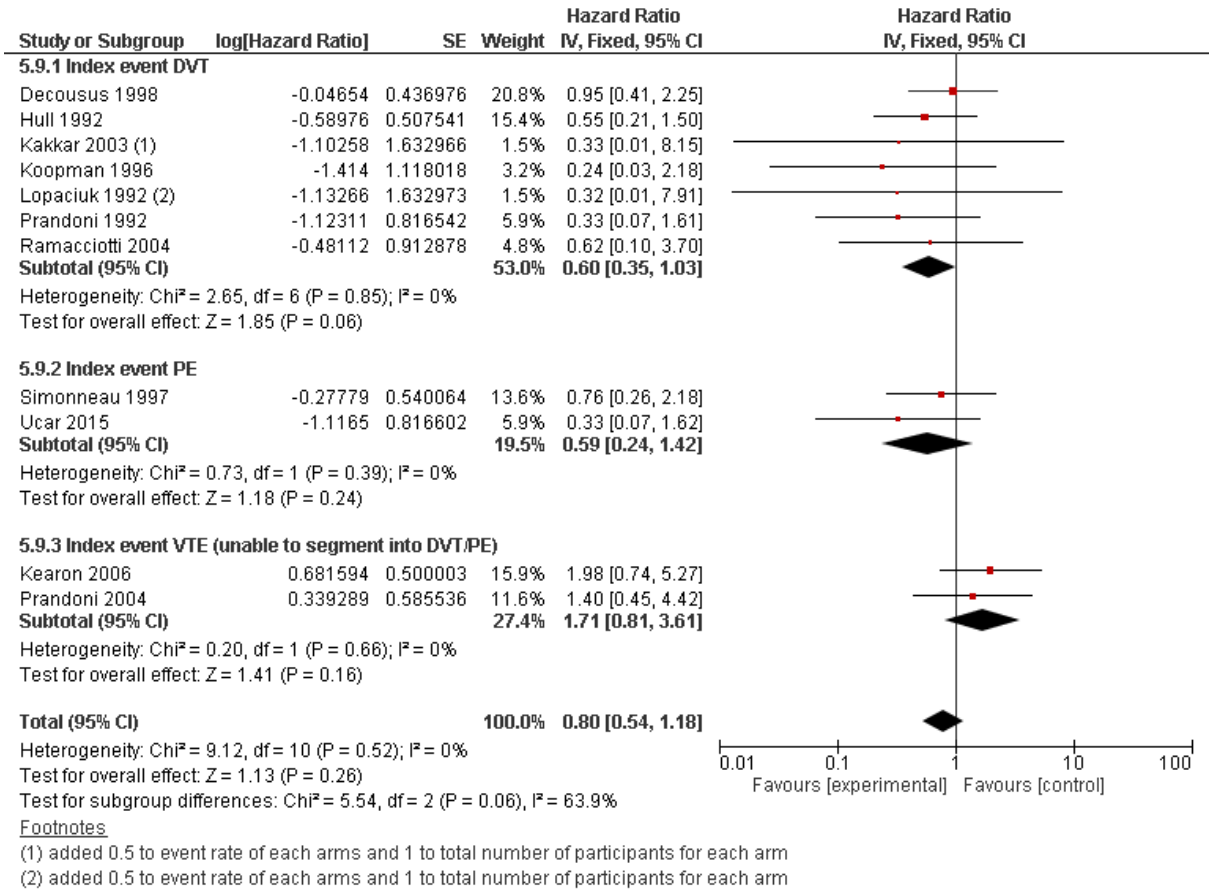


Figure 166: Clinically relevant non-major bleeding (converted from event data)

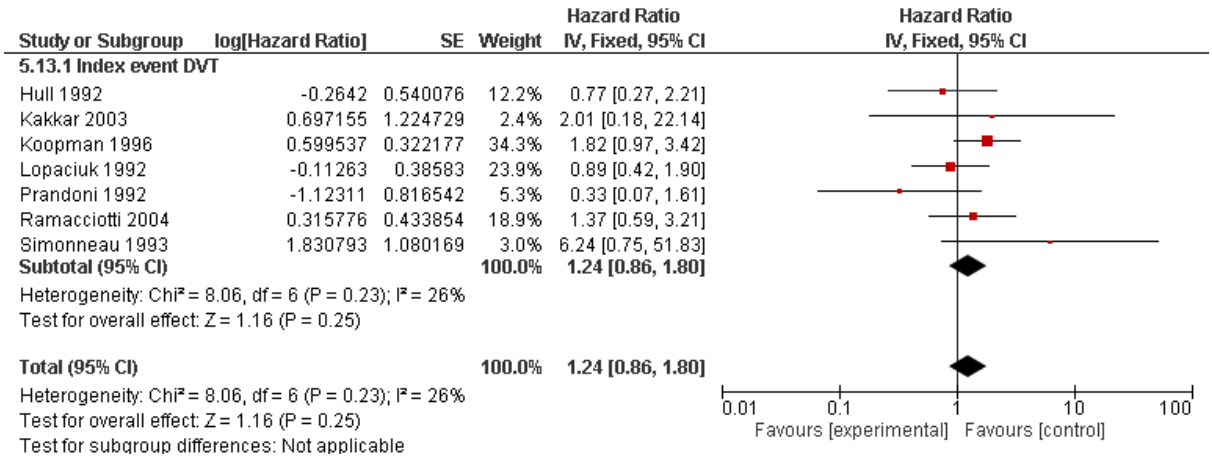
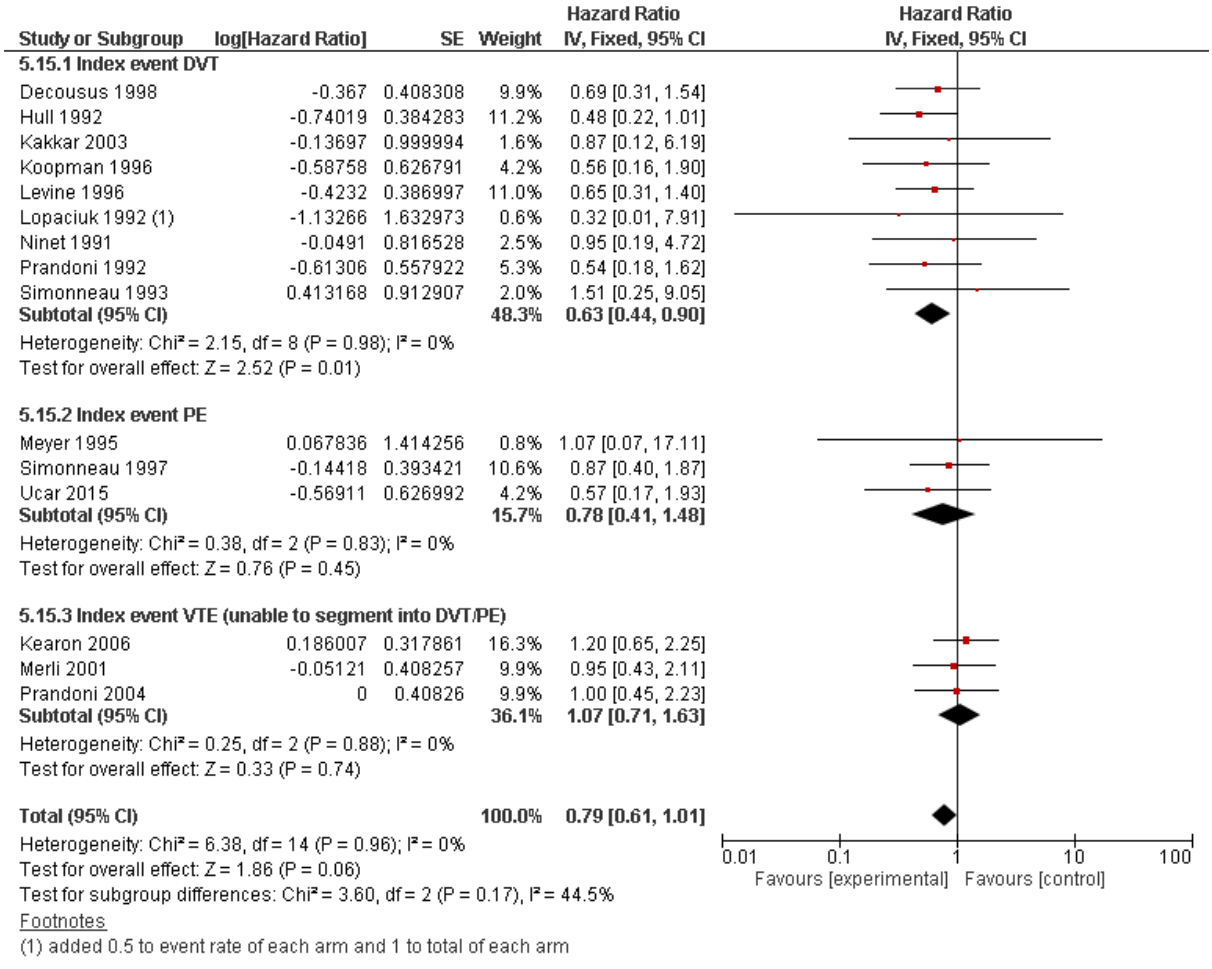
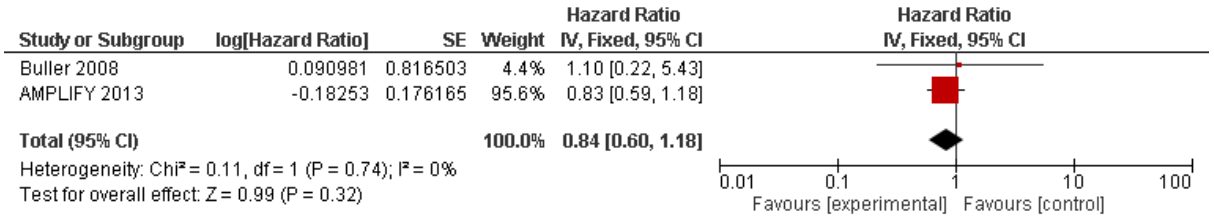


Figure 167: All-cause mortality (converted from event data)



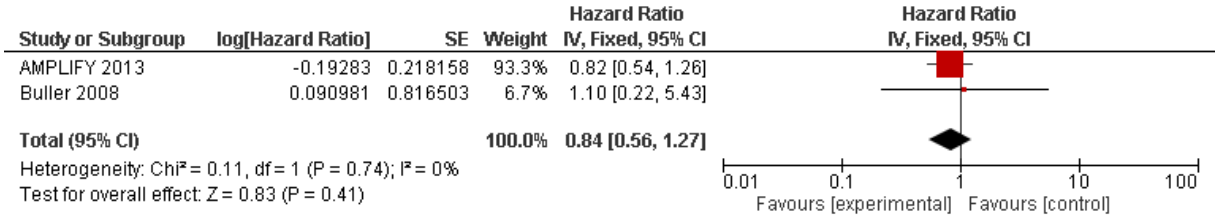
Apixaban (5/10mg twice daily for 7 days followed by 5mg twice daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Figure 168: VTE-recurrence (converted from event data)



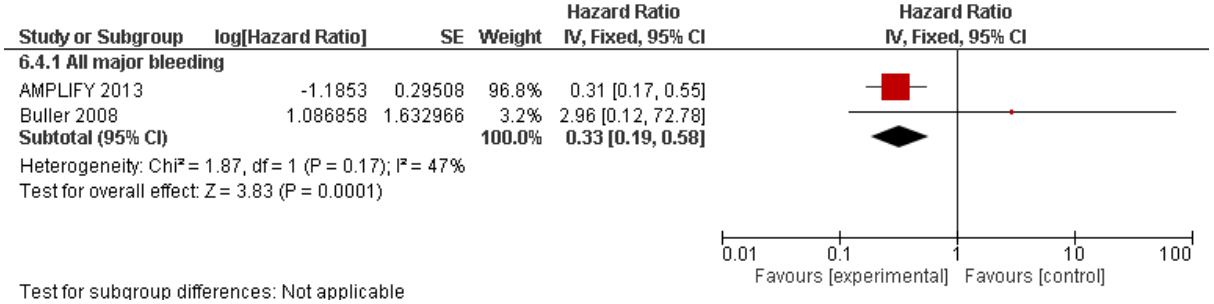
1

2 **Figure 169: VTE-recurrence (subgroup analysis of only DVT patients; converted from**
3 **event data)**



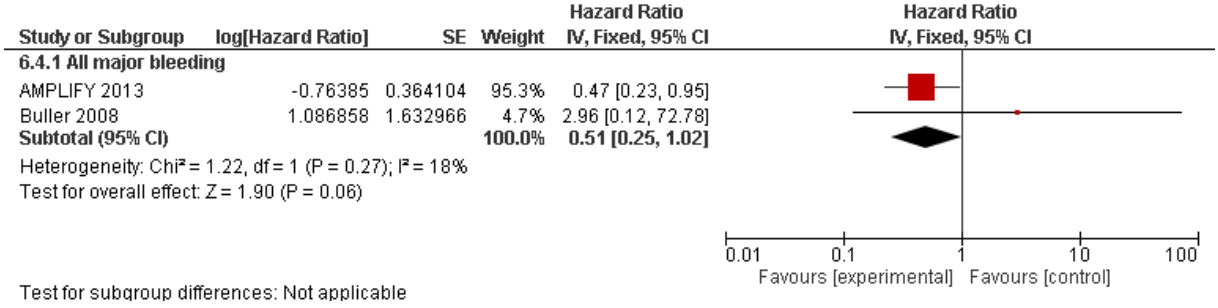
4

5 **Figure 170: Major bleeding (converted from event data)**



6 Test for subgroup differences: Not applicable

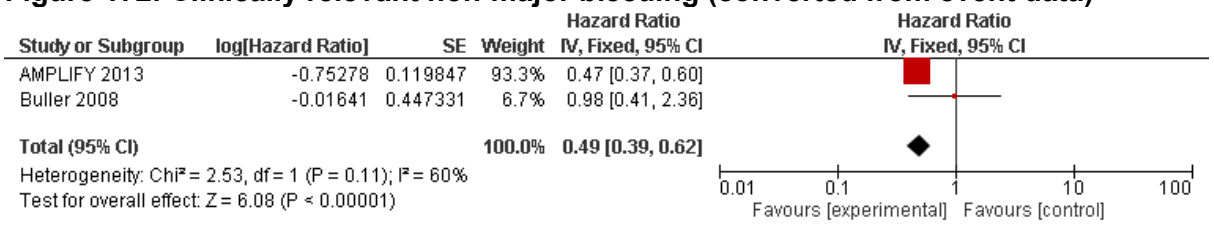
7 **Figure 171:Major bleeding (subgroup analysis of only DVT patients; converted from**
8 **event data)**



9 Test for subgroup differences: Not applicable

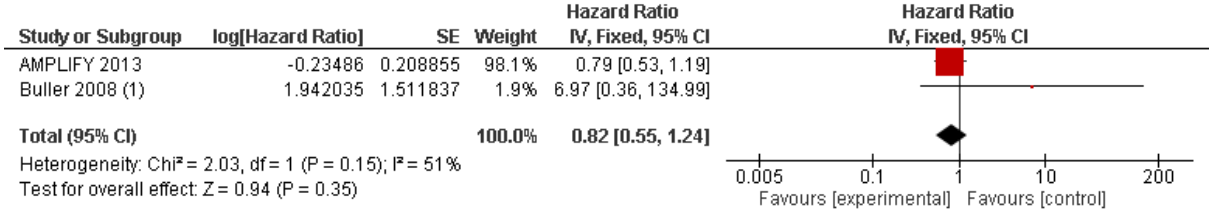
10

11 **Figure 172: Clinically relevant non-major bleeding (converted from event data)**



12

Figure 173: All-cause mortality (converted from event data)



Footnotes

(1) added 0.5 to event rate of each arm and 1 to total of each arm

Dabigatran (150mg twice daily) versus LMWH + VKA for VTE

Figure 174: Clinically relevant non major bleeding (converted from event data)

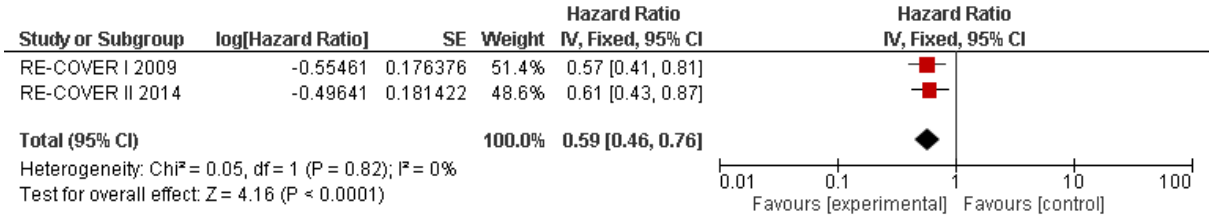
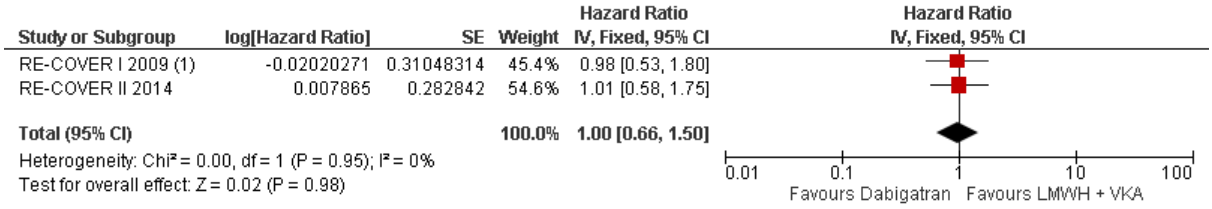


Figure 175: All-cause mortality (converted from event data)

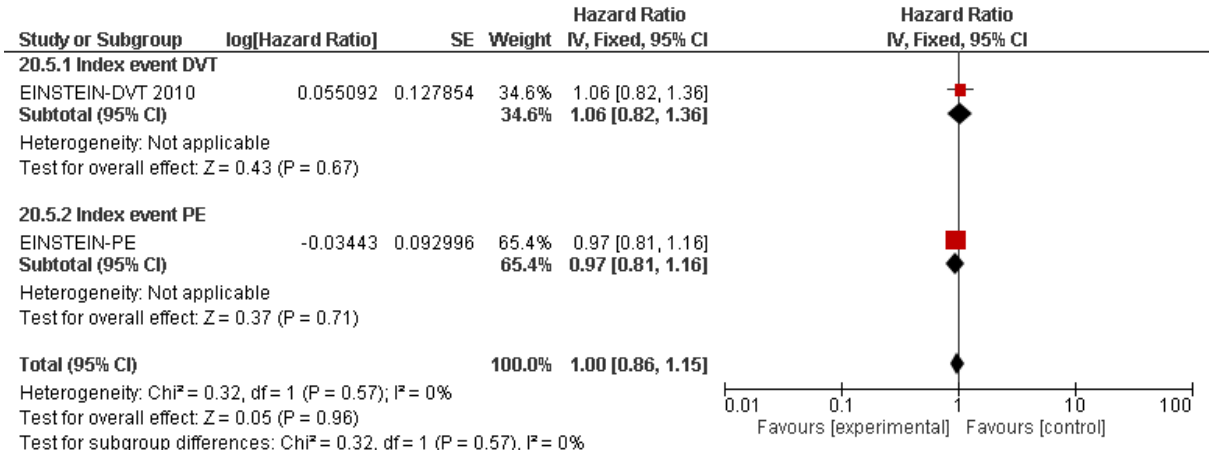


Footnotes

(1) Taken directly from study (not converted from event data)

Rivaroxaban (15mg twice daily for 3 weeks followed by 20mg once daily) versus LMWH + VKA for the initial treatment of VTE (DVT and/or PE)

Figure 176: Clinically relevant non-major bleeding (converted from event data)



Warfarin (INR 2.0-3.0) versus placebo for the extended therapy of VTE (DVT and/or PE)

Figure 177: Major bleeding (converted from event data)

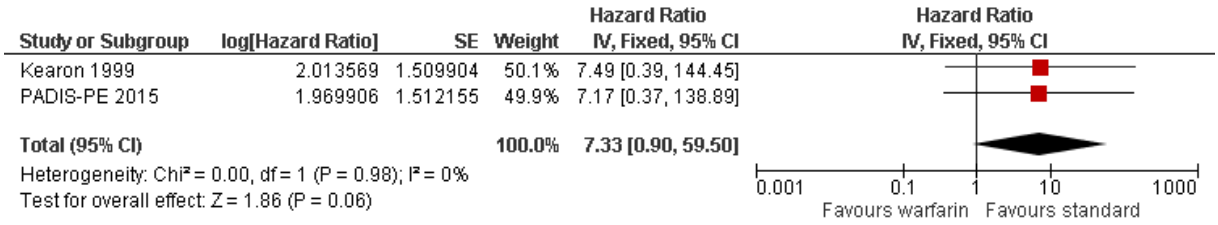
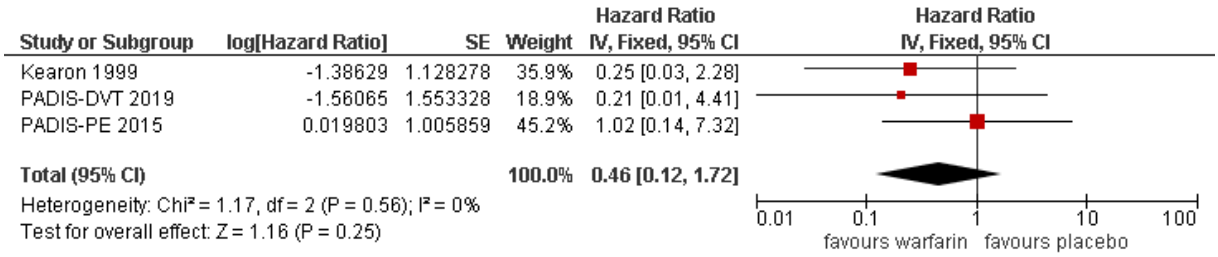


Figure 178: All-cause mortality (converted from event data)



Aspirin (100mg) versus placebo for the extended therapy of VTE (DVT and/or PE)

Figure 179: VTE-recurrence

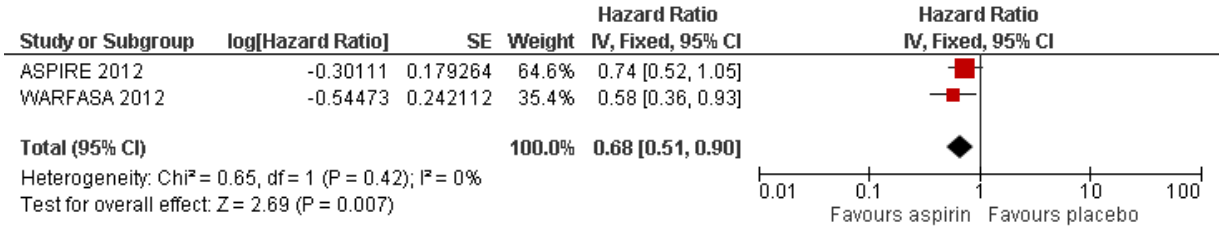


Figure 180: VTE-recurrence (converted from event data)

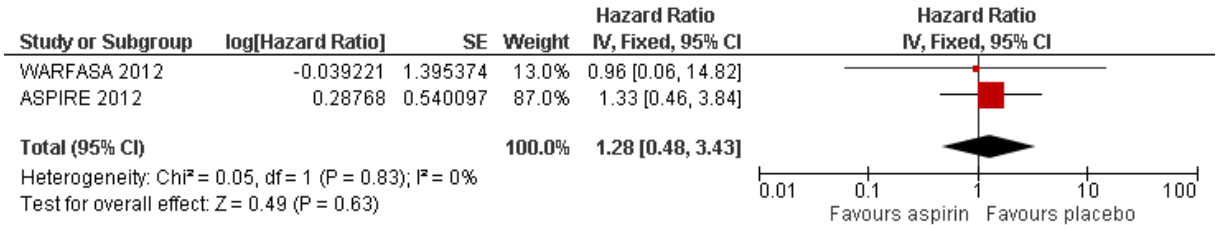
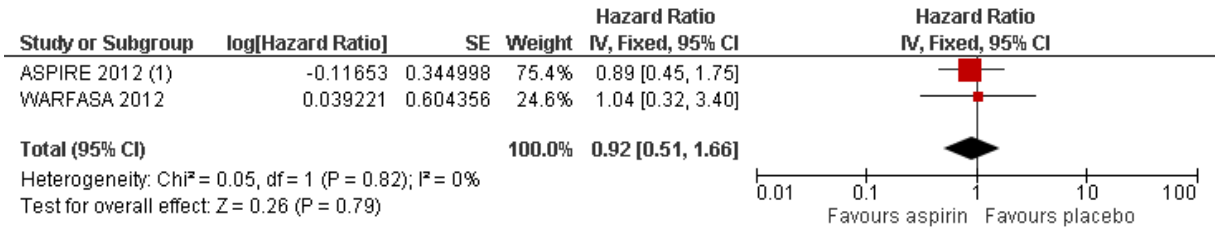
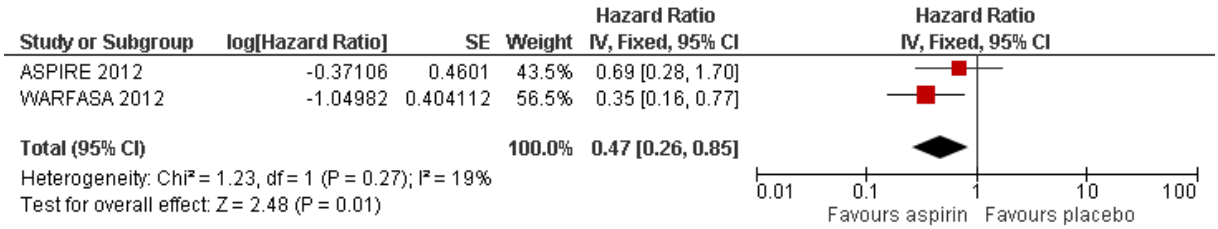


Figure 181: All-cause mortality (converted from event data)



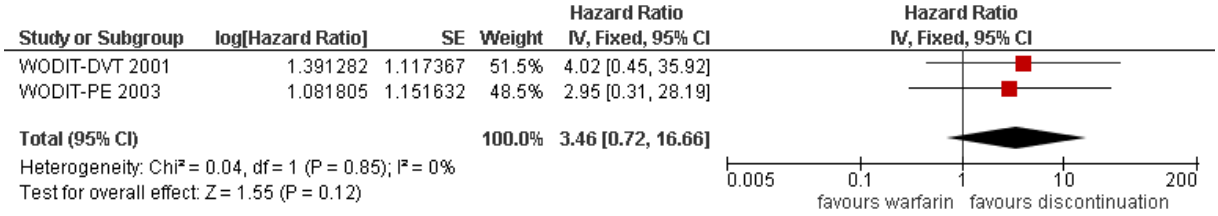
Footnotes
(1) converted from event data -0.11653

Figure 182: (Subgroup analysis: index PE without or without DVT) VTE-recurrence (converted from event data)

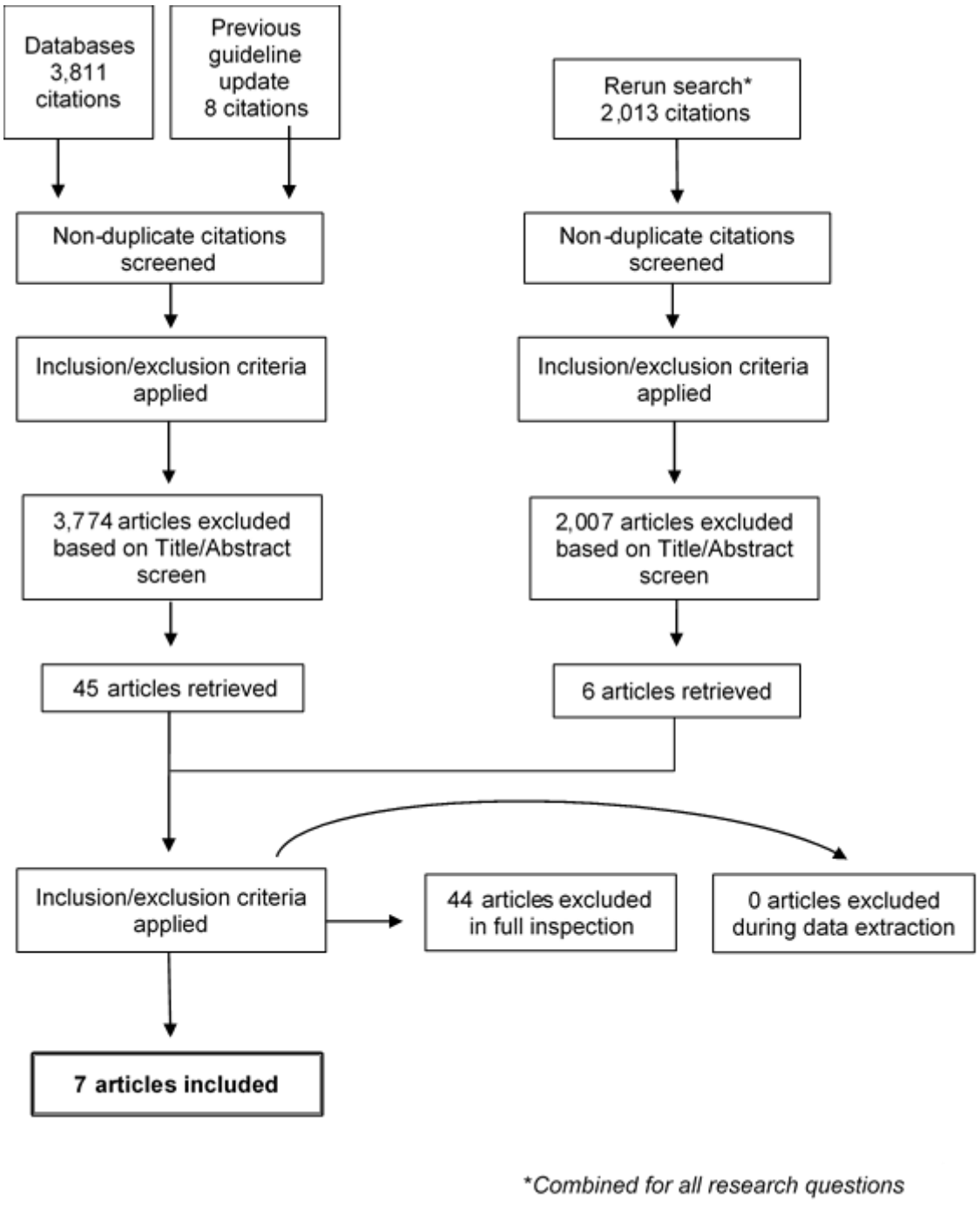


Warfarin (INR 2.0-3.0) versus discontinuation for the extended therapy of VTE (DVT and/or PE)

Figure 183: Major bleeding



Appendix K – Economic evidence study selection



Appendix L – Economic evidence tables

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Bamber et al. (2015)	1. Partially applicable[(a)] 2. Potentially serious limitations[(b)]	Rivaroxaban versus LMWH/VKA	UK	Lifetime 3.5% for costs and health effects	Rivaroxaban produces an ICER of: • £8,677/QALY in patients with a DVT • £7,072/QALY in patients with a PE	Probabilistic sensitivity analysis shows that rivaroxaban has a >81% probability of being cost effective at a £20,000/QALY threshold in both groups

(b) Only includes two of the interventions of interest
(c) Potential conflict of interest (funded by the manufacturer of rivaroxaban)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Lanitis et al. (2016)	1. Partially applicable[(a)] 2. Potentially serious limitations[(b)]	• Apixaban • Rivaroxaban • Dabigatran • LMWH/VKA	UK	Lifetime 3.5% for costs and health effects	Apixaban dominates rivaroxaban and dabigatran, and produces an ICER of £2,520/QALY compared to LMWH/VKA	Probabilistic sensitivity analysis shows that rivaroxaban has a >85% probability of being cost effective at a £20,000/QALY. Scenario analyses exploring different treatment durations and in PE/DVT subgroups found that apixaban remains cost effective.

(a) Does not evaluate the entire decision space (edoxaban not included)
(b) Potential conflict of interest (funded by the manufacturer of apixaban)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty

Lanitis et al. (2017)	1. Partially applicable[a] 2. Potentially serious limitations[b]	• Apixaban – 12 months anticoagulation • LMWH/VKA – 6 months anticoagulation • LMWH/VKA – 12 months anticoagulation	UK	Lifetime 3.5% for costs and health effects	Apixaban produces an ICER of: • £6,692/QALY compared to 12 months of LMWH/VKA • £8,528/QALY compared to 6 months of LMWH/VKA	Probabilistic sensitivity analysis showed that apixaban has a 94% probability of being cost-effective at a threshold of £20,000/QALY

(a) Only includes 2 of the interventions of interest
(b) Potential conflict of interest (funded by the manufacturer of apixaban)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Jugrin et al. (2015)	1. Partially applicable[a] 2. Potentially serious limitations[b]	Dabigatran versus LMWH/warfarin in patients anticoagulated for up to 6 months and up to 24 months	UK	Lifetime 3.5% for costs and health effects	Dabigatran produces an ICER of: • £767/QALY in patients treated for up to 6 months • £7,877/QALY in patients treated for up to 24 months	Dabigatran remained cost effective in DVT/PE subgroups for both treatment durations. Probabilistic sensitivity analysis showed that dabigatran has a 79%-94% probability of being cost effective at a £20,000/QALY threshold across all patient groups

(a) Only includes 2 of the interventions of interest
(b) Potential conflict of interest (funded by the manufacturer of dabigatran)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Jugrin et al. (2016)	1. Partially applicable[a]	Dabigatran versus rivaroxaban in patients treated	UK	Lifetime	Dabigatran dominates rivaroxaban in both treatment duration groups	Dabigatran remained cost effective in DVT/PE subgroups for both treatment durations.

	2. Potentially serious limitations[b]	with 6 months of anticoagulation and with extended anticoagulation	3.5% for costs and health effects			Probabilistic sensitivity analysis showed that dabigatran has a 61%-88% probability of being cost effective at a £20,000/QALY threshold across all patient groups

(a) Only includes 2 of the interventions of interest
(b) Potential conflict of interest (funded by the manufacturer of dabigatran)

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Sterne et al. (2017)	1. Directly applicable 2. Potentially serious limitations[a]	**Acute treatment:** • LMWH/warfarin • Rivaroxaban • Dabigatran • Apixaban • Edoxaban **Secondary prevention:** • Warfarin • Rivaroxaban • Dabigatran • Apixaban 2.5 mg bd • Apixaban 5 mg bd • Aspirin • No pharmacotherapy	UK	Lifetime 3.5% for costs and health effects	**Acute treatment:** apixaban produces an ICER of £800 per QALY compared to LMWH/warfarin. All other options are dominated **Secondary prevention:** dabigatran produces an ICER of £64,660 compared to aspirin. All other options are dominated	**Acute treatment:** Probabilistic sensitivity analysis shows that apixaban has a probability of ~54% of being cost-effective at a threshold of £20,000-£30,000/QALY. All other treatments have probabilities <25%. **Secondary prevention:** Probabilistic sensitivity analysis shows that aspirin and no pharmacotherapy have non-trivial probabilities of being cost effective at a threshold of £20,000 per QALY (~70% and ~30%, respectively)

(a) Assumes equal intracranial bleeding rates across DOACs in acute treatment model, uses atrial fibrillation treatment effects for intracranial bleeding in secondary prevention model, introduces unnecessary uncertainty to model results by including treatment effects on mortality, assumes that all bleeding-related mortality is due to intracranial bleeding, no list price was available at the time for edoxaban so cost assumed equal to dabigatran

Study	1. Applicability 2. Limitations	Comparison(s)	Setting	Duration Discount rate(s)	Results / conclusion	Uncertainty
Clay et al. (2018)	1. Partially applicable[(a)] 2. Potentially serious limitations[(b)]	Edoxaban versus LMWH/VKA as acute treatment of VTE (6 months) and lifelong treatment of recurrent VTE	UK	Lifetime 3.5% for costs and health effects	Edoxaban dominates LMWH/VKA in both treatment duration groups	Edoxaban remained cost effective in DVT/PE subgroups for both treatment durations. Probabilistic sensitivity analysis showed that edoxaban has a 99.5% probability of being cost effective at a £20,000/QALY threshold.

(a) Only includes 2 of the interventions of interest
(b) Potential conflict of interest (funded by the manufacturer of edoxaban)

Appendix M –Excluded studies

Clinical studies (main search)

Author (year)	Title	Reason for exclusion
Adam (2012)	Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review	• Systematic review used as a source of primary studies
Agnelli (2007)	Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study	• Drug not given at a clinically relevant dosage
Agnelli (2013)	Apixaban reduced recurrence and did not increase major bleeding in previously treated VTE. Annals of Internal Medicine 158(8): jc3	• Conference abstract
Agnelli (2013)	Apixaban for extended treatment of venous thromboembolism. New England Journal of Medicine 368(8): 699-708	• Conference abstract
Agnelli (2015)	Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial	• Associated study
Akl (2008)	Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer.	• Systematic review used as a source of primary studies
Akl (2008)	Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer.	• Systematic review used as a source of primary studies
Akl (2008)	Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer	• Systematic review used as a source of primary studies
Akl (2008)	Low-molecular-weight heparins are superior to vitamin K antagonists for the long term treatment of venous thromboembolism in patients with cancer: A cochrane systematic review	• Systematic review used as a source of primary studies
Akl (2014)	Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer	• Systematic review used as a source of primary studies
Almutairi (2017)	Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Alotaibi (2014)	Dabigatran, rivaroxaban and apixaban for extended venous thromboembolism treatment: network meta-analysis	• More recent NMA available
Andras (2017)	Vitamin K antagonists versus low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism	• Systematic review used as a source of primary studies
Anonymous (2010)	Dabigatran as effective as warfarin for treatment of acute venous thromboembolism	• Conference abstract
Anonymous (2017)	Erratum: Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: A randomized clinical trial (JAMA (2015) 314:7 (677-686) DOI: 10.1001/jama.2015.9243)	• Conference abstract
Antoniazzi (2013)	Risk of major bleeding with dabigatran versus active controls: a systematic review and meta-analysis of randomised clinical trials	• Conference abstract
Bamber (2013)	Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis	• Associated study
Bauersachs (2013)	No need for a rivaroxaban dose reduction in renally impaired patients with symptomatic venous thromboembolism	• Conference abstract
Bauersachs (2018)	Renal Impairment, Recurrent Venous Thromboembolism and Bleeding in Cancer Patients with Acute Venous Thromboembolism-Analysis of the CATCH Study	• Cancer only study
Becattini (2012)	Aspirin for preventing the recurrence of venous thromboembolism: editorial comment	• Editorial comment
Becattini (2012)	Aspirin reduced recurrence of venous thromboembolism (VTE) after a first-ever, unprovoked VTE. Annals of Internal Medicine 157(8): JC4-JC3	• Conference abstract
Becattini (2012)	Aspirin after oral anticoagulants for prevention of recurrence in patients with unprovoked venous thromboembolism. the warfasa study. Blood 118(21)	• Conference abstract
Beckman (2003)	Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism.	• Comparator in study does not match that specified in protocol [Info] Study compared LMWH montherapy to UFH (with VKA)
Belcaro (1999)	Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis.	• Randomised controlled trial

Author (year)	Title	Reason for exclusion
Bleker (2016)	Clinical presentation and course of bleeding events in patients with venous thromboembolism, treated with apixaban or enoxaparin and warfarin. Results from the AMPLIFY trial	• Associated study
Bleker (2017)	Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists. An individual patient data meta-analysis	• Systematic review used as a source of primary studies
Bloom (2014)	Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran	• Systematic review used as a source of primary studies
Boehringer (2012)	Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp Venous Thromboembolism (VTE)	• Conference abstract
Bookhart (2014)	Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program	• Associated study
Bova (2016)	Extended anticoagulation and mortality in venous thromboembolism. A meta-analysis of six randomized trials	• Systematic review used as a source of primary studies
Bratt (1990)	Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT).	• Comparator in study does not match that specified in protocol [Info] compared heparin monotherapies that unlikely used VKA or oral anticoagulant
Brekelmans (2016)	Clinical impact and course of major bleeding with edoxaban versus vitamin K antagonists	• Associated study
Brekelmans (2017)	Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin	• Associated study
Brighton (2012)	Aspirin for the prevention of recurrent venous thromboembolism after a first unprovoked event: results of the ASPIRE randomized controlled trial. Circulation 126(23): 2777	• Conference abstract
Brighton (2013)	Aspirin did not reduce recurrence after a first-ever, unprovoked venous thromboembolism. Annals of Internal Medicine 158(6): jc2	• Conference abstract
Buller (2003)	Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism.[Erratum appears in N Engl J Med. 2004 Jan 22;350(4):423]	• Erratum that accompanies an included study
Buller (2008)	A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in	• Drug not given at a clinically relevant dosage

Author (year)	Title	Reason for exclusion
	the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study	
Buller (2010)	Oral rivaroxaban for the acute and continued treatment of symptomatic venous thromboembolism. The einstein-DVT and einstein-extension study	• Conference abstract
Buller (2012)	Enoxaparin followed by once-weekly idrabiotaparinux versus enoxaparin plus warfarin for patients with acute symptomatic pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial	• Comparator in study does not match that specified in protocol
Buller (2013)	Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism	• Associated study
Caldeira (2015)	Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Caldeira (2015)	Risk of Substantial Intraocular Bleeding With Novel Oral Anticoagulants: Systematic Review and Meta-analysis	• Systematic review used as a source of primary studies
Caldeira (2015)	Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants	• Systematic review used as a source of primary studies
Camm (2009)	The RE-LY study: Randomized Evaluation of Long-term anticoagulant therapY: Dabigatran vs. warfarin	• Does not contain a population of people with confirmed VTE
Carrier (2014)	Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Castellucci (2013)	Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis	• Systematic review used as a source of primary studies
Castellucci (2014)	Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Chai-Adisaksopha (2015)	Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Cheung (2015)	Post thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep vein thrombosis	• Conference abstract
Chitsike (2012)	Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: Results from the REVERSE study	• Not a relevant study design Non-randomised
Chong (2005)	Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis.	• Data not reported in an extractable format
Cohen (2015)	Rivaroxaban in antiphospholipid syndrome (RAPS) protocol: a prospective, randomized controlled phase II/III clinical trial of rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without SLE	• Not a relevant study design
Cohen (2015)	Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis	• More recent NMA available.
Cohen (2015)	Comparison of apixaban, dabigatran, rivaroxaban, and edoxaban in the acute treatment and prevention of venous thromboembolism: systematic review and network meta-analysis	• Conference abstract
Cohen (2016)	Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial	• Data not reported in an extractable format Data was reported at day 210 only, with treatment having been stopped at day 180.
Cohen (2016)	Comparison of the Non-VKA Oral Anticoagulants Apixaban, Dabigatran, and Rivaroxaban in the Extended Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis	• More recent NMA available
Cohen (2016)	Comparison of the Non-VKA Oral Anticoagulants Apixaban, Dabigatran, and Rivaroxaban in the Extended Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis. PLoS ONE [Electronic Resource] 11(8): e0160064	• More recent NMA available
Coleman (2017)	Effectiveness and safety of rivaroxaban versus warfarin for treatment and prevention of recurrence of venous thromboembolism	• Review article but not a systematic review
Coleman (2018)	Effectiveness and Safety of Rivaroxaban Versus Warfarin in Frail Patients with Venous Thromboembolism	• Review article but not a systematic review

Author (year)	Title	Reason for exclusion
Cortes-Hernandez (2017)	Rivaroxaban versus warfarin as secondary thromboprophylaxis in patients with antiphospholipid syndrome protocol: a randomized, multicentre, open-label, clinical trial	• Conference abstract
Cosmi (2012)	A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis: STEFLUX (Superficial ThromboEmbolism and Fluxum)	• Population not applicable to the review question
Costantino (2012)	Bleeding risk during treatment of acute thrombotic events with subcutaneous LMWH compared to intravenous unfractionated heparin; a systematic review	• Systematic review used as a source of primary studies
Cully (2013)	Long-term dabigatran therapy reduces the risk of recurrent venous thromboembolism	• Review article but not a systematic review
Das (1996)	Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial.	• Drug comparison not of interest to this review
Daskalopoulos (2005)	Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial.	• Comparator in study does not match that specified in protocol Study compared warfarin (monotherapy) versus LMWH (monotherapy) in a non-cancer population
De Alba (2015)	Randomized clinical trial of rivaroxaban in the prevention of post-thrombotic syndrome	• Study not reported in English
De Martino (2012)	A meta-analysis of anticoagulation for calf deep venous thrombosis	• Systematic review used as a source of primary studies
Dentali (2015)	Non-vitamin K oral anticoagulants in patients with pulmonary embolism: a systematic review and meta-analysis of the literature	• Systematic review used as a source of primary studies
Di Minno (2015)	Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
	venous thromboembolism: a meta-analysis of randomized controlled trials	
Di Minno (2015)	Direct oral anticoagulants for the treatment of unprovoked venous thromboembolism: a meta-analysis of randomised controlled trials	• Systematic review used as a source of primary studies
Di Minno (2017)	Direct oral anticoagulants for the treatment of acute venous thromboembolism in patients with cancer: a meta-analysis of randomised controlled trials	• Systematic review used as a source of primary studies
Diaz (2015)	Low-molecular-weight hepar in treatment of deep-vein thrombosis: a network meta-analysis	• Conference abstract
Douketis (2014)	Approach to the new oral anticoagulants in family practice: part 1: comparing the options	• Systematic review used as a source of primary studies
Dranitsaris (2017)	Dalteparin versus vitamin K antagonists for the prevention of recurrent venous thromboembolism in patients with cancer and renal impairment: a Canadian pharmacoeconomic analysis	• Study does not contain any of the outcomes of interest
Dunn (2017)	In VTE, extending anticoagulation with rivaroxaban vs aspirin reduced recurrence without increasing bleeding. Annals of Internal Medicine 166(12): jc65	• Conference abstract
Eerenberg (2015)	Clinical impact and course of major bleeding with rivaroxaban and vitamin K antagonists	• Associated study
Faivre (1987)	[Efficacy of a very low molecular weight heparin fragment (CY 222) compared to standard heparin in patients with deep venous thrombosis. A randomized study].	• Drug comparison not of relevance to this review.
Farge (2018)	Quality of life in cancer patients undergoing anticoagulant treatment with LMWH for venous thromboembolism: The QUAVITEC study on behalf of the Groupe Francophone Thrombose et Cancer (GFTC)	• Not a relevant study design Non-randomised
Fox (2012)	Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials	• Systematic review used as a source of primary studies
Frank (2018)	Emergency Department Discharge of Pulmonary Embolus Patients	• Drug comparison not of relevance to this review Comparator drug not defined.

Author (year)	Title	Reason for exclusion
Frey (2010)	Warfarin pharmacodynamics and pharmacokinetics are not affected by the soluble guanylate cyclase stimulator riociguat (bay 63-2521): results of a randomized, controlled trial	• Conference abstract
Galanis (2014)	The new oral anticoagulants for the treatment of venous thromboembolism: a new paradigm shift in antithrombotic therapy	• Systematic review used as a source of primary studies
Ganji (2016)	Comparison of Dabigatran vs. Warfarin in Acute Vnous Thromboemboly: Systematic Review	• Systematic review used as a source of primary studies
Gomez-Outes (2014)	Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Gomez-Outes (2018)	Causes of Death in Patients with Venous Thromboembolism Anticoagulated with Direct oral anticoagulants: A Systematic Review and Meta-Analysis	• Systematic review used as a source of primary studies
Gonzalez-Fajardo (1999)	Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis.	• Original guideline papers
Gonzalez-Fajardo (2008)	Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: Comparative study of enoxaparin versus coumarin.	• Comparator in study does not match that specified in protocol Study compared warfarin monotherapy versus LMWH monotherapy
Granziera (2014)	Randomised controlled trial: Evidence suggests dabigatran is an effective and safe treatment for patients with VTE requiring early parenteral therapy	• Conference abstract
Greig (2014)	Dabigatran etexilate: a review of its use in the treatment of acute venous thromboembolism and prevention of venous thromboembolism recurrence	• Systematic review used as a source of primary studies
Greig (2016)	Apixaban: A Review in Venous Thromboembolism	• Systematic review used as a source of primary studies
Hakoum (2018)	Anticoagulation for the initial treatment of venous thromboembolism in people with cancer	• Systematic review used as a source of

Author (year)	Title	Reason for exclusion
		primary studies
Handeland (1990)	Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin.	• Not a relevant study design Non-randomised
Harel (2015)	Comparison of novel oral anticoagulants versus vitamin K antagonists in patients with chronic kidney disease	• Systematic review used as a source of primary studies
Harenberg (1990)	Therapeutic application of subcutaneous low-molecular-weight heparin in acute venous thrombosis	• Data not reported in an extractable format
Ho (2009)	Milestone results in RE-COVERTM study - Novel oral direct thrombin inhibitor dabigatran etexilate - As effective as well-controlled warfarin with less bleeding in treatment of acute venous thromboembolism	• Full text paper not available
Holster (2013)	New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Holy (2014)	Direct oral anticoagulants in the management of venous thromboembolism--evidence from major clinical trials	• Systematic review used as a source of primary studies
Hong (2018)	Effect of anticoagulants on admission rates and length of hospital stay for acute venous thromboembolism: A systematic review of randomized control trials	• Systematic review used as a source of primary studies
Hull (2000)	Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. American-Canadian Thrombosis Study Group.	• Comparator in study does not match that specified in protocol
Hull (2007)	Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms.	• Comparator in study does not match that specified in protocol Study compared LMWH monotherapy versus UFH + VKA
Hull (2009)	Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome.	• Comparator in study does not match that specified in protocol Study compared LMWH monotherapy versus LMWH + VKA

Author (year)	Title	Reason for exclusion
Imberti (2018)	Real-Life Management of Venous Thromboembolism With Rivaroxaban: Results From EXperience VTE, an Italian Epidemiological Survey	• Not a relevant study design Non-randomized
Jiang (2018)	Comparative efficacy and safety of low-intensity warfarin therapy in preventing unprovoked recurrent venous thromboembolism: A systematic review and meta-analysis	• Systematic review used as a source of primary studies
Johnson (2015)	Continuing warfarin for 18 months after unprovoked PE reduces risk of recurrent VTE	• Conference abstract
Kakkar (2003)	Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis.	• Original guideline papers
Kakkos (2014)	Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials	• Systematic review used as a source of primary studies
Kamphuisen (2018)	Clinically relevant bleeding in cancer patients treated for venous thromboembolism from the CATCH study	• Associated study
Kaymaz (2017)	EINSTEIN CHOICE: comparison of rivaroxaban treatment and prophylactic doses with aspirin in the extended treatment of patients with venous thromboembolism. Turk Kardiyoloji Dernegi arsivi 45(suppl4): 1-7	• Not reported in english
Kearon (2006)	Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism.	• Duplicate reference
Kraaijpoel (2016)	Clinical impact and course of anticoagulant-related major bleeding in cancer patients	• Conference abstract
Kraaijpoel (2018)	Clinical Impact and Course of Anticoagulant-Related Major Bleeding in Cancer Patients	• Systematic review used as a source of primary studies
Kucher (2005)	Extended enoxaparin monotherapy for acute symptomatic pulmonary embolism.	• Comparator in study does not match that specified in protocol
Kurtoglu (2010)	Long-term efficacy and safety of once-daily enoxaparin plus warfarin for the outpatient ambulatory treatment of	• Comparator in study does not match that specified in protocol

Author (year)	Title	Reason for exclusion
	lower-limb deep vein thrombosis in the TROMBOTEK trial	
Laporte (2012)	Long-term treatment of venous thromboembolism with tinzaparin compared to vitamin K antagonists: a meta-analysis of 5 randomized trials in non-cancer and cancer patients	• Systematic review used as a source of primary studies
Laporte (2017)	Assessment of clinically relevant bleeding as a surrogate outcome for major bleeding: validation by meta-analysis of randomized controlled trials	• Systematic review used as a source of primary studies
Larsen (2014)	Non-vitamin K antagonist oral anticoagulants and the treatment of venous thromboembolism in cancer patients: a semi systematic review and meta-analysis of safety and efficacy outcomes	• Systematic review used as a source of primary studies
Lee (2013)	CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients	• Secondary publication of an included study that does not provide any additional relevant information
Lee (2016)	Effectiveness of Adaptive Statistical Iterative Reconstruction for 64-Slice Dual-Energy Computed Tomography Pulmonary Angiography in Patients With a Reduced Iodine Load: comparison With Standard Computed Tomography Pulmonary Angiography	• Study does not contain any relevant interventions
Lega (2014)	Consistency of safety profile of new oral anticoagulants in patients with renal failure	• Systematic review used as a source of primary studies
Li (2018)	Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis	• Systematic review used as a source of primary studies
Liakishev (2010)	Dabigatran versus warfarin in the treatment of acute venous thromboembolism. Results of the RE-COVER study	• Study not reported in English
Liu (2013)	Apixaban reduces hospitalization in patients with venous thromboembolism: an analysis of the amplify-ext trial	• Conference abstract
Liu (2015)	Apixaban Reduces Hospitalizations in Patients With Venous Thromboembolism: An Analysis of the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) Trial	• Associated study
Liu (2016)	Extended anticoagulation with apixaban reduces hospitalisations in patients with venous	• Study does not contain any of the

Author (year)	Title	Reason for exclusion
	thromboembolism. An analysis of the AMPLIFY-EXT trial	outcomes of interest
Loffredo (2015)	New oral anticoagulants for the treatment of acute venous thromboembolism: are they safer than vitamin K antagonists? A meta-analysis of the interventional trials	• More recent systematic review included that covers the same topic
London (2010)	Oral fixed-dose rivaroxaban slashes risk of recurrent VTE	• Review article but not a systematic review
Lopaciuk (1999)	Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis.	• Duplicate reference
Lopez-Beret (2001)	Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis.	• Drug comparison not of relevance to this review.
Lopez-Lopez (2015)	Network meta-analysis of oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation	• NMA used as a source of primary studies
Lyman (2015)	Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014	• Systematic review used as a source of primary studies
Majeed (2016)	Bleeding events with dabigatran or warfarin in patients with venous thromboembolism	• Secondary publication of an included study that does not provide any additional relevant information
Mak (2012)	Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomised trials	• Systematic review used as a source of primary studies
Manganaro (2000)	[Evolution in the pharmacological treatment of venous thrombosis according to evidence-based medicine].	• Review article (non-systematic)
Marcy (2015)	Comparing Direct oral anticoagulants and Warfarin for Atrial Fibrillation, Venous Thromboembolism, and Mechanical Heart Valves	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Martinez-Zapata (2018)	Tinzaparin for Long-Term Treatment of Venous Thromboembolism in Patients With Cancer: A Systematic Review and Meta-Analysis	• Systematic review used as a source of primary studies
Marik (2015)	Extended Anticoagulant and Aspirin Treatment for the Secondary Prevention of Thromboembolic Disease: A Systematic Review and Meta-Analysis. PLoS ONE [Electronic Resource] 10(11): e0143252	• Systematic review used as a source of primary studies
Marvig (2015)	Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants	• Comparator in study does not match that specified in protocol
Mazilu (2014)	Venous thromboembolism: secondary prevention with dabigatran vs.acenocumarolin patients with paraneoplastic deep vein thrombosis. Results from a small prospective study in Romania	• Conference abstract
McBane (2017)	Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE Trial	• Design and methods only
McBride (2017)	Safety and efficacy of direct oral anticoagulants (DOAC) in cancer patients: metaanalysis of randomized controlled trials (RCT)	• Conference abstract
Mearns (2015)	Index clinical manifestation of venous thromboembolism predicts early recurrence type and frequency: a meta-analysis of randomized controlled trials	• Systematic review used as a source of primary studies
Medina (2017)	Outpatient Management in Patients with Venous Thromboembolism with Edoxaban: A Post Hoc Analysis of the Hokusai-VTE Study. Thrombosis and Haemostasis 117(12): 2406-2414	• Review article but not a systematic review
Meyer (2002)	Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study.	• Duplicate reference
Miller (2017)	Risk of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants: A Systematic Review and Meta-analysis	• Systematic review used as a source of primary studies
Minor (2015)	Edoxaban, a Novel Oral Factor Xa Inhibitor	• Systematic review used as a source of primary studies
Munoz-Corcuera (2016)	Dabigatran: A new oral anticoagulant. Guidelines to follow in oral surgery procedures. A systematic review of the literature	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Nakamura (2011)	Multidetector-row computed tomography-based clinical assessment of fondaparinux for treatment of acute pulmonary embolism and acute deep vein thrombosis in Japanese patients	• Review article but not a systematic review
Nct (2008)	Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp Venous Thromboembolism (VTE)	• Conference abstract
Nct (2014)	Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic VTE(Venous Thromboembolism) (EinsteinChoice)	• Conference abstract
Nct (2014)	Rivaroxaban in Thrombotic Antiphospholipid Syndrome	• Conference abstract
Nct (2015)	Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban	• Conference abstract
Nct (2016)	Pradaxa or Warfarin for Prevention of Recurrent VTE in Patients With Angiographically Confirmed Acute Massive Pulmonary Embolism undergoIng Endovascular Mechanical Fragmentation and Thrombolytic Therapy	• Conference abstract
Nct (2017)	A Randomized Phase II Study to Compare the Safety and Efficacy of Dalteparin vs. Rivaroxaban for Cancer-associated Venous Thromboembolism	• Conference abstract
Nct (2017)	Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer	• Conference abstract
Nct (2017)	Comparison of Oral Anticoagulants for Extended VEnous Thromboembolism	• Conference abstract
Nct (2017)	The Danish Non-vitamin K Antagonist Oral Anticoagulation Study in Patients With Venous Thromboembolism (DANNOAC-VTE)	• Conference abstract
Nct (2017)	Comparison of Bleeding Risk Between Rivaroxaban and Apixaban for the Treatment of Acute Venous Thromboembolism	• Conference abstract
Nct (2018)	Rivaroxaban With Diosmine in Long-term Treatment of DVT	• Conference abstract
Nijkeuter (2004)	Pentasaccharides in the prophylaxis and treatment of venous thromboembolism: a systematic review	• Systematic review used as a source of primary studies
Nisio (2016)	Risk of major bleeding in patients with venous thromboembolism treated with rivaroxaban or with heparin and vitamin K antagonists	• Secondary publication of an included study that does not provide any additional relevant information
Noble (2015)	A feasibility study to inform the design of a randomised controlled trial to identify the most clinically effective and cost-effective length of Anticoagulation with Low-	• Rationale and design only

Author (year)	Title	Reason for exclusion
	molecular-weight heparin In the treatment of Cancer-Associated Thrombosis (ALICAT)	
Peacock (2017)	Multicenter trial of rivaroxaban for early discharge of pulmonary embolism from the emergency department	• Comparator in study does not match that specified in protocol
Pebanco (2013)	New pharmacologic methods to prevent venous thromboembolism in older adults: a meta-analysis	• Systematic review used as a source of primary studies
Perez-de-Llano (2010)	Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study.	• Comparator in study does not match that specified in protocol
Peternel (2002)	Markers of hemostatic system activation during treatment of deep vein thrombosis with subcutaneous unfractionated or low-molecular weight heparin.	• Comparator in study does not match that specified in protocol
Piazza (2014)	A randomized, open-label, multicenter study of the efficacy and safety of edoxaban monotherapy versus low-molecular weight heparin/warfarin in patients with symptomatic deep vein thrombosis-edoxaban thrombus reduction imaging study (etris)	• Conference abstract
Pini (1994)	Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis.	• Comparator in study does not match that specified in protocol study compared LMWH monotherapy versus LMWH + VKA
Piovella (2017)	Extended non-vitamin K antagonist oral anticoagulation therapy for prevention of recurrent venous thromboembolism	• Systematic review used as a source of primary studies
Plitt (2014)	Edoxaban: Review of pharmacology and key phase I to III clinical trials	• Systematic review used as a source of primary studies
Posch (2015)	Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants	• More recent NMA available
Prins (2011)	The EINSTEIN DVT study: does localization of the initial DVT affect the occurrence of recurrent VTE while patients are on anticoagulation?	• Conference abstract

Author (year)	Title	Reason for exclusion
Prins (2012)	Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic pulmonary embolism	• Conference abstract
Prins (2014)	Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials	• Associated study
Prins (2015)	Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of pulmonary embolism; results from the EINSTEIN PE trial	• Associated study
Raskob (2011)	Risk assessment for recurrent venous thromboembolism (VTE) after 6-14 months of anticoagulant treatment	• Conference abstract
Raskob (2013)	Edoxaban for the long-term treatment of venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study--methodological implications for clinical trials	• Rationale and design only
Raskob (2016)	Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial	• Associated study
Raskob (2016)	Early time courses of recurrent thromboembolism and bleeding during apixaban or enoxaparin/warfarin therapy. A sub-analysis of the AMPLIFY trial	• Secondary publication of an included study that does not provide any additional relevant information
Raskob (2016)	Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study	• Associated study
Raskob (2018)	Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism.	• Cancer only study
Ridker (2003)	Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism.	• Associated study
Riess (2015)	CONKO-011: evaluation of patient satisfaction with the treatment of acute venous thromboembolism with rivaroxaban or low molecular weight heparin in cancer patients. A randomized phase III study	• Study not reported in English
Righini (2016)	Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial	• Review article but not a systematic review
Rivaroxaban for the... (2018)	Rivaroxaban for the treatment of venous thromboembolism in patients with nephrotic syndrome and low AT-III: a pilot study	• Data not reported in an extractable format

Author (year)	Title	Reason for exclusion
Robertson (2017)	Secondary prevention of recurrent venous thromboembolism after initial oral anticoagulation therapy in patients with unprovoked venous thromboembolism	• Systematic review used as a source of primary studies
Robertson (2017)	Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism	• Systematic review used as a source of primary studies
Rollins (2014)	Evaluation of oral anticoagulants for the extended treatment of venous thromboembolism using a mixed-treatment comparison, meta-analytic approach	• Systematic review used as a source of primary studies
Romualdi (2011)	Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study)	• Randomised controlled trial
Rong (2017)	Comparative clinical efficacy and safety of low-intensity warfarin therapy in preventing recurrent venous thromboembolism: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Rosenberg (2011)	Oral rivaroxaban for acute DVT, or long term for VTE, is as effective as enoxaparin followed by a vitamin K antagonist for preventing recurrence, with no increase in bleeding complications	• Secondary publication of an included study that does not provide any additional relevant information
Sadlon (2016)	Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions	• Systematic review used as a source of primary studies
Salla (2016)	Venous Thromboembolism in Patients Diagnosed With Lung Cancer	• Systematic review used as a source of primary studies
Sardar (2013)	Efficacy and safety of new oral anticoagulants for extended treatment of venous thromboembolism: systematic review and meta-analyses of randomized controlled trials	• Systematic review used as a source of primary studies
Sardar (2014)	Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials	• Systematic review used as a source of primary studies
Sardar (2014)	New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Sardar (2015)	Risk of major bleeding in different indications for new oral anticoagulants: insights from a meta-analysis of approved dosages from 50 randomized trials	• Systematic review used as a source of primary studies
Sardar (2015)	New oral anticoagulants in patients with cancer: current state of evidence	• Systematic review used as a source of primary studies
Sarratt (2017)	Safety Outcomes of Apixaban Compared With Warfarin in Patients With End-Stage Renal Disease	• Systematic review used as a source of primary studies
Schellong (2016)	Safety and efficacy of dabigatran compared with warfarin in patients with acute venous thromboembolism enrolled in RE-COVER/RE-COVER IITM in Western Europe	• Conference abstract
Schulman (2011)	A randomized trial of dabigatran versus warfarin in the treatment of acute venous thromboembolism (RE-COVER II)	• Conference abstract
Schulman (2011)	Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism	• Conference abstract
Schulman (2011)	Dabigatran vs. placebo for extended maintenance therapy of venous thromboembolism	• Conference abstract
Schulman (2012)	Benefit of extended maintenance therapy for venous thromboembolism with dabigatran etexilate is maintained over 1 year of post-treatment follow-up	• Conference abstract
Schulman (2012)	Treatment of venous thromboembolism with dabigatran	• Review article but not a systematic review
Schulman (2014)	Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis	• Duplicate reference
Schulman (2015)	Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer	• Associated study
Schutgens (2004)	Low molecular weight heparin (dalteparin) is equally effective as unfractionated heparin in reducing coagulation activity and perfusion abnormalities during the early treatment of pulmonary embolism	• Study does not contain any of the outcomes of interest
Senoo (2017)	Safety and efficacy of direct oral anticoagulants over warfarin in Japanese patients with acute venous thromboembolism: A meta-analysis	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Shah (2016)	Direct oral anticoagulants in patients with cancer	• Conference abstract
Simes (2014)	Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. Circulation 130(13): 1062-71	• Individual patient data only
Sindet-Pedersen (2015)	Safety and efficacy of direct oral anticoagulants compared to warfarin for extended treatment of venous thromboembolism -a systematic review and meta-analysis	• Systematic review used as a source of primary studies
Sobieraj (2015)	Comparative efficacy and safety of anticoagulants and aspirin for extended treatment of venous thromboembolism: A network meta-analysis. Thrombosis Research 135(5): 888-96	• More recent NMA available
Skaistis (2015)	Risk of fatal bleeding in episodes of major bleeding with new oral anticoagulants and Vitamin K antagonists: A systematic review and meta-Analysis	• Systematic review used as a source of primary studies
Sprynger (2013)	Hokusai-VTE: edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism	• Conference abstract
Sterne (2017)	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	• duplicate reference
Suchkov (2018)	Comparison of Once-Daily Bemiparin with Twice-Daily Enoxaparin for Acute Deep Vein Thrombosis: A Multicenter, Open-Label, Randomized Controlled Trial	• Comparator in study does not match that specified in protocol
Sullivan (2011)	Health-related quality of life after venous thromboembolism	• Conference abstract
Sun (2017)	Risk of Intraocular Bleeding With Novel Oral Anticoagulants Compared With Warfarin: A Systematic Review and Meta-analysis	• Systematic review used as a source of primary studies
Tahir (2013)	The new oral anti-coagulants and the phase 3 clinical trials - a systematic review of the literature	• Systematic review used as a source of primary studies
Tomkowski (2017)	Extended use of sulodexide, apixaban, rivaroxaban and dabigatran in venous thromboembolism: indirect comparison of clinical trials	• Systematic review used as a source of primary studies
Touma (2015)	A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Treatment of proximal... (2000)	Treatment of proximal deep vein thrombosis with a novel synthetic compound (SR90107A/ORG31540) with pure anti-factor Xa activity: A phase II evaluation. The Rembrandt Investigators.	• Comparator in study does not match that specified in protocol
Tromeur (2018)	Novel Anticoagulant Treatment for Pulmonary Embolism with Direct oral anticoagulants Phase 3 Trials and Clinical Practice	• Conference abstract
Turpie (2017)	Analysis of patients with deep vein thrombosis switched from standard therapy to rivaroxaban in the non-interventional XALIA study	• Not a relevant study design
van der Heijden (2002)	Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism.	• Systematic review used as a source of primary studies
van der Hulle (2014)	Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis	• Systematic review used as a source of primary studies
van der Hulle (2014)	Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism	• Systematic review used as a source of primary studies
van Doormaal (2010)	Idraparinux versus standard therapy in the treatment of deep venous thrombosis in cancer patients: a subgroup analysis of the Van Gogh DVT trial.	• Comparator in study does not match that specified in protocol
van Es (2014)	Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials	• Systematic review used as a source of primary studies
Vanassche (2018)	Impact of age, comorbidity, and polypharmacy on the efficacy and safety of edoxaban for the treatment of venous thromboembolism: An analysis of the randomized, double-blind Hokusai-VTE trial. Thrombosis Research 162: 7-14	• Review article but not a systematic review
Vandell (2017)	Genetics and clinical response to warfarin and edoxaban in patients with venous thromboembolism. Heart 103(22): 1800-1805	• Associated study
Vasanthamohan (2018)	Vasanthamohan, L., Boonyawat, K., Chai-Adisaksopha, C. et al. (2018) Reduced-dose direct oral anticoagulants in the extended treatment of venous thromboembolism: a systematic review and meta-analysis. Journal of Thrombosis & Haemostasis 16(7): 1288-1295	• Systematic review used as a source of primary studies

Author (year)	Title	Reason for exclusion
Veiga (2000)	Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial.	• Comparator in study does not match that specified in protocol Study compared warfarin (monotherapy) versus LMWH (monotherapy) in a non-cancer population
Verhamme (2016)	Dose reduction of edoxaban preserves efficacy and safety for the treatment of venous thromboembolism. An analysis of the randomised, double-blind HOKUSAI VTE trial	• Study does not contain any of the outcomes of interest
Weitz (2017)	Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism	• Duplicate reference
Wellington (2001)	Reviparin: a review of its efficacy in the prevention and treatment of venous thromboembolism	• Systematic review used as a source of primary studies
Wells (2015)	Long-term anticoagulation with rivaroxaban for the prevention of recurrent deep venous thrombosis and pulmonary embolism: a benefit-risk analysis on the EINSTEIN EXTENSION trial	• Conference abstract
Whitlock (2016)	A randomised, double blind comparison of tecarfarin, a novel vitamin k antagonist, with warfarin the embraceac trial	• Comparator in study does not match that specified in protocol
Wu (2015)	Wu, C., Alotaibi, G. S., Alsaleh, K. et al. (2015) Case-fatality of recurrent venous thromboembolism and major bleeding associated with aspirin, warfarin, and direct oral anticoagulants for secondary prevention. Thrombosis Research 135(2): 243-8	• Systematic review used as a source of primary studies
Xu (2015)	Initial thrombolysis treatment compared with anticoagulation for acute intermediate-risk pulmonary embolism: a meta-analysis	• Systematic review used as a source of primary studies
Young (2016)	OC-11 - Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism	• Conference abstract
Zondag (2013)	Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis	• Systematic review used as a source of primary studies

Clinical studies (search update)

Author (year)	Title	Reason for exclusion
Couturaud (2019)	Two years versus six months of oral anticoagulation after a first episode of unprovoked proximal depp vein thrombosis: the PADIS DVT multicenter, double-blind, randomized trial	• Abstract only
Farge (2018)	Quality of life in cancer patients undergoing anticoagulant treatment with LMWH for venous thromboembolism: The QUAVITEC study on behalf of the Groupe Francophone Thrombose et Cancer (GFTC).	• Not a relevant study design Non-randomized
Hutchinson (2018)	Patient and carer experience of oral and injected anticoagulation for cancer-associated thrombosis: select-d trial qualitative sub-study.	• Abstract only

Economic studies

Author (year)	Title	Reason for exclusion
Aguirre et al. (2015)	Cost-Effectiveness Analysis of Bemiparin Used As Acute Treatment For Deep Venous Thrombosis Without Pulmonary Embolism	Conference abstract
Al Saleh et al. (2017)	Direct oral anticoagulants and Vitamin K Antagonists for Treatment of Deep Venous Thrombosis and Pulmonary Embolism in the Outpatient Setting: Comparative Economic Evaluation	Not conducted in a UK setting
Anonymous et al. (2013)	Cost-effectiveness of prevention and treatment of VTE	Review article
Aujesky et al. (2005a)	Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism	Not conducted in a UK setting
Aujesky et al. (2005b)	Cost-effectiveness of low-molecular-weight heparin for treatment of pulmonary embolism	Not conducted in a UK setting
Bryden et al. (2015)	A Cost-Effectiveness Analysis of Novel Oral Anticoagulants For Acute Treatment And Secondary Prevention Of Venous Thromboembolic Disease	Conference abstract
Caro et al. (2002)	Cost effectiveness of tinzaparin sodium versus unfractionated heparin in the treatment of proximal deep vein thrombosis	Not conducted in a UK setting
Coleman et al. (2014)	Cost-effectiveness analysis of extended duration anticoagulation with rivaroxaban to prevent recurrent venous thromboembolism	Not conducted in a UK setting
Connell et al. (2017)	Low-molecular weight heparin versus vitamin K antagonists for the treatment of cancer-associated thrombosis: A cost-effectiveness analysis	Not conducted in a UK setting
Connell et al. (2018)	Cost-effectiveness of edoxaban versus dalteparin for treatment of cancer-associated thrombosis	Not conducted in a UK setting
de Jong et al. (2017)	Cost-effectiveness Analysis for Apixaban in the Acute Treatment and Prevention of Venous Thromboembolism in the Netherlands	Not conducted in a UK setting
de Jong et al. (2018)	Extended Treatment with Apixaban for Venous Thromboembolism Prevention in the Netherlands: Clinical and Economic Effects	Not conducted in a UK setting

Author (year)	Title	Reason for exclusion
De Andres-Nogales et al. (2017)	Cost-effectiveness and cost-utility analysis of apixaban versus dabigatran and rivaroxaban in the treatment and secondary prevention of venous thromboembolism	Not conducted in a UK setting
Dranitsaris et al. (2006)	Dalteparin versus warfarin for the prevention of recurrent venous thromboembolic events in cancer patients: a pharmacoeconomic analysis	Not conducted in a UK setting
Elias et al. (2016)	Cost-effectiveness analysis of apixaban compared to low-molecular weight heparins and vitamin k antagonists for treatment and secondary prevention of venous thromboembolism	Not conducted in a UK setting
Fenf et al. (2018)	Cost-effectiveness of rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist for the treatment of pulmonary embolism in China	Not conducted in a UK setting
Gomez-Outes et al. (2006)	Cost-effectiveness of bemiparin in the prevention and treatment of venous thromboembolism	Review article
Gomez-Outes et al. (2006)	Cost Effectiveness of Bemiparin Sodium versus Unfractionated Heparin and Oral Anticoagulants in the Acute and Long-Term Treatment of Deep Vein Thrombosis	Not conducted in a UK setting
Gould et al. (1999)	Low molecular-weight heparins compared with unfractionated heparin for treatment of acute deep vein thrombosis. A cost effectiveness analysis	Not conducted in a UK setting
Gourzoulidis et al. (2017)	Cost-Effectiveness Analysis of Rivaroxaban for Treatment of Deep Vein Thrombosis and Pulmonary Embolism in Greece	Not conducted in a UK setting
Heisen et al. (2017)	Cost-effectiveness analysis of rivaroxaban for treatment and secondary prevention of venous thromboembolism in the Netherlands	Not conducted in a UK setting
Helwick et al. (2013)	Rivaroxaban more cost-effective than warfarin for recurrent VTE prevention	Not conducted in a UK setting
Jimenez et al. (2015)	Cost-effectiveness of rivaroxaban in the treatment of venous thromboembolism in Spain	Not conducted in a UK setting
Jimenez et al. (2015)	Is Edoxaban A Cost-Effective Alternative To Venous Thromboembolim Patients Treated With Vitamin K Antagonists In Spain?	Review article
Jugrin et al. (2014)	The Cost-Effectiveness Of Dabigatran Etexilate Compared With Warfarin In The Treatment And Secondary Prevention Of Acute Venous Thromboembolism In The Uk	Conference abstract
Kahler et al. (2015)	Cost of Treating Venous Thromboembolism With Heparin and Warfarin Versus Home Treatment With Rivaroxaban	Not conducted in a UK setting
Lanitis et al. (2014)	Cost-Effectiveness Of Apixaban Compared To Other Anticoagulants For Lifetime Treatment And Prevention Of Recurrent Venous Thromboembolism	Conference abstract
Lanitis et al. (2015)	Cost-Effectiveness of Apixaban Compared to Low Molecular Weight Heparin/ Edoxaban for Treatment and Prevention of Recurrent Venous Thromboembolism	Conference abstract
Lefebvre et al. (2014)	Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism	Not conducted in a UK setting
Ma et al. (2018)	Cost-effectiveness of edoxaban compared with daltepar in for the treatment of cancer-associated venous thromboembolism	Not conducted in a UK setting

Author (year)	Title	Reason for exclusion
Maervoet et al. (2015)	Cost effectiveness of Rivaroxaban versus low molecular weight heparin and vitamin K antagonists for the treatment of deep-vein thrombosis in the Belgian healthcare setting	Not conducted in a UK setting
Marchetti et al. (2001a)	Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis	Not conducted in a UK setting
Perez-de-Llano et al. (2010)	Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study	Not conducted in a UK setting. Cost consequence analysis.
Preblick et al. (2015)	Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study	Not conducted in a UK setting
Quon et al. (2016)	Clinical and economic benefits of extended treatment with apixaban for the treatment and prevention of recurrent venous thromboembolism in Canada	Not conducted in a UK setting
Rosselli et al. (2014)	Cost-Effectiveness of Dabigatran Compared With Warfarin, Apixaban, Rivaroxaban And Low Molecular Weight Heparins For The Treatment And Secondary Prevention Of Venous Thromboembolism In Colombia	Conference abstract
Rudakova et al. (2015)	Cost-effectiveness of new oral anticoagulants in the treatment and secondary prevention of venous thromboembolism	Not conducted in a UK setting
Seaman et al. (2013)	Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: a U.S. perspective	Not conducted in a UK setting
Shane et al. (2016)	Dalteparin vs. Vitamin K antagonist (VKA) for the prevention of recurrent venous thromboembolism (VTE) in cancer patients with renal insufficiency: A patient level pharmacoeconomic analysis in three European countries.	Conference abstract
Stern et al. (2015)	Cost-Utility Analysis of Apixaban in the Acute Treatment And Prevention of Venous Thromboembolism In France	Conference abstract
Stevanovic et al. (2016)	Dabigatran for the Treatment and Secondary Prevention of Venous Thromboembolism; A Cost-Effectiveness Analysis for the Netherlands	Not conducted in a UK setting
Valette et al. (1995)	Economic evaluation of the use of tinzaparin in the treatment of deep vein thrombosis.	Cost consequence analysis
van Leent et al. (2015)	Cost-Effectiveness of Dabigatran Compared to Vitamin-K Antagonists for the Treatment of Deep Venous Thrombosis in the Netherlands Using Real-World Data	Not conducted in a UK setting
Yang et al. (2018)	Cost-effectiveness of rivaroxaban compared with enoxaparin plus warfarin for the treatment of acute deep vein thrombosis in China	Not conducted in a UK setting

Appendix N – References

Included clinical studies

Agnelli, G., Prandoni, P., Santamaria, M. G., Bagatella, P., Iorio, A., Bazzan, M., ... & Scannapieco, G. (2001). Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *New England Journal of Medicine*, *345*(3), 165-169.

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Becattini, C., & Agnelli, G. (2014). Aspirin for prevention and treatment of venous thromboembolism. *Blood reviews*, *28*(3), 103-108.

Brighton, T. A., Eikelboom, J. W., Mann, K., Mister, R., Gallus, A., Ockelford, P., ... & Kirby, A. (2012). Low-dose aspirin for preventing recurrent venous thromboembolism. *New England Journal of Medicine*, *367*(21), 1979-1987.

Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, van den Berg-Segers AE, Cariou R, Leeuwenkamp O, and Lensing AW (2003) Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism.. The New England journal of medicine 349(18), 1695-702

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Appendix O- NMA models

Models for combining hazard ratio and event rate data

Fixed effect model

```
# Shared parameter model: Binomial/cloglog; Normal/id
# (cloglog truncation not required)
# Fixed effects model
model{                              # *** PROGRAM STARTS
# Binomial likelihood, cloglog link model for number of events data
for(i in 1:nsBi){                   # LOOP THROUGH STUDIES WITH BINOMIAL DATA
  mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
  for (k in 1:na[i]) {              # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
    # model for linear predictor
    cloglog(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
    # cloglog truncated to avoid arithmetic overflow when close to 0 or 1
    # see Ntzoufras(2009, Chapter 7)
#    eta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#    cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-
xi2))
#       -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    # Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  # summed residual deviance contribution for each trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
# cloglog truncation values
#xi1 <- 10
#xi2 <- 3
#
# Normal likelihood, identity link for data given as lnHR
for(i in 1:nsNo){                   # LOOP THROUGH 2-ARM STUDIES
  y[i,2] ~ dnorm(delta[i+nsBi,2],prec[i,2]) # normal likelihood for 2-arm
trials
  # Deviance contribution for trial i
  resdev[i+nsBi]<- (y[i,2]-delta[i+nsBi,2])*(y[i,2]-
delta[i+nsBi,2])*prec[i,2]
 }
#
for(i in (nsNo+1):(nsNo+ns3)){      # LOOP THROUGH 3-ARM STUDIES
  for (k in 1:(naNo[i]-1)){         # set variance-covariance matrix
    for (j in 1:(naNo[i]-1)){
      Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
     }
   }
  # Precision matrix
  Omega[i,1:(naNo[i]-1),1:(naNo[i]-1)] <- inverse(Sigma[i,,])
  # multivariate normal likelihood for 3-arm trials
  y[i,2:naNo[i]] ~ dmnorm(delta[i+nsBi,2:naNo[i]],Omega[i,1:(naNo[i]-
1),1:(naNo[i]-1)])
  # Deviance contribution for trial i
  for (k in 1:(naNo[i]-1)){         # multiply vector & matrix
    ydiff[i,k]<- y[i,(k+1)] - delta[i+nsBi,(k+1)]
    z[i,k]<- inprod2(Omega[i,k,1:(naNo[i]-1)], ydiff[i,1:(naNo[i]-1)])
   }
```

```
  resdev[i+nsBi]<- inprod2(ydiff[i,1:(naNo[i]-1)], z[i,1:(naNo[i]-1)])
 }
#
for(i in 1:(nsNo+ns3)){      # LOOP THROUGH ALL STUDIES (Normal lik.)
  delta[i+nsBi,1] <- 0           # treatment effect is zero for control arm
  for (k in 2:naNo[i]){          # LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)   # calculate variances
    prec[i,k] <- 1/var[i,k]      # set precisions
   }
  for (k in 2:naNo[i]){          # LOOP THROUGH ARMS
    # trial-specific treat effects distributions
    delta[i+nsBi,k] <- d[tNo[i,k]] - d[tNo[i,1]]
   }
 }
#
totresdevBi <- sum(resdev[1:nsBi]) # res dev for Binomial data
totresdevNo <- sum(resdev[(nsBi+1):(nsBi+nsNo+ns3)]) # res dev for Normal
data
totresdev <- sum(resdev[])     # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
for (c in 1:(nt-1)){
  for (k in (c+1):nt){
    lhr[c,k] <- (d[k]-d[c])
    log(hr[c,k]) <- lhr[c,k]
   }
 }
# ranking on relative scale
for (k in 1:nt) {
#  rk[k] <- nt+1-rank(d[],k)     # assumes events are "good"
  rk[k] <- rank(d[],k)           # assumes events are "bad"
  best[k] <- equals(rk[k],1)     # Rank 1 is best
  # calculates probability that treat k is h-th best
  for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
 }

# new line added here by NICE GUT
for (k in 1:nt) { log(caterpillar2[k]) <- d[k]-d[1] }


}                              # *** PROGRAM ENDS
```

Random effects model

```
  # Shared parameter model: Binomial/cloglog; Normal/id
  # (cloglog truncation not required)
  # Random effects model for multi-arm trials
  model{                              # *** PROGRAM STARTS
  # Binomial likelihood, cloglog link model for number of events data
  for(i in 1:nsBi){                   # LOOP THROUGH STUDIES WITH BINOMIAL DATA
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0                   # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
    for (k in 1:na[i]) {              # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
      # model for linear predictor
      cloglog(p[i,k]) <- mu[i] + delta[i,k]
      # cloglog truncated to avoid arithmetic overflow when close to 0 or 1
      # see Ntzoufras(2009, Chapter 7)
  #    eta[i,k] <- mu[i] + delta[i,k]
  #    cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-
  xi2))
  #         -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      # Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
    # summed residual deviance contribution for each trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {              # LOOP THROUGH ARMS
      # trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      # mean of RE distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
      # precision of RE distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
      # adjustment, multi-arm trials
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
   }
  # cloglog truncation values
  #xi1 <- 10
  #xi2 <- 3
  #
  # Normal likelihood, identity link for data given as lnHR
  for(i in 1:nsNo){                   # LOOP THROUGH 2-ARM STUDIES
    y[i,2] ~ dnorm(delta[i+nsBi,2],prec[i,2]) # normal likelihood for 2-arm
  trials
    # Deviance contribution for trial i
    resdev[i+nsBi]<- (y[i,2]-delta[i+nsBi,2])*(y[i,2]-
  delta[i+nsBi,2])*prec[i,2]
   }
  #
  for(i in (nsNo+1):(nsNo+ns3)){    # LOOP THROUGH 3-ARM STUDIES
    for (k in 1:(naNo[i]-1)){       # set variance-covariance matrix
      for (j in 1:(naNo[i]-1)){
        Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
     }
    # Precision matrix
```

```
  Omega[i,1:(naNo[i]-1),1:(naNo[i]-1)] <- inverse(Sigma[i,,])
  # multivariate normal likelihood for 3-arm trials
  y[i,2:naNo[i]] ~ dmnorm(delta[i+nsBi,2:naNo[i]],Omega[i,1:(naNo[i]-
1),1:(naNo[i]-1)])
  # Deviance contribution for trial i
  for (k in 1:(naNo[i]-1)){ # multiply vector & matrix
    ydiff[i,k]<- y[i,(k+1)] - delta[i+nsBi,(k+1)]
    z[i,k]<- inprod2(Omega[i,k,1:(naNo[i]-1)], ydiff[i,1:(naNo[i]-1)])
   }
  resdev[i+nsBi]<- inprod2(ydiff[i,1:(naNo[i]-1)], z[i,1:(naNo[i]-1)])
 }

#
for(i in 1:(nsNo+ns3)){      # LOOP THROUGH ALL STUDIES (Normal lik.)
  w[i+nsBi,1] <- 0 # adjustment for multi-arm trials is zero for control
arm
  delta[i+nsBi,1] <- 0           # treatment effect is zero for control arm
  for (k in 2:naNo[i]){          # LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)   # calculate variances
    prec[i,k] <- 1/var[i,k]      # set precisions
   }
  for (k in 2:naNo[i]){          # LOOP THROUGH ARMS
    # trial-specific treat effects distributions
    delta[i+nsBi,k] ~ dnorm(md[i+nsBi,k],taud[i+nsBi,k])
    # mean of RE distributions (with multi-arm trial correction)
    md[i+nsBi,k] <- d[tNo[i,k]] - d[tNo[i,1]] + sw[i+nsBi,k]
    # precision of RE distributions (with multi-arm trial correction)
    taud[i+nsBi,k] <- tau *2*(k-1)/k
    # adjustment for multi-arm trials
    w[i+nsBi,k] <- (delta[i+nsBi,k] - d[tNo[i,k]] + d[tNo[i,1]])
    # cumulative adjustment for multi-arm trials
    sw[i+nsBi,k] <- sum(w[i+nsBi,1:k-1])/(k-1)
   }
 }
#
totresdevBi <- sum(resdev[1:nsBi]) # resdev for Binomial data
totresdevNo <- sum(resdev[nsBi+1:nsBi+nsNo+ns3]) # resdev for Normal data
totresdev <- sum(resdev[])        # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment
effects
sd ~ dunif(0,2)                   # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
#
# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
  for (k in (c+1):nt)  {
    lhr[c,k] <- (d[k]-d[c])
    log(hr[c,k]) <- lhr[c,k]
   }
 }
# ranking on relative scale
for (k in 1:nt) {
#  rk[k] <- nt+1-rank(d[],k)     # assumes events are "good"
  rk[k] <- rank(d[],k)           # assumes events are "bad"
  best[k] <- equals(rk[k],1)     # calculate probability that treat k is
best
  # calculates probability that treat k is h-th best
  for (h in 1:nt){  prob[h,k] <- equals(rk[k],h)  }
 }
```

```
# new line added here by NICE GUT
for (k in 1:nt) { log(caterpillar2[k]) <- d[k]-d[1] }

}                                   # *** PROGRAM ENDS
```

Models for event rate data

Fixed effect model

Binomial likelihood, logit link
Fixed effects model

```
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # LOOP THROUGH ARMS 62
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
 logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects


for (z in 1:(nt-1))
{
caterpillar[z] <- exp(d[z+1])-d[1]
}

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}

# change distribution A below for each outcome of interest
A ~ dnorm(-4.76583024600087, 5.70128914942992)
for (k in 1:nt) { logit(T[k]) <- A + d[k] }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
RRR[c,k] <- T[k]/T[c]
}
}

} # *** PROGRAM ENDS
```

Random effects model

Binomial likelihood, logit link
Random effects model for multi-arm trials

```
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
 w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
 delta[i,1] <- 0 # treatment effect is zero for control arm
```

```
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # LOOP THROUGH ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
 logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
 for (k in 2:na[i]) { # LOOP THROUGH ARMS
 delta[i,k] ~ dnorm(md[i,k],taud[i,k]) # trial-specific LOR distributions
 md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions (with multi-arm trial correction)
 taud[i,k] <- tau *2*(k-1)/k # precision of LOR distributions (with multi-arm trial correction)
 w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
 sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
 }
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1] <- 0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects
sd ~ dunif(0,5) # vague prior for between-trial SD. ALTERNATIVES BELOW
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}

# change distribution A below for each outcome of interest
A ~ dnorm(-4.76583024600087, 5.70128914942992)
for (k in 1:nt) { logit(T[k]) <- A + d[k] }

# Provide estimates of number needed to treat NNT[k], Risk Difference RD[k],
# and Relative Risk RR[k], for each treatment, relative to treatment 1
RR[1] <- 1
for (k in 2:nt) {
RR[k] <- T[k]/T[1]
}

for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
RRR[c,k] <- T[k]/T[c]
}
}

} # *** PROGRAM ENDS
```

Appendix P- NMA inconsistency checking

This work was accrued out by the TSU on behalf of the NICE Guideline Updates Team.

Introduction

The purpose of this analysis was to assess the consistency assumption in the network meta-analysis (NMA) models used to estimate the comparative effectiveness of pharmacological interventions for treating venous thromboembolism (VTE).

Methods

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts [1, 2]. There should be no meaningful differences between these two sources of evidence.

To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an "inconsistency", or unrelated mean effects, model [1, 2]. The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 or more treatments that are informed by at least 3 independent sources of evidence [3]. This was not the case for the following networks of evidence:

- Initial treatment of VTE patients: VTE-related mortality
- Initial treatment of DVT patients: VTE-recurrence
- Initial treatment of DVT patients: Major bleeding
- Initial treatment of DVT patients: CRNMB
- Initial treatment of DVT patients: All-cause mortality
- Initial treatment of PE patients: VTE-recurrence
- Initial treatment of VTE in patients 65 years and older
- Initial treatment of VTE in patients who are obese

and so it was not possible to assess consistency assumption for those networks.

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model [4]. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study contributes 1 data point per arm in the case of arm-level data, 1 point per relative effect in the case of contrast-level data) [4].

In addition to assessing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean deviance and the effective number of parameters, and thus penalizes model fit with model complexity [4]. Lower values are preferred and differences of 3 points were considered meaningful [4].

Where the base-case model assumes random effects, if the inconsistency model has smaller heterogeneity (measured by the posterior median between-study standard deviation) compared to the consistency model, then this indicates potential inconsistency in the data.

To visually assess if specific data-points are contributing to inconsistency, we plot contributions to the posterior mean residual deviance for each data-point for the inconsistency model vs the

consistency model. Points lying below the line of equality indicate data-points contributing to inconsistency.

We performed further checks for evidence of inconsistency through node-splitting either using the gemtc package [1, 3, 5, 6], or through the R2WinBUGS package in R [7] (see code in Appendix 1). This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared [3, 5].

Results

Main analyses

3.1. Initial treatment of VTE: VTE Recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 1). The deviance contributions plot (Figure 1) shows no data-points where the inconsistency model better predicted data points (no points below the line of equality).

Table 1: Model fit statistics for VTE Recurrence after initial treatment of VTE

Model[a]	**Posterior total residual deviance**[b]	**DIC**[c]
Consistency model - FE	42.63	220.61
Inconsistency model - FE	44.74	224.46

[a] Continuity correction applied to studies containing zero cells
[b] Posterior mean residual deviance compared to 47 total data points
[c] Deviance information criteria (DIC) – lower values preferred

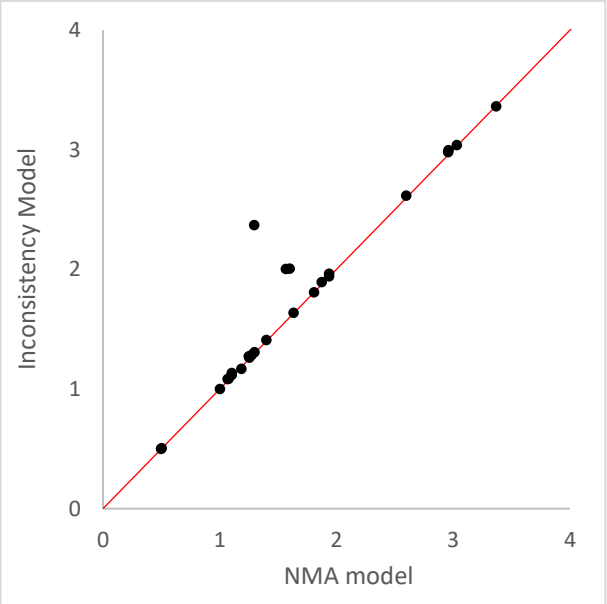

Figure 1: Deviance contributions for the fixed effect consistency and inconsistency models: VTE Recurrence after initial treatment of VTE.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 2, Table 2). Although there is some difference between the direct and indirect point estimates of Apixaban vs. LMWH + VKA (4 vs. 1) and Apixaban vs. UFH + VKA (4 vs. 3) (Figure 2), the direct Apixaban vs. UFH + VKA (4 vs. 3) comparison is extremely imprecisely estimated, so that indirect estimate is compatible with the direct estimate (similarly for 4 vs 1).

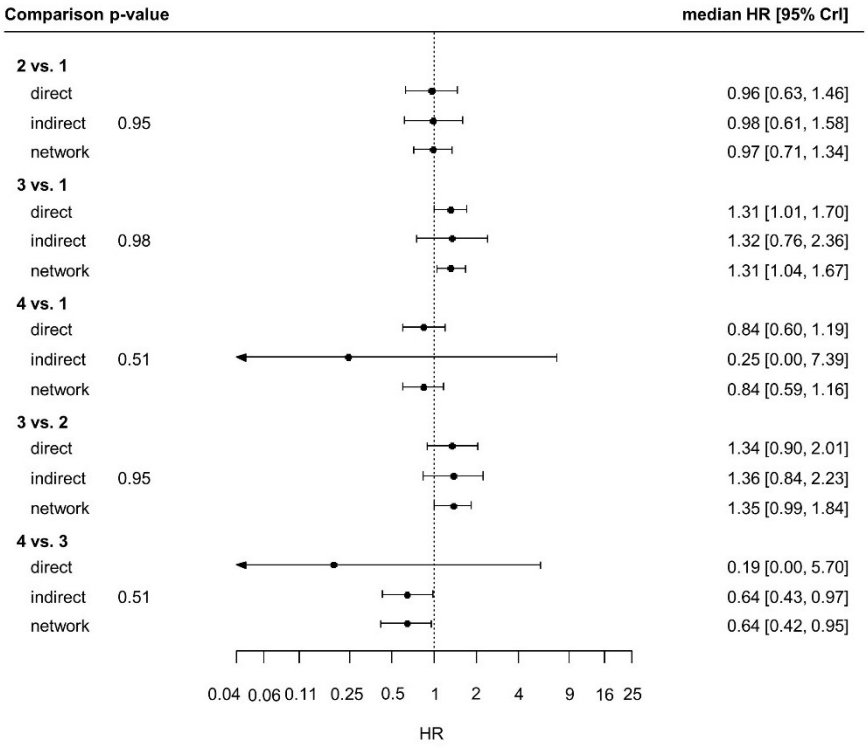

Figure 2: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – LMWH + VKA, 2 – Fondaparinux + VKA, 3 – UFH + VKA, 4 – Apixaban.

Table 2: Model fit statistics for VTE Recurrence after initial treatment of VTE

Node split model[a]	**Posterior total residual deviance**[b]	**DIC**	**p-value**[c]
Fondaparinux + VKA vs. LMWH + VKA (2 vs. 1)	43.64	222.64	0.95
UFH + VKA vs. LMWH + VKA (3 vs. 1)	43.67	222.69	0.98
Apixaban vs. LMWH + VKA (4 vs. 1)	43.73	222.44	0.51
UFH + VKA vs. Fondaparinux + VKA (3 vs. 2)	43.67	222.70	0.95
Apixaban vs. UFH + VKA (4 vs. 3)	43.72	222.41	0.51
NMA (no nodes split)	**42.63**	**220.61**	**---**

[a] Continuity correction applied to studies containing zero cells

[b] Posterior mean residual deviance compared to 47 total data points

[c] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.2. Initial treatment of VTE: Major Bleeding

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model

assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 3). The deviance contributions plot (Figure 3) shows no data-points where the inconsistency model better predicted data points (no points below the line of equality).

Table 3: Model fit statistics for major bleeding after initial treatment of VTE

Model[a]	**Posterior total residual deviance**[b]	**DIC**[c]
Consistency model - FE	35.39	161.27
Inconsistency model - FE	37.66	165.27

[a] Continuity correction applied to studies containing zero cells
[b] Posterior mean residual deviance compared to 37 total data points
[c] Deviance information criteria (DIC) – lower values preferred

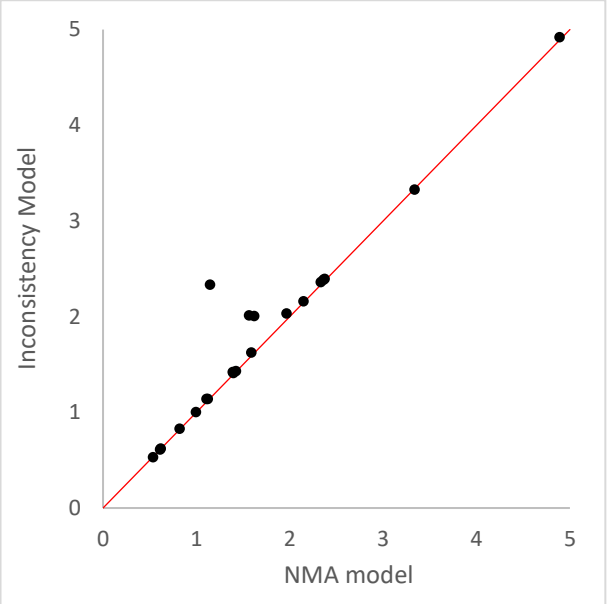

Figure 3: Deviance contributions for the fixed effect consistency and inconsistency models: Major bleeding after initial treatment of VTE.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 4, Table 4). Although there are some differences between the direct and indirect estimates of Apixaban vs. LMWH + VKA (4 vs. 1) and Apixaban vs. UFH + VKA (4 vs. 3) (Figure 4), the direct Apixaban vs. UFH + VKA (4 vs. 3) comparison is extremely imprecisely estimated, so that indirect estimate is compatible with the direct estimate (similarly for 4 vs 1).

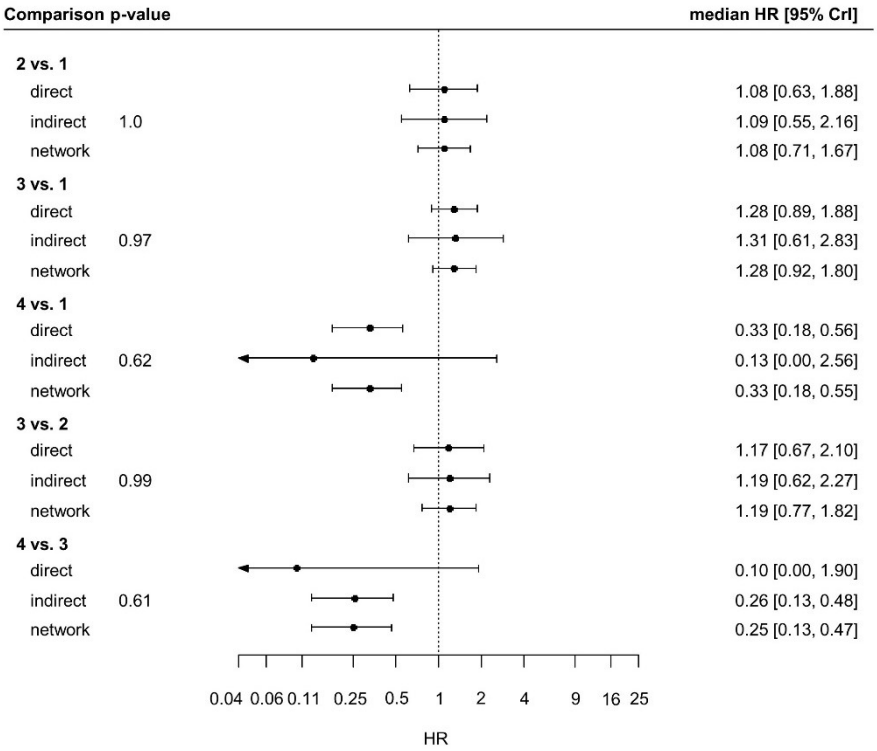

Figure 4: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – LMWH + VKA, 2 – Fondaparinux + VKA, 3 – UFH + VKA, 4 – Apixaban.

Table 4: Node split model fit statistics for major bleeding after initial treatment of VTE

Node split model[a]	**Posterior total residual deviance**[b]	**DIC**	**p-value**[c]
Fondaparinux + VKA vs. LMWH + VKA (2 vs. 1)	36.42	163.32	1.00
UFH + VKA vs. LMWH + VKA (3 vs. 1)	36.42	163.31	0.97
Apixaban vs. LMWH + VKA (4 vs. 1)	36.61	163.23	0.62
UFH + VKA vs. Fondaparinux + VKA (3 vs. 2)	36.41	163.29	0.99
Apixaban vs. UFH + VKA (4 vs. 3)	36.66	163.29	0.61
NMA (no nodes split)	35.39	161.27	**---**

[a] Continuity correction applied to studies containing zero cells

[b] Posterior mean residual deviance compared to 37 total data points

[c] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.3. Initial treatment of VTE: Clinically relevant non-major bleeding

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 5). The deviance contributions plot (Figure 5) shows only a few data-points where the inconsistency model better predicted data points (points below the line of equality), but the differences are small.

Table 5: Model fit statistics for clinically relevant non-major bleeding after Initial treatment of VTE

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	36.22	208.64
Inconsistency model - FE	37.79	212.18

[a] Posterior mean residual deviance compared to 33 total data points

[b] Deviance information criteria (DIC) – lower values preferred

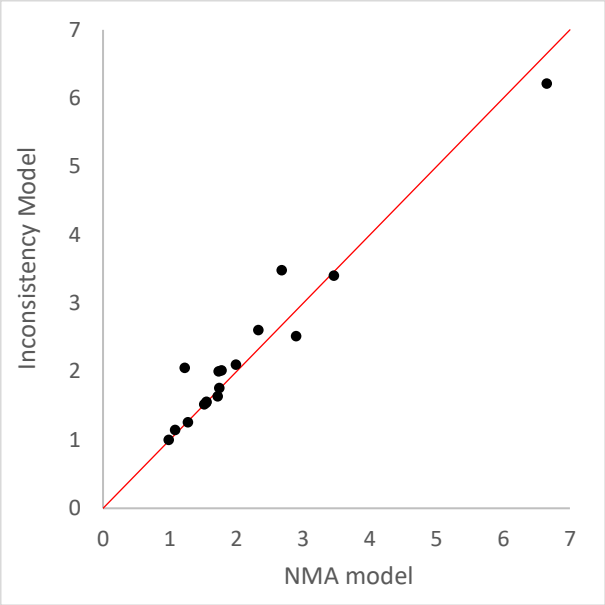

Figure 5: Deviance contributions for the fixed effect consistency and inconsistency models: Clinically relevant non-major bleeding after initial treatment of VTE.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 6, Table 6).

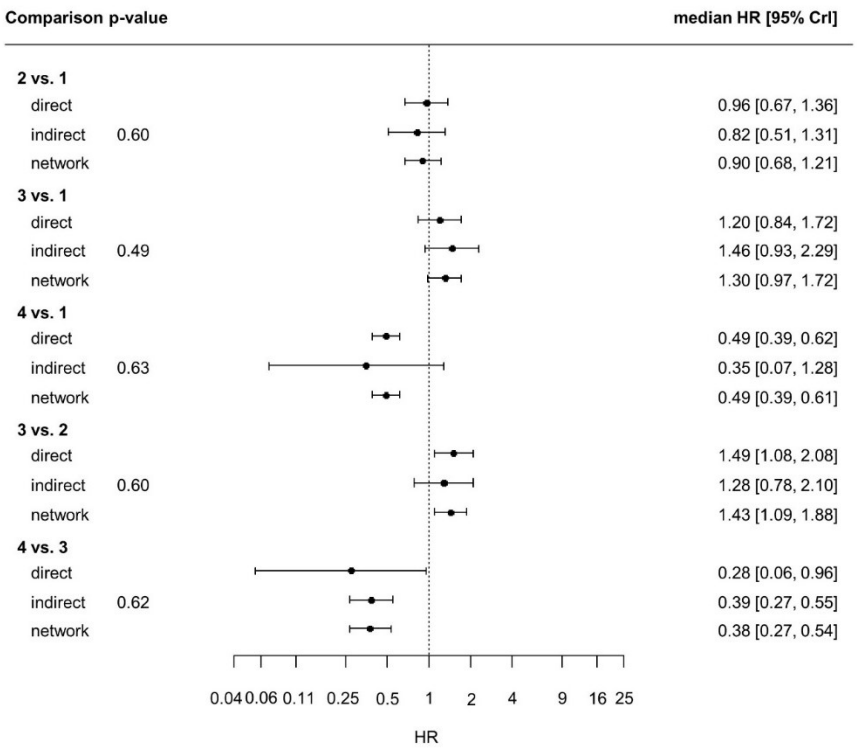

Figure 6: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – LMWH + VKA, 2 – Fondaparinux + VKA, 3 – UFH + VKA, 4 – Apixaban.

Table 6: Node split model fit statistics for clinically relevant non-major bleeding after initial treatment of VTE

Node split model	Posterior total residual deviance[a]	DIC	p-value[b]
Fondaparinux + VKA vs. LMWH + VKA (2 vs. 1)	36.98	210.41	0.60
UFH + VKA vs. LMWH + VKA (3 vs. 1)	36.79	210.23	0.49
Apixaban vs. LMWH + VKA (4 vs. 1)	37.15	210.57	0.63
UFH + VKA vs. Fondaparinux + VKA (3 vs. 2)	36.98	210.41	0.60
Apixaban vs. UFH + VKA (4 vs. 3)	37.16	210.57	0.62
NMA (no nodes split)	**36.22**	**208.64**	**---**

[a] Posterior mean residual deviance compared to 33 total data points

[b] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.4. Initial treatment of VTE: All-cause Mortality

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 7). The deviance contributions plot (Figure 7) shows only one data-point where the inconsistency model better predicted data points (points below the line of equality), but the difference is small.

Table 7: Model fit statistics for all-cause mortality after Initial treatment of VTE

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	43.35	232.60
Inconsistency model - FE	43.99	234.23

[a] Posterior mean residual deviance compared to 45 total data points

[b] Deviance information criteria (DIC) – lower values preferred

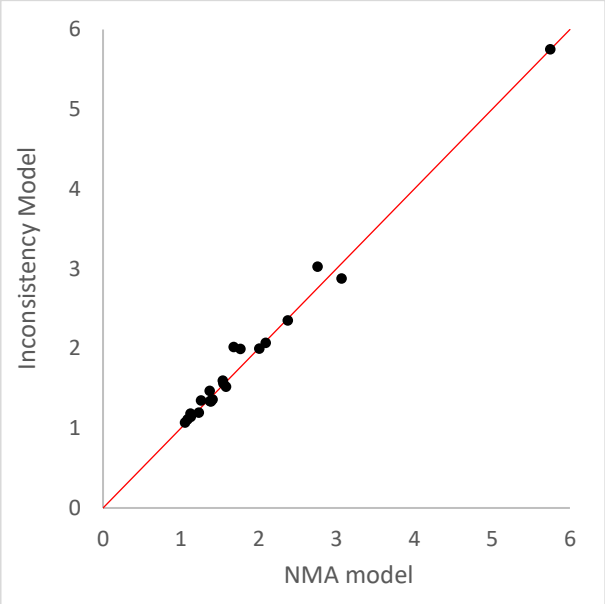

Figure 7: Deviance contributions for the fixed effect consistency and inconsistency models: All-cause mortality after initial treatment of VTE.

3.5. Initial treatment of VTE: VTE-related Mortality

Inconsistency assessments were not possible for this outcome, since there were no closed loops in the network.

3.6. Extended treatment of VTE: Recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 8). The deviance contributions plot (Figure 8) shows only one data-point where the inconsistency model better predicted data points (points below the line of equality), but the difference is small.

Table 8: Model fit statistics for VTE Recurrence after extended treatment of VTE

Model	Posterior total residual deviance[b]	DIC[c]
Consistency model - FE	15.32	49.15
Inconsistency model - FE	17.21	54.06

[b] Posterior mean residual deviance compared to 17 total data points

[c] Deviance information criteria (DIC) – lower values preferred

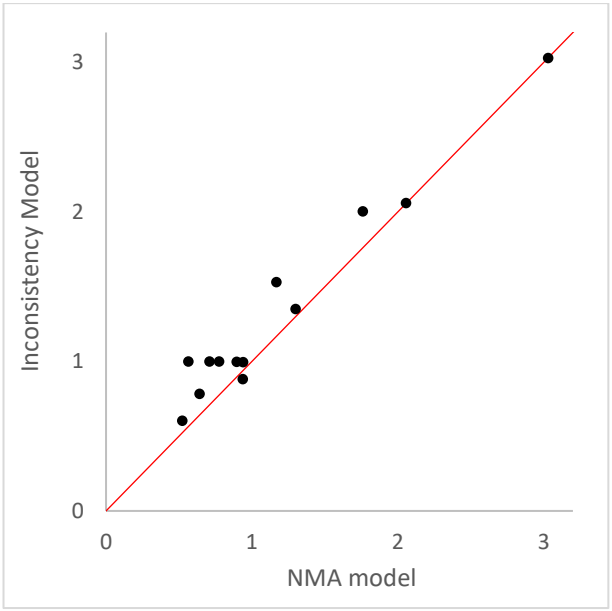

Figure 8: Deviance contributions for the fixed effect consistency and inconsistency models: VTE Recurrence after extended treatment of VTE.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 9, Table 9).

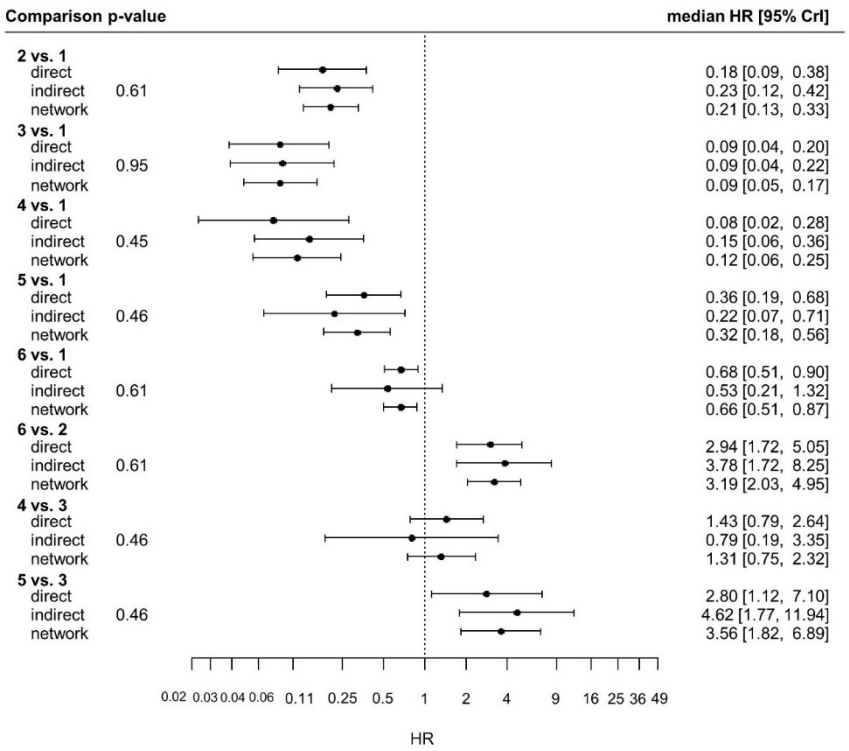

Figure 9: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – Placebo, 2 – Rivaroxaban (20 mg), 3 – Warfarin (2.0), 4 – Dabigatran, 5 – Warfarin (1.5 INR), 6 – Aspirin (100 mg).

Table 9: Node split model fit statistics for VTE Recurrence after extended treatment of VTE

Node split model	Posterior total residual deviance[a]	DIC	p-value[b]
Rivaroxaban (20 mg) vs. Placebo (2 vs. 1)	16.05	51.24	0.61
Warfarin (2.0) vs. Placebo (3 vs. 1)	16.28	51.46	0.95
Dabigatran vs. Placebo (4 vs. 1)	15.74	50.94	0.45
Warfarin (1.5 INR) vs. Placebo (5 vs. 1)	15.77	50.97	0.46
Aspirin (100 mg) vs. Placebo (6 vs. 1)	16.05	51.25	0.61
Aspirin (100 mg) vs. Rivaroxaban (20 mg) (6 vs. 2)	16.04	51.25	0.61
Dabigatran vs. Warfarin (2.0) (4 vs. 3)	15.75	50.96	0.46
Warfarin (1.5 INR) vs. Warfarin (2.0) (5 vs. 3)	15.76	50.95	0.46
NMA (no nodes split)	**15.32**	**49.16**	**---**

[a] Posterior mean residual deviance compared to 17 total data points

[b] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.7. Extended treatment of VTE: Major bleeding

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 10). The deviance contributions plot (Figure 10) shows only a few data-points where the inconsistency model better predicted data points (points below the line of equality), but the differences are very small.

Table 10: Model fit statistics for major bleeding after extended treatment of VTE

Model[a]	Posterior total residual deviance[b]	DIC[c]
Consistency model - FE	20.54	89.17
Inconsistency model - FE	22.53	93.55

[a] Continuity correction applied to all studies with a zero cell

[b] Posterior mean residual deviance compared to 24 total data points

[c] Deviance information criteria (DIC) – lower values preferred

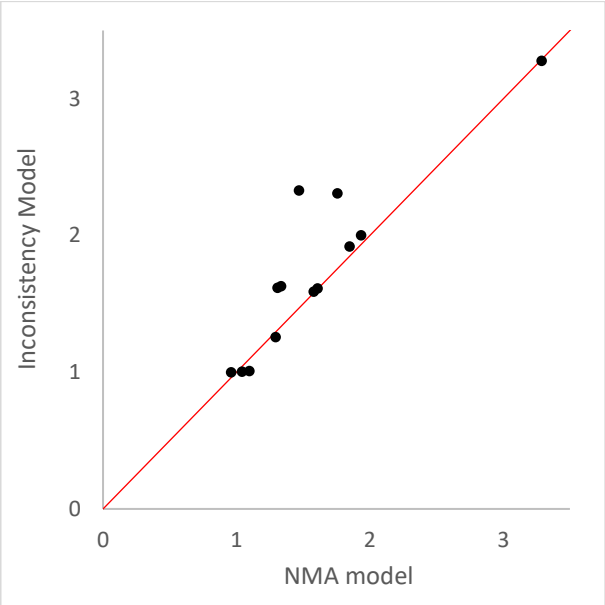

Figure 10: Deviance contributions for the fixed effect consistency and inconsistency models: Major bleeding after extended treatment of VTE.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 11, Table 11).

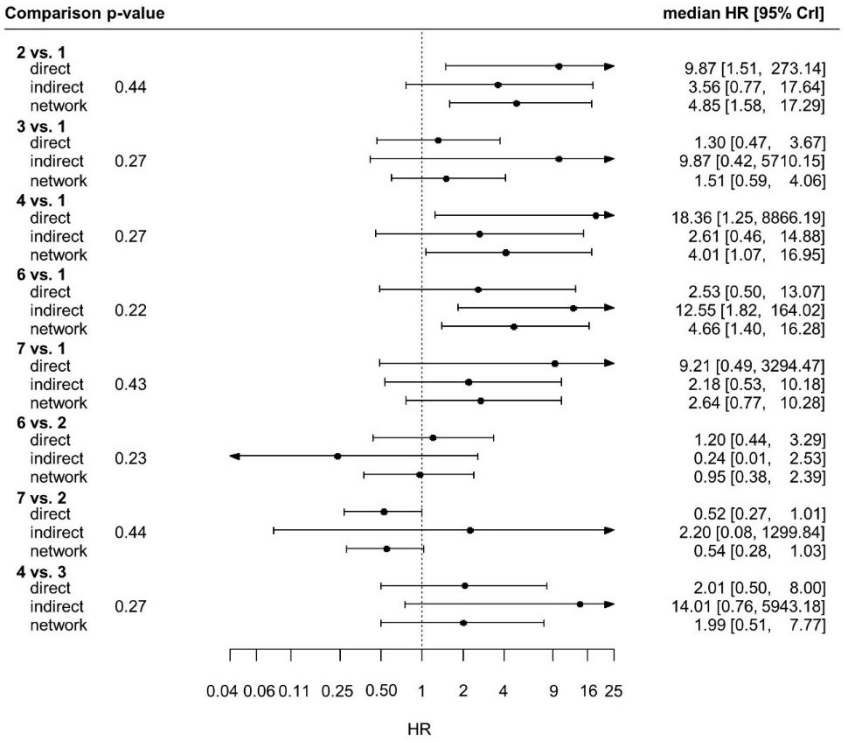

Figure 11: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – Placebo, 2 – Warfarin (2.0), 3 – Aspirin (100 mg), 4 – Rivaroxaban (20 mg), 5 – Rivaroxaban (10 mg), 6 – Warfarin (1.5 INR), 7 – Dabigatran.

Table 11: Node split model fit statistics for major bleeding after extended treatment of VTE

Node split model[a]	Posterior total residual deviance[b]	DIC	p-value[c]
Warfarin (2.0) vs. Placebo (2 vs. 1)	21.3	90.76	0.44
Aspirin (100 mg) vs. Placebo (3 vs. 1)	21.2	90.55	0.27
Rivaroxaban (20 mg) vs. Placebo (4 vs. 1)	21.2	90.57	0.27
Warfarin (1.5 INR) vs. Placebo (6 vs. 1)	20.54	90.04	0.22
Dabigatran vs. Placebo (7 vs. 1)	21.49	90.84	0.43
Warfarin (1.5 INR) vs. Warfarin (2.0) (6 vs. 2)	20.54	90.06	0.23
Dabigatran vs. Warfarin (2.0) (7 vs. 2)	21.53	90.90	0.44
Rivaroxaban (20 mg) vs. Aspirin (100 mg) (4 vs. 3)	21.17	90.56	0.27
NMA (no nodes split)	**20.54**	**89.17**	**---**

[a] Continuity correction applied to all studies with a zero cell

[b] Posterior mean residual deviance compared to 24 total data points

[c] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.8. Extended treatment of VTE: Clinically relevant non-major bleeding

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for all models after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 3 [8].

There are no meaningful differences between the fit of the fixed effect consistency models. Similarly, there were no meaningful differences between the fit of the consistency and inconsistency models (Table 12). The deviance contributions plot (Figure 12) shows only a few data-points where the inconsistency model better predicted data points (points below the line of equality), but the differences are small.

Table 12: Model fit statistics for clinically relevant non-major bleeding after extended treatment of VTE

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model – FE	15.67	103.11
Inconsistency model – FE	16.15	104.50

[a] Posterior mean residual deviance compared to 16 total data points

[b] Deviance information criteria (DIC) – lower values preferred

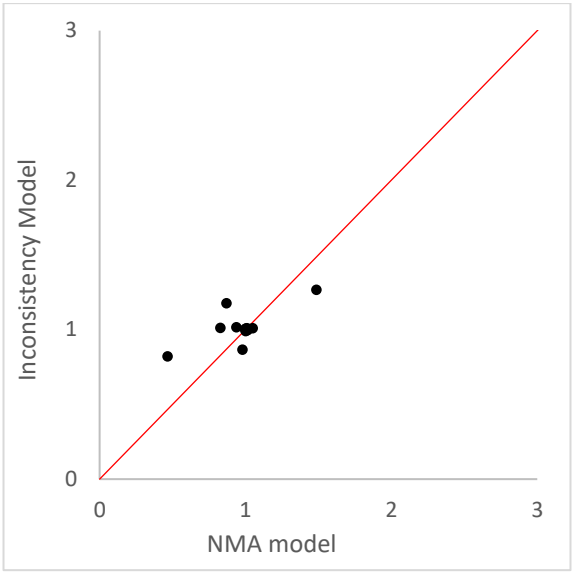

Figure 12: Deviance contributions for the fixed effect consistency and inconsistency models: Clinically relevant non-major bleeding after extended treatment of VTE.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 13, Table 13).

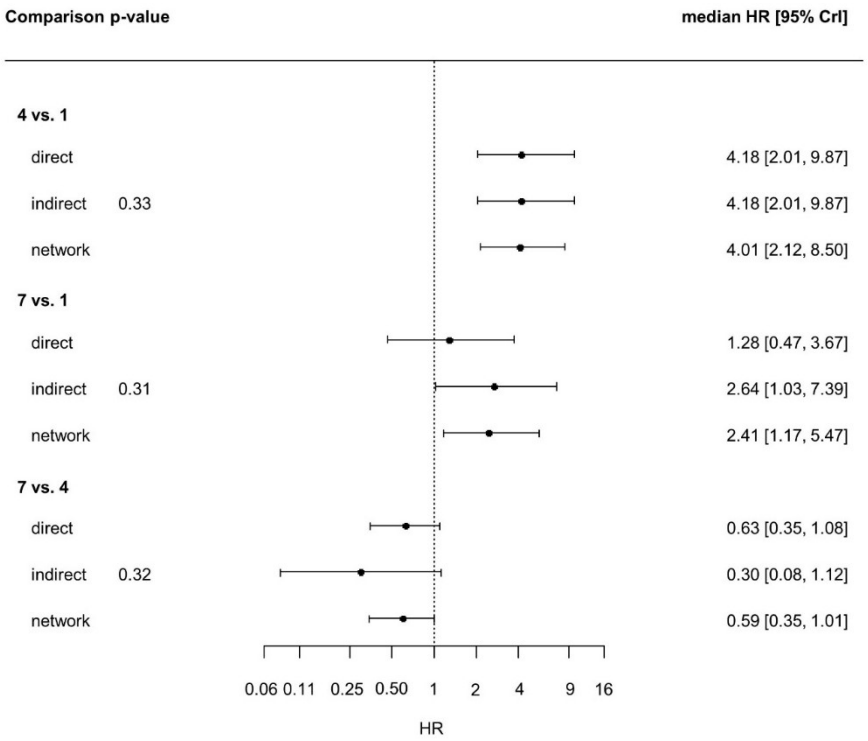

Figure 13: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – Placebo, 4 – Rivaroxaban (20 mg), 7 – Aspirin (100 mg).

Table 13: Node split model fit statistics for clinically relevant non-major bleeding after extended treatment of VTE

Node split model	Posterior total residual deviance[a]	DIC	p-value[a]
Rivaroxaban (20 mg) vs. Placebo (4 vs. 1)	16.34	30.78	0.33
Aspirin (100 mg) vs. Placebo (7 vs. 1)	16.39	30.84	0.31
Aspirin (100 mg) vs. Rivaroxaban (20 mg) (7 vs. 4)	15.35	28.79	0.32
NMA (no nodes split)	**15.93**	**29.44**	**---**

[a] Posterior mean residual deviance compared to 16 total data points

[b] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.9. Extended treatment of VTE: All-cause Mortality

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 14). The deviance contributions plot (Figure 14) shows only one data-point where the inconsistency model better predicted data points (points below the line of equality), but the difference is small.

Table 14: Model fit statistics for all-cause mortality after extended treatment of VTE

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	17.32	78.10
Inconsistency model - FE	18.94	81.54

[a] Posterior mean residual deviance compared to 19 total data points

[b] Deviance information criteria (DIC) – lower values preferred

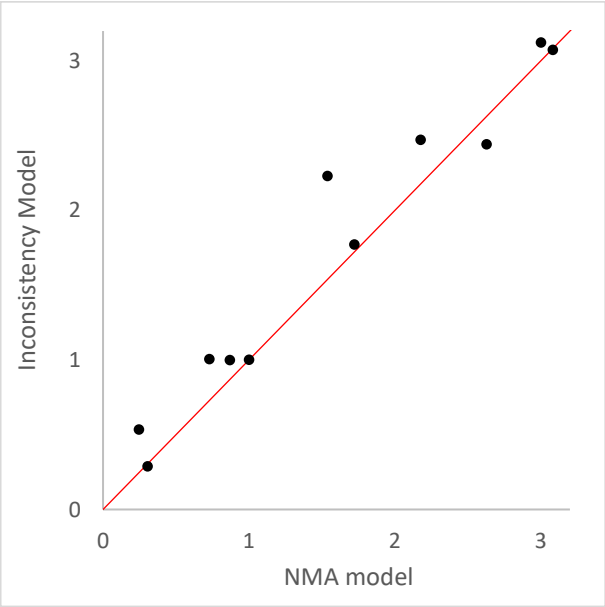

Figure 14: Deviance contributions for the fixed effect consistency and inconsistency models: All-cause mortality after extended treatment of VTE.

3.10. Extended treatment of VTE: VTE-related Mortality

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Both models were run in OpenBUGS. Convergence was satisfactory for all models after 40,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 80,000 iterations on three chains. WinBUGS/OpenBUGS code for the inconsistency model is provided in Appendix 3 [8].

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 15). The deviance contributions plot (Figure 15) shows no data-points where the inconsistency model better predicted data points (points below the line of equality).

Table 15: Model fit statistics for VTE-related mortality after extended treatment of VTE

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	12.46	51.65
Inconsistency model - FE	13.47	53.5

[a] Posterior mean residual deviance compared to 12 total data points

[b] Deviance information criteria (DIC) – lower values preferred

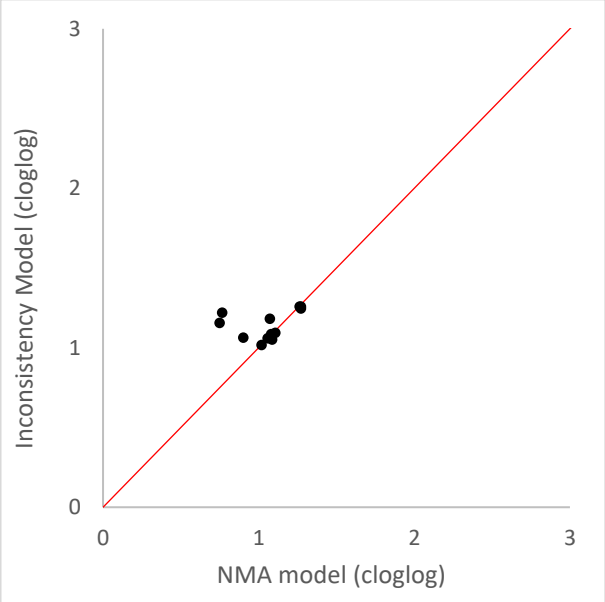

Figure 15: Deviance contributions for the fixed effect consistency and inconsistency models: All-cause mortality after extended treatment of VTE.

3.11. Initial treatment of VTE in people with cancer: VTE Recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 16). The area below the line of equality in Figure 16 highlights where the inconsistency model better predicted data points, for which there were some minor improvements in the predication of data in Clot 2003 (comparing LMWH + VKA (1) and LMWH alone (2)), Select-d 2018 (comparing LMWH alone (2) and Rivaroxaban (3)), EINSTEIN trials (comparing LMWH + VKA (1) and Rivaroxaban (3)).

Table 16: Model fit statistics for VTE Recurrence after initial treatment of VTE in people with cancer

Model	**Posterior total residual deviance[a]**	**DIC[b]**
Consistency model - FE	12.77	46.16
Inconsistency model - FE	12.04	46.40

[a] Posterior mean residual deviance compared to 14 total data points

[b] Deviance information criteria (DIC) – lower values preferred

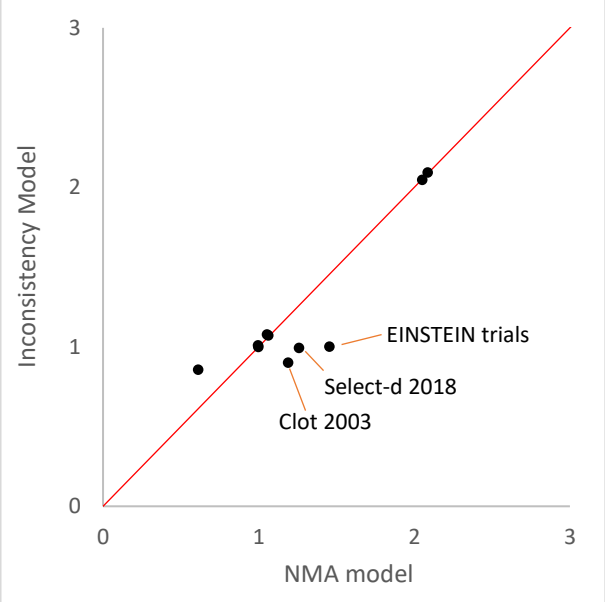

Figure 16: Deviance contributions for the fixed effect consistency and inconsistency models: VTE-recurrence after initial treatment of VTE in people with cancer.

Further checks for inconsistency using the node-splitting method (fixed effect model) did not find any evidence of inconsistency between the direct and indirect estimates (Figure 17, Table 17). There are some notable differences between the direct and indirect estimates of LMWH alone vs. LMWH + VKA (2 vs. 1) (Figure 17), however, the NMA estimate is similar to the direct estimate.

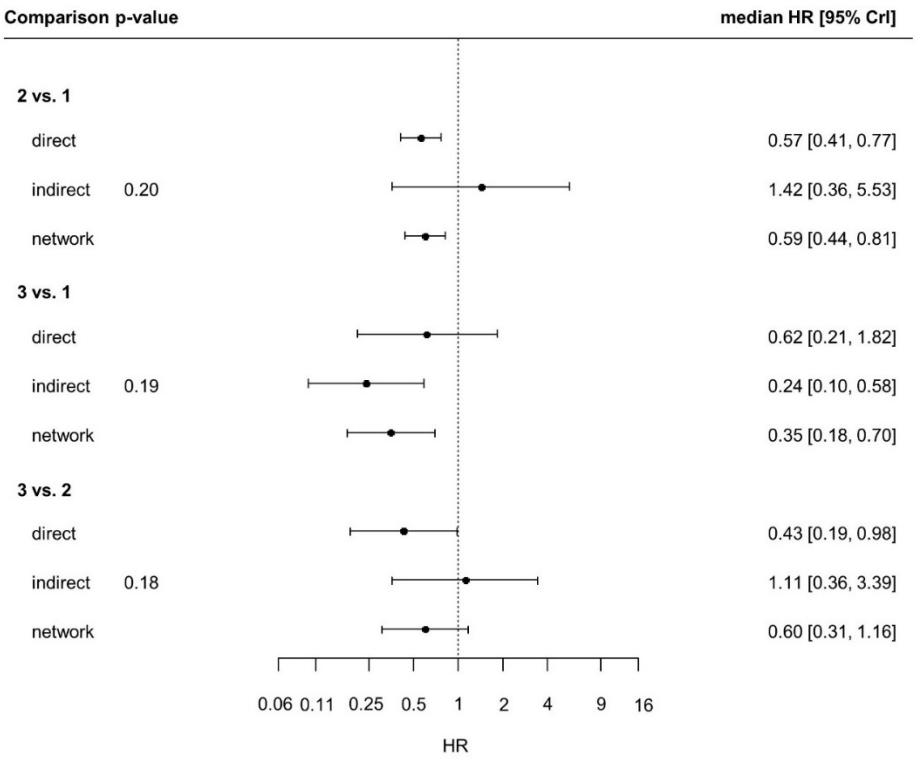

Figure 17: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – LMWH + VKA, 2 – LMWH alone, 3 – Rivaroxaban.

Table 17: Node split model fit statistics for VTE recurrence after initial treatment of VTE in people with cancer

Node split model	Posterior total residual deviance[a]	DIC	p-value[b]
LMWH alone vs. LMWH + VKA (2 vs. 1)	12.05	46.43	0.20
Rivaroxaban vs. LMWH + VKA (3 vs. 1)	12.02	46.35	0.19
Rivaroxaban vs. LMWH alone (3 vs. 2)	12.02	46.36	0.18
NMA (no nodes split)	**12.77**	**46.12**	**---**

[a] Posterior mean residual deviance compared to 14 total data points

[b] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.12. Initial treatment of VTE in people with cancer: Major Bleeding

Inconsistency checks were performed using the fixed effect model. Although the random effects model improved the fit of the model (based on the total residual deviance – see Table 12), there was not enough evidence to fully estimate the between-study standard deviation (SD). Placing an informative prior on the between-study variance (log-Normal(-3.95, 1.79^2) [9] improved the estimation of the between-study standard deviation, but there were no meaningful differences between the fixed and random effects model with an informative prior in terms of the posterior mean residual deviance and DIC (Table 12).

Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 18). The area below the line of equality in Figure 18 highlights where the inconsistency model better predicted data points, for which there were notable improvements in the data predicted in the studies contributing data in the form of log hazard ratios.

Table 18: Model fit statistics for major bleeding after initial treatment of VTE in people with cancer

Model	**Posterior total residual deviance[a]**	**DIC[b]**
Consistency model - FE	21.78	81.03
Consistency model - RE	17.08	79.70
Consistency model – RE (informative prior)	19.67	80.42
Inconsistency model - FE	19.69	79.91

[a] Posterior mean residual deviance compared to 16 total data points
[b] Deviance information criteria (DIC) – lower values preferred

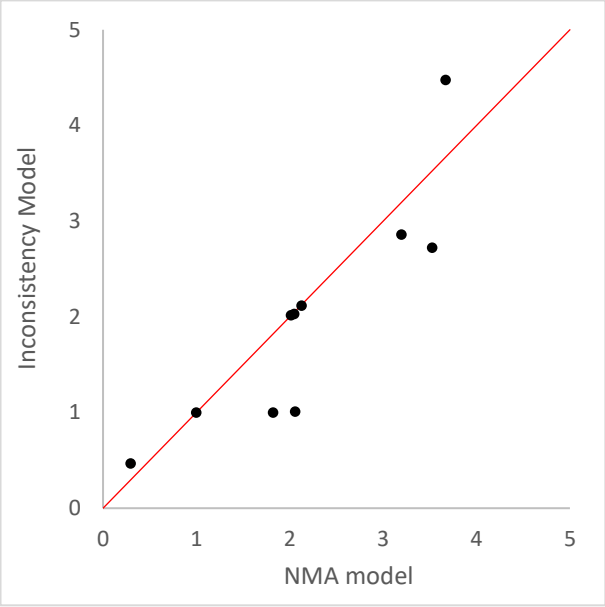

Figure 18: Deviance contributions for the fixed effect consistency and inconsistency models: major bleeding after initial treatment of VTE in people with cancer.

Although there are no meaningful differences between the fit of the node split models and the consistency model (Table 19), there are some notable differences between the direct and indirect estimates of LMWH alone vs. LMWH + VKA (2 vs. 1), Rivaroxaban vs. LMWH + VKA (3 vs. 1), and Rivaroxaban vs. LMWH alone (3 vs. 2) (Figure 19). The NMA estimate for LMWH alone vs. LMWH + VKA (2 vs. 1) is similar to the direct estimate, and the other NMA estimates seem to be balanced between the direct and indirect estimates (Figure 19).

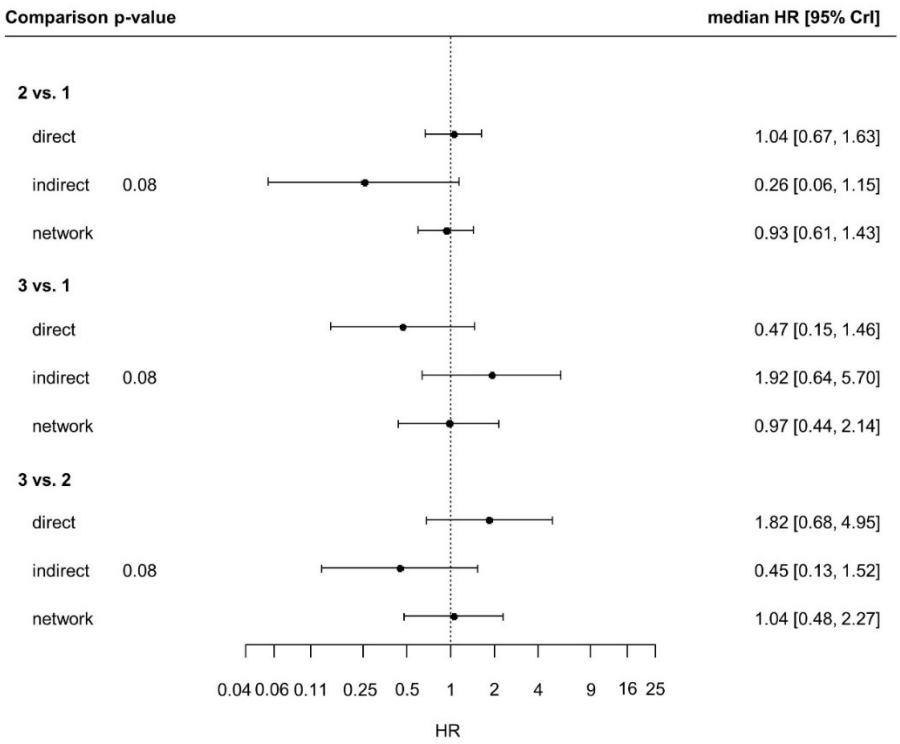

Figure 19: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – LMWH + VKA, 2 – LMWH alone, 3 – Rivaroxaban.

Table 19: Node split model fit statistics for major bleeding after initial treatment of VTE in people with cancer

Node split model	Posterior total residual deviance[a]	DIC	p-value[b]
LMWH alone vs. LMWH + VKA (2 vs. 1)	19.69	79.92	0.08
Rivaroxaban vs. LMWH + VKA (3 vs. 1)	19.72	79.97	0.08
Rivaroxaban vs. LMWH alone (3 vs. 2)	19.69	79.92	0.08
NMA (no nodes split)	**21.78**	**81.03**	**---**

[a] Posterior mean residual deviance compared to 16 total data points

[b] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.13. Initial treatment of VTE in people with cancer: Clinically relevant non-major bleeding

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 20). The area below the line of equality in Figure 20 highlights where the inconsistency model better predicted data points, for which there were some minor improvements in the predication of data in Select-d 2018 (comparing LMWH alone (2) and Rivaroxaban (3)) and EINSTEIN trials (comparing LMWH + VKA (1) and Rivaroxaban (3)).

Table 20: Model fit statistics for clinically relevant non-major bleeding after Initial treatment of VTE in people with cancer

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	12.82	68.61
Inconsistency model - FE	12.12	68.94

[a] Posterior mean residual deviance compared to 12 total data points

[b] Deviance information criteria (DIC) – lower values preferred

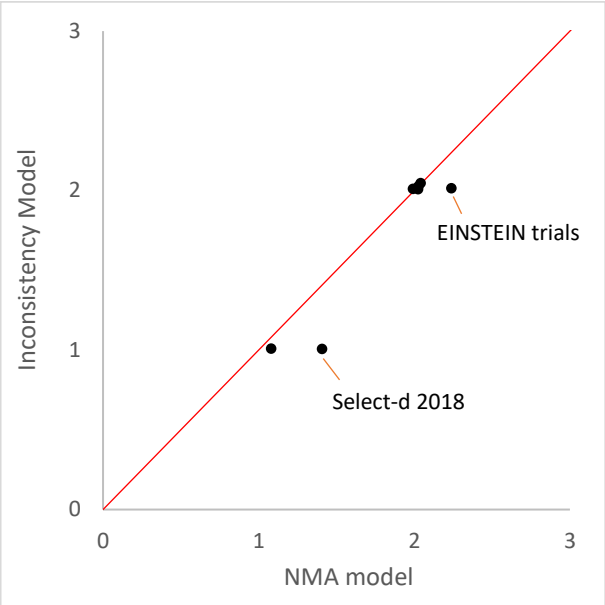

Figure 20: Deviance contributions for the fixed effect consistency and inconsistency models: clinically relevant non-major bleeding after initial treatment of VTE in people with cancer.

There are no meaningful differences between the fit of the node split models and the consistency model (Table 21), and direct estimates are compatible with indirect estimates (Figure 21).

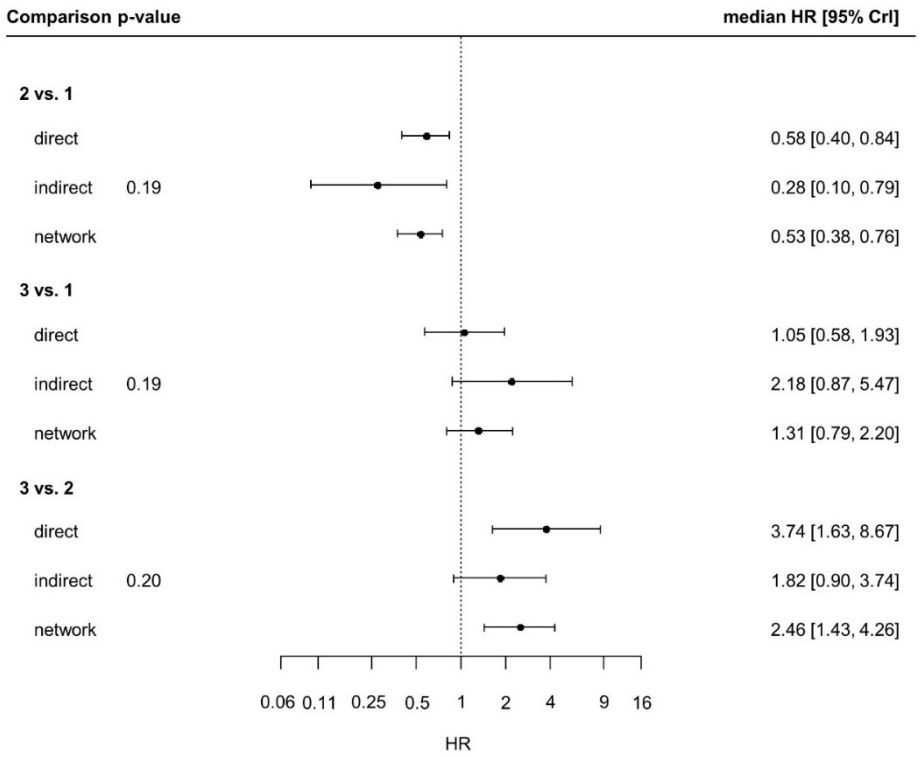

Figure 21: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – LMWH + VKA, 2 – LMWH alone, 3 – Rivaroxaban.

Table 21: Node split model fit statistics for clinically relevant non-major bleeding after initial treatment of VTE in people with cancer

Node split model	**Posterior total residual deviance[a]**	**DIC**	**p-value[a]**
LMWH alone vs. LMWH + VKA (2 vs. 1)	12.12	68.94	0.19
Rivaroxaban vs. LMWH + VKA (3 vs. 1)	12.11	68.92	0.19
Rivaroxaban vs. LMWH alone (3 vs. 2)	12.12	68.94	0.20
NMA (no nodes split)	12.82	68.61	---

[a] Posterior mean residual deviance compared to 12 total data points

[b] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.14. Initial treatment of VTE in people with cancer: All-cause Mortality

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 22). The deviance contributions plot (Figure 22) shows no data-points where the inconsistency model better predicted data points (points below the line of equality).

Table 22: Model fit statistics for all-cause mortality after Initial treatment of VTE in people with cancer

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	14.71	67.35
Inconsistency model - FE	15.75	69.41

[a] Posterior mean residual deviance compared to 14 total data points

[b] Deviance information criteria (DIC) – lower values preferred

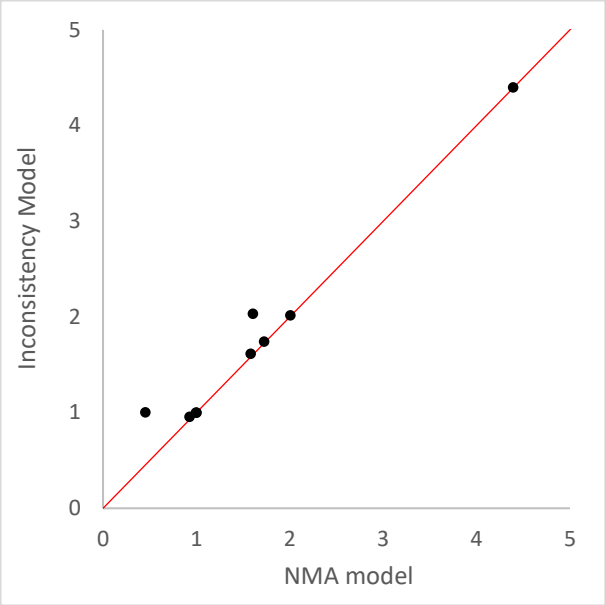

Figure 22: Deviance contributions for the fixed effect consistency and inconsistency models: all-cause mortality after initial treatment of VTE in people with cancer.

Subgroup Analyses

3.15. Initial treatment of DVT: VTE-recurrence, major bleeding, clinically relevant non-major bleeding, all-cause mortality.

Inconsistency assessments were not possible for these outcomes, since there were no closed loops in the networks.

3.16. Initial treatment of PE: VTE-recurrence

Inconsistency assessments were not possible for this outcome, since there were no closed loops in the network.

3.17. Initial treatment of PE: Major bleeding

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 23). The deviance contributions plot (Figure 23) shows no data-points where the inconsistency model better predicted the data points (points below the line of equality).

Table 23: Model fit statistics for major bleeding after initial treatment of PE

Model[a]	Posterior total residual deviance[b]	DIC[c]
Consistency model - FE	10.07	53.96
Inconsistency model - FE	11.26	55.92

[a] Continuity correction applied to studies containing zero cells
[b] Posterior mean residual deviance compared to 11 total data points
[c] Deviance information criteria (DIC) – lower values preferred

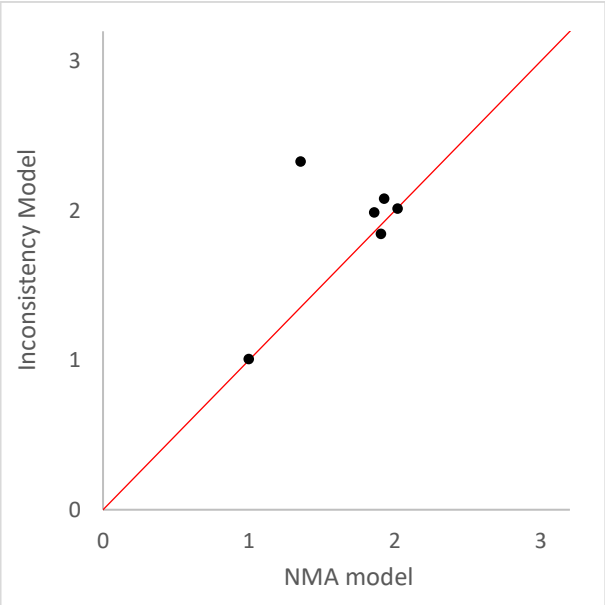

Figure 23: Deviance contributions for the fixed effect consistency and inconsistency models: Major bleeding after initial treatment of PE.

3.18. Extended treatment of DVT: VTE-recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 24). The deviance contributions plot (Figure 24) shows only two data-points where the inconsistency model better predicted data points (points below the line of equality), but the differences are small.

Table 24: Model fit statistics for VTE-recurrence after extended treatment of DVT

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	18.59	115.42
Inconsistency model - FE	18.58	116.47

[a] Posterior mean residual deviance compared to 20 total data points

[b] Deviance information criteria (DIC) – lower values preferred

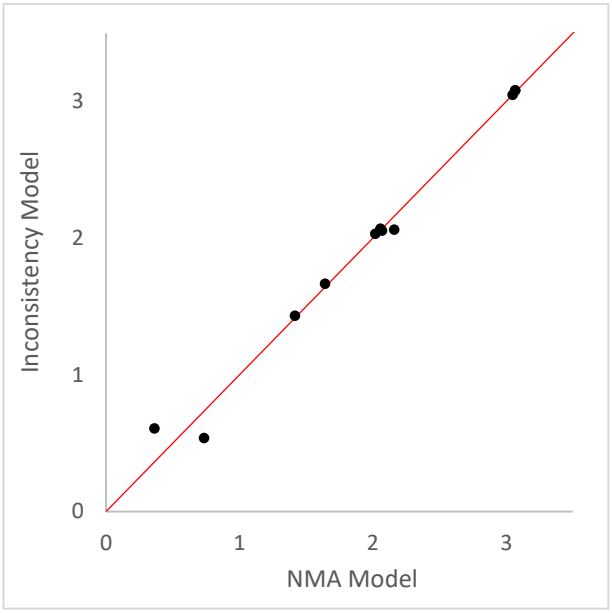

Figure 24: Deviance contributions for the fixed effect consistency and inconsistency models: VTE-recurrence after extended treatment of DVT.

3.19. Extended treatment of PE: VTE-recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 2.

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 25). The area below the line of equality in Figure 25 highlights

where the inconsistency model better predicted data points, for which there was some improvement in PADIS-PE (comparing placebo and standard warfarin).

Table 25: Model fit statistics for VTE-recurrence after extended treatment of PE

Model[a]	**Posterior total residual deviance**[b]	**DIC**[c]
Consistency model - FE	19.23	98.85
Inconsistency model - FE	17.44	97.82

[a] Continuity correction applied to studies containing zero cells
[b] Posterior mean residual deviance compared to 17 total data points
[c] Deviance information criteria (DIC) – lower values preferred

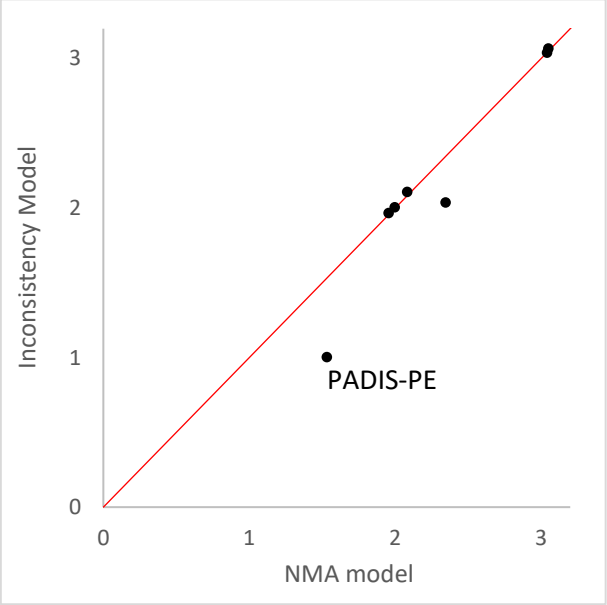

Figure 25: Deviance contributions for the fixed effect consistency and inconsistency models: VTE-recurrence after extended treatment of PE.

Although there are no meaningful differences between the fit of the node split models and the consistency model (Table 26), there are differences between the direct and indirect estimates of Warfarin (standard) vs. Placebo (2 vs. 1), Dabigatran vs. Placebo (5 vs.1), and Apixaban vs. UFH + VKA (5 vs. 2) (Figure 26).

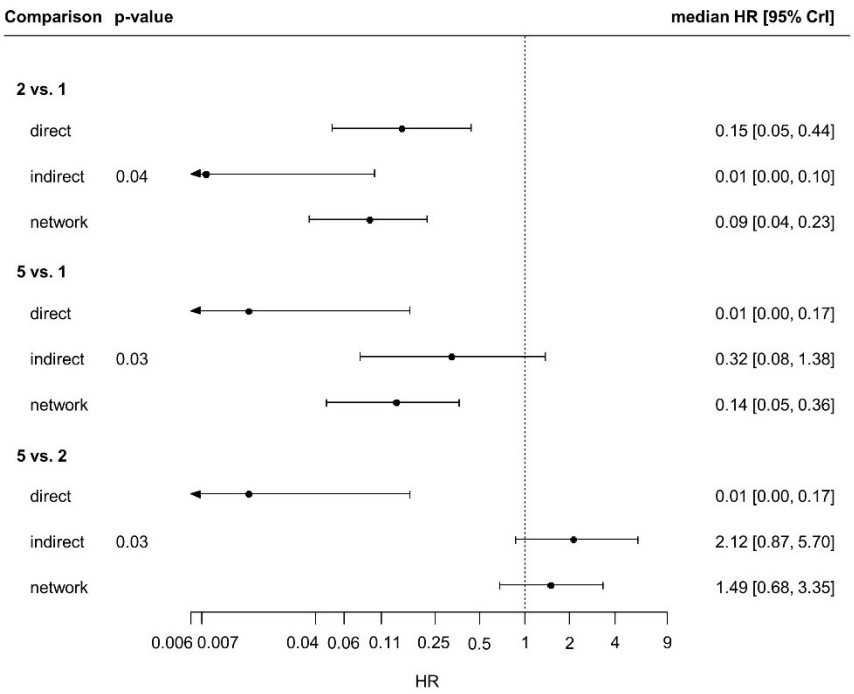

Figure 26: Direct, indirect, and network estimates of relative treatment effects based on node-splitting results. Treatments codes: 1 – Placebo, 2 – Warfarin (standard), 5 – Dabigatran.

Table 26: Node split model fit statistics for clinically relevant non-major bleeding after initial treatment of VTE in people with cancer

Node split model[a]	**Posterior total residual deviance[b]**	**DIC**	**p-value[c]**
Warfarin (standard) vs. Placebo (2 vs. 1)	17.41	97.84	0.04
Dabigatran vs. Placebo (5 vs. 1)	17.49	97.88	0.03
Dabigatran vs. Warfarin (standard) (5 vs. 2)	17.49	97.88	0.03
NMA (no nodes split)	19.23	98.85	---

[a] Continuity correction applied to studies containing zero cells

[b] Posterior mean residual deviance compared to 17 total data points

[c] p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates

3.20. Initial treatment of VTE patients at least 65 years old: VTE-recurrence

Inconsistency assessments were not possible for this outcome, since there were no closed loops in the network.

3.21. Initial treatment of VTE patients who are obese: VTE-recurrence

Inconsistency assessments were not possible for this outcome, since there were no closed loops in the network.

3.22. Extended treatment of VTE patients at least 65 years old: VTE-recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming consistency after 40,000 iterations, and the model assuming inconsistency after 60,000 iterations. The consistency and inconsistency models were compared using results

based on samples from a further 80,000 and 120,000 iterations, respectively, on three chains. WinBUGS code for the inconsistency model is provided in Appendix 3 [8].

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 27). The deviance contributions plot (Figure 27) shows only a few data-points where the inconsistency model better predicted data points (points below the line of equality), but the differences are very small.

Table 27: Model fit statistics for VTE-recurrence after extended treatment of VTE patients at least 65 years old

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	16.43	93.62
Inconsistency model - FE	16.65	94.88

[a] Posterior mean residual deviance compared to 16 total data points

[b] Deviance information criteria (DIC) – lower values preferred

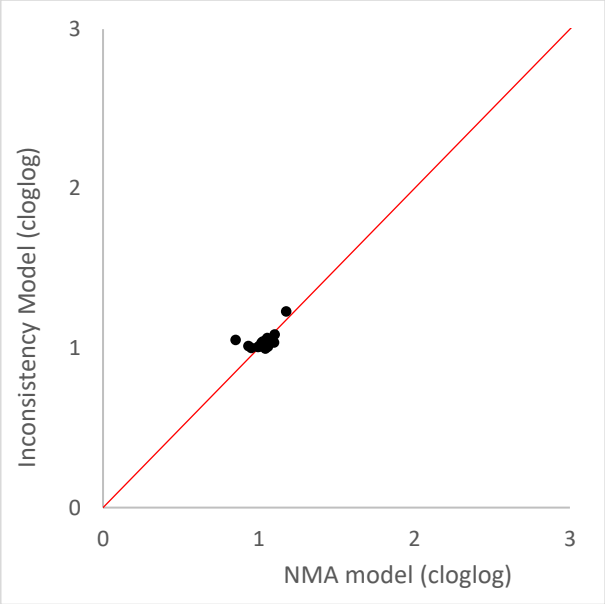

Figure 27: Deviance contributions for the fixed effect consistency and inconsistency models: VTE-recurrence after extended treatment of VTE patients at least 65 years old

3.23. Extended treatment of VTE patients who are obese: VTE-recurrence

Inconsistency checks were performed using the fixed effect model, as there were no meaningful differences between the fixed and random effects model in terms of the posterior mean residual deviance and DIC. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided in Appendix 3 [8].

There are no meaningful differences between the fit of the fixed effect consistency and inconsistency models (Table 28). The deviance contributions plot (Figure 28) shows no data-points where the inconsistency model better predicted data points (points below the line of equality).

Table 28: Model fit statistics for VTE-recurrence after extended treatment of VTE patients who are obese

Model	Posterior total residual deviance[a]	DIC[b]
Consistency model - FE	9.05	46.07
Inconsistency model - FE	8.99	46.00

[a] Posterior mean residual deviance compared to 9 total data points

[b] Deviance information criteria (DIC) – lower values preferred

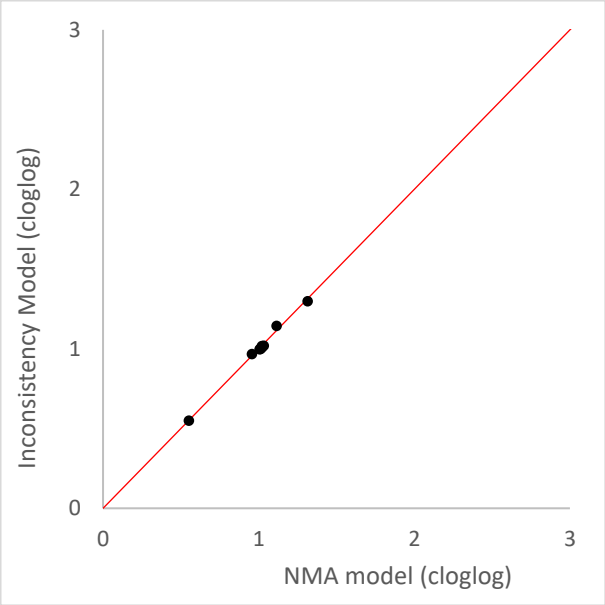

Figure 28: Deviance contributions for the fixed effect consistency and inconsistency models: VTE-recurrence after extended treatment of VTE patients who are obese

Appendices

Appendix 1 – Example model file for node-splitting – to run in R2WinBUGS package in R

```
model{
# MTC Fixed effects model
for(i in 1:(ns-ns.hr)){
      delta[i,bi[i]] <- 0
      mu[i] ~ dnorm(0,.0001)             # vague priors for trial baselines
       for (k in 1:na[i])  {
              # Likelihood
              r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])       # binomial likelihood

              # model
              cloglog(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]

              index[i,k] <- split[i] * (equals(t[i,k], pair[1]) + equals(t[i,k],
pair[2]))

              # Deviance for observed events
              rhat[i,k] <- p[i,t[i,k]] * n[i,k] # expected value of the numerators
              # Deviance contribution
              dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
                     +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
       }

       # summed residual deviance contribution for each trial
       resdev[i] <- sum(dev[i,1:na[i]])

       for (k in 2:na[i]) {
              # trial-specific LHR distributions, split into direct and indirect
(through MTC)
              delta[i,si[i,k]] <-  (d[si[i,k]] - d[bi[i]] )*(1-index[i,m[i,k]]) +
direct*index[i,m[i,k]]
       }
  }

for(i in (ns-ns.hr+1):(ns-ns.hr3)){
  delta[i,bi[i]] <- 0
  var[i,1] <- pow(se[i,1],2)   # calculate variances
  prec[i,1] <- 1/var[i,1]      # set precisions

  # normal likelihood for 2-arm trials
  y[i,1] ~ dnorm(delta[i,t[i,2]],prec[i,1])

  for(k in 1:na[i]){
       index[i,k] <- split[i] * (equals(t[i,k], pair[1]) + equals(t[i,k], pair[2]))
       }

  # Deviance contribution for trial i
  resdev[i] <- (y[i,1]-delta[i,t[i,2]])*(y[i,1]-delta[i,t[i,2]])*prec[i,1]

  for (k in 2:2){          # LOOP THROUGH ARMS
    # trial-specific treat effects distributions
    delta[i,si[i,k]] <- (d[si[i,k]] - d[bi[i]] )*(1-index[i,m[i,k]]) +
direct*index[i,m[i,k]]
   }
 }

for(i in (ns-ns.hr3+1):ns){
  delta[i,bi[i]] <- 0
  for (k in 1:2){                  # set variance-covariance matrix
    for (j in 1:2){
```

```
      Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k]*equals(j,k)
     }
   }
  Omega[i,1:2,1:2] <- inverse(Sigma[i,,]) # Precision matrix

  # multivariate normal likelihood for 3-arm trials
  # Note treatment codes in delta[i,6:7]
  y[i,1:2] ~ dmnorm(delta[i,6:7],Omega[i,1:2,1:2])

  for(k in 1:na[i]){
       index[i,k] <- split[i] * (equals(t[i,k], pair[1]) + equals(t[i,k], pair[2]))
       }

  # Deviance contribution for trial i
  for (k in 1:2){                  # multiply vector & matrix
    ydiff[i,k] <- y[i,k] - delta[i,t[i,(k+1)]]
    z[i,k] <- inprod2(Omega[i,k,1:2], ydiff[i,1:2])
   }
  resdev[i] <- inprod2(ydiff[i,1:2], z[i,1:2])

  for (k in 1:2){           # LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)    # calculate variances
    prec[i,k] <- 1/var[i,k]       # set precisions
   }

  for (k in 2:3){           # LOOP THROUGH ARMS
    # trial-specific treat effects distributions
    delta[i,si[i,k]] <- (d[si[i,k]] - d[bi[i]] )*(1-index[i,m[i,k]]) +
direct*index[i,m[i,k]]
   }
 }

d[1]<-0
direct ~ dnorm(0,1.0E-6)                  # vague prior for direct comparison
parameter
for (k in 2:nt){d[k] ~ dnorm(0,.0001) }   # vague priors for basic parameters

# Total Residual Deviance
totresdev <- sum(resdev[])   # observed events

# pairwise HRs
for (c in 1:(nt-1)) {  for (k in (c+1):nt)  { hr[c,k] <- exp(d[k] - d[c] )
                                              lhr[c,k]<-(d[k]-d[c])}  }
# calculate probability (direct >= indirect)
prob <- step(direct - lhr[pair[1], pair[2]])
}
```

Appendix 2 – Code for unrelated mean effects model, where event data and log-HRs data are combined through a shared parameter – to run in WinBUGS or Open BUGS

```
# Shared parameter model: Binomial/cloglog; Normal/id
# (cloglog truncation not required)
# Fixed effects model
model{                              # *** PROGRAM STARTS
# Binomial likelihood, cloglog link model for number of events data
for(i in 1:nsBi){                   # LOOP THROUGH STUDIES WITH BINOMIAL DATA
  mu[i] ~ dnorm(0,.0001)            # vague priors for all trial baselines
  for (k in 1:na[i]) {              # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
    # model for linear predictor
    cloglog(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]
    # cloglog truncated to avoid arithmetic overflow when close to 0 or 1
    # see Ntzoufras(2009, Chapter 7)
```

```
#    eta[i,k] <- mu[i] + d[t[i,1],t[i,k]]
#    cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-
xi2))
#       -xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
    rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
    # Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  # summed residual deviance contribution for each trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
# cloglog truncation values
#xi1 <- 10
#xi2 <- 3
#
# Normal likelihood, identity link for data given as lnHR
for(i in 1:nsNo){                  # LOOP THROUGH 2-ARM STUDIES
  y[i,2] ~ dnorm(delta[i+nsBi,2],prec[i,2]) # normal likelihood for 2-arm
trials
  # Deviance contribution for trial i
  resdev[i+nsBi]<- (y[i,2]-delta[i+nsBi,2])*(y[i,2]-
delta[i+nsBi,2])*prec[i,2]
 }
#
for(i in (nsNo+1):(nsNo+ns3)){    # LOOP THROUGH 3-ARM STUDIES
  for (k in 1:(naNo[i]-1)){       # set variance-covariance matrix
    for (j in 1:(naNo[i]-1)){
      Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
     }
   }
  # Precision matrix
  Omega[i,1:(naNo[i]-1),1:(naNo[i]-1)] <- inverse(Sigma[i,,])
  # multivariate normal likelihood for 3-arm trials
  y[i,2:naNo[i]] ~ dmnorm(delta[i+nsBi,2:naNo[i]],Omega[i,1:(naNo[i]-
1),1:(naNo[i]-1)])
  # Deviance contribution for trial i
  for (k in 1:(naNo[i]-1)){       # multiply vector & matrix
    ydiff[i,k]<- y[i,(k+1)] - delta[i+nsBi,(k+1)]
    z[i,k]<- inprod2(Omega[i,k,1:(naNo[i]-1)], ydiff[i,1:(naNo[i]-1)])
   }
  resdev[i+nsBi]<- inprod2(ydiff[i,1:(naNo[i]-1)], z[i,1:(naNo[i]-1)])
 }
#
for(i in 1:(nsNo+ns3)){       # LOOP THROUGH ALL STUDIES (Normal lik.)
  delta[i+nsBi,1] <- 0            # treatment effect is zero for control arm
  for (k in 2:naNo[i]){           # LOOP THROUGH ARMS
    var[i,k] <- pow(se[i,k],2)    # calculate variances
    prec[i,k] <- 1/var[i,k]       # set precisions
   }
  for (k in 2:naNo[i]){           # LOOP THROUGH ARMS
    # trial-specific treat effects distributions
    delta[i+nsBi,k] <- d[tNo[i,1],tNo[i,k]]
   }
 }
#
totresdevBi <- sum(resdev[1:nsBi]) # res dev for Binomial data
totresdevNo <- sum(resdev[(nsBi+1):(nsBi+nsNo+ns3)]) # res dev for Normal
data
totresdev <- sum(resdev[])     # Total Residual Deviance
```

```
# vague priors for treatment effects
for(c in 1:nt){ d[c,c]<-0 }
for(c in 1:(nt-1)){
      for(k in (c+1):nt){
            d[c,k]~dnorm(0,0.0001)
            log(hr[c,k]) <- d[c,k]
            d[k,c] <- -d[c,k]
            }
      }

}                              # *** PROGRAM ENDS
```

Appendix 3 – Code for unrelated mean effects model, binomial likelihood and cloglog link – to run in WinBUGS or Open BUGS

```
# Binomial likelihood, cloglog link
# Fixed effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)                # vague priors for all trial baselines
  for (k in 1:na[i]) {                  # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])        # Binomial likelihood
# model for linear predictor
    cloglog(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]
# cloglog truncated to avoid arithmetic overflow when close to 0 or 1
# see Ntzoufras(2009, Chapter 7) - use only when required
#    eta[i,k] <- mu[i] + d[t[i,1],t[i,k]]
#    cloglog(p[i,k]) <- eta[i,k]*(1-step(-xi1-eta[i,k]))*(1-step(eta[i,k]-
xi2))-xi1*step(-xi1-eta[i,k])+ xi2*step(eta[i,k]-xi2)
    rhat[i,k] <- p[i,k] * n[i,k]        # expected value of the numerators
#Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
#  summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])              # Total Residual Deviance

# cloglog truncation values - use only when required
#xi1 <- 15
#xi2 <- 3

# vague priors for treatment effects
for(c in 1:nt){ d[c,c]<-0 }
for(c in 1:(nt-1)){
      for(k in (c+1):nt){
            d[c,k]~dnorm(0,0.0001)
            log(hr[c,k]) <- d[c,k]
            d[k,c] <- -d[c,k]
            }
      }

}                                       # *** PROGRAM ENDS
```

Appendix 4- References

1. Dias, S., et al., *Evidence Synthesis for Decision Making 4: Inconsistency in networks of evidence based on randomized controlled trials.* Medical Decision Making, 2013. **33**: p. 641-656.
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3. van Valkenhoef, G., et al., *Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis.* Research Synthesis Methods, 2016. **7**: p. 80-93.
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5. Dias, S., et al., *Checking Consistency in Mixed Treatment Comparison Meta-analysis.* Statistics In Medicine, 2010. **29**: p. 932-944.
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7. Sturtz, S., U. Ligges, and A. Gelman, *R2WinBUGS: A package for running WinBUGS from R.* Journal of Statistical Software, 2005. **12**(3): p. 1-16 (http://www.jstatsoft.org/v12/i03).
8. Dias, S., et al., *Network meta-analysis for decision making*. Statistics in Practice. 2018, Hoboken, NJ: Wiley.
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Appendix Q – Research recommendations

Research recommendation 1

Research question	What is the optimal pharmacological treatment strategy for DVT or PE in people who use intravenous drugs?
Population	Adult (aged 18+) IV drug users with confirmed VTE.
Intervention(s)	• Edoxaban • Apixaban • Dabigatran • Rivaroxaban • Subcutaneous Low Molecular Weight Heparin (LMWH) • Note that intravenous LMWH will not be included as it is in not licensed in the UK • Subcutaneous or intravenous unfractionated heparin (UFH) • Synthetic pentasacharides • Vitamin K antagonists
Comparators	Each other
Outcomes	• All-cause mortality • VTE-related mortality • Recurrence of VTE • Split by recurrent DVT and recurrent PE if data is available • Length of hospital stay • Quality of life • Generic and disease-specific measures will be reported • Overall score will be reported (data on subscales will not be reported) • Post-thrombotic syndrome • Adverse events • Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. • Major bleeding (as defined by International Society on Thrombosis and Haemostasis) • Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis) • Intracranial haemorrhage • Liver injury • Heparin induced thrombocytopenia • Adherence
Outcome measures	Risk ratios/hazard ratios, mean differences
Study design	An RCT compares these different treatment options to each other, for the treatment of VTE in adult IV drug users.

Potential criterion	Explanation
Importance to patients, service users or the population	It is unclear what the best treatment strategies are for treating people with VTE who are IV drug users. These people are prone to have problems with adherence and often have poor access to treatment. A trial comparing treatment options in this population should clarify what are the most effectives treatment and this will hopefully lead to improvements in the health of the IV drug users who have VTE.

Potential criterion	Explanation
Relevance to NICE guidance	Low priority: This trial is of interest and will help to create recommendations for which treatment option(s) should be used in this group of people.
Current evidence base	There is difficult treating VTE in people who are IV drugs users, with no RCT evidence available comparing strategies for this population. There is clinical uncertainty as to the clinical and cost effectiveness of the different treatment strategies in this population, including the treatment agent and dose.
Equality	IV drug users are a difficult to treat population in the context of VTE and there is limited literature in this area exploring different strategies.
Feasibility	It is unclear how large this population of people is and some issues with recruitment are expected.

1 Research recommendation 2

Research question	What is the clinical and cost effectiveness of direct-acting oral anticoagulants compared with each other, and with LMWH+VKA, LMWH alone, placebo or aspirin for the initial and long-term treatment of DVT or PE based on individual patient data from existing trials?
Population	Adult (aged 18+) with confirmed VTE
Intervention(s)	• Edoxaban • Apixaban • Dabigatran • Rivaroxaban • LMWH+VKA • LMWH alone • Placebo • Aspirin
Comparator	• Each other
Outcomes	• All-cause mortality • VTE-related mortality • Recurrence of VTE • Split by recurrent DVT and recurrent PE if data is available • Length of hospital stay • Quality of life • Generic and disease-specific measures will be reported • Overall score will be reported (data on subscales will not be reported) • Post-thrombotic syndrome • Adverse events • Total serious adverse events (as defined by the European medicines agency) will be reported if data is available. • Major bleeding (as defined by International Society on Thrombosis and Haemostasis) • Clinically relevant non-major bleeding (as defined by International Society on Thrombosis and Haemostasis) • Intracranial haemorrhage • Liver injury • Heparin induced thrombocytopenia
Outcome measures	Event data, risk ratios, hazard ratios, mean differences
Study design	Re-analysis of the results of the existing DOAC trials and those of relevant comparator treatments (listed above) using individual participant data (IPD) to determine the relative effectiveness of the treatment options. This would require the collection, checking and re-analysis of the original data for each participant in each study followed by indirect comparisons (using NMAs) of the relative effectiveness of the treatments for key outcomes.
Subgroups	• People with cancer • People with a body weight less than 50kg or more than 120kg • Older people (defined as people over the age of 65) • People who have restricted movement • People with learning disabilities • Intravenous drug users

Research question	What is the clinical and cost effectiveness of direct-acting oral anticoagulants compared with each other, and with LMWH+VKA, LMWH alone, placebo or aspirin for the initial and long-term treatment of DVT or PE based on individual patient data from existing trials?
	• People in a care home / nursing home • People who have stage 3 to 5 chronic kidney disease

1

Potential criterion	Explanation
Importance to patients, service users or the population	The DOACs offer a more convenient treatment option for VTE, as they do not require INR monitoring, however there is still uncertainty about the relative effectiveness of the different DOACs in people with confirmed VTE, and those people with VTE and cancer or with VTE who Have a body weight less than 50kg or more than 120kg. A direct trial comparing all of the DOACs with LMWH+VKA or LMWH alone in the same population of people with VTE would help determine the most effective treatment options for the population as a whole and for specific subgroups, but this is unlikely to be performed by any of the drug manufacturers. Individual patient data from trials that have been already published would allow selection of comparable participants and enable the relative effectiveness of the treatments to be determined with increased certainty. This in turn would allow greater certainty about which DOACs were most beneficial to people with VTE and could improve the effectives of their treatment and as a result, improve their quality of life.
Relevance to NICE guidance	High priority: recommendations were made using current evidence, however there were concerns regarding the comparability of the different DOAC trials due to differences in the inclusion criteria. There were additional concerns associated with trials for people with VTE and cancer and very limited evidence for the effectiveness of DOACS as treatments in people with VTE and obesity. In the absence of a single trial comparing the different DOACs, this re-analysis of existing trial data has the potential to change recommendations substantially.
Current evidence base	There is evidence comparing different treatment strategies for VTE, however no studies directly compare the different DOACs to each other during either the initial or extended treatment of VTE. In addition, differences in trial design (particularly due to differing inclusion/exclusion criteria) limit certainty in the results of indirect comparisons between the DOAC trials. There is some evidence comparing different treatment strategies for VTE in people with active cancer. Edoxaban and rivaroxaban have both been compared to LMWH alone in large clinical trials in people with VTE and active cancer, and ongoing studies are looking at apixaban and dabigatran, as compared with LMWH. However, differences between the inclusion criteria for these trials are also an issue here. There are concerns that anticoagulants work differently in people with low (<50kg) and high (>120kg) body weight and there is not a clear understanding of which treatment options, and which doses, are most optimal for these people. Evidence for the use of DOACs in people with obesity is available from subgroup analyses (of people with BMI≥30mg/kg^2) of trials in the general population of people with VTE. However, this data is most limited to the outcome of VTE-recurrence and was unable to differentiate between comparators for this outcome. Additionally, the cut-off of 30mg/kg^2 was not considered to be useful by the committee because it will contain some people who would not have problems with conventional treatment. The committee

Potential criterion	Explanation
	agreed that a cut-off using an absolute body weight cut-off of 120kg (and another cut-off <50kg for people with low body weight) would better capture the groups of people who may require different treatment options, dosing and monitoring due to their body weight.
Equality	Obese people are a difficult to treat population in the context of VTE due to a lack of information about the effectiveness of newer anticoagulants in these people. It is the intention of this research recommendation to also provide information on this group of people.
Feasibility	A sufficient number of relevant RCTs are already published in this area and a re-analysis using individual patient data is feasible, although difficulty obtaining consent and access to IPD from pharmacological companies and study authors is foreseen. In addition, IPD may not be available for older studies.

1