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

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Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of deep vein thrombosis.
Cochrane Database of Systematic Reviews 2023, Issue 4. Art. No.: CD010956.
DOI: 10.1002/14651858.CD010956.pub3.

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[Intervention Review]

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

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Editorial group: Cochrane Vascular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2023.

Citation: Wang X, Ma Y, Hui X, Li M, Li J, Tian J, Wang Q, Yan P, Li J, Xie P, Yang K, Yao L. Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of deep vein thrombosis. *Cochrane Database of Systematic Reviews* 2023, Issue 4. Art. No.: CD010956. DOI: 10.1002/14651858.CD010956.pub3.

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 one in 1000 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 direct oral anticoagulants (DOACs) have been developed: oral direct thrombin inhibitors (DTIs) and oral factor Xa inhibitors, which have characteristics that may be favourable compared to conventional treatment, including oral administration, a predictable effect, lack of frequent monitoring or dose adjustment and few known drug interactions. DOACs are now commonly being used for treating DVT: recent guidelines recommended DOACs over conventional anticoagulants for both DVT and PE treatment. This Cochrane Review was first published in 2015. It was the first systematic review to measure the effectiveness and safety of these drugs in the treatment of DVT. This is an update of the 2015 review.

Objectives

To assess the effectiveness and safety of oral DTIs and oral factor Xa inhibitors versus conventional anticoagulants for the long-term treatment of DVT.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 1 March 2022.

Selection criteria

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

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were recurrent venous thromboembolism (VTE), recurrent DVT and PE. Secondary outcomes included all-cause mortality, major bleeding, post-thrombotic syndrome (PTS) and quality of life (QoL). We used GRADE to assess the certainty of evidence for each outcome.

Main results

We identified 10 new studies with 2950 participants for this update. In total, we included 21 RCTs involving 30,895 participants. Three studies investigated oral DTIs (two dabigatran and one ximelagatran), 17 investigated oral factor Xa inhibitors (eight rivaroxaban, five apixaban and four edoxaban) and one three-arm trial investigated both a DTI (dabigatran) and factor Xa inhibitor (rivaroxaban). Overall, the studies were of good methodological quality.

Meta-analysis comparing DTIs to conventional anticoagulation showed no clear difference in the rate of recurrent VTE (odds ratio (OR) 1.17, 95% confidence interval (CI) 0.83 to 1.65; 3 studies, 5994 participants; moderate-certainty evidence), recurrent DVT (OR 1.11, 95% CI 0.74 to 1.66; 3 studies, 5994 participants; moderate-certainty evidence), fatal PE (OR 1.32, 95% CI 0.29 to 6.02; 3 studies, 5994 participants; moderate-certainty evidence), non-fatal PE (OR 1.29, 95% CI 0.64 to 2.59; 3 studies, 5994 participants; moderate-certainty evidence) or all-cause mortality (OR 0.66, 95% CI 0.41 to 1.08; 1 study, 2489 participants; moderate-certainty evidence). DTIs reduced the rate of major bleeding (OR 0.58, 95% CI 0.38 to 0.89; 3 studies, 5994 participants; high-certainty evidence).

For oral factor Xa inhibitors compared with conventional anticoagulation, meta-analysis demonstrated no clear difference in recurrent VTE (OR 0.85, 95% CI 0.71 to 1.01; 13 studies, 17,505 participants; moderate-certainty evidence), recurrent DVT (OR 0.70, 95% CI 0.49 to 1.01; 9 studies, 16,439 participants; moderate-certainty evidence), fatal PE (OR 1.18, 95% CI 0.69 to 2.02; 6 studies, 15,082 participants; moderate-certainty evidence), non-fatal PE (OR 0.93, 95% CI 0.68 to 1.27; 7 studies, 15,166 participants; moderate-certainty evidence) or all-cause mortality (OR 0.87, 95% CI 0.67 to 1.14; 9 studies, 10,770 participants; moderate-certainty evidence). Meta-analysis showed a reduced rate of major bleeding with oral factor Xa inhibitors compared with conventional anticoagulation (OR 0.63, 95% CI 0.45 to 0.89; 17 studies, 18,066 participants; high-certainty evidence).

Authors' conclusions

The current review suggests that DOACs may be superior to conventional therapy in terms of safety (major bleeding), and are probably equivalent in terms of efficacy. There is probably little or no difference between DOACs and conventional anticoagulation in the prevention of recurrent VTE, recurrent DVT, pulmonary embolism and all-cause mortality. DOACs reduced the rate of major bleeding compared to conventional anticoagulation. The certainty of evidence was moderate or high.

PLAIN LANGUAGE SUMMARY

Are direct oral anticoagulants (a type of 'blood thinner') better than conventional anticoagulation for treating people with a blood clot in a deep vein?

What is deep vein thrombosis?

Deep vein thrombosis (DVT) is when a blood clot forms, usually in a deep vein of the leg or pelvis. Approximately 1 in 1000 people will develop a DVT. If it is not treated, the clot can travel in the blood and block the blood vessels in the lungs. This life-threatening condition is called a pulmonary embolism. It occurs in approximately 3 to 4 people per 10,000 people. The chances of getting a DVT are increased if you have certain risk factors. These include previous clots, prolonged periods of immobility (such as travelling on aeroplanes or taking 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 by determining the risk factors and performing an ultrasound of the leg veins.

How is deep vein thrombosis treated?

If a DVT is confirmed, people are treated with an anticoagulant: a medicine that either treats or prevents blood clots, often called a 'blood thinner'. Previously, the medicines of choice were heparin, fondaparinux and vitamin K antagonists, known as 'conventional anticoagulants'. However, these medicines can cause side effects and have limitations.

Two types of anticoagulant have been developed: direct thrombin inhibitors (DTI) and factor Xa inhibitors. These anticoagulants are given orally (that is, by mouth, in the form of a pill), have a predictable effect, do not require frequent monitoring or re-dosing (taking multiple doses), and have few known interactions with other medicines. For these reasons, direct oral anticoagulants have become the medicines of choice for treating DVT.

What did we want to find out?

We wanted to find out if direct oral anticoagulants are useful and safe for treating people with DVT compared with conventional treatments.

What did we do?

We searched for studies in which people with a confirmed DVT were randomly allocated to one of two treatment groups. These types of studies give the most reliable evidence about treatment effects. People in the experimental groups received an oral direct thrombin inhibitor or an oral factor Xa inhibitor, and their results were compared to the results of people given conventional anticoagulation. All participants were given long-term treatment of DVT (minimum duration of 3 months).

What did we find?

After searching for relevant studies, we found 21 studies with 30,895 participants. We combined the data from the studies and found that there was no clear difference in the incidence of:

- recurrent venous thromboembolism (DVT, pulmonary embolism, or both);
- recurrent DVT;
- pulmonary embolism (blood clot in the lungs); or
- death

between people treated with oral direct thrombin inhibitors or oral factor Xa inhibitor compared to those given conventional anticoagulants.

Compared to conventional treatment, both direct thrombin inhibitors and factor Xa inhibitors reduced the major bleeding which happened during the treatment of DVT.

What are the limitations of the evidence?

Our confidence in the evidence is generally moderate because few people overall experienced the outcomes. The evidence answered the question we addressed directly and the results of the studies were consistent. However, further studies are needed to explore how one direct oral anticoagulant compares with another. Future well-designed studies may also provide important evidence for post-thrombotic syndrome (a condition that can happen to people who have had a DVT of the leg, causing chronic pain, swelling and other symptoms in the leg) and quality of life.

How up to date is this evidence?

This review updates a previous Cochrane Review. The evidence is up to date to 1 March 2022.

Key messages

When treating people with a DVT, current evidence shows there is probably a similar effect between direct oral anticoagulants and conventional anticoagulants for preventing recurrent venous thromboembolism, recurrent DVT, pulmonary embolism and death. Direct oral anticoagulants reduced major bleeding compared to conventional anticoagulation.

SUMMARY OF FINDINGS

Summary of findings 1. Oral DTIs versus conventional anticoagulation for participants with diagnosed DVT

Oral DTIs versus conventional anticoagulation for participants with diagnosed DVT

Patient or population: participants with diagnosed DVT
Setting: hospital
Intervention: oral DTIs
Comparison: conventional anticoagulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional anticoagulation	Risk with oral DTIs				
Recurrent VTE (7 months)	Study population 21 per 1000	25 per 1000 (18 to 35)	**OR 1.17 (0.83 to 1.65)**	5994 (3 RCTs[a])	⊕⊕⊕⊖ Moderate[b]	
Recurrent DVT (7 months)	Study population 15 per 1000	17 per 1000 (11 to 25)	**OR 1.11 (0.74 to 1.66)**	5994 (3 RCTs[a])	⊕⊕⊕⊖ Moderate[b]	
Fatal PE (7 months)	Study population 1 per 1000	1 per 1000 (0 to 6)	**OR 1.32 (0.29 to 6.02)**	5994 (3 RCTs[a])	⊕⊕⊕⊖ Moderate[b]	
Non-fatal PE (7 months)	Study population 5 per 1000	6 per 1000 (3 to 12)	**OR 1.29 (0.64 to 2.59)**	5994 (3 RCTs[a])	⊕⊕⊕⊖ Moderate[b]	
All-cause mortality (7 months)	Study population 34 per 1000	22 per 1000 (14 to 36)	**OR 0.66 (0.41 to 1.08)**	2489 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	

Major bleeding (7 months)	Study population 19 per 1000	11 per 1000 (7 to 17)	**OR 0.58 (0.38 to 0.89)**	5994 (3 RCTs[a])	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **DTIs:** direct thrombin inhibitors; **DVT**: deep vein thrombosis; **OR:** odds ratio; **PE**: pulmonary embolism; **RCT**: randomised controlled trial; **VTE**: venous thromboembolism

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The data from RE-COVER 2009 and RE-COVER II 2014 were taken from one pooled analysis and are therefore shown as one study in our analyses
[b]We downgraded one level for imprecision due to the low number of events and a small sample size; the possibility of publication bias is not excluded but we did not consider it sufficient to downgrade the certainty of evidence.

Summary of findings 2. Oral factor Xa inhibitors compared to conventional anticoagulation for participants with diagnosed DVT

Oral factor Xa inhibitors versus conventional anticoagulation for participants with diagnosed DVT

Patient or population: participants with diagnosed DVT
Setting: hospital
Intervention: oral factor Xa inhibitors
Comparison: conventional anticoagulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional anticoagulation	Risk with oral factor Xa				
Recurrent VTE (3 to 12 months)	Study population 34 per 1000	29 per 1000 (24 to 34)	**OR 0.85 (0.71 to 1.01)**	17,505 (13 RCTs)	⊕⊕⊕⊖ Moderate[a]	One of the 13 studies reported no events

Recurrent DVT (3 to 12 months)	Study population 16 per 1000	12 per 1000 (8 to 17)	**OR 0.70 (0.49 to 1.01)**	16,439 (9 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Fatal PE (3 to 12 months)	Study population 3 per 1000	4 per 1000 (2 to 6)	**OR 1.18 (0.69 to 2.02)**	15,082 (6 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Non-fatal PE (3 to 12 months)	Study population 11 per 1000	10 per 1000 (8 to 14)	**OR 0.93 (0.68 to 1.27)**	15,166 (7 RCTs)	⊕⊕⊕⊖ Moderate[a]	
All-cause mortality (3 to 6 months)	Study population 23 per 1000	20 per 1000 (16 to 27)	**OR 0.87 (0.67 to 1.14)**	10,770 (9 RCTs)	⊕⊕⊕⊖ Moderate[a]	Three of the nine studies reported no events
Major bleeding (3 to 12 months)	Study population 17 per 1000	11 per 1000 (8 to 15)	**OR 0.63 (0.45 to 0.89)**	18,066 (17 RCTs)	⊕⊕⊕⊕ High	Five of 17 studies reported no events

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT**: deep vein thrombosis; **OR:** odds ratio; **PE**: pulmonary embolism; **RCT**: randomised controlled trial; **VTE**: venous thromboembolism

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded one level for imprecision due to the low number of events and a small sample size; the possibility of publication bias is not excluded but we did not consider it sufficient to downgrade the quality of evidence.

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. DVT and pulmonary embolism (PE) occur with an incidence of approximately one per 1000 annually in adults (Cushman 2007; White 2003); the incidence of DVT in the general population is around five per 10,000 per annum (Fowkes 2003). 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 four to 12 per 10,000 people, but this is likely to be underestimated and the incidence has been increasing steadily (Barco 2021; Bělohlávek 2013; Keller 2020; Konstantinides 2020; Wendelboe 2016). The two interrelated conditions, DVT and PE, are different clinical manifestations of venous thromboembolism (VTE). Among VTE, about two-thirds of cases manifest as DVT only and one-third as PE with or without DVT (Stone 2017). Another complication of DVT is post-thrombotic syndrome (PTS). PTS is a long-term condition caused by the reduction in the return of venous blood to the heart. 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 60%; PTS added an additional 75% to the cost of treating DVT (Ashrani 2009; Kahn 2014).

There are many risk factors for DVT. When a risk factor is transient (such as major surgery), DVT is termed "provoked". DVT occurring in the absence of transient risk factors is termed "unprovoked" (Kearon 2012). Provoked DVT occurs following surgery or by a non-surgical transient risk factor, such as the history of 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 an individual's medical history and physical examination. The UK National Institute for Health and Care Excellence (NICE) recommends that people presenting with a suspected DVT should be assessed for pre-test probability of DVT using the 2-level DVT Wells score (NICE 2020; 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 (ACCP) recommends 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; Wells 2003). 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; Wells 2003).

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 or a raised D-dimer level, including cancer, disseminated intravascular coagulation, pregnancy, inflammation and infection (NICE 2020). 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 non-invasive diagnostic imaging technique that uses sound waves to produce images of structures within the body. 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 high sensitivity and specificity for detecting proximal DVT (NICE 2020). Guidelines recommend completing either proximal or whole-leg ultrasound, determined by local practice, access to testing and cost (Bates 2012).

Description of the intervention

Anticoagulation is an essential component of therapy for DVT, which can prevent the progression of DVT to PE and the recurrence of thrombosis. The 30-day mortality rate exceeds 3% in people with DVT who are not anticoagulated; this mortality risk is as high as 31% in people with PE (Sogaard 2014). The conventional treatment of DVT is with an indirect thrombin inhibitor, namely unfractionated heparin (UFH), or low molecular weight heparin (LMWH), followed by vitamin K antagonists (VKAs). 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). Although heparin and VKAs are effective anticoagulants, there are limitations associated with each. Heparin-induced thrombocytopenia (HIT) is a rare, potentially life-threatening, reaction to heparin (Ortel 2022). Approximately 50% of people with isolated HIT develop further thrombosis (Warkentin 1996). 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 direct oral anticoagulants (DOACs) have been developed: direct thrombin inhibitors (DTIs) and factor Xa inhibitors. Oral DTIs and factor Xa inhibitors have characteristics that may be favourable over heparin and VKAs, including oral administration, a predictable effect, lack of frequent monitoring or dose adjustment, and few known drug interactions (Almutairi 2017; Fox 2012).

Anticoagulant therapy for VTE (DVT and PE) can be divided into three stages: initiation phase (five to 21 days) with initial provision of anticoagulants after diagnosis; treatment phase (three months), the period that completes treatment for the acute VTE following initiation; and the extended phase (three months to no planned stop date) for secondary prevention, with anticoagulant use at full or reduced dose (Stevens 2021). Previous ACCP guidelines recommend initial therapy for DVT with a parenteral anticoagulant (UFH or LMWH or fondaparinux) and initial VKA initiation; recommendations include the use of LMWH or fondaparinux over UFH for initial therapy of DVT (Kearon 2012). The latest updates of ACCP guidelines recommended apixaban, dabigatran, edoxaban

or rivaroxaban over VKA as treatment-phase (first three months) anticoagulant therapy for people with VTE (DVT of the leg or PE), and recommended an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy for acute VTE associated with cancer (Kearon 2016; Stevens 2021). Similarly, the 2019 European Society of Cardiology (ESC) guidelines recommended DOACs in preference to VKAs in eligible individuals ready for an oral anticoagulant (Konstantinides 2020). The NICE 2020 guidelines recommended offering either apixaban or rivaroxaban as initial choices, and suggested other regimens only for people suitable for neither: consider a DOAC for people with active cancer and confirmed proximal DVT or PE, and consider other strategies when DOAC is unsuitable.

According to research by Lutsey and colleagues, the use of DOACs (especially rivaroxaban and apixaban) to treat VTE has increased dramatically in the USA since the US Food and Drug Administration (FDA) approved them for this application (Lutsey 2019). Drawing on individual health insurance data for 2012 to 2017, they found that DOACs accounted for less than 2% of the prescriptions for VTE treatment at the beginning of 2012 and increased to more than 80% by the fourth quarter of 2017 (Lutsey 2019).

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, but only one available for clinical use.

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 stroke prevention in atrial fibrillation (Calkins 2017; Cannon 2017; Connolly 2009), acute coronary syndromes (Oldgren 2011), prevention of thrombosis following orthopaedic surgery (Eriksson 2007; Van der Veen 2021), and in people with mechanical heart valves (Eikelboom 2013; Van de Werf 2012). In common with the other DOACs, dabigatran was associated with a lower incidence of intracranial haemorrhage (compared with VKAs). However, again compared with VKAs, dabigatran showed a higher incidence of indigestion, heartburn and gastrointestinal bleeding (Schulman 2014).

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), especially with prolonged use (Testa 2007), and was never licensed.

Oral factor Xa inhibitors

Factor Xa inhibitors bind directly to the active site of factor Xa, thus blocking the activity of this 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 VKAs but without the need for regular blood test monitoring. They appear to have fewer drug interactions (compared with VKAs) 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; the dose can be reduced to 10 mg once daily beyond six months (Skelley 2018). The absorption of rivaroxaban (the 15 mg and 20 mg dosage) is predicated on giving it with food; therefore, rivaroxaban is recommended to be taken with food (Skelley 2018; Stampfuss 2013).

Apixaban

Apixaban is an oral, small molecule, reversible inhibitor of factor Xa with a plasma half-life of eight to 15 hours (Eriksson 2009). The recommended dosage for apixaban is 10 mg twice daily for one week, then 5 mg twice daily. For people with severe renal impairment (creatinine clearance (CrCL) of 15 mL/min to 29 mL/min), apixaban should be used with caution (Leung 2022).

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). Betrixaban is only labelled for VTE prophylaxis, not treatment (Skelley 2018). For the prophylaxis of VTE, the recommended dose of betrixaban is an initial single dose of 160 mg starting on day 1, followed by 80 mg once daily taken for 35 to 42 days at the same time each day with food. For people with severe renal impairment (CrCL 15 mL/min to 29 mL/min computed by Cockcroft-Gault using actual body weight), the recommended dose of betrixaban is an initial single dose of 80 mg followed by 40 mg once daily (FDA 2017).

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). The recommended dose is 60 mg once daily after parenteral anticoagulation for five to 10 days (Leung 2022).

Why it is important to do this review

Given the relatively high incidence and serious consequence of DVT, and the emergence and adoption of these DOACs, it is important to establish the safety and effectiveness of these treatments. Multiple non-Cochrane systematic reviews have examined the effectiveness of DTIs and factor Xa inhibitors versus VKAs in the treatment of

VTE (Almutairi 2017; Fox 2012; Mulder 2020). However, their primary outcome was VTE and they did not present results for DVT and PE separately.

This review was originally conducted in 2015 and included 11 randomised controlled trials of 27,945 participants. It examined the effectiveness of oral DTIs and oral factor Xa inhibitors in the treatment of DVT alone, and showed that they are potentially effective and safe alternatives to conventional anticoagulation treatment for acute DVT (Robertson 2015). However, none of the included studies in the previous version focused on and measured important outcomes, such as PTS or health-related quality of life, and all-cause mortality has yet to be estimated for DVT treated with dabigatran (the only FDA-approved DTI). In addition, data were limited for important subgroups (e.g. people with cancer). Further, no study compared one DOAC with another, a fact highlighted in both NICE and ACCP guidelines (NICE 2020; Stevens 2021).

Since 2015, many new randomised controlled trials on this topic have been published (AMPLIFY-J 2015; Farhan 2019; Ohmori 2019; PRAIS 2019; Raskob 2018), with some reporting on quality of life (Sukovatykh 2017) and PTS (de Athayde 2019), and more studies focused on cancer-associated DVT (Caravaggio 2020; Hokusai VTE Cancer 2018; Mokadem 2021). Further, the previous version included data published only in a conference abstract for the eTRIS 2016 study. As DOACs are now ubiquitous in the context of primary treatment for VTE, there is a continued need to assess their comparative effectiveness, and to explore and understand how to optimise their management in high-risk situations. It is important to update the evidence presented in this Cochrane Review to include any newly available data, providing trustworthy evidence synthesis for more informed decision-making.

OBJECTIVES

To assess the effectiveness and safety of oral DTIs and oral factor Xa inhibitors versus conventional anticoagulants for the long-term treatment of DVT.

METHODS

Criteria for considering studies for this review

Types of studies

We included 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 lasted 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

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

Types of interventions

We included the following 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).

We included the following comparisons:

- 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.

Treatment had to be for a minimum duration of three months as this is conventional anticoagulation practice for a DVT.

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)
- Recurrent DVT, confirmed by standard imaging techniques, including proximal leg vein ultrasound scan or D-dimer test
- PE (fatal/non-fatal), confirmed by CTPA or V/Q scan

Secondary outcomes

- All-cause mortality
- Major bleeding (an adverse event; 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.
- PTS as defined by Kahn 2016
- Health-related quality of life (as reported in studies)

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases, from inception to 1 March 2022, for randomised controlled trials and controlled clinical trials without language, publication year or publication status restrictions:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2022) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE);
- Embase Ovid;
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) EBSCO.

We developed search strategies for other databases from the search strategy designed for MEDLINE. Where appropriate, they were combined with adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 4 (Lefebvre 2021). Search strategies for major databases are provided in Appendix 1.

We searched the following trials registries:

- the World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch);
- ClinicalTrials.gov (clinicaltrials.gov).

The most recent searches were carried out on 1 March 2022.

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

Pairs of reviewers (XW, YM, ML, JL, XH, QW, LY), independently and in duplicate, used the selection criteria to identify trials for inclusion. We resolved any disagreements by discussion.

Data extraction and management

Two pairs of review authors (ML, YM, JL, XH) independently extracted the data from the included studies. We recorded information about the trial design; exclusions post-randomisation; losses to follow-up; duration of study; unit of randomisation; country and setting; number of participants; age and sex of participants; participant inclusion and exclusion criteria; intervention and control group sample sizes, type, dose and duration of intervention; diagnosis of DVT; baseline characteristics of participants; funding source and declarations of interest declared by study authors. We recorded recurrent VTE, recurrent DVT and PE (fatal and non-fatal) data as the primary outcome measures. We also collected data on all-cause mortality, major bleeding, PTS and health-related quality of life 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 discussions with a third review author (XW) if required.

Assessment of risk of bias in included studies

Two pairs of review authors (ML, YM, JL, XH) independently used Cochrane's risk of bias tool to assess risk of bias for each of the included studies (Higgins 2017). 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 2017, and provided support for each judgement. We presented the conclusions in a risk of bias table. We resolved any disagreements by discussion with a third review author (XW) if required.

Measures of treatment effect

We based the analysis on intention-to-treat data from the individual clinical trials.

For dichotomous outcomes, we used odds ratios (ORs) as the effect measure, with 95% confidence intervals (CIs). For continuous data, we calculated mean differences (MDs) with 95% CIs. If similar outcomes were measured using different scales, we planned to calculate the standardised mean difference (SMD).

Unit of analysis issues

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

Dealing with missing data

We sought information about dropouts, 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: visually examining forest plots to check for overlap among CIs; using the Chi^2 test for homogeneity with a 10% level of significance; and using 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 2022).

Assessment of reporting biases

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

Data synthesis

One review author (XW) entered the data into RevMan Web (RevMan Web 2019), and a second review author (XH) cross-checked data entry. We resolved any discrepancies by consulting the source publication.

We used a random-effects model to synthesise the data, even when low heterogeneity was indicated by small I^2 values. This was because we expected that clinical heterogeneity across studies may exist, such as different oral factor Xa inhibitors (e.g. apixaban, rivaroxaban, edoxaban), different indirect thrombin inhibitors in the control group (e.g. warfarin, dalteparin), and different treatment durations (e.g. three, six and 12 months).

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis only when each subgroup was reported by at least two studies. Due to the limited

number of included studies in each subgroup, we were not able to perform the following subgroup analyses:

- history of VTE;
- age;
- pregnancy;
- major surgery requiring general or regional anaesthesia in the previous 12 weeks;
- recent period of immobility (bedridden for three or more days in the previous 12 weeks);
- thrombophilia (genetic or acquired).

We performed subgroup analysis by duration of treatment to identify treatment effects of three months of treatment and more than three months of treatment. We also conducted subgroup analysis by different oral Xa factor inhibitors since individual drugs may have potential differences in effectiveness and safety. For treatment effects by populations with active cancer versus no cancer, we carried out subgroup analysis when sufficient data were available.

Sensitivity analysis

We performed sensitivity analyses by excluding studies that we judged to be at high risk of bias in any domain. We also performed sensitivity analyses by excluding the study that gave participants ximelagatran, as this drug is no longer available.

Summary of findings and assessment of the certainty of the evidence

We developed summary of finding tables using GRADEpro GDT software (GRADEpro GDT). We created one table for the comparisons 'Oral DTIs versus conventional anticoagulation for participants with diagnosed DVT' and 'Oral factor Xa inhibitors compared to conventional anticoagulation for participants with diagnosed DVT'. We assessed the certainty of the body of evidence for each outcome as high, moderate, low or very low by considering the risk of bias, inconsistency, indirectness, imprecision and publication bias, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022). We assessed the certainty of evidence for the following outcomes: recurrent VTE, recurrent DVT, fatal PE, non-fatal PE, all-cause mortality and major bleeding. We included footnotes to justify decisions to downgrade the certainty of the evidence.

RESULTS

Description of studies

Results of the search

See Figure 1.

Figure 1. Study flow diagram

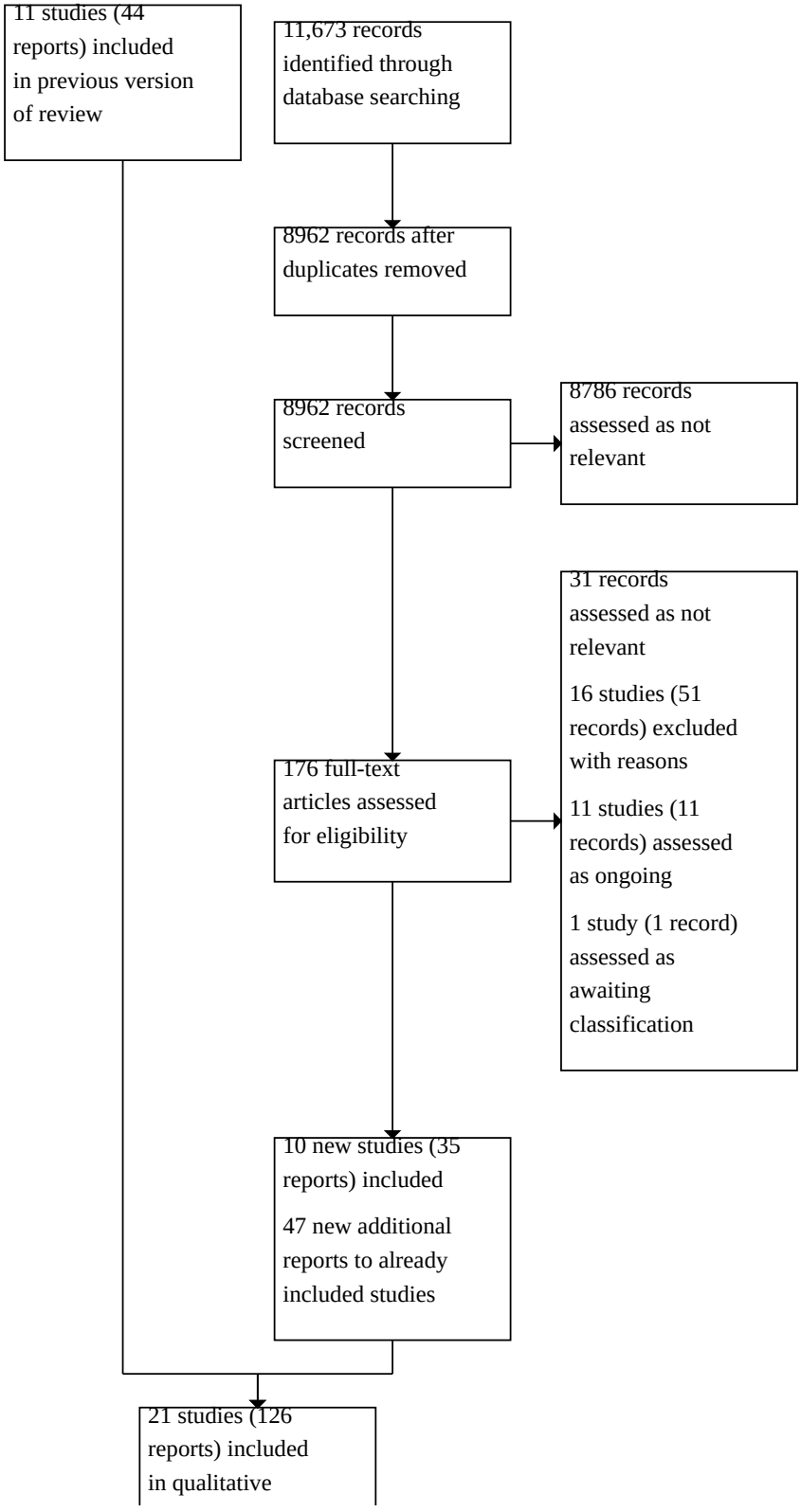
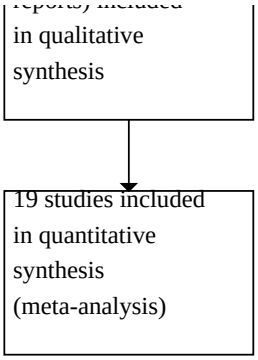


Figure 1. (Continued)



For this update, the searches identified 11,673 records, leaving 8962 records after deduplication. We assessed 8786 records as not relevant based on the title and abstract screening. We assessed 176 potentially relevant records by screening full-text publications. We identified 10 new studies (35 reports) eligible for inclusion in the review, and 47 additional reports for already included studies. The previous version of the review included 11 studies (44 reports); therefore, we ultimately included a total of 21 studies (126 reports) in this review update. See Characteristics of included studies. Five references reported on more than one study and are listed more than once, making the total count of reports of included studies 131. We excluded 16 studies (51 reports) with reasons; we identified 11 ongoing studies (11 reports); and we assessed one study (one report) as awaiting classification. We assessed the remaining thirty-one records as not relevant.

Included studies

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

Twenty-one studies (30,895 participants) met the criteria and were included in the review (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai-VTE 2013; Hokusai VTE Cancer 2018; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2019; PRAIS 2019; RE-COVER 2009; RE-COVER II 2014; Sukovatykh 2017; THRIVE 2005). All studies were two-arm trials with the exception of one, the Sukovatykh 2017 study, which was a three-arm trial, comparing both a DTI (dabigatran) and factor Xa inhibitor (rivaroxaban) to conventional anticoagulation.

Four studies (7691 participants) compared oral DTIs with conventional anticoagulation (RE-COVER 2009; RE-COVER II 2014; Sukovatykh 2017; THRIVE 2005). One study tested ximelagatran (THRIVE 2005). The THRIVE 2005 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. Three studies tested dabigatran (RE-COVER 2009; RE-COVER II 2014; Sukovatykh 2017). RE-COVER 2009 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 2014). Sukovatykh 2017 was a clinical trial in which 95 participants were randomly divided into the dabigatran (150 mg twice daily for six months), rivaroxaban (15 mg twice daily for three weeks, then 20 mg once daily until end of the six-month course) or warfarin group. All studies measured recurrent VTE; three studies measured recurrent DVT, PE (fatal and non-fatal), all-cause mortality and major clinically relevant bleeding (RE-COVER 2009; RE-COVER II 2014; THRIVE 2005); one reported quality of life measured by the 36-item Short Form Health Survey (SF-36) (Sukovatykh 2017).

Eighteen studies (30,895 participants) tested oral factor Xa inhibitors (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2019; PRAIS 2019; Sukovatykh 2017). Of these studies, nine investigated rivaroxaban (de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Farhan 2019; J-EINSTEIN DVT and PE 2015; ODIXa-DVT 2007; PRAIS 2019; Sukovatykh 2017), five investigated apixaban (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; Mokadem 2021), and four investigated edoxaban (eTRIS 2016; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; Ohmori 2019). Four studies were dose-ranging (Botticelli DVT 2008; EINSTEIN-DVT dose 2008; J-EINSTEIN DVT and PE 2015; ODIXa-DVT 2007), while the remaining 14 studies were fixed dose (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT 2010; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; Mokadem 2021; Ohmori 2019; PRAIS 2019; Sukovatykh 2017). The control treatment was heparin combined with VKA in 12 studies (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; ODIXa-DVT 2007; PRAIS 2019), LMWH in three studies (Caravaggio 2020; Hokusai VTE Cancer 2018; Mokadem 2021), and VKA in three studies (de Athayde 2019; Ohmori 2019; Sukovatykh 2017). Sukovatykh 2017 was a three-arm trial comparing dabigatran, rivaroxaban and warfarin. Duration of treatment was 12 weeks in five studies (Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; eTRIS 2016;

ODIXa-DVT 2007), 5.5 to 6.5 months in 12 studies (AMPLIFY 2013; AMPLIFY-J 2015; Caravaggio 2020; de Athayde 2019; EINSTEIN-PE 2012; Farhan 2019; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; Ohmori 2019; PRAIS 2019; Sukovatykh 2017), 12 months in one study (Ohmori 2019), and six to 12 months in one study (Hokusai VTE Cancer 2018).

Thirteen oral factor Xa inhibitor studies measured recurrent VTE (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007), nine measured recurrent DVT (AMPLIFY 2013; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai-VTE 2013; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019), six measured fatal PE (AMPLIFY 2013; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; Hokusai-VTE 2013; ODIXa-DVT 2007), seven measured non-fatal PE (AMPLIFY 2013; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; eTRIS 2016; Hokusai-VTE 2013; ODIXa-DVT 2007), nine measured all-cause mortality (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019), and 17 measured major bleeding (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2019; PRAIS 2019). The Sukovatykh 2017 study reported quality of life and de Athayde 2019 reported PTS.

We included the EINSTEIN-PE 2012 study, as 25% of participants had concurrent symptomatic DVT. We contacted the authors of this 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. We included four studies in participants with either DVT, PE or both (AMPLIFY-J 2015; Caravaggio 2020; Hokusai VTE Cancer 2018; Hokusai-VTE 2013). For these studies, we collected reported data from the subgroup of people with an index DVT (44 participants in AMPLIFY-J 2015, 517 in Caravaggio 2020, 4921 in Hokusai-VTE 2013, and 389 in Hokusai VTE Cancer 2018). We were unable to obtain outcome data on all-cause mortality from the authors of the Hokusai-VTE 2013 study.

Excluded studies

See Characteristics of excluded studies.

We excluded 16 studies from this review (ADAM VTE trial 2020; AMPLIFY Extended Study 2013; Borsi 2021; CASTA DIVA Trial 2022; COBRRA 2017; CONKO-011 study 2015; DIVERSITY 2021; EINSTEIN-CHOICE 2017; EINSTEIN-Jr 2020; Peacock 2018; PRIORITY 2022; REMEDY 2013; RE-SONATE 2013; SELECT-D 2018; THRIVE I 2003; THRIVE III 2003).

Participants in the AMPLIFY Extended Study 2013 had already taken part in the included AMPLIFY 2013 study. Similarly, REMEDY 2013 and RE-SONATE 2013 were extended treatment studies and participants had already taken part in the RE-COVER 2009 and RE-COVER II 2014 studies. We excluded the THRIVE I 2003 study as treatment was only for four weeks. We excluded THRIVE III 2003 as the control group was administered a placebo, which did not fit as an intervention in this review. We excluded nine studies as, although all participants had venous thromboembolism, specific data on the subgroup with a DVT were not published (ADAM VTE trial 2020; Borsi 2021; CASTA DIVA Trial 2022; COBRRA 2017; CONKO-011 study 2015; DIVERSITY 2021; EINSTEIN-Jr 2020; PRIORITY 2022; SELECT-D 2018). We made attempts to contact the authors for these data but were unsuccessful. We excluded EINSTEIN-CHOICE 2017 as the comparator was aspirin. We excluded Peacock 2018 as participants had PE only.

Studies awaiting classification

We assessed one trial as 'awaiting classification'; there are currently insufficient details to assess its eligibility for inclusion (NCT01780987).

Ongoing studies

Eleven trials are ongoing and there are currently no suitable data available for review (EudraCT 2014-002606-20; NCT01516840; NCT02464969; NCT02664155; NCT02744092; NCT02798471; NCT02829957; NCT03129555; NCT03266783; NCT04066764; NCT05171049). See Characteristics of ongoing studies.

Risk of bias in included studies

See Figure 2 and Figure 3.

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

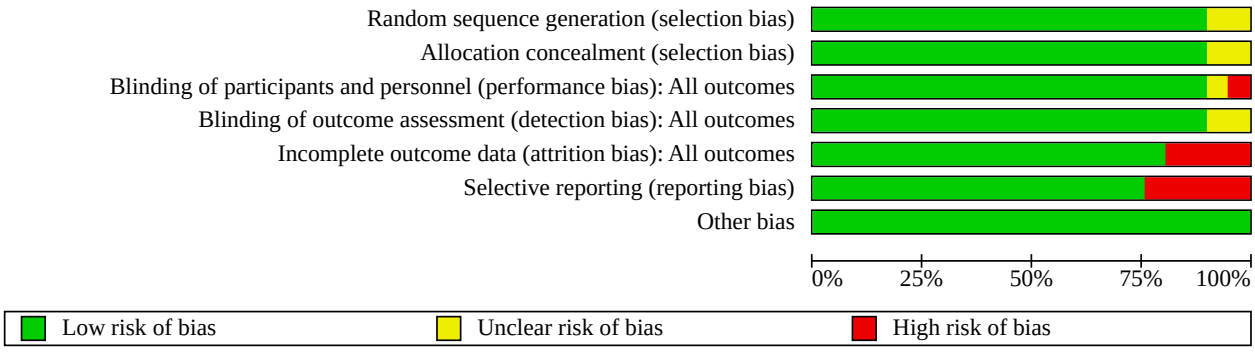


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

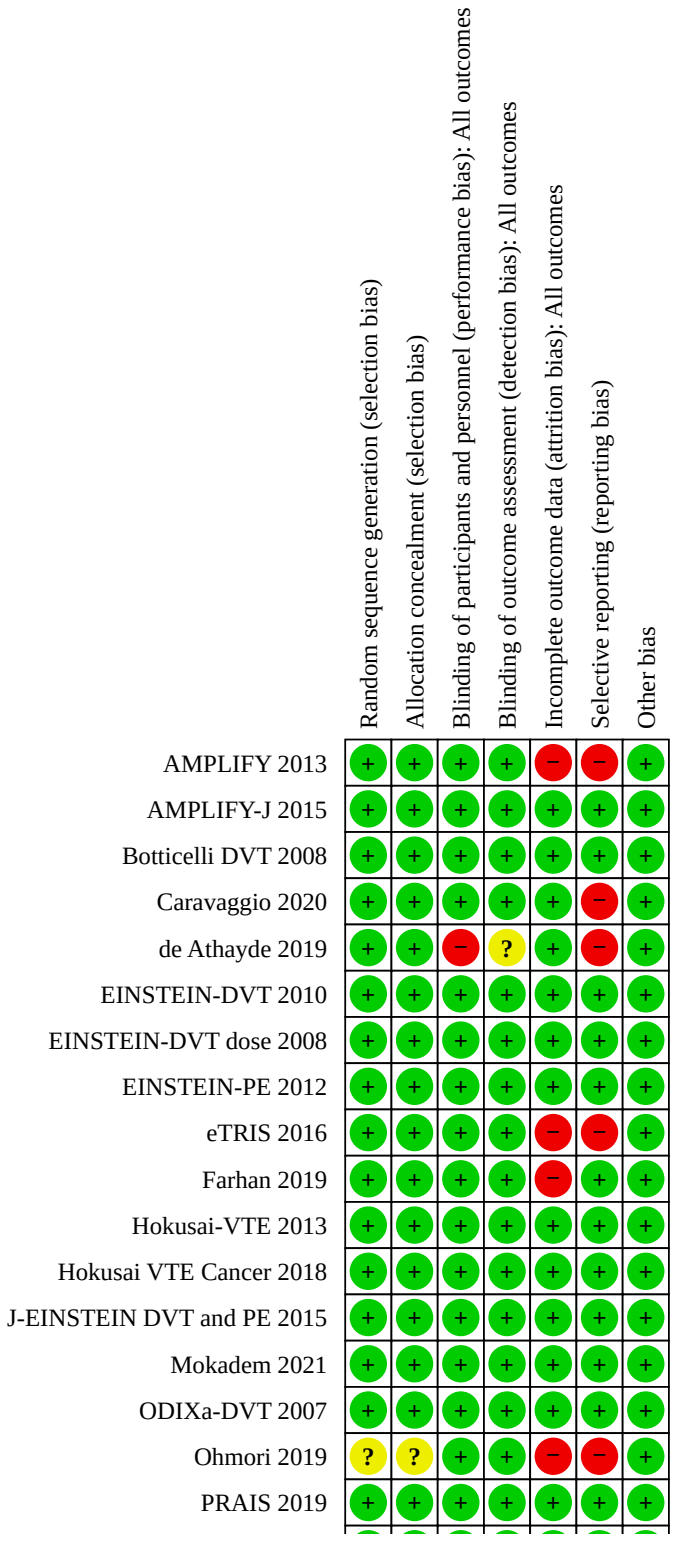
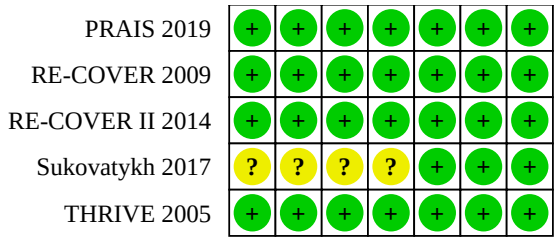


Figure 3. (Continued)



Allocation

Nineteen studies were at low risk of bias for sequence generation as they used a computerised system to generate the randomisation sequence (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019; RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). Two studies were at unclear risk of bias: Ohmori 2019 used block randomisation (1:1) but did not describe the process in detail, and Sukovatykh 2017 did not report information about randomisation.

Similarly, 19 studies adequately concealed the treatment allocation with the use of a computerised system and we judged them to be at low risk of selection bias for allocation concealment (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019; RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). Two studies were at an unclear risk because of insufficient information (Ohmori 2019; Sukovatykh 2017). The eTRIS 2016 study was reported as an abstract in the previous version of the review and we have now included the full-text report. This did not provide clear information regarding allocation concealment. However, personal communication with the study author revealed that treatment allocation was concealed with the use of a computerised system and, therefore, we judged this study to be at low risk of bias.

Blinding

We assessed 14 studies to be at low risk of bias for blinding (AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2019; PRAIS 2019). They either did not blind participants and personnel to the control treatment or did not report blinding, but we judged that the lack of blinding in the control group was unlikely to have affected the outcomes of this review. A further five studies were double-blinded and used placebo tablets or injection so were at low risk of bias (AMPLIFY 2013; Hokusai-VTE 2013; RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). Therefore, we judged 19 studies to be at low risk of performance bias. The de Athayde 2019 study reported PTS but provided no information about blinding for participants. The PTS score included participants' self-reported domains (such as pain, cramps, heaviness, pruritus and paraesthesia), so we judged the risk of blinding for participants and personnel as high, as knowing what treatment group they were in may have affected the outcome. The Sukovatykh 2017 study measured quality of life using SF-36, which is a participant self-reported instrument. We judged the risk of blinding for both participants and personnel as unclear as no information was provided, and knowing what treatment group participants were in may have affected the outcome.

Fourteen studies blinded outcome assessors to treatment, and we judged them to be at low risk of detection bias (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; ODIXa-DVT 2007; RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). We rated a further five studies that either did not blind outcome assessors or reported insufficient information on this to be at low risk of detection bias, as a lack of blinding was unlikely to have affected the objective outcome (eTRIS 2016; Farhan 2019; PRAIS 2019; Mokadem 2021; Ohmori 2019). The de Athayde 2019 study blinded the physician responsible for data assessment; however, the PTS score included participants' self-reported domains, so we judged this study to have an unclear risk of detection bias. The Sukovatykh 2017 study did not provide enough information for an assessment of detection bias to be made so we also judged it to be at an unclear risk of detection bias.

Incomplete outcome data

Seventeen studies sufficiently reported missing outcome data and were balanced across treatment groups. Therefore, we judged these studies to be at low risk of attrition bias (AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019; RE-COVER 2009; RE-COVER II 2014; Sukovatykh 2017; THRIVE 2005). The AMPLIFY 2013 inappropriately excluded a number of randomised participants from the intention-to-treat analysis. Furthermore, a large number of participants within each treatment group were classified as discontinuing the study for "other reasons" with no explanation given. We therefore deemed this study to be at high risk of attrition bias. We also judged the risk of attrition bias as high for the eTRIS 2016, Farhan 2019 and Ohmori 2019 studies, as they all lost more than 20% of participants and did not clarify if the loss was balanced across groups.

Selective reporting

Sixteen studies clearly stated and reported their pre-specified outcomes and, therefore, we judged these to be at low risk of

reporting bias (AMPLIFY-J 2015; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019; RE-COVER 2009; RE-COVER II 2014; Sukovatykh 2017; THRIVE 2005). We judged five studies to be at high risk of reporting bias (AMPLIFY 2013; Caravaggio 2020; de Athayde 2019; eTRIS 2016; Ohmori 2019). The AMPLIFY 2013 study pre-defined minor bleeding as a secondary outcome but data were not reported in the paper. In addition, this study analysed non-inferiority using an ITT analysis. When compared with the per-protocol analysis, ITT favoured the finding of non-inferior results. This may have skewed the result in favour of increased efficacy of apixaban. The Caravaggio 2020 study defined quality of life as a secondary outcome in its protocol but no information was reported in the full text. This study also stated that a "significant interaction was noted between age subgroups and treatment for recurrent venous thromboembolism", but no result was found in the paper and appendix. Both the de Athayde 2019 and Ohmori 2019 studies failed to report the pre-defined secondary outcome complications in their full report. The eTRIS 2016 study planned to report the number of participants with major adverse cardiovascular events (MACE) when registered; however, this outcome was not provided in the full text. Protocols were available for eight studies (AMPLIFY 2013; Caravaggio 2020; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; Ohmori 2019).

Other potential sources of bias

We judged the other risk of bias for all included studies as low as no potential risks were detected.

Effects of interventions

See: **Summary of findings 1** Oral DTIs versus conventional anticoagulation for participants with diagnosed DVT; **Summary of findings 2** Oral factor Xa inhibitors compared to conventional anticoagulation for participants with diagnosed DVT

Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation

In the meta-analysis of oral DTIs versus conventional anticoagulation, we used data from Goldhaber 2016, as it reported the separate deep vein thrombosis (DVT) data for RE-COVER 2009 and RE-COVER II 2014. It combined these studies, which is reflected in the data analysis tables and Summary of findings 1 by showing only one study for this comparison.

Recurrent venous thromboembolism (VTE)

Meta-analysis of three studies (5994 participants) showed no clear difference in the rate of recurrent VTE between the groups treated with a DTI and conventional anticoagulation with heparin and a VKA (RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). The incidence was 2.37% (71 events/2998 participants) in the DTI group and 2.04% (61 events/2996 participants) in the conventional anticoagulation group, leading to an odds ratio (OR) of 1.17 (95% confidence interval (CI) 0.83 to 1.65; 3 studies, 5994 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.1).

Recurrent deep vein thrombosis

Three studies reported recurrent DVT (RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). The incidence was 1.70% (51 events/2998 participants) in the DTI group and 1.54% (46 events/2996 participants) in the conventional anticoagulation group, leading to an OR of 1.11 (95% CI 0.74 to 1.66; 3 studies, 5994 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.2).

Fatal pulmonary embolism

The same three studies reported fatal PE. The incidence of fatal PE was 0.13% (4 events/2998 participants) in the DTI group compared with 0.10% (3 events/2996 participants) in the conventional anticoagulation group (OR 1.32, 95% CI 0.29 to 6.02; 3 studies, 5994 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.3).

Non-fatal pulmonary embolism

The same three studies reported non-fatal PE, which occurred in 0.60% (18 events/2998 participants) of DTI participants and 0.47% (14 events/2996 participants) of conventional anticoagulation participants (OR 1.29, 95% CI 0.64 to 2.59; 3 studies, 5994 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.4).

All-cause mortality

We could not obtain the all-cause mortality data from RE-COVER 2009 and RE-COVER II 2014 from any report or by contacting authors. There was no difference in the rate of all-cause mortality between the two treatment groups based on data from THRIVE 2005. The incidence was 2.26% (28 events/1240 participants) in the DTI (ximelagatran) group and 3.36% (42 events/1249 participants) in the conventional anticoagulation group, with an OR of 0.66 (95% CI 0.41 to 1.08; 1 study, 2489 participants; moderate-certainty evidence; Analysis 1.5).

Major bleeding

Meta-analysis showed that DTIs were associated with fewer major bleeding episodes than conventional anticoagulation therapy. Of the DTI participants, 1.13% (34 events/2998 participants) had a major clinically relevant bleeding episode compared with 1.94% (58 events/2996 participants) of conventional anticoagulation participants, resulting in an OR of 0.58 (95% CI 0.38 to 0.89; 3 studies, 5994 participants; I^2 = 0%; high-certainty evidence; Analysis 1.6).

Post-thrombotic syndrome

None of the included studies measured PTS as an outcome.

Health-related quality of life

Sukovatykh 2017 used SF-36 scales to measure the quality of life (0 to 100 mm scales where a higher score indicates better health). The study authors did not report the overall score and baseline data, so we collected data as physical component of health and psychological component of health at 12 months as these were reported. Both indices appeared to be higher in the dabigatran group compared to the warfarin group: physical component: mean difference (MD) 6.75 (95% CI 2.37 to 11.13; 1 study, 75 participants; Analysis 1.7) and psychological component: MD 6.45 (95% CI 3.24 to 9.66; 1 study, 75 participants; Analysis 1.8).

Sensitivity analyses

As part of the planned sensitivity analysis, we removed the THRIVE 2005 study testing ximelagatran from the meta-analyses since the drug is no longer available (Analysis 2.1; Analysis 2.2; Analysis 2.3;

Analysis 2.4; Analysis 2.5). Excluding these results had little effect on the outcomes. The rate of recurrent VTE (OR 1.21, 95% CI 0.78 to 1.89), recurrent DVT (OR 1.24, 95% CI 0.76 to 2.03), fatal PE (OR 0.66, 95% CI 0.11 to 3.97) and non-fatal PE (OR 1.12, 95% CI 0.43 to 2.91) remained similar between participants treated with dabigatran and participants treated with a VKA. However, excluding the ximelagatran study resulted in a similar point estimate for major bleeding but was no longer statistically significant (OR 0.62, 95% CI 0.35 to 1.08) due to insufficient statistical power.

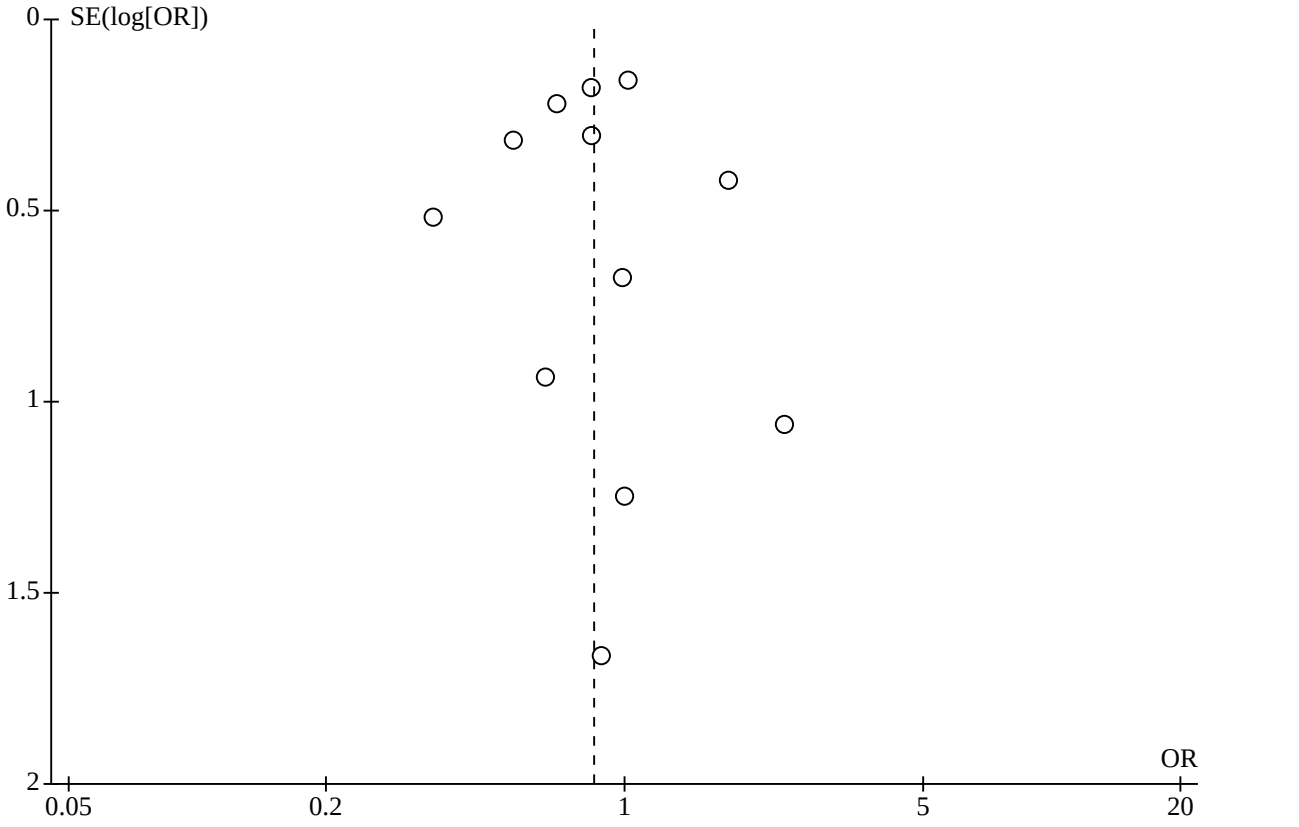
We deemed no studies to be at high risk of bias, therefore, we did not perform a sensitivity analysis excluding studies judged to be of high risk of bias.

Oral factor Xa inhibitors versus conventional anticoagulation

Recurrent venous thromboembolism

Meta-analysis of 13 studies (17,505 participants) demonstrated that there was no clear difference in the rate of recurrent VTE in participants treated with an oral factor Xa inhibitor compared with conventional anticoagulation (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007). The AMPLIFY-J 2015 study had no events in either group and so did not contribute to the analysis (not estimable). The incidence was 2.90% (267 events/9207 participants) in the factor Xa inhibitor group and 3.42% (283 events/8298 participants) in the conventional anticoagulation group, leading to an OR of 0.85 (95% CI 0.71 to 1.01; 13 studies, 17,505 participants; I^2 = 0%; moderate-certainty evidence; 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 conventional anticoagulation (OR 0.68, 95% CI 0.47 to 0.99; 5 studies, 5001 participants). There was no clear difference in the incidence between the two groups when duration of treatment was for longer than three months (OR 0.90, 95% CI 0.74 to 1.10; 8 studies, 12,460 participants) (test for subgroup differences: P = 0.20). Further, subgroup analysis of people experiencing DVT with cancer (OR 0.69, 95% CI 0.51 to 0.94; 4 studies, 4248 participants) versus without cancer (OR 0.82, 95% CI 0.59 to 1.15; 4 studies, 5579 participants) suggested no subgroup difference (test for subgroup differences: P = 0.45, Analysis 4.1). We produced a funnel plot and found no indication of publication bias (Figure 4). No subgroup effect was indicated when analysed by the three oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) (test for subgroup differences: P = 0.48, Analysis 5.1).

Figure 4. Funnel plot of oral factor Xa inhibitors versus conventional anticoagulants for recurrent VTE



Recurrent deep vein thrombosis

Data on recurrent DVT was available in nine studies (16,439 participants) (AMPLIFY 2013; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai-VTE 2013; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019). The authors of Hokusai-VTE 2013 kindly provided us with separate data on recurrent DVT and fatal and non-fatal PE. There was no

clear difference in rate of recurrent DVT between oral factor Xa inhibitors (1.26%, 109 events/8633 participants) and conventional anticoagulation (1.64%, 128 events/7806 participants), leading to an OR of 0.70 (95% CI 0.49 to 1.01; 9 studies, 16,439 participants; I^2 = 30%; moderate-certainty evidence; Analysis 3.2). When analysed according to treatment duration, there were no clear differences in the incidence of recurrent DVT between participants treated with factor Xa inhibitors and participants treated with conventional anticoagulation for either three months (OR 0.50, 95% CI 0.22 to 1.15; 4 studies, 4917 participants) or more than three months (OR 0.86, 95% CI 0.63 to 1.17; 5 studies, 11,522 participants). No subgroup differences were indicated (test for subgroup differences: P = 0.23). As a limited number of studies reporting on this outcome provided separate data for participants with or without cancer, we were not able to undertake subgroup analysis on this characteristic. No subgroup effect was indicated when analysed by the three oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) (test for subgroup differences: P = 0.20, Analysis 5.2).

Fatal pulmonary embolism

Six studies (15,082 participants) reported fatal PE (AMPLIFY 2013; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; Hokusai-VTE 2013; ODIXa-DVT 2007). There was no clear difference in the rate of fatal PE between the two treatment groups. Meta-analysis showed that fatal PE occurred in 0.42% (33 events/7945 participants) in the factor Xa inhibitor group versus 0.32% (23 events/7137 participants) in the conventional anticoagulation group (OR 1.18, 95% CI 0.69 to 2.02; 6 studies, 15,082 participants; I^2 = 0%; moderate-certainty evidence; Analysis 3.3). We found no clear difference in the incidence of fatal PE between participants treated with factor Xa inhibitors and conventional anticoagulation when treatment was for three months (OR 1.68, 95% CI 0.36 to 7.94; 4 studies, 4917 participants) and for more than three months (OR 1.15, 95% CI 0.54 to 2.44; 2 studies, 10,165 participants). No subgroup differences were indicated (test for subgroup differences: P = 0.67). As a limited number of studies reporting on this outcome provided separate data for participants with or without cancer, we were not able to undertake subgroup analysis on this characteristic. No subgroup effect was indicated when analysed by the three oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) (test for subgroup differences: P = 0.36, Analysis 5.3).

Non-fatal pulmonary embolism

Seven studies (15,166 participants) reported non-fatal PE (AMPLIFY 2013; Botticelli DVT 2008; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; eTRIS 2016; Hokusai-VTE 2013; ODIXa-DVT 2007). The incidence was 1.00% (80 events/8001 participants) in the factor Xa inhibitor group versus 1.11% (80 events/7165 participants) in the conventional anticoagulation group (OR 0.93, 95% CI 0.68 to 1.27; 7 studies, 15,166 participants; I^2 = 0%; moderate-certainty evidence; Analysis 3.4). There was no clear difference in incidence of non-fatal PE between factor Xa inhibitors and conventional anticoagulation when treatment was for three months (OR 0.87, 95% CI 0.51 to 1.48; 5 studies, 5001 participants) and for more than three months (OR 0.96, 95% CI 0.65 to 1.43; 2 studies, 10,165 participants). No subgroup differences were indicated (test for subgroup differences: P = 0.77). As a limited number of studies reporting on this outcome provided separate data for participants with or without cancer, we were not able to undertake subgroup analysis on this characteristic. No subgroup effect was indicated when analysed by the three oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) (test for subgroup differences: P = 0.84, Analysis 5.4).

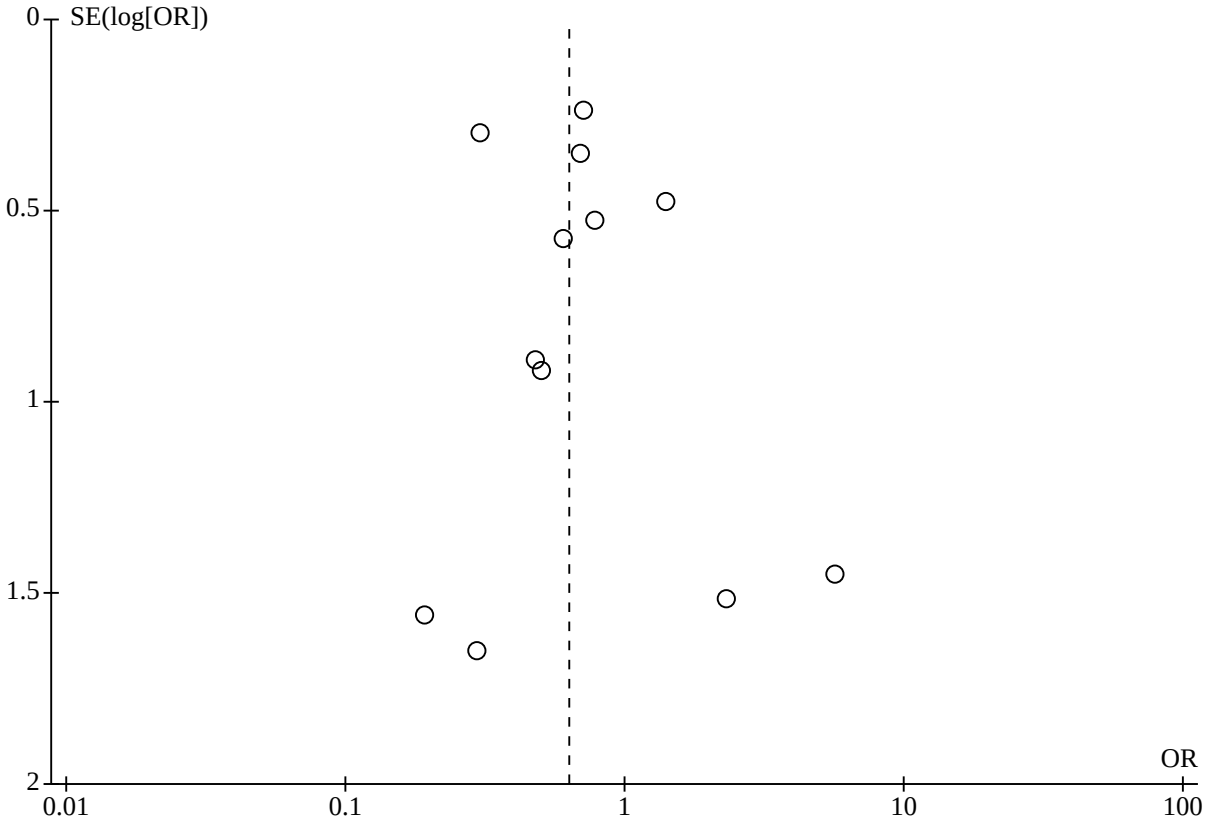
All-cause mortality

Nine studies (10,770 participants) reported all-cause mortality (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; Mokadem 2021; ODIXa-DVT 2007; PRAIS 2019). We did not include the EINSTEIN-PE 2012 as it was not possible to obtain the specific all-cause mortality data on participants with an index DVT. The AMPLIFY-J 2015, de Athayde 2019 and PRAIS 2019 studies had no events in either group and contributed no estimate in the forest plot. Meta-analysis showed no clear difference in the rate of all-cause mortality between the two treatment groups (OR 0.87, 95% CI 0.67 to 1.14; 9 studies, 10,770 participants; I^2 = 0%; moderate-certainty evidence; Analysis 3.5). The incidence was 2.12% (126 events/5834 participants) in the factor Xa inhibitor group and 2.35% (118 events/4936 participants) in the conventional anticoagulation group. Furthermore, there was no difference in the incidence of all-cause mortality between participants treated with factor Xa inhibitors and conventional anticoagulation when treatment was three months (OR 0.85, 95% CI 0.58 to 1.25; 4 studies, 5072 participants) or more than three months (OR 0.95, 95% CI 0.55 to 1.67; 5 studies, 5698 participants). No subgroup differences were indicated (test for subgroup differences: P = 0.75). As a limited number of studies reporting on this outcome provided separate data for participants with or without cancer, we were not able to undertake subgroup analysis on this characteristic. No subgroup effect was indicated when analysed by different oral factor Xa inhibitors (apixaban and rivaroxaban) (test for subgroup differences: P = 0.61, Analysis 5.5).

Major bleeding

We included 17 studies (18,066 participants) in the meta-analysis of major bleeding (AMPLIFY 2013; AMPLIFY-J 2015; Botticelli DVT 2008; Caravaggio 2020; de Athayde 2019; EINSTEIN-DVT dose 2008; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; eTRIS 2016; Farhan 2019; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2019; PRAIS 2019). Five studies reported zero events in both experimental and control groups and contributed no estimate to the pooled result (AMPLIFY-J 2015; de Athayde 2019; eTRIS 2016; J-EINSTEIN DVT and PE 2015; Ohmori 2019). The incidence was 1.04% (101 events/9536 participants) in the factor Xa inhibitor group and 1.68% (145 events/8530 participants) in the conventional anticoagulation group. This led to an OR of 0.63 (95% CI 0.45 to 0.89; 17 studies, 18,066 participants; I^2 = 18%; high-certainty evidence; Analysis 3.6), indicating that factor Xa inhibitors reduced the risk of major bleeding compared with conventional anticoagulation. We produced a funnel plot and found no indication of publication bias (Figure 5).

Figure 5. Funnel plot of oral factor Xa inhibitors versus conventional anticoagulants for major bleeding



When analysed according to treatment duration, no subgroup differences were indicated (test for subgroup differences: P = 0.48) between treatment for three months (OR 0.78, 95% CI 0.42 to 1.43; 5 studies, 5170 participants) or for more than three months (OR 0.60, 95% CI 0.39 to 0.91; 12 studies, 12,986 participants).

Additional analysis indicated a possible subgroup difference between people with cancer (OR 0.93, 95% CI 0.49 to 1.76; 3 studies, 1006 participants) and people without cancer (OR 0.30, 95% CI 0.17 to 0.52; 6 studies, 5795 participants) (test for subgroup differences: P = 0.009, Analysis 4.2). No subgroup effect was indicated when analysed by the three oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) (test for subgroup differences: P = 0.65, Analysis 5.6).

Post-thrombotic syndrome

The de Athayde 2019 study reported PTS as an outcome, and the results indicated that oral factor Xa inhibitor (rivaroxaban) had a lower rate of PTS events compared with warfarin. The incidence for rivaroxaban was 8.70% (4 events/46 participants) for both six months and 12 months; for warfarin, the incidence was 36.84% (14 events /38 participants) at six months, and 28.95% (11 events/38 participants) at 12 months. This led to an OR of 0.16 (95% CI 0.05 to 0.55; 1 study, 84 participants) and 0.23 (95% CI 0.08 to 0.46; 1 study, 84 participants; Analysis 3.7) at six months and 12 months, respectively.

Health-related quality of life

Sukovatykh 2017 used SF-36 scales (described above) to measure the quality of life of 65 participants. The factor Xa inhibitors group had a better score on the physical component of health (MD 5.55, 95% CI 1.18 to 9.92) and a similar score on the psychological component (MD 1.41, 95% CI -2.61 to 5.43) when compared with the warfarin group (Analysis 3.8; Analysis 3.9).

Sensitivity analyses

As planned, we excluded studies with a high risk of bias in sensitivity analysis (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5; Analysis 6.6). The rate of recurrent VTE (OR 0.89, 95% CI 0.70 to 1.13), recurrent DVT (OR 0.72, 95% CI 0.45 to 1.13), fatal PE (OR 1.73, 95% CI 0.81 to 3.69), non-fatal PE (OR 0.84, 95% CI 0.57 to 1.23) and all-cause mortality (OR 0.94, 95%CI 0.66 to 1.35) remained similar when excluding high risk studies. However, excluding these studies did alter the result for major bleeding to no difference between oral factor Xa inhibitors versus conventional anticoagulation (OR 0.76, 95% CI 0.55 to 1.05).

Oral direct thrombin inhibitor versus oral factor Xa inhibitor

Sukovatykh 2017 was the only study to compare an oral DTI with an oral factor Xa inhibitor, and the only outcome of interest reported was quality of life. Sukovatykh 2017 compared oral dabigatran to oral rivaroxaban for quality of life using SF-36 scales. The DTI group had a similar score on the physical component of health (MD 1.20, 95% CI -2.89 to 5.29; 1 study, 60 participants) and a higher score on the psychological component (MD 5.04, 95% CI 1.24 to 8.84; 1 study,

60 participants) compared to the factor Xa inhibitor group (Analysis 7.1; Analysis 7.2).

DISCUSSION

Summary of main results

We included an additional ten studies for this update, bringing the total to 21 included studies involving 30,895 participants. Compared with conventional anticoagulation, three studies investigated oral direct thrombin inhibitors (DTIs) (two dabigatran and one ximelagatran), 17 studies investigated oral factor Xa inhibitors (eight rivaroxaban, five apixaban and four edoxaban) and one study with three arms investigated both a DTI (dabigatran) and a factor Xa inhibitor (rivaroxaban).

Recurrent venous thromboembolism

Meta-analyses showed no clear difference between direct oral anticoagulants (DOACs) and conventional anticoagulation in the prevention of recurrent VTE during treatment. This is unsurprising as the incidence of recurrent events during treatment with vitamin K antagonists (VKAs) is low and often only occurs in people with an aggressive thrombotic tendency, such as people with metastatic malignancy.

The duration of treatment in the included studies varied, from three months (Botticelli DVT 2008; EINSTEIN-DVT dose 2008; eTRIS 2016; ODIXa-DVT 2007), four months (EINSTEIN-DVT 2010), six months (AMPLIFY 2013; AMPLIFY-J 2015; Caravaggio 2020; de Athayde 2019; Farhan 2019; J-EINSTEIN DVT and PE 2015; Mokadem 2021; PRAIS 2019; RE-COVER 2009; RE-COVER II 2014; Sukovatykh 2017; THRIVE 2005), six to 12 months (Hokusai VTE Cancer 2018), and 12 months (EINSTEIN-PE 2012; Hokusai-VTE 2013; Ohmori 2019). Our analyses showed little or no statistical heterogeneity amongst the included studies. We performed subgroup analyses by grouping studies where treatment was for three months only and for longer than three months. No differences were observed for oral factor Xa versus conventional anticoagulation. 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).

We did not detect any subgroup differences between DVT associated with cancer versus without cancer. A review by Kahale 2018 found that compared to low molecular weight heparin (LMWH), DOACs may reduce VTE but may increase risk of major bleeding in people with cancer. However, the Mulder 2020 review did not find a difference in these outcomes in cancer-associated venous thromboembolism (Mulder 2020).

Recurrent deep vein thrombosis

There is no clear difference between DOACs and conventional anticoagulation in the prevention of recurrent DVT.

Fatal pulmonary embolism

Meta-analyses showed no clear difference in the rate of fatal pulmonary embolism (PE) between DOACs and conventional anticoagulation, indicating that neither was more or less effective. This association was unaffected by the length of treatment. However, it is important to note that the confidence intervals (CIs) were wide for both DTIs and factor Xa inhibitors due to the small number of events overall.

Non-fatal pulmonary embolism

Meta-analyses also showed no clear difference in the rate of non-fatal PE between DOACs and conventional anticoagulation regardless of treatment duration, indicating that neither was more or less effective. However, it is important to note that the CIs were wide due to the small number of non-fatal PE events overall.

All-cause mortality

There is no clear difference in preventing all-cause mortality between the DOACs tested in this review (apixaban, rivaroxaban and ximelagatran) and conventional anticoagulants; no clear difference was observed between treatment durations of three months and longer. This result is unsurprising as current treatment with heparin and VKAs is associated with very low mortality.

Major bleeding

Results of our meta-analysis indicated that DOACs were associated with a reduction in major bleeding compared with conventional 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 the International Society on Thrombosis and Haemostasis (ISTH) (Schulman 2005), except for the de Athayde 2019 study, which did not report the definition. For factor Xa inhibitors compared with conventional anticoagulation, no subgroup difference was indicated by treatment duration, but there may be a difference between participants with cancer and those without. We cannot draw conclusions from these subgroup analyses as both were heavily dependent on one trial with a high risk of bias in selective reporting and missing data. In addition, research from observational studies showed that apixaban decreased risk of major and minor bleeding events compared with rivaroxaban in VTE patients (Aryal 2019; Ballestri 2023; Liu 2022), while the subgroup analysis based on randomised controlled trials (RCTs) included in this review did not show a difference.

Post-thrombotic syndrome

Only one small study comparing oral factor Xa inhibitor (rivaroxaban) with conventional anticoagulation measured post-thrombotic syndrome (PTS). The incidence was lower in the oral factor Xa inhibitor group versus the warfarin group; however, the PTS score was partially self-reported by participants, who were not blinded in this study. This prevents us from drawing any strong conclusions on this outcome.

Health-related quality of life

Only one small study measured participants' quality of life. It did not report baseline data so we could not conclude whether DOACs improved quality of life versus conventional anticoagulation. This was also the only study we found that compared a DTI (dabigatran) with a factor Xa inhibitor (rivaroxaban).

Overall completeness and applicability of evidence

This review assessed whether DOACs, such as DTIs and factor Xa inhibitors, reduced the rate of recurrent VTE, recurrent DVT, fatal PE, non-fatal PE, all-cause mortality, major bleeding and PTS, and whether DOACs improved quality of life in people with a DVT. Three

studies explored DTIs, 17 studies explored factor Xa inhibitors, and one explored both. All studies included similar study populations, with three focused on cancer-associated DVT. The trials analysed and reported all of the addressed outcomes, with PTS and health-related quality of life reported in only one study with a small sample size. 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.

We could not perform subgroup analyses according to history of VTE, age, pregnancy, major surgery requiring general or regional anaesthesia in the previous 12 weeks, recent period of immobility, and thrombophilia because of the lack of participant-level data. Additionally, the treatment effect may differ between DVT in unusual sites (e.g. upper limbs) and lower limbs, considering different clinical symptoms and risk (Ageno 2019; Cote 2017); however, almost all the participants from included studies had been diagnosed with DVT in lower limbs. Thus, we could not address this issue in this review. These analyses might be important to guide the clinical management of people with different risk factors for DVT.

In the subgroup analysis based on participants with cancer versus without cancer, most included trials for DOACs included only small numbers of participants with cancer, and likely included those with only lower-risk malignancies. Dedicated cancer-associated DVT trials have not been performed for DTIs, and results in this review relating to their use in cancer-associated thrombosis should therefore be interpreted with caution.

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. An update of the review on the effectiveness of oral DTIs and factor Xa inhibitors for the treatment of PE is ongoing (Li 2023).

We found no studies comparing:

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

While DOACs are more expensive than VKAs, these costs are offset by reduced bleeding and laboratory monitoring costs (Chen 2020). The UK's National Institute for Health and Care Excellence (NICE) conducted a recent cost-effectiveness analysis of DOACs versus conventional anticoagulation for the treatment of DVT and PE (NICE 2020). Within the DOACs, apixaban appeared to be the most cost-effective, both in people with a DVT and people with a PE. Rivaroxaban had the next most favourable effect on major bleeding and generated the second highest total quality-adjusted life years (QALYs). The cost of the two drugs was similar and the difference in total costs was mainly led by differences in the number of bleeding events.

Certainty of the evidence

We created summary of findings tables for both our main comparisons and reported recurrent VTE, recurrent DVT, fatal PE, non-fatal PE, all-cause mortality and major bleeding. We assessed the certainty of the evidence using GRADE criteria (Schünemann 2022).

Summary of findings 1 presented the result of oral DTIs versus conventional anticoagulation used for the treatment of DVT. We found moderate-certainty evidence suggesting that DTIs were not inferior to conventional anticoagulation for reducing recurrent VTE, recurrent DVT, fatal PE, non-fatal PE, and all-cause mortality when used for treating DVT. We downgraded the certainty by one level for all of these outcomes because of imprecision due to the low number of events. High-certainty evidence indicated that DTIs had a lower rate of major bleeding. This difference became unclear when we excluded the study on ximelagatran in sensitivity analysis. Ximelagatran was not approved and not used in practice.

Summary of findings 2 presented the result of oral factor Xa inhibitors versus conventional anticoagulation used for the treatment of DVT. We found moderate-certainty evidence indicating no clear difference between oral factor Xa inhibitors and conventional anticoagulation in preventing recurrent VTE, recurrent DVT, fatal PE, non-fatal PE and all-cause mortality. We downgraded the certainty by one level for all of these outcomes because of imprecision due to small sample size or the low number of events. High-certainty evidence indicated that oral factor Xa inhibitors had a lower rate of major bleeding.

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. Pairs of review authors independently performed study selection and data extraction in duplicate 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 2014). We performed data collection according to the process suggested by Cochrane. We also followed Cochrane processes as described by Higgins 2017 for assessing the risk of bias. Furthermore, we used the GRADE approach, which enabled us to rate the certainty of evidence systematically and interpret the data appropriately. For two of the included studies, RE-COVER 2009 and RE-COVER II 2014, we could only obtain data for DVT participants from a pooled analysis from Goldhaber 2016. We were able to obtain all outcomes, except all-cause mortality, from both trials. Evidence regarding all-cause mortality of DTIs versus control is therefore supported by only one study.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review of RCTs, now updated, to measure the efficacy and safety of oral anticoagulants in people with a DVT. We found 12 other systematic reviews that assessed the same oral anticoagulants but in people with a VTE (Antoniazzi 2014; Castellucci 2013; Di Minno 2015; Fox 2012; Gomez-

Outes 2014; Hirschl 2014; Kakkos 2014; Kang 2014; Loffredo 2015; Sardar 2013; Senoo 2017; Van der Huille 2014). Five reviews found similar results to this review: that DOACs are associated with less bleeding than conventional treatment (Antoniazzi 2014; Fox 2012; Gomez-Outes 2014; Hirschl 2014; Kakkos 2014; Loffredo 2015; Senoo 2017; Van der Huille 2014).

The review by Fox 2012 included eight of the 11 studies that we included in the 2015 version of this review. The Fox 2012 review did not include the remaining studies (AMPLIFY 2013; Hokusai-VTE 2013), but did not state the reasons for this in the review. 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 episodes (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. They excluded three as they were phase II trials (Botticelli DVT 2008; ODIXa-DVT 2007; THRIVE 2005), and one as it had not been published in a peer-reviewed journal at the time of the review (RE-COVER II 2014). Therefore, only five studies were included in the review (AMPLIFY 2013; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai-VTE 2013; RE-COVER 2009). Meta-analysis showed no difference between the two treatment groups in terms of recurrent VTE, fatal PE and all-cause mortality. However, the DOACs were associated with a 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 DOACs and conventional treatment regarding recurrent VTE and mortality (AMPLIFY 2013; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai-VTE 2013; RE-COVER 2009; RE-COVER II 2014). However, they reported 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 reviews by Gomez-Outes 2014 and Kang 2014 included the same six studies as Hirschl 2014. Gomez-Outes 2014 found no difference in the risk of recurrent VTE between the two treatment groups (RR 0.91, 95% CI 0.79 to 1.06) and DOACs were associated with reduced major bleeding (absolute risk difference -0.6%, 95% CI -1.0% to -0.3%). Kang 2014 reported that DOACs did not differ in the risk of mortality or recurrent VTE. However, an indirect comparison suggested that 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 from Kakkos 2014 also included these six studies on treatment for VTE and reached similar conclusions.

Di Minno 2015 focused on the treatment of unprovoked or provoked VTE and included five studies (EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai-VTE 2013; RE-COVER 2009; RE-COVER II 2014). This review found that DOACs and VKAs had equal efficacy in treating VTE.

The Loffredo 2015 review included seven studies (AMPLIFY 2013; EINSTEIN-DVT 2010; EINSTEIN-PE 2012; Hokusai-VTE 2013; RE-COVER 2009; RE-COVER II 2014; THRIVE 2005). The results suggested that DOACs for participants with acute VTE are not inferior to conventional therapy for recurrent VTE and all-cause mortality, and reduced major bleeding (RR 0.63, 95% CI 0.47 to 0.83). However, there might be an increased incidence of myocardial infarction.

Senoo 2017 focused on Japanese participants only and included three studies (AMPLIFY-J 2015; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015). This review found that DOACs had a decreased risk for all bleeding (RR 0.69, 95% CI 0.50 to 0.95), without any significant differences in recurrent VTE (RR 0.84, 95% CI 0.29 to 2.43).

The review by Antoniazzi 2014 included people with VTE and atrial fibrillation. The review was only available as an abstract report and included eight studies. Its 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 of VTE rather than treatment.

Several systematic reviews focused on cancer-associated VTE have been published in recent years, but these made no separate results for DVT available (Desai 2020; Kahale 2018; Li 2019; Mulder 2020; Yang 2019). The results differed slightly among these reviews, but all suggested a similar trend: that DOACs likely reduce recurrent VTE but may increase the risk of major bleeding in participants with cancer-associated VTE.

AUTHORS' CONCLUSIONS

Implications for practice

The current review suggests that direct oral anticoagulants (DOACs) may be superior to conventional therapy in terms of safety (major bleeding), and are probably equivalent in terms of efficacy (recurrent venous thromboembolism (VTE), recurrent deep vein thrombosis (DVT), fatal and non-fatal pulmonary embolism (PE) and mortality). The clear practical benefit of DOACs is the ease of use. This may provide clinical and economic benefits in the avoidance of the warfarin-loading phase of treatment (as shown in some of the studies), with its concomitant use of parenteral anticoagulants and frequent international normalised ratio (INR) testing. However, precautions are required with the use of DOACs. They are all, to some extent, renally excreted, and there is evidence of wide inter-individual variation in anticoagulant response.

Implications for research

There is evidence of wide inter-individual variation in anticoagulant effect from the fixed doses of DOACs currently prescribed. This may be of clinical importance, and further research is needed to investigate dosage adjustment for various subgroups, including people with: malignancy, DVT in unusual sites (e.g. upper limbs), travel-associated DVT, thrombophilic abnormality (e.g. anti-phospholipid syndrome), obesity or renal impairment. Further research is also needed to investigate any impact on the decision to use extended phase anticoagulation and interruption of procedures with DOAC use. Furthermore, future studies should directly compare one DOAC to another to determine which is most effective and safe, especially given that research from observational studies has shown that apixaban decreased risk of major bleeding events compared with rivaroxaban in people with VTE. For outcomes, studies rarely analysed quality of life and post-thrombotic syndrome (PTS). Future studies should consider recording and reporting these important outcomes. Finally, as we

noted above, all-cause mortality has yet to be estimated for DVT treated with dabigatran, so more research is needed in this area.

ACKNOWLEDGEMENTS

We thank Lindsay Robertson, James McCaslin and colleagues for their contribution to previous versions of this review. We thank Cathryn Broderick and other Cochrane Vascular editors for their assistance and advice in completing this review. We thank Candida Fenton for searching the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases, the World Health Organization International Clinical Trials Registry Platform and the ClinicalTrials.gov trials registers. We thank Shitong Xie for helping with the input for economic comment. We would also like to thank Dr Vahid Ashoorion for helping confirm study eligibility and verifying data within a Persian publication. The review authors and the Cochrane Vascular editorial base are grateful to the following peer reviewers for their time and comments: Scott M Stevens MD, Professor of Medicine, Intermountain Healthcare and the University of Utah; Rhys Morris, Cardiff and Vale University Health Board, Cardiff, Wales, UK; Ashok Pai MD, Department of Hematology/ Oncology, Kaiser Permanente Oakland Medical Center, Oakland, California; Davide Imberti, Head of Haemostasis and Thrombosis Centre Internal Medicine Department Piacenza Hospital Italy; Brian Duncan.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

AMPLIFY 2013

Study characteristics	
Methods	**Study design:** randomised double-blind trial
	Duration of study: 6 months
Participants	**Setting:** hospital
	Country: multinational
	Number of participants: 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

AMPLIFY 2013 *(Continued)*

	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 IV 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 CrCL < 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. **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
Funding	Quote: "Supported by Pfizer and Bristol-Myers Squibb." Comment: Pfizer Inc and Bristol-Myers Squibb were the pharmaceutical companies that developed apixaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Dr. Agnelli reports receiving personal fees from Boehringer Ingelheim, Sanofi, Daiichi-Sankyo, and Bayer. Dr. Buller reports receiving grant support from Bayer, Sanofi, and Daiichi-Sankyo. Dr. Cohen reports receiving payment for board membership from Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, Pfizer, Portola Pharmaceuticals, and Sanofi, and consulting fees, lecture fees, travel support, and payment for the development of educational presentations from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Glaxo-SmithKline, Johnson & Johnson, Mitsubishi Pharma, Pfizer, Portola Pharmaceuticals, Sanofi, Schering-Plough, and Takeda. Drs. Curto, Johnson, Masiukiewicz, Pak, and Thompson report being employees of Pfizer. Dr. Gallus reports receiving consulting fees from Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, Bayer, and Boehringer Ingelheim. Dr. Raskob reports receiving consulting fees and travel support from Bayer, Janssen Pharmaceuticals, Daiichi-Sankyo, and Quintiles. Dr. Weitz reports receiving consulting fees from Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Pfizer, Bristol-Myers Squibb, Merck, Janssen Pharmaceuticals, and Portola Pharmaceuticals. No other potential conflict of interest relevant to this article was reported."
Notes	None

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 voice-response system". Comment: study judged at low risk of bias.

AMPLIFY 2013 *(Continued)*

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 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. 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 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." Comment: study judged at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	A number of randomised participants were inappropriately excluded from the ITT analysis. Additionally, 144/377 of apixaban participants and 142/413 participants given conventional treatment were classified as discontinuing for "other reasons", with no given explanations. Comment: study judged at high risk of attrition bias.
Selective reporting (reporting bias)	High risk	Comment: study protocol was available. Minor bleeding was a pre-defined secondary outcome but the data on this outcome were not reported in the paper. In addition, the trial analysed non-inferiority using an ITT analysis. When compared with the per-protocol analysis, ITT favoured the finding of non-inferior results. This may have skewed the result in favour of an increased efficacy of apixaban. Therefore, we deemed the risk of reporting bias to be high.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

AMPLIFY-J 2015

Study characteristics	
Methods	**Study design:** a randomised, active-controlled, open-label study **Duration of study:** 5.5 months
Participants	**Setting:** hospital **Country:** Japan **Number of participants:** 80; apixaban 40, UFH/warfarin 40 **Age, mean (SD) years:** apixaban 64.3 (13.4) years, UFH/warfarin 66.1 (17.7) years **Sex:** apixaban 22 M/18 F, UFH/warfarin 17 M/23 F

AMPLIFY-J 2015 *(Continued)*

	Inclusion criteria: Japanese patients, ≥ 20 years of age and who had objectively confirmed, symptomatic proximal DVT or PE (with or without DVT). Proximal DVT was defined as thrombosis involving at least the popliteal vein or a more proximal vein. **Exclusion criteria:** participants were excluded if they had thrombectomy or used fibrinolytic agent, had active bleeding, a high risk of bleeding, or other contraindications to treatment with UFH and warfarin; if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, or treatment with aspirin > 165 mg daily. Other key exclusion criteria were > 2 doses of fondaparinux, or continuous infusion of UFH > 36 hours, and > 2 doses of oral VKA before first administration of the study drug. Additional exclusion criteria were haemoglobin < 9 g/dL, platelet count < 100,000/mm^3, and CrCL < 25 mL/min.
Interventions	**Intervention 1:** received 10 mg twice daily apixaban for 7 days as an initial therapy, followed by 5 mg twice daily apixaban for 23 weeks as long-term therapy. **Intervention 2:** given a continuous IV infusion of UFH to maintain the aPTT in the range 1.5–2.5-fold the control value. Warfarin was also concomitantly administered. UFH was continuously given until the effect of warfarin was stabilised; after which, participants were given warfarin alone. UFH was given for at least 5 days consecutively and was discontinued at once if the PT-INR was ≥ 1.5. If PT-INR exceeded 2.0 within the initial 5 days of administration, UFH could be discontinued based on the investigator's judgement. The warfarin dose was adjusted to maintain INR between 1.5 and 2.5 in accordance with Japan PE/DVT treatment guidelines. Treatment was administered for 24 weeks (5.5 months). **Follow-up:** 0, 2, 12, 24 and 28 weeks
Outcomes	**Primary:** the incidence of the adjudicated composite of ISTH-defined major bleeding and CRNM bleeding during the treatment period **Secondary:** the incidence of the adjudicated ISTH-defined major bleeding events and all bleeding events (ISTH major, CRNM and minor) during the treatment period, composite endpoint of adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death during 24 weeks, thrombotic burden deterioration at 2, 12 and 24 weeks.
Funding	Quote: "This study was funded by Pfizer Inc and Bristol-Myers Squibb." Comment: Pfizer Inc and Bristol-Myers Squibb were the pharmaceutical companies that developed apixaban, and the results of the primary outcome favoured the apixaban group. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "M. Nakamura has received remuneration from Daiichi Sankyo, Bayer Yakuhin. M. Nishikawa has received remuneration and research funds from Daiichi Sankyo. I. Komuro has received remuneration from Daiichi Sankyo, Nippon Boehringer Ingelheim, and scholarship funds from Astellas Pharma, Daiichi Sankyo, Takeda Pharmaceutical, Nippon Boehringer Ingelheim, Bristol-Myers Squibb. I. Kitajima has received remuneration from Nippon Boehringer Ingelheim. H.O. has received remuneration from AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim Japan, Bristol-Myers Squibb, Daiichi Sankyo, Mitsubishi Tanabe Pharma, MSD, Pfizer Japan, Sanofi, Takeda Pharmaceutical and Teijin Pharma, and has received research funds from Bayer Yakuhin, Daiichi Sankyo and Novartis Pharma, and has received scholarship funds from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kowa, MSD, Otsuka Pharmaceutical, Pfizer Japan, Sanofi, Shionogi and Takeda Pharmaceutical. Y.U., T.Y., H.M., R.Y. have no conflict of interest."
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was centrally performed through an interactive online system." Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "An interactive voice response system was used for randomisation".

AMPLIFY-J 2015 *(Continued)*

		Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: blinding of participants and personnel was not conducted. However, review authors judged that the lack of blinding was unlikely to have affected the outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All outcome events were adjudicated by an event adjudication committee in a blinded manner so as to maintain validity of assessment." Comment: blinding was performed adequately, study judged at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the apixaban group: 3 did not complete the overall trial period (2 were no longer willing to participate in study, 1 had other reason); in the UFH/warfarin group: 2 did not complete the overall trial period (1 withdrawn from the study prior to the initiation of study treatment, 1 had other reason). Comment: fewer than 20% of participants dropped out or withdrew, and the study author performed ITT analysis; study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Botticelli DVT 2008

Study characteristics	
Methods	**Study design:** veiled randomised, parallel-group, dose-ranging study **Duration of study:** 12 weeks
Participants	**Setting:** hospital **Country:** the Netherlands **Number of participants:** 520; apixaban 5 mg 130, 10 mg 134, 10 mg 128, 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 CrCL < 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 contraindicating treatment with LMWH, fondaparinux or VKA; systolic BP > 200 mm Hg or diastolic BP > 110 mm Hg; use of acetylsalicylic acid (aspirin) > 165 mg/day; child-bearing potential without effective contraception; pregnancy; breastfeeding and any other contraindication list-

Botticelli DVT 2008 *(Continued)*

	ed 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 CRNM 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. CRNM 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
Funding	Quote: "This study was sponsored by Bristol-Myers Squibb and Pfizer Inc." Comment: Pfizer Inc and Bristol-Myers Squibb were the pharmaceutical companies that developed apixaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Medical writing assistance was provided by Jaya Kolipaka of PPSI, a division of PAREXEL Inc., and funded by Bristol-Myers Squibb and Pfizer Inc."
Notes	None

Risk of bias

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 bias.
Allocation concealment (selection bias)	Low risk	Quote: "An interactive voice response system was used for randomisation". Comment: study judged at low risk of 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 SC 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. Study judged at low risk of performance bias.
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.

Botticelli DVT 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Caravaggio 2020

Study characteristics	
Methods	**Study design:** multinational, randomised, controlled, investigator initiated, open-label, non-inferiority trial **Duration of study:** 6 months
Participants	**Setting:** multicentre **Country:** multinational (119 centres in 11 countries: Belgium, France, Germany, Israel, Italy, Poland, Portugal, Spain, the Netherlands, United Kingdom, United States of America) **Number of participants:** 1155; apixaban 576, dalteparin 579 **Age, mean (SD) years:** apixaban 67.2 (11.3) years, dalteparin 67.2 (10.9) years **Sex:** apixaban 292 M/284 F, dalteparin 276 M/303 F **Inclusion criteria:** consecutive adults with cancer who had a newly diagnosed symptomatic or incidental proximal lower-limb DVT or PE were eligible to participate in the trial. People with confirmed cancer other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumour, known intracerebral metastases or acute leukaemia were eligible to participate in the trial. **Exclusion criteria:** patients' clinical characteristics, issues related to anticoagulant treatment, bleeding risk and standard issues from clinical trials of anticoagulant agents.
Interventions	**Intervention 1:** apixaban was given orally at a dose of 10 mg twice daily for the first 7 days and 5 mg twice daily thereafter. Treatment was administered for 6 months. **Intervention 2:** dalteparin was given subcutaneously at a dose of 200 IU/kg of body weight once daily for the first month, after which the dose was reduced to 150 IU/kg daily. The maximum daily dose allowed for dalteparin was 18,000 IU. Treatment was administered for 6 months. **Follow-up:** trial visits were scheduled at enrolment and at 4 weeks, 3 months, 6 months and 7 months after randomisation.
Outcomes	**Primary:** recurrent VTE, recurrent DVT, recurrent PE, fatal PE, major bleeding, major gastrointestinal bleeding, major nongastrointestinal bleeding **Secondary:** recurrent VTE or major bleeding, CRNM bleeding, death from any cause, event-free survival
Funding	Quote: "Supported by the Bristol-Myers Squibb–Pfizer Alliance." Comment: the study was supported by the Bristol-Myers Squibb–Pfizer Alliance, the pharmaceutical companies that developed apixaban and dalteparin, respectively, and the results of primary outcome

Caravaggio 2020 *(Continued)*

	supported the non-inferiority hypothesis of apixaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Dr. Agnelli reports receiving lecture fees from Pfizer and Bayer Healthcare and serving as chair of a registry for Daiichi Sankyo; Dr. Becattini, receiving lecture fees and consulting fees from Bayer Healthcare, Bristol-Myers Squibb, and Daiichi Sankyo; Dr. Meyer, receiving grant support and travel support from Leo Pharma, Bristol-Myers Squibb–Pfizer, Stago, and Bayer Healthcare; Dr. Muñoz, receiving grant support, consulting fees, lecture fees, advisory board fees, and travel support from Sanofi and Celgene, lecture fees and advisory board fees from AstraZeneca, Servier, Bristol-Myers Squibb–Pfizer, Daiichi Sankyo, Bayer, and Merck Sharp & Dohme, lecture fees, advisory board fees, and travel support from Roche, grant support, lecture fees, and advisory board fees from Leo Pharma, advisory".
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was centrally performed through an interactive online system". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centrally performed through an interactive online system". Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: blinding of participants and personnel was not conducted. However, review authors judged that the lack of blinding was unlikely to have affected the outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded adjudication of the outcomes" Comment: blinding was performed adequately, study judged at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the apixaban group: 177 did not complete the overall trial period (137 died, 12 were lost to follow-up, 28 had other reason); in the dalteparin group: 197 did not complete the overall trial period (149 died, 8 were lost to follow-up, 40 had other reason). Comment: fewer than 20% of participants dropped out or withdrew, and the study author performed ITT analysis; study judged at low risk of attrition bias.
Selective reporting (reporting bias)	High risk	Comment: study protocol was available. Quality of life was a pre-defined secondary outcome but the data on this outcome were not reported in the paper. In addition, it was stated that a "significant interaction was noted between age subgroups and treatment for recurrent venous thromboembolism", but no results were found in the paper and appendix. Therefore the risk of reporting bias was deemed to be high.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

de Athayde 2019

Study characteristics	
Methods	**Study design:** a prospective, randomised, consecutive, blind cohort study **Duration of study:** 6 months
Participants	**Setting:** hospital **Country:** Brazil **Number of participants:** 84 (88 randomised but 4 were excluded with diagnosis of cancer); rivaroxaban 46, warfarin 38 **Age, mean (SD) years:** rivaroxaban 54.9 (3.1) years, warfarin 55.6 (2.3) years **Sex:** rivaroxaban 20 M/26 F, warfarin 21 M/17 F **Inclusion criteria:** people treated for acute iliofemoral or femoropopliteal DVT of a lower limb at the Division of Vascular and Endovascular Surgery, Hospital do Servidor Público Estadual, Sao Paulo, Brazil, between March 2016 and July 2018. **Exclusion criteria:** the pre-randomisation exclusion criteria were pregnancy, age < 18 years or > 80 years, chronic renal failure, chronic hepatic failure, inferior vena cava thrombosis, contraindication for any type of anticoagulation, previous DVT on the ipsilateral affected limb, any type of active cancer and refusing to participate in the study. The post-randomisation exclusion criteria were pre-defined before the start of the study and were defined as several haemorrhagic complications that required the discontinuation of anticoagulation, death after < 30 days, allergic reaction to any anticoagulant, a diagnosis of active cancer during follow-up, loss to follow-up, difficulty in achieving proper anticoagulation owing to patient non-adherence to the treatment protocol and incomplete data.
Interventions	All participants received initial anticoagulation with subcutaneous enoxaparin (1 mg/kg/dose) every 12 hours (12/12 hours) or intravenous unfractionated heparin (IUH; loading dose 80 UI/kg, and 18 UI/kg/h) for at least 48 to 72 hours. **Intervention 1:** after the initial admission, participants received oral rivaroxaban, with a loading dose of 15 mg every 12 hours for 21 days after the initial dose and 20 mg/day for 6 months. **Intervention 2:** participants received oral warfarin, sufficient to maintain an INR of 2 to 3 for 6 months **Follow-up:** all participants were followed up with outpatient visits at 1, 3, 6 and 12 months after discharge.
Outcomes	**Primary:** DUS-detected recanalisation rates; the occurrence of PTS (a diagnosis of PTS was made with the Villalta scale. Each of the scale's components (5 symptoms and 6 signs) were rated on a 4-point severity scale, and the points were summed to produce a total score. A score > 4 indicated PTS. The 5 symptoms (pain, cramps, heaviness, pruritus and paraesthesia) were assessed by patient self-report, and the 6 signs (oedema, skin induration, hyperpigmentation, venous ectasia, redness and pain during calf compression) were evaluated by a clinician.) **Secondary:** the prevalence of PE, death and complications of treatment
Funding	Quote: "This research received no specific funding."
Declarations of interest	Quote: "The authors declare that they have no conflicts of interest."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include information for 4 participants who were excluded during follow-up with diagnosis of cancer.

de Athayde 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization protocol was performed by a computer-generated program." Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization protocol was performed by a computer-generated program." Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: no information Comment: treatments were two oral drugs with control group being kept in the hospital on SC enoxaparin or IUH until their INR was 2 to 3. So it was not possible to blind participants or personnel. The subjective and self-reported outcome PTS was likely to be influenced by the lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Data assessment by a physician blinded to the type of drug therapy." Comment: even though the data-assessment physician was blinded, the PTS score included some self-reported domains (such as pain, cramps, heaviness, pruritus and paraesthesia) by participants who were not blinded. These domains may be influenced by the lack of blinding for participants and personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four participants were excluded from the study during follow-up. Comment: fewer than 20% of participants dropped out or withdrew; study judged at low risk of attrition bias.
Selective reporting (reporting bias)	High risk	Commen: complications of treatment was a pre-defined secondary outcome but the data on this outcome were not reported in the paper. Study judged at high risk of reporting bias.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

EINSTEIN-DVT 2010

Study characteristics	
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 **Number of participants:** 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

EINSTEIN-DVT 2010 *(Continued)*

	Inclusion criteria: people of legal age for consent with 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 for 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 SC 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 ≥ 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 CNRM 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.
Funding	Quote: "Funded by Bayer Schering Pharma and Ortho-McNeil." Comment: Bayer HealthCare was the pharmaceutical company that developed rivaroxaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "L Bamber, AWA Lensing and MY Wang are employees of Bayer HealthCare AG. MH Prins has received honoraria from Bayer Pharma AG. C Ciniglio is an employee of Janssen Global Services, LLC, and owns stocks and shares in Janssen. R Bauersachs has received honoraria for lectures or consultancies from Novartis, LEO, Bayer Pharma AG, Boehringer Ingelheim and Bristol-Myers Squibb. SJ Cano was supported in part through a grant from Bayer Pharma AG and has received honoraria for lectures or consultancies from Novartis, PMI International, Eisai, Pfizer and Merck/ - Serono."
Notes	None

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 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 bias.
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.

EINSTEIN-DVT 2010 *(Continued)*

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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: the study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

EINSTEIN-DVT dose 2008

Study characteristics	
Methods	**Study design:** randomised dose-ranging, phase II, double-blind study **Duration of study:** 84 days
Participants	**Setting:** hospital **Country:** the Netherlands **Number of participants:** 543; rivaroxaban 20 mg 136, 30 mg 134, 40 mg 136, LMWH/VKA 137 **Age, mean (range) years:** rivaroxaban 20 mg 58 (22 to 87) years, 30 mg 57 (18 to 89) years, 30 mg 60 (22 to 94) years, LMWH/VKA 57 (21 to 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 BP > 200 mm Hg or diastolic BP > 110 mm Hg); CrCL < 30 mL/minute; impaired liver function (ALT > 2 x the ULN); 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 SC once daily) or enoxaparin (1.5 mg/kg SC once daily, or 1.0 mg/kg SC 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.

EINSTEIN-DVT dose 2008 *(Continued)*

	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
Funding	Quote: "This work was sponsored by Bayer HealthCare. The Executive Committee and Study Management and Coordination Committee (including 2 non-voting representatives of the sponsor) had final responsibility for the study design, protocol, statistical analysis plan, study oversight, verification of data, and data analyses. The data were gathered and maintained by the sponsor." Comment: Bayer HealthCare was the pharmaceutical company that developed rivaroxaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "A.W.A.L. and F.M. are employees of Bayer HealthCare, and F.M. owns stocks in the company. The remaining authors (except A.S.) were members of the Einstein Executive Committee and received an honorarium from Bayer HealthCare for their involvement in this committee. A.S. is an employee of International Clinical Trial Organization and Management (ICTOM), which received consultancy fees from Bayer HealthCare for the coordination and management of the study."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for one participant who was not treated as planned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised, via an interactive voice response system". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised, via an interactive voice response system". Comment: study judged at low risk of 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 SC 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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: the study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way.

EINSTEIN-DVT dose 2008 *(Continued)*

Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

EINSTEIN-PE 2012

Study characteristics	
Methods	**Study design:** randomised, open-label, event-driven, non-inferiority trial **Duration of study:** 12 months
Participants	**Setting:** hospital **Country:** 38 countries **Number of participants:** 4832 (4833 randomised but 1 was excluded because of invalid informed consent); 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 aged 18 or older who had 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 CrCL < 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 BP > 180 mm Hg or a diastolic BP > 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 ≥ 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 CRNM bleeding. **Secondary:** major bleeding, death from any cause, vascular events (acute coronary syndrome, ischaemic stroke, transient ischaemic attack or systemic embolism) and net clinical benefit (defined as a composite of the primary efficacy outcome and major bleeding, as assessed in the ITT population).
Funding	Quote: "Supported by Bayer HealthCare and Janssen Pharmaceuticals." Comment: the study was funded by Bayer HealthCare, the pharmaceutical company that developed rivaroxaban. It is possible that this may have influenced the timeframe of reported safety outcomes.

EINSTEIN-PE 2012 *(Continued)*

Declarations of interest	Disclosure forms provided by the authors are available at: www.nejm.org/doi/suppl/10.1056/NEJMoa1113572/suppl_file/nejmoa1113572_disclosures.pdf
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include information for participants who were excluded because of invalid informed consent.

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 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 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 assignments 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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: the study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

eTRIS 2016

Study characteristics

Methods	**Study design:** a randomised, open-label, parallel-group, active-control, multicenter trial **Duration of study:** 12 weeks
Participants	**Setting:** multicentre **Country:** USA **Number of participants:** 84 (85 people randomised but 1 who did not receive intervention as planned was excluded); edoxaban 56, LMWH/warfarin 28

eTRIS 2016 *(Continued)*

	Age, mean (SD) years: edoxaban 55.6 (14.1) years, LMWH/warfarin 53.1 (12.0) years **Sex:** edoxaban 41 M/15 F, LMWH/warfarin 21 M/7 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 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; calculated significant liver disease; people 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 BP > 170 mm Hg or diastolic BP > 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; people 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; people in whom MRI would be contraindicated (e.g. those with metal implants) or for whom the use of a gadolinium-based contrast agent such as gadofosveset trisodium (Ablavar) would be contraindicated; individual has previously entered this study or another edoxaban study.
Interventions	**Intervention 1:** edoxaban 90 mg once daily for 10 days (± 2 days) followed by 60 mg once daily for approximately 90 days. After randomisation, participants assigned to edoxaban monotherapy were stratified by need for dose reduction (body weight ≤ 60 kg or CrCL between 30 mL/min and 50 mL/min). Participants stratified to the dose reduction arm received 45 mg once daily for 10 days followed by 30 mg once daily for a total of approximately 90 days. The study protocol allowed for concomitant aspirin use up to 100 mg daily. **Intervention 2:** SC enoxaparin (1 mg/kg twice daily or 1.5 mg/kg once daily) or IV UFH was administered as soon as possible after randomisation for at least 5 days. Open-label warfarin was started approximately at the same time as enoxaparin or UFH. As soon as an INR ≥ 2 was achieved on two consecutive days or a single INR > 3 was achieved, parenteral anticoagulation was stopped, and warfarin was continued to maintain the INR target range of 2.0–3.0. **Follow-up:** post-randomisation Day 10 ± 2, Day 14–21, Day 45 ± 4, Day 90 ± 7, and Day 120 ± 7 (30 days post-study drug completion).
Outcomes	**Primary:** relative change in magnetic resonance venogram-quantified thrombus volume, and major or CRNM bleeding **Secondary:** recurrent VTE (defined as a composite of adjudicated recurrent DVT, PE, or VTE-related death), and change from baseline to Day 14–21 in the presence or absence of thrombus by venous segment as detected by MRV; non-fatal PE
Funding	**Quote:** "The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: research grant from Daiichi Sankyo." Comment: Daiichi-Sankyo was the pharmaceutical company that developed edoxaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	**Quote:** "Dr Piazza receives research grant support from Daiichi Sankyo, EKOS, a BTG International Group company, Bristol Myers Squibb, and Janssen. Dr Mani receives consulting fees from Tursiop Inc. and research grant support from Novartis AG and Daiichi Sankyo. Dr Goldhaber receives research

eTRIS 2016 *(Continued)*

	grant support from Daiichi Sankyo, EKOS, a BTG International Group company, Bristol Myers Squibb, and Janssen. Drs Grosso, Mercuri, Lanz, Hsu, and Chinigo and Mr Schussler receive salary from Daiichi Sankyo. Drs Ritchie, Nadar, Cannon, Pullman, Concha, Schul, and Fayad receive research grant support from Daiichi Sankyo."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for participants who did not receive interventions as planned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from personal communication with the author: "centralized computer generated randomisation scheme". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized with a web-based system in a 2:1 allocation ratio." Quote from personal communication with the author indicated that participants were blinded appropriately. Comment: study judged at low risk of 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	Low risk	Comment: all index DVT and all recurrent DVT, bleeding, major adverse cardiac events, death, and hepatic events were evaluated via a centralised, blinded adjudication process. All bleeding events were adjudicated by a Clinical Endpoints Committee blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 6/28 and 6/56 lost from control and experimental groups, respectively. Reasons differed, with 3/28 in control group with unclear 'other' reasons.
Selective reporting (reporting bias)	High risk	Comment: authors planned to collect the number of participants with MACE. However, the authors failed to report any information in the full text. Thus, we judged this as high risk of bias.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Farhan 2019

Study characteristics

Methods	**Study design:** open-label, randomised controlled study **Duration of study:** 6 months
Participants	**Setting:** hospital **Country:** Pakistan

Farhan 2019 *(Continued)*

	Number of participants: 151 (183 randomised but 32 were lost to follow-up); rivaroxaban 76, warfarin 75 **Age, mean (SD) years:** rivaroxaban 37.1 (10.4) years, warfarin 32.9 (12.7) years **Sex:** rivaroxaban 44 M/32F, warfarin 22 M/53 F **Inclusion criteria:** people of both genders between 18 and 60 years of age, with DVT confirmed on DUS, were included in the study after written informed consent was obtained. **Exclusion criteria:** people with a previous history of DVT or post-phlebitis syndrome were excluded. People with advanced liver disease (those with ascites, varices, portal hypertension and bilirubin of 2 mg/dL or more), or liver disease with abnormal liver synthetic function (baseline PT > 6 seconds and albumin levels < 2.5 mg/dL), people with renal disease with a creatinine > 3 mg/dL or GFR < 30 mL/min, people with underlying malignancy, those with a platelets count < 50,000/µL, pregnant women and those with a positive thrombophilia screen
Interventions	**Intervention 1:** participants received oral rivaroxaban (xceptR) at doses of 15 mg twice daily for 3 weeks followed by 20 mg once daily for 6 months **Intervention 2:** participants received conventional heparin 7500 IU SC 4 times daily for 3 to 5 days along with warfarin 10 mg once daily for 2 days followed by warfarin 5 mg once daily for 6 months **Follow-up:** participants were followed for 6 months at 3-weekly intervals
Outcomes	**Primary:** vessel patency as determined by Doppler and duplex ultrasound at the end of 3 and 6 months. Parameters determining vessel patency included clot lysis and present or absence of blood flow. **Secondary:** any major or minor bleeding
Funding	Not reported
Declarations of interest	Quote: "No author has declared any sort of financial or other kind of support from anybody."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for 32 participants who were lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised into two groups by the android mobile software statistics and sample size version 10". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised into two groups by the android mobile software statistics and sample size version 10". Comment: the method used was unlikely to induce bias on the final observed effect.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: blinding of participants and personnel was not conducted. The outcome is major bleeding. Review authors judged that the lack of blinding was unlikely to have affected the outcome.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Only the investigator performing Doppler/duplex ultrasound was blinded."

Farhan 2019 *(Continued)*

All outcomes		Comment: the outcome measurement was not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	In the rivaroxaban group, 12 participants were lost to follow-up; in the warfarin group, 20 were lost to follow-up. Comment: more than 20% of participants dropped out or withdrew; study judged at high risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Hokusai VTE Cancer 2018

Study characteristics	
Methods	**Study design:** a multinational, prospective, randomised, open-label, blinded endpoint, non-inferiority study **Duration of study:** 6 to 12 months
Participants	**Setting:** multicentre **Country:** multinational (114 centres in 13 countries: Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, New Zealand, Spain, United States) **Number of participants:** 1046; edoxaban 522, dalteparin 524 **Age, mean (SD) years:** edoxaban 64.3 (11.0) years, dalteparin 63.7 (11.7) years **Sex:** edoxaban 277 M/245 F, dalteparin 263 M/261 F **Inclusion criteria:** adults with cancer were eligible for inclusion in the trial if they had acute symptomatic or incidentally detected DVT involving the popliteal, femoral or iliac vein or the inferior vena cava; acute symptomatic PE that was confirmed by means of diagnostic imaging; or incidentally detected PE involving segmental or more proximal pulmonary arteries. **Exclusion criteria:** thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE; more than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, UFH, and fondaparinux per local labelling), oral direct anticoagulants or VKA prior to randomisation to treat the current (index) episode; treatment with therapeutic doses of an anticoagulant including dalteparin for an indication other than VTE prior to randomisation; active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban; an ECOG Performance Status of 3 or 4 at the time of randomisation; calculated CrCL < 30 mL/min; history of heparin associated thrombocytopenia; acute hepatitis, chronic active hepatitis, liver cirrhosis; hepatocellular injury with concurrent transaminase (ALT/AST > 3 x ULN) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation; life expectancy < 3 months; platelet count < 50,000/mL; uncontrolled hypertension as judged by the investigator (e.g. systolic BP > 170 mm Hg or diastolic BP > 100 mm Hg despite antihypertensive treatment); women of childbearing potential without proper contraceptive measures, and women who are pregnant or breastfeeding.
Interventions	**Intervention 1:** edoxaban was administered orally at a fixed dose of 60 mg once daily, with or without food. It was administered at a lower dose (30 mg once daily) in participants with a CrCL of 30 to 50 mL/min or a body weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors. Treatment was administered for 6 to 12 months, median duration was 7 months.

Hokusai VTE Cancer 2018 *(Continued)*

	Intervention 2: dalteparin was given SC at a dose of 200 IU/kg of body weight once daily for 30 days, with a maximum daily dose of 18,000 IU. Thereafter, dalteparin was given at a dose of 150 IU/kg once daily. If the platelet count declined to less than 100,000 per µL during treatment, the dose of dalteparin was temporarily reduced. Treatment was administered for 6 to 12 months, median duration was 6 months. **Follow-up:** participants underwent assessment, in the clinic or by telephone, on day 31 after randomisation and at months 3, 6, 9 and 12.
Outcomes	**Primary:** a composite of recurrent VTE or major bleeding; death **Secondary:** recurrent VTE; major bleeding; CRNM bleeding; major + CRNM bleeding; event-free survival, VTE-related death, mortality from all causes, recurrent DVT, recurrent PE
Funding	Quote: "Funded by Daiichi Sankyo." Comment: this study was funded by Daiichi Sankyo, the pharmaceutical company that developed edoxaban, and the result of the primary outcome supported the non-inferiority hypothesis of edoxaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Disclosure forms provided by the authors are available at: www.nejm.org/doi/suppl/10.1056/NEJMoa1711948/suppl_file/nejmoa1711948_disclosures.pdf
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with the use of an interactive Web-based system". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with the use of an interactive Web-based system". Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: blinding of participants and personnel was not conducted. However, review authors judged that the lack of blinding was unlikely to have affected the objective outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All events were adjudicated by a committee whose members were unaware of the treatment assignments." Comment: blinding was performed adequately, study judged at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the edoxaban group: 16 did not complete the overall trial period (3 did not receive the assigned treatment, 10 withdrew consent, 3 were lost to follow-up); in the dalteparin group: 18 did not complete the overall trial period (1 did not receive the assigned treatment, 12 withdrew consent, 5 were lost to follow-up). Comment: fewer than 20% of participants dropped out or withdrew, and the study author performed intention-to-treat analysis. Study judged at low risk of attrition bias.

Hokusai VTE Cancer 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Hokusai-VTE 2013

Study characteristics	
Methods	**Study design:** randomised, double-blind, non-inferiority study **Duration of study:** 12 months
Participants	**Setting:** multicentre **Country:** multinational **Number of participants:** 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 CrCL < 30 mL/minute.
Interventions	**Intervention 1:** oral edoxaban 60 mg once daily or 30 mg once daily in people with a CrCL 30 to 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 an 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 CRNM) **Secondary:** none
Funding	Quote: "Funded by Daiichi-Sankyo." Comment: the study was funded by Daiichi-Sankyo, the pharmaceutical company that developed edoxaban. It is possible that this may have influenced the timeframe of reported safety outcomes.
Declarations of interest	Quote: "Dr. Büller reports receiving consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Isis Pharmaceuticals, and ThromboGenics, and grant support from Bayer and Pfizer. Dr. Décousus reports receiving fees for board membership from Bayer and Daiichi Sankyo, lecture fees from GlaxoSmithKline, and grant support from Bayer, Bristol-Myers Squibb–Pfizer, Boehringer Ingelheim, and Portola. Drs. Grosso, Mercuri, Schwocho, and Shi report being employees of Daiichi Sankyo. Dr. Middeldorp reports receiving consulting fees from Bayer and Bristol-Myers Squibb–Pfizer, lecture fees

Hokusai-VTE 2013 *(Continued)*

	from Bayer, GlaxoSmithKline, Bristol- Myers Squibb–Pfizer, and Boehringer Ingelheim, and grant support from GlaxoSmithKline, Bristol-Myers Squibb–Pfizer, and Sanquin. Dr. Prins reports receiving consulting fees from Bayer, Pfizer, and Boehringer Ingelheim, and lecture fees from Bayer. Dr. Raskob reports receiving consulting fees and travel support from Bayer, Bristol-Myers Squibb, Janssen, Johnson & Johnson, Pfizer, Sanofi- Aventis, and Takeda. Dr. Schellong reports receiving consulting fees from Bayer and Boehringer Ingelheim, and lecture fees from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb–Pfizer. Dr. Segers reports receiving fees for the scientific management of the studies as director of the International Clinical Trial Organization and Management (ICTOM) academic research organization from Bayer, Isis Pharmaceuticals, and Pfizer. Dr. Verhamme re- ports receiving consulting fees from Bayer, Boehringer Ingelheim, ThromboGenics, and Pfizer, lecture fees from Bayer, Boehringer Ingelheim, Leo Pharma, Sanofi-Aventis, and Pfizer, and grant support from Bayer, Boehringer Ingelheim, Leo Pharma, and Sanofi-Aventis. Dr. Wells reports receiving lecture fees from Bayer, Boehringer Ingelheim, Biomerieux, and Bristol-Myers Squibb– Pfizer. No other potential conflict of interest relevant to this article was reported."
Notes	None

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 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 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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: the study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

J-EINSTEIN DVT and PE 2015

Study characteristics

Methods	**Study design:** an open-label, randomised trial

J-EINSTEIN DVT and PE 2015 *(Continued)*

	Duration of study: 6.5 months
Participants	**Setting:** multicentre **Country:** Japan (30 centres) **Number of participants:** 97; rivaroxaban 78, UFH/warfarin 19 **Age, mean (SD) years:** rivaroxaban (10 mg twice daily/ 15 mg once daily) 65.0 (9.9) years, rivaroxaban (15 mg twice daily/ 15 mg once daily) 68.8 (12.2) years, UFH/warfarin 63.4 (18.3) years **Sex:** rivaroxaban (10 mg twice daily/ 15 mg once daily) 16 M/7 F, rivaroxaban (15 mg twice daily/ 15 mg once daily) 25 M/30 F, UFH/warfarin 10 M/9 F **Inclusion criteria:** people older than 20 years who had acute, objectively confirmed symptomatic proximal DVT and/or PE **Exclusion criteria:** people were excluded if they had received heparin or fondaparinux treatment for longer than 48 hours or more than a single dose of warfarin. Other exclusion criteria were: thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent for the current episode; any contraindication listed in the local labelling of UFH or warfarin or another indication for the use of UFH or warfarin; CrCL < 30 mL/min; significant hepatic disease or ALT > 3 times ULN; bacterial endocarditis; active bleeding or a high risk of bleeding contraindicating treatment with UFH or warfarin; a systolic BP of more than 180 mm Hg or a diastolic BP of more than 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy, or breast-feeding; concomitant use of strong cytochrome P450 3A4 inhibitors (i.e. azole-antimycotics or HIV protease inhibitors); and a life expectancy of less than 3 months.
Interventions	**Intervention 1:** participants received rivaroxaban 15 mg twice daily for a total of 3 weeks in a double-blind fashion, followed by open-label rivaroxaban 15 mg once daily. Treatment was continued for 3, 6 or 12 months, as decided by the treating physician. The mean treatment duration was 195 days. **Intervention 2:** participants assigned to control treatment received IV UFH, with the dose adjusted to prolong the activated partial thromboplastin time to 1.5–2.5-fold that of controls, for at least 5 days, overlapping with and followed by INR (range 1.5–2.5)-titrated warfarin. UFH was discontinued when the INR was 1.5 or more for two consecutive measurements at least 24 hours apart. Initially, the INR was measured every 2 to 3 days and, when stable, at least once per month. Treatment was continued for 3, 6 or 12 months, as decided by the treating physician. The mean treatment duration was 200 days. **Follow-up:** day 22 and at the end of the 3, 6 or 12 months' intended treatment period.
Outcomes	**Primary:** the occurrence of symptomatic recurrent VTE or asymptomatic deterioration **Secondary:** venous ultrasound and spiral CT, major bleeding, CRNM bleeding
Funding	Quote: "The program was sponsored by Bayer Yakuhin Ltd." Comment: the program was sponsored by Bayer Yakuhin Ltd, Japan, which was the pharmaceutical company that developed rivaroxaban. Some authors received funding from some pharmaceutical companies. The results showed similar efficacy and safety profiles with rivaroxaban and control treatment. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Bayer Yakuhin supported this study, was involved in the design of the trial, and collected and analysed the data. MHP has received research support and honoraria, and has participated in advisory boards for Bayer HealthCare, Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, Daiichi Sankyo, LEO Pharma, ThromboGenics, and Pfizer. AWAL, MKato, JO, YM, KI, and MKajikawa are employees of Bayer HealthCare Pharmaceuticals. NY has received honoraria for oral presentations from Daiichi Sankyo. AH has received research grants from Astellas Pharmaceuticals, AstraZeneka, MSD, Otsuka Pharmaceutical, Kissei Pharmaceutical, Kyowa Hakko Kirin, Kowa Pharmaceuticals, Sanofi, Daiichi Sankyo, Takeda Pharmaceuticals, Mitsubishi Tanabe Pharma, Boehringer Ingelheim, Nihon Medi-Physics, and Bayer Yakuhin, and has received funding from Sanofi, Daiichi Sankyo, Toa Eiyo, Novartis, and Bayer Yakuhin for participation in clinical trials. AH has received funding for endowed courses from Otsuka Pharmaceutical, Fukuda Denshi, Hokushin Medical, Boston Scientific, and Vega Life Cor-

J-EINSTEIN DVT and PE 2015 *(Continued)*

	poration. SS has received funding from Bayer Yakuhin, Daiichi Sankyo, Takeda Pharmaceuticals, Otsuka Pharmaceutical, Novartis Pharma, and Boehringer Ingelheim for participation in clinical trials. The other authors declare that they have no competing interests."
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done centrally, using an interactive web response system". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done centrally, using an interactive web response system". Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: blinding of participants and personnel was not conducted. However, review authors judged that the lack of blinding was unlikely to have affected the objective outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Use objective and validated tests to confirm suspected recurrent VTE and the use of an independent committee, whose members were blinded to treatment assignment to adjudicate outcome events." Comment: blinding was performed adequately, study judged at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three participants from a single site were excluded from all analyses because of serious non-compliance with the protocol/Good Clinical Practice guidelines. Comment: fewer than 20% of participants dropped out or withdrew, and the study author performed intention-to-treat analysis. Study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Mokadem 2021

Study characteristics

Methods	**Study design:** a prospective randomised clinical study **Duration of study:** 6 months
Participants	**Setting:** hospital **Country:** Egypt

Mokadem 2021 *(Continued)*

	Number of participants: 100 (138 randomised but 38 were excluded); apixaban 50, enoxaparin 50 **Age, mean (SD) years:** apixaban 61.3 (11.2) years, enoxaparin 59.9 (9.7) years **Sex:** apixaban 20 M/30 F, enoxaparin 22 M/28 F **Inclusion criteria:** people with active malignancy presenting with acute DVT and still treated with chemotherapy **Exclusion criteria:** (1) people with PE and haemodynamic instability requiring thrombolytic therapy; (2) people with previous DVT or VTE; (3) people who received LMWH or UFH before randomisation; (4) people with brain tumours, cerebral metastasis; (5) people with hepatic impairment Child-Pugh B or C; (6) people with recent or current active or life- threatening bleeding (e.g. intracranial haemorrhage or gastrointestinal bleeding; (7) people with thrombocytopenia (platelets < 100 x109 L); (8) people with severe chronic kidney disease (estimated GFR < 30 mL/min); (9) pregnant women.
Interventions	**Intervention 1:** apixaban 10 mg twice daily dose for 7 days followed by apixaban 5 mg twice daily or LMWH. Apixaban dose was adjusted to be 2.5 mg twice daily in participants with serum creatinine ≥ 1.5 mg/dL, elderly participants ≥ 80 years or those with body weight ≤ 60 kg. **Intervention 2:** participants received enoxaparin (1mg/kg/SC every 12h). **Follow-up:** all participants were followed up for 6 months.
Outcomes	**Primary:** occurrence of fatal or major bleeding **Secondary:** recurrent DVT or VTE, occurrence of non-fatal or minor bleeding, mortality related to massive PE
Funding	Quote: "The author(s) received no financial support for the research, authorship, and/or publication of this article."
Declarations of interest	Quote: "The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for participants who died or were lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized according to a computer-based program (random number generators) using {Math.random} method". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized according to a computer-based program (random number generators) using {Math.random} method". Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No information Comment: blinding was not possible in this study because of the different nature of the two medications (oral versus SC). However, review authors judged that the lack of blinding was unlikely to have affected the objective outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: no information

Mokadem 2021 *(Continued)*

		Comment: blinding was not possible in this study because of the different nature of the two medications (oral versus SC). However, review authors judged that the lack of blinding was unlikely to have affected the objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the edoxaban group, 4 participants were lost to follow-up; in the control group, 8 participants were lost to follow-up. Comment: fewer than 20% of participants dropped out or withdrew; study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

ODIXa-DVT 2007

Study characteristics	
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 **Number of participants:** 604 (613 randomised but 9 were not treated or had no data and were excluded); rivaroxaban 478 (10 mg 119, 20 mg 117, 30 mg 121, 40 mg 121), enoxaparin/VKA 126 **Age, mean (SD) years:** rivaroxaban 10 mg 58.5 (15.3) years, 20 mg 57.5 (15.9) years, 30 mg 61.4 (15.9) years, 40 mg 59.5 (16.9) years, enoxaparin/VKA 58.4 (18.3) years **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 aPTT; 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 CrCL 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 SC injection and a VKA (warfarin, phenprocoumon or acenocoumarol) for 12 weeks **Follow-up:** day 21, 84 and 114

ODIXa-DVT 2007 *(Continued)*

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.
Funding	Quote: "Sponsored by Bayer HealthCare AG." Comment: Bayer HealthCare was the pharmaceutical company that developed rivaroxaban. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Drs Agnelli, Gallus, Goldhaber, Haas, Huisman, Hull, and Kakkar received reimbursement as members of the ODIXa-DVT steering committee. Dr Gallus received a research grant for the ASPIRE trial investigating aspirin for the secondary prevention of venous thromboembolism and received honoraria as a consultant to Bayer HealthCare, GlaxoSmithKline, sanofi-aventis, AstraZeneca, Astellas, and Progen. Dr Haas received a research grant from Lilly for a phase IIa study with a factor Xa inhibitor, received honoraria from AstraZeneca, and is a member of a speakers' bureau for sanofi-aventis and GlaxoSmithKline; she also has participated as an expert witness for German medicolegal cases. Dr Kakkar has received research grants from AstraZeneca to support the PERCIEVE registry and from sanofi-aventis for basic research on a low–molecular-weight heparin; he is a consultant to Bayer, sanofi-aventis, and Emisphere, for which he has received honoraria, and has also received honoraria from Pfizer, Merck, and Boehringer Ingelheim. Dr Schellong was reimbursed as a member of the ODIXa-DVT adjudication committee and was a consultant on the study; he also received a research grant to undertake a substudy of phase II prevention of venous thromboembolism trials with rivaroxaban to validate an ultrasound method. Dr Misselwitz is an employee of Bayer HealthCare AG and owns stock in the company."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for 9 participants who were not treated as planned or had no data.

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 bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised by central computer". Comment: study judged at low risk of 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 SC 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.

ODIXa-DVT 2007 *(Continued)*

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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Ohmori 2019

Study characteristics	
Methods	**Study design:** a multicenter, open-label, randomised controlled trial **Duration of study:** 12 months
Participants	**Setting:** multicenter **Country:** Japan (16 centres) **Number of participants:** 14; edoxaban 8, warfarin 6 **Age, mean (range) years:** edoxaban 63 (44 to 69) years, warfarin 48 (37 to 59) years **Sex:** edoxaban 4 M/1 F, warfarin 4 M/2 F **Inclusion criteria:** 1) adult (aged 20 years or older) SMID patients with Oshima's classification grades 1 to 4; 2) people with DVT evaluated by lower extremity venous ultrasonography; 3) those who provided written informed consent through a legally acceptable representative. **Exclusion criteria:** 1) people who were considered by the principle investigator and sub-investigator to be ineligible for the study; 2) people whose CrCL decreased to less than 15 mL/min; and 3) people taking agents contraindicated for coadministration with the study drug.
Interventions	**Intervention 1:** the normal daily dose was 60 mg (or 30 mg below 60 kg body weight) taken once orally. At one month of treatment, or depending on renal function and concomitant medication, the dose was adjusted to 30 mg orally once daily. Treatment was administered for 12 months. **Intervention 2:** following the once daily oral administration of the initial dose of warfarin, the dose was adjusted to ensure that it was within the target therapeutic range using a blood coagulation test over a few weeks, and a maintenance dose was selected. Treatment was administered for 12 months. **Follow-up:** trial visits were scheduled at enrolment and at 0, 3 months, 6 months, 9 months and 12 months after randomisation.
Outcomes	**Primary:** incidence of hemorrhagic events (major bleeding and clinically important bleeding) **Secondary:** a composite of DVT changes (including the size, location and number), DVT scores
Funding	Quote: "Supported by a Grant-in-Aid for Clinical Research from the National Hospital Organization."

Ohmori 2019 *(Continued)*

	Comment: the source of funding for the trial did not come from any parties, but two authors received honoraria from Daiichi Sankyo company, a company that produces edoxaban tosilate hydrate. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Mashio Nakamura and Yukihiro Koretsune received honoraria from Daiichi Sankyo Company, Limited. The other authors do not have any conflicts of interest to declare."
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized 1:1 to the warfarin and edoxaban tosilate hydrate groups by block randomization adjusted by the presence of either tracheostomy, gastric tube insertion, or urethral balloon insertion." Comment: insufficient information to permit judgement of low or high risk of bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "Block randomization." Comment: there was insufficient information to assess whether the method used was likely to induce bias on the estimate of effect.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: no blinding for two oral treatments, but the outcome or the outcome measurement was unlikely to be influenced by the lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Open label" Comment: no blinding for two oral treatments, but the outcome or the outcome measurement was unlikely to be influenced by the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	In the edoxaban group, 3/8 participants were lost to follow-up with no explanations given. Comment: more than 20% of participants dropped out or withdrew; study judged at high risk of attrition bias.
Selective reporting (reporting bias)	High risk	Comment: 'adverse events' was a predefined secondary outcome in protocol and described in abstract of full text, but the data for this outcome were not reported. Study judged at high risk of reporting bias.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

PRAIS 2019

Study characteristics

Methods	**Study design:** a pilot randomised, open-label, parallel, multicenter study **Duration of study:** 6 months
Participants	**Setting:** multicentre (7 centres in South Korea: Seoul National University Hospital, Gachon University Gil Medical Center, Daegu Catholic University Medical Center, Bundang Seoul National University Hos-

PRAIS 2019 *(Continued)*

	pital, Seoul Metropolitan Government Seoul National University Boramae Hospital, Catholic University of Korea Seoul Saint Mary's Hospital, and Yeouido Saint Mary's Hospital) **Country:** South Korea **Number of participants:** 67 (72 participants randomised but 5 were excluded who were not treated with the intervention); rivaroxaban 35, enoxaparin and VKA 32 **Age, mean (SD) years:** rivaroxaban 57.3 (11.1) years, enoxaparin and VKA 60.1 (10.9) years **Sex:** rivaroxaban 15M/20F, enoxaparin and VKA 13M/19F **Inclusion criteria:** people were included if they were of legal age (18 to 75 years) for consent and had the first episode of objectively verified iliofemoral DVT by imaging of CT or DUS, and the onset of symptoms within the past 21 days. Successful catheter-directed thrombolysis. **Exclusion criteria:** people were excluded if they had: remnant thrombus more than 50% or with blood flow restriction on completion venography after the intervention; contraindications to anticoagulation; VKA treatment within 7 days before enrolment or other indication for VKA; CrCL < 30 mL/min; clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis or cirrhosis); liver enzyme level > 3 X the ULN range; bacterial endocarditis; active bleeding or a high risk of bleeding; systolic BP > 180 mm Hg or diastolic BP > 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy, or breastfeeding; malignant disease needing chemotherapy.
Interventions	**Intervention 1:** rivaroxaban group received 15 mg twice daily for the initial 3 weeks, followed by 20 mg once daily for 6 months. **Intervention 2:** participants randomised to standard therapy received enoxaparin and VKA. Target range of INR was 2.0–3.0. **Follow-up:** day 21, day 90 and day 180
Outcomes	**Primary:** recurrent VTE, recurrent DVT, acute PE **Secondary:** major bleeding or CRNM bleeding, all-cause mortality and vascular events (acute coronary syndrome, ischaemic stroke, transient ischaemic attack or systemic embolism)
Funding	Quote: "Funding for this research was provided by Bayer Korea." Comment: the sponsor of the study had no role in the conduct of the analysis or drafting of the report.
Declarations of interest	Quote: "The authors declare no competing interests."
Notes	Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for participants who were not treated as planned due to consent withdrawal or active cancer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was performed using a web-based randomization program supplied by Medical Research Collaborating Center in Seoul National University Hospital after checking for inclusion and exclusion criteria". Comment: study judged at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was performed using a web-based randomization program supplied by Medical Research Collaborating Center in Seoul National University Hospital after checking for inclusion and exclusion criteria".

PRAIS 2019 *(Continued)*

		Comment: study judged at low risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No information Comment: blinding was not possible in this study because of the different nature of the two medications (oral versus SC). However, review authors judged that the lack of blinding was unlikely to have affected the objective outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information Comment: blinding was not possible in this study because of the different nature of the two medications (oral versus SC). However, review authors judged that the lack of blinding was unlikely to have affected the objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the rivaroxaban group, 5 participants were lost to follow-up; in the standard therapy group, 5 participants were lost to follow-up. Comment: fewer than 20% of participants dropped out or withdrew; study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

RE-COVER 2009

Study characteristics	
Methods	**Study design:** randomised, double-blind, double-dummy, non-inferiority trial **Duration of study:** 7 months
Participants	**Setting:** 228 clinical centres **Country:** 29 countries **Number of participants:** 2539; dabigatran 1273, warfarin 1266 **Age, mean (range) years:** dabigatran 56 (18 to 93) years, warfarin 55 (18 to 97) years **Sex:** dabigatran 738 M/535 F, warfarin 746 M/520 F **Inclusion criteria:** people aged ≥ 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 2 x ULN range, an estimated CrCL < 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 an INR 2.0-3.0 and dabigatran-like placebo. **Follow-up:** participants were assessed at 7 days and then monthly until 6 months; an additional follow-up visit was scheduled for 30 days after completion of the study.

RE-COVER 2009 *(Continued)*

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
Funding	Quote: "Supported by Boehringer Ingelheim." Comment: the study was funded by Boehringer-Ingelheim, the pharmaceutical company that developed dabigatran. It is possible that this may have influenced the timeframe of reported safety outcomes.
Declarations of interest	Quote: "Dr. Schulman reports receiving consulting fees from AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, GlaxoSmithKline, and Sanofi-Aventis, lecture fees from LEO Pharma, Sanofi-Aventis, and Boehringer Ingelheim, and grant support from Bayer HealthCare; Dr. Kearon, consulting fees from Boehringer Ingelheim; Dr. Kakkar, consulting fees and honoraria from Boehringer Ingelheim, Bayer Schering Pharma, SanofiAventis, Bristol-Myers Squibb, Pfizer, ARYx Therapeutics, Canyon Pharmaceuticals, and Eisai, lecture fees from Sanofi-Aventis, Bayer Schering Pharma, Boehringer Ingelheim, GlaxoSmithKline, Eisai, and Pfizer, and grant support from Sanofi-Aventis, Boehringer Ingelheim, Pfizer, and Bayer Schering Pharma; Dr. Mismetti, consulting fees and lecture fees from Boehringer Ingelheim, Sanofi-Aventis, and GlaxoSmithKline; Dr. Schellong, lecture fees and consulting fees from Bayer HealthCare, Boehringer Ingelheim, and GlaxoSmithKline and consulting fees from Sanofi-Aventis; Dr. Eriksson, consulting fees and lecture fees from Boehringer Ingelheim, Pfizer, AstraZeneca, Bayer HealthCare, LEO Pharma, and Sanofi-Aventis; and Dr. Goldhaber, clinical research support from Sanofi-Aventis, BristolMyers Squibb, and Boehringer Ingelheim, and consulting fees from Sanofi-Aventis, Boehringer Ingelheim, Merck, MEDRAD Interventional/Possis, Bristol-Myers Squibb, Genentech, and Medscape. Mr. Baanstra and Dr. Schnee report being employees of Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported."
Notes	None

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 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 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.... 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.

RE-COVER 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

RE-COVER II 2014

Study characteristics	
Methods	**Study design:** randomised, double-blind, double-dummy trial **Duration of study:** 7 months
Participants	**Setting:** 208 study sites **Country:** 31 countries worldwide **Number of participants:** 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 ≥ 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 CrCL < 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 **Follow-up:** participants were assessed at 7 days and then monthly until 6 months; an additional follow-up visit was scheduled for 30 days after completion of the study.
Outcomes	**Primary:** recurrent VTE objectively verified, preferably with the same method as for the index event **Secondary:** major bleeding defined according to the ISTH criteria
Funding	Quote: "The study was funded by Boehringer-Ingelheim." Comment: Boehringer-Ingelheim is the pharmaceutical company that developed dabigatran. It is possible that this may have influenced the timeframe of reported safety outcomes.
Declarations of interest	Quote: "Dr. Schulman reports receiving consulting fees from Boehringer Ingelheim and grant support from Bayer Healthcare. Dr. Kakkar discloses consultancy for Sanofi Aventis, Pfizer, Eisai Inc, GSK, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb, and payment for lec-

RE-COVER II 2014 *(Continued)*

	tures (inc. speakers bureaus) from Sanofi Aventis, Pfizer, Eisai Inc, GSK, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb. His institution has received grants from Sanofi Aventis, Pfizer, Eisai Inc, GSK, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and BristolMyers Squibb. Dr. Goldhaber reports receiving clinical research support from Sanofi Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim, and consulting fees from Sanofi Aventis, Boehringer Ingelheim, Merck, Possis, Bristol-Myers Squibb, Genentech, and Medscape. Ms. Christiansen, Dr. Schellong reports receiving speaker fees and consulting honoraria from Bayer Healthcare, Boehringer Ingelheim, GlaxoSmithKline, and consulting fees from Sanofi Aventis. Dr. Eriksson reports receiving consultant fees and lecture fees from Boehringer Ingelheim, Pfizer, Bayer Healthcare, Leo Pharma, and Bristol-Myers Squibb. Dr. Mismetti reports receiving consulting fees and lecture fees from Boehringer Ingelheim, Sanofi Aventis, and GlaxoSmithKline. Ms. Christiansen, Ms. Le Maulf, Dr. Friedman, and Ms. Peter are employees of Boehringer Ingelheim. Dr. Kearon reports receiving consulting fees from Boehringer Ingelheim."
Notes	None

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 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 2009), which was judged at low risk of selection bias. Comment: study judged at low risk of 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 2009), 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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

Sukovatykh 2017

Study characteristics	
Methods	**Study design:** randomised study **Duration of study:** 12 months
Participants	**Setting:** hospital **Country:** Russia **Number of participants:** 95; dabigatran 30, rivaroxaban 30, VKA/warfarin 35 **Age, mean (SD) years:** 57.4 (1.2) years **Sex:** 56M/39F **Inclusion criteria:** unilateral or bilateral acute lower extremity DVT involving proximal veins without/or in combination with PE, confirmed by instrumental imaging methods; age > 18 years old; the duration of the disease is not more than 2 weeks; signed informed consent of individual to participate in the study. **Exclusion criteria:** PE with unstable haemodynamics requiring immediate thrombolysis; presence of contraindications to anticoagulant therapy; severe concomitant diseases of the heart; liver and kidneys in the decompensation stage
Interventions	**Intervention 1:** dabigatran etexilate 150 mg twice daily for 6 months. **Intervention 2:** rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily before the end of the 6-month course of treatment. **Intervention 3:** no later than 48 hours after the start of parenteral anticoagulant therapy, participants started taking warfarin at a dose of 5 mg. On day 3 from the moment warfarin was prescribed, the INR was determined and dose adjustments were made. In subsequent days, INR was monitored daily with warfarin dose adjustment until optimal values in the range of 2.0–3.0, after which heparin was cancelled. After discharge from hospital, participants took warfarin at the correct dose for 6 months with INR control 1 time in 10 days in a polyclinic at place of residence. **Follow-up:** 6 and 12 months
Outcomes	Relapses of the disease, haemorrhagic complications, quality of life
Funding	Not reported
Declarations of interest	Not reported
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the study did not specify the method of randomisation; insufficient information to permit judgement of high or low risk of bias.
Allocation concealment (selection bias)	Unclear risk	Comment: the study did not specify the method of randomisation and allocation concealment; insufficient information to permit judgement of high or low risk of bias.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: the study did not specify the method of blinding; insufficient information to permit judgement of high or low risk of bias.

Sukovatykh 2017 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of high or low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: the outcomes reported in method section were also reported in the result section; study judged at low risk of reporting bias.
Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

THRIVE 2005

Study characteristics	
Methods	**Study design:** multicentre, randomised, double-blind, non-inferiority trial **Duration of study:** 28 weeks
Participants	**Setting:** 279 centres **Country:** 28 countries **Number of participants:** 2489 (2528 participants randomised but 39 who did not receive interventions were excluded); ximelagatran 1240, enoxaparin/warfarin 1249 **Age, mean (range) years:** ximelagatran 57 (18 to 93) years, enoxaparin/warfarin 57 (18 to 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 CrCL < 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 for 6 months. **Intervention 2:** enoxaparin 1.0 mg/kg SC 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 mm to 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

THRIVE 2005 *(Continued)*

	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.
Funding	Quote: "This study was funded by AstraZeneca." Comment: AstraZeneca was the pharmaceutical company that developed ximelagatran. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Drs Fiessinger, Huisman, and Bounameaux have served as consultants for AstraZeneca. Dr Davidson has been a clinical investigator in anticoagulant research with AstraZeneca, Sanofi, Organon, Aventis, and Bristol-Myers Squibb, and has served as a consultant or occasional speaker (sometimes for honoraria) for each of these sponsors. Dr Francis has served as a consultant for AstraZeneca. Dr Eriksson has served as a consultant for AstraZeneca. Dr Ginsberg has received funding from AstraZeneca for consultation on ximelagatran or as unencumbered educational or research grants."
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 This drug is no longer on the market but we included the study for completeness, and performed sensitivity analysis. Number of participants with basic information was smaller than number of participants randomised because authors did not include the information for participants who did not receive interventions as planned due to ineligibility, withdrawal of consent or other reasons.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized 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 bias.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized 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 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 Comment: study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	Comment: all of the study's pre-specified outcomes were reported in the pre-specified way.

THRIVE 2005 *(Continued)*

Other bias	Low risk	Comment: we did not find any methodological issues that might directly lead to a risk of bias.

ALT: alanine aminotransferase
AST: aspartate aminotransferase
aPTT: activated partial thromboplastin time
BP: blood pressure
(C)CUS: (complete) compression ultrasound
CrCL: creatinine clearance
CRNM: clinically relevant non-major
CT: computed tomography
CUS: compression ultrasonography
DUS: duplex ultrasound
DVT: deep vein thrombosis
ECOG: Eastern Cooperative Oncology Group
F: female
GFR: glomerular filtration rate
INR: international normalised ratio
ISTH: International Society on Thrombosis and Haemostasis
ITT: intention-to-treat
IUH: intravenous unfractionated heparin
IV: intravenous
LMWH: low molecular weight heparin
M: male
MACE: major adverse cardiovascular events
MRI: magnetic resonance imaging
MRV: magnetic resonance venography
PE: pulmonary embolism
PLS: perfusion lung scan
PT: prothrombin time
PT-INR: prothrombin time-international normalised ratio
PTS: post thrombotic syndrome
SC: subcutaneous
SMID: severe motor and intellectual disabilities
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
ADAM VTE trial 2020	Unable to obtain specific outcome data for participants with a DVT
AMPLIFY Extended Study 2013	Extended study testing prophylaxis rather than treatment; participants had already taken part in the AMPLIFY 2013
Borsi 2021	Unable to obtain specific outcome data for participants with a DVT
CASTA DIVA Trial 2022	Unable to obtain specific outcome data for participants with a DVT
COBRRA 2017	Unable to obtain specific outcome data for participants with a DVT
CONKO-011 study 2015	Unable to obtain specific outcome data for participants with a DVT

Study	Reason for exclusion
DIVERSITY 2021	Unable to obtain specific outcome data for participants with a DVT
EINSTEIN-CHOICE 2017	Comparator was aspirin
EINSTEIN-Jr 2020	Unable to obtain specific outcome data for participants with a DVT
Peacock 2018	Participants with a DVT were excluded from the study
PRIORITY 2022	Unable to obtain specific outcome data for participants with a DVT
RE-SONATE 2013	Participants were already included in RE-COVER 2009 and RE-COVER II 2014
REMEDY 2013	Participants were already included in the RE-COVER 2009 and RE-COVER II 2014 studies
SELECT-D 2018	Unable to obtain specific outcome data for participants with a DVT
THRIVE I 2003	Treatment duration was only for four weeks
THRIVE III 2003	Control group were given a placebo

DVT: deep vein thrombosis

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT01780987

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 BP > 180 mm Hg or diastolic BP > 110 mm Hg) and people 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 CRNM bleeding **Secondary:** symptomatic VTE or VTE-related death, major bleeding and all bleeding
Notes	

aPTT: activated partial thromboplastin time
BP: blood pressure
CRNM: clinically relevant non major
DVT: deep vein thrombosis
INR: international normalised ratio

PE: pulmonary embolism
UFH: unfractionated heparin
VKA: vitamin K antagonist
VTE: venous thromboembolism

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

EudraCT 2014-002606-20

Study name	A randomised, open-label, active-controlled, safety and descriptive efficacy study in paediatric subjects requiring anticoagulation for the treatment of a venous thromboembolic event
Methods	**Study design**: randomised, open-label, active controlled study
Participants	**Setting**: not reported **Country**: Austria, Canada, Germany, Italy, Russian Federation, Ukraine, United States **Inclusion criteria**: "1. Children 12 to < 18 years of age at the time of consent (Age Group 1). An approved amended protocol will be implemented prior to enrolment of each subsequent age group (Age Groups 2, 3, and 4). 2. Presence of an index VTE which is confirmed by imaging. Index VTE include, but are not limited to, DVT, PE, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, and splanchnic thrombosis. 3. Intention to manage the index VTE with anticoagulation treatment for at least 12 weeks or intention to manage the index VTE with anticoagulation treatment in neonates for at least 6 weeks. 4. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study. Depending on local regulations, whenever the minor is able to give assent, the minor's assent must also be obtained. 5. Subjects/legally acceptable representatives who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. 6. Female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 28 days after the last dose of assigned treatment." **Exclusion criteria**: "1. Anticoagulant treatment for the index VTE for greater than 7 days prior to randomisation. 2. Thrombectomy, thrombolytic therapy, or insertion of a caval filter to treat the index VTE. 3. A mechanical heart valve. 4. Active bleeding or high risk of bleeding (e.g. central nervous system tumours) at the time of randomisation. 5. Intracranial bleed, including intraventricular haemorrhage, within 3 months prior to randomisation. 6. Abnormal baseline liver function (ALT > 3 x ULN or conjugated bilirubin > 2 x ULN) at randomisation. 7. At the time of randomisation, inadequate renal function. 8. Platelet count < 50 x 10^9 per L at randomisation. 9. At the time of randomisation, uncontrolled severe hypertension. 10. At the time of randomisation, use of prohibited concomitant medication as listed for apixaban. 11. Known allergy to apixaban. 12. Female subjects who are either pregnant or breastfeeding a child. 13. Geographically unavailable for follow-up. 14. Family members who are either investigational site staff members directly involved in the conduct of this trial or site staff members otherwise supervised by the Investigator. Family members who are Pfizer or Bristol Myers Squibb employees directly involved in the conduct of this trial. 15. Taking an investigational drug in other studies within 30 days before the first dose of apixaban and/or during study participation. N.B. using marketed medications commonly used in usual and customary practice, though not labelled for use in children, is acceptable. 16. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study."
Interventions	**Intervention 1**: oral apixaban **Intervention 2**: not reported
Outcomes	**Primary**: the composite of major and CRNM bleeding; all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including DVT, PE and paradoxical embolism and VTE-related mortality

EudraCT 2014-002606-20 *(Continued)*

	Secondary: all-cause death, index VTE status (e.g. progression, regression or resolution), stroke, new symptomatic or asymptomatic DVT, new symptomatic PE, apixaban concentrations, anti-FXa activity
Starting date	April 2015
Contact information	Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Notes	

NCT01516840

Study name	Venous thromboembolism treatment study in Japanese deep vein thrombosis 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 CrCL < 30 mL/minute, people 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 BP > 180 mm Hg or diastolic BP > 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 PT-INR values target range (1.5-2.5)
Outcomes	**Primary:** number of participants with new 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 new onset of symptomatic VTE or asymptomatic deterioration of thrombus
Starting date	March 2012
Contact information	Bayer Health
Notes	

NCT02464969

Study name	Apixaban for the acute treatment of venous thromboembolism in children

NCT02464969 *(Continued)*

Methods	**Study design**: randomised, open-label, parallel, active controlled study
Participants	**Setting**: hospital, clinic, research centre **Country**: United States, Australia, Canada, France, Germany, Israel, Mexico, Russian Federation, Spain, Turkey, Ukraine, United Kingdom **Inclusion criteria**: "1. Birth to < 18 years of age with a minimum weight of 2.6 kg at the time of randomisation. 2. Presence of an index VTE which is confirmed by imaging. 3. Intention to manage the index VTE with anticoagulation treatment for at least 6 to 12 weeks. Subjects able to tolerate oral feeding, nasogastric, gastric feeding for at least 5 days." **Exclusion criteria**: "1. Anticoagulant treatment for the index VTE for greater than 14 days prior to randomisation. Neonates that are enrolled into the PK cohort must be on a minimum of 5 days and a maximum of 14 days SOC anticoagulation prior to randomisation. Neonates that are enrolled into the post PK cohort may receive SOC anticoagulation for up to 14 days prior to randomisation. 2. Thrombectomy, thrombolytic therapy, or insertion of a caval filter to treat the index VTE. 3. A mechanical heart valve. 4. Active bleeding or high risk of bleeding at the time of randomisation. 5. Intracranial bleed, including intraventricular haemorrhage, within 3 months prior to randomisation. 6. Abnormal baseline liver function at randomisation. 7. Inadequate renal function at the time of randomisation. 8. Platelet count <50 x 109 per L at randomisation. 9. Uncontrolled severe hypertension at the time of randomisation. 10. Use of prohibited concomitant medication at the time of randomisation. 11. Female subjects who are either pregnant or breastfeeding a child. 12. Use of aggressive life-saving therapies such as ventricular assist devices or extracorporeal membrane oxygenation at the time of enrolment. 13. Unable to take oral or enteric medication via the nasogastric or gastric tube. 14. Known inherited or acquired antiphospholipid syndrome. 15. Known inherited bleeding disorder or coagulopathy with increased bleeding risk (e.g., haemophilia, von Willebrand disease, etc.)."
Interventions	**Intervention 1**: "oral apixaban - participants between birth to <18 years will be dosed on a body weight tiered regimen. Participants ≥35kg will receive 10mg twice daily for 7 days followed by 5mg twice daily thereafter; <35kg to 25kg will receive 8mg twice daily for 7 days followed by 4mg twice daily thereafter; <25 to 18kg will receive 6mg twice daily for 7 days and then 3mg twice daily thereafter;<18 to 12kg will receive 4mg twice daily for 7 days and then 2mg twice daily thereafter; <12 to 9kg will receive 3mg twice daily for 7 days and then 1.5mg twice daily thereafter; < 9kg to 6kg will receive 2 mg twice daily for 7 days and 1mg twice daily thereafter; <6kg to 5kg will receive 1mg twice daily for 7 days and 0.5mg twice daily thereafter; <5kg to 4kg will receive 0.6mg twice daily for 7 days and 0.3mg twice daily thereafter; PK cohort neonates ≥ 2.6kg will receive 0.1mg twice daily. Dose will be adjusted as determined by PK measurements (i.e., to 0.2mg twice daily, 0.1mg daily or dose will stay the same). For the post PK cohort neonates <4kg to 2.6kg, if confirmed by PK subanalysis, subjects will receive 0.2mg twice daily for 7 days and 0.1mg twice daily thereafter." **Intervention 2**: SOC - UFH, LMWH and/or a VKA. For participants under 2 years of age, SOC will be limited to UFH or LMWH.
Outcomes	**Primary**: the composite of major and CRNM bleeding; a composite of all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE and VTE related mortality **Secondary**: apixaban concentration; anti-Xa levels
Starting date	November 2015
Contact information	Pfizer CT.gov Call Center 1-800-718-1021 ClinicalTrials.gov_Inquiries@pfizer.com
Notes	

NCT02664155

Study name	Venous thromboembolism in renally impaired patients and direct oral anticoagulants
Methods	**Study design**: randomised, open-label, parallel controlled trial
Participants	**Setting**: hospital **Country**: France **Inclusion criteria**: people with a moderate renal insufficiency defined by a CrCL between 30 to 50 mL/min (Cockcroft and Gault formulae) or a severe renal insufficiency (between 15 to 29 mL/min); people with acute objectively confirmed symptomatic proximal DVT or PE (with or without DVT), planned to be treated for at least 3 months; >18 years of age; life expectancy of greater than 3 months; social security affiliation; signed informed consent **Exclusion criteria**: indication for anticoagulants other than VTE; active bleeding or a high risk of bleeding contraindicating anticoagulant treatment; a systolic BP of more than 180 mm Hg or a diastolic BP of more than 110 mm Hg; anticoagulation for more than 72 hours prior to randomisation; chronic liver disease or chronic hepatitis; at high risk of bleeding; CrCL < 15 mL/min or end-stage renal disease or indication for extra-renal dialysis; need for concomitant anti-platelet therapy other than aspirin 75-325 mg per day. However concomitant treatment with aspirin is discouraged in this population at bleeding risk; concomitant use of a strong inhibitor of cytochrome P-450 3A4 (CYP3A4) (e.g. a protease inhibitor for human immunodeficiency virus infection or azole-antimycotics agents ketoconazole, itraconazole, voriconazole, posaconazole) or a CYP3A4 inducer (e.g. rifampin, carbamazepine or phenytoin); active pregnancy or expected pregnancy or no effective contraception; any contraindication listed in the local labelling of UFH, LMWH or VKA or oral anticoagulant; cancer-associated VTE requiring long-term treatment with LMWH; life expectancy of less than 3 months
Interventions	**Intervention 1**: oral apixaban and rivaroxaban. Apixaban (Eliquis tablet) 10 mg twice daily for 7 days then 2.5 mg twice daily for 3 months. Rivaroxaban (Xarelto tablet) 15 mg twice daily for 21 days then 15 mg once daily for 3 months **Intervention 2**: control group receiving the SOC, i.e. heparins/VKA regimen. Participants will receive the current recommended therapy: SC or IV UFH/VKA in case of severe renal insufficiency and SC LMWH/VKA in case of moderate renal insufficiency for at least 5 days. VKA will begin concomitantly and continue for 3 months
Outcomes	**Primary**: non-inferiority of reduced doses of DOACs **Secondary**: bleeding events; VTE events
Starting date	October 2016
Contact information	Centre Hospitalier Universitaire de Saint Etienne; Ministry of Health, France
Notes	

NCT02744092

Study name	Direct oral anticoagulants versus LMWH +/- warfarin for VTE in cancer
Methods	**Study design**: randomised, open-label, parallel study
Participants	**Setting**: hospital **Country**: United States

NCT02744092 *(Continued)*

	Inclusion criteria: diagnosis of advanced solid tumour cancer, lymphoma or myeloma (no time restrictions or limitations) or diagnosis of early stage solid tumour cancer, lymphoma or myeloma ≤ 12 months prior to study enrolment; diagnosis of VTE ≤ 30 days prior to study enrolment for which potential benefits of anticoagulation therapy to prevent recurrence of VTE are felt by the treating physician to exceed the potential harms; any anticoagulation drug/strategy may be used to treat the index VTE; protocol treatment will begin ≤ 30 days after the index VTE diagnosis date; treating physician intends to put participant on anticoagulation therapy for at least three months; age ≥ 18 years; platelet count is ≥ 50,000/mm^3 (≤ 7 days prior to enrolment); CrCL is ≥ 15 mL/min (≤ 7 days prior to enrolment) **Exclusion criteria**: diagnosis of acute leukaemia or scheduled to receive an allogeneic hematopoietic stem cell transplantation; people who have ever received an autologous hematopoietic stem cell transplantation are eligible; patients who are scheduled to receive an autologous hematopoietic stem cell transplantation are not eligible; ongoing, clinically significant bleeding (CTCAE grade 3 or 4); ongoing therapy with a P-glycoprotein inhibitor (e.g. nelfinavir, indinavir or saquinavir-protease inhibitors for HIV) as these drugs interact with the factor Xa inhibitors; therapy with any azole antifungals (e.g. itraconazole, ketaconazole, voriconazole) at the time of enrolment
Interventions	**Intervention 1**: randomised Arm 1 will get anticoagulation therapy with a DOAC. There are four FDA-approved DOAC drugs that may be used for this study: rivaroxaban, apixaban, edoxaban or dabigatran. The treatment (including dosage form, dosage, frequency and duration) should be administered in accordance with the drug's FDA package insert, and all modifications are at the discretion of the treating investigator. **Intervention 2**: randomised Arm 2 will get anticoagulation therapy with LMWH with or without a transition to warfarin. There are three FDA-approved LMWH drugs that may be used for this study: dalteparin, enoxaparin or fondaparinux. The treatment (including dosage form, dosage, frequency and duration) should be administered in accordance with the drug's FDA package insert, and all modifications are at the discretion of the treating investigator.
Outcomes	**Primary**: cumulative VTE recurrence reported by participants (via study-specific questionnaire) or clinicians (via study-specific case report form) **Secondary**: cumulative rates of major bleeding reported by participants (via study-specific questionnaire) or clinicians (via study-specific case report form); health-related quality of life reported by participants via the Optum SF-12v2 Health Survey questionnaire; burden of anticoagulation therapy reported by participants via the Anti-Clot Treatment Scale (ACTS) questionnaire; mortality reported by participants' surrogates (via study-specific questionnaire) or clinicians (via study-specific case report form)
Starting date	December 2016
Contact information	CANVAS@AllianceFoundationTrials.org
Notes	

NCT02798471

Study name	Hokusai study in pediatric patients with confirmed venous thromboembolism
Methods	**Study design:** randomised, open-label, parallel, multicentre study
Participants	**Setting:** hospital **Country:** United States, Argentina, Brazil, Bulgaria, Canada, Chile, Croatia, Czechia, Denmark, El Salvador, France, Germany, Guatemala, Hungary, India, Israel, Kenya, Korea, Lebanon, Malaysia,

NCT02798471 *(Continued)*

	the Netherlands, Norway, Panama, Portugal, Romania, Russian Federation, Serbia, Singapore, Slovenia, Spain, China, Thailand, Turkey, Ukraine **Inclusion criteria:** "male or female paediatric subjects between birth (defined as 38 weeks gestational age) and less than 18 years of age at the time of consent; paediatric subjects with the presence of documented VTE confirmed by appropriate diagnostic imaging and requiring anticoagulant therapy for at least 90 days; participants must have received at least 5 days of heparin therapy prior to randomisation to treat the newly identified index VTE. In addition, prior to being randomised to edoxaban or SOC, participants initially treated with VKA are recommended to have an INR < 2.0; participant and/or parent(s)/legal guardian(s) or legally acceptable representative is informed and provides signed consent for the child to participate in the study; female subjects who have menarche must test negative for pregnancy at screening and must consent to avoid becoming pregnant by using an approved contraception method throughout the study." **Exclusion criteria:** "subjects with active bleeding or high risk of bleeding contraindicating treatment with LMWH, SP Xa inhibitors, VKAs, or DOACs; identified high risk of bleeding during prior experimental administration of DOACs; participants who have been or are being treated with thrombolytic agents, thrombectomy or insertion of a caval filter for the newly identified index VTE; administration of antiplatelet therapy is contraindicated in both arms except for low dose aspirin defined as 1-5 mg/Kg/day with maximum of 100 mg/day; administration of rifampin is prohibited during the study and subjects on concomitant use of rifampin are excluded; participants with hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk (aPTT > 50 seconds or INR > 2.0 not related to anticoagulation therapy) or ALT > 5 x ULN or total bilirubin > 2 × ULN with direct bilirubin > 20% of the total at screening visit; participants with GFR < 30% of normal for age and size as determined by the Schwartz formula; participants with stage 2 hypertension defined as BP systolic and/or diastolic confirmed > 99th percentile + 5 mmHg; participant with thrombocytopenia < 50 × 109/L at screening visit. Subjects with a history of heparin-induced thrombocytopenia may be enrolled in the study at the Investigator's discretion; life expectancy less than the expected study treatment duration (3 months); participants who are known to be pregnant or breastfeeding; participants with any condition that, as judged by the Investigator, would place the subject at increased risk of harm if he/she participated in the study, including contraindicated medications; participants who participated in another clinical study or treated with an experimental therapy with less than a 30 day washout period prior to identifying the qualifying index VTE."
Interventions	**Intervention 1**: 15 mg or 30 mg tablets for participants 12 years of age to < 18, and 60 mg edoxaban suspension for oral administration to participants under 12 years of age **Intervention 2**: SOC could include LMWH, VKA or synthetic pentasaccharide Xa inhibitors
Outcomes	**Primary**: symptomatic recurrent VTE; death as a result of VTE; no change or extension of thrombotic burden **Secondary**: major bleeding; CRNM bleeding; symptomatic recurrent VTE, death as a result of VTE and major and CRNM bleeding; peak plasma concentration (Cmax); area under the plasma concentration versus time curve (AUC); apparent systemic clearance (CL/F); apparent volume of distribution (V/F); PT; aPTT; anti-activated factor X (anti-FXa)
Starting date	March 2017
Contact information	Daiichi Sankyo Contact for Clinical Trial Information, 908-992-6400, CTRinfo@dsi.com
Notes	

NCT02829957

Study name	Rivaroxaban vs. apixaban for heavy menstrual bleeding (RAMBLE)
Methods	**Study design**: randomised, parallel, open-label study
Participants	**Setting**: hospital

NCT02829957 *(Continued)*

	Country: United States **Inclusion criteria**: non-pregnant women, age 18 to 50. For study purposes, evidence of negative pregnancy is accounted for by the treating physician's initiation of treatment with oral anticoagulants; objectively diagnosed VTE or atrial fibrillation/flutter; patient-reported active menstruation - does not apply to women who were recently pregnant; clinical plan and participant agreement to treat with oral anticoagulation for 3 months or longer; participants must have a working telephone **Exclusion criteria**: package insert exclusions for Eliquis (apixaban) or Xarelto (rivaroxaban): active pathological bleeding or severe hypersensitivity reaction to Eliquis (apixaban) or Xarelto (e.g. anaphylactic reactions); plan to become pregnant in the next 3 months; concomitant prescribed use of aspirin or thienopyridenes or other platelet inhibiting drugs; plan for surgical hysterectomy or endometrial ablation; known uterine cancer; Von Willebrand's disease, or haemophilia; known coagulopathy from liver disease; conditions likely to preclude adherence to study procedures: active IV drug use, known alcoholism, homelessness or uncontrolled psychiatric illness
Interventions	**Intrvention 1**: rivaroxaban, 15 mg twice daily for 7 days, then 20 mg daily for 3 months **Intervention 2**: apixaban, 10 mg twice daily for 7 days, then 5 mg twice daily for 3 months
Outcomes	**Primary**: PBAC scores (< 100 normal) **Secondary**: "rate of discontinuation; number of participants that held drug for menorrhagia; rate of major haemorrhage; rate of recurrent VTE; rate of crossover to another anticoagulant; rate of CRNM bleeding; haemoglobin concentration; Physical component summary of standard form 36"
Starting date	September 2016
Contact information	Patti Hogan, hoganpr@iu.edu Kate Pettit, klpettit@iu.edu
Notes	

NCT03129555

Study name	The Danish non-vitamin K antagonist oral anticoagulation study in patients with venous thromboembolism (DANNOAC-VTE)
Methods	**Study design:** cluster-randomised cross-over study
Participants	**Setting:** hospital **Country:** Denmark **Inclusion criteria:** a diagnosis of VTE in outpatient clinic or as discharge diagnosis after hospitalisation; a claimed prescription of a NOAC from a Danish pharmacy within 14 days of discharge or outpatient clinic visit **Exclusion criteria:** a prescription of a NOAC within 90 days prior to hospitalisation or outpatient clinic visit for VTE; patients with NOAC preference apart from preference consistent with current cluster-randomised NOAC; other contraindications mentioned in the "Summary of Product Characteristics" for the respective NOAC
Interventions	**Intervention 1:** dabigatran etexilate oral capsule - to all patients with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months, one at a time. **Intervention 2:** rivaroxaban oral tablet - to all patients with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months, one at a time.

NCT03129555 *(Continued)*

	Intervention 3: edoxaban oral tablet - all patients with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months, one at a time. **Intervention 4:** apixaban oral tablet - all patients with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months, one at a time.
Outcomes	**Primary:** a composite endpoint of new VTE or all-cause death **Secondary:** new VTE; all-cause death; bleeding requiring hospitalisation **Other outcome measure:** discontinuation of therapy; adherence to therapy
Starting date	May 2017
Contact information	Casper N Bang, MD, PhD +4570250000 caspernfb@hjerteforeningen.dk Gunnar H Gislason, MD, PhD +4570250000 gunnar.gislason@hjerteforeningen.dk
Notes	

NCT03266783

Study name	Comparison of bleeding risk between rivaroxaban and apixaban for the treatment of acute venous thromboembolism
Methods	**Study design:** randomised, open-label, parallel study
Participants	**Setting**: hospital **Country**: Canada **Inclusion criteria**: confirmed newly diagnosed symptomatic acute VTE (proximal power extremity DVT or segmental or greater PE); age ≥ 18 years old; informed consent obtained **Exclusion criteria**: have received > 72 hours of therapeutic anticoagulation; CrCL < 30 mL/min calculated with the Cockcroft-Gault formula; any contraindication for anticoagulation with apixaban or rivaroxaban as determined by the treating physician such as, but not limited to: active bleeding; active malignancy, defined as a) diagnosed with cancer within the past 6 months; or b) recurrent, regionally advanced or metastatic disease; or c) currently receiving treatment or have received any treatment for cancer during the 6 months prior to randomisation; or d) a hematologic malignancy not in complete remission; weight > 120 kg; liver disease (Child-Pugh Class B or C); use of contraindicated medications; another indication for long-term anticoagulation (e.g. atrial fibrillation); pregnant or breastfeeding
Interventions	**Intervention 1**: apixaban, 10 mg orally twice daily for 1 week, then 5 mg orally twice daily for 3 months of treatment **Intervention 2**: rivaroxaban, 15 mg orally twice daily for 3 weeks, then 20 mg orally twice daily for 3 months of treatment
Outcomes	**Primary**: the rate of adjudicated clinically relevant bleeding events **Secondary**: adjudicated major bleeding events; adjudicated major bleeding events; adjudicated recurrent VTE events; adjudicated recurrent VTE events; all-cause mortality; medication adherence; QALYs gained; impact of verbal consent on patient participation in comparison with participants from sites using written informed consent
Starting date	December 2017
Contact information	Lana Castellucci, MD, FRCPC 613-737-8899 ext, 74641 lcastellucci@toh.ca

NCT03266783 *(Continued)*

	Veronica Bates, BSc, CCRP 613-737-8899 ext, 71068 vebates@ohri.ca
Notes	

NCT04066764

Study name	Efficacy and safety of rivaroxaban in patients with inferior vena cava filter placement without anticoagulation contraindications (EPICT): a prospective randomised controlled trial study protocol
Methods	**Study design:** randomised, parallel, open-label study
Participants	**Setting**: hospital **Country**: China **Inclusion criteria**: "all patients aged 18 – 75 years, diagnosed with DVT of the lower extremity and implanted with an IVC filter from the 10 participating hospitals will be recruited. Patients with typical symptoms will be screened through D-dimer testing, colour Doppler ultrasound, CT venography, magnetic resonance venography or venography with digital subtraction angiography to objectively confirm DVT." The inclusion criteria were patients with a definite DVT diagnosis who will receive an IVC filter to prevent fatal PE. As some indications are not absolute for IVC filter implantation, those who refused to insert an IVC filter were not enroled. **Exclusion criteria**: "patients were excluded if they were (1) aged <18 or >75 years, (2) had obvious contraindications for anticoagulation therapy, (3) were allergic to iodine contrast agents, (4) had concomitant diseases requiring high-intensity anticoagulation and the anticoagulation intensity is higher than that of the patients with only an IVC filter, (5) had a CrCL below 30 mL/min, (6) had clinically significant liver disease (e.g., acute hepatitis, chronic active hepatitis or cirrhosis) or an ALT level that was > 3 x ULN, (7) had bacterial endocarditis, (8) had active bleeding or a potential bleeding risk, (9) were pregnant or breast-feeding, (10) had a systolic BP of more than 180 mm Hg or diastolic BP of more than 110 mm Hg, (11) had malignant tumours and a life expectancy of <1 year or (12) taking CYP-450 3A4 inhibitors or inducers."
Interventions	**Intrvention 1**: rivaroxaban, 20 mg once daily for 4 months **Intervention 2**: enoxaparin and VKA, 1.0 mg/kg of body weight of nadroparin SC twice daily plus 3 mg of warfarin orally once daily after the IVC filter insertion. Enoxaparin will be discontinued when the INR is between 2.0 and 3.0 or more for two consecutive days; participants will receive at least 5 days of enoxaparin treatment.
Outcomes	**Primary**: death of any cause, PE-related death, bleeding and recurrent PE/ DVT **Secondary**: vascular events, IVC filter retrieval failure and net clinical benefits
Starting date	Not started
Contact information	Zhenjie Liu lawson4001@zju.edu.cn
Notes	

NCT05171049

Study name	A study comparing abelacimab to apixaban in the treatment of cancer-associated VTE
Methods	**Study design**: randomised, multicenter, open-label, parallel study

NCT05171049 *(Continued)*

Participants	**Setting**: hospital **Country**: United States **Inclusion criteria**: "Male or female subjects ≥18 years old or other legal maturity age according to the country of residence; confirmed diagnosis of cancer (by histology, adequate imaging modality), other than basal-cell or squamous-cell carcinoma of the skin alone with one of the following: active cancer, defined as either locally active, regionally invasive, or metastatic cancer at the time of randomisation and/or currently receiving or having received anticancer therapy (radiotherapy, chemotherapy, hormonal therapy, any kind of targeted therapy or any other anticancer therapy) in the last 6 months; confirmed symptomatic or incidental proximal lower limb acute DVT (i.e., popliteal, femoral, iliac, and/or inferior vena cava thrombosis) and/or a confirmed symptomatic PE, or an incidental PE in a segmental, or larger pulmonary artery. Patients are eligible within 72 hours from diagnosis of the qualifying VTE. Anticoagulation therapy with a therapeutic dose of DOAC for at least 6 months is indicated. Able to provide written informed consent" **Exclusion criteria**: "thrombectomy, insertion of a caval filter or use of a fibrinolytic agent to treat the current (index) DVT and/or PE; more than 72 hours of pre-treatment with therapeutic doses of UFH, LMWH, fondaparinux, DOAC, or other anticoagulants; an indication to continue treatment with therapeutic doses of an anticoagulant other than that VTE treatment prior to randomisation (e.g., atrial fibrillation, mechanical heart valve, prior VTE); platelet count <50,000/mm3; PE leading to haemodynamic instability BP <90 mmHg or shock; acute ischaemic or haemorrhagic stroke or intracranial haemorrhage within the 4 weeks preceding screening; brain trauma or a cerebral or spinal cord surgery within 4 weeks of screening; need for aspirin in a dosage of >100 mg/day or any other antiplatelet agent alone or in combination with aspirin; primary brain cancer or untreated intracranial metastases at baseline; acute myeloid or lymphoid leukaemia; bleeding requiring medical attention at the time of randomisation or in the preceding 4 weeks; planned major surgery at baseline; ECOG performance status of 3 or 4 at screening; life expectancy <3 months at randomisation; CrCl <30 mL/min (Cockcroft-Gault equation); haemoglobin <8 g/dL; acute hepatitis, chronic active hepatitis, liver cirrhosis; or an ALT ≥3 x and/or bilirubin ≥2 x ULN in absence of clinical explanation; uncontrolled hypertension (systolic BP>180 mm Hg or diastolic BP >100 mm Hg despite antihypertensive treatment); women of child-bearing potential who are unwilling or unable to use highly effective contraceptive measures during the study from screening up to 3 days after last treatment of apixaban or 100 days after administration of abelacimab; sexually active males with sexual partners of childbearing potential must agree to use a condom or other reliable contraceptive measure up to 3 days after last treatment of apixaban or 100 days after administration of abelacimab; pregnant or breast-feeding women; patients known to be receiving strong dual inducers or inhibitors of both CYP3A4 and P gp; history of hypersensitivity to any of the study drugs (including apixaban) or excipients, to drugs of similar chemical classes, or any contraindication listed in the label for apixaban; participants with any condition that in the Investigator's judgement would place the subject at increased risk of harm if he/she participated in the study; use of other investigational (not registered) drugs within 5 half-lives prior to enrolment or until the expected pharmacodynamic(s) effect has returned to baseline, whichever is longer. Participation in academic non-interventional studies or interventional studies, comprising testing different strategies or different combinations of registered drugs is permitted"
Interventions	**Intervention 1**: apixaban administered orally twice a day, 10 mg followed by 5 mg **Intervenyion 2**: abelacimab IV administration followed by monthly administration of the same dose SC
Outcomes	**Primary**: time to first event of centrally adjudicated VTE recurrence consisting of new proximal DVT, new PE or fatal PE, including unexplained death for which PE cannot be ruled out **Secondary**: time to first event of ISTH-adjudicated major or CRNM bleeding events; net clinical benefit defined as survival without VTE recurrence, or major or CRNM bleeding
Starting date	May 2022
Contact information	Nancy Widener 239-284-3741, Nancy.w@anthostherapeutics.com

NCT05171049 *(Continued)*

Deb Freedholm 609-439-8246, Deb.f@anthostherapeutics.com

Notes

ALT: alanine aminotransferase
aPTT: activated partial thromboplastin time
AST: aspartate aminotransferase
BP: blood pressure
COX-1: cyclo-oxygenase-1
COX-2: cyclo-oxygenase-2
CrCL: creatinine clearance
CRNM: clinically relevant non-major
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
CUS: compression ultrasonography
DOACs: direct oral anticoagulants
DVT: deep vein thrombosis
ECOG: Eastern Cooperative Oncology Group
GFR: glomerular filtration rate
HIV: human immunodeficiency virus
INR: international normalised ratio
ISTH: international society on thrombosis and haemostasis
IV: intravenous
IVC: inferior vena cava
LMWH: low molecular weight heparin
MACE: major adverse cardiovascular events
MDRD: modification of diet in renal disease
MRI: magnetic resonance imaging
NOAC: non-vitamin K antagonist oral anticoagulant
PBAC: Pictoral Blood Loss Assessment Chart
PE: pulmonary embolism
PK: pharmacokinetic
PT-INR: prothrombin time-international normalised ratio
QALYs: quality-adjusted life years
SC: subcutaneous
SOC: standard of care
UFH: unfractionated heparin
ULN: upper level of normal
VKA: vitamin K antagonist
VTE: venous thromboembolism

DATA AND ANALYSES

Comparison 1. Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation

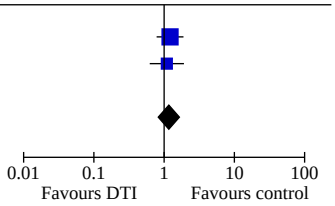
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Recurrent venous thromboembolism	2	5994	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.83, 1.65]
1.2 Recurrent deep vein thrombosis	2	5994	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.74, 1.66]
1.3 Fatal pulmonary embolism	2	5994	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.29, 6.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Non-fatal pulmonary embolism	2	5994	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.64, 2.59]
1.5 All-cause mortality	1	2489	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.41, 1.08]
1.6 Major bleeding	2	5994	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.38, 0.89]
1.7 Health-related quality of life: SF-36 physical component	1	65	Mean Difference (IV, Random, 95% CI)	6.75 [2.37, 11.13]
1.8 Health-related quality of life: SF-36 psychological component	1	65	Mean Difference (IV, Random, 95% CI)	6.45 [3.24, 9.66]

Analysis 1.1. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 1: Recurrent venous thromboembolism

	DTI		Conventional anticoagulation			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
RE-COVER 2009 (1)	45	1758	37	1747	61.9%	1.21 [0.78 , 1.89]	
THRIVE 2005	26	1240	24	1249	38.1%	1.09 [0.62 , 1.91]	
Total (95% CI)		**2998**		**2996**	**100.0%**	**1.17 [0.83 , 1.65]**	
Total events:	71		61				

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable

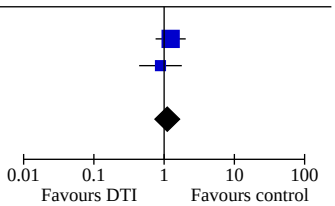


Footnotes
(1) Separate data for DVT from both RE-COVER 2009 and RE-COVER II 2014 were only reported in Goldhaber 2016. Therefore only one study visible in forest plot.

Analysis 1.2. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 2: Recurrent deep vein thrombosis

	DTI		Conventional anticaogulation			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
RE-COVER 2009 (1)	36	1758	29	1747	66.7%	1.24 [0.76 , 2.03]	
THRIVE 2005	15	1240	17	1249	33.3%	0.89 [0.44 , 1.78]	
Total (95% CI)		**2998**		**2996**	**100.0%**	**1.11 [0.74 , 1.66]**	
Total events:	51		46				

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable

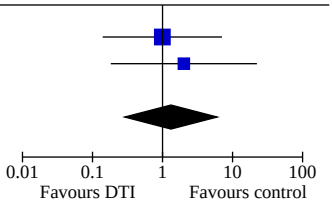


Footnotes
(1) Separate data for DVT from both RE-COVER 2009 and RE-COVER II 2014 were only reported in Goldhaber 2016. Therefore only one study visible in forest plot.

Analysis 1.3. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 3: Fatal pulmonary embolism

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
RE-COVER 2009 (1)	2	1758	2	1747	60.0%	0.99 [0.14 , 7.06]
THRIVE 2005	2	1240	1	1249	40.0%	2.02 [0.18 , 22.26]
Total (95% CI)		**2998**		**2996**	**100.0%**	**1.32 [0.29 , 6.02]**
Total events:	4		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable

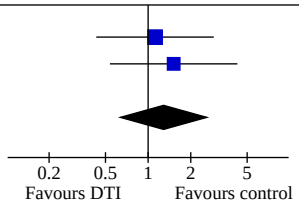


Footnotes
(1) Separate data for DVT from both RE-COVER 2009 and RE-COVER II 2014 were only reported in Goldhaber 2016. Therefore only one study visible in forest plot.

Analysis 1.4. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 4: Non-fatal pulmonary embolism

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
RE-COVER 2009 (1)	9	1758	8	1747	54.1%	1.12 [0.43 , 2.91]
THRIVE 2005	9	1240	6	1249	45.9%	1.51 [0.54 , 4.27]
Total (95% CI)		**2998**		**2996**	**100.0%**	**1.29 [0.64 , 2.59]**
Total events:	18		14			

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable

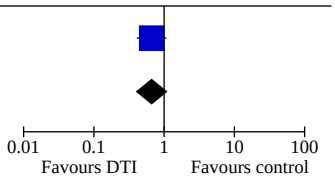


Footnotes
(1) Separate data for DVT from both RE-COVER 2009 and RE-COVER II 2014 were only reported in Goldhaber 2016. Therefore only one study visible in forest plot.

Analysis 1.5. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 5: All-cause mortality

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
THRIVE 2005	28	1240	42	1249	100.0%	0.66 [0.41 , 1.08]
Total (95% CI)		**1240**		**1249**	**100.0%**	**0.66 [0.41 , 1.08]**
Total events:	28		42			

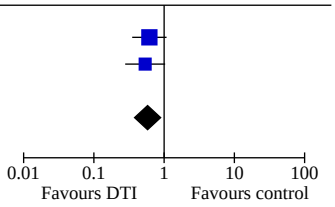
Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 6: Major bleeding

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
RE-COVER 2009 (1)	20	1758	32	1747	57.5%	0.62 [0.35 , 1.08]
THRIVE 2005	14	1240	26	1249	42.5%	0.54 [0.28 , 1.03]
Total (95% CI)		**2998**		**2996**	**100.0%**	**0.58 [0.38 , 0.89]**
Total events:	34		58			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable

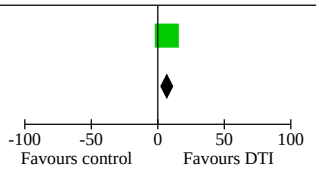


Footnotes
(1) Separate data for DVT from both RE-COVER 2009 and RE-COVER II 2014 were only reported in Goldhaber 2016. Therefore only one study visible in forest plot.

Analysis 1.7. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 7: Health-related quality of life: SF-36 physical component

Study or Subgroup	DTI Mean	DTI SD	DTI Total	Conventional anticoagulation Mean	Conventional anticoagulation SD	Conventional anticoagulation Total	Weight	Mean Difference IV, Random, 95% CI
Sukovatykh 2017	66.3	8.1	30	59.55	9.9	35	100.0%	6.75 [2.37 , 11.13]
Total (95% CI)			**30**			**35**	**100.0%**	**6.75 [2.37 , 11.13]**

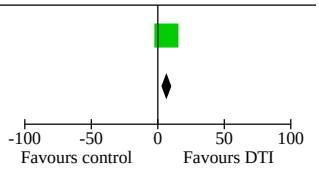
Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation, Outcome 8: Health-related quality of life: SF-36 psychological component

Study or Subgroup	DTI Mean	DTI SD	DTI Total	Conventional anticoagulation Mean	Conventional anticoagulation SD	Conventional anticoagulation Total	Weight	Mean Difference IV, Random, 95% CI
Sukovatykh 2017	62.1	5.8	30	55.65	7.4	35	100.0%	6.45 [3.24 , 9.66]
Total (95% CI)			**30**			**35**	**100.0%**	**6.45 [3.24 , 9.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.94 (P < 0.0001)
Test for subgroup differences: Not applicable



Comparison 2. Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation (sensitivity analysis excluding ximelagatran)

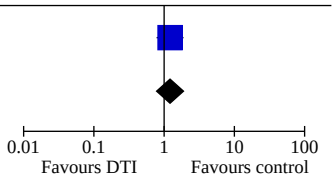
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Recurrent venous thromboembolism	1	3505	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.78, 1.89]
2.2 Recurrent deep vein thrombosis	1	3505	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.76, 2.03]
2.3 Fatal pulmonary embolism	1	3505	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Non-fatal pulmonary embolism	1	3505	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.43, 2.91]
2.5 Major bleeding	1	3505	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.35, 1.08]

Analysis 2.1. Comparison 2: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 1: Recurrent venous thromboembolism

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
RE-COVER 2009 (1)	45	1758	37	1747	100.0%	1.21 [0.78 , 1.89]
Total (95% CI)		**1758**		**1747**	**100.0%**	**1.21 [0.78 , 1.89]**
Total events:	45		37			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

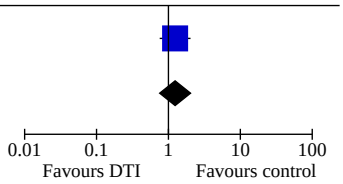


Footnotes
(1) Data on DVT groups for RE-COVER 2009 and RE-COVER II 2014 studies is from the Goldhaber 2016 study, as it is the only paper reported separate DVT data fro l

Analysis 2.2. Comparison 2: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 2: Recurrent deep vein thrombosis

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RE-COVER 2009 (1)	36	1758	29	1747	100.0%	1.24 [0.76 , 2.03]
Total (95% CI)		**1758**		**1747**	**100.0%**	**1.24 [0.76 , 2.03]**
Total events:	36		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable

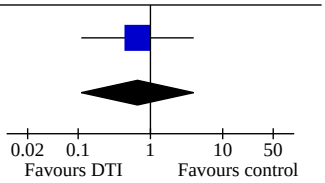


Footnotes
(1) Data on DVT groups for RE-COVER 2009 and RE-COVER II 2014 studies is from the Goldhaber 2016 study, as it is the only paper reported separate DVT data

Analysis 2.3. Comparison 2: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 3: Fatal pulmonary embolism

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RE-COVER 2009 (1)	2	1758	3	1747	100.0%	0.66 [0.11 , 3.97]
Total (95% CI)		**1758**		**1747**	**100.0%**	**0.66 [0.11 , 3.97]**
Total events:	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



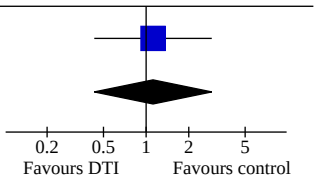
Footnotes

(1) Data on DVT groups for RE-COVER 2009 and RE-COVER II 2014 studies is from the Goldhaber 2016 study, as it is the only paper reported separate DVT data

Analysis 2.4. Comparison 2: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 4: Non-fatal pulmonary embolism

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
RE-COVER 2009 (1)	9	1758	8	1747	100.0%	1.12 [0.43 , 2.91]
Total (95% CI)		**1758**		**1747**	**100.0%**	**1.12 [0.43 , 2.91]**
Total events:	9		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



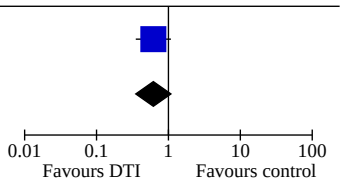
Footnotes

(1) Data on DVT groups for RE-COVER 2009 and RE-COVER II 2014 studies is from the Goldhaber 2016 study, as it is the only paper reported separate DVT data fro l

Analysis 2.5. Comparison 2: Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation (sensitivity analysis excluding ximelagatran), Outcome 5: Major bleeding

Study or Subgroup	DTI Events	DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RE-COVER 2009 (1)	20	1758	32	1747	100.0%	0.62 [0.35 , 1.08]
Total (95% CI)		**1758**		**1747**	**100.0%**	**0.62 [0.35 , 1.08]**
Total events:	20		32			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



Footnotes

(1) Data on DVT groups for RE-COVER 2009 and RE-COVER II 2014 studies is from the Goldhaber 2016 study, as it is the only paper reported separate DVT data

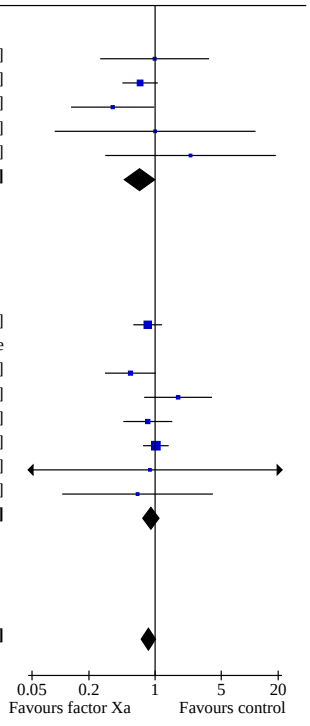
Comparison 3. Oral factor Xa inhibitors versus conventional anticoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Recurrent venous thromboembolism	13	17461	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.01]
3.1.1 Treatment duration 3 months	5	5001	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.47, 0.99]
3.1.2 Treatment duration > 3 months	8	12460	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.10]
3.2 Recurrent deep vein thrombosis	9	16439	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.49, 1.01]
3.2.1 Treatment duration 3 months	4	4917	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.22, 1.15]
3.2.2 Treatment duration > 3 months	5	11522	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.17]
3.3 Fatal pulmonary embolism	6	15082	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.69, 2.02]
3.3.1 Treatment duration 3 months	4	4917	Odds Ratio (M-H, Random, 95% CI)	1.68 [0.36, 7.94]
3.3.2 Treatment duration > 3 months	2	10165	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.54, 2.44]
3.4 Non-fatal pulmonary embolism	7	15166	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.68, 1.27]
3.4.1 Treatment duration 3 months	5	5001	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.51, 1.48]
3.4.2 Treatment duration > 3 months	2	10165	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.65, 1.43]
3.5 All-cause mortality	9	10770	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.14]
3.5.1 Treatment duration 3 months	4	5072	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.58, 1.25]
3.5.2 Treatment duration > 3 months	5	5698	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.67]
3.6 Major bleeding	17	18066	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.89]
3.6.1 Treatment duration 3 months	5	5170	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.42, 1.43]
3.6.2 Treatment duration > 3 months	12	12896	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7 Post-thrombotic syndrome	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
3.7.1 6 months	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
3.7.2 12 months	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
3.8 Health-related quality of life: SF-36 physical component	1	65	Mean Difference (IV, Fixed, 95% CI)	5.55 [1.18, 9.92]
3.9 Health-related quality of life: SF-36 psychological component	1	65	Mean Difference (IV, Fixed, 95% CI)	1.41 [-2.61, 5.43]

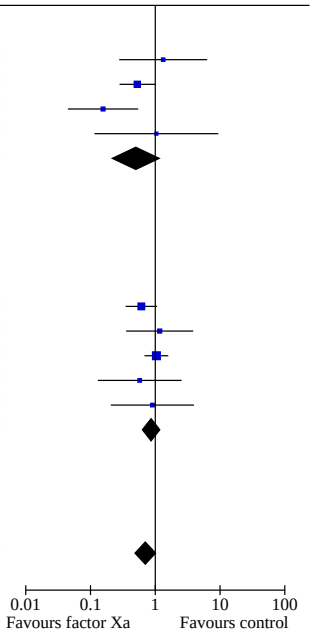
Analysis 3.1. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 1: Recurrent venous thromboembolism

Study or Subgroup	Oral factor Xa inhibitor Events	Oral factor Xa inhibitor Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 Treatment duration 3 months						
Botticelli DVT 2008	9	358	3	118	1.7%	0.99 [0.26 , 3.71]
EINSTEIN-DVT 2010	36	1731	51	1718	16.2%	0.69 [0.45 , 1.07]
EINSTEIN-DVT dose 2008	9	348	7	101	2.9%	0.36 [0.13 , 0.98]
eTRIS 2016	2	56	1	28	0.5%	1.00 [0.09 , 11.52]
ODIXa-DVT 2007	9	431	1	112	0.7%	2.37 [0.30 , 18.88]
Subtotal (95% CI)		**2924**		**2077**	**22.1%**	**0.68 [0.47 , 0.99]**
Total events:	65		63			
Heterogeneity: Tau² = 0.00; Chi² = 3.38, df = 4 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
3.1.2 Treatment duration > 3 months						
AMPLIFY 2013	59	2609	71	2635	24.7%	0.84 [0.59 , 1.19]
AMPLIFY-J 2015	0	22	0	22		Not estimable
Caravaggio 2020	18	272	28	245	7.9%	0.55 [0.30 , 1.02]
EINSTEIN-PE 2012	16	603	9	587	4.4%	1.75 [0.77 , 3.99]
Hokusai VTE Cancer 2018	23	194	27	195	8.5%	0.84 [0.46 , 1.52]
Hokusai-VTE 2013	83	2468	81	2453	31.2%	1.02 [0.75 , 1.39]
J-EINSTEIN DVT and PE 2015	1	43	0	12	0.3%	0.88 [0.03 , 23.03]
Mokadem 2021	2	50	3	50	0.9%	0.65 [0.10 , 4.09]
Subtotal (95% CI)		**6261**		**6199**	**77.9%**	**0.90 [0.74 , 1.10]**
Total events:	202		219			
Heterogeneity: Tau² = 0.00; Chi² = 5.90, df = 6 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**9185**		**8276**	**100.0%**	**0.85 [0.71 , 1.01]**
Total events:	267		282			
Heterogeneity: Tau² = 0.00; Chi² = 10.93, df = 11 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Test for subgroup differences: Chi² = 1.66, df = 1 (P = 0.20), I² = 39.9%						



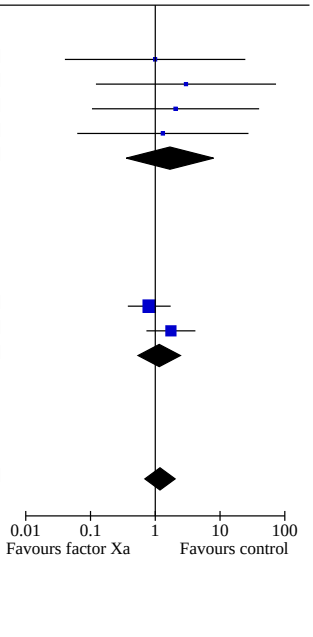
Analysis 3.2. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 2: Recurrent deep vein thrombosis

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.2.1 Treatment duration 3 months						
Botticelli DVT 2008	8	358	2	118	4.9%	1.33 [0.28 , 6.33]
EINSTEIN-DVT 2010	15	1731	28	1718	18.7%	0.53 [0.28 , 0.99]
EINSTEIN-DVT dose 2008	4	348	7	101	7.1%	0.16 [0.04 , 0.54]
ODIXa-DVT 2007	4	431	1	112	2.6%	1.04 [0.12 , 9.40]
Subtotal (95% CI)		**2868**		**2049**	**33.3%**	**0.50 [0.22 , 1.15]**
Total events:	31		38			
Heterogeneity: Tau² = 0.31; Chi² = 5.29, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 1.63 (P = 0.10)						
3.2.2 Treatment duration > 3 months						
AMPLIFY 2013	20	2609	33	2635	21.3%	0.61 [0.35 , 1.06]
EINSTEIN-PE 2012	6	603	5	587	7.7%	1.17 [0.36 , 3.85]
Hokusai-VTE 2013	45	2468	43	2453	27.0%	1.04 [0.68 , 1.59]
Mokadem 2021	3	50	5	50	5.3%	0.57 [0.13 , 2.55]
PRAIS 2019	4	35	4	32	5.4%	0.90 [0.21 , 3.96]
Subtotal (95% CI)		**5765**		**5757**	**66.7%**	**0.86 [0.63 , 1.17]**
Total events:	78		90			
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 4 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Total (95% CI)		**8633**		**7806**	**100.0%**	**0.70 [0.49 , 1.01]**
Total events:	109		128			
Heterogeneity: Tau² = 0.08; Chi² = 11.42, df = 8 (P = 0.18); I² = 30%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Test for subgroup differences: Chi² = 1.44, df = 1 (P = 0.23), I² = 30.4%						



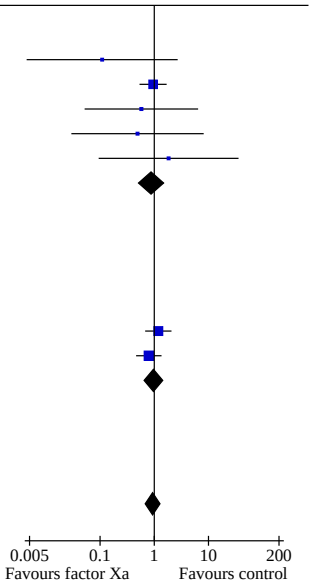
Analysis 3.3. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 3: Fatal pulmonary embolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.3.1 Treatment duration 3 months						
Botticelli DVT 2008	1	358	0	118	2.8%	0.99 [0.04 , 24.58]
EINSTEIN-DVT 2010	1	1731	0	1718	2.8%	2.98 [0.12 , 73.18]
EINSTEIN-DVT dose 2008	3	348	0	101	3.3%	2.06 [0.11 , 40.14]
ODIXa-DVT 2007	2	431	0	112	3.1%	1.31 [0.06 , 27.47]
Subtotal (95% CI)		**2868**		**2049**	**12.0%**	**1.68 [0.36 , 7.94]**
Total events:	7		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 3 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
3.3.2 Treatment duration > 3 months						
AMPLIFY 2013	12	2609	15	2635	49.9%	0.81 [0.38 , 1.73]
Hokusai-VTE 2013	14	2468	8	2453	38.1%	1.74 [0.73 , 4.16]
Subtotal (95% CI)		**5077**		**5088**	**88.0%**	**1.15 [0.54 , 2.44]**
Total events:	26		23			
Heterogeneity: Tau² = 0.12; Chi² = 1.71, df = 1 (P = 0.19); I² = 41%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)		**7945**		**7137**	**100.0%**	**1.18 [0.69 , 2.02]**
Total events:	33		23			
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 5 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%						



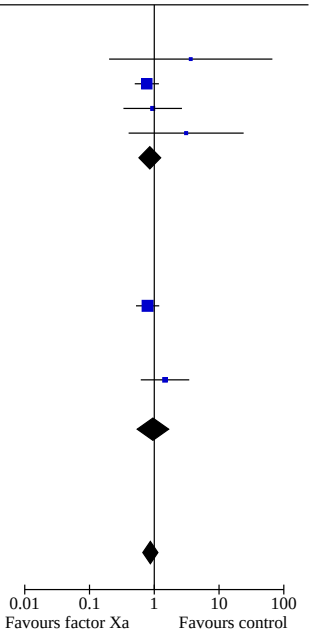
Analysis 3.4. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 4: Non-fatal pulmonary embolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.4.1 Treatment duration 3 months						
Botticelli DVT 2008	0	358	1	118	1.0%	0.11 [0.00 , 2.70]
EINSTEIN-DVT 2010	23	1731	24	1718	29.7%	0.95 [0.53 , 1.69]
EINSTEIN-DVT dose 2008	2	348	1	101	1.7%	0.58 [0.05 , 6.44]
eTRIS 2016	1	56	1	28	1.2%	0.49 [0.03 , 8.15]
ODIXa-DVT 2007	3	431	0	112	1.1%	1.84 [0.09 , 35.84]
Subtotal (95% CI)		**2924**		**2077**	**34.7%**	**0.87 [0.51 , 1.48]**
Total events:	29		27			
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 4 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
3.4.2 Treatment duration > 3 months						
AMPLIFY 2013	27	2609	23	2635	31.5%	1.19 [0.68 , 2.08]
Hokusai-VTE 2013	24	2468	30	2453	33.8%	0.79 [0.46 , 1.36]
Subtotal (95% CI)		**5077**		**5088**	**65.3%**	**0.96 [0.65 , 1.43]**
Total events:	51		53			
Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Total (95% CI)		**8001**		**7165**	**100.0%**	**0.93 [0.68 , 1.27]**
Total events:	80		80			
Heterogeneity: Tau² = 0.00; Chi² = 3.34, df = 6 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						

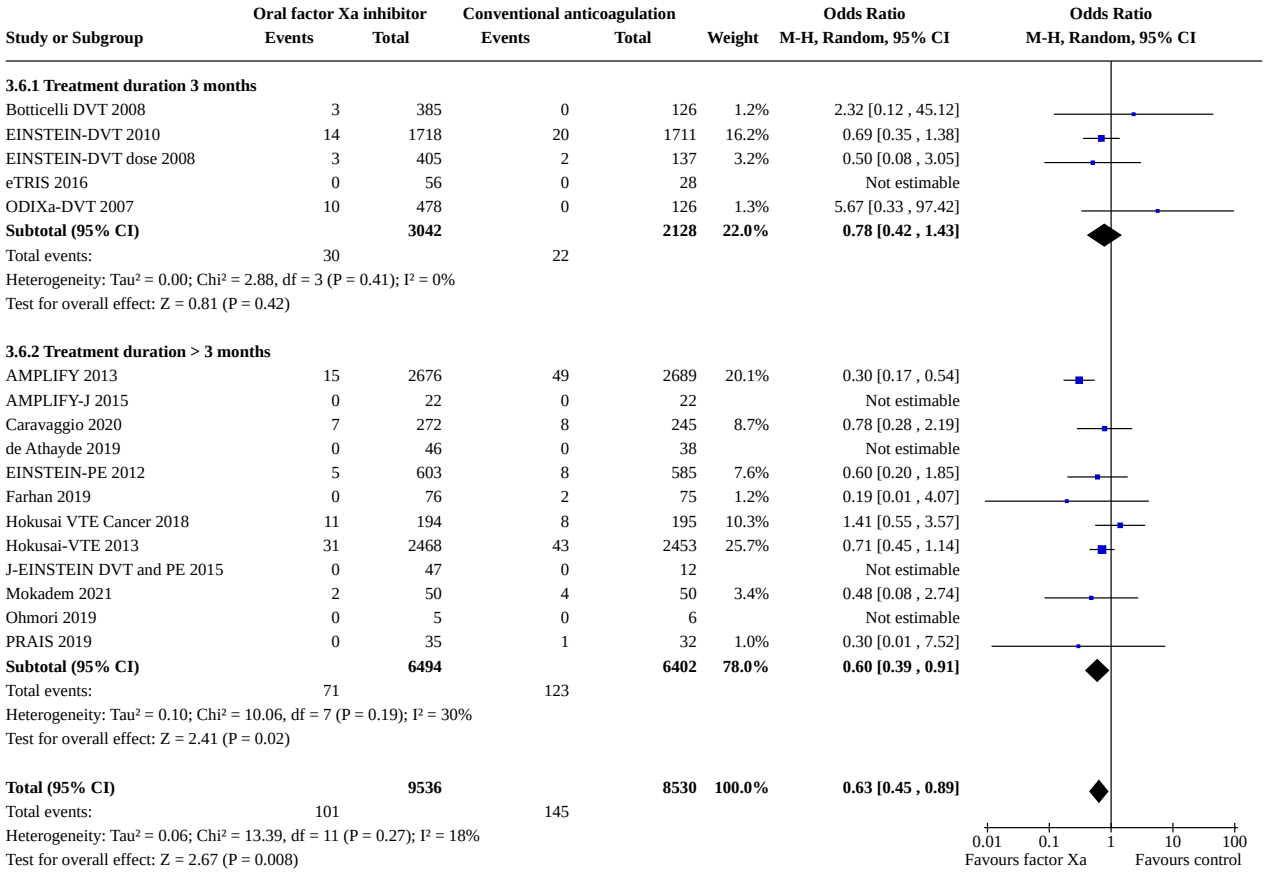


Analysis 3.5. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 5: All-cause mortality

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.5.1 Treatment duration 3 months						
Botticelli DVT 2008	5	385	0	126	0.9%	3.66 [0.20 , 66.60]
EINSTEIN-DVT 2010	38	1718	49	1711	39.0%	0.77 [0.50 , 1.18]
EINSTEIN-DVT dose 2008	14	405	5	137	6.6%	0.95 [0.33 , 2.67]
ODIXa-DVT 2007	13	478	1	112	1.7%	3.10 [0.40 , 23.97]
Subtotal (95% CI)		**2986**		**2086**	**48.2%**	**0.85 [0.58 , 1.25]**
Total events:	70		55			
Heterogeneity: Tau² = 0.00; Chi² = 2.82, df = 3 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						
3.5.2 Treatment duration > 3 months						
AMPLIFY 2013	41	2676	52	2689	42.1%	0.79 [0.52 , 1.19]
AMPLIFY-J 2015	0	22	0	22		Not estimable
de Athayde 2019	0	46	0	38		Not estimable
Mokadem 2021	15	69	11	69	9.7%	1.46 [0.62 , 3.47]
PRAIS 2019	0	35	0	32		Not estimable
Subtotal (95% CI)		**2848**		**2850**	**51.8%**	**0.95 [0.55 , 1.67]**
Total events:	56		63			
Heterogeneity: Tau² = 0.07; Chi² = 1.61, df = 1 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.17 (P = 0.87)						
Total (95% CI)		**5834**		**4936**	**100.0%**	**0.87 [0.67 , 1.14]**
Total events:	126		118			
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						

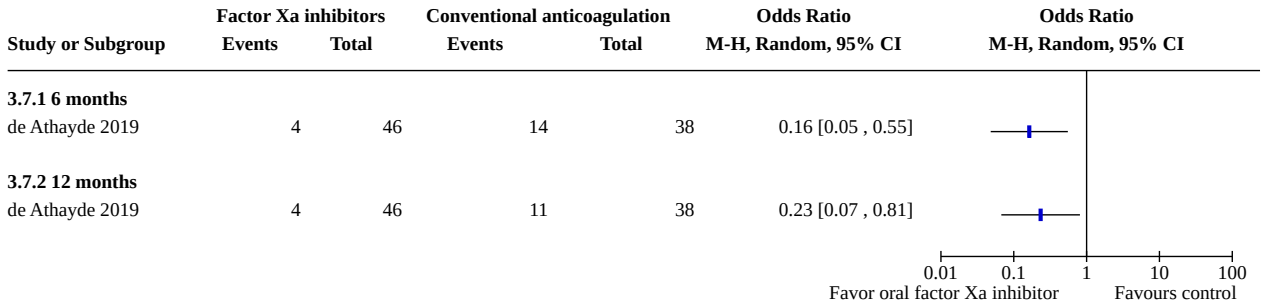


Analysis 3.6. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 6: Major bleeding



Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.6.1 Treatment duration 3 months						
Botticelli DVT 2008	3	385	0	126	1.2%	2.32 [0.12 , 45.12]
EINSTEIN-DVT 2010	14	1718	20	1711	16.2%	0.69 [0.35 , 1.38]
EINSTEIN-DVT dose 2008	3	405	2	137	3.2%	0.50 [0.08 , 3.05]
eTRIS 2016	0	56	0	28		Not estimable
ODIXa-DVT 2007	10	478	0	126	1.3%	5.67 [0.33 , 97.42]
Subtotal (95% CI)		**3042**		**2128**	**22.0%**	**0.78 [0.42 , 1.43]**
Total events:	30		22			
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						
3.6.2 Treatment duration > 3 months						
AMPLIFY 2013	15	2676	49	2689	20.1%	0.30 [0.17 , 0.54]
AMPLIFY-J 2015	0	22	0	22		Not estimable
Caravaggio 2020	7	272	8	245	8.7%	0.78 [0.28 , 2.19]
de Athayde 2019	0	46	0	38		Not estimable
EINSTEIN-PE 2012	5	603	8	585	7.6%	0.60 [0.20 , 1.85]
Farhan 2019	0	76	2	75	1.2%	0.19 [0.01 , 4.07]
Hokusai VTE Cancer 2018	11	194	8	195	10.3%	1.41 [0.55 , 3.57]
Hokusai-VTE 2013	31	2468	43	2453	25.7%	0.71 [0.45 , 1.14]
J-EINSTEIN DVT and PE 2015	0	47	0	12		Not estimable
Mokadem 2021	2	50	4	50	3.4%	0.48 [0.08 , 2.74]
Ohmori 2019	0	5	0	6		Not estimable
PRAIS 2019	0	35	1	32	1.0%	0.30 [0.01 , 7.52]
Subtotal (95% CI)		**6494**		**6402**	**78.0%**	**0.60 [0.39 , 0.91]**
Total events:	71		123			
Heterogeneity: Tau² = 0.10; Chi² = 10.06, df = 7 (P = 0.19); I² = 30%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Total (95% CI)		**9536**		**8530**	**100.0%**	**0.63 [0.45 , 0.89]**
Total events:	101		145			
Heterogeneity: Tau² = 0.06; Chi² = 13.39, df = 11 (P = 0.27); I² = 18%						
Test for overall effect: Z = 2.67 (P = 0.008)						
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%						

Analysis 3.7. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 7: Post-thrombotic syndrome

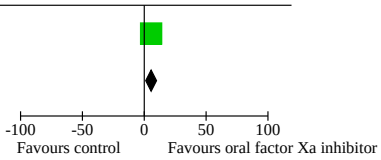


Study or Subgroup	Factor Xa inhibitors Events	Total	Conventional anticoagulation Events	Total	Odds Ratio M-H, Random, 95% CI
3.7.1 6 months					
de Athayde 2019	4	46	14	38	0.16 [0.05 , 0.55]
3.7.2 12 months					
de Athayde 2019	4	46	11	38	0.23 [0.07 , 0.81]

Analysis 3.8. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 8: Health-related quality of life: SF-36 physical component

Study or Subgroup	Oral Xa inhibitor Mean	SD	Total	Conventional anticoagulation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sukovatykh 2017	65.1	8.05	30	59.55	9.9	35	100.0%	5.55 [1.18 , 9.92]
Total (95% CI)			**30**			**35**	**100.0%**	**5.55 [1.18 , 9.92]**

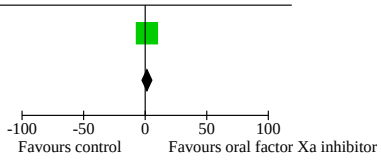
Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 9: Health-related quality of life: SF-36 psychological component

Study or Subgroup	Oral Xa inhibitor Mean	SD	Total	Conventional anticoagulation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sukovatykh 2017	57.06	8.9	30	55.65	7.4	35	100.0%	1.41 [-2.61 , 5.43]
Total (95% CI)			**30**			**35**	**100.0%**	**1.41 [-2.61 , 5.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

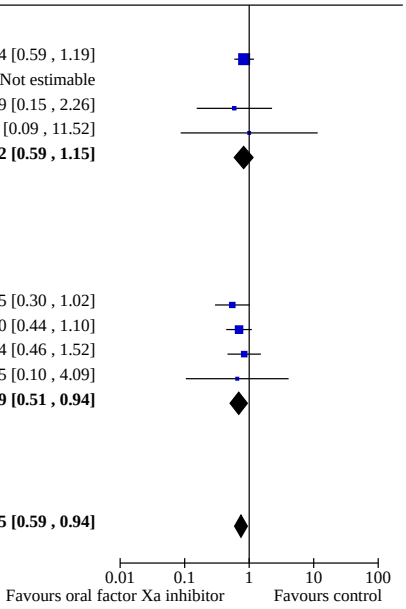


Comparison 4. Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis of participants with versus without active cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Recurrent VTE	7	9827	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.94]
4.1.1 Participants without cancer	4	5579	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.59, 1.15]
4.1.2 Participant with Cancer	4	4248	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.94]
4.2 Major bleeding	9	6801	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.27, 1.08]
4.2.1 Participants without cancer	6	5795	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.17, 0.52]
4.2.2 Participant with Cancer	3	1006	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.49, 1.76]

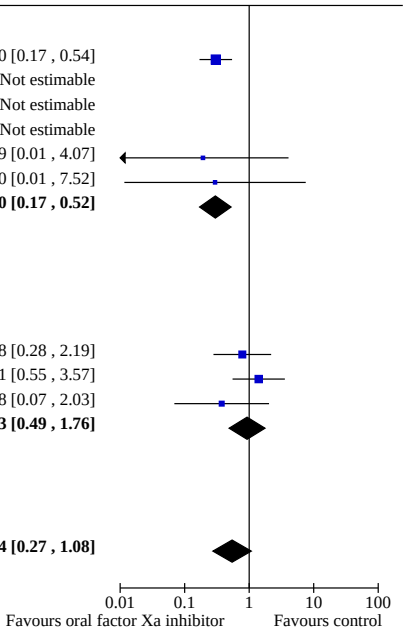
Analysis 4.1. Comparison 4: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis of participants with versus without active cancer, Outcome 1: Recurrent VTE

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4.1.1 Participants without cancer						
AMPLIFY 2013	59	2609	71	2635	42.1%	0.84 [0.59 , 1.19]
AMPLIFY-J 2015	0	22	0	22		Not estimable
EINSTEIN-DVT 2010	4	118	5	89	2.8%	0.59 [0.15 , 2.26]
eTRIS 2016	2	56	1	28	0.9%	1.00 [0.09 , 11.52]
Subtotal (95% CI)		**2805**		**2774**	**45.8%**	**0.82 [0.59 , 1.15]**
Total events:	65		77			
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
4.1.2 Participant with Cancer						
Caravaggio 2020	18	272	28	245	13.4%	0.55 [0.30 , 1.02]
EINSTEIN-DVT 2010	32	1613	46	1629	24.7%	0.70 [0.44 , 1.10]
Hokusai VTE Cancer 2018	23	194	27	195	14.5%	0.84 [0.46 , 1.52]
Mokadem 2021	2	50	3	50	1.5%	0.65 [0.10 , 4.09]
Subtotal (95% CI)		**2129**		**2119**	**54.2%**	**0.69 [0.51 , 0.94]**
Total events:	75		104			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**4934**		**4893**	**100.0%**	**0.75 [0.59 , 0.94]**
Total events:	140		181			
Heterogeneity: Tau² = 0.00; Chi² = 1.77, df = 6 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.53 (P = 0.01)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						



Analysis 4.2. Comparison 4: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis of participants with versus without active cancer, Outcome 2: Major bleeding

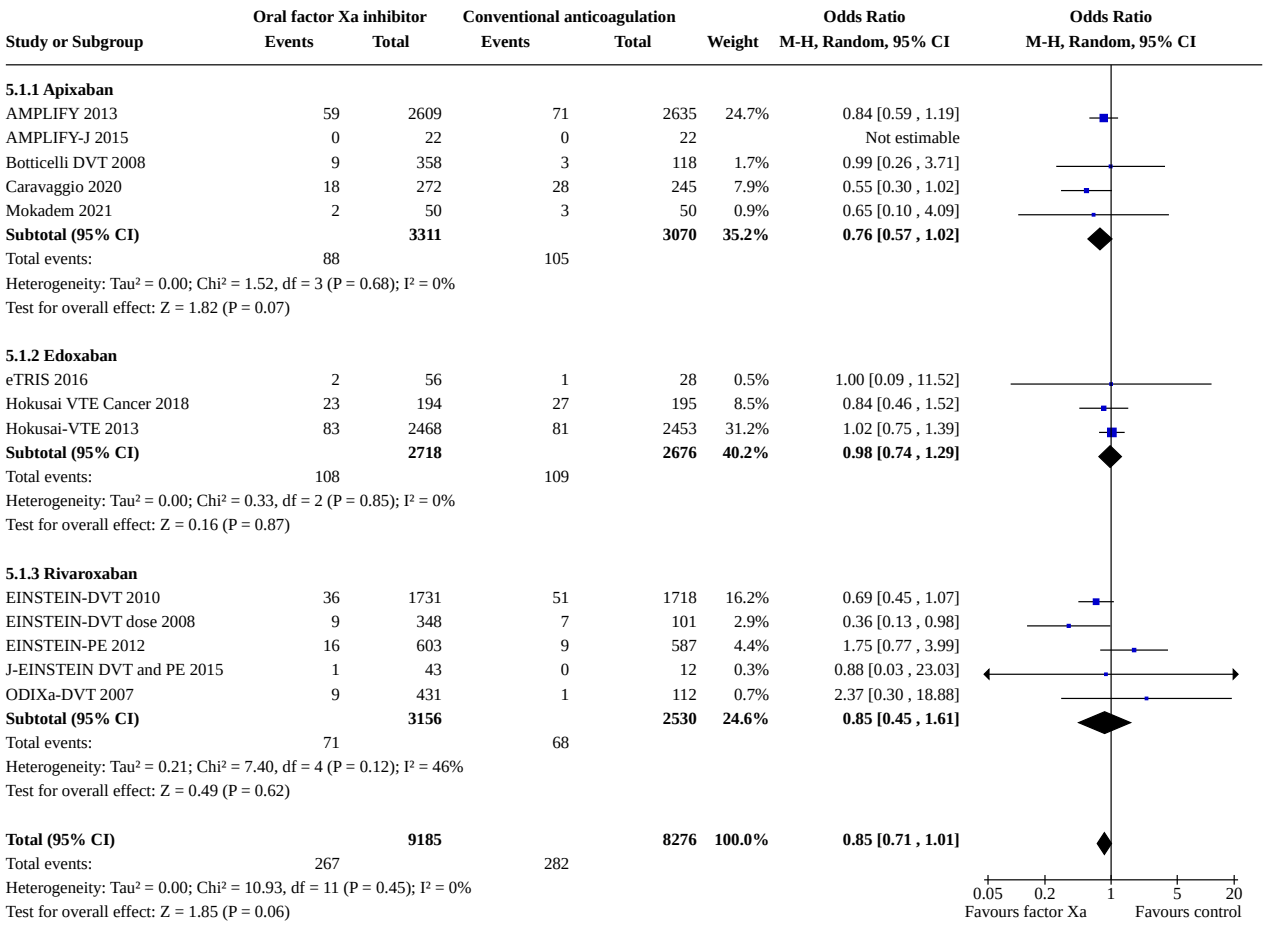
Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4.2.1 Participants without cancer						
AMPLIFY 2013	15	2676	49	2689	33.3%	0.30 [0.17 , 0.54]
AMPLIFY-J 2015	0	22	0	22		Not estimable
de Athayde 2019	0	46	0	38		Not estimable
eTRIS 2016	0	56	0	28		Not estimable
Farhan 2019	0	76	2	75	4.5%	0.19 [0.01 , 4.07]
PRAIS 2019	0	35	1	32	4.1%	0.30 [0.01 , 7.52]
Subtotal (95% CI)		**2911**		**2884**	**41.9%**	**0.30 [0.17 , 0.52]**
Total events:	15		52			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
4.2.2 Participant with Cancer						
Caravaggio 2020	7	272	8	245	22.0%	0.78 [0.28 , 2.19]
Hokusai VTE Cancer 2018	11	194	8	195	24.2%	1.41 [0.55 , 3.57]
Mokadem 2021	2	50	5	50	11.9%	0.38 [0.07 , 2.03]
Subtotal (95% CI)		**516**		**490**	**58.1%**	**0.93 [0.49 , 1.76]**
Total events:	20		21			
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 2 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**3427**		**3374**	**100.0%**	**0.54 [0.27 , 1.08]**
Total events:	35		73			
Heterogeneity: Tau² = 0.28; Chi² = 8.87, df = 5 (P = 0.11); I² = 44%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Chi² = 6.79, df = 1 (P = 0.009), I² = 85.3%						



Comparison 5. Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Recurrent venous thromboembolism	13	17461	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.01]
5.1.1 Apixaban	5	6381	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.57, 1.02]
5.1.2 Edoxaban	3	5394	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.29]
5.1.3 Rivaroxaban	5	5686	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.61]
5.2 Recurrent deep vein thrombosis	9	16439	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.49, 1.01]
5.2.1 Apixaban	3	5820	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.40, 1.07]
5.2.2 Edoxaban	1	4921	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.68, 1.59]
5.2.3 Rivaroxaban	5	5698	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.29, 1.09]
5.3 Fatal pulmonary embolism	6	15082	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.69, 2.02]
5.3.1 Apixaban	2	5720	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.39, 1.71]
5.3.2 Edoxaban	1	4921	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.73, 4.16]
5.3.3 Rivaroxaban	3	4441	Odds Ratio (M-H, Random, 95% CI)	1.98 [0.34, 11.62]
5.4 Non-fatal pulmonary embolism	7	15166	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.68, 1.27]
5.4.1 Apixaban	2	5720	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.08, 4.98]
5.4.2 Edoxaban	2	5005	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.46, 1.32]
5.4.3 Rivaroxaban	3	4441	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.64]
5.5 All-cause mortality	9	10770	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.14]
5.5.1 Apixaban	4	6058	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.59, 1.65]
5.5.2 Rivaroxaban	5	4712	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.56, 1.23]
5.6 Major bleeding	17	18066	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.89]
5.6.1 Apixaban	6	7141	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.27, 1.42]
5.6.2 Edoxaban	4	5405	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.48, 1.64]
5.6.3 Rivaroxaban	7	5520	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.36, 1.05]

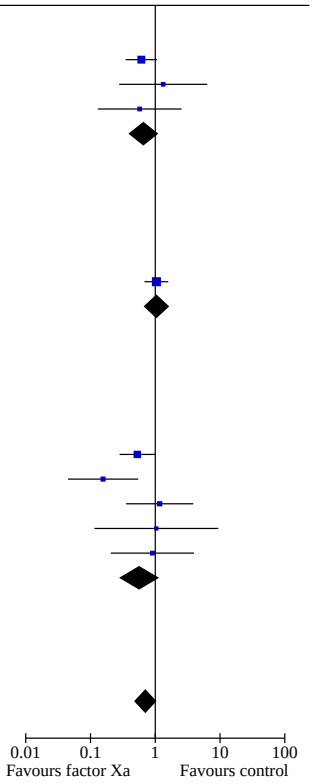
Analysis 5.1. Comparison 5: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors, Outcome 1: Recurrent venous thromboembolism



Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
5.1.1 Apixaban						
AMPLIFY 2013	59	2609	71	2635	24.7%	0.84 [0.59 , 1.19]
AMPLIFY-J 2015	0	22	0	22		Not estimable
Botticelli DVT 2008	9	358	3	118	1.7%	0.99 [0.26 , 3.71]
Caravaggio 2020	18	272	28	245	7.9%	0.55 [0.30 , 1.02]
Mokadem 2021	2	50	3	50	0.9%	0.65 [0.10 , 4.09]
Subtotal (95% CI)		**3311**		**3070**	**35.2%**	**0.76 [0.57 , 1.02]**
Total events:	88		105			
Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 3 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
5.1.2 Edoxaban						
eTRIS 2016	2	56	1	28	0.5%	1.00 [0.09 , 11.52]
Hokusai VTE Cancer 2018	23	194	27	195	8.5%	0.84 [0.46 , 1.52]
Hokusai-VTE 2013	83	2468	81	2453	31.2%	1.02 [0.75 , 1.39]
Subtotal (95% CI)		**2718**		**2676**	**40.2%**	**0.98 [0.74 , 1.29]**
Total events:	108		109			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
5.1.3 Rivaroxaban						
EINSTEIN-DVT 2010	36	1731	51	1718	16.2%	0.69 [0.45 , 1.07]
EINSTEIN-DVT dose 2008	9	348	7	101	2.9%	0.36 [0.13 , 0.98]
EINSTEIN-PE 2012	16	603	9	587	4.4%	1.75 [0.77 , 3.99]
J-EINSTEIN DVT and PE 2015	1	43	0	12	0.3%	0.88 [0.03 , 23.03]
ODIXa-DVT 2007	9	431	1	112	0.7%	2.37 [0.30 , 18.88]
Subtotal (95% CI)		**3156**		**2530**	**24.6%**	**0.85 [0.45 , 1.61]**
Total events:	71		68			
Heterogeneity: Tau² = 0.21; Chi² = 7.40, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Total (95% CI)		**9185**		**8276**	**100.0%**	**0.85 [0.71 , 1.01]**
Total events:	267		282			
Heterogeneity: Tau² = 0.00; Chi² = 10.93, df = 11 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Test for subgroup differences: Chi² = 1.48, df = 2 (P = 0.48), I² = 0%						

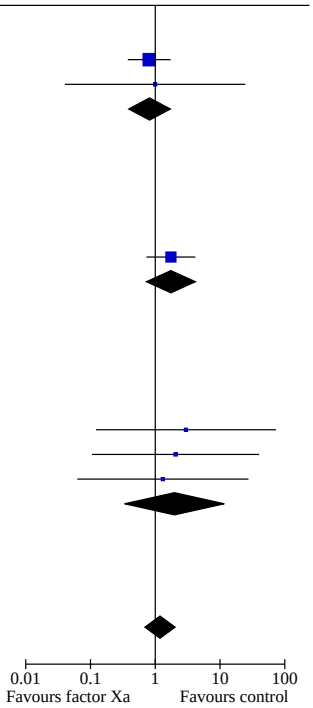
Analysis 5.2. Comparison 5: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors, Outcome 2: Recurrent deep vein thrombosis

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
5.2.1 Apixaban						
AMPLIFY 2013	20	2609	33	2635	21.3%	0.61 [0.35 , 1.06]
Botticelli DVT 2008	8	358	2	118	4.9%	1.33 [0.28 , 6.33]
Mokadem 2021	3	50	5	50	5.3%	0.57 [0.13 , 2.55]
Subtotal (95% CI)		**3017**		**2803**	**31.4%**	**0.65 [0.40 , 1.07]**
Total events:	31		40			
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
5.2.2 Edoxaban						
Hokusai-VTE 2013	45	2468	43	2453	27.0%	1.04 [0.68 , 1.59]
Subtotal (95% CI)		**2468**		**2453**	**27.0%**	**1.04 [0.68 , 1.59]**
Total events:	45		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.19 (P = 0.85)						
5.2.3 Rivaroxaban						
EINSTEIN-DVT 2010	15	1731	28	1718	18.7%	0.53 [0.28 , 0.99]
EINSTEIN-DVT dose 2008	4	348	7	101	7.1%	0.16 [0.04 , 0.54]
EINSTEIN-PE 2012	6	603	5	587	7.7%	1.17 [0.36 , 3.85]
ODIXa-DVT 2007	4	431	1	112	2.6%	1.04 [0.12 , 9.40]
PRAIS 2019	4	35	4	32	5.4%	0.90 [0.21 , 3.96]
Subtotal (95% CI)		**3148**		**2550**	**41.5%**	**0.56 [0.29 , 1.09]**
Total events:	33		45			
Heterogeneity: Tau² = 0.20; Chi² = 6.22, df = 4 (P = 0.18); I² = 36%						
Test for overall effect: Z = 1.69 (P = 0.09)						
Total (95% CI)		**8633**		**7806**	**100.0%**	**0.70 [0.49 , 1.01]**
Total events:	109		128			
Heterogeneity: Tau² = 0.08; Chi² = 11.42, df = 8 (P = 0.18); I² = 30%						
Test for overall effect: Z = 1.90 (P = 0.06)						
Test for subgroup differences: Chi² = 3.20, df = 2 (P = 0.20), I² = 37.5%						



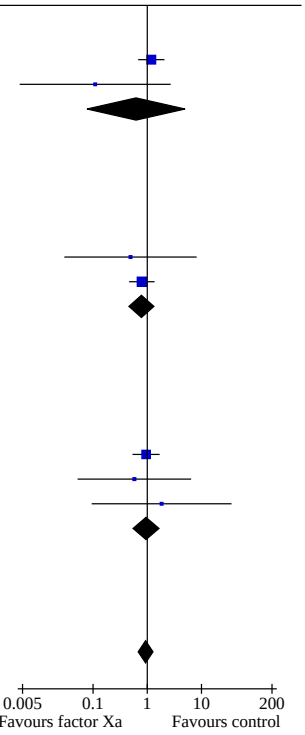
Analysis 5.3. Comparison 5: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors, Outcome 3: Fatal pulmonary embolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
5.3.1 Apixaban						
AMPLIFY 2013	12	2609	15	2635	49.9%	0.81 [0.38 , 1.73]
Botticelli DVT 2008	1	358	0	118	2.8%	0.99 [0.04 , 24.58]
Subtotal (95% CI)		**2967**		**2753**	**52.7%**	**0.82 [0.39 , 1.71]**
Total events:	13		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
5.3.2 Edoxaban						
Hokusai-VTE 2013	14	2468	8	2453	38.1%	1.74 [0.73 , 4.16]
Subtotal (95% CI)		**2468**		**2453**	**38.1%**	**1.74 [0.73 , 4.16]**
Total events:	14		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
5.3.3 Rivaroxaban						
EINSTEIN-DVT 2010	1	1731	0	1718	2.8%	2.98 [0.12 , 73.18]
EINSTEIN-DVT dose 2008	3	348	0	101	3.3%	2.06 [0.11 , 40.14]
ODIXa-DVT 2007	2	431	0	112	3.1%	1.31 [0.06 , 27.47]
Subtotal (95% CI)		**2510**		**1931**	**9.2%**	**1.98 [0.34 , 11.62]**
Total events:	6		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.45)						
Total (95% CI)		**7945**		**7137**	**100.0%**	**1.18 [0.69 , 2.02]**
Total events:	33		23			
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 5 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.5%						



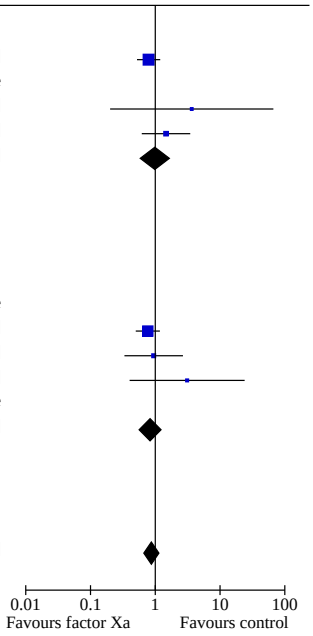
Analysis 5.4. Comparison 5: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors, Outcome 4: Non-fatal pulmonary embolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
5.4.1 Apixaban						
AMPLIFY 2013	27	2609	23	2635	31.5%	1.19 [0.68 , 2.08]
Botticelli DVT 2008	0	358	1	118	1.0%	0.11 [0.00 , 2.70]
Subtotal (95% CI)		**2967**		**2753**	**32.5%**	**0.62 [0.08 , 4.98]**
Total events:	27		24			
Heterogeneity: Tau² = 1.47; Chi² = 2.07, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 0.45 (P = 0.65)						
5.4.2 Edoxaban						
eTRIS 2016	1	56	1	28	1.2%	0.49 [0.03 , 8.15]
Hokusai-VTE 2013	24	2468	30	2453	33.8%	0.79 [0.46 , 1.36]
Subtotal (95% CI)		**2524**		**2481**	**35.0%**	**0.78 [0.46 , 1.32]**
Total events:	25		31			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
5.4.3 Rivaroxaban						
EINSTEIN-DVT 2010	23	1731	24	1718	29.7%	0.95 [0.53 , 1.69]
EINSTEIN-DVT dose 2008	2	348	1	101	1.7%	0.58 [0.05 , 6.44]
ODIXa-DVT 2007	3	431	0	112	1.1%	1.84 [0.09 , 35.84]
Subtotal (95% CI)		**2510**		**1931**	**32.5%**	**0.95 [0.55 , 1.64]**
Total events:	28		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**8001**		**7165**	**100.0%**	**0.93 [0.68 , 1.27]**
Total events:	80		80			
Heterogeneity: Tau² = 0.00; Chi² = 3.34, df = 6 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 0.34, df = 2 (P = 0.84), I² = 0%						

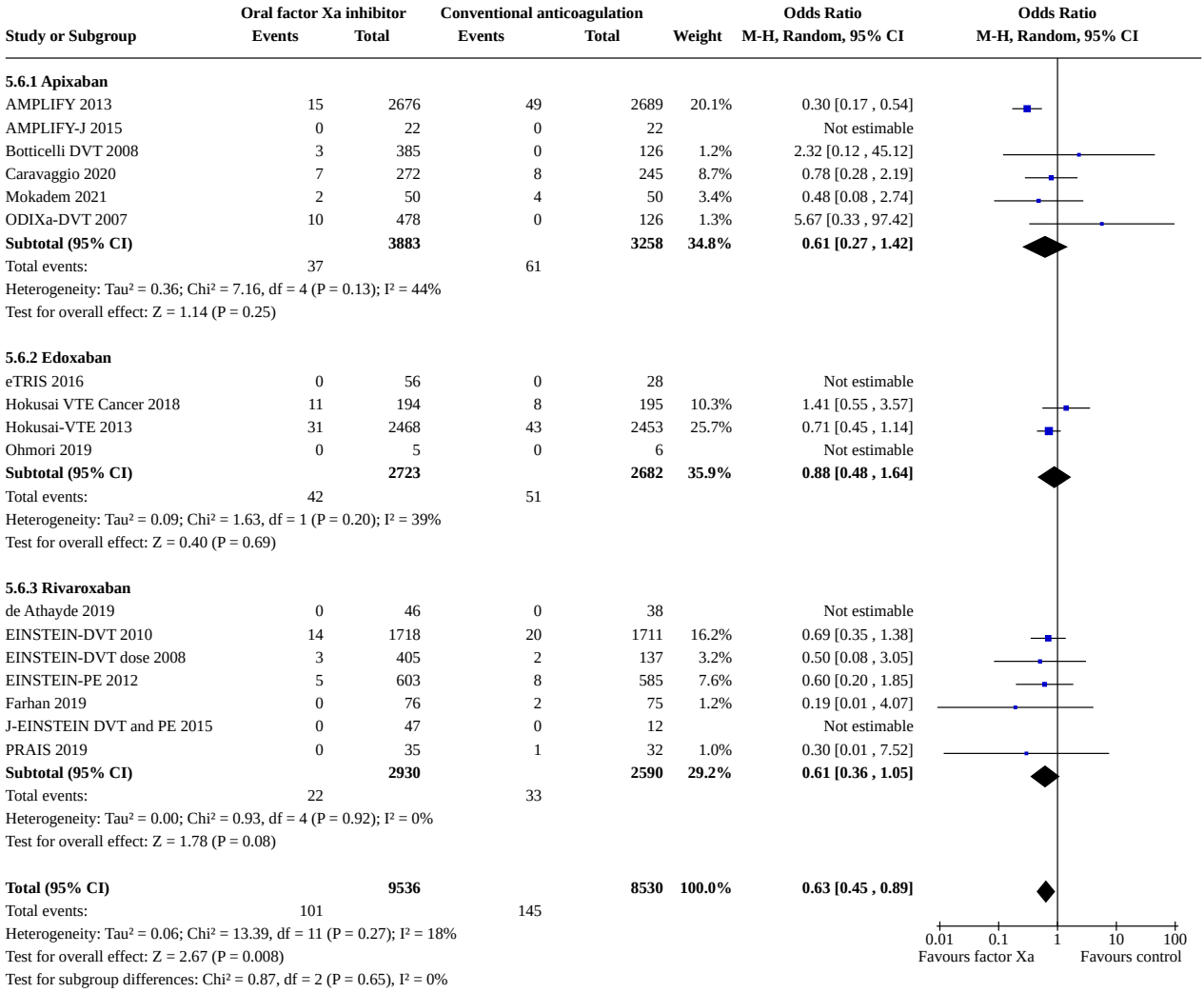


Analysis 5.5. Comparison 5: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors, Outcome 5: All-cause mortality

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
5.5.1 Apixaban						
AMPLIFY 2013	41	2676	52	2689	42.1%	0.79 [0.52 , 1.19]
AMPLIFY-J 2015	0	22	0	22		Not estimable
Botticelli DVT 2008	5	385	0	126	0.9%	3.66 [0.20 , 66.60]
Mokadem 2021	15	69	11	69	9.7%	1.46 [0.62 , 3.47]
Subtotal (95% CI)		**3152**		**2906**	**52.6%**	**0.98 [0.59 , 1.65]**
Total events:	61		63			
Heterogeneity: Tau² = 0.06; Chi² = 2.52, df = 2 (P = 0.28); I² = 21%						
Test for overall effect: Z = 0.06 (P = 0.95)						
5.5.2 Rivaroxaban						
de Athayde 2019	0	46	0	38		Not estimable
EINSTEIN-DVT 2010	38	1718	49	1711	39.0%	0.77 [0.50 , 1.18]
EINSTEIN-DVT dose 2008	14	405	5	137	6.6%	0.95 [0.33 , 2.67]
ODIXa-DVT 2007	13	478	1	112	1.7%	3.10 [0.40 , 23.97]
PRAIS 2019	0	35	0	32		Not estimable
Subtotal (95% CI)		**2682**		**2030**	**47.4%**	**0.83 [0.56 , 1.23]**
Total events:	65		55			
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**5834**		**4936**	**100.0%**	**0.87 [0.67 , 1.14]**
Total events:	126		118			
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						



Analysis 5.6. Comparison 5: Oral factor Xa inhibitors versus conventional anticoagulation: subgroup analysis by different oral factor Xa inhibitors, Outcome 6: Major bleeding



Comparison 6. Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies)

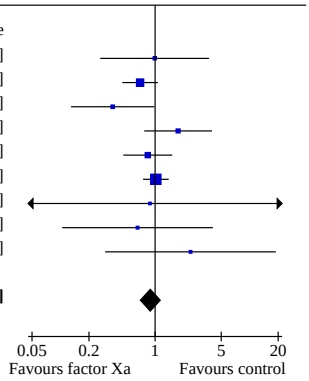
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Recurrent venous thromboembolism	10	11616	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.70, 1.13]
6.2 Recurrent deep vein thrombosis	8	11195	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.45, 1.13]
6.3 Fatal pulmonary embolism	5	9838	Odds Ratio (M-H, Random, 95% CI)	1.73 [0.81, 3.69]
6.4 Non-fatal pulmonary embolism	5	9838	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.23]
6.5 All-cause mortality	7	5321	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.66, 1.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.6 Major bleeding	11	11855	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.55, 1.05]

Analysis 6.1. Comparison 6: Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies), Outcome 1: Recurrent venous thromboembolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMPLIFY-J 2015	0	22	0	22		Not estimable
Botticelli DVT 2008	9	358	3	118	3.2%	0.99 [0.26 , 3.71]
EINSTEIN-DVT 2010	36	1731	51	1718	24.9%	0.69 [0.45 , 1.07]
EINSTEIN-DVT dose 2008	9	348	7	101	5.4%	0.36 [0.13 , 0.98]
EINSTEIN-PE 2012	16	603	9	587	8.0%	1.75 [0.77 , 3.99]
Hokusai VTE Cancer 2018	23	194	27	195	14.5%	0.84 [0.46 , 1.52]
Hokusai-VTE 2013	83	2468	81	2453	40.3%	1.02 [0.75 , 1.39]
J-EINSTEIN DVT and PE 2015	1	43	0	12	0.5%	0.88 [0.03 , 23.03]
Mokadem 2021	2	50	3	50	1.7%	0.65 [0.10 , 4.09]
ODIXa-DVT 2007	9	431	1	112	1.3%	2.37 [0.30 , 18.88]
Total (95% CI)		**6248**		**5368**	**100.0%**	**0.89 [0.70 , 1.13]**
Total events:	188		182			

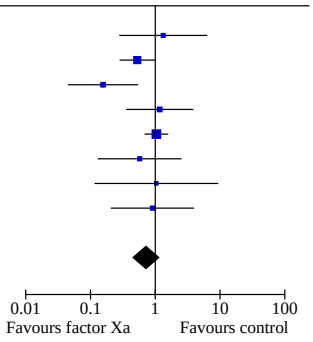
Heterogeneity: Tau² = 0.01; Chi² = 8.74, df = 8 (P = 0.36); I² = 8%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies), Outcome 2: Recurrent deep vein thrombosis

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Botticelli DVT 2008	8	358	2	118	7.0%	1.33 [0.28 , 6.33]
EINSTEIN-DVT 2010	15	1731	28	1718	22.9%	0.53 [0.28 , 0.99]
EINSTEIN-DVT dose 2008	4	348	7	101	10.0%	0.16 [0.04 , 0.54]
EINSTEIN-PE 2012	6	603	5	587	10.7%	1.17 [0.36 , 3.85]
Hokusai-VTE 2013	45	2468	43	2453	30.2%	1.04 [0.68 , 1.59]
Mokadem 2021	3	50	5	50	7.6%	0.57 [0.13 , 2.55]
ODIXa-DVT 2007	4	431	1	112	3.9%	1.04 [0.12 , 9.40]
PRAIS 2019	4	35	4	32	7.7%	0.90 [0.21 , 3.96]
Total (95% CI)		**6024**		**5171**	**100.0%**	**0.72 [0.45 , 1.13]**
Total events:	89		95			

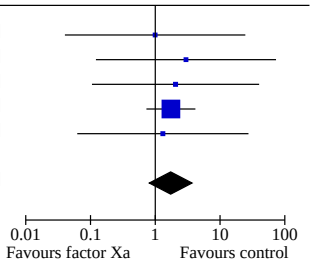
Heterogeneity: Tau² = 0.13; Chi² = 10.79, df = 7 (P = 0.15); I² = 35%
Test for overall effect: Z = 1.43 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6: Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies), Outcome 3: Fatal pulmonary embolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Botticelli DVT 2008	1	358	0	118	5.6%	0.99 [0.04 , 24.58]
EINSTEIN-DVT 2010	1	1731	0	1718	5.6%	2.98 [0.12 , 73.18]
EINSTEIN-DVT dose 2008	3	348	0	101	6.5%	2.06 [0.11 , 40.14]
Hokusai-VTE 2013	14	2468	8	2453	76.0%	1.74 [0.73 , 4.16]
ODIXa-DVT 2007	2	431	0	112	6.2%	1.31 [0.06 , 27.47]
Total (95% CI)		**5336**		**4502**	**100.0%**	**1.73 [0.81 , 3.69]**
Total events:	21		8			

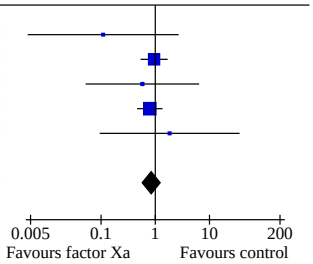
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6: Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies), Outcome 4: Non-fatal pulmonary embolism

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Botticelli DVT 2008	0	358	1	118	1.4%	0.11 [0.00 , 2.70]
EINSTEIN-DVT 2010	23	1731	24	1718	44.1%	0.95 [0.53 , 1.69]
EINSTEIN-DVT dose 2008	2	348	1	101	2.5%	0.58 [0.05 , 6.44]
Hokusai-VTE 2013	24	2468	30	2453	50.3%	0.79 [0.46 , 1.36]
ODIXa-DVT 2007	3	431	0	112	1.7%	1.84 [0.09 , 35.84]
Total (95% CI)		**5336**		**4502**	**100.0%**	**0.84 [0.57 , 1.23]**
Total events:	52		56			

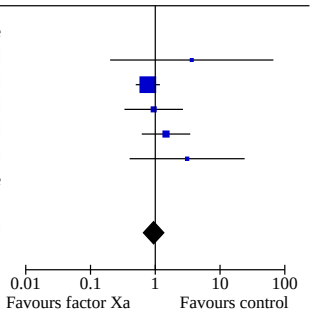
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6: Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies), Outcome 5: All-cause mortality

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMPLIFY-J 2015	0	22	0	22		Not estimable
Botticelli DVT 2008	5	385	0	126	1.6%	3.66 [0.20 , 66.60]
EINSTEIN-DVT 2010	38	1718	49	1711	65.9%	0.77 [0.50 , 1.18]
EINSTEIN-DVT dose 2008	14	405	5	137	12.0%	0.95 [0.33 , 2.67]
Mokadem 2021	15	69	11	69	17.4%	1.46 [0.62 , 3.47]
ODIXa-DVT 2007	13	478	1	112	3.1%	3.10 [0.40 , 23.97]
PRAIS 2019	0	35	0	32		Not estimable
Total (95% CI)		**3112**		**2209**	**100.0%**	**0.94 [0.66 , 1.35]**
Total events:	85		66			

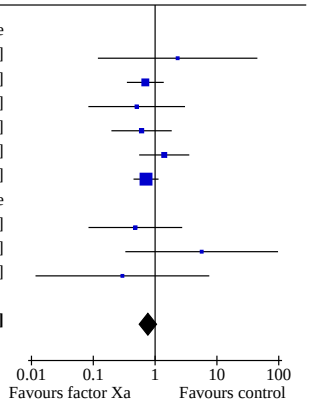
Heterogeneity: Tau² = 0.00; Chi² = 4.06, df = 4 (P = 0.40); I² = 2%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Oral factor Xa inhibitors versus conventional anticoagulation (sensitivity analysis excluding high risk of bias studies), Outcome 6: Major bleeding

Study or Subgroup	Oral factor Xa inhibitor Events	Total	Conventional anticoagulation Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
AMPLIFY-J 2015	0	22	0	22		Not estimable
Botticelli DVT 2008	3	385	0	126	1.2%	2.32 [0.12 , 45.12]
EINSTEIN-DVT 2010	14	1718	20	1711	22.0%	0.69 [0.35 , 1.38]
EINSTEIN-DVT dose 2008	3	405	2	137	3.2%	0.50 [0.08 , 3.05]
EINSTEIN-PE 2012	5	603	8	586	8.2%	0.60 [0.20 , 1.86]
Hokusai VTE Cancer 2018	11	194	8	195	11.9%	1.41 [0.55 , 3.57]
Hokusai-VTE 2013	31	2468	43	2453	47.9%	0.71 [0.45 , 1.14]
J-EINSTEIN DVT and PE 2015	0	47	0	12		Not estimable
Mokadem 2021	2	50	4	50	3.4%	0.48 [0.08 , 2.74]
ODIXa-DVT 2007	10	478	0	126	1.3%	5.67 [0.33 , 97.42]
PRAIS 2019	0	35	1	32	1.0%	0.30 [0.01 , 7.52]
Total (95% CI)		**6405**		**5450**	**100.0%**	**0.76 [0.55 , 1.05]**
Total events:	79		86			

Heterogeneity: Tau² = 0.00; Chi² = 5.26, df = 8 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



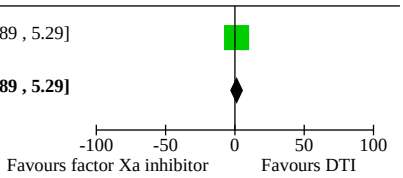
Comparison 7. Oral direct thrombin inhibitor (DTI) versus oral factor Xa inhibitor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Health-related quality of life: SF-36 physical component	1	60	Mean Difference (IV, Random, 95% CI)	1.20 [-2.89, 5.29]
7.2 Health-related quality of life: SF-36 psychological component	1	60	Mean Difference (IV, Random, 95% CI)	5.04 [1.24, 8.84]

Analysis 7.1. Comparison 7: Oral direct thrombin inhibitor (DTI) versus oral factor Xa inhibitor, Outcome 1: Health-related quality of life: SF-36 physical component

Study or Subgroup	DTI Mean	SD	Total	Factor Xa inhibitor Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sukovatykh 2017	66.3	8.1	30	65.1	8.05	30	100.0%	1.20 [-2.89 , 5.29]
Total (95% CI)			**30**			**30**	**100.0%**	**1.20 [-2.89 , 5.29]**

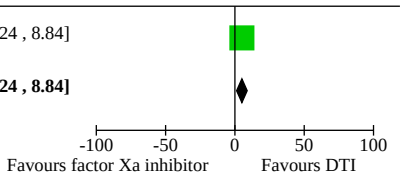
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Oral direct thrombin inhibitor (DTI) versus oral factor Xa inhibitor, Outcome 2: Health-related quality of life: SF-36 psychological component

Study or Subgroup	DTI Mean	DTI SD	DTI Total	Factor Xa inhibotor Mean	Factor Xa inhibotor SD	Factor Xa inhibotor Total	Weight	Mean Difference IV, Random, 95% CI
Sukovatykh 2017	62.1	5.8	30	57.06	8.9	30	100.0%	5.04 [1.24 , 8.84]
Total (95% CI)			**30**			**30**	**100.0%**	**5.04 [1.24 , 8.84]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Sources searched and search strategies

Source		Search strategy	Hits retrieved
1. VASCULAR REGISTER IN CRSW (Date of most recent search: 1 March 2022)		#1 rivaroxaban OR apixaban OR dabigatran OR ximelagatran OR betrixaban OR edoxaban AND INREGISTER	Sep 2018: 130 MARCH 2022: 384
2. CENTRAL via CRSO (Date of most recent search: 1 March 2022)	#1	MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES	Sep 2018: 1310 MARCH 2022: 2042
	#2	MESH DESCRIPTOR Hirudin Therapy	
	#3	(thrombin near3 inhib*):TI,AB,KY	
	#4	hirudin*:TI,AB,KY	
	#5	(dabigatran or Pradaxa or Rendix):TI,AB,KY	
	#6	(BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI,AB,KY	
	#7	(ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY 152	
	#8	(AZD0837 or AZD-0837):TI,AB,KY	
	#9	(S35972 or S-35972):TI,AB,KY	
	#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	
	#11	MESH DESCRIPTOR Factor Xa Inhibitors	
	#12	(Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY	
	#13	(FX* near4 (antag* or inhib* or block*)):TI,AB,KY	
	#14	(10* near4 (antag* or inhib* or block*)):TI,AB,KY	
	#15	#11 OR #12 OR #13 OR #14	
	#16	rivaroxaban or Xarelto	
	#17	Bay-597939 or Bay597939	
	#18	betrixaban or PRT054021	
	#19	apixaban	

(Continued)

	#20 BMS-562247 or BMS-562247 or ELIQUIS #21 DU-176b or DU176b #22 PRT-054021 or PRT054021 #23 YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176* #24 GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893 #25 edoxaban or lixiana #26 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 #27 #10 OR #15 OR #26 #28 MESH DESCRIPTOR Thrombosis #29 MESH DESCRIPTOR Thromboembolism #30 MESH DESCRIPTOR Venous Thromboembolism #31 MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES #32 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):TI,AB,KY #33 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES 882 #34 (PE or DVT or VTE):TI,AB,KY #35 (((vein* or ven*) near thromb*)):TI,AB,KY #36 (blood near3 clot*):TI,AB,KY #37 (pulmonary near3 clot*):TI,AB,KY #38 (lung near3 clot*):TI,AB,KY #39 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 #40 #27 AND #39	
3. Clinicaltrials.gov (Date of most recent search: 1 March 2022)	rivaroxaban OR apixaban OR dabigatran OR ximelagatran OR betrixaban OR edoxaban	Sep 2018: 335 MARCH 2022: 347
4. ICTRP Search Portal (Date of most recent search: 1 March 2022)	rivaroxaban OR apixaban OR dabigatran OR ximelagatran OR betrixaban OR edoxaban	Sep 2018: 504 MARCH 2022: 468
5. MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) 1946 to present (Date of most recent search: 1 March 2022)	1 exp ANTITHROMBINS/ 2 Hirudin Therapy/ 3 (thrombin adj3 inhib*).ti,ab. 4 hirudin*.ti,ab. 5 (dabigatran or Pradaxa or Rendix).ti,ab. 6 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab.	Sep 2018: 906 MARCH 2022: 2582

(Continued)

7 (ximelagatran or Exanta or Exarta or melagatran).ti,ab.

8 (AZD0837 or AZD-0837).ti,ab.

9 (S35972 or S-35972).ti,ab.

10 Factor Xa Inhibitors/

11 (Factor X* adj4 (antag* or inhib* or block*)).ti,ab.

12 (FX* adj4 (antag* or inhib* or block*)).ti,ab.

13 (FX* adj4 (antag* or inhib* or block*)).ti,ab.

14 (10* adj4 (antag* or inhib* or block*)).ti,ab.

15 (rivaroxaban or Xarelto).ti,ab.

16 (Bay-597939 or Bay597939).ti,ab.

17 (betrixaban or PRT054021).ti,ab.

18 apixaban.ti,ab.

19 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab.

20 (DU-176b or DU176b).ti,ab.

21 (PRT-054021 or PRT054021).ti,ab.

22 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab.

23 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab.

24 (edoxaban or lixiana).ti,ab.

25 or/1-21

26 THROMBOSIS/

27 THROMBOEMBOLISM/

28 exp Venous Thromboembolism/

29 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab.

30 exp Pulmonary Embolism/

31 (PE or DVT or VTE).ti,ab.

32 ((vein* or ven*) adj thromb*).ti,ab.

33 (blood adj3 clot*).ti,ab.

34 (pulmonary adj3 clot*).ti,ab.

35 (lung adj3 clot*).ti,ab.

36 or/26-35

37 25 and 36

38 randomized controlled trial.pt.

39 controlled clinical trial.pt.

(Continued)

	40 randomized.ab. 41 placebo.ab. 42 drug therapy.fs. 43 randomly.ab. 44 trial.ab. 45 groups.ab. 46 or/38-45 47 exp animals/ not humans.sh. 48 46 not 47 49 37 and 48	
6. Embase 1974 to present (Date of most recent search: 1 March 2022)	1 exp antithrombin/ 2 anticoagulant therapy/ 3 (thrombin adj3 inhib*).ti,ab. 4 hirudin*.ti,ab. 5 (dabigatran or Pradaxa or Rendix).ti,ab. 6 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab. 7 (ximelagatran or Exanta or Exarta or melagatran).ti,ab. 8 (AZD0837 or AZD-0837).ti,ab. 9 (S35972 or S-35972).ti,ab. 10 blood clotting factor 10a inhibitor/ 11 (Factor X* adj4 (antag* or inhib* or block*)).ti,ab. 12 (FX* adj4 (antag* or inhib* or block*)).ti,ab. 13 (10* adj4 (antag* or inhib* or block*)).ti,ab. 14 (rivaroxaban or Xarelto).ti,ab. 15 (Bay-597939 or Bay597939).ti,ab. 16 (betrixaban or PRT054021).ti,ab. 17 apixaban.ti,ab. 18 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab. 19 (DU-176b or DU176b).ti,ab. 20 (PRT-054021 or PRT054021).ti,ab. 21 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab. 22 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab. 23 (edoxaban or lixiana).ti,ab.	Sep 2018: 2394 MARCH 2022: 5402

(Continued)

24 or/1-23

25 thrombosis/

26 thromboembolism/

27 venous thromboembolism/

28 exp vein thrombosis/

29 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab.

30 exp lung embolism/

31 (DVT or VTE).ti,ab.

32 ((vein* or ven*) adj thromb*).ti,ab.

33 (blood adj3 clot*).ti,ab.

34 (pulmonary adj3 clot*).ti,ab.

35 (lung adj3 clot*).ti,ab.

36 or/25-35

37 24 and 36

38 randomized controlled trial/

39 controlled clinical trial/

40 random$.ti,ab.

41 randomization/

42 intermethod comparison/

43 placebo.ti,ab.

44 (compare or compared or comparison).ti.

45 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

46 (open adj label).ti,ab.

47 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

48 double blind procedure/

49 parallel group$1.ti,ab.

50 (crossover or cross over).ti,ab.

51 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

52 (assigned or allocated).ti,ab.

53 (controlled adj7 (study or design or trial)).ti,ab.

54 (volunteer or volunteers).ti,ab.

55 trial.ti.

(Continued)

	56 or/38-55 57 37 and 56	
7. CINAHL via EBSCO (Date of most recent search: 1 March 2022)	S47 S33 AND S46 S46 S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 S45 MH "Random Assignment" S44 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies" S43 MH "Crossover Design" S42 MH "Factorial Design" S41 MH "Placebos" S40 MH "Clinical Trials" S39 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" S38 TX crossover OR "cross-over" S37 AB placebo* S36 TX random* S35 TX trial* S34 TX "latin square" S33 S22 AND S32 S32 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 S31 TX (lung n3 clot*) S30 TX (pulmonary n3 clot*) S29 TX (blood n3 clot*) S28 TX ((vein* or ven*) n thromb*) S27 TX thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* S26 (MH "Venous Thrombosis+") S25 (MH "Venous Thromboembolism") S24 (MH "Thromboembolism") S23 (MH "Thrombosis") S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 S21 TX edoxaban or lixiana S20 TX GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893 S19 TX YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*	Sep 2018: 78 MARCH 2022: 448

(Continued)

	S18 TX PRT-054021 or PRT054021 S17 TX DU-176b or DU176b S16 TX BMS-562247 or BMS-562247 or ELIQUIS S15 TX apixaban S14 TX betrixaban or PRT054021 S13 TX Bay-597939 or Bay597939 S12 TX rivaroxaban or Xarelto S11 TX (10* n4 (antag* or inhib* or block*)) S10 TX (FX* n4 (antag* or inhib* or block*)) S9 TX (Factor X* n4 (antag* or inhib* or block*)) S8 TX S35972 or S-35972 S7 TX AZD0837 or AZD-0837 S6 TX ximelagatran or Exanta or Exarta or melagatran S5 TX BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048 S4 TX Antithrombins S3 TX dabigatran or Pradaxa or Rendix 945 S2 TX hirudin* S1 TX thrombin n3 inhib*	
8. AMED via Ovid (Date of most recent search: 1 March 2022)	1 (thrombin adj3 inhib*).ti,ab. 2 hirudin*.ti,ab. 3 (dabigatran or Pradaxa or Rendix).ti,ab. 4 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab. 5 (ximelagatran or Exanta or Exarta or melagatran).ti,ab. 6 (AZD0837 or AZD-0837).ti,ab. 7 (S35972 or S-35972).ti,ab. 8 blood clotting factor 10a inhibitor/ 0 9 (Factor X* adj4 (antag* or inhib* or block*)).ti,ab. 10 (FX* adj4 (antag* or inhib* or block*)).ti,ab. 11 (10* adj4 (antag* or inhib* or block*)).ti,ab. 12 (rivaroxaban or Xarelto).ti,ab. 13 (Bay-597939 or Bay597939).ti,ab. 14 (betrixaban or PRT054021).ti,ab. 15 apixaban.ti,ab. 16 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab.	Sep 2018: 0 MARCH 2022: 0

(Continued)

17 (DU-176b or DU176b).ti,ab.

18 (PRT-054021 or PRT054021).ti,ab.

19 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab.

20 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab.

21 (edoxaban or lixiana).ti,ab.

22 or/1-21

23 Thrombosis/

24 Thromboembolism/

25 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab.

26 exp Pulmonary embolism/

27 (PE or DVT or VTE).ti,ab.

28 ((vein* or ven*) adj thromb*).ti,ab.

29 (blood adj3 clot*).ti,ab.

30 (pulmonary adj3 clot*).ti,ab.

31 (lung adj3 clot*).ti,ab.

32 or/23-31

33 22 and 32

34 exp CLINICAL TRIALS/

35 RANDOM ALLOCATION/

36 DOUBLE BLIND METHOD/

37 Clinical trial.pt.

38 (clinic* adj trial*).tw.

39 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw.

40 PLACEBOS/

41 placebo*.tw.

42 random*.tw.

43 PROSPECTIVE STUDIES/

44 or/34-43

45 33 and 44 2

TOTAL before deduplication	Sep 2018: 5372 MARCH 2022: 11673
TOTAL after deduplication	Sep 2018: 3990

(Continued)

FEEDBACK

Feedback on risk of bias, 4 July 2015

Summary

Thank-you for your systematic review of the oral direct thrombin inhibitors and factor Xa inhibitors for the treatment of deep vein thrombosis. As part of our pharmacy residency, we are critically appraising Cochrane Reviews, with a focus on risk of bias assessment. We are hoping to clarify a few discrepancies found in your review. Although we used examples from the AMPLIFY trial (Agnelli 2013A), the issues described below are also present in the other risk of bias tables. A revision of the risk of bias assessment for all of the trials included is suggested.

1. Random sequence generation (selection bias)
The review states, "randomisation was performed with the use of an interactive voice-response system. Comment: study judged at low risk." However, this captures only allocation concealment, not the method of random sequence generation. From the Cochrane Handbook (Ch 8.10.2), "methods for allocation concealment refer to techniques used to implement the sequence, not to generate it". The AMPLIFY protocol (Agnelli 2013B pg. 5) elaborates, stating, "subjects will be randomized (1:1 ratio) to groups 1 or 2 using a central interactive voice response system (IVRS)". The randomization methods are still unclear, and the authors should be contacted for clarification. The Cochrane Handbook (Ch 8.9.2.3) suggests that, "if there is doubt, then the adequacy of sequence generation should be considered to be unclear" (Higgins 2011). In our opinion, we cannot be confident that the incompletely defined randomization approach can be considered low risk; at this point, it seems to be unclear.

2. Blinding of participants and personnel (performance bias)
The review states, "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." The AMPLIFY protocol (Agnelli 2013B pg. 47) states "subjects, investigators, members of any of the administrative and adjudicating committees, and the sponsor's staff conducting the study, will not have access to individual subject treatment assignments". However, it is unclear if all healthcare providers involved in the care the subjects were included under 'investigators'. The bias rating may be considered 'unclear risk' if the AMPLIFY authors are unable to provide this information. Additionally, INR blinding was addressed under, 'blinding of outcome assessment (detection bias)'. In our opinion, as INR unblinding would influence performance bias, the description may be more appropriate there. Furthermore, blinding was considered 'impossible' due to LMWH SC injections and VKA administration for a number of trials, and judged to be 'low risk'. However, the AMPLIFY trial was successfully blinded in this regard (Agnelli 2013A). The risk of bias assessments should reflect the inadequate blinding in these trials as blinding was possible.

3. Incomplete outcome data (attrition bias)
The review states "no missing outcome data" and is categorized as 'low risk' of bias. However, we disagree with this categorization as a number of randomized subjects were inappropriately excluded from the intention-to-treat (ITT) analysis (Agnelli 2013A fig 1). Additionally, the denominators in each of the treatment groups were not the same (Agnelli 2013A). From the safety analysis, the apixaban and conventional groups had 2676 and 2689 patients, respectively (Agnelli 2013A table 2). In comparison to the efficacy outcome, only 2609 and 2635 subjects in each group, respectively, were analyzed (Agnelli 2013A table 2). The AMPLIFY supplementary appendix attempted to address this issue with a sensitivity analysis (Agnelli 2013D table S1). However, the authors assumed that none of missing subjects experienced a first recurrent VTE or VTE-related death. A graded scale of assumptions (ie. 0, 25, 50, or 100%) would more accurately reflect how the missing subjects could have influenced the end-points. In addition, with regards to the number of subjects who discontinue study treatment, we noted that while both treatment arms had similar numbers, a high proportion of patients (apixaban 144/377; conventional 142/413) were classified as discontinuing for 'other reasons' with no given explanations (Agnelli 2013A fig 3). The Cochrane Handbook (Ch 8.13.1) suggests that, "missing outcome data...raise the possibility that the observed effect estimate is biased" (Higgins 2011). Given the large proportion of subjects discontinuing for 'other reasons', the reasons should be known and deemed appropriate. At this point we suggest that, until clarification is sought from the authors, the classification should be changed to unclear risk.

4. Selective reporting (reporting bias)
The review states, "study protocol was available and all of the study's pre-specified outcomes were reported in the pre-specified way". However, we noted a few discrepancies that we would like to have clarified.
a. The number of subjects who died in the AMPLIFY trial (apixaban 41/2676; conventional 52/2689) do not match the 'all-cause mortality' forest plot (apixaban 29/2676; conventional 36/2689) on pg. 70 of the review (Agnelli 2013A; Robertson 2015). Interestingly, the number of deaths excluded is the exact sum of the fatal PEs and deaths for which PE could not be ruled out. Is it possible that these categories were excluded? If so, we suggest they be included. The exclusion of deaths from the meta-analysis may skew the results towards better safety outcomes for apixaban.
b. We noted that the safety analyses period in the AMPLIFY trial encompassed the time from administration of the first dose up until 48 hours after the last dose (Agnelli 2013A). Given that bleeds may occur later than 48 hours, any bleeding events after 48 hours of drug

discontinuation are not reflected in the trial results, which may underestimate apixaban's risk of harm. Follow-up continued for 30 days after the end of the intended treatment period (Agnelli 2013A pg. 5), therefore, it is likely the authors have this data. One approach would be to acquire the data from the authors, if available, and include it in your review. At minimum, we suggest this category be rated high risk due to this outcome alone, simply because the major bleed risk is likely underestimated and readers should be made aware.
c. There are several secondary efficacy and safety endpoints, from the Statistical Analysis Plan (SAP) that were not reported in the AMPLIFY trial, such as minor bleeding, which may under-report the bleeding risk (Agnelli 2013C pg 15-22). Additionally, pre-planned demographic variables (ie. race/ethnicity) are also missing from the trial (Agnelli 2013C pg 22), which have the potential to mislead the readers of the harm or lack of benefit in racial subgroup populations. The Cochrane Handbook (Ch 8.14.2) suggests that "when there is suspicion of or direct evidence for selective outcome reporting it is desirable to ask the study authors for additional information" (Higgins 2011). We were uncertain if the authors of the AMPLIFY trial were contacted regarding these discrepancies.

5. Other bias
The review categorized other bias as "unclear risk. Comment: The study was funded by Pfizer and Bristol-Myers Squibb, the pharmaceutical companies that developed apixaban." While we agree that there is no tool to assess funding bias, it is possible that funding influenced the timeframe of reported safety endpoints, which may inaccurately suggest a lower risk of bleeding as detailed above. Additionally, the AMPLIFY trial analyzed non-inferiority using an ITT analysis (Agnelli 2013A). When compared with the preferred per-protocol analysis, ITT favors the finding of non-inferior results. This may have skewed the result in favor of an increased efficacy of apixaban. The Cochrane Handbook (Ch 8.15.1.5) suggests these types of uncertainties should be commented on in the 'Other Bias' section (Higgins 2011).

Overall, if the discussed issues are not corrected the results would inaccurately reflect more favorable efficacy and safety outcomes for apixaban. We hope you will modify the review based on our suggestions and reflect this change in your assessment of the quality of evidence.
Thank-you for your time.

References:

AMPLIFY study
Agnelli 2013A: Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013 Aug 29;369(9):799-808.
Agnelli 2013B: Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism (Protocol). N Engl J Med. 2013 Aug 29;369(9):799-808.
Agnelli 2013C: Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism (Statistical Analysis Plan). N Engl J Med. 2013 Aug 29;369(9):799-808.
Agnelli 2013D: Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism (Supplementary Appendix). N Engl J Med. 2013 Aug 29;369(9):799-808.

Higgins 2011: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Robertson 2015: Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis (Review). Cochrane Database Syst Rev. 2015 Jun 30;6:CD010956.

Reply

1. Random sequence generation (selection bias)
We agree and the review has been changed so that the risk of selection bias has been deemed to be unclear due to inadequate description of the random sequence generation.

2. Blinding of participants and personnel (performance bias)
In response to your first comment regarding whether all healthcare providers were included under investigators, we assumed that only those personnel directly involved with a trial were considered investigators. Therefore, it is very likely that other healthcare providers were not considered as such. We do not think the risk of the risk of detection bias should be changed to unclear due to the fact that, as treatments were double blind, it is unlikely that other healthcare providers had access to treatment assignments.

With regard to the second comment that INR blinding would influence performance bias, we agree and this has been moved to within the risk of bias table in the review.

In reference to your third comment that some open-label trials could be prone to performance bias, we respectfully disagree. We are aware that blinding in these trials was possible, as shown in the AMPLIFY trial. However, given that all outcomes in this review were clinical (DVT, PE, death, bleeding), we feel that unblinded treatment would not have affected these outcomes. The only way open-label treatment could introduce bias would be if those assessing the outcome were not blinded to the treatment allocation. In all of these studies, outcome assessors were blinded and therefore there is little to no risk of bias. We feel that this is adequately described in both the risk of bias tables and the text of the review.

3. Incomplete outcome data (attrition bias)

In response to your first comment regarding missing outcome data, we agree that in the AMPLIFY study, a number of randomised patients were inappropriately excluded from the intention-to-treat analysis. Therefore the review has been changed so that the risk of attrition bias is unclear for this study.

In response to your second comment regarding different denominators in the AMPLIFY study, the efficacy analysis was "based on patients in the intention-to-treat population for whom the outcome status at 6 months was documented". While the safety analysis was from "patients during study treatment, defined as the time from the administration of the first dose until 48 hours after the last dose was administered". Therefore we assumed that the efficacy analysis would be based on fewer patients as those who had discontinued treatment, been withdrawn, died etc. within those 6 months would be excluded. The trialists have reported as planned in their protocol but this is not ITT.

In response to your third comment regarding the number of subjects who discontinued study treatment, we agree and the risk of bias table has been changed to reflect this. A statement has also been added to the review under attrition bias.

4. Selective reporting (reporting bias)
a. We agree that outcome all-cause mortality should include all causes of death even if they are already included and reported as another outcome e.g. fatal PE. This has been amended for all studies in the review.

b. The 48 hours after the last dose of apixaban covers 4 half-lives of the drug (i.e. down to 6.25% of the therapeutic level). Causes of prolonged half-life of apixaban were dealt with in the exclusion criteria. Thus, any bleeding after 48 hours from the last dose (especially as this was after 6 months of therapy) would be extremely unlikely to be due to the drug.

c. We realise that minor bleeding was not reported even though it was a pre-defined outcome. The risk of bias table for the AMPLIFY study has been changed to reflect this. However, it should be noted that the definition of 'minor bleeding' is one of exclusion (not in any other of the bleeding categories) and as such is an extremely weak measure of risk, depending as it does on whether the patient can remember to report the event. Subgroup analyses were not included in the original study protocol; nor in the main publication; and therefore, not in this meta-analysis.

5. Other bias
We agree and a sentence has been added to the risk of bias table for the AMPLFY study and also in the main text of the review.

Contributors

Feedback: Carly Hoffman BSc, BScPharm, Gary Kwan BSc, BScPharm, Candice Leung BScPharm, Aaron M Tejani, BSc(Pharm), PharmD
AMT: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback

Reply: Lindsay Robertson and Patrick Kesteven

WHAT'S NEW

Date	Event	Description
14 April 2023	New citation required but conclusions have not changed	Search updated, 10 new studies included, 16 studies excluded and 11 studies ongoing. New team involved. Text updated to reflect current Cochrane recommendations. Summary of findings tables added.
14 April 2023	New search has been performed	Search updated, 10 new studies included, 16 studies excluded and 11 studies ongoing.

HISTORY

Protocol first published: Issue 2, 2014
Review first published: Issue 6, 2015

Date	Event	Description
25 November 2015	Amended	Declarations of interest statement amended for clarification and transparency on request of Cochrane Funding Arbiter
5 August 2015	Feedback has been incorporated	Feedback addressed by review authors and review text amended
9 July 2015	Feedback has been incorporated	Feedback submitted

CONTRIBUTIONS OF AUTHORS

XW: selected studies for inclusion, extracted data, assessed the risk of bias of studies, performed data analysis and interpretation, created the summary of findings tables using GRADE approach, and updated the review.
YM: selected studies for inclusion, extracted data, assessed the risk of bias of the studies, performed data analysis and interpretation, and updated the review.
XH: selected studies for inclusion, extracted data, assessed the risk of bias of the studies, and updated the review.
ML: selected studies for inclusion, extracted data, assessed the risk of bias of the studies, contacted authors for missing data, and commented on the review.
JL: selected studies for inclusion, extracted data, assessed the risk of bias of the studies, and commented on the review.
JT: commented on the review.
QW: selected studies for inclusion, extracted data, and commented on the review.
PY: commented on the review.
JFL: provided clinical consultation during update process.
PX: provided clinical consultation during update process.
KY: commented on the review.
LY: selected studies for inclusion, commented on the review, and provided methodological guidance during update process.

DECLARATIONS OF INTEREST

XW: none known.
YM: none known.
XH: none known.
ML: none known.
JL: none known.
JT: none known.
QW: none known.
PY: none known.
JFL: none known.
PX: none known.
KY: none known.
LY: none known.

SOURCES OF SUPPORT

Internal sources

- -, Other

  No internal sources of support

External sources

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

  The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2022 version

For this update, we used a random-effects model for all analyses as we expected clinical heterogeneity across studies. This may be due to different oral factor Xa inhibitors (e.g. apixaban, rivaroxaban, edoxaban), different indirect thrombin inhibitors in the control group (e.g. warfarin, dalteparin), different treatment durations (e.g. three, six or 12 months). We amended 'standard anticoagulation' to 'conventional anticoagulation' throughout for consistency. We redefined 'adverse effects' as 'major bleeding' to allow GRADE assessment and reordered the position of this in the secondary outcomes due to its clinical importance. We used the GRADE approach to assess the certainty of evidence and added summary of finding tables.

2015 version

In a change from the protocol (Robertson 2014), we excluded studies where treatment lasted 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).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [adverse effects]; Antithrombins [adverse effects]; Dabigatran [adverse effects]; Factor Xa Inhibitors [adverse effects]; Hemorrhage [chemically induced]; Neoplasm Recurrence, Local [drug therapy]; *Pulmonary Embolism [drug therapy] [prevention & control]; Rivaroxaban [adverse effects]; *Venous Thromboembolism [prevention & control]; *Venous Thrombosis [complications]

MeSH check words

Humans