Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis (Review)

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[Intervention Review]

Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

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ABSTRACT

Background

Deep vein thrombosis (DVT) is a condition in which a clot forms in the deep veins, most commonly of the leg. It occurs in approximately 1 in 1,000 people. If left untreated, the clot can travel up to the lungs and cause a potentially life-threatening pulmonary embolism (PE). Previously, a DVT was treated with the anticoagulants heparin and vitamin K antagonists. However, two forms of novel oral anticoagulants (NOACs) have been developed: oral direct thrombin inhibitors (DTI) and oral factor Xa inhibitors. The new drugs have characteristics that may be favourable over conventional treatment, including oral administration, a predictable effect, lack of frequent monitoring or re-dosing and few known drug interactions. To date, no Cochrane review has measured the effectiveness and safety of these drugs in the treatment of DVT.

Objectives

To assess the effectiveness of oral DTIs and oral factor Xa inhibitors for the treatment of DVT.

Search methods

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched January 2015) and the Cochrane Register of Studies (last searched January 2015). We searched clinical trials databases for details of ongoing or unpublished studies and the reference lists of relevant articles retrieved by electronic searches for additional citations.

Selection criteria

We included randomised controlled trials in which people with a DVT confirmed by standard imaging techniques, were allocated to receive an oral DTI or an oral factor Xa inhibitor for the treatment of DVT.

Data collection and analysis

Two review authors (LR, JM) independently extracted the data and assessed the risk of bias in the trials. Any disagreements were resolved by discussion with the third review author (PK). We performed meta-analyses when we considered heterogeneity low. The two primary outcomes were recurrent VTE and PE. Other outcomes included all-cause mortality and major bleeding. We calculated all outcomes using an odds ratio (OR) with a 95% confidence interval (CI).

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Main results

We included 11 randomised controlled trials of 27,945 participants. Three studies tested oral DTIs (two dabigatran and one ximelagatran), while eight tested oral factor Xa inhibitors (four rivaroxaban, two apixaban and two edoxaban). We deemed all included studies to be of high methodological quality and low risk of bias. The quality of the evidence was graded as high as the outcomes were direct and effect estimates were consistent and precise, as reflected in the narrow CIs around the ORs. Meta-analysis of three studies (7596 participants) comparing oral DTIs with standard anticoagulation groups showed no difference in the rate of recurrent VTE (OR 1.09; 95% CI 0.80 to 1.49), recurrent DVT (OR 1.08; 95% CI 0.74 to 1.58), fatal PE (OR 1.00; 95% CI 0.27 to 3.70), non-fatal PE (OR 1.12; 95% CI 0.66 to 1.90) or all-cause mortality (OR 0.82; 95% CI 0.60 to 1.13). However, oral DTIs were associated with reduced bleeding (OR 0.68; 95% CI 0.47 to 0.98). Meta-analysis of eight studies (16,356 participants) comparing oral factor Xa inhibitors with standard anticoagulation demonstrated a similar rate of recurrent VTE between the two treatments (OR 0.89; 95% CI 0.73 to 1.07). Oral factor Xa inhibitors were associated with a lower rate of recurrent DVT (OR 0.75; 95% CI 0.57 to 0.98). However, this was a weak association, heavily dependent on one study. The rate of fatal (OR 1.20; 95% CI 0.71 to 2.03), non-fatal PE (OR 0.94; 95% CI 0.68 to 1.28) and all-cause mortality (OR 0.90; 95% CI 0.65 to 1.23) was similar between the two treatment groups. Oral factor Xa inhibitors were also associated with reduced bleeding (OR 0.57; 95% CI 0.43 to 0.76). None of the included studies measured post-thrombotic syndrome or health-related quality of life.

Authors' conclusions

NOACs such as DTIs and factor Xa inhibitors may be an effective and safe alternative to conventional anticoagulation treatment for acute DVT.

PLAIN LANGUAGE SUMMARY

Novel oral anticoagulants for the treatment of deep vein thrombosis

Background

Deep vein thrombosis (DVT) is a condition in which a blood clot forms in the deep vein of the leg or pelvis. It affects approximately 1 in 1000 people. If it is not treated, the clot can travel in the blood and block the arteries in the lungs. This life-threatening condition is called a pulmonary embolism (PE) and occurs in approximately 3 to 4 per 10,000 people. The chances of getting a DVT can be increased if people have certain risk factors. These include previous clots, prolonged periods of immobility (such as travelling on aeroplanes or bed rest), cancer, exposure to oestrogens (pregnancy, oral contraceptives or hormone replacement therapy), trauma and blood disorders such as thrombophilia (abnormal blood clotting). A DVT is diagnosed through determining the risk factors and performing an ultrasound of the leg veins. If a DVT is confirmed, people are treated with an anticoagulant. This medicine prevents further clots from forming. Until recently, the drugs of choice were heparin, fondaparinux and vitamin K antagonists. However, these drugs can cause side effects and have limitations. Two further classes of novel oral anticoagulants have been developed: these are called direct thrombin inhibitors (DTI) and factor Xa inhibitors. There are particular reasons why oral DTIs and factor Xa inhibitors might now be better medicines to use. They can be given orally, they have a predictable effect, they do not require frequent monitoring or re-dosing and they have few known drug interactions. This review measures the effectiveness and safety of these new drugs with conventional treatment.

Key results

After searching for relevant studies up to January 2015, we found 11 studies with 27,945 participants. Studies compared DTIs or factor Xa inhibitors with conventional treatment. We looked at whether they prevented blood clots and PE. The main safety outcomes included death and side effects such as bleeding. This review showed that both oral DTIs and oral factor Xa inhibitors had similar effects on preventing blood clots and PE than standard anticoagulation treatment. However, fewer people experienced bleeding who were given either of the drugs. None of the included studies measured post-thrombotic syndrome (a complication of DVT) or health-related quality of life.

Quality of the evidence

The quality of the evidence was high as the studies were of good quality, they answered the question we addressed directly, the results of the studies were consistent and the effect estimates were precise. We do not believe that further research will change the results we have presented.

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BACKGROUND

Description of the condition

Deep vein thrombosis (DVT) occurs when a blood clot or thrombus forms in the deep venous system. This is most commonly observed in the veins in the leg or pelvis. It is a relatively common condition affecting approximately 1 in 1000 people (SIGN 2010). If left untreated, the thrombus can dislodge and travel in the blood to the pulmonary arteries blocking the supply of blood to the lungs. This is termed a pulmonary embolism (PE) and is a life-threatening condition. The incidence of PE is approximately 3 to 4 per 10,000 people but this is likely to be underestimated as it is based on clinical data. DVT is present in approximately 70% to 80% of people with a PE, yet only 15% of PE cases have symptoms of DVT (Huerta 2007). Another complication of DVT is post-thrombotic syndrome (PTS). PTS is long-term condition caused by the reduction in the return of venous blood to the heart and symptoms include chronic pain, skin discolouration, oedema and, in severe cases, varicose veins and venous ulceration (Kahn 2002). The incidence of PTS after a symptomatic DVT is estimated to be between 12% and 50% (Kahn 2014)

According to guidelines by the American College of Chest Physicians, risk factors for DVT are classified as provoked or unprovoked (Kearon 2012). Provoked DVT occurs following surgery or by a non-surgical transient risk factor such as history of venous thromboembolism (VTE), venous insufficiency, chronic heart failure, thrombophilia, obesity, immobility (such as prolonged travel, acute medical illness or hospitalisation), cancer, oestrogens (pregnancy, use of oral contraceptives or hormone replacement therapy) and trauma (SIGN 2010).

Diagnosis of DVT is made by general assessment of the person's medical history and physical examination. The UK National Institute for Health and Care Excellence (NICE) recommend that people presenting with a suspected DVT should be assessed for pre-test probability of DVT using a two-level Wells score (NICE 2012a; Wells 2003). Points are awarded to clinical features present including active cancer, recent immobilisation or surgery, tenderness or swelling and history of DVT in order to estimate the clinical probability of a DVT. The American College of Chest Physicians recommend that people with a low pre-test probability of a first lower extremity DVT should undergo initial testing with D-dimer or ultrasound of the proximal veins (Bates 2012). People with moderate pre-test probability should undergo D-dimer, proximal compression or whole-leg ultrasound, while people with a high pre-test probability should undergo proximal compression or whole-leg ultrasound (Bates 2012).

A D-dimer test is based on the principle that the formation of a thrombus is followed by an immediate fibrinolytic response including the release of fibrin degradation products, predominantly D-dimer, into the circulation. Therefore, a negative D-dimer suggests that thrombosis is not occurring and thus is a useful tool in excluding DVT along with clinical scores and imaging. It is important to consider that while a positive result can indicate DVT, there are other potential reasons for a positive D-dimer including liver disease, inflammation, malignancy, pregnancy, trauma and recent surgery (NICE 2012a). Furthermore, D-dimer assays vary in sensitivity and the choice of assay used by an institution is based on cost and availability.

Ultrasound is a diagnostic imaging technique in which high-frequency sound waves are transmitted into the body and the speed at which it is reflected back to the transducer forms an image. Compression ultrasound involves using the probe to try to compress the vascular lumen. If the lumen is fully compressible it indicates that a thrombus has not occurred. Duplex ultrasound is similar but it involves the use of the Doppler signal to determine blood flow properties. In addition, colour imaging can be used to augment the images. Ultrasound is non-invasive and has a high sensitivity and specificity for detecting proximal DVT (NICE 2012a). Guidelines recommend completing either proximal or whole-leg ultrasound determined by local practice, access to testing and cost (Bates 2012).

Description of the intervention

Until recently, standard treatment of a DVT was with an indirect thrombin inhibitor, namely unfractionated heparin (UFH), or low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKA). These drugs block the action of thrombin either by "activating naturally occurring thrombin inhibitors or by inhibiting specific factors in the coagulation system that subsequently impact on thrombin generation or activity" (Weitz 2003). Present guidelines recommend initial therapy for DVT with a parenteral anticoagulant (UFH or LMWH or fondaparinux) and initial VKA initiation (Kearon 2012). Recommendations include the use of LMWH or fondaparinux over UFH for initial therapy of DVT. Although heparin and VKAs are effective anticoagulants, there are limitations associated with each. Heparin-induced thrombocytopenia (HIT) is a severe immune-mediated condition in which the effect of heparin is reversed (Koster 2007). Approximately 50% of people with isolated HIT develop a further thrombosis (Warkentin 1996). HIT is managed by discontinuing heparin but alternative anticoagulation must be administered to treat the thrombosis and prevent a recurrence (Lewis 2001). Meanwhile, VKAs have a narrow therapeutic window, require frequent monitoring and dosage adjustments, and have multiple interactions with other drugs (Ageno 2012).

Two further classes of novel oral anticoagulants (NOACs) have been developed: direct thrombin inhibitors (DTI) and factor Xa inhibitors. Oral DTIs and factor Xa inhibitors have characteristics that may be favourable over heparin and VKA, including oral administration, a predictable effect, lack of frequent monitoring or re-dosing and few known drug interactions (Fox 2012).

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How the intervention might work

Oral direct thrombin inhibitors

Oral DTIs work by binding directly to the enzyme thrombin without the need for a co-factor such as antithrombin. Unlike heparins and VKAs, DTIs can inhibit both soluble thrombin and fibrin-bound thrombin (Kam 2005). Other advantages include a more predictable anticoagulant effect because of their lack of binding to other proteins, an antiplatelet effect and the absence of HIT (Lee 2011). There are several types of oral DTIs.

Dabigatran

Dabigatran etexilate is a reversible oral DTI that is metabolised to its active ingredient, dabigatran, in the gastrointestinal tract (Ageno 2012). It does not require anticoagulation monitoring, is excreted by the kidneys and has a half-life of 12 to 17 hours. As well as a treatment for venous thrombosis, this drug has been involved in many large randomised studies of atrial fibrillation (Connolly 2009), acute coronary syndromes (Oldgren 2011), and prevention of thrombosis following orthopaedic surgery (Eriksson 2007), and in people with mechanical heart valves (Van de Werf 2012). In common with the other NOACs, dabigatran was associated with a lower incidence of intracranial haemorrhage (compared with VKA). However, again compared with VKA, dabigatran showed a higher incidence of indigestion, heartburn and gastrointestinal bleeding. Dabigatran, in the atrial fibrillation studies, showed a tendency (although ultimately not statistically significant) to increased incidence of myocardial infarction (Baetz 2008).

Ximelagatran

Ximelagatran is a prodrug that is metabolised to melagatran as it is better absorbed from the gastrointestinal tract (Kam 2005). It has a plasma half-life of three hours, has a predictable response after oral administration and does not require coagulation monitoring. Ximelagatran was found to be effective in the treatment of VTE but caused unacceptable liver toxicity (Boudes 2006), and was, therefore, never licensed.

Oral factor Xa inhibitors

Factor Xa inhibitors bind directly to the active site of factor Xa, thus blocking the activity of the clotting factor. Unlike indirect factor Xa inhibitors such as fondaparinux, direct factor Xa inhibitors "inactivate free FXa and FXa incorporated with the prothrombinase complex equally well" and do not require interaction with the inhibitor antithrombin (Eriksson 2009). They have been shown to be non-inferior to VKA but without the need for regular blood test monitoring. They appear to have fewer drug interactions (compared with VKA) and no food or alcohol interactions.

Rivaroxaban

Rivaroxaban is a reversible oral direct factor Xa inhibitor with a half-life estimated to be eight to 10 hours (Spyropoulos 2012). For the initial treatment of acute DVT, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment and prevention of recurrence (NICE 2012b).

Apixaban

Apixaban is an oral, small molecule, reversible inhibitor of factor Xa with a plasma half-life of eight to 15 hours (Eriksson 2009).

Betrixaban

Betrixaban is an orally administered direct factor Xa inhibitor. It has a half-life of 15 hours, offers the convenience of once daily dosing and may exhibit fewer drug interactions than warfarin (Palladino 2013).

Edoxaban

Edoxaban is an oral direct inhibitor of activated factor X that is rapidly absorbed with a half-life of nine to 11 hours. Edoxaban has a dual mechanism of elimination with one-third eliminated via the kidneys and the remainder excreted in the faeces. It also offers the convenience of once-daily dosing (Eikelboom 2010), and is used in conjunction with LMWH for five days.

Why it is important to do this review

The effectiveness of oral DTIs and factor Xa inhibitors for the treatment of VTE has been studied in several randomised controlled trials (EINSTEIN-DVT study (EINSTEIN Investigators), ODIXa-DVT study (Agnelli 2007), Botticelli study (Botticelli Investigators), AMPLIFY study (Agnelli 2013), RE-COVER II study (Schulman 2011), THRIVE studies (Eriksson 2003)). One non-Cochrane systematic review has examined the effectiveness of DTIs and factor Xa inhibitors versus VKAs in the treatment of acute VTE (Fox 2012). The primary outcome was VTE and results were not presented for DVT and PE separately. To date, no systematic review has been conducted examining the effectiveness of oral inhibitors in the treatment of DVT alone. Given the relatively high incidence of DVT and the emergence of these new anticoagulants, it is important to establish the safety and effectiveness of these new treatments.

We are currently conducting another Cochrane systematic review to determine the effectiveness of oral DTIs and oral factor Xa inhibitors for the treatment of PE (Robertson 2014a).

OBJECTIVES

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To assess the effectiveness of oral DTIs and oral factor Xa inhibitors for the treatment of DVT.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials in which people with a confirmed DVT were allocated to receive an oral DTI or an oral factor Xa inhibitor for the treatment of DVT. We included published studies and studies in progress if preliminary results were available. We also included non-English studies in the review. There was no restriction on publication status. We excluded DTIs and factor Xa inhibitors that were not given by the oral route. We also excluded studies where treatment was for less than three months as a meta-analysis of DVT treatment strategies has demonstrated an increased rate of recurrence after less than three months of anticoagulation but no significant difference with various longer periods of treatment (Boutitie 2011).

Types of participants

People with a DVT, confirmed by standard imaging techniques (venography, impedance plethysmography, whole-leg compression ultrasound, proximal compression ultrasound).

Types of interventions

- Oral DTIs (e.g. dabigatran, ximelagatran) (although ximelagatran was withdrawn from the market in 2006 due to safety issues, we included it in the review to make the results as comprehensive as possible).
- Oral factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban).
- Other anticoagulants (e.g. LMWH, UFH or VKAs).

Comparisons included:

- Oral DTI or oral factor Xa inhibitor versus another anticoagulant.
- One oral DTI versus another oral DTI.
- One oral factor Xa inhibitor versus another oral factor Xa inhibitor.
- Oral DTI versus oral factor Xa inhibitor.

Types of outcome measures

Primary outcomes

- Recurrent VTE (clinically overt DVT confirmed by standard imaging techniques including proximal leg vein ultrasound scan or D-dimer test, or both; or clinically overt PE confirmed by computed tomography pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) scan, or both).
- PE (fatal/non-fatal), confirmed by CTPA or V/Q scan.

Secondary outcomes

- All-cause mortality.
- PTS.
- Adverse effects of treatment including major bleeding (as defined by the International Society on Thrombosis and Haemostasis (ISTH); Schulman 2005);
    - fatal bleeding;
    - symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome;
    - bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells;
    - any combination of the above.
- Health-related quality of life (as reported in studies).

Search methods for identification of studies

Electronic searches

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched January 2015) and the Cochrane Register of Studies (CRS) (www.metaxis.com/CRSWeb/Index.asp) (last searched January 2015). See Appendix 1 for details of the search strategy used to search CRS. The Specialised Registeris maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

The TSC also searched the following trial databases for details of ongoing and unpublished studies using the terms apixaban or betrixaban or dabigatran or edoxaban or rivaroxaban or ximelagatran:

- World Health Organization International Clinical Trials Registry (apps.who.int/trialsearch/);
- ClinicalTrials.gov (clinicaltrials.gov/);
- Current Controlled Trials (www.controlled-trials.com/);

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Searching other resources

We searched the reference lists of relevant articles retrieved by electronic searches for additional citations.

Data collection and analysis

Selection of studies

One review author (LR) used the selection criteria to identify trials for inclusion and a second review author (PK or JM) independently confirmed this selection. We resolved any disagreements by discussion.

Data extraction and management

Two review authors (LR, JM) independently extracted the data from the included studies. We recorded information about the trial design, diagnosis of DVT, baseline characteristics of participants and type of prophylaxis. Recurrent DVT and PE (fatal and non-fatal) data were recorded as the primary outcome measures. Data on all-cause mortality, PTS, adverse effects of treatment including clinically relevant bleeding and health-related quality of life were also collected in accordance with the secondary outcome measures. We contacted authors of included studies where further information or clarification was required. We resolved any disagreements in data extraction and management by discussion with the third review author (PK) if required.

Assessment of risk of bias in included studies

Two review authors (LR, JM) independently used The Cochrane Collaboration's 'Risk of bias' tool to assess risk of bias for each of the included studies (Higgins 2011). The tool provides a protocol for judgements on sequence generation, allocation methods, blinding, incomplete outcome data, selective outcome reporting and any other relevant biases. We judged each of these domains as high, low or unclear risk of bias according to Higgins 2011, and provided support for each judgement. We presented the conclusions in a 'Risk of bias' table. Any disagreements were resolved by discussion with the third review author (PK) if required.

Measures of treatment effect

We based the analysis on intention-to-treat data from the individual clinical trials. As the primary and secondary outcomes were all binary measures, we computed odds ratios (ORs) using a fixed-effect model and calculated the 95% confidence intervals (CI) of the effect sizes.

Unit of analysis issues

The unit of analysis in this review was the individual participant.

Dealing with missing data

We sought information about drop-outs, withdrawals and other missing data and, if not reported, we contacted study authors for this information.

Assessment of heterogeneity

We assessed heterogeneity between the trials by visual examination of the forest plot to check for overlapping CIs, the Chi^2 test for homogeneity with a 10% level of significance and we used the I^2 statistic to measure the degree of inconsistency between the studies. An I^2 result of greater than 50% may represent moderate to substantial heterogeneity (Deeks 2011).

Assessment of reporting biases

We planned to assessed publication bias by funnel plots if a sufficient number of studies (10 or more) were available in the meta-analyses. There are many reasons for funnel plot asymmetry, and we planned to consult the *Cochrane Handbook for Systematic Reviews of Interventions* to aid the interpretation of the results (Sterne 2011).

Data synthesis

The review authors independently extracted the data. One review author (LR) inputted the data into Review Manager 5 (RevMan 2012), and the second review author (JM) cross-checked data entry. We resolved any discrepancies by consulting the source publication.

We used a fixed-effect model to meta-analyse the data. If the I^2 statistic indicated heterogeneity greater than 50%, we performed a random-effects model analysis instead of a fixed-effect model analysis.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses.

- History of VTE.
- Age.
- Active cancer (treatment within last six months or palliative).
- Pregnancy.
- Major surgery requiring general or regional anaesthesia in the previous 12 weeks.
- Recent period of immobility (bedridden three or more days in the previous 12 weeks).
- Thrombophilia (genetic or acquired).

We performed additional subgroup analysis by duration of treatment to identify treatment effects of treatment duration of three months and more than three months.

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Sensitivity analysis

We planned to perform sensitivity analyses by excluding studies that were judged to be at high risk of bias. We also performed sensitivity analyses with and without ximelagatran a priori given that this drug is no longer available.

RESULTS

Description of studies

Results of the search

See Figure 1.

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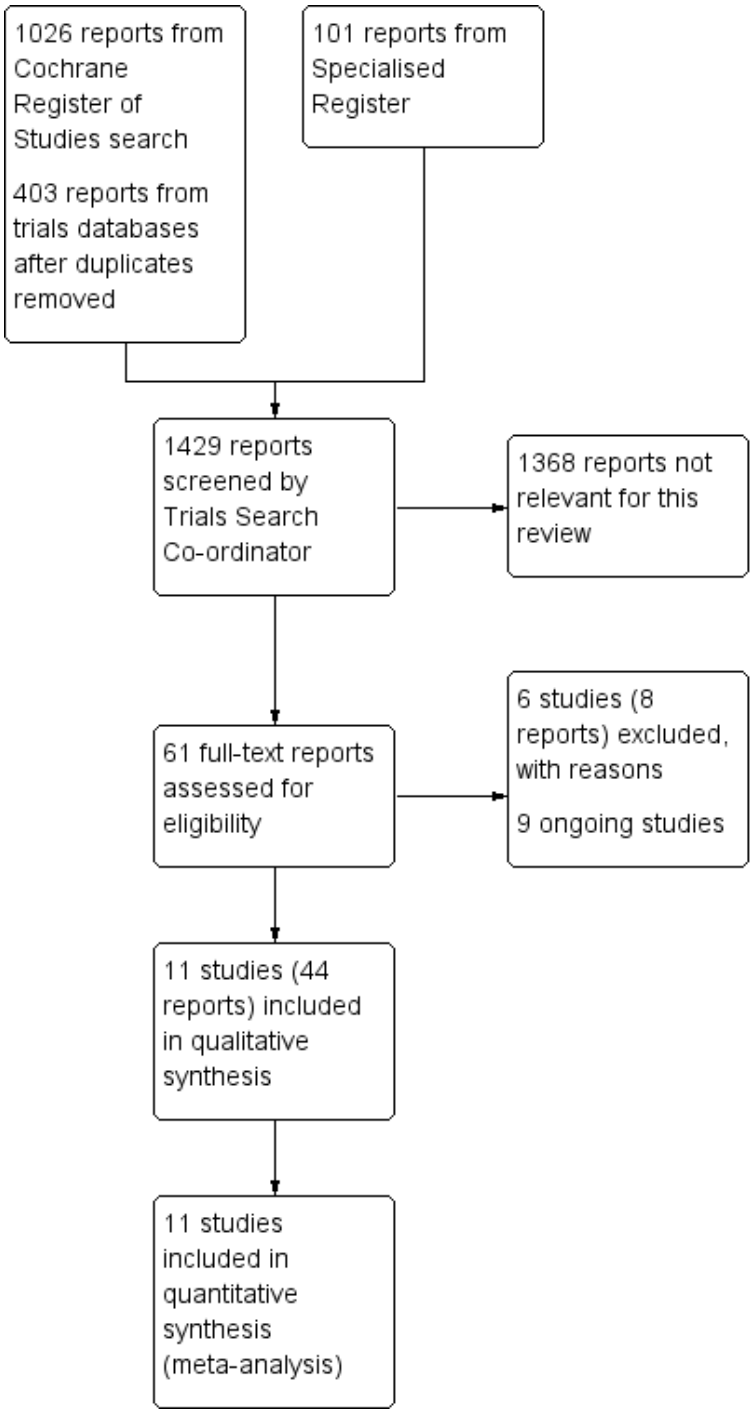
Figure 1. Study flow diagram.



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We included 11 studies in the review.

Included studies

The Characteristics of included studies table presents details of the included studies.

Eleven studies (27,945 participants) met the criteria and were included in the review (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study; Piazza 2014; RE-COVER; RE-COVER II; THRIVE I).

Three studies (7596 participants) compared oral DTIs with standard anticoagulation (RE-COVER; RE-COVER II; THRIVE I). One study tested ximelagatran (THRIVE I). The THRIVE I study was a phase III double-blind, double-dummy, dose-guiding study in which 2489 people with a VTE were given ximelagatran 24 mg, 36 mg, 48 mg or 60 mg twice daily for six months. The control treatment was LMWH (enoxaparin or dalteparin) followed by warfarin. Two studies tested dabigatran (RE-COVER; RE-COVER II). RE-COVER was a phase III non-inferiority, double-blind, double-dummy trial in which 2539 people with a VTE were given dabigatran 150 mg twice daily or warfarin. Treatment was for six months and included sham monitoring of international normalised ratio (INR) and sham titration of warfarin in the control group. To gain regulatory approval, the study was repeated with an identical design (RE-COVER II).

Eight studies (20,349 participants) tested oral factor Xa inhibitors (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study; Piazza 2014). Four studies tested rivaroxaban (ODIXa-DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study), two tested apixaban (AMPLIFY study; Botticelli DVT study), and two tested edoxaban (Hokusai-VTE study; Piazza 2014). Three studies were dose ranging (Botticelli DVT study; Einstein-DVT dose study; ODIXa-DVT study), while the remaining five studies were fixed dose (AMPLIFY study; Botticelli DVT study; Einstein-DVT study; Hokusai-VTE study; Piazza 2014). The control treatment was enoxaparin followed by a VKA in all eight studies. Duration of treatment was 12 weeks in five studies (Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; ODIXa-DVT study; Piazza 2014), and six months in three studies (AMPLIFY study; Einstein-PE study; Hokusai-VTE study). Seven studies measured recurrent DVT, PE (fatal and non-fatal), all-cause mortality and major clinically relevant bleeding (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study). The Piazza 2014 study measured recurrent VTE. The Einstein-PE study was included as 25% of participants had concurrent symptomatic DVT. We contacted the authors of the study who provided us with the data for the subgroup of people with DVT. However, it was not possible to obtain data on fatal PE, non-fatal PE and all-cause mortality from the study authors. The Hokusai-VTE study was also included but data were taken from the subgroup of 4921 people with an index DVT. It was not possible to obtain outcome data on all-cause mortality from the authors of this study.

Excluded studies

See Characteristics of excluded studies.

We excluded six studies (Ageno 2014; AMPLIFY EXTENDED STUDY; REMEDY; RE-SONATE; THRIVE; THRIVE III) from this review. The Xalia study by Ageno 2014 was not a randomised controlled trial. In the AMPLIFY EXTENDED STUDY, participants had already taken part in the AMPLIFY study. Similarly, the RE-SONATE study was an extended treatment study and participants had already taken part in the RE-COVER and RE-COVER II studies. We excluded the THRIVE study as treatment was only for four weeks. We excluded the REMEDY and THRIVE III studies as the control groups were administered a placebo and this did not fit as an intervention in this review.

Risk of bias in included studies

See Figure 2 and Figure 3.

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Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

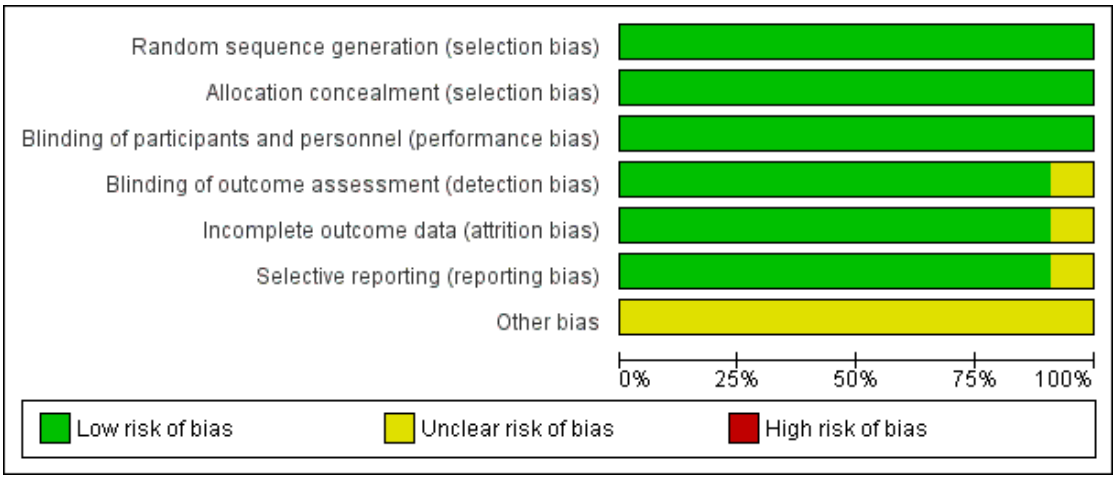

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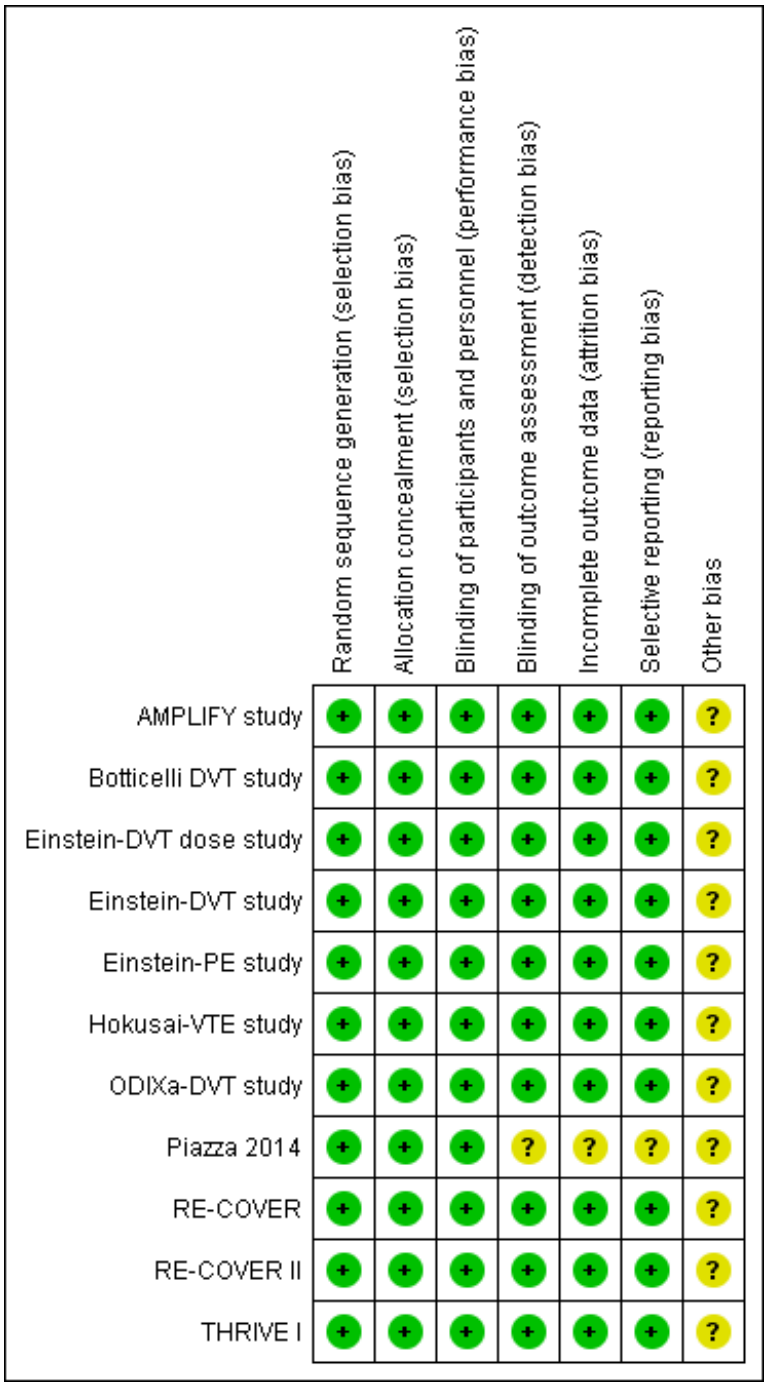
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

All 11 included studies reported using a computerised system to generate the randomisation sequence and conceal treatment allocation and we, therefore, judged them at low risk of selection bias (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study; Piazza 2014; RE-COVER; RE-COVER II; THRIVE I). The Piazza 2014 study was an abstract and details of the randomisation process were not reported. However, personal communication with the author revealed that the randomisation process was computerised and, therefore, we judged this study at low risk of bias.

Blinding

Six studies did not blind participants and personnel to the control treatment as it comprised a subcutaneous injection of heparin (Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; ODIXa-DVT study; Piazza 2014). However, we judged that the lack of blinding in the control group was unlikely to have affected the outcomes of this review. The remaining five studies were double-blinded and used placebo tablets or injection (AMPLIFY study; Hokusai-VTE study; RE-COVER; RE-COVER II; THRIVE I). Therefore, we judged all 11 studies at low risk of performance bias.

Ten studies blinded outcome assessors to treatment and we judged them at low risk of detection bias (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study; RE-COVER; RE-COVER II; THRIVE I). The study by Piazza 2014 did not provide enough information for an assessment about detection bias to be made.

Incomplete outcome data

Ten studies sufficiently reported missing outcome data and were balanced across treatment groups and, therefore, we judged them at low risk of attrition bias (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study; RE-COVER; RE-COVER II; THRIVE I). The study by Piazza 2014 did not provide enough information for an assessment about the level of attrition bias to be made.

Selective reporting

Ten studies clearly stated and reported the pre-specified outcomes and, therefore, we deemed them at low risk of reporting bias (AMPLIFY study; Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; ODIXa-DVT study; RE-COVER; RE-COVER II; THRIVE I). The Piazza 2014 study did not provide enough information for an assessment about reporting bias to be made. Protocols were available for five studies (AMPLIFY study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study).

Other potential sources of bias

All 11 included studies were funded by the pharmaceutical company that developed the particular drug being tested and, therefore, could potentially have biased design, collection or reporting of results.

Effects of interventions

We identified only studies investigating DTIs or factor Xa inhibitors and not the other comparisons set out in the review.

Oral direct thrombin inhibitors versus another anticoagulant

Recurrent venous thromboembolism

Meta-analysis of three studies (7596 participants) showed that the rate of recurrent VTE was similar between the groups treated with a DTI and standard anticoagulation with heparin and a VKA. The incidence was 2.26% (86 events/3793 participants) in the DTI group and 2.08% (79 events/3803 participants) in the standard anticoagulation group, leading to an OR of 1.09 (95% CI 0.80 to 1.49, I^2 = 0%; Analysis 1.1). When analysed according to duration of treatment, there was no difference in the incidence of recurrent VTE between participants treated with DTIs and standard anticoagulation for three months (OR 1.09; 95% CI 0.62 to 1.91) or for more than three months (OR 1.09; 95% CI 0.76 to 1.58) compared with standard anticoagulation.

Recurrent deep vein thrombosis

The incidence of recurrent DVT was 1.48% (56 events/3793 participants) in the DTI group and 1.37% (52 events/3803 participants) in the standard anticoagulation group, leading to an OR of 1.08 (95% CI 0.74 to 1.58, I^2 = 0%; Analysis 1.2). The incidence of recurrent DVT was similar between DTIs and standard anticoagulation when treatment was for three months (OR 0.89; 95% CI 0.44 to 1.78) and more than three months (OR 1.18; 95% CI 0.75 to 1.85).

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Fatal pulmonary embolism

The incidence of fatal PE was 0.10% (4 events/3793 participants) in the DTI group compared with 0.10% (4 events/3803 participants) in the standard anticoagulation group (OR 1.00; 95% CI 0.27 to 3.70, I^2 = 0%; Analysis 1.3). The incidence of fatal PE was similar between DTIs and standard anticoagulation when treatment was for three months (OR 2.02; 95% CI 0.18 to 22.26) and for more than three months (OR 0.71; 95% CI 0.14 to 3.61).

Non-fatal pulmonary embolism

Non-fatal PE occurred in 0.76% (29 events/3793 participants) of DTI participants and 0.68% (26 events/3803 participants) of standard anticoagulation participants (OR 1.12; 95% CI 0.66 to 1.90, I^2 = 48%; Analysis 1.4). The incidence of non-fatal PE was similar between DTIs and standard anticoagulation when treatment was for three months (OR 1.51; 95% CI 0.54 to 4.27) and for more than three months (OR 1.00; 95% CI 0.54 to 1.86).

All-cause mortality

There was no difference in the rate of all-cause mortality between the two treatment groups. The incidence was 1.84% (70 events/3792 participants) in the DTI group and 2.23% (85 events/3804 participants) in the standard anticoagulation group), leading to an OR of 0.82 (95% CI 0.60 to 1.13, I^2 = 0%; Analysis 1.5). When analysed according to treatment duration, the incidence was similar between participants treated with DTIs and standard anticoagulation for three months (OR 0.66; 95% CI 0.41 to 1.08) and for more than three months (OR 0.98; 95% CI 0.64 to 1.50).

Post-thrombotic syndrome

None of the included studies measured PTS as an outcome.

Adverse effects of treatment

Meta-analysis showed that DTIs were associated with fewer major bleeding episodes than standard anticoagulation therapy. Of the DTI participants, 1.29% (49 events/3793 participants) had a major clinically relevant bleeding episode compared with 1.89% (72 events/3803 participants) of standard anticoagulation participants, resulting in a significant OR 0.68 (95% CI 0.47 to 0.98, I^2 = 0%; Analysis 1.6). However, when analysed according to treatment duration, there was no difference in the incidence of major bleeding between participants treated with DTIs and standard anticoagulation for three months (OR 0.54; 95% CI 0.28 to 1.03) or for more three months (OR 0.76; 95% CI 0.49 to 1.18).

Health-related quality of life

Health-related quality of life was not an outcome in any of the included studies.

Sensitivity analyses

As part of the planned sensitivity analysis, we removed one study (THRIVE I) testing ximelagatran from the meta-analyses (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6) since the drug is no longer available. Excluding these results had little effect on the outcomes. The rate of recurrent VTE (OR 1.09; 95% CI 0.76 to 1.58), recurrent DVT (OR 1.18; 95% CI 0.75 to 1.85), fatal PE (OR 0.71; 95% CI 0.14 to 3.61), non-fatal PE (OR 1.00; 95% CI 0.30 to 3.35) and all-cause mortality (OR 0.98; 95% CI 0.64 to 1.50) remained similar between participants treated with dabigatran and participants treated with a VKA. However, excluding the ximelagatran study did produce a result for major bleeding that was no longer significant (OR 0.76, 95% CI 0.49 to 1.18).

We deemed no studies to be of high risk of bias, therefore, we did not perform a sensitivity analysis excluding studies judged to be of high risk of bias.

Oral factor Xa inhibitors versus another anticoagulant

Recurrent venous thromboembolism

Meta-analysis of eight studies (16,356 participants) demonstrated that the rate of recurrent VTE was similar in participants treated with an oral factor Xa inhibitor compared with standard anticoagulation. The incidence was 2.60% (223 events/8604 participants) in the factor Xa inhibitor group and 2.92% (226 events/7752 participants) in the standard anticoagulation group, leading to an OR 0.89 (95% CI 0.73 to 1.07, I^2 = 26%; Analysis 3.1). When analysed according to duration of treatment, the incidence of recurrent VTE was slightly lower in participants treated with factor Xa inhibitors for three months compared with participants treated with standard anticoagulation (OR 0.69; 95% CI 0.48 to 0.99) but there was no difference in the incidence between the two groups when duration of treatment was over three months (OR 0.97; 95% CI 0.78 to 1.22).

Recurrent deep vein thrombosis

Data on recurrent DVT was available in 10 of the 11 included studies. The Piazza 2014 study did not present recurrent DVT data. We attempted to obtain these data but personal communication with the author revealed that it was not available. Oral factor Xa inhibitors were associated with a lower rate of recurrent DVT (1.19%, 102 events/8548 participants) than standard anticoagulation (1.54%, 119 events/7724 participants), leading to an OR of 0.75 (95% CI 0.57 to 0.98, I^2 = 47%; Analysis 3.2). When analysed according to treatment duration, the incidence of recurrent DVT was lower in participants treated with factor Xa inhibitors for three months compared with participants treated with standard

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anticoagulation (OR 0.51; 95% CI 0.31 to 0.84). However, when treatment was for three months or more, there was no difference in the incidence of recurrent DVT between participants treated with factor Xa inhibitors and standard anticoagulation (OR 0.87; 95% CI 0.63 to 1.20).

Fatal pulmonary embolism

The rate of fatal PE was similar between the two treatment groups. The Hokusai-VTE study was not included in the meta-analysis for this outcome as authors only reported overall PE rather than data on fatal and non-fatal PE. We attempted to contact the authors for these specific data but they did not respond. The Piazza 2014 study did not report fatal PE data and, therefore, was not included in the meta-analysis. Meta-analysis of six studies showed that fatal PE occurred in 0.41% (33 events/7945 participants) in the factor Xa inhibitor group versus 0.32% (23 events/7137 participants) in the standard anticoagulation group (OR 1.20; 95% CI 0.71 to 2.03; I^2 = 0%; Analysis 3.3). The incidence of fatal PE was similar between participants treated with factor Xa inhibitors and standard anticoagulation when treatment was for three months (OR 1.73; 95% CI 0.37 to 8.13) and for more than three months (OR 1.13; 95% CI 0.65 to 1.99).

Non-fatal pulmonary embolism

The incidence of non-fatal PE was 0.99% (79 events/7945 participants) in the factor Xa inhibitor group versus 1.10% (79 events/7137 participants) in the standard anticoagulation group (OR 0.94; 95% CI 0.68 to 1.28; I^2 = 0%; Analysis 3.4). The incidence of non-fatal PE was similar between factor Xa inhibitors and standard anticoagulation when treatment was for three months (OR 0.89; 95% CI 0.52 to 1.52) and for more than three months (OR 0.96; 95% CI 0.65 to 1.42). The Piazza 2014 study did not report non-fatal PE data and, therefore, was not included in the meta-analysis.

All-cause mortality

Five studies reported all-cause mortality. We did not include the Einstein-PE study; Hokusai-VTE study; and Piazza 2014 studies as it was not possible to get the specific all-cause mortality data on participants with an index DVT. Meta-analysis showed no difference in the rate of all-cause mortality between the two treatment groups (OR 0.90; 95% CI 0.65 to 1.23, I^2 = 0%; Analysis 3.5). The incidence was 1.58% (88 events/ 5562 participants) in the factor Xa inhibitor group and 1.65% (79 events/4775 participants) in the standard anticoagulation group. Furthermore, there was no difference in the incidence of all-cause mortality between participants treated with factor Xa inhibitors and standard anticoagulation when treatment was three months (OR 0.97; 95% CI 0.64 to 1.46) or more than three months (OR 0.81; 95% CI 0.49 to 1.32).

Post-thrombotic syndrome

None of the included studies measured PTS as an outcome.

Adverse effects of treatment

We included eight studies in the meta-analysis of major bleeding. The incidence was 0.92% (81 events/8789 participants) in the factor Xa inhibitor group and 1.57% (123 events/7856 participants) in the standard anticoagulation group. This led to an OR of 0.57 (95% CI 0.43 to 0.76; I^2 = 28%; Analysis 3.6), indicating that factor Xa inhibitors reduces the risk of major bleeding compared with standard anticoagulation. When analysed according to treatment duration, there was no difference in the incidence of major bleeding between the two groups when treatment was for three months (OR 0.83; 95% CI 0.47 to 1.45). However, when treatment was for more than three months, participants treated with factor Xa inhibitors had a lower incidence of major bleeding compared to those treated with standard anticoagulation (OR 0.50; 95% CI 0.36 to 0.71).

Health-related quality of life

Health-related quality of life was not measured in any of the included studies.

Sensitivity analyses

We deemed no studies to be of high risk of bias; therefore, we did not perform a sensitivity analysis excluding studies judged to be of high risk of bias.

DISCUSSION

Summary of main results

Recurrent venous thromboembolism

Meta-analyses showed no difference between NOACs and standard anticoagulation in the prevention of recurrent VTE during treatment between the NOACs or compared with VKA anticoagulants. This is unsurprising as the incidence of recurrent events during treatment with VKA is low and often only occurs in people with an overwhelming thrombotic tendency, such as people with metastatic malignancy.

Durations of treatment in the included studies varied between three (Botticelli DVT study; Einstein-DVT dose study; ODIXa-DVT study; Piazza 2014), four (Einstein-DVT study), six (AMPLIFY study; RE-COVER; RE-COVER II; THRIVE I),

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and 12 (Einstein-PE study; Hokusai-VTE study) months. Our analyses showed little or no statistical heterogeneity between the included studies. Nevertheless, subgroup analysis was performed by grouping studies where treatment was for three months only and for longer than three months. No difference was observed. This is consistent with findings from previous studies, which have also indicated that there is little difference in outcomes between three, six and 12 months' treatment, although recurrence rates after treatment rose if anticoagulated for less than three months (Boutitie 2011).

Recurrent deep vein thrombosis

Meta-analyses showed oral factor Xa inhibitors to be marginally more effective in preventing recurrent DVT when treatment was for three months. However, this was a weak association, heavily dependent on one study. Therefore, firm conclusions could not really be drawn from this finding, particularly when there was no benefit when treatment was for longer than three months

Fatal pulmonary embolism

Meta-analyses showed that the rate of fatal PE was similar between NOACs and standard anticoagulation, indicating that neither was more or less effective. This association was unaffected by the length of treatment and was consistent with findings from previous studies, which have also indicated that there is little difference in outcomes between three, six and 12 months' treatment, although recurrence rates after treatment rose if anticoagulated for less than three months (Boutitie 2011). However, it is important to note that the CIs were wide due to the small number of fatal PEs.

Non-fatal pulmonary embolism

Meta-analyses also showed that the rate of non-fatal PE was similar between NOACs and standard anticoagulation, indicating that neither was more or less effective. This association was also unaffected by the length of treatment and was consistent with findings from previous studies, which have also indicated that there is little difference in outcomes between three, six and 12 months' treatment, although recurrence rates after treatment rose if anticoagulated for less than three months (Boutitie 2011). However, it is important to note that the CIs were wide due to the small number of non-fatal PEs.

All-cause mortality

The NOACs tested in this review (apixaban, dabigatran, edoxaban, rivaroxaban and ximelagatran) were no more or less effective in preventing all-cause mortality. This result is unsurprising as current treatment with heparin and VKAs is associated with a very low mortality.

Major bleeding

Results of our meta-analysis indicated that NOACs were associated with a significant reduction in major bleeding compared with standard anticoagulation. This appears to be a class effect and may be due to the different mechanisms of action. The included studies all used the strict definition of major bleeding provided by ISTH (Schulman 2005).

Overall completeness and applicability of evidence

This review assessed whether new oral anticoagulants, such as DTIs and factor Xa inhibitors, reduced the rate of recurrent VTE, all-cause mortality and major bleeding in people with a DVT. Three studies tested DTIs and seven studies tested factor Xa inhibitors, all within similar study populations. With the exception of PTS and health-related quality of life, the trialists analysed and reported all of the addressed outcomes. Statistical heterogeneity was low for all outcomes. This was expected as each individual study had strict inclusion criteria, which resulted in the overall participant population of this review having almost identical conditions. Furthermore, for each particular drug, the concentrations used across studies were similar.

Subgroup analyses could not be performed because of the lack of participant-level data. These analyses might be important to guide the clinical management in people with different risk factors for DVT.

Although many researchers consider DVT and PE to be manifestations of the same disorder, we elected to study these two conditions separately as there is evidence of clinically significant differences between them. The majority of recurrent events occur at the same site as the original thrombosis (in other words, in a person presenting with a PE, a recurrent event after treatment is much more likely to be another PE); both oral contraceptive use and Factor V Leiden mutation are more likely to be associated with DVT than PE; and, for example, lung disease is much more likely to be associated with PE. A review on the effectiveness of oral DTIs and factor Xa inhibitors for the treatment of PE is ongoing (Robertson 2014a).

We found no studies comparing:

- one oral DTI versus another oral DTI;
- one oral factor Xa inhibitor versus another oral factor Xa inhibitor;
- oral DTI versus oral factor Xa inhibitor.

One cost-effectiveness analysis conducted by the NICE used data from the RE-COVER, RESONATE and REMEDY trials to measure the cost-effectiveness of NOACs versus standard anticoagulation for the treatment of DVT and PE (NICE 2014). While dabigatran and rivaroxaban were not compared directly, the report found no difference in efficacy between the two drugs and that the costs were also very similar.

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Quality of the evidence

With the exception of funding bias, the risk of bias was low in all 11 included studies (see Figure 2), reflecting good methodological quality. Six of the 11 included studies were open label because of the complexity of monitoring INR in the standard anticoagulation arm (Botticelli DVT study; Einstein-DVT dose study; Einstein-DVT study; Einstein-PE study; ODIXa-DVT study; Piazza 2014). However, all outcomes were assessed by observers who were blinded to the treatment and all safety outcomes were adjudicated by a central independent committee in each study. We could not investigate publication bias because we could not assess asymmetry in a funnel plot with the limited number of studies included in the meta-analysis. All 11 included studies were funded by the pharmaceutical company that formulated the particular drug being tested in the study. This could have led to funding bias. Currently there is no Cochrane tool to estimate the risk of this so we classified this as a potential other risk of bias.

For the majority of primary and secondary outcomes, the quality of evidence was graded as high as the outcomes were direct and effect estimates were consistent and precise, as reflected in the narrow CIs around the ORs. However, for the fatal and non-fatal PE outcomes, the quality of the evidence was lower as the effect estimates were less precise due to the wide CIs based on the small number of events.

Potential biases in the review process

The search was as comprehensive as possible and we are confident that we have included all relevant studies. However, the possibility remains that some relevant trials, particularly in the 'grey' literature (e.g. conference proceedings), have been missed. Two review authors independently performed study selection and data extraction in order to minimise bias in the review process. The inclusion and exclusion criteria set out in the protocol were strictly adhered to in order to limit subjectivity (Robertson 2014b). We performed data collection according to the process suggested by The Cochrane Collaboration. We also followed Cochrane processes as described by Higgins 2011 for assessing the risk of bias.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first review to measure the efficacy and safety of oral anticoagulants in people with a DVT. We found eight other systematic reviews that assessed the same oral anticoagulants but in people with a VTE (Antoniazzi 2013; Castellucci 2013; Fox 2012; Gomez-Outes 2014; Hirschl 2014; Kang 2014; Sardar 2013; van der Huille 2014). Five reviews found similar results to this review; that NOACs are associated with less bleeding than conventional treatment (Antoniazzi 2013; Fox 2012; Gomez-Outes 2014; Hirschl 2014; van der Huille 2014).

The review by Fox 2012 included eight of the 10 studies that we included in our review. Two studies were not included but the reasons are not stated in the review (AMPLIFY study; Hokusai-VTE study). Meta-analysis was done by brand rather than class of drug. Fox 2012 found no difference in recurrent VTE between the two treatment groups. Rivaroxaban was the only drug found to be significantly associated with fewer major bleeding episode (OR 0.57; 95% CI 0.39 to 0.84). All-cause mortality did not differ between the two treatment groups.

The review by van der Huille 2014 excluded four studies that were included in our review (Botticelli DVT study; ODIXa-DVT study; RE-COVER II; THRIVE I). We excluded three as they were phase II trials (Botticelli DVT study; ODIXa-DVT study; THRIVE I). We excluded the RE-COVER II study as, at the time of the review, it had not been published in a peer-reviewed journal. Therefore only five studies were included in the review (AMPLIFY study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; RE-COVER). Meta-analysis showed no difference between the two treatment groups in terms of recurrent VTE, fatal PE and all-cause mortality. However, the NOACs were associated with a significant reduced risk of major bleeding (risk ratio (RR) 0.60; 95% CI 0.41 to 0.88) and fatal bleeding (RR 0.36; 95% CI 0.15 to 0.87).

Hirschl 2014 included six studies and found no differences between NOACs and standard treatment regarding recurrent VTE and mortality (AMPLIFY study; Einstein-DVT study; Einstein-PE study; Hokusai-VTE study; RE-COVER; RE-COVER II). However, bleeding was reduced by rivaroxaban (RR 0.55; 95% CI 0.38 to 0.81), apixaban (RR 0.31; 95% CI 0.17 to 0.55) and edoxaban (RR 0.81; 95% CI 0.71 to 0.93).

The review by Gomez-Outes 2014 included six studies. The risk of recurrent VTE was similar between the two treatment groups (RR 0.91; 95% CI 0.709 to 1.06) but the NOACs were associated with reduced major bleeding (absolute risk difference -0.6%, 95% CI -1.0% to -0.3%).

The review by Kang 2014 also included six studies and found that NOACs did not differ in the risk of mortality or recurrent VTE. However, dabigatran was associated with increased major bleeding compared to apixaban (RR 2.69; 95% CI 1.19 to 6.07) and edoxaban also had a higher bleeding rate compared with apixaban (RR 2.74; 95% CI 1.40 to 5.39).

The review by Antoniazzi 2013 included people with VTE and atrial fibrillation. The review included eight studies and results showed that the risk of major bleeding was lower in people treated with dabigatran (RR 0.83; 95% CI 0.78 to 0.97).

The reviews by Castellucci 2013 and Sardar 2013 compared oral anticoagulants with antiplatelet drugs but the focus was on the secondary prevention on VTE rather than treatment.

AUTHORS' CONCLUSIONS

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Implications for practice

The clear benefit of all novel oral anticoagulants (NOACs) is ease of use. In the short term, this may provide clinical and economic benefits in the avoidance of the warfarin-loading phase of treatment (as shown with some of the studies) with its concomitant use of parenteral anticoagulants and frequent international normalised ratio (INR) testing. The ease of administration of NOACs associated with reduced incidence of major bleeding may open the opportunity to prescribe long-term treatment for people in whom the risk of a recurrent event after stopping anticoagulants is impossible to determine. However, precautions are required with the use of NOACs. They are all, to some extent, renally excreted; and there is evidence of wide inter-individual variation in anticoagulant response.

Implications for research

The lack of an antidote is of concern to some clinicians and patients. This is obviously a very serious problem although fortunately, relatively rare as the NOACs have a short half-life (if renal function is maintained). Antidotes to each of the NOACs are currently under trial, results of which are required urgently.

There is evidence of wide inter-individual variation in anticoagulant effect from the fixed doses of NOACs currently prescribed. This is of great clinical importance, not only in emergencies or in people requiring surgical or investigational interventions, but to answer the very basic questions: is this patient both safely and adequately anticoagulated?

Further research is required in categories of venous thrombosis not specifically examined in the studies included here, such as those with malignancy, travel-associated or people carrying thrombophilic abnormality such as the anti-phospholipid syndrome. The ease of administration of these anticoagulants associated with reduced incidence of major bleeding may open the opportunity to prescribe long-term treatment for people in whom the risk of a recurrent event after stopping anticoagulants is impossible to determine. Furthermore, future studies should compare the NOACs directly with one another to determine which one is most effective and safe.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AMPLIFY study

Methods	**Study design :** randomised double-blind trial **Duration of study :** 6 months
Participants	**Setting :** hospital **Country :** multinational **No :** 5395; apixaban 2691, enoxaparin + warfarin 2704 **Age, mean (SD) years :** apixaban 57.2 (16.0) years, enoxaparin + warfarin 56.7 (16.0) years **Sex :** apixaban 1569 M/1122 F; placebo 1598 M/1106 F **Inclusion criteria :** people ≥ 18 years of age with an objectively confirmed, symptomatic proximal DVT or PE (with or without DVT) **Exclusion criteria :** active bleeding, a high risk of bleeding, or other contraindications to treatment with enoxaparin and warfarin; if they had cancer and long-term treatment with LMWH was planned; if their DVT or PE was provoked in the absence of a persistent risk factor for recurrence; if < 6 months of anticoagulant treatment was planned; or if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin at a dose > 165 mg daily, or treatment with potent inhibitors of cytochrome P-450 3A4; if they had received > 2 doses of a once-daily LMWH regimen, fondaparinux, or a VKA; > 3 doses of a twice daily LMWH regimen; or more than 36 hours of continuous intravenous heparin. Additional exclusion criteria were a haemoglobin level < 9 mg/dL, a platelet count < 100,000/mm^3, a serum creatinine level > 2.5 mg/dL (220 μmol/L), or a calculated creatinine clearance < 25 mL/minute
Interventions	**Intervention 1 :** apixaban 10 mg twice daily for the first 7 days, followed by 5 mg twice daily for 6 months **Intervention 2 :** enoxaparin 1 mg/kg body weight every 12 hours for at least 5 days and warfarin concomitantly for 6 months. Warfarin dose was adjusted to maintain the INR 2.0-3.0. Enoxaparin or placebo was discontinued when a blinded INR of ≥ 2.0 was achieved **Follow-up :** weeks 2, 4, 8, 12, 16, 20 and 24 after randomisation and 30 days after the end of the intended treatment period
Outcomes	**Primary :** composite of recurrent symptomatic VTE (fatal or non-fatal PE and DVT), and mortality related to VTE; major bleeding; major bleeding **Secondary :** recurrent symptomatic VTE, mortality related to VTE, mortality from cardiovascular causes, mortality from any cause and the composite of major bleeding and clinically relevant non-major bleeding
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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AMPLIFY study (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive voice-response system" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive voice-response system" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind. Patients were assigned to receive apixaban tablets plus placebo enoxaparin injections and placebo warfarin tablets or conventional therapy with enoxaparin injections and warfarin tablets plus placebo apixaban tablets" Comment: study judged at low risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent committee, whose members were unaware of the study-group assignments, adjudicated the qualifying diagnosis, the anatomical extent of the initial deep vein thrombosis or pulmonary embolism, and all suspected outcomes. The study used blinded INR monitoring with a point-of-care device that generated an encrypted code for INR results. Investigators reported the code to the interactive voice-response system and received either an actual INR value (for patients assigned to warfarin) or a sham INR value (for patients receiving apixaban)" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Pfizer and Bristol-Myers Squibb, the pharmaceutical companies that developed apixaban

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Botticelli DVT study

Methods	**Study design :** veiled randomised, parallel group dose-ranging study **Duration of study :** 12 weeks
Participants	**Setting :** hospital **Country :** Netherlands **No :** 520; apixaban 392, LMWH/VKA 128 **Age, mean (SD) years :** apixaban 58 (15) years, LMWH/VKA 59 (16) years **Sex :** apixaban 242 M/150 F, LMWH/VKA 81 M/47 F **Inclusion criteria :** people with acute symptomatic proximal DVT or extensive calf vein thrombosis, involving at least the upper third of the deep calf vein (trifurcation area) confirmed by CUS or venography **Exclusion criteria :** symptomatic PE; calculated creatinine clearance < 30 mL/minute; impaired liver function (ALT ≥ 3 times the upper limit of normal); bacterial endocarditis; life-expectancy < 6 months; thrombectomy; insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT; indications for VKAs other than DVT; > 24 hours of pre-randomisation treatment with therapeutic doses of UFH, LMWH or fondaparinux or more than a single starting dose of VKA prior to randomisation; active bleeding or high risk of bleeding contraindication treatment with LMWH, fondaparinux or VKA; systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg; use of acetylsalicylic acid (aspirin) > 165 mg/day; child-bearing potential without effective contraception; pregnancy; breastfeeding and any other contraindication listed in the local labelling of enoxaparin, tinzaparin, fondaparinux, warfarin, acenocoumarol or phenprocoumon
Interventions	**Intervention 1 :** apixaban 5 or 10 mg twice daily or 20 mg once daily for 12 weeks **Intervention 2 :** LMWH/VKA. LMWH included tinzaparin 175 IU/kg, enoxaparin 1.5 mg/kg once daily or 1.0 mg/kg twice daily and fondaparinux for a minimum of 5 days. VKAs included warfarin, acenocoumarol or phenprocoumon, which were started within 48 hours after randomisation and continued for 12 weeks. VKA treatment was adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0-3.0). LMWH was continued until a stable INR > 2 was observed on 2 measurements at least 24 hours apart. The choice of LMWH/VKA was made per centre **Follow-up :** days 7, 14, 21, 49 and 84
Outcomes	**Primary :** composite of symptomatic recurrent VTE (recurrent DVT, fatal or non-fatal PE), asymptomatic deterioration in the thrombotic burden as assessed by repeat bilateral CUS and PLS and composite of major and clinically relevant, non-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 ≥ 2 units of packed red blood cells or whole blood. 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, (temporary) cessation of study treatment, or associated with any other discomfort for the participant, such as pain, or impairment of activities of daily life **Secondary :** any bleeding and all-cause mortality.
Notes	
Risk of bias	

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Botticelli DVT study (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An interactive voice response system was used for randomisation" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "An interactive voice response system was used for randomisation" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study was double-blind for the different doses of apixaban and open-label for the LMWH/VKA comparator" Comment: participants and study personnel were blinded to the dose of apixaban. It was impossible to double-blind the control group as treatment comprised enoxaparin by subcutaneous injection and administration of a VKA. However, review authors judge that the lack of blinding in the control group was unlikely to have affected the outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All potential study outcomes were assessed by an independent committee, whose members were unaware of treatment assignment" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Bristol-Myers Squibb, the pharmaceutical company that developed apixaban

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Einstein-DVT dose study

Methods	**Study design :** randomised dose-ranging, phase II double-blind study **Duration of study :** 84 days
Participants	**Setting :** hospital **Country :** Netherlands **No :** 543; rivaroxaban 20 mg 135, 30 mg 134, 40 mg 136, LMWH/VKA 137 **Age, mean (range) years :** rivaroxaban 20 mg 58 (22-87) years, 30 mg 57 (18-89) years, 30 mg 60 (22-94) years, LMWH/VKA 57 (21-92) years **Sex :** rivaroxaban 20 mg 64 M/71 F, 30 mg 69 M/65 F, 40 mg 71 M/65 F, LMWH/VKA 73 M/64 F **Inclusion criteria :** adults with acute symptomatic DVT (i.e. proximal or isolated extensive calf vein thrombosis involving at least the upper one-third of the calf veins) confirmed by CUS or venography. The sole criterion for the presence of DVT was non-compressibility on ultrasound or an intraluminal filling defect on venography **Exclusion criteria :** people with concomitant symptomatic PE; treated for > 36 hours before randomisation with therapeutic doses of UFH or LMWH, or received > 1 dose of a VKA; active bleeding or high risk of bleeding; thrombectomy; insertion of a caval filter or use of a fibrinolytic agent to treat the current episode of DVT; other indications for VKA; life expectancy < 3 months; uncontrolled hypertension (systolic blood pressure > 200 mm Hg or diastolic blood pressure > 110 mm Hg); creatinine clearance < 30 mL/minute; impaired liver function (ALT > 2 x the upper limit of normal; participation in another pharmacotherapeutic study within the previous 30 days; pregnancy or child-bearing potential without effective contraceptive measures; any other contraindication listed on the labelling or permitted anticoagulants; systemic treatment with azole compounds or other strong CYP3A4 inhibitors such as human immunodeficiency virus-protease inhibitors within 4 days before randomisation or during the study
Interventions	**Intervention 1 :** rivaroxaban 20 mg, 30 mg or 40 mg once daily for 12 weeks **Intervention 2 :** LMWH and VKA. Heparins permitted for initial treatment were UFH (5000 IU bolus and 1250 IU/hour infusion), tinzaparin (175 IU/kg subcutaneously once daily) or enoxaparin (1.5 mg/kg subcutaneously once daily, or 1.0 mg/kg subcutaneously twice daily). Minimum duration of heparin was 5 days. Permitted VKAs included warfarin, acenocoumarol, phenprocoumon and fluindione. VKA treatment was started within 48 hours after randomisation, adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0-3.0) and continued for 12 weeks **Follow-up :** days 8, 15, 22, 43 and 84
Outcomes	**Primary :** symptomatic recurrent DVT, symptomatic fatal or non-fatal PE, asymptomatic deterioration in thrombotic burden; major and clinically relevant but non-major bleeding **Secondary :** all-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Einstein-DVT dose study (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised, via an interactive voice response system" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised, via an interactive voice response system" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind for rivaroxaban doses and open-label for the LMWH/VKA comparator" Comment: participants and study personnel were blinded to the dose of rivaroxaban. It was impossible to double-blind the control group as treatment comprised enoxaparin by subcutaneous injection and administration of a VKA. However, review authors judged that the lack of blinding in the control group was unlikely to have affected the outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded outcome assessment for all groups. An independent adjudication committee, unaware of treatment allocation, evaluated all suspected thromboembolic complications, deaths, baseline and repeat ultrasound and perfusion lung scans, as well as all episodes of suspected bleeding" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Bayer HealthCare, the pharmaceutical company that developed rivaroxaban

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Einstein-DVT study

Methods	**Study design :** open-label, randomised, event-driven, non-inferiority phase III study **Duration of study :** 15 weeks
Participants	**Setting :** 300 centres **Country :** over 30 countries **No :** 3449; rivaroxaban 1731, enoxaparin/VKA 1718 **Age, mean (SD) years :** rivaroxaban 55.8 (16.4) years, enoxaparin/VKA 56.4 (16.3) years **Sex :** rivaroxaban 993 M/738 F, enoxaparin/VKA 967 M/751 F **Inclusion criteria :** people of a legal age for consent and had acute, symptomatic, objectively confirmed proximal DVT, without symptomatic PE **Exclusion criteria :** people who had received therapeutic doses of LMWH, fondaparinux or UFH for > 48 hours or if they had received more than a single dose of a VKA before randomisation; if they had been treated with thrombectomy, a vena cava filter, or a fibrinolytic agent fort the current episode of thrombosis; or if they had any contraindication listed in the labelling of enoxaparin, warfarin or acenocoumarol
Interventions	**Intervention 1 :** oral rivaroxaban 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily for 12 weeks **Intervention 2 :** standard therapy with subcutaneous enoxaparin, 1.0 mg/kg body weight twice daily, and either warfarin or acenocoumarol, started within 48 hours after randomisation. Enoxaparin was discontinued when the INR was $\geq$ 2.0 for 2 consecutive days and the person had received at least 5 days of enoxaparin
Outcomes	**Primary :** symptomatic recurrent VTE, defined as the composite of DVT or non-fatal or fatal PE and clinically relevant bleeding, defined as the composite of major or clinically relevant non-major bleeding **Secondary :** all-cause mortality, vascular events (acute coronary syndrome, ischaemic stroke, transient ischaemic attack or systemic embolism), and net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding). In addition, analyses of the treatment effects and bleeding were performed in pre-specified subgroups
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to a study group with the use of a computerised voice-response system Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote (from protocol): "Allocation to treatment was done centrally by interactive voice response system" Comment: study judged at low risk of selection bias

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Einstein-DVT study (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label study" Comment: only 1 dose of rivaroxaban was given and as the comparison was enoxaparin/VKA, blinding of participants and personnel was not possible. However, review authors judged that the lack of blinding in the control group was unlikely to have affected the outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected outcome events were classified by a central adjudication committee whose members were unaware of the treatment assignments" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Bayer HealthCare, the pharmaceutical company that developed rivaroxaban

Einstein-PE study

Methods	**Study design :** randomised, open-label, event-driven, non-inferiority trial **Duration of study :** 12 months
Participants	**Setting :** hospital **Country :** 38 countries **No :** 4832; rivaroxaban 2419, enoxaparin 2413 **Age, mean (SD) years :** rivaroxaban 57.9 (7.3) years, enoxaparin 57.5 (7.2) years **Sex :** rivaroxaban 1309 M/1110 F, 1247 M/ 1166 F **Inclusion criteria :** people of a legal age with an acute, symptomatic PE with objective confirmation, with or without symptomatic DVT **Exclusion criteria :** people who had received a therapeutic dose of LMWH, fondaparinux or UFH for > 48 hours or if they had received > 1 dose of a VKA before randomisation; if thrombectomy had been performed, a vena cava filter placed, or a fibrinolytic agent administered for treatment of the current episode; or if they had any contraindication listed in the local labelling of enoxaparin, warfarin or acenocoumarol; another indication for a VKA; a creatinine clearance < 30 mL/minute; clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis or cirrhosis) or an alanine aminotransferase level that was > 3 x upper limit of normal; bacterial endocarditis; active bleeding or a high risk of bleeding contraindicating anticoagulant treatment; a systolic blood pressure > 180

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Einstein-PE study (*Continued*)

	mm Hg or a diastolic blood pressure > 110 mm Hg; child-bearing potential without effective contraceptive measures, pregnancy or breastfeeding; concomitant use of a strong inhibitor of cytochrome P-450 3A4 or a CYP3A4 inducer; participation in another experimental pharmacotherapeutic programme within 30 days; or a life expectancy < 3 months
Interventions	**Intervention 1 :** rivaroxaban 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily **Intervention 2 :** enoxaparin 1.0 mg/kg body weight twice daily and either warfarin or acenocoumarol, started within 48 hours of randomisation. Enoxaparin was discontinued when the INR was $\geq$ 2.0 for 2 consecutive days and the person had received at least 5 days of enoxaparin treatment. The dose of the VKA was adjusted to maintain an INR of 2.0-3.0, determined at least once a month **Follow-up :** 3, 6 and 12 months
Outcomes	**Primary :** symptomatic recurrent VTE, defined as a composite of fatal or non-fatal PE or DVT and clinically relevant bleeding defined as a composite of major or clinically relevant non-major bleeding **Secondary :** mortality due to PE, bleeding or other established diagnoses
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of a computerised voice-response system Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of a computerised voice-response system Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: only 1 dose of rivaroxaban was given and as the comparison was enoxaparin/VKA, blinding of participants and personnel was not possible. However, review authors judged that the lack of blinding in the control group was unlikely to have affected the outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A central committee whose members were unaware of the study-group as-

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Einstein-PE study (*Continued*)

		signments adjudicated the results of all baseline lung-imaging tests and all suspected outcome events" Comment: study at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Bayer HealthCare, the pharmaceutical company that developed rivaroxaban

Hokusai-VTE study

Methods	**Study design :** randomised, double-blind, non-inferiority study **Duration of study :** 12 months
Participants	**Setting :** multicentre **Country :** multinational **No :** 4921; edoxaban 2468, warfarin 2453 **Age, mean (SD) years :** edoxaban 55.7 (16.3) years, warfarin 55.9 (16.2) years **Sex :** edoxaban 2360 M/1758 F, warfarin 2356 M/1766 F **Inclusion criteria :** people aged ≥ 18 years who had objectively diagnosed, acute, symptomatic DVT involving the popliteal, femoral or iliac veins or acute, symptomatic PE (with or without DVT) **Exclusion criteria :** contraindications to heparin or warfarin, had received treatment for > 48 hours with therapeutic doses of heparin, had received > 1 dose of a VKA, had cancer for which long-term treatment with LMWH was anticipated, had another indication for warfarin therapy, continued to receive treatment with aspirin at a dose > 100 mg daily or dual antiplatelet therapy, or had a creatinine clearance < 30 mL/minute
Interventions	**Intervention 1 :** oral edoxaban 60 mg once daily or 30 mg once daily in people with a creatinine clearance 30-50 mL/minute or a body weight ≤ 60 kg or in people who were receiving concomitant treatment with potent P-glycoprotein inhibitors **Intervention 2 :** dose-adjusted warfarin therapy to achieve and INR of 2.0-3.0 and dabigatran-like placebo **Follow-up :** days 5, 12, 30 and 60 after randomisation, monthly while on study drug or every 3 months after discontinuing the study drug and finally at 12 months
Outcomes	**Primary :** incidence of symptomatic recurrent VTE (DVT and fatal or non-fatal PE), clinically relevant bleeding (major or clinically relevant non-major) **Secondary :** none

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Hokusai-VTE study (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive Web-base system" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive Web-base system" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Edoxaban or warfarin was administered in a double-blind fashion" Comment: study judged at low risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent committee, whose members were unaware of the study-group assignments, adjudicated all suspected outcome and the results of baseline imaging tests and assessed the anatomical extent of thrombosis" Comment: study judged at low risk of performance bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Daiichi-Sankyo, the pharmaceutical company that developed edoxaban

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ODIXa-DVT study

Methods	**Study design :** randomised, partially blinded, parallel-group, phase II, dose-finding trial **Duration of study :** 16 weeks (12 weeks' treatment and follow-up examination at 16 weeks)
Participants	**Setting :** multicentre **Country :** multinational **No :** 604; rivaroxaban 478 (10 mg 119, 20 mg twice daily 117, 30 mg 121, 40 mg 121) , enoxaparin/VKA 126 **Age, mean (SD) years :** rivaroxaban 10 mg 58.5 (15.3), 20 mg 57.5 (15.9), 30 mg 61. 4 (15.9), 40 mg 59.5 (16.9), enoxaparin/VKA 58.4 (18.3) **Sex :** rivaroxaban 291 M/187 F, enoxaparin/VKA 77 M/49 F **Inclusion criteria :** people with symptomatic acute thrombosis of the popliteal or more proximal veins, confirmed by CCUS aged ≥ 18 years, had no signs of PE, had not received a VKA, and had received no more than 36 hours of treatment with UFH or an LMWH (3 doses 12 hours apart or 2 doses 24 hours apart) **Exclusion criteria :** cerebral ischaemia; intracerebral bleeding or gastrointestinal bleeding within the past 6 months; neurosurgery within the past 4 weeks or other surgery within the past 10 days; an active peptic ulcer; a known bleeding disorder; prolonged INR or activated partial thromboplastin time; a platelet count below 100 x 10^9/L; known brain metastasis; cytotoxic chemotherapy; life expectancy < 6 months; body weight < 45 kg; severe heart failure (New York Heart Association class III-IV); uncontrolled severe hypertension (> 200/100 mm Hg); a derived creatinine clearance of < 30 mL/min or serum creatinine > 1.5 x ULN; impaired liver function (transaminases > 2 x ULN); a likelihood of reduced oral drug absorption (severe inflammatory bowel disease, short gut syndrome); child-bearing potential without effective contraception; required thrombolytic therapy or treatment with antiplatelet agents, non-steroidal anti-inflammatory drugs with a half-life > 17 hours or potent CYP3A4 inhibitors such as ketoconazole
Interventions	**Intervention 1 :** oral rivaroxaban 10 mg, 20 mg or 30 mg twice daily or 40 mg once daily for 12 weeks **Intervention 2 :** enoxaparin 1 mg/kg twice daily for at least 5 days by subcutaneous injection and a VKA (warfarin, phenprocoumon or acenocoumarol) for 12 weeks **Follow up :** day 21, 84 and 114
Outcomes	**Primary :** improvement in thrombotic burden at mean day 21 (defined as a ≥ 4-point reduction in the thrombus score as measured by CCUS) without confirmed symptomatic extension or recurrence of DVT, confirmed symptomatic PE, or VTE-related death; incidence of major bleeding with onset no later than 2 days after the last dose of study drug. Bleeding was considered major if it was fatal, affected a critical organ (retroperitoneal, intracranial, intraocular or intra-articular), or was clinically overt and led to treatment cessation, a fall in blood haemoglobin ≥ 2 g/dL, or transfusion of ≥ 2 units of packed red blood cells or whole blood **Secondary :** improvement in thrombus score ≥ 4 points as measured by CCUS or an improved perfusion lung scan on day 21 without deterioration in the other and without symptomatic recurrence of VTE, or both; an improvement in CCUS examination score at 3 months; incidence of symptomatic and confirmed PE or DVT (recurrence or extension) during the 3 months of study therapy; incidence of minor bleeding events
Notes	

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ODIXa-DVT study (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by central computer" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised by central computer" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Partially blinded. Patients received double-blinded doses of rivaroxaban. Patients in the open-label standard-anticoagulation group received enoxaparin and a VKA" Comment: participants and study personnel were blinded to the dose of rivaroxaban. It was impossible to double-blind the control group as treatment comprised enoxaparin by subcutaneous injection and administration of a VKA. However review authors judged that the lack of blinding in the control group was unlikely to have affected the outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All clinically suspected VTE, bleeding events, deaths, and paired perfusion lung scans were adjudicated, without knowledge of the treatment group, by an independent central adjudication committee. CCUS videos were assessed centrally by 2 independent readers" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Bayer HealthCare, the pharmaceutical company that developed rivaroxaban

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Piazza 2014

Methods	**Study design :** randomised, open-label multicentre trial **Duration of study :** 12 weeks
Participants	**Setting :** multicentre **Country :** USA **No :** 85; edoxaban 56, LMWH/warfarin 29 **Age, mean (SD) years :** edoxaban 55.6 (14.1), LMWH/warfarin 53.1 (12.0) **Sex :** edoxaban 41 M/15 F, LMWH/warfarin 21 M/8 F **Inclusion criteria :** people with acute symptomatic proximal DVT involving the popliteal, femoral or iliac veins confirmed by CUS or other appropriate imaging techniques (such as venography or spiral/contrast CT) with symptom onset ≤ 1 week prior to randomisation **Exclusion criteria :** concomitant PE known to the investigator at the time of randomisation; thrombectomy, insertion of a caval filter or use of a fibrinolytic agent to treat the current episode of DVT; indication for warfarin other than DVT; > 48 hours pretreatment with therapeutic dosages of anticoagulant treatment (LMWH, UFH, fondaparinux, VKA, factor Xa inhibitor or other anticoagulant per local labelling) prior to randomisation to treat the current episode; treatment with any investigational drug within 30 days prior to randomisation; calculated significant liver disease; subjects with active cancer for whom long-term treatment with LMWH is anticipated, life expectancy < 3 months; active bleeding or high risk for bleeding contraindicating treatment with LMWH or warfarin; uncontrolled hypertension as judged by the investigator (e.g. systolic blood pressure > 170 mm Hg or diastolic blood pressure > 100 mm Hg despite antihypertensive medications confirmed by repeat measurement); women of child-bearing potential without effective contraceptive measures (i.e. a method of contraception with a failure rate < 1 % during the course of the study including the observational period) and women who are pregnant or breastfeeding; any contraindication listed in the local labelling of LMWH, UFH or warfarin; chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs ≥ 4 days/week anticipated to continue during the study; treatment with aspirin in a dosage > 100 mg/day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study; known history of positive hepatitis B antigen or hepatitis C antibody; subjects with any condition that, as judged by the investigator, would put the person at increased risk of harm if he/she participated in the study, including, but not limited to, subjects at increased risk of harm if given a gadolinium-based contrast agent such as gadofosveset trisodium and person has previously entered this study or another edoxaban study
Interventions	**Intervention 1 :** oral edoxaban 90 mg/day for 10 days followed by 60 mg/day for 3 months **Intervention 2 :** LMWH/warfarin for 3 months **Follow up :** day 14-21
Outcomes	**Primary :** relative change in magnetic resonance venogram-quantified thrombus volume **Secondary :** recurrent VTE and major or clinically relevant non-major bleeding
Notes	

Risk of bias

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Piazza 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from personal communication with the author: "Computer generated randomisation scheme" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote from personal communication with the author: "Computer generated randomisation scheme" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: only 1 dose of edoxaban was given and as the comparison was LMWH/warfarin, blinding of participants and personnel was not possible. However review authors judged that the lack of blinding in the control group was unlikely to have affected the outcome
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of high or low risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of high or low risk
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement of high or low risk
Other bias	Unclear risk	The study was funded by Daiichi-Sankyo, the pharmaceutical company that developed edoxaban

RE-COVER

Methods	**Study design : r**andomised, double-blind, double-dummy non-inferiority trial **Duration of study :** 6 months
Participants	**Setting :** 228 clinical centres **Country :** 29 countries **No :** 2539; dabigatran 1273, warfarin 1266 **Age, mean (range) years :** dabigatran 56 (18-93) years, warfarin 55 (18-97) years **Sex :** dabigatran 738 M/535 F, warfarin 746 M/520 F **Inclusion criteria :** people aged $\geq$ 18 years who had acute, symptomatic, objectively

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	verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered an appropriate treatment **Exclusion criteria : d**uration of symptoms > 14 days, PE with haemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was 2 x ULN range, an estimated creatinine clearance < 20 mL/minute, a life expectancy < 6 months, contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, requirement for long-term anticoagulant therapy
Interventions	**Intervention 1 :** oral dabigatran 150 mg twice daily and warfarin-like placebo **Intervention 2 :** dose-adjusted warfarin therapy to achieve and INR 2.0-3.0 and dabigatran-like placebo **Follow-up :** 6 months
Outcomes	**Primary :** recurrent VTE evaluated using the same diagnostic methods used for the initial diagnosis **Secondary :** bleeding that was defined as major if it was clinically overt and if it was associated with a fall in the haemoglobin level ≥ 20 g/L, resulted in the need for transfusion of ≥ 2 units of red cells, involved a critical site, or was fatal
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated randomisation scheme" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Staff members at the clinical centres called an interactive voice-response system that randomly assigned subjects to one of the supplied medication kits. The treatment-group assignment was concealed from all the investigators and their staff at the coordinating centre and the clinical centres and from the clinical monitors" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind. The treatment-group assignment was concealed from all the investigators and their staff at the coordinating centre and the clinical centres and from the clinical monitors. Warfarin or a placebo that looked identical to warfarin....

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RE-COVER (*Continued*)

		..Administration of dabigatran or a placebo that looked identical to dabigatran" Comment: study judged at low risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected outcome events and deaths were classified by central adjudication committees, whose members were unaware of the treatment assignments" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by Boehringer-Ingelheim, the pharmaceutical company that developed dabigatran

RE-COVER II

Methods	**Study design :** randomised, double-blind, double-dummy trial **Duration of study :** 6 months
Participants	**Setting :** 208 study sites **Country :** 31 countries worldwide **No :** 2568; dabigatran 1280, warfarin 1288 **Age, mean (SD) years :** dabigatran 54.7 (16.2) years, warfarin 55.1 (16.3) years **Sex :** dabigatran 781 M/499 F, warfarin 776 M/512 F **Inclusion criteria :** people aged $\geq$ 18 years who had acute, symptomatic, objectively verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered an appropriate treatment **Exclusion criteria :** duration of symptoms > 14 days, PE with haemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was 3 x ULN range, an estimated creatinine clearance < 20 mL/minute, a life expectancy < 6 months, a contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, requirement for long-term anticoagulant therapy
Interventions	**Intervention 1 :** oral dabigatran 150 mg twice daily and warfarin-like placebo for 6 months **Intervention 2 :** active warfarin adjusted to achieve an INR of 2.0-3.0 and dabigatran-like placebo for 6 months

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RE-COVER II (*Continued*)

Outcomes	**Primary :** recurrent VTE objectively verified, preferably with the same method as for the index event **Secondary :** major bleeding defined according to the International Society on Thrombosis and Haemostasis criteria
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by use of an interactive voice response system and a computer-generated randomisation scheme in blocks of 4" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Comment: no information given about how treatment allocation was concealed but study authors stated that "the design of the trial was essentially identical to that of the first study with dabigatran for the treatment of acute VTE" (RE-COVER), which was judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind" Comment: stated as double blind. No other information given about how blinding was maintained but study authors state that "the design of the trial was essentially identical to that of the first study with dabigatran for the treatment of acute VTE" (RE-COVER), which as judged at low risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A central adjudication committee, the members of which were unaware of the treatment assignments, classified all suspected outcome events, bleeding events, and deaths" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes were reported in the pre-specified way

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RE-COVER II (*Continued*)

Other bias	Unclear risk	The study was funded by Boehringer-Ingelheim, the pharmaceutical company that developed dabigatran

THRIVE I

Methods	**Study design :** multicentre, randomised, double-blind, non-inferiority trial **Duration of study :** 28 weeks
Participants	**Setting :** 279 centres **Country :** 28 countries **No :** 2489; ximelagatran 1240, enoxaparin/warfarin 1249 **Age, mean (range) years :** ximelagatran 56.7 (18-93) years, enoxaparin/warfarin 57.1 (18-97) years **Sex :** ximelagatran 654 M/586 F, enoxaparin/warfarin 665 M/584 F **Inclusion criteria :** people aged ≥ 18 years, with acute, objectively confirmed DVT, with or without PE, for whom anticoagulant therapy was planned for at least 6 months. The diagnosis of DVT was based on a clear-cut non-compressible proximal venous segment identified by venous ultrasonography or a persistent intraluminal filling defect in the calf or proximal veins identified by contrast venography **Exclusion criteria :** symptoms of DVT > 2 weeks, contraindications to anticoagulants, weight > 140 kg, clinically significant bleeding disorder/ stroke within the previous 30 days, haemodynamically unstable PE, platelet count < 90 x 10^3/µL, calculated creatinine clearance < 30 mL/minute (0.501 mL/second), clinically significant liver disease or levels of aminotransferases persistently increased to > 2 x ULN, thoracic or central nervous system surgery within the previous 2 weeks or planned major surgery during the study, expected survival of < 6 months or treatment with thrombolytic agents within 14 days before randomisation
Interventions	**Intervention 1 :** oral ximelagatran, 36 mg twice daily **Intervention 2 :** enoxaparin 1.0 mg/kg subcutaneously twice daily for at least 5 days (maximum 20 days) and concomitantly, encapsulated warfarin (1.0 and 2.5 mg) once daily and adjusted to maintain an INR 2.0-3.0. Enoxaparin was stopped after 2 consecutive INR measurements reached the target range
Outcomes	**Primary :** recurrent VTE (DVT diagnosed by ultrasonography if there was a new non-compressible venous segment in the proximal veins, an increase of ≥ 4 mm in thrombus diameter with compression, or an increase of 1-4 mm in diameter combined with an extension of at least 4 cm in length) **Secondary :** bleeding, combined endpoint of recurrent VTE or major bleeding, all-cause mortality. Major bleeding was defined as fatal bleeding, bleeding in critical sites, or overt bleeding with a reduction in haemoglobin of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of blood or packed red cells. Minor bleeding was defined as clinically significant bleeding that did not meet the criteria for major bleeding
Notes	Concomitant use of other anticoagulant or fibrinolytic agents was not allowed. Acetylsalicylic acid (aspirin), non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors were discouraged but permitted at the lowest effective dose

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THRIVE I (*Continued*)

	This drug is no longer on the market but that the study was included for completeness and that sensitivity analysis are performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised using an adaptive balancing algorithm. Randomization was undertaken by phoning a central number to obtain the treatment allocation for an enrolled patient" Comment: study judged at low risk of selection bias
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised using an adaptive balancing algorithm. Randomization was undertaken by phoning a central number to obtain the treatment allocation for an enrolled patient. Study medication was centrally labelled and distributed to the sites" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind. INR results were sent to an independent study monitor who provided the attending physicians with an actual INR to maintain blinding" Comment: study judged at low risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected recurrences were adjudicated by an independent committee that reviewed the diagnostic testing" Comment: study judged at low risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes were reported in the pre-specified way
Other bias	Unclear risk	The study was funded by AstraZeneca, the pharmaceutical company that developed ximelagatran

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ALT: alanine transaminase; CCUS: complete compression ultrasound; CT: computed tomography; CUS: compression ultrasonography; DVT: deep vein thrombosis; F: female; INR: international normalised ratio; IU: international units; LMWH: low molecular weight heparin; M: male; No: number of participants; PE: pulmonary embolism; PLS: perfusion lung scan; SD: standard deviation; UFH: unfractionated heparin; ULN: upper limit of normal; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ageno 2014	Not a randomised controlled trial
AMPLIFY EXTENDED STUDY	Extended study testing prophylaxis rather than treatment
RE-SONATE	Participants were already included in the RE-COVER I and RE-COVER II studies
REMEDY	Extended study testing prophylaxis rather than treatment
THRIVE	Treatment was for less than 3 months
THRIVE III	Control group were given a placebo

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-TRC-14005223

Trial name or title	Efficacy and Safety of Rivaroxaban or Warfarin on Venous Thromboembolic Disease: a Randomised Controlled Trial
Methods	**Study design :** randomised, parallel-control trial
Participants	**Setting :** hospitals **Country :** China **Inclusion criteria :** people diagnosed with non-high-risk pulmonary thromboembolism with/without DVT **Exclusion criteria :** people with active bleeding, high risk for bleeding complications or considered to be high-risk pulmonary thromboembolism. AST and ALT > 3 x ULN in liver function test and ≤ 30 mL/minute in kidney function test; systemic blood pressure < 90/50 mm Hg, or people with uncontrolled dangerous hypertension (blood pressure > 170/110 mm Hg); people who have to take azole antifungals, HIV protease inhibitors or strong CYP3A4 inducers during the period of treatment; pregnant, lactational women or may be pregnant during the period of treatment
Interventions	**Intervention 1 :** rivaroxaban **Intervention 2 :** warfarin
Outcomes	**Primary :** thromboembolic events **Secondary :** bleeding events

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ChiCTR-TRC-14005223 (*Continued*)

Starting date	Not stated
Contact information	Chunli Liu, chunli@gird.cn
Notes	

NCT01516840

Trial name or title	Venous Thromboembolism (VTE) Treatment Study in Japanese Deep Vein Thrombosis (DVT) Patients
Methods	**Study design :** randomised, double-blind trial
Participants	**Setting :** 19 hospitals **Country :** Japan **Inclusion criteria :** men and women ≥ 20 years with confirmed acute symptomatic proximal DVT without symptomatic PE **Exclusion criteria :** thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of DVT, > 48 hours pre-randomisation treatment with therapeutic dosages of anticoagulant treatment or > 1 dose of warfarin from the onset of the current episode of DVT to randomisation, calculated creatinine clearance < 30 mL/minute, subjects with hepatic disease that is associated with coagulopathy leading to a clinically relevant bleeding risk, active bleeding or high risk for bleeding contraindicating treatment with UFH or warfarin, systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg
Interventions	**Intervention 1 :** rivaroxaban 10 mg twice daily for 21 days, followed by 15 mg once daily **Intervention 2 :** rivaroxaban 15 mg twice daily for 21 days, followed by 15 mg once daily **Intervention 3 :** UFH to be adjusted to maintain the aPTT prolongation (1.5-2.5 times the control) **Intervention 4 :** warfarin to be adjusted on the basis of prothrombin time-international normalised ratio (PT-INR) values target range (1.5-2.5)
Outcomes	**Primary :** number of participants with newly onset of symptomatic VTE and number of clinically relevant bleedings **Secondary :** number of participants with deterioration or improvement in thrombotic burden and number of participants with the composite of newly onset of symptomatic VTE or asymptomatic deterioration of thrombus
Starting date	March 2012
Contact information	Bayer Health
Notes	

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NCT01662908

Trial name or title	A Randomised, Open-Label, Parallel-Group, Multi-Centre Study for the Evaluation of Efficacy and Safety of Edoxaban Monotherapy versus Low Molecular Weight (LMW) Heparin/Warfarin in Subjects with Symptomatic Deep-Vein Thrombosis (eTRIS)
Methods	**Study design :** randomised, open-label study
Participants	**Setting :** 33 hospitals **Country :** USA and Canada **Inclusion criteria :** men and women aged ≥ 18 years with acute symptomatic proximal DVT involving the popliteal, femoral or iliac veins confirmed by CUS or other appropriate imaging techniques (such as venography or spiral/contrast CT) with symptom onset ≤ 1 week prior to randomisation **Exclusion criteria :** concomitant PE known to the investigator at the time of randomisation; thrombectomy, insertion of a caval filter or use of a fibrinolytic agent to treat the current episode of DVT; indication for warfarin other than DVT; > 48 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, UFH, fondaparinux, VKA, factor Xa inhibitor or other anticoagulant per local labelling) prior to randomisation to treat the current episode; treatment with any investigational drug within 30 days prior to randomisation; significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALT ≥ 2 x ULN, or total bilirubin ≥ 1.5 times the ULN; subjects with active cancer for whom long-term treatment with LMWH is anticipated; life expectancy < 3 months; active bleeding or high risk for bleeding contraindicating treatment with LMWH or warfarin; uncontrolled hypertension as judged by the investigator (e.g. systolic blood pressure > 170 mm Hg or diastolic blood pressure > 100 mm Hg despite antihypertensive medications confirmed by repeat measurement); women of child-bearing potential without effective contraceptive measures (i.e. a method of contraception with a failure rate < 1% during the course of the study including the observational period) and women who are pregnant or breastfeeding; any contraindication listed in the local labelling of LMWH, UFH or warfarin; chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs including both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX- 2) inhibitors for ≥ 4 days/week anticipated to continue during the study; treatment with aspirin in a dosage of > 100 mg/day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study; known history of positive hepatitis B antigen or hepatitis C antibody; subjects with any condition that, as judged by the investigator, would put the person at increased risk of harm if he/she participated in the study, including, but not limited to, subjects at increased risk of harm if given a gadolinium-based contrast agent such as gadofosveset trisodium (Ablavar®); subjects for whom MRI would be contraindicated (e.g. subjects with metal implants) or for whom the use of a gadolinium-based contrast agent such as gadofosveset trisodium (Ablavar®) would be contraindicated; people who have previously entered this study or another edoxaban study
Interventions	**Intervention 1 :** edoxaban 90 mg once daily for 10 days followed by 60 mg once daily for a total of approximately 90 days **Intervention 2 :** enoxaparin administered by subcutaneous injection; 1 mg/kg/ twice daily or UFH 1.5 mg/kg once daily started with 5000 IU bolus intravenous administration, 1300 IU/hour continuous infusion, minimum of 5 days of treatment and stopped when target INR (2.0-3.0) is achieved plus warfarin daily dosage, adjusted to maintain INR 2.0-3.0 for 90 days
Outcomes	**Primary :** relative change from baseline in thrombus volume assessed by MRI (14-21 days post randomisation) **Secondary :** clinically relevant bleeding (i.e. major or clinically relevant non-major bleeding, recurrence of VTE, major adverse cardiovascular events defined as a composite of non-fatal myocardial infarction, non-fatal stroke, non-fatal systemic embolic event and cardiovascular death and change from baseline in the presence or absence of thrombus by vessel

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NCT01662908 (*Continued*)

Starting date	August 2012
Contact information	Samuel Z Goldhaber, Brigham and Women's Hospital
Notes	

NCT01684423

Trial name or title	Oral Rivaroxaban in Children with Venous Thrombosis (EINSTEINJunior)
Methods	**Study design :** randomised, open-label study
Participants	**Setting :** 56 hospitals **Country :** USA, Australia, Austria, Canada, France, Germany, Israel, Italy, Netherlands and Switzerland **Inclusion criteria :** children aged 6 to < 18 years who were treated for at least 2 months or, in case of catheter-related thrombosis, for at least 6 weeks with LMWH, fondaparinux, VKA or a combination for documented symptomatic or asymptomatic venous thrombosis and who will enter their last month of intended anticoagulant treatment **Exclusion criteria :** active bleeding or high risk for bleeding contraindicating anticoagulant therapy; symptomatic progression of venous thrombosis during preceding anticoagulant treatment; planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study treatment; hepatic disease that is associated with coagulopathy leading to a clinically relevant bleeding risk or ALT > 5 x ULN or total bilirubin > 2 x ULN with direct bilirubin > 20% of the total, platelet count < 100 x 10^9/L, hypertension defined as > 95th age percentile; life expectancy < 3 months; concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), i.e. all HIV protease inhibitors and the following azole antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically and concomitant use of strong inducers of CYP3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine
Interventions	**Intervention 1 :** rivaroxaban according to an age- and body weight-adjusted dosing schedule to achieve a similar exposure in children as that observed in adults treated for VTE with rivaroxaban 20 mg daily. Rivaroxaban will be provided as a tablet for children aged 12-18 years. Once the age- and body weight-adjusted dosing regimen has been finally confirmed for the age group 6 to < 12 years, rivaroxaban will be provided as tablets (and subsequently as oral suspension) for this age group **Intervention 2 :** children randomised to the comparator group will continue with the anticoagulant treatment that was used prior to study randomisation
Outcomes	**Primary :** composite number of major and clinically relevant non-major bleeding events after 31 days and composite number of major and clinically relevant non-major bleeding events after 60 days **Secondary :** composite number of all recurrent VTEs and asymptomatic deterioration after 31 days and composite number of all recurrent VTEs after 60 days
Starting date	February 2013
Contact information	Bayer Clinical Trials Contact
Notes	

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NCT01780987

Trial name or title	A Study to Evaluate Safety and Efficacy of Apixaban In Japanese Acute Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) Patients
Methods	**Study design :** randomised, multicentre, open-label study
Participants	**Setting :** 20 hospitals **Country :** Japan **Inclusion criteria :** men or women aged ≥ 20 years with acute symptomatic proximal DVT with evidence of proximal thrombosis or acute symptomatic PE with evidence of thrombosis in segmental or more proximal branches **Exclusion criteria :** active bleeding or high risk for bleeding contraindicating treatment with UFH and a VKA, uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg) and subjects requiring dual anti-platelet therapy
Interventions	**Intervention 1 :** apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily for 23 weeks **Intervention 2 :** UFH, dose adjustment based on APTT 1.5-2.5 x the control value, and until INR ≥ 1.5 for ≥ 5 days plus warfarin for 24 weeks at a dose to target INR range 1.5-2.5
Outcomes	**Primary :** major bleeding and clinically relevant non-major bleeding **Secondary :** symptomatic VTE or VTE-related death, major bleeding and all bleeding
Starting date	January 2013
Contact information	Pfizer CT.gov Call Centre
Notes	

NCT01895777

Trial name or title	Open Label Study Comparing Efficacy and Safety of Dabigatran Etexilate to Standard of Care in Paediatric Patients with Venous Thromboembolism (VTE)
Methods	**Study design :** randomised, open-label study
Participants	**Setting :** 61 hospitals **Country :** Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Finland, France, Greece, Israel, Italy, Lithuania, Mexico, Norway, Russia, Slovakia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine **Inclusion criteria :** male or female subjects aged < 18 years at the time of informed consent, body weight ≤ 40 kg, with a documented diagnosis of VTE per investigator judgement initially treated (generally 5-7 days) with an UFH or a LMWH and clinical indication for 3 months of treatment with anticoagulants for the VTE episode defined under the above inclusion criterion **Exclusion criteria :** conditions associated with an increased risk of bleeding, renal dysfunction or requirement for dialysis, active infective endocarditis, subjects with a mechanical or a biological heart valve prosthesis, hepatic disease
Interventions	**Intervention 1 :** dabigatran at an age- and weight-appropriate dose given in capsules (50, 75 and 110 mg) pellets or oral liquid formulation given twice daily in an open-label manner for 3 months

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NCT01895777 (*Continued*)

	Intervention 2 : LMWH or VKA prescribed in an open-label manner for 3 months
Outcomes	**Primary :** combined efficacy endpoint of complete thrombus resolution plus freedom from recurrent VTE plus freedom from mortality related to VTE and freedom from major bleeding events **Secondary :** freedom from thrombus progression at baseline and at days 21 and 84 after randomisation; freedom from recurrence of VTE at 6, 9 and 12 months; freedom from occurrence of post-thrombotic syndrome at 6, 9 and 12 months; all bleeding events and all-cause mortality
Starting date	September 2013
Contact information	clintriage.rdg@boehringer-ingelheim.com
Notes	

NCT01986192

Trial name or title	Prevention of Recurrence after Thrombolysis in Acute Iliofemoral Venous Thrombosis (PRAIS) Study
Methods	**Study design :** randomised, open-label study
Participants	**Setting :** hospital **Country :** Korea **Inclusion criteria :** aged 18-75 years; onset of symptoms within the past 21 days; objectively verified (by CT venography) DVT localised in the iliofemoral segment and complete catheter-directed thrombolysis, a vena cava, venous stent insertion, or a combination **Exclusion criteria :** incomplete catheter-directed thrombolysis, if people received > 1 dose of warfarin before randomisation, contraindicating anticoagulant treatment, another indication for a warfarin, an estimated glomerular filtration rate by MDRD equation < 30 mL/minute, clinically significant liver disease (acute hepatitis, chronic active hepatitis, cirrhosis), ALT > 3 x ULN range, bacterial endocarditis, active bleeding or high risk of bleeding, pregnancy or breastfeeding
Interventions	**Intervention 1 :** rivaroxaban 15 mg twice daily for 3 weeks and 20 mg once daily for 6 months **Intervention 2 :** enoxaparin 1 mg/kg twice daily overlapping with warfarin (target PT INR 2.0-3.0) for 6 months
Outcomes	**Primary :** recurrent VTE **Secondary :** vascular events (acute coronary syndrome, ischaemic stroke, transient Ischaemic attack or systemic embolism) and all-cause mortality
Starting date	November 2013
Contact information	Seung-Kee Min, Seoul National University Hospital, surgeonmsi@gmail.com
Notes	

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NCT02234843

Trial name or title	EINSTEIN Junior Phase III: Oral Rivaroxaban in Children with Venous Thrombosis (EINSTEIN Jr)
Methods	**Study design :** randomised, open-label study
Participants	**Setting :** hospital **Country :** 20 countries **Inclusion criteria :** children aged 6 months to < 18 years with confirmed VTE who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days **Exclusion criteria :** active bleeding or high risk for bleeding contraindicating anticoagulant therapy, estimated glomerular filtration rate < 30 mL/minute/1.73 m^2, hepatic disease that is associated with either coagulopathy leading to a clinically relevant bleeding risk, or ALT > 5 x ULN or total bilirubin > 2 x ULN with direct bilirubin > 20% of the total, platelet count < 50 x 10^9/L, hypertension defined as > 95th age percentile, life expectancy < 3 months, concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), concomitant use of strong inducers of CYP3A4, child-bearing potential without effective contraceptive measures, pregnancy or breastfeeding, hypersensitivity or any other contraindication listed in the local labelling for the comparator treatment or experimental treatment
Interventions	**Intervention 1 :** age and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with rivaroxaban 20 mg **Intervention 2 :** subcutaneous LMWH, subcutaneous fondaparinux, oral VKA, or a combination
Outcomes	**Primary :** composite number of all symptomatic recurrent VTE and composite number of overt major and clinically relevant non-major bleeding **Secondary :** composite number of all symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging
Starting date	November 2014
Contact information	clinical-trials-contact@bayerhealthcare.com
Notes	

NCT02309411

Trial name or title	EINSTEIN Junior Phase II: Oral Rivaroxaban in Young Children with Venous Thrombosis (EINSTEIN Jr)
Methods	**Study design :** randomised, open-label study
Participants	**Setting :** hospital **Country :** 20 countries **Inclusion criteria :** children aged 6 months to < 6 years who were treated for at least 2 months or, in case of catheter-related thrombosis, for at least 6 weeks with LMWH, fondaparinux, VKA, or a combination for documented symptomatic or asymptomatic venous thrombosis and who will enter their last month of intended anticoagulant treatment, haemoglobin, platelets, creatinine, ALT and bilirubin evaluated within 10 days prior to randomisation and informed consent provided **Exclusion criteria :** active bleeding or high risk for bleeding contraindicating anticoagulant therapy, symptomatic progression of venous thrombosis during preceding anticoagulant treatment, planned invasive proce-

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NCT02309411 (*Continued*)

	dures including lumbar puncture and removal of non-peripherally placed central lines during study treatment, an estimated glomerular filtration rate < 30 mL/minute/1.73 m^2, hepatic disease that is associated with either coagulopathy leading to a clinically relevant bleeding risk or ALT> 5 x ULN or total bilirubin > 2 x ULN with direct bilirubin > 20% of the total, platelet count < 100 x 10^9/L, hypertension defined as > 95th age percentile, life expectancy < 3 months, concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), concomitant use of strong inducers of CYP3A4, hypersensitivity or any other contraindication listed in the local labelling for the comparator treatment or experimental treatment, inability to co-operate with the study procedures, previous randomisation to this study and participation in a study with an investigational drug or medical device within 30 days prior to randomisation
Interventions	**Intervention 1 :** age- and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with rivaroxaban 20 mg **Intervention 2 :** children randomised to the comparator group will continue with the anticoagulant treatment that was used prior to study randomisation (e.g. UFH, LMWH, fondaparinux, VKA therapy)
Outcomes	**Primary :** composite number of all symptomatic recurrent VTE and composite number of overt major and clinically relevant non-major bleeding **Secondary :** composite number of all symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging
Starting date	January 2015
Contact information	clinical-trials-contact@bayerhealthcare.com
Notes	

ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CT: computed tomography; CUS: compression ultrasonography; DVT: deep vein thrombosis; HIV: human immunodeficiency virus; INR: international normalised ratio; LMWH: low molecular weight heparin; MDRD: modification of diet in renal disease; MRI: magnetic resonance imaging; PE: pulmonary embolism; UFH: unfractionated heparin; ULN: upper level of normal; VKA: vitamin K antagonist; VTE: venous thromboembolism.

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DATA AND ANALYSES

Comparison 1. Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent venous thromboembolism	3	7596	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.80, 1.49]
1.1 Treatment duration 3 months	1	2489	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.62, 1.91]
1.2 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.76, 1.58]
2 Recurrent deep vein thrombosis	3	7596	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.74, 1.58]
2.1 Treatment duration 3 months	1	2489	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.44, 1.78]
2.2 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.75, 1.85]
3 Fatal pulmonary embolism	3	7596	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.27, 3.70]
3.1 Treatment duration 3 months	1	2489	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.18, 22.26]
3.2 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.61]
4 Non-fatal pulmonary embolism	3	7596	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.66, 1.90]
4.1 Treatment duration 3 months	1	2489	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.54, 4.27]
4.2 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.54, 1.86]
5 All-cause mortality	3	7596	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.13]
5.1 Treatment duration 3 months	1	2489	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.41, 1.08]
5.2 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.64, 1.50]
6 Major bleeding	3	7596	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.47, 0.98]
6.1 Treatment duration 3 months	1	2489	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.28, 1.03]
6.2 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.18]

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Comparison 2. Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent venous thromboembolism	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.76, 1.58]
2 Recurrent deep vein thrombosis	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.75, 1.85]
3 Fatal pulmonary embolism	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.61]
3.1 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.61]
4 Non-fatal pulmonary embolism	2	5107	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.30, 3.35]
4.1 Treatment duration > 3 months	2	5107	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.30, 3.35]
5 All-cause mortality	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.64, 1.50]
6 Major bleeding	2	5107	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.18]

Comparison 3. Oral factor Xa inhibitor versus standard anticoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent venous thromboembolism	8	16356	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.07]
1.1 Treatment duration 3 months	5	5001	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.48, 0.99]
1.2 Treatment duration > 3 months	3	11355	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.22]
2 Recurrent deep vein thrombosis	7	16272	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.57, 0.98]
2.1 Treatment duration 3 months	4	4917	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.31, 0.84]
2.2 Treatment duration > 3 months	3	11355	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.20]
3 Fatal pulmonary embolism	6	15082	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.71, 2.03]
3.1 Treatment duration 3 months	4	4917	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.37, 8.13]
3.2 Treatment duration > 3 months	2	10165	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.65, 1.99]
4 Non-fatal pulmonary embolism	6	15082	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.28]
4.1 Treatment duration 3 months	4	4917	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.52, 1.52]
4.2 Treatment duration > 3 months	2	10165	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.42]
5 All-cause mortality	5	10437	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.23]
5.1 Treatment duration 3 months	4	5072	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.64, 1.46]

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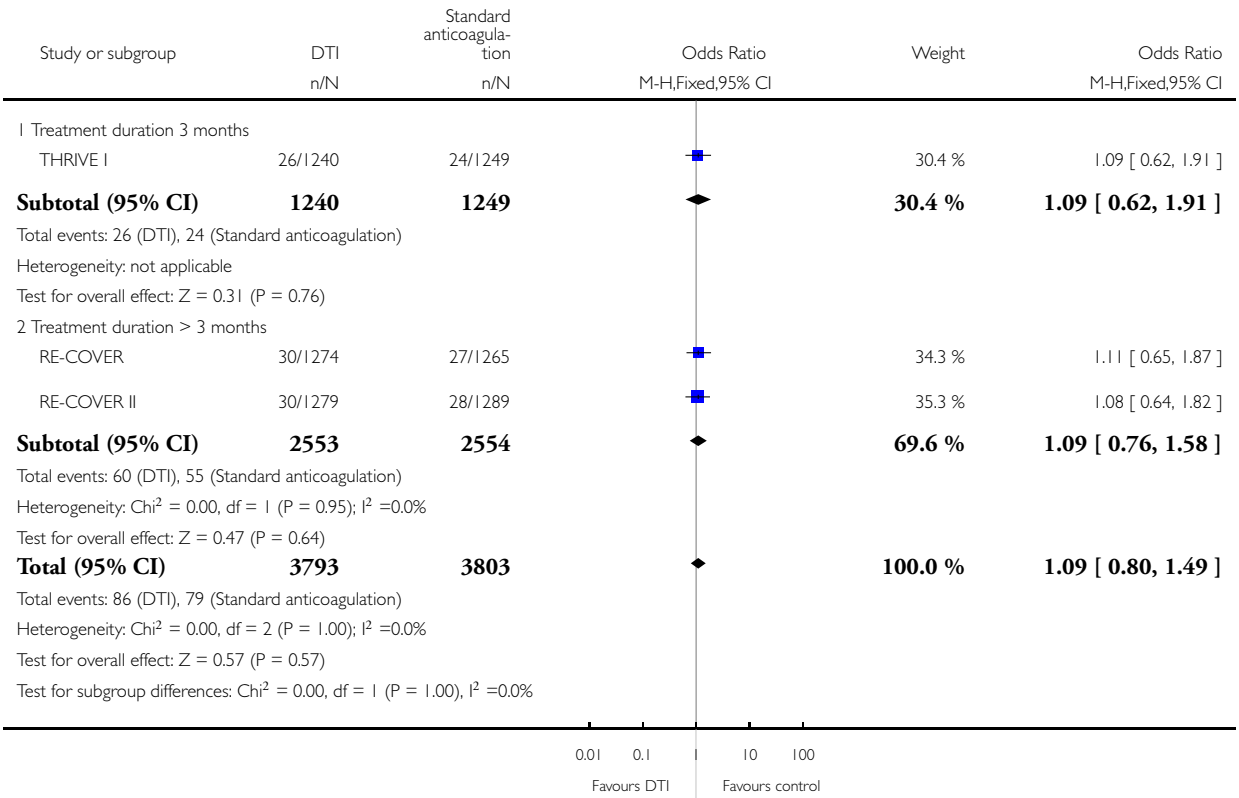
5.2 Treatment duration > 3 months	1	5365	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.49, 1.32]
6 Major bleeding	8	16645	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.43, 0.76]
6.1 Treatment duration 3 months	5	5171	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.47, 1.45]
6.2 Treatment duration > 3 months	3	11474	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.36, 0.71]

Analysis 1.1. Comparison 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation, Outcome 1 Recurrent venous thromboembolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome: 1 Recurrent venous thromboembolism



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Analysis 1.2. Comparison 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation, Outcome 2 Recurrent deep vein thrombosis.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome: 2 Recurrent deep vein thrombosis

Study or subgroup	DTI n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Treatment duration 3 months					
THRIVE I	15/1240	17/1249		32.7 %	0.89 [0.44, 1.78]
Subtotal (95% CI)	**1240**	**1249**		**32.7 %**	**0.89 [0.44, 1.78]**
Total events: 15 (DTI), 17 (Standard anticoagulation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.74)					
2 Treatment duration > 3 months					
RE-COVER	16/1274	18/1265		34.9 %	0.88 [0.45, 1.74]
RE-COVER II	25/1279	17/1289		32.4 %	1.49 [0.80, 2.78]
Subtotal (95% CI)	**2553**	**2554**		**67.3 %**	**1.18 [0.75, 1.85]**
Total events: 41 (DTI), 35 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 1.26, df = 1 (P = 0.26); I^2 =21%					
Test for overall effect: Z = 0.70 (P = 0.49)					
Total (95% CI)	**3793**	**3803**		**100.0 %**	**1.08 [0.74, 1.58]**
Total events: 56 (DTI), 52 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 1.69, df = 2 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Chi^2 = 0.44, df = 1 (P = 0.51), I^2 =0.0%					

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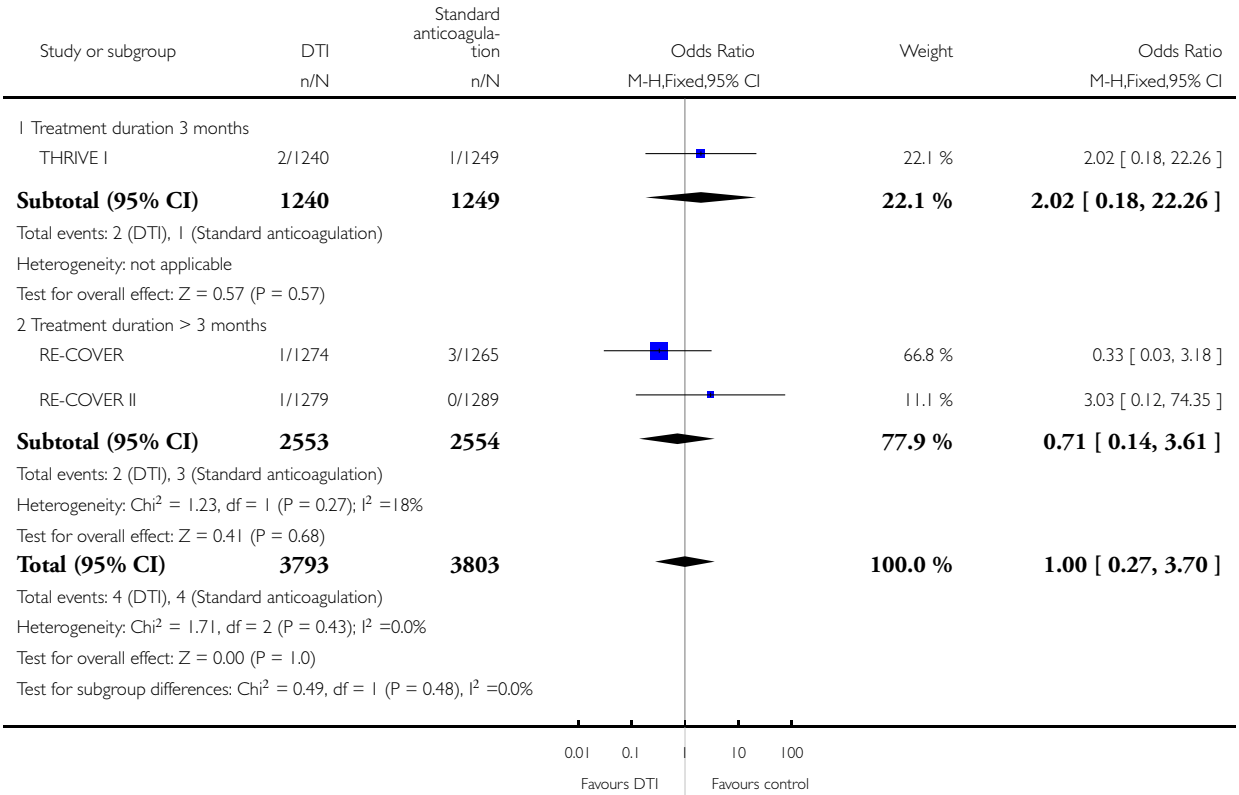
Analysis 1.3. Comparison 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation, Outcome 3 Fatal pulmonary embolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome: 3 Fatal pulmonary embolism



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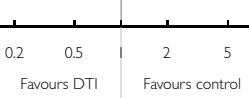
Analysis 1.4. Comparison 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation, Outcome 4 Non-fatal pulmonary embolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome: 4 Non-fatal pulmonary embolism

Study or subgroup	DTI n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Treatment duration 3 months					
THRIVE I	9/1240	6/1249		23.0 %	1.51 [0.54, 4.27]
Subtotal (95% CI)	**1240**	**1249**		**23.0 %**	**1.51 [0.54, 4.27]**
Total events: 9 (DTI), 6 (Standard anticoagulation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
2 Treatment duration > 3 months					
RE-COVER	13/1274	7/1265		27.0 %	1.85 [0.74, 4.66]
RE-COVER II	7/1279	13/1289		50.0 %	0.54 [0.21, 1.36]
Subtotal (95% CI)	**2553**	**2554**		**77.0 %**	**1.00 [0.54, 1.86]**
Total events: 20 (DTI), 20 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 3.43, df = 1 (P = 0.06); I^2 =71%					
Test for overall effect: Z = 0.00 (P = 1.0)					
Total (95% CI)	**3793**	**3803**		**100.0 %**	**1.12 [0.66, 1.90]**
Total events: 29 (DTI), 26 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 3.87, df = 2 (P = 0.14); I^2 =48%					
Test for overall effect: Z = 0.41 (P = 0.68)					
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%					



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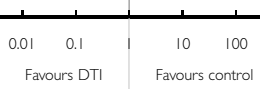
Analysis 1.5. Comparison 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation, Outcome 5 All-cause mortality.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome: 5 All-cause mortality

Study or subgroup	DTI n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Treatment duration 3 months					
THRIVE I	28/1240	42/1249		49.2 %	0.66 [0.41, 1.08]
Subtotal (95% CI)	**1240**	**1249**		**49.2 %**	**0.66 [0.41, 1.08]**
Total events: 28 (DTI), 42 (Standard anticoagulation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.098)					
2 Treatment duration > 3 months					
RE-COVER	20/1273	18/1266		21.4 %	1.11 [0.58, 2.10]
RE-COVER II	22/1279	25/1289		29.4 %	0.88 [0.50, 1.58]
Subtotal (95% CI)	**2552**	**2555**		**50.8 %**	**0.98 [0.64, 1.50]**
Total events: 42 (DTI), 43 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.10 (P = 0.92)					
Total (95% CI)	**3792**	**3804**		**100.0 %**	**0.82 [0.60, 1.13]**
Total events: 70 (DTI), 85 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 1.63, df = 2 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 1.19 (P = 0.23)					
Test for subgroup differences: Chi^2 = 1.38, df = 1 (P = 0.24), I^2 =27%					



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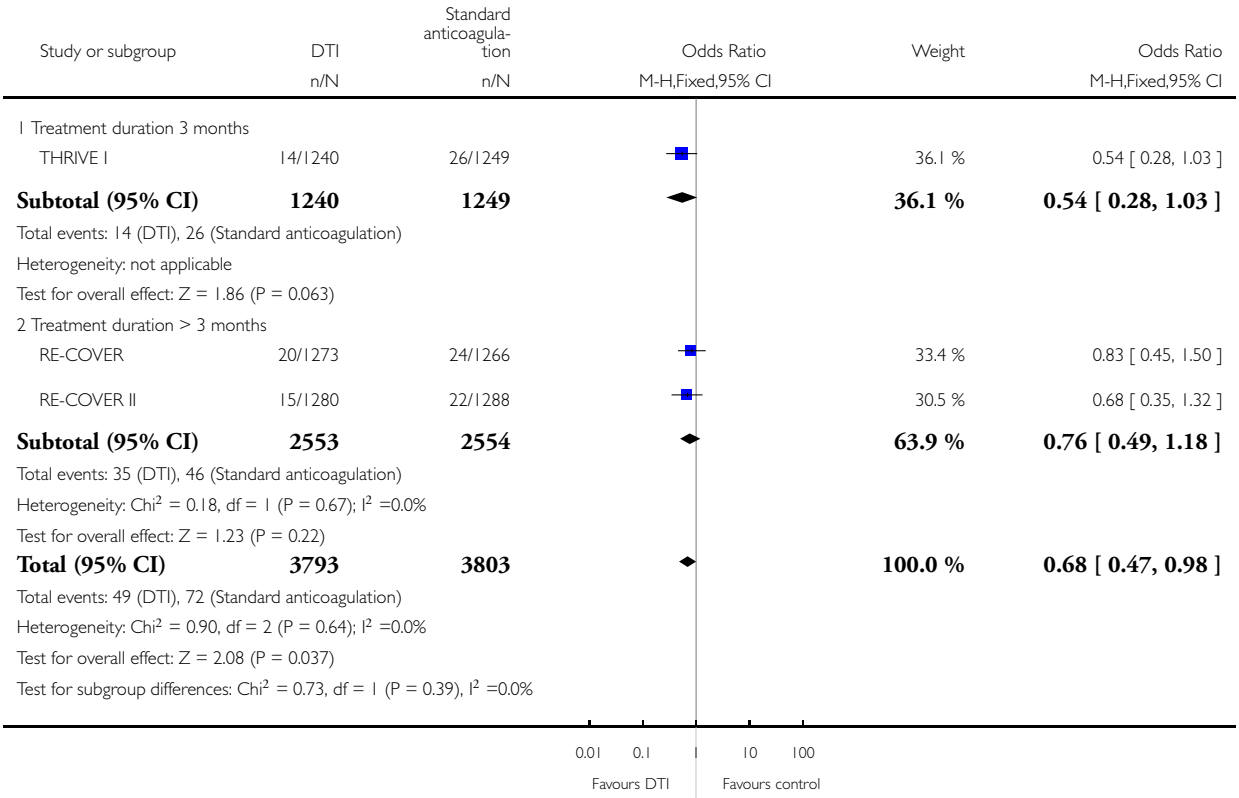
Analysis 1.6. Comparison 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation, Outcome 6 Major bleeding.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 1 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation

Outcome: 6 Major bleeding



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Analysis 2.1. Comparison 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 1 Recurrent venous thromboembolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome: 1 Recurrent venous thromboembolism

Study or subgroup	DTI	Standard anticoagulation	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
RE-COVER	30/1274	27/1265		49.3 %	1.11 [0.65, 1.87]
RE-COVER II	30/1279	28/1289		50.7 %	1.08 [0.64, 1.82]
Total (95% CI)	**2553**	**2554**		**100.0 %**	**1.09 [0.76, 1.58]**

Total events: 60 (DTI), 55 (Standard anticoagulation)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

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Analysis 2.2. Comparison 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 2 Recurrent deep vein thrombosis.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome: 2 Recurrent deep vein thrombosis

Study or subgroup	DTI n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
RE-COVER	16/1274	18/1265		51.8 %	0.88 [0.45, 1.74]
RE-COVER II	25/1279	17/1289		48.2 %	1.49 [0.80, 2.78]
Total (95% CI)	**2553**	**2554**		**100.0 %**	**1.18 [0.75, 1.85]**

Total events: 41 (DTI), 35 (Standard anticoagulation)

Heterogeneity: $Chi^2 = 1.26$, df = 1 (P = 0.26); $I^2 = 21\%$

Test for overall effect: Z = 0.70 (P = 0.49)

Test for subgroup differences: Not applicable

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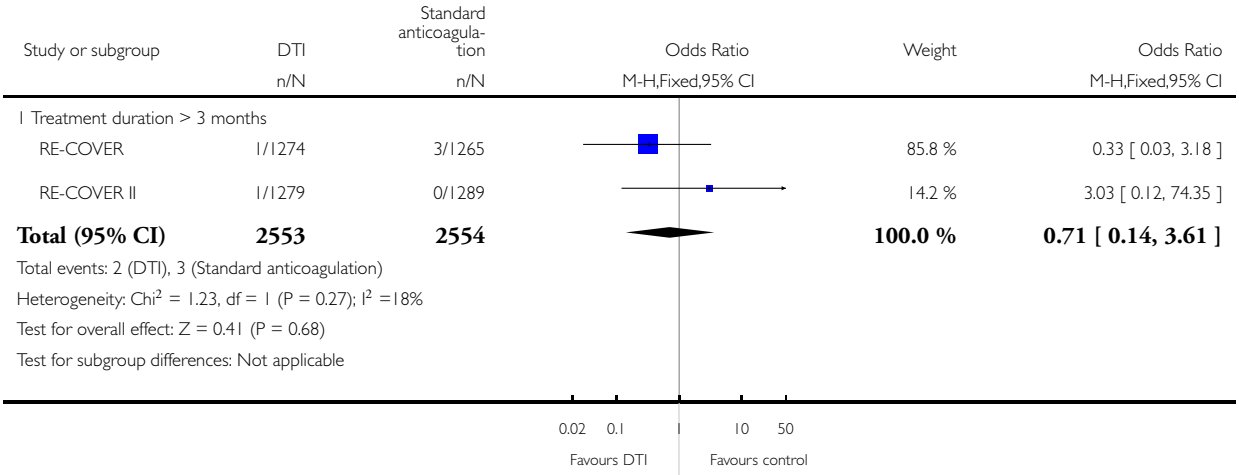
Analysis 2.3. Comparison 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 3 Fatal pulmonary embolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome: 3 Fatal pulmonary embolism



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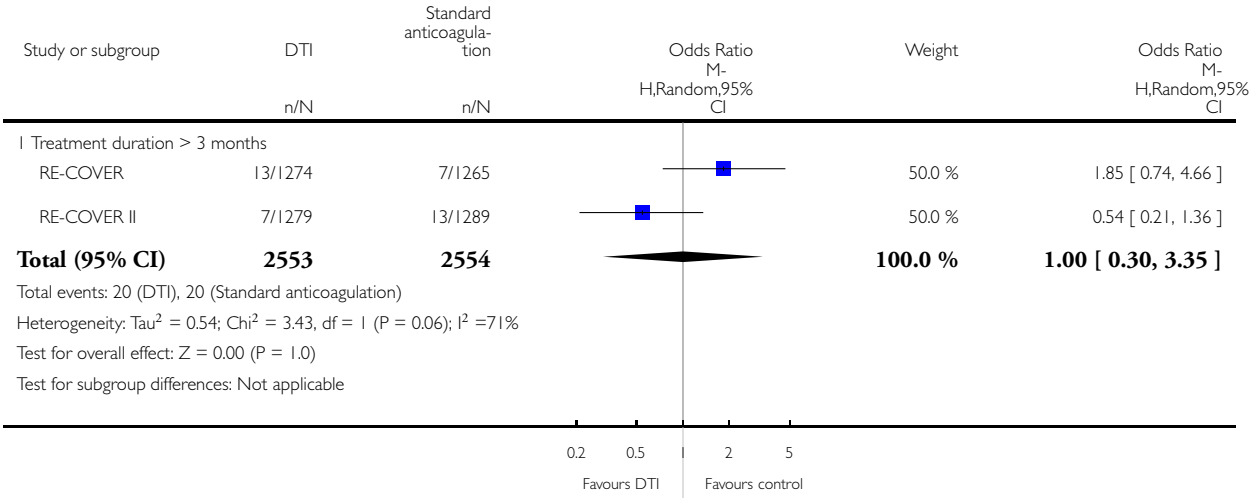
Analysis 2.4. Comparison 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 4 Non-fatal pulmonary embolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome: 4 Non-fatal pulmonary embolism



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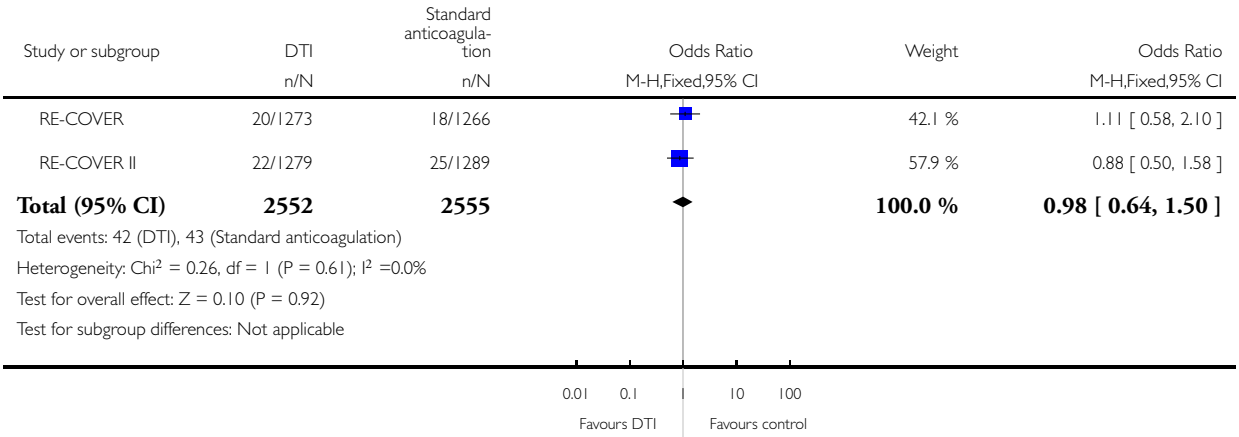
Analysis 2.5. Comparison 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 5 All-cause mortality.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome: 5 All-cause mortality



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Analysis 2.6. Comparison 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 6 Major bleeding.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 2 Oral direct thrombin inhibitor (DTI) versus standard anticoagulation (sensitivity analysis excluding ximelagatran)

Outcome: 6 Major bleeding

Study or subgroup	DTI n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
RE-COVER	20/1273	24/1266		52.2 %	0.83 [0.45, 1.50]
RE-COVER II	15/1280	22/1288		47.8 %	0.68 [0.35, 1.32]
Total (95% CI)	**2553**	**2554**		**100.0 %**	**0.76 [0.49, 1.18]**

Total events: 35 (DTI), 46 (Standard anticoagulation)

Heterogeneity: $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

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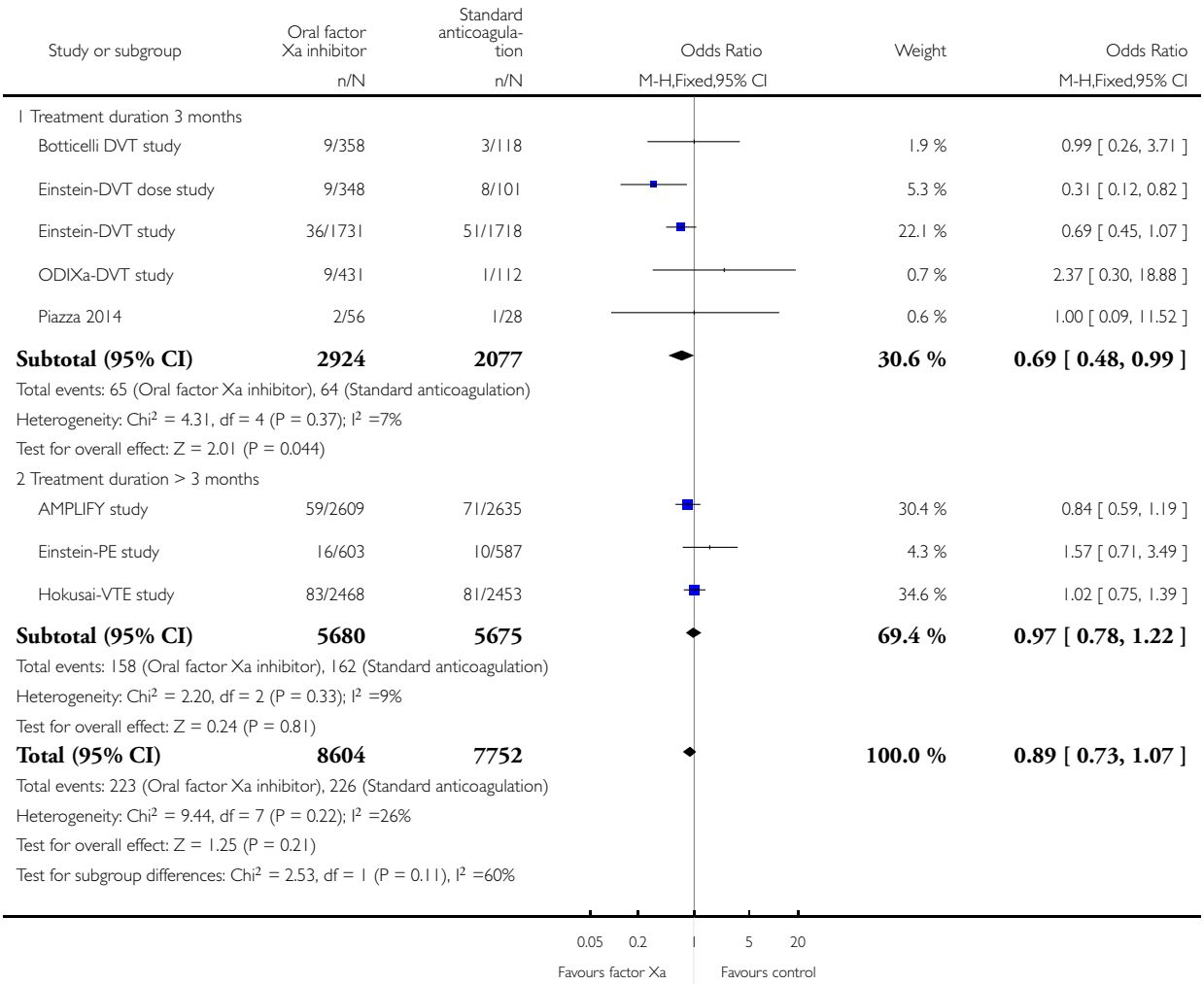
Analysis 3.1. Comparison 3 Oral factor Xa inhibitor versus standard anticoagulation, Outcome 1 Recurrent venous thromboembolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 3 Oral factor Xa inhibitor versus standard anticoagulation

Outcome: 1 Recurrent venous thromboembolism



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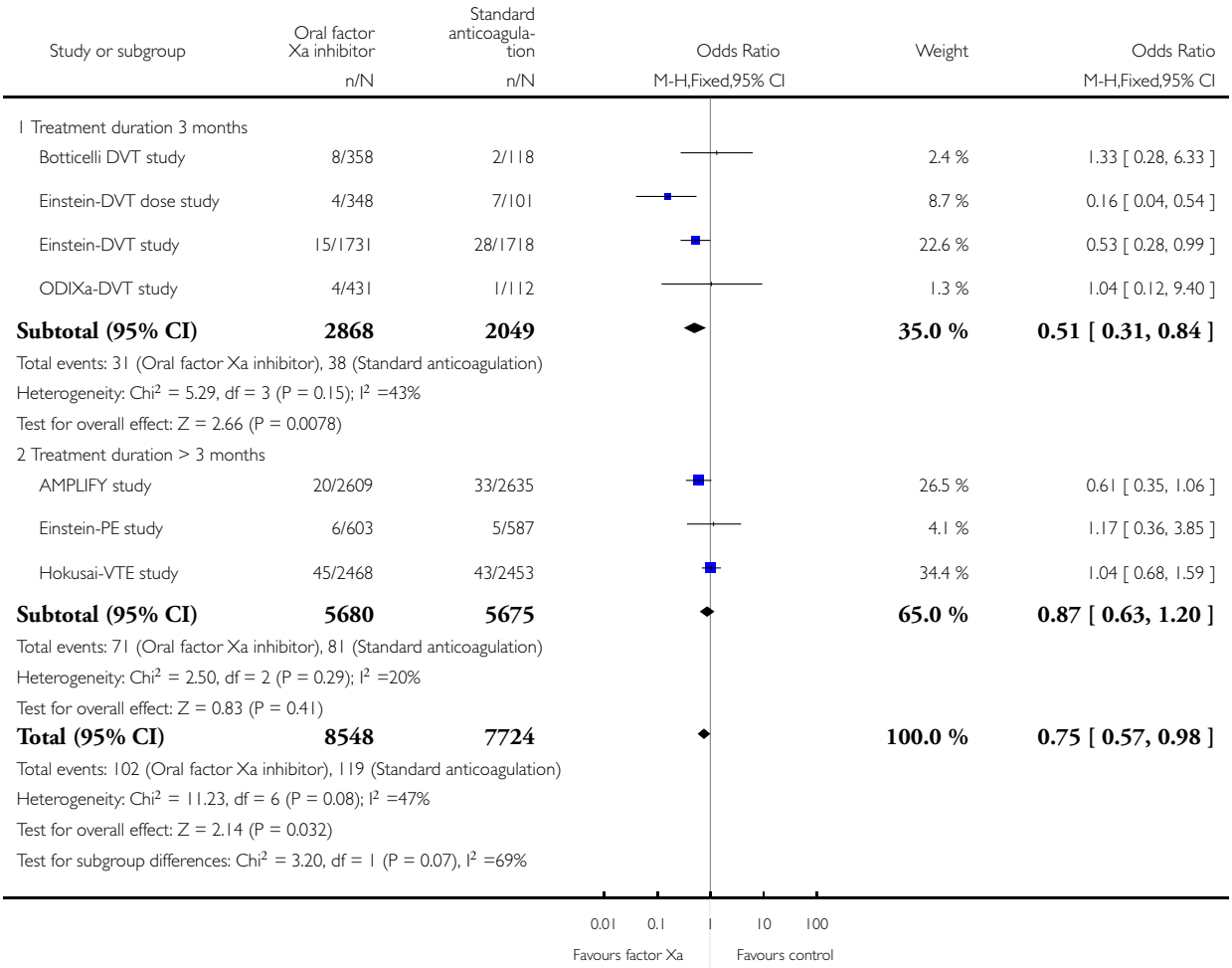
Analysis 3.2. Comparison 3 Oral factor Xa inhibitor versus standard anticoagulation, Outcome 2 Recurrent deep vein thrombosis.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 3 Oral factor Xa inhibitor versus standard anticoagulation

Outcome: 2 Recurrent deep vein thrombosis



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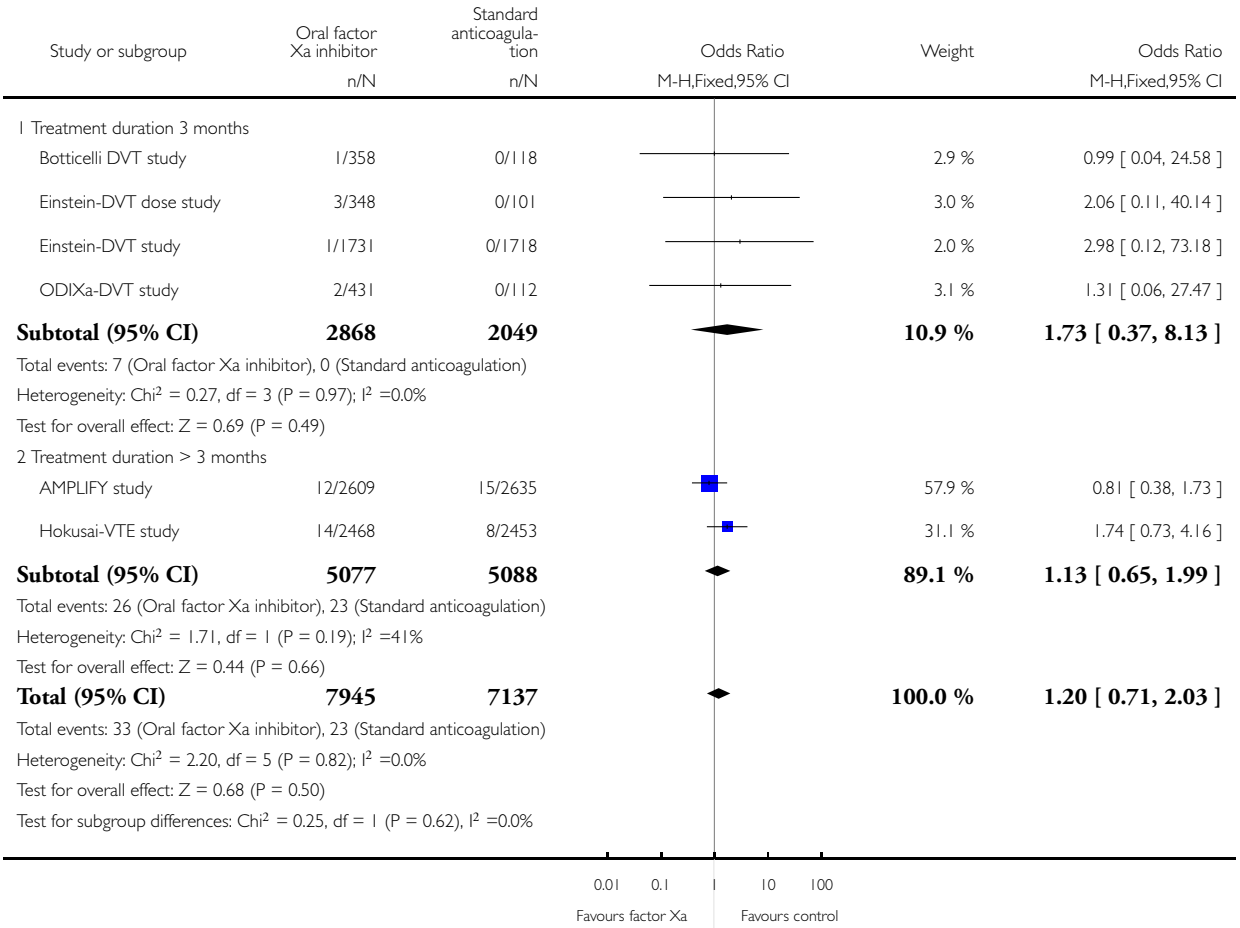
Analysis 3.3. Comparison 3 Oral factor Xa inhibitor versus standard anticoagulation, Outcome 3 Fatal pulmonary embolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 3 Oral factor Xa inhibitor versus standard anticoagulation

Outcome: 3 Fatal pulmonary embolism



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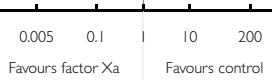
Analysis 3.4. Comparison 3 Oral factor Xa inhibitor versus standard anticoagulation, Outcome 4 Non-fatal pulmonary embolism.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 3 Oral factor Xa inhibitor versus standard anticoagulation

Outcome: 4 Non-fatal pulmonary embolism

Study or subgroup	Oral factor Xa inhibitor n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Treatment duration 3 months					
Botticelli DVT study	0/358	1/118		2.8 %	0.11 [0.00, 2.70]
Einstein-DVT dose study	2/348	1/101		1.9 %	0.58 [0.05, 6.44]
Einstein-DVT study	23/1731	24/1718		29.4 %	0.95 [0.53, 1.69]
ODIXa-DVT study	3/431	0/112		1.0 %	1.84 [0.09, 35.84]
Subtotal (95% CI)	**2868**	**2049**		**35.1 %**	**0.89 [0.52, 1.52]**
Total events: 28 (Oral factor Xa inhibitor), 26 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 2.05, df = 3 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.43 (P = 0.66)					
2 Treatment duration > 3 months					
AMPLIFY study	27/2609	23/2635		28.0 %	1.19 [0.68, 2.08]
Hokusai-VTE study	24/2468	30/2453		36.9 %	0.79 [0.46, 1.36]
Subtotal (95% CI)	**5077**	**5088**		**64.9 %**	**0.96 [0.65, 1.42]**
Total events: 51 (Oral factor Xa inhibitor), 53 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%					
Test for overall effect: Z = 0.19 (P = 0.85)					
Total (95% CI)	**7945**	**7137**		**100.0 %**	**0.94 [0.68, 1.28]**
Total events: 79 (Oral factor Xa inhibitor), 79 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 3.14, df = 5 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.81), I^2 =0.0%					



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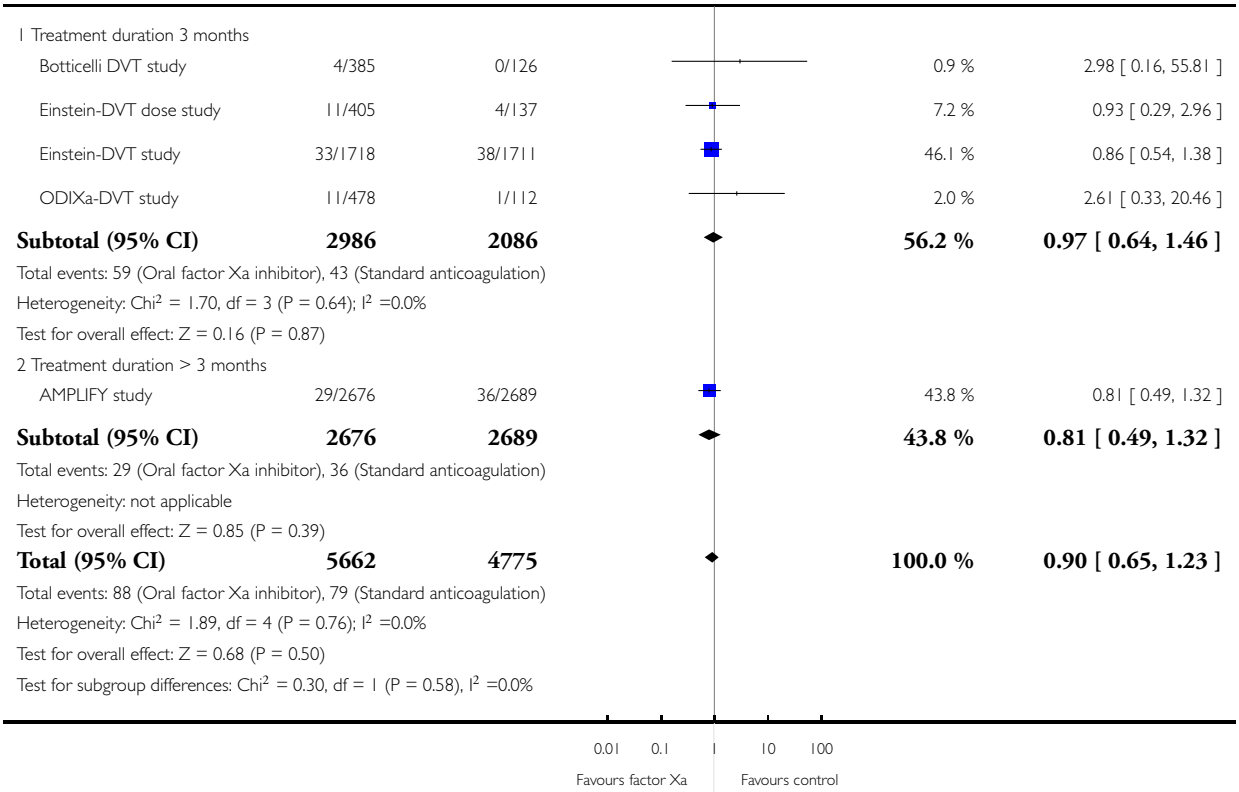
Analysis 3.5. Comparison 3 Oral factor Xa inhibitor versus standard anticoagulation, Outcome 5 All-cause mortality.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 3 Oral factor Xa inhibitor versus standard anticoagulation

Outcome: 5 All-cause mortality

Study or subgroup	Oral factor Xa inhibitor n/N	Standard anticoagulation n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Treatment duration 3 months					
Botticelli DVT study	4/385	0/126		0.9 %	2.98 [0.16, 55.81]
Einstein-DVT dose study	11/405	4/137		7.2 %	0.93 [0.29, 2.96]
Einstein-DVT study	33/1718	38/1711		46.1 %	0.86 [0.54, 1.38]
ODIXa-DVT study	11/478	1/112		2.0 %	2.61 [0.33, 20.46]
Subtotal (95% CI)	**2986**	**2086**		**56.2 %**	**0.97 [0.64, 1.46]**
Total events: 59 (Oral factor Xa inhibitor), 43 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 1.70, df = 3 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.16 (P = 0.87)					
2 Treatment duration > 3 months					
AMPLIFY study	29/2676	36/2689		43.8 %	0.81 [0.49, 1.32]
Subtotal (95% CI)	**2676**	**2689**		**43.8 %**	**0.81 [0.49, 1.32]**
Total events: 29 (Oral factor Xa inhibitor), 36 (Standard anticoagulation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
Total (95% CI)	**5662**	**4775**		**100.0 %**	**0.90 [0.65, 1.23]**
Total events: 88 (Oral factor Xa inhibitor), 79 (Standard anticoagulation)					
Heterogeneity: Chi^2 = 1.89, df = 4 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.58), I^2 =0.0%					



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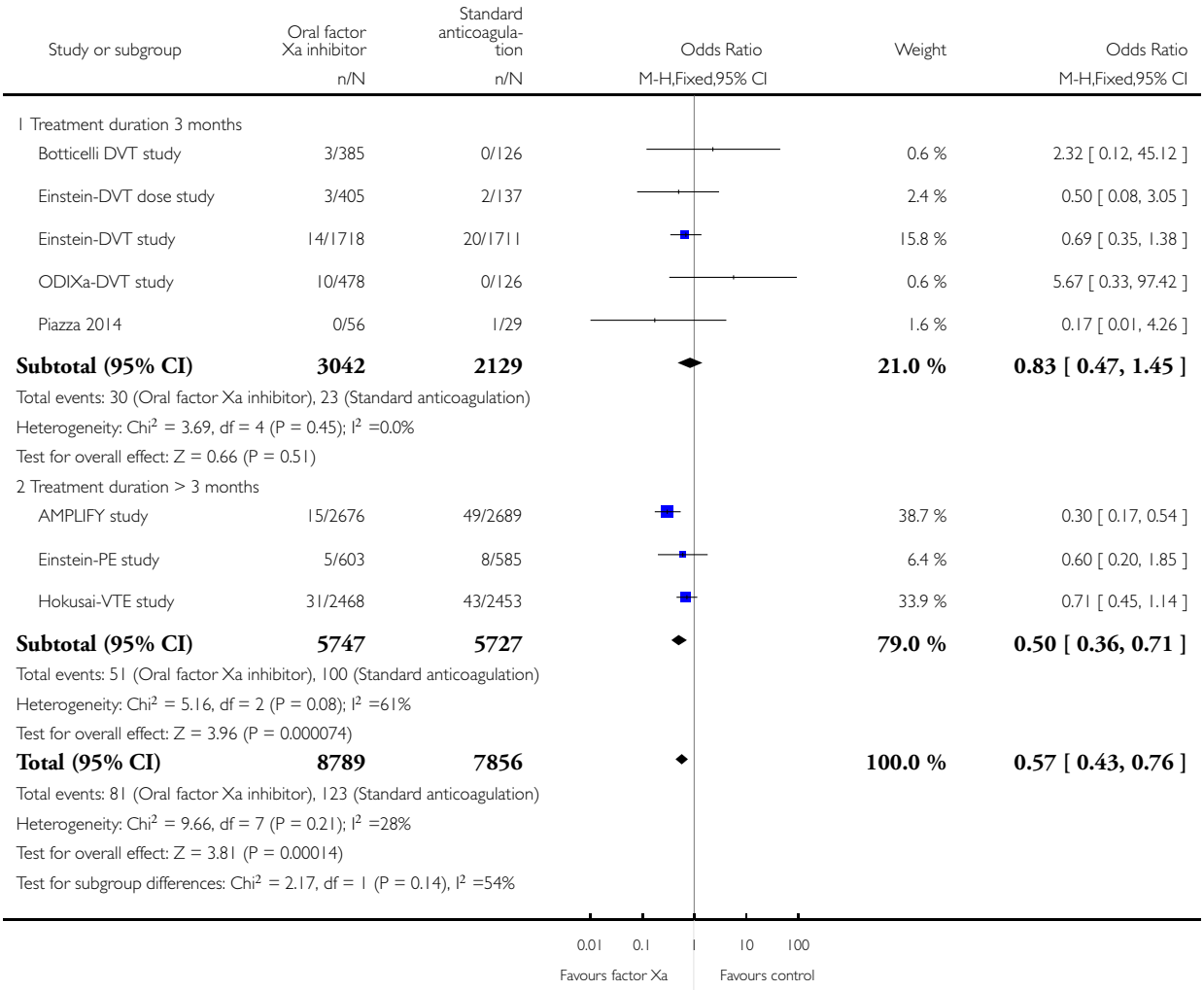
Analysis 3.6. Comparison 3 Oral factor Xa inhibitor versus standard anticoagulation, Outcome 6 Major bleeding.

Review: Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis

Comparison: 3 Oral factor Xa inhibitor versus standard anticoagulation

Outcome: 6 Major bleeding



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APPENDICES

Appendix 1. Cochrane Register of Studies search strategy

	Search run on Wed 28 January 2015	
#1	MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES	790
#2	MESH DESCRIPTOR Hirudin Therapy	75
#3	(thrombin near3 inhib*):TI,AB,KY	444
#4	hirudin*:TI,AB,KY	327
#5	(dabigatran or Pradaxa or Rendix):TI,AB,KY	199
#6	(BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI, AB,KY	9
#7	(ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY	147
#8	(AZD0837 or AZD-0837):TI,AB,KY	12
#9	(S35972 or S-35972):TI,AB,KY	0
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	1387
#11	MESH DESCRIPTOR Factor Xa Inhibitors	1
#12	(Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY	415
#13	(FX* near4 (antag* or inhib* or block*)):TI,AB,KY	33
#14	(10* near4 (antag* or inhib* or block*)):TI,AB,KY	842
#15	#11 OR #12 OR #13 OR #14	1237
#16	(rivaroxaban or Xarelto):TI,AB,KY	251
#17	(Bay-597939 or Bay597939):TI,AB,KY	0
#18	(betrixaban or PRT054021):TI,AB,KY	14
#19	apixaban:TI,AB,KY	134
#20	(BMS-562247 or BMS-562247 or ELIQUIS):TI,AB,KY	0

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(*Continued*)

#21	(DU-176b or DU176b):TI,AB,KY	11
#22	(PRT-054021 or PRT054021):TI,AB,KY	1
#23	(YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*):TI,AB,KY	38
#24	(GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893):TI,AB,KY	3
#25	edoxaban or lixiana	51
#26	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	456
#27	#10 OR #15 OR #26	2793
#28	MESH DESCRIPTOR Thrombosis	1133
#29	MESH DESCRIPTOR Thromboembolism	841
#30	MESH DESCRIPTOR Venous Thromboembolism	159
#31	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	1857
#32	(thrombus* or thrombotic* or thrombolic* or thromboembol* or thrombos* or embol*):TI,AB,KY	13382
#33	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	676
#34	(PE or DVT or VTE):TI,AB,KY	3057
#35	((vein* or ven*) near thromb*):TI,AB,KY	5003
#36	(blood near3 clot*):TI,AB,KY	1305
#37	(pulmonary near3 clot*):TI,AB,KY	5
#38	(lung near3 clot*):TI,AB,KY	3
#39	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	16505
#40	#27 AND #39	1026

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Appendix 2. Trials databases

World Health Organization
182 records for 66 trials found for: apixaban
387 records for 157 trials found for: rivaroxaban
349 records for 142 trials found for: dabigatran
9 records for 3 trials found for: ximelagatran
63 records for 22 trials found for: edoxaban
22 records for 7 trials found for: betrixaban
Clinicaltrials.gov
144 studies found for: rivaroxaban
66 studies found for: apixaban
160 studies found for: dabigatran
3 studies found for: ximelagatran
7 studies found for: betrixaban
25 studies found for: edoxaban
ISRCTN
Apixaban 0
Rivaroxaban 3
Dabigatran 2
Ximelagatran 1
Edoxaban 0
Betrixaban 0

CONTRIBUTIONS OF AUTHORS

LR: drafted the protocol, selected studies for inclusion, extracted data, assessed the quality of studies, performed data analysis and wrote the review.

PK: commented on the protocol, selected studies for inclusion, resolved disagreements between LR and JM, where necessary, regarding extracted data and assessment of the quality of the studies and commented on the review.

JM: selected studies for inclusion, extracted data, assessed the quality of the studies and commented on the review.

DECLARATIONS OF INTEREST

LR: none known.

PK: I have received consultancy fees for attendance at advisory boards of Boehringer-Ingelheim, Bayer, and Daiitchi-Sankyo and payment from Bayer for lectures at the 2013 anticoagulation master class. My institution was paid travel/accommodation/meeting expenses by Boehringer-Ingelheim for my attendance at the 2013 ISTH meeting and staff and NHS costs by Boehringer-Ingelheim and Daiitchi-Sankyo for involvement in phase III trials of novel anticoagulants in venous thrombosis. Since Summer 2014 I have declined all invitations to advisory boards, or lectures on behalf of the pharmaceutical industry.

JM: I received travel, course fees, accommodation and meals from Medtronic as part of the Medtronic University program. This is an educational program, and includes registration and attendance at the European Vascular Course 2012. No financial remuneration was received by myself, other than costs of travel, accommodation, course fees and meals.

I received sponsorship to attend the Vascular Society annual meeting 2012 and 2014 in the form of registration fees and accommodation / travel costs.

I received sponsorship to attend a stenting master class, the Verve clinical meeting in 2013, and a technology forum in Phoenix, Arizona from Gore. This was in the form of travel, accommodation and meals. No other financial remuneration was received.

I received sponsorship to attend the LINC 2015 meeting in Leipzig, Germany from Abbott medical in the form of registration, accommodation, travel and meals.

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I am a co-founder of UKETS, a trainee initiative which receives funding through sponsorship from endovascular technology and simulation companies. The majority of this is non-financial (i.e. the companies supply trainers on the courses or allow use of their simulators), although some direct financial input is received from Vasctutek and Mentice and is used to run events. No profit is derived from this initiative.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a change from the protocol (Robertson 2014b), we excluded studies where treatment was for less than three months because a meta-analysis of DVT treatment strategies has demonstrated an increased rate of recurrence after less than three months' anticoagulation but no significant difference with various longer periods of treatment (Boutitie 2011).

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