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Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of pulmonary embolism (Review)

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Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of pulmonary embolism.
Cochrane Database of Systematic Reviews 2023, Issue 4. Art. No.: CD010957.
DOI: 10.1002/14651858.CD010957.pub3.

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[Intervention Review]

Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of pulmonary embolism

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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: Li M, Li J, Wang X, Hui X, Wang Q, Xie S, Yan P, Tian J, Li J, Xie P, Yang K, Yao L. Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of pulmonary embolism. *Cochrane Database of Systematic Reviews* 2023, Issue 4. Art. No.: CD010957. DOI: 10.1002/14651858.CD010957.pub3.

ABSTRACT

Background

Pulmonary embolism (PE) is a potentially life-threatening condition in which a clot can migrate from the deep veins, most commonly in the leg, to the lungs. Conventional treatment of PE used unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, and vitamin K antagonists (VKAs). Recently, two forms of direct oral anticoagulants (DOACs) have been developed: oral direct thrombin inhibitors (DTIs) and oral factor Xa inhibitors. DOACs have characteristics that may be favourable to conventional treatment, including oral administration, a predictable effect, no need for frequent monitoring or re-dosing, and few known drug interactions. This review reports the efficacy and safety of these drugs in the long-term treatment of PE (minimum duration of three months). This is an update of a Cochrane Review first published in 2015.

Objectives

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

Search methods

The Cochrane Vascular Information Specialist searched 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 to 2 March 2022. We checked the reference lists of relevant articles for additional studies.

Selection criteria

We included randomised controlled trials (RCTs) in which people with a PE confirmed by standard imaging techniques were allocated to receive an oral DTI or an oral factor Xa inhibitor compared with a conventional anticoagulant or compared with each other for the long-term treatment of PE (minimum duration three months).

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were recurrent PE, recurrent venous thromboembolism (VTE), and deep vein thrombosis (DVT). Secondary outcomes were all-cause mortality, major bleeding, and health-related quality of life. We used GRADE to assess the certainty of evidence for each outcome.

Main results

We identified five additional RCTs with 1484 participants for this update. Together with the previously included trials, we have included ten RCTs with a total of 13,073 participants. Two studies investigated an oral DTI (dabigatran) and eight studies investigated oral factor Xa inhibitors (three rivaroxaban, three apixaban, and two edoxaban). The studies were of good methodological quality overall.

Meta-analysis showed no clear difference in the efficacy and safety of oral DTI compared with conventional anticoagulation in preventing recurrent PE (odds ratio (OR) 1.02, 95% confidence interval (CI) 0.50 to 2.04; 2 studies, 1602 participants; moderate-certainty evidence), recurrent VTE (OR 0.93, 95% CI 0.52 to 1.66; 2 studies, 1602 participants; moderate-certainty evidence), DVT (OR 0.79, 95% CI 0.29 to 2.13; 2 studies, 1602 participants; moderate-certainty evidence), and major bleeding (OR 0.50, 95% CI 0.15 to 1.68; 2 studies, 1527 participants; moderate-certainty evidence). We downgraded the certainty of evidence by one level for imprecision due to the low number of events.

There was also no clear difference between the oral factor Xa inhibitors and conventional anticoagulation in the prevention of recurrent PE (OR 0.92, 95% CI 0.66 to 1.29; 3 studies, 8186 participants; moderate-certainty evidence), recurrent VTE (OR 0.83, 95% CI 0.66 to 1.03; 8 studies, 11,416 participants; moderate-certainty evidence), DVT (OR 0.77, 95% CI 0.48 to 1.25; 2 studies, 8151 participants; moderate-certainty evidence), all-cause mortality (OR 1.16, 95% CI 0.79 to 1.70; 1 study, 4817 participants; moderate-certainty evidence) and major bleeding (OR 0.71, 95% CI 0.36 to 1.41; 8 studies, 11,447 participants; low-certainty evidence); the heterogeneity for major bleeding was significant (I^2 = 79%). We downgraded the certainty of the evidence to moderate and low because of imprecision due to the low number of events and inconsistency due to clinical heterogeneity. None of the included studies measured health-related quality of life.

Authors' conclusions

Available evidence shows there is probably little or no difference between DOACs and conventional anticoagulation in the prevention of recurrent PE, recurrent VTE, DVT, all-cause mortality, and major bleeding. The certainty of evidence was moderate or low. Future large clinical trials are required to identify if individual drugs differ in effectiveness and bleeding risk, and to explore effect differences in subgroups, including people with cancer and obesity.

PLAIN LANGUAGE SUMMARY

Are direct oral anticoagulants (a type of 'blood thinner') better than traditional anticoagulants for treating a pulmonary embolism (a blood clot in the lung)?

What is a pulmonary embolism?

A pulmonary embolism occurs when a piece of blood clot breaks off from a clot somewhere else in the body and travels in the blood to the lungs. This can be life-threatening and occurs in approximately 4 to 12 per 10,000 people. The chances of getting a pulmonary embolism can increase with risk factors, including 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), blood disorders (thrombophilia), and trauma.

How is a pulmonary embolism treated?

Until recently, the standard treatment for a pulmonary embolism was an anticoagulant: a medicine that either treats or prevents blood clots, often called a 'blood thinner'. Conventional anticoagulants include heparin, fondaparinux, and vitamin K antagonists. However, these drugs can cause side effects and have limitations.

Two types of anticoagulant have been developed: direct thrombin inhibitors (DTIs) 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 a pulmonary embolism, compared with conventional anticoagulants. We looked at whether 3 months' treatment or longer prevented further blood clots (recurrent deep vein thrombosis (DVT), when a clot forms in a deep vein, usually in the leg), recurrent pulmonary embolism, and pulmonary embolisms. The main safety outcomes included death and unwanted, harmful adverse events, such as major bleeding.

What did we do?

We searched for studies in which people with a pulmonary embolism confirmed by standard imaging techniques 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 DTI 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 pulmonary embolism (a minimum duration of 3 months).

What did we find?

After searching for relevant studies, we included 10 studies with a combined total of 13,073 participants. Studies compared oral DTIs and factor Xa inhibitors with conventional anticoagulation. We combined the data from the studies and found that there was no clear difference in the incidence of:

- recurrent pulmonary embolism;
- recurrent deep vein thrombosis (DVT: when a blood clot forms, usually in a deep vein of the leg or pelvis);
- recurrent venous thromboembolism (when DVT and pulmonary embolism occur together);
- death;
- major bleeding

This review showed that there was no clear difference between the direct oral anticoagulants and conventional treatment in preventing recurrent PE, recurrent VTE, DVT, mortality, and major bleeding. No study measured health-related quality of life.

What are the limitations of the evidence?

We are moderately confident in this evidence. This was because the number of events involved in the studies was small and there were differences in how individual studies were carried out.

How up to date is this evidence?

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

Key messages

Current evidence shows there is probably little or no difference between direct oral anticoagulants and conventional anticoagulation for preventing recurrent pulmonary embolism, recurrent venous thromboembolism (VTE), deep vein thrombosis (DVT), all-cause mortality, and major bleeding in people who are being treated for a pulmonary embolism.

SUMMARY OF FINDINGS

Summary of findings 1. Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation for the treatment of pulmonary embolism

Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation for the treatment of pulmonary embolism

Patient or population: people with a pulmonary embolism, confirmed by standard imaging techniques
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 DTI				
Recurrent PE[a] Follow-up: 6 months	Study population 20 per 1000	20 per 1000 (10 to 40)	**OR 1.02** (0.50 to 2.04)	1602 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	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.
Recurrent VTE[c] Follow-up: 6 months	Study population 31 per 1000	29 per 1000 (16 to 50)	**OR 0.93** (0.52 to 1.66)	1602 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	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.
DVT[d] Follow-up: 6 months	Study population 11 per 1000	9 per 1000 (3 to 23)	**OR 0.79** (0.29 to 2.13)	1602 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	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.
All-cause mortality	See comment		See comment	See comment	-	RE-COVER 2009 and RE-COVER II 2014 did not report on all-cause mortality.

Major bleeding[e] Follow-up: 6 months	Study population		**OR 0.50** (0.15 to 1.68)	1527 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	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.
	10 per 1000	5 per 1000 (2 to 17)				
Health-related quality of life	See comment		See comment	See comment	-	RE-COVER 2009 and RE-COVER II 2014 did not measure health-related quality of life.

*__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; **CTPA:** computed tomographic pulmonary angiography; **DVT**: deep vein thrombosis; **ISTH**: International Society on Thrombosis and Haemostasis; **OR:** odds ratio; **PE:** pulmonary embolism; **RCT:** randomised controlled trial; **V/Q:** ventilation/perfusion; **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]Confirmed by V/Q lung scanning, pulmonary angiography, or CTPA
[b]We downgraded one level for imprecision due to the low number of events. The possibility of publication bias is not excluded but we did not consider it sufficient to downgrade the certainty of evidence.
[c]VTE includes clinically overt DVT and PE. Clinically overt DVT, confirmed by standard imaging techniques (venography, impedance plethysmography, whole-leg compression ultrasound, proximal compression ultrasound); or clinically overt PE, confirmed by V/Q lung scanning, pulmonary angiography, or CTPA.
[d]Clinically overt DVT confirmed by standard imaging techniques (venography, impedance plethysmography, whole-leg compression ultrasound, proximal compression ultrasound).
[e]As defined by the ISTH (Schulman 2005): 1. Fatal bleeding, and/or 2. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or 3. 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 packed red cells.

Summary of findings 2. Oral factor Xa inhibitors versus conventional anticoagulation for the treatment of pulmonary embolism

Oral factor Xa inhibitors versus conventional anticoagulation for the treatment of pulmonary embolism

Patient or population: people with a pulmonary embolism, confirmed by standard imaging techniques
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 inhibitors				
Recurrent PE[a] Follow-up: 0 to 12 months	Study population		**OR 0.92** (0.66 to 1.29)	8186 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	-
	18 per 1000	16 per 1000 (12 to 23)				
Recurrent VTE[c] Follow-up: 0 to 12 months	Study population		**OR 0.83** (0.66 to 1.03)	11,416 (8 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	2 of 8 studies reported no events
	32 per 1000	26 per 1000 (21 to 33)				
DVT[d] Follow-up: 5 days to 12 months	Study population		**OR 0.77** (0.48 to 1.25)	8151 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	-
	10 per 1000	7 per 1000 (5 to 12)				
All-cause mortality Follow-up: 0 to 12 months	Study population		**OR 1.16** (0.79 to 1.70)	4817 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	-
	21 per 1000	24 per 1000 (16 to 35)				
Major bleeding[e] Follow-up: 0 to 12 months	Study population		**OR 0.71** (0.36 to 1.41)	11,447 (8 RCTs)	⊕⊕⊖⊖ **Low**[b,f]	2 of 8 studies reported no events
	23 per 1000	16 per 1000 (8 to 32)				
Health-related quality of life	See comment		See comment	See comment	-	The studies did not measure

				health-related quality of life.

*__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; **CTPA:** computed tomographic pulmonary angiography; **DVT:** deep vein thrombosis; **ISTH:** International Society on Thrombosis and Haemostasis; **OR:** odds ratio; **PE:** pulmonary embolism; **RCT:** randomised controlled trial; **V/Q:** ventilation/perfusion; **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]Confirmed by V/Q lung scanning, pulmonary angiography, or CTPA.
[b]We downgraded one level for imprecision due to the low number of events. The possibility of publication bias is not excluded but we did not consider it sufficient to downgrade the certainty of evidence.
[c]VTE includes clinically overt DVT and PE. Clinically overt DVT, confirmed by standard imaging techniques (venography, impedance plethysmography, whole-leg compression ultrasound, proximal compression ultrasound); or clinically overt PE, confirmed by V/Q lung scanning, pulmonary angiography, or CTPA.
[d]Clinically overt DVT confirmed by standard imaging techniques (venography, impedance plethysmography, whole-leg compression ultrasound, proximal compression ultrasound).
[e]As defined by the ISTH (Schulman 2005): 1. Fatal bleeding, and/or 2. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or 3. 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 packed red cells.
[f]We downgraded one level for serious inconsistency (I^2 = 79% due to clinical heterogeneity).

BACKGROUND

Description of the condition

Pulmonary embolism (PE) is a potentially life-threatening condition in which a blood clot blocks the supply of blood to the lungs. PE is often a consequence of a thrombus in the deep veins of the legs (deep vein thrombosis, DVT) that dislodges and migrates in the blood to the pulmonary arteries. The incidence of PE has been estimated as 4 to 12 per 10,000 people annually (Keller 2020; Konstantinides 2020; Wendelboe 2016), and longitudinal studies have revealed that the annual PE prevalence rates tend to rise over time (Dentali 2016; de Miguel-Diez 2014; Keller 2020; Lehnert 2018). DVT is present in approximately 70% to 80% of people with PE, yet only 15% of PE cases have symptoms of DVT (Huerta 2007). One long-term complication of PE is chronic thromboembolic pulmonary hypertension (CTPH). CTPH occurs when the clot obstructs the pulmonary arteries, causing excessive pressure in the pulmonary artery and stress to the right ventricle. CTPH is uncommon but it can result in heart failure (NICE 2020). It is estimated that up to a quarter of all PE patients present with sudden death (Heit 2015). In the USA, PE is one of the leading causes of cardiovascular mortality, contributing to nearly 300,000 deaths annually (Wendelboe 2016).

Risk factors for PE are similar to those for DVT and are classified as provoked or unprovoked (Kearon 2012). For unprovoked PE, no clear precipitating risk factor can be identified; risk factors are either hereditary or more often acquired. For provoked PE, risk factors include cancer, acute medical illness, surgery, trauma, immobility (often in hospital and lasting at least three days), obesity, inflammatory diseases/infection, hormone therapy (oestrogen-containing), pregnancy (particularly the postpartum period), long-distance travel, recent hospitalisation, and antiphospholipid syndrome (APS) (Kakkos 2021).

People presenting with signs or symptoms of PE, such as chest pain, shortness of breath, or coughing up blood, will have their general medical history assessed, undergo a physical examination, and may be offered a chest X-ray to exclude other causes (NICE 2020). However, it can be particularly challenging to diagnose PE as the symptoms (dyspnoea, pleuritic chest pain, retrosternal chest pain, cough, and haemoptysis) are not specific (NICE 2020). In severe cases, right ventricle failure leads to dizziness, syncope, tachypnoea, tachycardia, hypoxia, elevated jugular venous pressure, systemic hypotension, and cardiogenic shock (NICE 2020). The UK National Institute for Health and Care Excellence (NICE) recommends that people presenting with suspected PE should be assessed using a two-level PE Wells score (NICE 2020; Wells 2000). Points are awarded for the presence of clinical features, including clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins), heart rate greater than 100 beats per minute, immobilisation for more than three days or surgery in the previous four weeks, previous DVT/PE, haemoptysis, and malignancy (on treatment, treated in the last six months, or palliative) (NICE 2020). For people with a low pre-test probability, the use of a D-dimer assay combined with a clinical prediction rule has a high negative predictive value and avoids the need for unnecessary imaging (Qaseem 2007). However, for people who have an intermediate or high pre-test probability of PE, imaging is essential. People with a score of greater than four are judged to be likely to have had a PE and should undergo immediate diagnostic imaging. If this cannot be performed immediately, patients should be given immediate interim parenteral anticoagulant therapy until the imaging test is done. Those with a negative diagnosis in whom a DVT is likely should be given a proximal leg vein ultrasound scan (NICE 2020).

There are three types of imaging techniques used to diagnose PE: computed tomography pulmonary angiogram (CTPA), ventilation-perfusion (V/Q) scan, and pulmonary angiography.

CTPA involves injecting a contrast agent intravenously and performing a computed tomography (CT) scan of the chest to visualise the pulmonary arteries and detect any thrombi in the pulmonary arteries down to the subsegmental branches. The procedure has over 90% specificity and sensitivity in diagnosing PE in the main, lobar, and segmental pulmonary arteries (Riedel 2004). However, the radiation dose administered to the individual is much larger than that of a V/Q scan, and thus people who have a CTPA may be at an increased lifetime risk of cancer (Anderson 2009). CTPA use is limited in people with iodine allergy, hyperthyroidism, those who are pregnant and breastfeeding, and is contraindicated in people with severe renal failure (Konstantinides 2020).

A V/Q scan comprises two parts: the ventilation part, where the patient breathes in a radioisotope (in the form of a gas or an aerosol) and the perfusion part, where the patient is given an intravenous injection of the isotope. A gamma camera is used to detect where the isotopes are in the lungs and the images show which areas of the lungs are ventilated but not perfused (NICE 2020). Another version of this test, the V/Q single photon emission computed tomography (V/Q SPECT) has been developed. The camera is rotated around the patient, thus generating three-dimensional images and leading to a more accurate diagnosis (Laurence 2012).

Pulmonary angiography is an imaging method that uses x-rays and a special dye to see how blood flows through the lung. The procedure is invasive, with related risks of mortality and complications, especially for people with haemodynamic compromise or respiratory failure (Stein 1992). For several decades, pulmonary angiography was the "gold standard" for diagnosing or ruling out acute PE, but it is now rarely used because less-invasive CTPA provides comparable diagnostic accuracy (Konstantinides 2020).

Description of the intervention

Conventional treatment of PE used unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, or 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 heparins and VKAs are effective anticoagulants, there are limitations associated with each. LMWH must be administered parenterally and may be associated with an increased risk of bleeding, loss of bone strength, elevated liver enzymes, and heparin-induced thrombocytopenia (Konstantinides 2020). Meanwhile, VKAs have a narrow therapeutic window, require frequent monitoring and dosage adjustments, and can have multiple interactions with other drugs (Ageno 2012).

Two further classes of oral anticoagulants have been developed: direct thrombin inhibitors (DTIs) and factor Xa inhibitors. DTIs and factor Xa inhibitors have characteristics that may be favourable to heparin and VKAs, including ease of oral administration, a predictable effect, lack of frequent monitoring or re-dosing, and fewer known drug interactions (compared with VKA) (Fox 2012).

The latest American College of Chest Physicians (ACCP) guidelines recommended apixaban, dabigatran, edoxaban, or rivaroxaban over VKAs 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 recommend 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

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, lack of an antiplatelet effect, and no suspected concern of heparin-induced thrombocytopenia (HIT) (Lee 2011). There are several types of DTIs.

Dabigatran

Dabigatran etexilate is a reversible oral DTI that is metabolised to its active ingredient, dabigatran, in the gastrointestinal tract (Ageno 2012). It does not require anticoagulation monitoring, is excreted by the kidneys, and has a half-life of 12 to 17 hours. As well as a treatment for venous thrombosis, this drug has been involved in many large randomised studies of atrial fibrillation (Connolly 2009), acute coronary syndromes (Oldgren 2011), prevention of thrombosis following orthopaedic surgery (Eriksson 2007), and in people with mechanical heart valves (Van de Werf 2012). In common with the other DOACs, dabigatran is associated with a lower incidence of intracranial haemorrhage (compared with VKAs). However, again compared with VKAs, dabigatran showed a higher incidence of indigestion and heartburn and a higher incidence of gastrointestinal bleeding (Baetz 2008). For the treatment of PE in people with creatinine clearance (CrCL) of more than 30 mL/min, the recommended dosage of dabigatran is 150 mg twice daily following at least five days of initial therapy with a parenteral anticoagulant. For people aged 80 years or older and for people having verapamil, the recommended dose is 110 mg twice daily. In people aged 75 to 80 years, people with moderately reduced kidney function, people with gastritis, oesophagitis or gastro-oesophageal reflux, and people at increased risk of bleeding, either dose (300 mg or 220 mg) can be given, based on an individual assessment. Dabigatran is not recommended in people with CrCL of less than 30 mL/min (Konstantinides 2020; NICE 2020).

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 venous thromboembolism but caused unacceptable liver toxicity (Boudes 2006), and, therefore, was never licensed. For the treatment of PE, the usual dosing of ximelagatran for adults is 48 mg twice daily (Ho 2006).

Oral factor Xa inhibitors

Factor Xa inhibitors bind directly to the active site of factor Xa, thus blocking the activity of the clotting factor. Unlike indirect factor Xa inhibitors such as fondaparinux, direct factor Xa inhibitors "inactivate free FXa and FXa incorporated with the prothrombinase complex equally well" and do not require interaction with the inhibitor antithrombin (Eriksson 2009). They have been shown to be non-inferior to 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 direct factor Xa inhibitor. The plasma half-life is estimated to be eight to 10 hours if renal function is normal (Spyropoulos 2012). For the treatment of PE, the recommended dosage of rivaroxaban is 15 mg twice daily for the first 21 days followed by 15 mg once daily in people with moderate (CrCL 30 mL/min to 49 mL/min) or severe (CrCL 15 mL/min to 29 ml/min) renal impairment, if their risk of bleeding outweighs the risk of recurrent DVT or PE (NICE 2020).

Apixaban

Apixaban is an oral, small molecule, reversible inhibitor of factor Xa with a plasma half-life of eight to 15 hours. For the treatment of PE, the recommended dosage of apixaban is 10 mg twice daily for the first seven days followed by 5 mg twice daily for continued treatment (NICE 2020). For people with severe renal impairment (CrCL 15 mL/min to 29 mL/min), apixaban should be used with caution (Eriksson 2009).

Betrixaban

Betrixaban is an orally administered direct factor Xa inhibitor. It has a half-life of 19 to 27 hours (Palladino 2013). For the prophylaxis of PE, 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 30 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 (Eikelboom 2010). For the treatment of PE, the recommended dose of edoxaban is 60 mg taken orally once daily following at least five days of initial therapy with a parenteral anticoagulant. The edoxaban dose should be reduced to 30 mg once daily in people with CrCL 15 mL/min to 50 mL/min, those who weigh less than or equal to 60 kg, or those who are taking certain concomitant P-glycoprotein inhibitor medications (NICE 2020).

Why it is important to do this review

The efficacy and safety of oral DTIs and oral factor Xa inhibitors for the treatment of VTE has been examined in several randomised controlled trials (the EINSTEIN-PE study (EINSTEIN-PE 2012), the ODIXa-DVT study (Agnelli 2007), the Botticelli study (Botticelli Investigators 2008), the AMPLIFY study (Agnelli 2013), the RE-COVER II study (Schulman 2011), and the THRIVE studies (Eriksson 2003)). Several non-Cochrane systematic reviews have examined the benefits and harms of DTIs and factor Xa inhibitors versus VKAs in the treatment of acute VTE (Fox 2012; Samaranayake 2022; Song 2021; Wu 2022). However, specific data on people with PE were not reported, and appropriate subgroup analyses that considered some clinical factors (such as the history of VTE, age, and active cancer) were lacking. It is important to assess the efficacy and safety of oral DTIs and oral factor Xa inhibitors for the treatment of PE to help both healthcare professionals and people with PE choose the most appropriate treatment. Since the first version of this review was completed (Robertson 2015a), several new RCTs have been published (AMPLIFY-J 2015; Caravaggio 2020; Hokusai VTE Cancer 2018; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018). Thus, it is necessary to update the review and present the most up-to-date evidence to aid decision-making in clinical practice. For this update, due to the limited number of included studies, subgroup analyses were only possible for active cancer and the different types of factor Xa inhibitors.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in which participants with a confirmed pulmonary embolism (PE) were allocated to receive an oral direct thrombin inhibitor (DTI) or an oral factor Xa inhibitor for the treatment of PE. We included studies published and in progress if preliminary results were available. We placed no restrictions on publication status and non-English studies were eligible for inclusion in the review. We excluded DTIs and factor Xa inhibitors that were not given by the oral route.

Types of participants

We included participants with a PE, confirmed by standard imaging techniques (CTPA, V/Q scan, or pulmonary angiography).

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, betrixaban, edoxaban);
- other anticoagulants (e.g. LMWH, UFH, VKAs).

We included the following comparisons:

- 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;
- oral DTI or oral factor Xa inhibitor versus another anticoagulant.

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

Types of outcome measures

Primary outcomes

- Recurrent PE, confirmed by standard imaging techniques (CTPA, V/Q scan, or pulmonary angiography)
- Recurrent venous thromboembolism (VTE, clinically overt DVT, confirmed by standard imaging techniques, including venography, impedance plethysmography, whole-leg compression ultrasound, or proximal compression ultrasound; or clinically overt PE, confirmed by CTPA, V/Q scan, or pulmonary angiography)
- Clinically overt DVT, confirmed by standard imaging techniques (venography, impedance plethysmography, whole-leg compression ultrasound, or proximal compression ultrasound).

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases, from inception to 2 March 2022, for RCTs 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 RCTs 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 2 March 2022.

Searching other resources

We reviewed the reference lists of relevant articles for potential additional citations.

Data collection and analysis

Selection of studies

We used Covidence to screen retrieved records (Covidence). Seven review authors (ML, JL, XH, LY, XW, QW, SX), working in pairs, independently screened all titles and abstracts based on the specified inclusion and exclusion criteria, and then reviewed full-text records of all potentially eligible articles. We linked together multiple reports of the same study and used the most comprehensive report as the primary reference. We resolved any disagreements by discussion. We illustrated the study selection process in a PRISMA diagram (Page 2021). We listed studies excluded after full-text assessment in the Characteristics of excluded studies table, and provided the reasons for exclusion.

Data extraction and management

Six review authors (ML, JL, XW, XH, QW, SX) independently extracted the data from the included studies, using a modified version of the Cochrane Vascular standard data extraction form. We resolved any disagreements in data extraction and management through discussion and we sought the opinion of a third author (LY or KY), when necessary. We collected the following data:

- study details (e.g. trial name, year, country, authors);
- methods (e.g. study design, number of participants and study centres, withdrawals and drop-outs, treatment duration, follow-up time);
- participant characteristics (e.g. country, setting, age, sex, inclusion and exclusion criteria, history of VTE, previous major surgery, active cancer, pregnancy, recent period of immobility, hereditary or acquired thrombophilia);
- interventions (e.g. oral DTIs, oral factor Xa inhibitors);
- comparisons (e.g. other anticoagulants, i.e. LMWH, UFH, VKAs);
- outcomes (e.g. recurrent PE, recurrent VTE, clinically overt DVT, all-cause mortality, major bleeding, health-related quality of life);
- funding source;
- declarations of interest of the study authors.

Assessment of risk of bias in included studies

Pairs of reviewers (ML, JL, XW, XH) independently assessed the risk of bias using the Cochrane risk of bias tool, as described in section 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (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 either 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 in included studies table. We resolved any disagreements through discussions with a third author (LY or KY).

Measures of treatment effect

For dichotomous outcomes, we used odds ratios (ORs) as the effect measure, with 95% confidence intervals (CIs). For continuous data, we planned to calculate 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 each participant recruited into each included study.

Dealing with missing data

We based the analysis on intention-to-treat (ITT) data from the individual clinical trials whenever possible. We adopted the 'available-case analysis' if the primary studies did not use ITT analysis. We contacted the study authors for additional information where there were missing or unavailable data. One study author provided missing outcome data when requested (Hokusai-VTE 2013). In addition, some studies only reported overall data about VTE, with no specific data on PE. We contacted these study authors for detailed information. When we did not get a response within one month, we excluded these studies for the reason "unable to obtain specific outcome data for people with a pulmonary embolism" (see Characteristics of excluded studies table).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by checking the study details. We assessed statistical heterogeneity between the trials: by visually examining the forest plots to check for overlapping CIs; with the Chi^2 test for homogeneity with a 10%

level of significance; and by using the I^2 statistic to measure the degree of inconsistency between the studies (Higgins 2022). We interpreted I^2 as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022):

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

We planned to investigate the reasons for significant heterogeneity where I^2 was greater than 50% by examining the characteristics of included articles, including participants, interventions, comparisons, outcomes, and study design.

Assessment of reporting biases

We planned to assess publication bias by funnel plots if a sufficient number of studies (10 or more) were available in the meta-analyses. In order to investigate any potential selective reporting bias, we compared the full-text reports of the included studies with the registration information and protocols, and we also searched for eligible studies that had been registered and should have been completed, but were without available published data.

Data synthesis

We used Review Manager Web (RevMan Web) to synthesise the data with a meta-analysis, following the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022; RevMan Web 2022). One review author (ML) entered the data into RevMan Web, and the second review author (JL) cross-checked the data entry. We resolved any discrepancies by consulting the source publication. We used a random-effects model to synthesise the data, even with a small I^2, as we expected clinical heterogeneity across studies to exist, due to different oral factor Xa inhibitors (e.g. apixaban, rivaroxaban, edoxaban), different conventional thrombin inhibitors in the control group (e.g. warfarin, dalteparin), different treatment durations (e.g. three, six, and 12 months). If meta-analysis was not appropriate or possible, we planned to report the results using a narrative synthesis (McKenzie 2002).

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis for the factors below if there were two or more studies in each subgroup. We planned to analyse the subgroup differences using the Chi^2 test, set at a P value of 0.05.

- History of VTE.
- Age.
- Active cancer (treatment within the last six months or palliative).
- 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 (hereditary or acquired).
- Treatment duration (three months or more than three months).
- Types of factor Xa inhibitors.

For this update, due to the limited number of included studies, subgroup analyses were only possible for active cancer and the types of factor Xa inhibitors.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the robustness of the results. We intended to exclude studies that we judged to be at high risk of bias (defined as high risk in any domain). We also planned to perform sensitivity analyses with and without studies in ximelagatran, given that this drug is no longer available. However, we found no studies that tested ximelagatran in people with PE.

Summary of findings and assessment of the certainty of the evidence

We developed summary of findings tables, using GRADEpro GDT software, to present the results of this review (GRADEpro GDT; Schünemann 2022a). We created one table each for our two comparisons: 'Oral DTIs versus conventional anticoagulation for the treatment of PE' and 'Oral factor Xa inhibitors versus conventional anticoagulation for the treatment of PE'. 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 2022b). We assessed the certainty of evidence for the following outcomes: recurrent PE, recurrent VTE, DVT, all-cause mortality, major bleeding, and health-related quality of life, as described in the Types of outcome measures section.

RESULTS

Description of studies

See Figure 1.

Figure 1. Study flow diagram

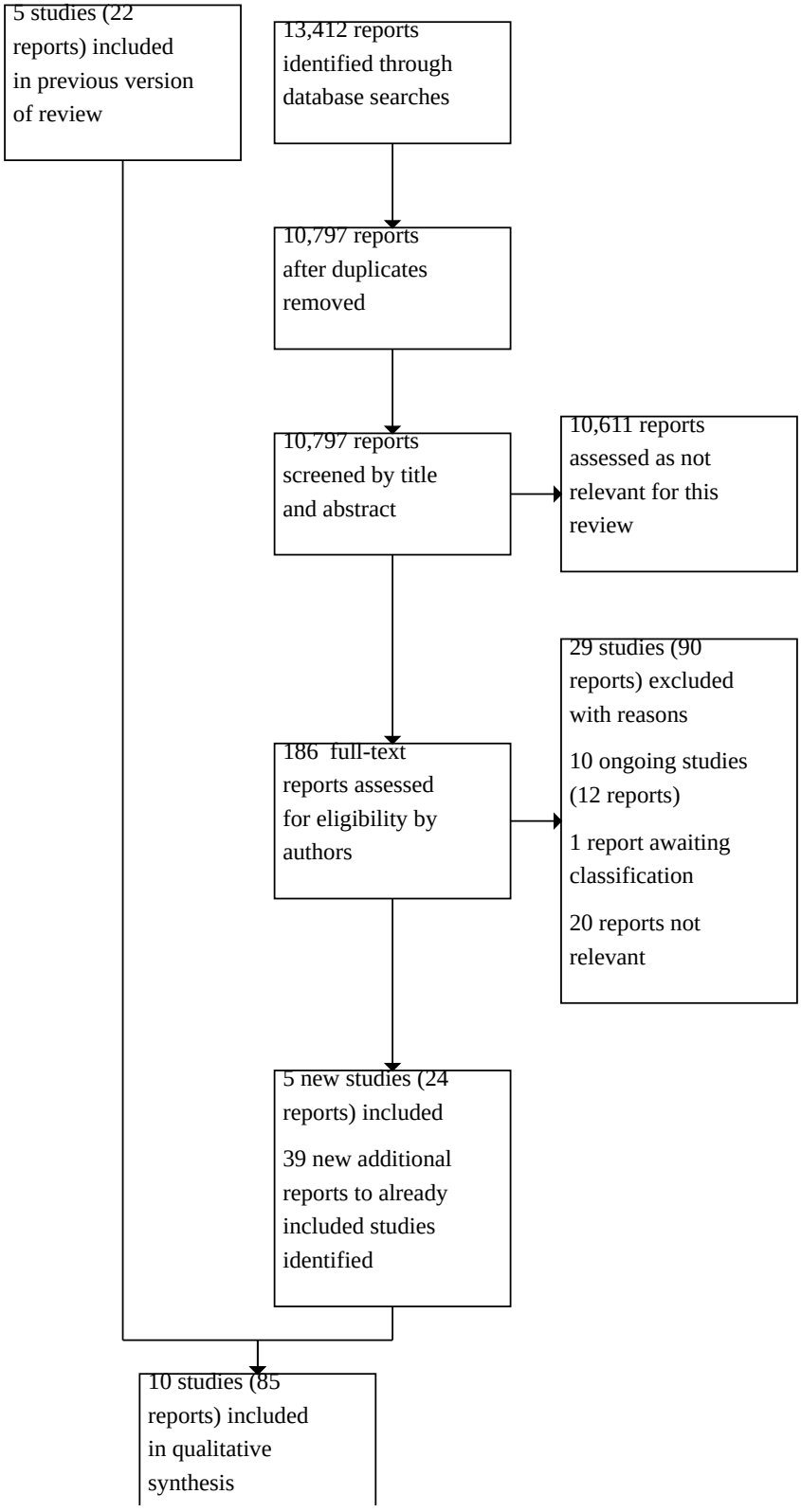
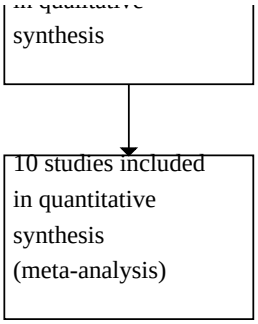


Figure 1. (Continued)



Results of the search

For this update, the searches identified 13,412 records, leaving 10,797 records after deduplication. We assessed 10,611 records as not relevant, based on the title and abstract screening. We assessed 186 potentially relevant records by full text. We identified five new included studies (24 reports) and 39 additional reports to already included studies. We excluded 29 studies (90 reports) with reasons, and discarded 20 further reports as not relevant. We identified one study (one report) as awaiting classification, and 10 ongoing studies (12 reports). The previous version of this review included five studies (22 reports). Thus, a total of 10 studies (85 reports) are now included in this review. If an article reported on two studies, we listed the article as an additional publication under each study, which makes both the counts of total reports in included and excluded studies 91. See Figure 1, Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Included studies

Ten RCTs involving 13,073 adults met the inclusion criteria for this review (AMPLIFY 2013; AMPLIFY-J 2015; Caravaggio 2020; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018; RE-COVER 2009; RE-COVER II 2014). See Characteristics of included studies.

AMPLIFY 2013 was a double-blind study in which 5395 participants with a deep vein thrombosis (DVT) or pulmonary embolism (PE) were randomised to receive oral apixaban 10 mg twice daily for the first seven days, followed by 5 mg twice daily for six months or enoxaparin 1 mg/kg of body weight every 12 hours for at least five days and warfarin concomitantly for six months. Participants were followed up for six months. Outcomes included a composite of recurrent symptomatic venous thromboembolism (VTE) (fatal or non-fatal PE and DVT), mortality related to VTE, major bleeding, and clinically relevant non-major bleeding.

AMPLIFY-J 2015 was a randomised, active-controlled, open-label study in which 80 participants with a DVT or PE were randomised to receive oral apixaban 10 mg for seven days as an initial therapy, followed by 5 mg for 23 weeks (n = 40) or continuous infusion of unfractionated heparin (UFH) for at least five days and warfarin concomitantly for 24 weeks (n = 40). Participants were followed up at zero, two, 12, 24, and 28 weeks. Outcomes included major bleeding, clinically relevant non-major bleeding, all bleeding events, adjudicated recurrent symptomatic VTE (non-fatal DVT or non-fatal PE) or VTE-related death during 24 weeks, and thrombotic burden deterioration at two, 12, and 24 weeks.

Caravaggio 2020 was a multinational, randomised, controlled, investigator-initiated, open-label, non-inferiority trial in which 1155 people with a cancer-associated DVT or PE were randomised to receive oral apixaban 10 mg twice daily for the first seven days, followed by 5 mg twice daily for six months (n = 576) or dalteparin 200 IU/kg of body weight once daily for the first month, followed by 150 IU/kg of body weight daily for six months (n = 579). Participants were followed up at enrolment and at four weeks, then at three, six, and seven months after randomisation. Outcomes included recurrent VTE, recurrent DVT, recurrent PE, fatal PE, major bleeding, major gastrointestinal bleeding, major non-gastrointestinal bleeding, clinically relevant non-major bleeding, death from any cause, and event-free survival.

EINSTEIN-PE 2012 was an open-label study in which 4832 participants were randomised to receive oral rivaroxaban 15 mg twice daily for the first three weeks, followed by 20 mg once daily (n = 2419), or enoxaparin 1.0 mg/kg of body weight twice daily and either warfarin or acenocoumarol, started within 48 hours of randomisation (n = 2413). Participants were followed up at three, six, and 12 months. Outcomes included recurrent PE, recurrent DVT, major bleeding, and all-cause mortality.

Hokusai VTE Cancer 2018 was a multinational, prospective, randomised, open-label, blinded endpoint, non-inferiority study in which 1046 participants with a cancer-associated DVT or PE were randomised to receive oral edoxaban at a fixed dose of 60 mg or 30 mg once daily for six to 12 months (n = 522) or dalteparin 200 IU/kg of body weight once daily for 30 days, with a maximum daily dose of 18,000 IU, followed by dalteparin 150 IU/kg of body weight once daily for six to 12 months (n = 524). Participants were followed up on day 31 after randomisation and at three, six, nine, and 12 months. Outcomes included a composite of recurrent VTE, major bleeding, clinically relevant non-major bleeding, event-free survival, VTE-related death, mortality from all causes, recurrent DVT, and recurrent PE.

Hokusai-VTE 2013 was a double-blind study in which 3319 participants were randomised to receive 60 mg oral edoxaban once daily (n = 1650) or dose-adjusted warfarin therapy and edoxaban-like placebo (n = 1669). Outcomes were measured monthly for one year. Results were presented for all participants with VTE but

specific outcome data for the subset of participants with PE were obtained through communication with the author.

J-EINSTEIN DVT and PE 2015 was an open-label, randomised trial in which 40 participants with a DVT or PE were randomised to receive oral rivaroxaban 15 mg twice daily for a total of three weeks in a double-blind fashion, followed by open-label rivaroxaban 15 mg once daily for three, six, or 12 months (n = 33) or UFH for at least five days, overlapping with and followed by an international normalised ratio (INR) (range 1.5 to 2.5) titrated warfarin for three, six, or 12 months (n = 7). Participants were followed up on day 22 and at the end of the three, six, or 12 months' intended treatment period. Outcomes included the occurrence of symptomatic recurrent VTE or asymptomatic deterioration, venous ultrasound and spiral CT, major bleeding, and clinically relevant non-major bleeding.

MERCURY PE 2018 was a randomised, open-label, parallel-group, multicenter study in which 114 participants with PE were randomised to receive rivaroxaban with food, 15 mg twice daily for 21 days and then 20 mg once daily to study completion for three months (n = 51), or standard of care (any Food and Drug Administration (FDA)-approved anticoagulant strategy) for three months (n = 63). Participants were followed up at on day 30 and day 90. Outcomes included the total amount of time spent in the hospital, VTE, bleeding events, major bleeding, recurrent VTE, VTE-related death, satisfaction with anticlot treatment, total costs of care, and clinically relevant non-major bleeding.

RE-COVER 2009 was a phase III, non-inferiority, double-blind, double-dummy trial in which people with VTE (n = 2539) were given 150 mg dabigatran twice daily or warfarin. In addition, initial treatment with an approved parenteral anticoagulant (UFH administered intravenously or low molecular weight heparin (LMWH) administered subcutaneously) was started before participants were randomised. Treatment was for a period of six months and included sham monitoring of 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). RE-COVER 2009 and RE-COVER II 2014 only reported outcome data of VTE, not separate data for PE, so we took data from a pooled analysis published in an additional report (Goldhaber 2016).

Excluded studies

See Characteristics of excluded studies.

We excluded 29 studies (ADAM VTE trial 2020; AMPLIFY Extended 2013; Borsi 2021; Botticelli DVT 2008; CASTA DIVA Trial 2022; COBRRA pilot feasibility study 2017; CONKO-011 2015; de Athayde Soares 2019; DIVERSITY trial 2021; EINSTEIN-CHOICE trial 2017; Einstein-DVT Dose 2008; Einstein DVT 2013; EINSTEIN Extension 2007; EINSTEIN-Jr Trial 2020; Farhan 2019; IRIVASC-Trial 2022; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2018; Piazza 2014; PRAIS trial 2019; PRIORITY 2022; REMEDY 2013; RE-SONATE 2013; SELECT-D 2018; Sukovatykh 2017; THRIVE 2005; THRIVE I 2003; THRIVE III 2003). We excluded 11 studies as participants had DVT only (Botticelli DVT 2008; de Athayde Soares 2019; Einstein-DVT Dose 2008; Einstein DVT 2013; Farhan 2019; Mokadem 2021; ODIXa-DVT 2007; Ohmori 2018; Piazza 2014; PRAIS trial 2019; Sukovatykh 2017). We excluded 11 studies as although all participants had a VTE, specific data on the subgroup with PE were not published (ADAM VTE trial 2020; Borsi 2021; CASTA DIVA Trial 2022; COBRRA pilot feasibility study 2017; CONKO-011 2015; DIVERSITY trial 2021; EINSTEIN-Jr Trial 2020; IRIVASC-Trial 2022; PRIORITY 2022; SELECT-D 2018; THRIVE 2005). We made attempts to contact the authors for these data but were unsuccessful. We excluded three studies as they were extended studies testing the effectiveness of DOACs as prophylaxis rather than the treatment of PE (AMPLIFY Extended 2013; EINSTEIN Extension 2007; REMEDY 2013). We excluded the THRIVE I 2003 study as treatment was for less than three months, and the THRIVE III 2003 study as the control arm was a placebo. We excluded EINSTEIN-CHOICE trial 2017 as the control arm was aspirin. Finally, we excluded the REMEDY 2013 study from this review as participants were already included in the RE-COVER 2009 and RE-COVER II 2014 studies.

Studies awaiting classification

One trial record is awaiting classification as there are currently insufficient details to assess its eligibility for inclusion (NCT01780987).

Ongoing studies

Ten trials are ongoing and there are currently no suitable data available for including in this review (EudraCT 2014-002606-20; NCT02464969; NCT02664155; NCT02744092; NCT02798471; NCT03129555; NCT03266783; NCT05171049; Pettit 2018; UMIN000020069). 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

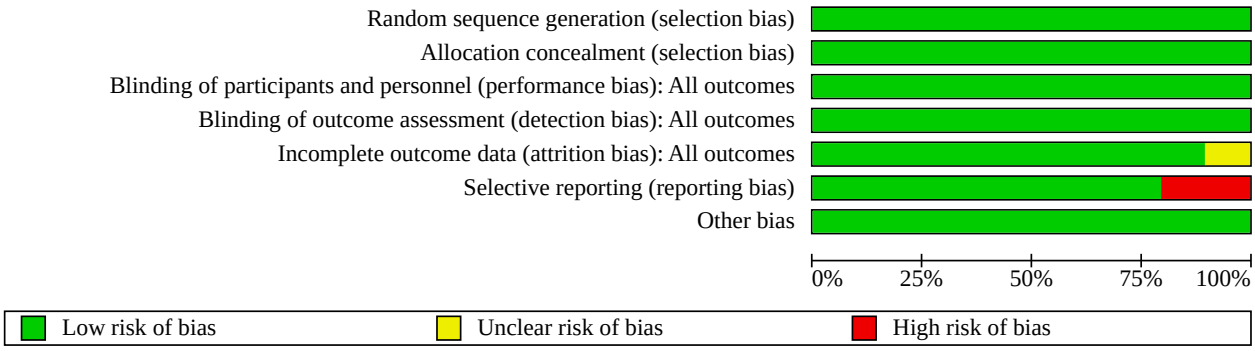
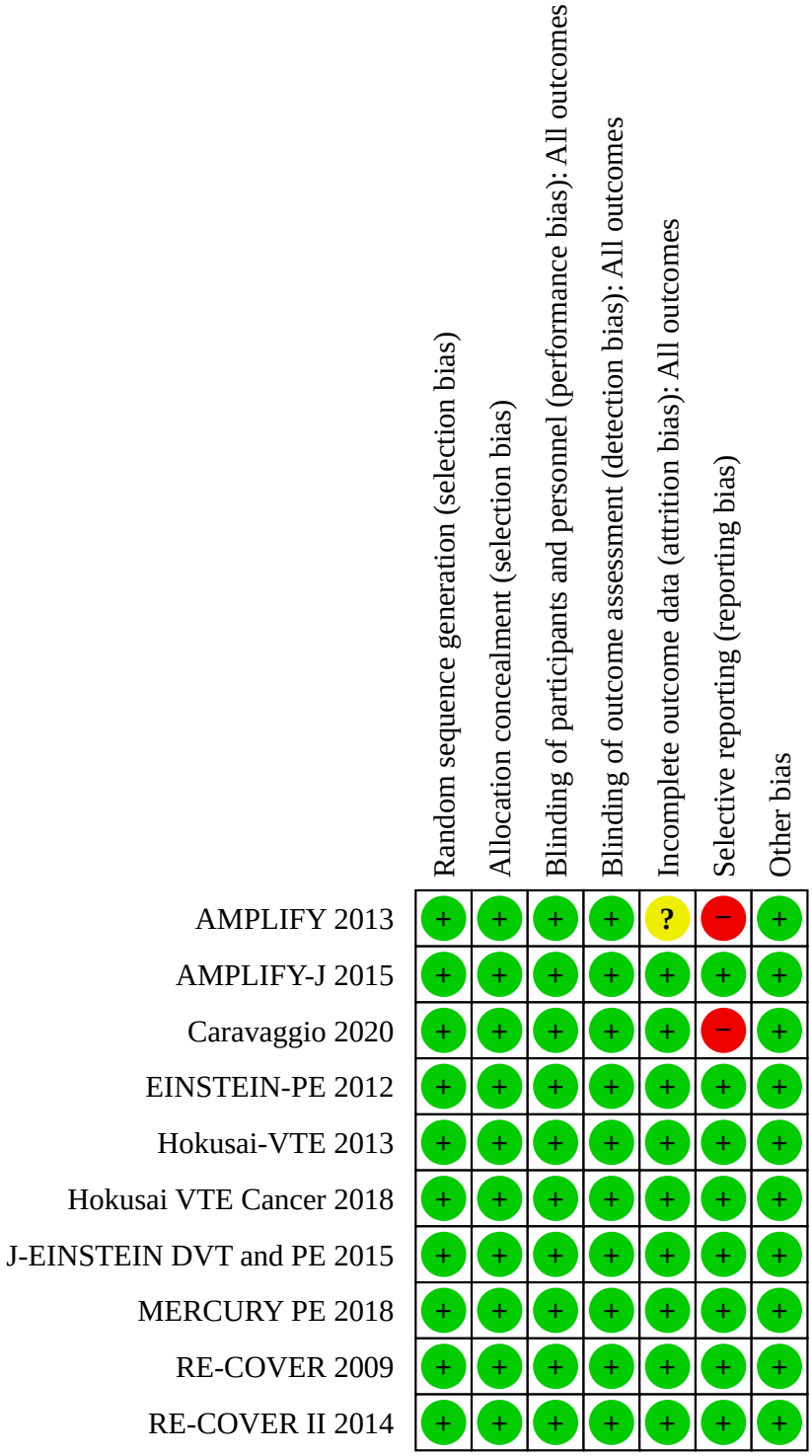


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

All 10 included studies stated that they used a computerised system to generate the random sequence, so we deemed the risk of selection bias relating to random sequence generation to be low. All 10 included studies reported that treatment allocation was concealed with the use of a computerised system, so we judged them to be at low risk of selection bias for allocation concealment (AMPLIFY 2013; AMPLIFY-J 2015; Caravaggio 2020; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018; RE-COVER 2009; RE-COVER II 2014).

Blinding

The AMPLIFY-J 2015, Caravaggio 2020, EINSTEIN-PE 2012, Hokusai VTE Cancer 2018, J-EINSTEIN DVT and PE 2015, and MERCURY PE 2018 studies were open-label: blinding of participants and personnel was not conducted. However, we judged that the lack of blinding in the control group was unlikely to have affected the outcome, and we thus judged these studies to have a low risk of performance bias. The AMPLIFY 2013, RE-COVER 2009, RE-COVER II 2014, and Hokusai-VTE 2013 studies were double-blind and therefore we judged them to be at low risk of performance bias.

All studies blinded outcome assessors to treatment; therefore, we judged them to be at low risk of detection bias.

Incomplete outcome data

Nine studies sufficiently reported that fewer than 20% of participants dropped out or withdrew, and these numbers were balanced across treatment groups. Therefore, we judged them to be at low risk of attrition bias (AMPLIFY-J 2015; Caravaggio 2020; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018; RE-COVER 2009; RE-COVER II 2014). The AMPLIFY 2013 study inappropriately excluded a number of randomised participants from the ITT analysis. Furthermore, a large number of participants within each treatment group were classified as discontinuing the study for "other reasons" with no explanations given, and we therefore deemed the risk of attrition bias to be unclear.

Selective reporting

Eight studies clearly pre-specified the study outcomes and data on the expected outcomes were presented (AMPLIFY-J 2015; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018; RE-COVER 2009; RE-COVER II 2014); we judged these studies to be at low risk of reporting bias. The AMPLIFY 2013 study pre-defined minor bleeding as a secondary outcome but data were not reported in the paper, and therefore we deemed the risk of reporting bias in this study to be high. The Caravaggio 2020 study pre-defined quality of life as a secondary outcome in the protocol but the data on this outcome were not reported in the paper; therefore we deemed the risk of reporting bias to be high.

Other potential sources of bias

We did not find any methodological issues that might directly lead to a risk of bias; therefore, we deemed the risk of other bias to be low in all 10 included studies.

Effects of interventions

See: **Summary of findings 1** Oral direct thrombin inhibitors (DTIs) versus conventional anticoagulation for the treatment of pulmonary embolism; **Summary of findings 2** Oral factor Xa inhibitors versus conventional anticoagulation for the treatment of pulmonary embolism

We identified two studies that compared an oral DTI versus conventional anticoagulation with warfarin (RE-COVER 2009; RE-COVER II 2014), and eight studies that compared an oral factor Xa inhibitor versus conventional anticoagulation with warfarin or dalteparin (AMPLIFY-J 2015; AMPLIFY 2013; Caravaggio 2020; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018). We did not find any studies comparing one DTI with another DTI, one factor Xa inhibitor with another factor Xa inhibitor, or an oral DTI with a factor Xa inhibitor. We used a random-effects model for all analyses due to clinical heterogeneity across studies (different oral factor Xa inhibitors, different conventional thrombin inhibitors in the control group, and different treatment durations).

Oral direct thrombin inhibitor versus conventional anticoagulation

In the meta-analysis of oral DTIs versus conventional anticoagulation, we used data from Goldhaber 2016, which reported combined data from the RE-COVER 2009 and RE-COVER II 2014 studies. This is reflected in the data analysis tables and Summary of findings 1 by showing only one study for this comparison.

Recurrent pulmonary embolism

Two studies with a combined total of 1602 participants measured recurrent pulmonary embolism (PE) (RE-COVER 2009; RE-COVER II 2014). There was no clear difference in the rate of recurrent PE between participants treated with dabigatran (16 events/795 participants) and those treated with conventional anticoagulation (16 events/807 participants) leading to an odds ratio (OR) of 1.02 (95% confidence interval (CI) 0.50 to 2.04; 2 studies, 1602 participants; moderate-certainty evidence; Analysis 1.1).

Recurrent venous thromboembolism

Two studies with a combined total of 1602 participants measured recurrent venous thromboembolism (VTE) (RE-COVER 2009; RE-COVER II 2014). There was no clear difference in the rate of recurrent VTE between participants treated with dabigatran (23 events/795 participants) and those treated with conventional anticoagulation (25 events/807 participants) leading to an OR of 0.93 (95% CI 0.52 to 1.66; 2 studies, 1602 participants; moderate-certainty evidence; Analysis 1.2).

Deep vein thrombosis

Two studies with a combined total of 1602 participants measured deep vein thrombosis (DVT) (RE-COVER 2009; RE-COVER II 2014). There was no clear difference in the rate of DVT between participants treated with dabigatran (7 events/795 participants) and those treated with conventional anticoagulation (9 events/807 participants) leading to an OR of 0.79 (95% CI 0.29 to 2.13; 2 studies, 1602 participants; moderate-certainty evidence; Analysis 1.3).

All-cause mortality

Neither study presented results on all-cause mortality for the specific group of participants with PE.

Adverse effects of treatment

Both RE-COVER 2009 and RE-COVER II 2014 measured major bleeding (as defined by the International Society on Thrombosis and Haemostasis (ISTH); Schulman 2005). There was no clear difference in the rate of major bleeding between participants treated with oral DTIs (4 events/759 participants) and those treated with conventional anticoagulation (8 events/768 participants) leading to an OR of 0.50 (95% CI 0.15 to 1.68; 2 studies, 1602 participants; moderate-certainty evidence; Analysis 1.4).

Health-related quality of life

Health-related quality of life was not a reported outcome in either RE-COVER 2009 or RE-COVER II 2014.

Oral factor Xa inhibitor versus conventional anticoagulation

See Summary of findings 2.

Recurrent pulmonary embolism

Data on recurrent PE was available in three studies with 8186 participants (AMPLIFY-J 2015; EINSTEIN-PE 2012; Hokusai-VTE 2013). The duration of treatment in all three studies was longer than three months. Meta-analysis showed no clear difference in the rate of recurrent PE between participants treated with oral factor Xa inhibitors (67 events/4087 participants) and those treated with conventional anticoagulation (73 events/4099 participants), leading to an OR of 0.92 (95% CI 0.66 to 1.29; I^2 = 0; 3 studies, 8186 participants; moderate-certainty evidence; Analysis 2.1).

Recurrent venous thromboembolism

We included eight studies with a combined total of 11,416 participants in a meta-analysis (AMPLIFY-J 2015; AMPLIFY 2013; Caravaggio 2020; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018). The treatment duration of MERCURY PE 2018 was three months, and the events in both groups were 0, so it was not estimated in the meta-analysis. The treatment duration of the other seven studies was longer than three months. Meta-analysis showed no clear difference in the rate of recurrent VTE between participants treated with oral factor Xa inhibitors (150 events/5698 participants) and those treated with conventional anticoagulation (183 events/5718 participants), leading to an OR of 0.83 (95% CI 0.66 to 1.03; I^2 = 0%; 8 studies, 11,416 participants; moderate-certainty evidence; Analysis 2.2).

Deep vein thrombosis

We included two studies with a combined total of 8151 participants in a meta-analysis (EINSTEIN-PE 2012; Hokusai-VTE 2013). There was no clear difference in the rate of recurrent DVT between participants treated with oral factor Xa inhibitors (30 events/4069 participants) and those treated with conventional anticoagulation (39 events/4082 participants), leading to an OR of 0.77 (95% CI 0.48 to 1.25; I^2 = 0; 2 studies, 8151 participants; moderate-certainty evidence; Analysis 2.3). The AMPLIFY 2013 study did not present DVT data for the subgroup of participants with a PE and therefore we did not include it in this meta-analysis.

All-cause mortality

Three studies measured all-cause mortality (AMPLIFY-J 2015; EINSTEIN-PE 2012; MERCURY PE 2018). In the AMPLIFY-J 2015 and MERCURY PE 2018 studies, the events in both groups were 0, so they were not estimated in the meta-analysis. There was no clear difference in the rate of all-cause mortality between participants treated with the oral factor Xa inhibitor rivaroxaban (2.40%; 58 events/2412 participants) and those treated with conventional anticoagulation (50 events/2405 participants), leading to an OR of 1.16 (95% CI 0.79 to 1.70; 1 study, 4817 participants; moderate-certainty evidence; Analysis 2.4).

Adverse effects of treatment

Eight studies measured major bleeding (as defined by ISTH, Schulman 2005) (AMPLIFY-J 2015; AMPLIFY 2013; Caravaggio 2020; EINSTEIN-PE 2012; Hokusai VTE Cancer 2018; Hokusai-VTE 2013; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018). There was no clear difference in the rate of major bleeding between participants treated with oral factor Xa inhibitors (95 events/5721 participants) and those treated with conventional anticoagulation (130 events/5726 participants) leading to an OR of 0.71 (95% CI 0.36 to 1.41; 8 studies, 11,447 participants; low-certainty evidence; Analysis 2.5). Considerable heterogeneity was detected between the studies (I^2 = 79%), likely due to clinical heterogeneity.

Health-related quality of life

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

Subgroup analysis

For this update, due to the limited number of included studies, subgroup analyses were only possible for participants who received oral factor Xa inhibitors. We performed subgroup analysis by active cancer and different types of factor Xa inhibitors for the outcome of recurrent VTE and major bleeding.

Results of subgroup analyses showed no clear difference in the incidence of recurrent VTE in participants without cancer (OR 0.89, 95% CI 0.68 to 1.17; 6 studies, 9898 participants; moderate-certainty evidence; Analysis 2.2) compared to participants with cancer (OR 0.65, 95% CI 0.42 to 1.01; 3 studies, 1518 participants; high-certainty evidence; Analysis 2.2). The test for subgroup differences did not indicate a difference (P = 0.23). For the subgroup analysis based on the different types of factor Xa inhibitors, there was also no clear difference in the incidence of recurrent VTE when participants received treatment with apixaban (OR 0.86, 95% CI 0.54 to 1.35; 3 studies, 2459 participants; moderate-certainty evidence; Analysis 2.6), rivaroxaban (OR 1.14, 95% CI 0.75 to 1.71; 3 studies, 4981 participants; moderate-certainty evidence; Analysis 2.6), and edoxaban (OR 0.66, 95% CI 0.48 to 0.92; 2 studies, 3976 participants; moderate-certainty evidence; Analysis 2.6) compared with conventional anticoagulation. The test for subgroup differences did not indicate a difference (P = 0.13).

Subgroup analysis of the incidence of major bleeding in participants without cancer (OR 0.45, 95% CI 0.19 to 1.06; 6 studies, 10,152 participants; low-certainty evidence; Analysis 2.5) versus participants with cancer (OR 1.51, 95% CI 0.84 to 2.71; 2 studies, 1295 participants; low-certainty evidence; Analysis 2.5) suggested a possible subgroup difference (test for subgroup differences: P = 0.02). Due to the limited number of studies in this analysis,

and as CIs overlap, this should be interpreted with caution. When analysed according to different types of factor Xa inhibitors, there was no clear difference in the incidence of major bleeding between apixaban and conventional anticoagulation (OR 0.36, 95% CI 0.07 to 1.91; 3 studies, 2503 participants; low-certainty evidence; Analysis 2.7), or between edoxaban and conventional anticoagulation (OR 1.44, 95% CI 0.80 to 2.58; 2 studies, 3976 participants; low-certainty evidence; Analysis 2.7). However, when treated with rivaroxaban, participants had a lower incidence of major bleeding compared to those treated with conventional anticoagulation (OR 0.49, 95% CI 0.31 to 0.79; 3 studies, 4968 participants; low-certainty evidence; Analysis 2.7). The test for subgroup differences indicated a possible difference (P = 0.01). Due to the limited number of studies in this analysis, and as CIs overlap, this should be interpreted with caution.

Sensitivity analysis

We performed sensitivity analysis by excluding studies we judged to be at high risk of bias (AMPLIFY 2013; Caravaggio 2020). Based on the available data, only sensitivity analyses of oral factor Xa inhibitors for PE in the incidence of recurrent VTE and major bleeding were possible. The results showed that oral factor Xa inhibitors versus conventional anticoagulation made no clear difference in reducing the incidence of recurrent VTE (OR 0.78, 95% CI 0.54 to 1.14; 6 studies, 8992 participants; moderate-certainty evidence; Analysis 2.8) and major bleeding (OR 0.91, 95% CI 0.42 to 1.97; 6 studies, 8979 participants; low-certainty evidence; Analysis 2.9). The results of the sensitivity analyses are consistent with the results of Analysis 2.2 and Analysis 2.5, which indicates that the results are robust.

DISCUSSION

We included an additional five studies for this update, bringing the total to 10 included studies involving 13,073 participants. Two studies investigated an oral DTI (dabigatran) and eight studies investigated oral factor Xa inhibitors (three rivaroxaban, three apixaban, and two edoxaban). Overall the studies were of good methodological quality. The certainty of the evidence was moderate or low.

Summary of main results

Recurrent pulmonary embolism

Moderate-certainty evidence showed no clear difference between both oral DTIs and factor Xa inhibitors compared to conventional anticoagulation in preventing recurrent pulmonary embolism (PE). We downgraded the certainty of the evidence by one level for imprecision.

Recurrent venous thromboembolism

Moderate-certainty evidence showed no clear difference between oral DTIs and conventional anticoagulation in the prevention of recurrent venous thromboembolism (VTE) during treatment, indicating that neither was more nor less effective. We downgraded the certainty of the evidence by one level for imprecision.

Similarly, for factor Xa inhibitors, moderate-certainty evidence showed no clear difference between factor Xa inhibitors and conventional anticoagulation in preventing recurrent VTE, indicating that neither was more nor less effective. We downgraded the certainty of the evidence by one level for imprecision.

Subgroup analyses showed no clear difference in the incidence of recurrent VTE between participants with and without cancer, and between participants who received different types of factor Xa inhibitors. Given the limited number of studies providing data in each subgroup, this may reflect a lack of information. More included studies may change the evidence in the future.

Deep vein thrombosis

Moderate-certainty evidence showed no clear difference between both oral DTIs and factor Xa inhibitors compared to conventional anticoagulation in preventing deep vein thrombosis (DVT). We downgraded the certainty of the evidence by one level for imprecision.

All-cause mortality

No study measured all-cause mortality in participants treated with oral DTIs. Moderate-certainty evidence showed no clear difference between oral factor Xa inhibitors and conventional therapy in preventing all-cause mortality. We downgraded the certainty of the evidence by one level for imprecision.

Major bleeding

Moderate-certainty evidence indicated no clear difference between oral DTIs and conventional anticoagulation in major bleeding. We downgraded the certainty of the evidence by one level for imprecision. For factor Xa inhibitors, low-certainty evidence showed no clear difference between factor Xa inhibitors and conventional anticoagulation in preventing major bleeding. We downgraded the certainty of the evidence by one level for serious inconsistency due to clinical heterogeneity and by one level for imprecision.

Subgroup analyses suggested possible subgroup differences in the incidence of major bleeding between participants without cancer versus those with cancer, and between participants receiving different types of factor Xa inhibitors. Due to the limited number of studies in the subgroups, and as CIs overlap, this should be interpreted with caution. More included studies may change the evidence in the future.

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

Overall completeness and applicability of evidence

This review assessed whether long-term treatment with oral anticoagulants – DTIs and factor Xa inhibitors – reduced the rate of recurrent PE, recurrent VTE, DVT, all-cause mortality, and major bleeding in people with PE. Two studies tested DTIs and eight studies tested factor Xa inhibitors within similar study populations. The included studies analysed and reported all of our outcomes of interest, except for health-related quality of life. Heterogeneity was high for major bleeding in the studies testing factor Xa inhibitors. As expected, this is likely due to clinical heterogeneity, because included studies varied in factor Xa inhibitors (three apixaban, three rivaroxaban, two edoxaban), comparators (six warfarin, two dalteparin), and treatment duration (three months (one study), five and a half months (one study), six months (two studies), 12 months (four studies)).

For this update, we performed subgroup analyses for active cancer and different types of factor Xa inhibitors. Limited data indicated

no clear difference in the incidence of recurrent VTE between participants with and without cancer, and between participants who received different types of factor Xa inhibitors. For major bleeding, both subgroup analyses (i.e. of people experiencing PE with versus without cancer, and subgroups of different types of factor Xa inhibitors) suggested possible subgroup differences. Bleeding risk is an important consideration when using DOACs for cancer patients, particularly in patients with gastrointestinal malignancies (Thapa 2019). A systematic review and meta-analysis of the Hokusai VTE Cancer 2018 and SELECT-D 2018 studies suggested that the risk of major bleeding in cancer patients was approximately doubled when using DOACs compared with LMWH (Li 2019). For factor Xa inhibitors, while efficacy with apixaban, edoxaban, and rivaroxaban versus dalteparin has been consistent in the treatment of cancer-associated VTE, one study showed heterogeneity is evident with respect to major gastrointestinal bleeding, with an increased risk with edoxaban and rivaroxaban but not apixaban (Athanazio 2022). All of these results are based on limited evidence; more evidence is needed to confirm these conclusions in the future.

We were unable to perform subgroup analyses for other factors because of the lack of participant-level data. More evidence is needed, as these analyses might be important to guide clinical management in people with different risk factors for PE.

Although many 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. First, the majority of recurrent events occur at the same site as the original thrombosis (in other words, in people presenting with a PE, a recurrent event after treatment is much more likely to be another PE). Second, both oral contraceptive use and Factor V Leiden mutation are more likely to be associated with DVT than PE. Third, lung disease is much more likely to be associated with PE. Consequently, a review on the effectiveness of oral DTIs and factor Xa inhibitors for the long-term treatment of DVT was published at the same time as the previous version of this review (Robertson 2015b). It has also now been updated (Wang 2023).

We did not find any studies comparing:

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

We identified no additional studies investigating DTIs for this update; therefore, this review cannot provide more evidence for this intervention. Given the recent clinical thinking that DOACs have a class effect, we will pool the results of all DTIs and factor Xa inhibitors in future updates. This may increase the power of the studies, reduce type II errors, and allow any effects to be determined clearly.

In 2020, the UK's National Institute for Health and Care Excellence (NICE) measured the cost-effectiveness of DOACs versus conventional anticoagulation for the treatment of DVT and PE (NICE 2020). Assuming that people remain on the same drug in the initial and extended phases of treatment, apixaban was highly cost-effective both in people with a DVT and people with a PE. 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 assessed the overall risk of bias as low in eight of 10 included studies, reflecting good methodological quality. We judged two studies to have a high risk of reporting bias. Six of the 10 included studies were open-label because of the complexity of monitoring international normalised ratio (INR) in the conventional anticoagulation arm. However, all outcomes were assessed by observers who were blinded to the treatment and all safety outcomes were adjudicated by a central independent committee in each included study. We could not investigate publication bias because we could not assess asymmetry in a funnel plot with the limited number of studies included in the meta-analysis.

For the comparison of oral DTIs versus conventional anticoagulation, we graded the certainty of the evidence as moderate, downgrading by one level for imprecision due to the low number of events. For oral factor Xa inhibitors versus conventional anticoagulation, we downgraded the evidence for recurrent PE, recurrent VTE, DVT, and all-cause mortality to moderate due to the low number of events. For this comparison, we downgraded the evidence for major bleeding by two levels to low, due to the low number of events and substantial clinical heterogeneity. See Summary of findings 1; Summary of findings 2.

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 (for example, conference proceedings), have been missed. Eight review authors independently performed study selection and data extraction in order to minimise bias in the review process. We strictly adhered to the inclusion and exclusion criteria set out in the protocol in order to limit subjectivity. We performed data collection according to the process suggested by Cochrane. We contacted study authors in an attempt to obtain PE-specific data. We also followed Cochrane processes as described by Higgins 2017 for assessing the risk of bias. Two of the included studies, RE-COVER 2009 and RE-COVER II 2014, only reported outcome data of VTE, not separate data for PE, so we took data from a pooled analysis published in an additional report (Goldhaber 2016). This was the best available evidence.

Agreements and disagreements with other studies or reviews

This review assesses the efficacy and safety of oral DTIs and oral factor Xa inhibitors for the long-term treatment of PE. A similar review by Dentali 2015 evaluated the difference in the safety and efficacy of DOACs compared to conventional treatment in participants presenting with DVT and with PE. The Dentali 2015 review included six studies (27,023 participants) and indicated that DOACs appear to have similar efficacy and safety profiles compared to VKAs for people with DVT and PE. Dentali 2015 focused on both PE and DVT, but did not include some more recent RCTs that are included in this update (AMPLIFY-J 2015; Caravaggio 2020; Hokusai VTE Cancer 2018; J-EINSTEIN DVT and PE 2015; MERCURY PE 2018).

Fourteen other systematic reviews have assessed the same oral anticoagulants (Antoniazzi 2013; Castellucci 2013; Cohen 2015; Fox 2012; Gómez-Outes 2014; Gómez-Outes 2015; Hirschl 2014; Kang 2014; Moik 2020; Samaranayake 2022; Sardar 2014; Song 2021; Van der Huille 2014; Wu 2022). However, these reviews focused on people with a VTE, and did not report specific data on the subgroup with a PE. Four reviews indicated that DOACs can decrease the risk of recurrent VTE compared to conventional treatment (Moik 2020; Samaranayake 2022; Song 2021; Wu 2022); seven reviews found that DOACs are associated with less bleeding than conventional treatment (Antoniazzi 2013; Fox 2012; Gómez-Outes 2014; Gómez-Outes 2015; Hirschl 2014; Van der Huille 2014; Wu 2022); one review found that DOACs are associated with lower all-cause mortality compared with those receiving conventional anticoagulants in people with venous thromboembolism (Wu 2022).

The Fox 2012 review performed meta-analysis by brand rather than class of drug and 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 (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.39 to 0.84). All-cause mortality did not differ between the two treatment groups.

The Van der Huille 2014 review showed no difference between the two treatment groups in terms of recurrent VTE, fatal PE, and all-cause mortality. However, DOACs were associated with a significantly reduced risk of major bleeding (relative risk (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 found no differences between DOACs and conventional treatment regarding recurrent VTE and death. However, bleeding was reduced by rivaroxaban (RR 0.55, 95% CI 0.38 to 0.81), apixaban (RR 0.31, 95% CI 0.17 to 0.55), and edoxaban (RR 0.81, 95% CI 0.71 to 0.93).

The Gómez-Outes 2014 review found no clear difference in the risk of recurrent VTE between the two treatment groups (RR 0.91, 95% CI 0.79 to 1.06), but DOACs were associated with reduced major bleeding (absolute risk difference of -0.6%, 95% CI -1.0% to -0.3%).

A network meta-analysis by Kang 2014 found that DOACs did not differ in the risk of mortality or recurrent VTE. However, dabigatran was associated with increased major bleeding compared to apixaban (RR 2.69, 95% CI 1.19 to 6.07), and edoxaban also had a higher bleeding rate compared to apixaban (RR 2.74, 95% CI 1.40 to 5.39).

The Wu 2022 review included 65 real-world evidence studies and found that, in people with VTE, rivaroxaban and apixaban are associated with a lower risk of recurrent VTE (rivaroxaban: HR 0.68, 95% CI 0.60 to 0.76; apixaban: HR 0.83, 95% CI 0.73 to 0.93), major bleeding events (rivaroxaban: HR 0.73, 95% CI 0.65 to 0.81; apixaban: HR 0.76, 95% CI 0.68 to 0.85), and all-cause mortality (HR 0.56, 95% CI 0.39 to 0.80) compared with those receiving conventional anticoagulants.

The Song 2021 review included four RCTs and 14 retrospective studies and found that DOACs decreased the risk of recurrent VTE (RCTs: OR 0.60, 95% CI 0.45 to 0.80; retrospective studies: OR 0.73, 95% CI 0.59 to 0.90) and recurrent DVT (RCTs: OR 0.54, 95% CI 0.36 to 0.80; retrospective studies: OR 0.20, 95% CI 0.06 to 0.63), but not PE recurrence (OR 0.75, 95% CI 0.53 to 1.05), fatal PE (OR 0.87, 95% CI 0.33 to 2.26), and major bleeding events (OR 1.04, 95% CI 0.84 to 1.28) compared with LMWHs in people with cancer.

The Samaranayake 2022 review conducted a network meta-analysis including four RCTs with 2907 participants with venous thromboembolism. They found that the overall risk of recurrent VTE was lower in the DOACs group compared to the dalteparin group (RR 0.63, 95% CI 0.44 to 0.91). There was no statistically significant difference in risk of major bleeding (RR 1.31, 95% CI 0.83 to 2.07) and all-cause mortality (RR 1.0, 95% CI 0.84 to 1.18) at six months' follow-up between DOACs and LMWH.

A review by Moik 2020 that included four RCTs (with 2894 participants with cancer-associated VTE) found that DOACs significantly reduced recurrent VTE compared to LMWHs (RR 0.62, 95% CI 0.43 to 0.91), but were associated with a non-significant increase in major bleeding (RR 1.31, 95% CI 0.83 to 2.08). Mortality risks were comparable between groups (RR 0.99, 95% CI 0.83 to 1.18).

The Gómez-Outes 2015 review found that DOACs were associated with lower major bleeding (RR 0.62, 95% CI 0.45 to 0.85), while there was no clear difference in recurrent VTE rate in people receiving DOACs or standard therapy (RR 0.91, 95% CI 0.79 to 1.05).

A review by Cohen 2015 conducted a network meta-analysis to compare the efficacy and safety of DOACs for the initial and long-term treatment of VTE. They found that apixaban was associated with a statistically significantly reduced risk of major bleeding compared with rivaroxaban (RR 0.47, 95% CI 0.36 to 0.61), dabigatran (RR 0.69, 95% CI 0.51 to 0.94), and edoxaban (RR 0.54, 95% CI 0.41 to 0.69). Dabigatran was associated with a significantly lower risk of major bleeding compared with rivaroxaban (RR 0.68, 95% CI 0.53 to 0.87) and edoxaban (RR 0.77, 95% CI 0.60 to 0.99). There were no clear differences between the DOACs with regard to the risk of VTE and related death.

The Antoniazzi 2013 review included participants with VTE and atrial fibrillation. Eight studies were included and results showed that the risk of major bleeding was lower in participants treated with dabigatran (RR 0.83, 95% CI 0.78 to 0.97) compared with the control group.

The reviews by Castellucci 2013, Cohen 2016, Sardar 2014, and Wang 2018 compared oral anticoagulants and antiplatelet drugs, but the focus was on the secondary prevention of venous thromboembolism rather than treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Available evidence shows there is little or no difference between direct oral anticoagulants (DOACs) and conventional anticoagulation in the prevention of recurrent pulmonary embolism (PE), recurrent venous thromboembolism (VTE), deep vein thrombosis (DVT), all-cause mortality, and major bleeding. According to GRADE criteria, the certainty of evidence was moderate to low. DOACs, such as direct thrombin inhibitors (DTIs) and factor Xa inhibitors, may therefore be an alternative to conventional anticoagulation treatment for acute pulmonary embolism. One potential practical advantage of DOACs over conventional anticoagulants is their ease of use due to fixed doses and no need for routine monitoring with blood tests.

Implications for research

There is some evidence of wide inter-individual variation in anticoagulant effect from the fixed doses of DOACs as currently prescribed. This may be of clinical importance, and further research is needed to compare DOACs directly with one another to see which one is most effective and safe, specifically in relation to bleeding risk in various subgroups, such as in people with cancer or obesity. Such studies would need to be very large and may not be considered financially viable to sponsoring drug companies. Any impact on the decision to use extended phase anticoagulation and interruption of procedures with DOAC use should also be investigated. Further research is also required to establish other factors associated with the use of DOACs, such as adherence, quality of life, cost-effectiveness, and tolerability. Finally, research is required in categories of venous thrombosis not specifically examined in the studies included here, such as in people with malignancy or a thrombophilic abnormality, as well as travel-associated venous thrombosis.

ACKNOWLEDGEMENTS

The review authors would like to thank Lindsay Robertson, James McCaslin, and colleagues for their contributions to previous versions of this review.

The review authors would like to thank Dr Cathryn Broderick, Dr Marlene Stewart and other Cochrane Vascular editors for their assistance and advice in completing this review. We thank Candida Fenton for designing and running the searches. We thank Yanfang Ma for helping select studies for inclusion.

The review authors would like to thank Faith Armitage for copy editing the review.

The review authors and the Cochrane Vascular editorial base are grateful to the following peer reviewers, and those who wished to remain anonymous, for their time and comments: Martin H Ellis MD, Hematology Institute and Blood Bank, Meir Medical Center, Kfar Saba and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; Daniel Schimmel MD, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA.

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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 (358 centres in 28 countries: United States, Argentina, Australia, Austria, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Hungary, India, Israel, Italy, Korea, Malaysia, Mexico, Norway, Poland, Portugal, Puerto Rico, Romania, Russia, Singapore, South Africa, Spain, Ukraine) **Number of participants:** 5395 (PE 1836, other VTE 3559); apixaban 2691 (PE 930, other VTE 1761), enoxaparin + warfarin 2704 (PE 906, DVT 1798) **Age, mean (SD) years:** apixaban 57.2 (16.0) years, enoxaparin + warfarin 56.7 (16.0) years **Sex:** apixaban 1569 M/1122 F; enoxaparin + warfarin 1598 M/1106 F **Inclusion criteria:** people ≥ 18 years of age with an objectively confirmed, symptomatic proximal DVT or PE (with or without DVT) **Exclusion criteria:** active bleeding, a high risk of bleeding, or other contraindications to treatment with enoxaparin and warfarin; if they had cancer and long-term treatment with LMWH was planned; if their DVT or PE was provoked in the absence of a persistent risk factor for recurrence; if < 6 months of anticoagulant treatment was planned; or if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin at a dose > 165 mg daily, or treatment with potent inhibitors of cytochrome P-450 3A4; if they had received > 2 doses of a once-daily LMWH regi-

AMPLIFY 2013 *(Continued)*

	men, 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 creatinine clearance < 25 mL/minute
Interventions	**Intervention 1:** oral 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 to 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	Results were presented for all participants with a VTE but specific recurrent VTE data for the subset of participants with a PE were available in the supplementary material

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 selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive voice-response system" Comment: study judged at low risk of selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind. Patients were assigned to receive apixaban tablets plus placebo enoxaparin injections and placebo warfarin tablets or conventional therapy with enoxaparin injections and warfarin tablets plus placebo apixaban tablets. 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

AMPLIFY 2013 *(Continued)*

		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	Unclear 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 explanations given. Therefore we deemed the risk of attrition bias to be unclear.
Selective reporting (reporting bias)	High risk	Study protocol was available. Minor bleeding was a pre-defined secondary outcome but the data on this outcome were not reported in the paper. Therefore we deemed the risk of reporting bias to be high.
Other bias	Low risk	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 (PE 35, other VTE 45); apixaban 40 (PE 18, other VTE 22), UFH/warfarin 40 (PE 17, other VTE 23) **Age, mean (SD) years:** apixaban 64.3 (13.40) years, UFH/warfarin 66.1 (17.72) years **Sex:** apixaban: 22 M/18 F, UFH/warfarin: 17 M/23 F **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:** people 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 creatinine clearance < 25 mL/min.
Interventions	**Intervention 1:** received apixaban 10 mg twice daily for 7 days as an initial therapy, followed by apixaban 5 mg twice daily for 23 weeks as long-term therapy **Intervention 2:** given a continuous IV infusion of UFH to maintain the activated partial thromboplastin time 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 judgment. 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).

AMPLIFY-J 2015 *(Continued)*

	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 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	Study characteristics were presented for all participants with a VTE but specific recurrent PE, recurrent VTE, all-cause mortality, and major bleeding with a PE were available.

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 selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "An interactive voice response system was used for randomisation" Comment: study judged at low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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 no longer willing to participant in study, 1 had other reason). In the UFH/warfarin group, 2 did not complete the overall trial period (1 withdrew 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	All the study's pre-specified outcomes were reported in the pre-specified way. Study judged at low risk of reporting bias.

AMPLIFY-J 2015 *(Continued)*

Other bias	Low risk	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 (PE 638, other VTE 517); apixaban 576 (PE 304, other VTE 272), dalteparin 579 (PE 334, other VTE 245) **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 non-gastrointestinal bleeding **Secondary:** recurrent VTE or major bleeding, clinically relevant non-major bleeding, major or clinically relevant non-major 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 the primary outcome 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	Results were presented for all participants with a VTE, but specific recurrent VTE and major bleeding data for the subset of participants with a PE were available in the supplementary material.

Caravaggio 2020 *(Continued)*

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 selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centrally performed through an interactive online system" Comment: study judged at low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label" Comment: 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 reasons). In the dalteparin group, 197 did not complete the overall trial period (149 died, 8 were lost to follow-up, 40 had other reasons). 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	Study protocol was available. Quality of life was a predefined 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 result was found in the paper and appendix. Therefore, the risk of reporting bias was deemed to be high.
Other bias	Low risk	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:** multinational (263 centres in 36 countries: Andorra, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Estonia, Finland, France, Germany, China Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Korea, Latvia, Lithuania, Malaysia, the Netherlands, New Zealand, Norway, Philippines, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, China Taiwan, Thailand, United Kingdom, USA) **Number of participants:** 4832 (all are PE); rivaroxaban 2419, warfarin 2413 **Age, mean (SD) years:** rivaroxaban 57.9 (7.3) years, warfarin 57.5 (7.2) years **Sex:** rivaroxaban 1309 M/1110 F, warfarin 1247 M/1166 F

EINSTEIN-PE 2012 *(Continued)*

	Inclusion criteria: aged 18 or older with an acute, symptomatic PE with objective confirmation, with or without symptomatic DVT **Exclusion criteria:** contraindications to heparin or warfarin, had received treatment for more than 48 hours with therapeutic doses of heparin, had received more than one 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 of more than 100 mg daily or dual antiplatelet therapy, or had a creatinine clearance of less than 30 mL per minute
Interventions	**Intervention 1:** oral rivaroxaban 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily **Intervention 2:** enoxaparin 1.0 mg/kg of body weight twice daily and either warfarin or aceno-coumarol, started within 48 hours of randomisation. Enoxaparin was discontinued when the INR was 2.0 or more for 2 consecutive days and the participants had received at least 5 days of enoxaparin treatment. The dose of VKA was adjusted to maintain an INR of 2.0 to 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 DVT or fatal or non-fatal PE and clinically relevant bleeding, defined as a composite of major or clinically relevant non-major bleeding. Death was classified as PE, bleeding or other established diagnoses. PE was considered the cause of death if there was objective documentation of the condition or if death could not be attributed to a documented cause and PE could not be confidently ruled out. Bleeding was defined as major if it was clinically overt and associated with a decrease in the haemoglobin level of 2.0 g per decilitre or more, if bleeding led to the transfusion of 2 or more units of red blood cells, or if bleeding was intracranial or retroperitoneal, occurred in another critical site, or contributed to death. CRNM bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life" **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 intention-to-treat 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.
Declarations of interest	"Dr. Agnelli reports receiving consulting fee, travel support, payment for writing or reviewing the manuscript, and lecture fees from Ictom/Bayer Healthcare. Dr. Berkowitz reports receiving travel support and employment from Bayer HealthCare Pharmaceuticals. Dr. Bounameaux reports receiving consulting fee, travel support, fees for participation in review activities, lecture fees and board membership from ICTOM/Bayer Healthcare, Pfizer, sanofi-aventis, GlaxoSmithKline, Boehringer-Ingelheim, and Daiichi-Sankyo. Dr. Buller reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, and Board membership from ICTOM/Bayer Healthcare, Pfizer, sanofi-aventis, GlaxoSmithKline, Boehringer-Ingelheim, and Daiichi-Sankyo. Dr. Chlumsky reports receiving consulting fee, travel support, fees for participation in review activities, and other fee from ICTOM/Bayer Healthcare. Dr. Cohen reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, and lecture fees from ICTOM/Bayer Healthcare, Astellas,AstraZeneca, Daiichi, Johnson and Johnson, Pfizer and other companies. Dr. Davidson reports receiving travel support, and fees for participation in review activities from Bayer. Dr. Decousus reports receiving fees for participation in review activities, payment for writing or reviewing the manuscript from Bayer. Dr. Gallus reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, from ICTOM/Bayer Health Care AG. Dr. Gallus reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript from ICTOM/Bayer Health Care AG. Dr. Jacobson reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript from Ictom/Bayer HealthCare AG. Dr. Lensing reports receiving travel support and employment from Bayer Healthcare. Dr. Minar reports receiving consulting fee, travel support, fees for participation in review activities, and lecture fees from BayerHealthcare/ ICTOM. Dr. Misselwitz is an employee of Bayer, the sponsor of the trial. Dr. Prins reports receiving consulting fee, travel support, payment for writing or reviewing the manuscript from

EINSTEIN-PE 2012 *(Continued)*

	ICTOM/BayerHeatltcare. Dr. Raskob reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, lecture fees, and payment for manuscript preparation from ICTOM/Bayer Healthcare, Daiichi Sankyo, BMS, and Pfizer. Dr. Schellong reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, lecture fees, and payment for development of educational presentations from ICTOM/Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, and other companies. Dr. Segers reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript from Bayer Healthcare. Dr. Verhamme reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, lecture fees from ICTOM/Bayer Healthcare, Boehringer Ingelheim, Sanofi-Aventis, and other companies. Dr. Verhamme reports receiving consulting fee, travel support, fees for participation in review activities, payment for writing or reviewing the manuscript, lecture fees from ICTOM/Bayer Healthcare, Boehringer Ingelheim, Pfizer." Disclosure forms provided by the authors are available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1113572/suppl_file/nejmoa1113572_disclosures.pdf
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of a computerised voice-response system" Comment: study judged at low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of a computerised voice-response system" Comment: study judged to be at a low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open-label" Comment: only one dose of rivaroxaban was given and as the comparison was enoxaparin/VKA, blinding of participants and personnel was not possible. However, we 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 judged to be at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the rivaroxaban group, 1 was excluded because of invalid informed consent, 7 did not receive rivaroxaban. In the standard therapy group, 8 did not receive standard therapy. 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	The study protocol is available and all of the study's pre-specified outcomes have been reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	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, Netherlands, New Zealand, Spain, USA) **Number of participants:** 1046 (PE 657, other VTE 389); edoxaban 522 (PE 328, other VTE 194), dalteparin 524 (PE 329, other VTE 195) **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:** people who met any of the following criteria were not eligible for enrolment: 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 mmHg or diastolic BP > 100 mmHg 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 creatinine clearance of 30 mL to 50 mL per minute or a body weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors. Treatment was administered for 6 to 12 months; median duration was 7 months. **Intervention 2:** dalteparin was given subcutaneously 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 venous thromboembolism or major bleeding; death **Secondary:** recurrent VTE; major bleeding; clinically relevant non-major (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	Quote: "Dr. Buller reports personal fees from Daiichi-Sankyo, during the conduct of the study; personal fees from Bayer Healthcare, personal fees from BMS/Pfizer, personal fees from Boehringer-Ingelheim, personal fees from Portola, personal fees from Medscape, personal fees from Eli Lilly, personal

Hokusai VTE Cancer 2018 *(Continued)*

	fees from Sanofi Aventis, and personal fees from Ionis outside the submitted work. Dr. Carrier reports personal fees from Daiichi Sankyo during the conduct of the study; grants and personal fees from BMS, grants and personal fees from LEO Pharma, personal fees from Pfizer, personal fees from Sanofi, and personal fees from Bayer outside the submitted work. Dr. Di Nisio reports personal fees from Daiichi Sankyo outside the submitted work. Dr. Garcia reports grants and personal fees from Daiichi Sankyo during the conduct of the study; personal fees from BMS, personal fees from Boehringer-Ingelheim, grants and personal fees from Janssen, personal fees from Pfizer, personal fees from Medscape, and grants and personal fees from Incyte outside the submitted work. Dr. Garcia reports grants and personal fees from Daiichi Sankyo during the conduct of the study; personal fees from BMS, personal fees from Boehringer-Ingelheim, grants and personal fees from Janssen, personal fees from Pfizer, personal fees from Medscape, and grants and personal fees from Incyte outside the submitted work. Dr. Kakkar reports personal fees from Daiichi Sankyo during the conduct of the study; grants and personal fees from Bayer AG, personal fees from Boehringer-Ingelheim, personal fees from Janssen Pharma, personal fees from Sanofi SA, and personal fees from Verseon outside the submitted work. Dr. Kovacs reports grants and personal fees from Pfizer, grants and personal fees from Bayer, grants from Daiichi Sankyo Pharma, and grants from Bristol Meyers Squibb outside the submitted work. Dr. Mercuri reports personal fees from Daiichi-Sankyo, outside the submitted work. Dr. Meyer reports non-financial support from Leo Pharma, grants and non-financial support from BMS-Pfizer, non-financial support from Stago, and non-financial support from Bayer Healthcare outside the submitted work. Dr. Raskob reports personal fees from Daiichi Sankyo during the conduct of the study; personal fees from Bayer Healthcare, personal fees from BMS, personal fees from Boehringer-Ingelheim, personal fees from Eli Lilly, personal fees from Janssen, personal fees from Johnson and Johnson, personal fees from Pfizer, personal fees from Portola, personal fees from Merck, and personal fees from Medscape outside the submitted work. Dr. Segers reports grants from Daiichi Sankyo during the conduct of the study; grants from IONIS Pharmaceuticals, grants from Daiichi Sankyo, and grants from Janssen Pharmaceuticals outside the submitted work. Dr. Shi reports personal fees from Daiichi Sankyo outside the submitted work. Dr. Verhamme reports grants and personal fees from Daiichi Sankyo, during the conduct of the study; grants and personal fees from Bayer Healthcare, personal fees from BMS, grants and personal fees from Boehringer-Ingelheim, personal fees from Portola, personal fees from Medscape, grants and personal fees from LeoPharma, grants from Sanofi, personal fees from Medtronic, personal fees from Pfizer, outside the submitted work. Dr. Wang reports non-financial support from Daiichi Sankyo during the conduct of the study. Dr. Weitz reports personal fees from Daiichi-Sankyo, during the conduct of the study; personal fees from Bayer Healthcare, personal fees from BMS, personal fees from Boehringer-Ingelheim, personal fees from Ionis Pharmaceuticals, personal fees from Janssen, personal fees from Johnson and Johnson, personal fees from Pfizer, personal fees from Portola, personal fees from Medscape, personal fees from Novartis outside the submitted work. Dr. Yeo reports grants and personal fees from Daiichi Sankyo during the conduct of the study; personal fees from Bayer Healthcare, personal fees from Pfizer, personal fees from Boerhringer Ingelheim, personal fees from Sanofi, and personal fees from Leo Pharma outside the submitted work. Dr. Zhang reports personal fees from Daiichi Sankyo outside the submitted work. Dr. Zhang reports personal fees from Daiichi Sankyo outside the submitted work." Disclosure forms provided by the authors are available at: www.nejm.org/doi/suppl/10.1056/NEJMoa1711948/suppl_file/nejmoa1711948_disclosures.pdf
Notes	Study characteristics were presented for all participants with a VTE, but specific recurrent VTE and major bleeding with a PE were available.

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 selection 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 selection bias.

Hokusai VTE Cancer 2018 *(Continued)*

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 ITT analysis. Study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes were reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	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 (439 centres in 36 countries: Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Estonia, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, China Taiwan, Thailand, Turkey, Ukraine, United Kingdom, USA) **Number of participants:** 3319 (all are PE); edoxaban 1650, warfarin 1669 **Age, mean (SD) years:** edoxaban 57.1 (16.6) years, warfarin 57.4 (16.5) years **Sex:** edoxaban 863 M/787 F, warfarin 875 M/794 F **Inclusion criteria:** people aged 18 or older 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 more than 48 hours with therapeutic doses of heparin, had received more than one 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 of more than 100 mg daily or dual antiplatelet therapy, or had a creatinine clearance of less than 30 mL per minute
Interventions	**Intervention 1:** oral edoxaban 60 mg once daily or 30 mg once daily in participants with a creatinine clearance of 30 mL to 50 mL per minute or a body weight of 60 kg or less or in participants who were receiving concomitant treatment with potent P-glycoprotein inhibitors **Intervention 2:** dose-adjusted warfarin therapy to achieve an INR of 2.0 to 3.0 and edoxaban-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

Hokusai-VTE 2013 *(Continued)*

Outcomes	**Primary:** incidence of symptomatic recurrent VTE (DVT and fatal or non-fatal PE), clinically relevant bleeding (major or clinically relevant non major) **Secondary:** none
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. Decousus 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 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 reports 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	We successfully contacted study authors for outcome data, including the rate of recurrent pulmonary embolism, deep vein thrombosis, and major bleeding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive Web-base system" Comment: study judged at low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of an interactive Web-base system" Comment: study judged to be at a low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Edoxaban or warfarin was administered in a double-blind fashion" Comment: study judged to be at a 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 to be at a low risk of performance bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the edoxaban group, 25 did not receive heparin–edoxaban, 181 did not complete the overall study period, 132 died, 36 withdrew consent, 7 were lost to follow-up, 6 had other reasons. In the warfarin group, 27 did not receive he-

Hokusai-VTE 2013 *(Continued)*

		parin–warfarin, 167 did not complete the overall study period, 126 died, 34 withdrew consent, 4 were lost to follow-up, 3 had other reasons. 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	The study protocol is available and all of the study's pre-specified outcomes have been reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	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 **Duration of study:** 6.5 months
Participants	**Setting:** multicentre **Country:** Japan (30 centres) **Number of participants:** 97 (PE 40, other VTE 57); rivaroxaban 78 (PE 33, other VTE 45), UFH (UFH)/warfarin 19 (PE 7, other VTE 12) **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; a creatinine clearance < 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 fewer 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 APPT 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 2 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."

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

	Comment: Bayer Yakuhin Ltd, Japan developed rivaroxaban. Some authors received funding from some pharmaceutical companies. The results showed a similar efficacy and safety profile 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 Corporation. 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	Results were presented for all participants with a VTE but specific recurrent VTE data for the subset of participants with a PE were available.

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 selection 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 selection 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 ITT analysis. Study judged at low risk of attrition bias.
Selective reporting (reporting bias)	Low risk	All the study's pre-specified outcomes were reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	We did not find any methodological issues that might directly lead to a risk of bias.

MERCURY PE 2018

Study characteristics	
Methods	**Study design:** randomised, open-label, parallel-group, multicenter study **Duration of study:** 3 months
Participants	**Setting:** multicentre (35 hospitals) **Country:** USA **Number of participants:** 114 (all were PE); rivaroxaban 51, standard of care 63 **Age, mean (SD) years:** rivaroxaban 49.14 (13.3) years, standard of care 47.56 (17.2) years **Sex:** rivaroxaban 24M/27F, standard of care 31M/32F **Inclusion criteria:** adults presenting to the emergency department (ED) with objectively confirmed, low-risk PE were eligible for enrolment. Low-risk PE was defined by the absence of any Hestia criteria, adapted for emergency medicine by removing 24-hour requirements. **Exclusion criteria:** people were excluded for a troponin level above the institutional upper reference level, contraindications to anticoagulation, or by investigator determination of barriers to treatment or follow-up. Although the Hestia criteria exclude haemodynamically unstable patients, instability is not defined and was determined per the physician's judgment.
Interventions	**Intervention 1:** participants randomised to early discharge on rivaroxaban were discharged within 24 hours of ED triage and were instructed to take rivaroxaban with food, 15 mg twice daily for 21 days and then 20 mg once daily to study completion. Treatment for 3 months **Intervention 2:** standard of care participants were treated per local protocol, which could include hospitalisation and any Food and Drug Administration (FDA)-approved anticoagulant strategy, including rivaroxaban. If receiving warfarin, the target INR was 2.0 to 3.0, with testing per local protocol. **Follow-up:** 30 days, 90 days
Outcomes	**Primary:** total amount of time spent in the hospital, expressed in hours for venous thromboembolic or bleeding events, in the 30 days after randomisation. The primary safety outcome was major bleeding within 90 days. **Secondary:** prespecified secondary efficacy endpoints included 90-day rates of new/recurrent VTE, VTE-related death, unplanned hospital or physician office visits for VTE
Funding	Quote: "Funding for this research was provided by Janssen Pharmaceuticals, Raritan, NJ" Comment: Janssen Pharmaceuticals, Raritan, NJ, manufactures rivaroxaban. The results showed a similar efficacy and safety profile with rivaroxaban and control treatment. It is possible that this may have influenced the report of outcomes.
Declarations of interest	Quote: "Consulting for commercial interests, including advisory board work-WFP, CC, DD, and AS have received funding personally from Janssen for consulting. WFP, and CC have received funding personally from Bayer, AG. JK has received grant funding from Janssen for a separate study. Payment for writing independent of grant funding—No author received payment from for writing any part of this manuscript. Employment—PW and JX are employed by Janssen, which manufactures rivaroxaban. Institutional Grant Receipt—WFP, CC, DD, SF, CKa, CKe, JM, and AS's institution has received funding from Janssen for this investigator-initiated research. Miscellaneous—DD has been a member of the SAEM board of directors. Author Contributions: WFP—study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical expertise, and acquisition of funding. CC—acquisition of the data, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, and statistical expertise. DD—study concept and design, acquisition of the data, and critical revision of the manuscript for important intellectual content. SK—acquisition of the data and critical revision of the manuscript for important intellectual content. CKa—study concept and design, analysis and interpretation of the data, and critical revision of the manuscript for important intellectual content. CKe—acquisition of the data and critical revision of the manuscript for important intellectual content. JK—study concept and design and critical revision of the manuscript for important intellectual content. JM—acquisition of the data and critical revision of the manuscript for important intellectual content. PW—study concept and design, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, statistical expertise, and acquisition of funding. JX—analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, and statistical expertise. AS—study concept and design, acquisition of the data, analysis and

MERCURY PE 2018 *(Continued)*

	interpretation of the data, critical revision of the manuscript for important intellectual content, statistical expertise, and acquisition of funding."
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to emergency department discharge on open-label rivaroxaban or standard care (as determined by the attending physician) by an interactive Web within 12 hours of diagnosis." Comment: study judged at low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centrally performed through an interactive online system." Comment: study judged at low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Open label, as participants could not be blinded to their own hospitalisation, to reduce observer bias clinical and safety endpoints were adjudicated by a panel blinded to treatment allocation." Comment: lack of blinding was unlikely to have affected the outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "As participants could not be blinded to their own hospitalisation, to reduce observer bias clinical and safety endpoints were adjudicated by a panel blinded to treatment allocation." Comment: blinding was performed adequately; study judged at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the rivaroxaban group, 7 dropouts (3 lost to follow-up, 0 withdrew consent, 4 other reasons). In the standard of care group: 8 dropouts (4 lost to follow-up, 2 withdrew consent, 2 other reasons). 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	All of the study's pre-specified outcomes were reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	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:** 6 months
Participants	**Setting:** multicentre **Country:** multinational (228 clinical centres in 29 countries: USA, Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, India, Israel, Italy, Mexico, the Netherlands, New Zealand, Norway, Portugal, Russian Federation, Slovakia, South Africa, Spain, Sweden, Turkey, Ukraine, United Kingdom) **Number of participants:** 2539 (PE 786, other VTE 1753); dabigatran 1273 (PE 391, other VTE 882), warfarin 1266 (PE 395, other VTE 871) **Age, mean (range) years:** dabigatran 55 (15.8) years, warfarin 54.4 (16.2) years **Sex:** dabigatran 738 M/535 F, warfarin 746 M/520 F

RE-COVER 2009 *(Continued)*

	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 ALT level that was 2 x ULN range, an estimated creatinine clearance < 20 mL/minute, a life expectancy < 6 months, contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, requirement for long-term anticoagulant therapy
Interventions	**Intervention 1:** oral dabigatran 150 mg twice daily and warfarin-like placebo **Intervention 2:** dose-adjusted warfarin therapy to achieve an INR of 2.0 to 3.0 and dabigatran-like placebo **Follow-up:** 6 months
Outcomes	**Primary:** recurrent VTE evaluated using the same diagnostic methods used for the initial diagnosis **Secondary:** bleeding that was defined as major if it was clinically overt and if it was associated with a fall in the haemoglobin level ≥ 20 g/L, resulted in the need for transfusion of ≥ 2 units of red cells, involved a critical site, or was fatal.
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, Sanofi-Aventis, 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, Bristol-Myers 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	2539 participants were recruited into the trial but only 1602 had a PE and were included in the analysis of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated randomisation scheme" Comment: study judged at low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Quote: "Staff members at the clinical centres called an interactive voice-response system that randomly assigned subjects to one of the supplied medication kits. The treatment-group assignment was concealed from all the investigators and their staff at the coordinating centre and the clinical centres and from the clinical monitors" Comment: study judged to be at low risk of selection bias.

RE-COVER 2009 *(Continued)*

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 to be 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 to be at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study drug was stopped before 6 months in 204 participants (16%) in the dabigatran group (126 because of an adverse event, 21 because of non-adherence, 9 because of loss to follow-up, 39 because of withdrawal of consent, and 9 for other reasons) and in 183 participants (14.5%) in the warfarin group (102 because of an adverse event, 35 because of non-adherence, 6 because of loss to follow-up, 36 because of withdrawal of consent, and 4 for other reasons). 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	All of the study's pre-specified outcomes have been reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	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:** 6 months
Participants	**Setting:** 208 study sites **Country:** multinational (228 clinical centres in 30 countries: USA, Australia, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, France, Hungary, India, Israel, Italy, Korea, Malaysia, the Netherlands, New Zealand, Norway, Philippines, Poland, Russian Federation, Singapore, Slovakia, South Africa, Spain, Sweden, China Taiwan, Thailand, Turkey, Ukraine, United Kingdom) **Number of participants:** 2568 (PE 816, other VTE 1752): dabigatran 1280 (PE 402, other VTE 878), warfarin 1288 (PE 414, other VTE 874) **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 or older who had acute, symptomatic, objectively verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment **Exclusion criteria:** duration of symptoms longer than 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 times the ULN range; an estimated creatinine clearance of less than 20 mL per minute; a life expectancy of less than 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 to 3.0 and dabigatran-like placebo for 6 months

RE-COVER II 2014 *(Continued)*

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	None
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by use of an interactive voice response system and a computer-generated randomisation scheme in blocks of 4" Comment: study judged at low risk of selection bias.
Allocation concealment (selection bias)	Low risk	Comment: no information given about how treatment allocation was concealed but study authors 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 we judged to be at low risk of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind" Comment: stated as double-blind. No other information given about how blinding was maintained but study authors state that "the design of the trial was essentially identical to that of the first study with dabigatran for the treatment of acute VTE", which we judged to be 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 to be at low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 participants in the dabigatran group and 7 in the warfarin group did not receive any study medication (10 did not meet the inclusion criteria or met the exclusion criteria, 9 withdrew consent, and 2 had an adverse event). 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	All of the study's pre-specified outcomes have been reported in the pre-specified way. Study judged at low risk of reporting bias.
Other bias	Low risk	We did not find any methodological issues that might directly lead to a risk of bias.

ALT/AST: alanine transaminase/aspartate aminotransferase
APTT: activated partial thromboplastin time
BP: blood pressure
CRNM: clinically relevant non-major
CT: computed tomography
DVT: deep vein thrombosis
ECOG: Eastern Cooperative Oncology Group
F: female
INR: international normalised ratio
ISTH: International Society on Thrombosis and Haemostasis
ITT: intention-to-treat

IV: intravenous
LMWH: low molecular weight heparin
M: male
PE: pulmonary embolism
PT-INR: prothrombin time-international normalised ratio
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 people with a pulmonary embolism
AMPLIFY Extended 2013	Extended study testing prophylaxis rather than treatment
Borsi 2021	Unable to obtain specific outcome data for people with a pulmonary embolism
Botticelli DVT 2008	People with a pulmonary embolism were excluded from the study
CASTA DIVA Trial 2022	Unable to obtain specific outcome data for people with a pulmonary embolism
COBRRA pilot feasibility study 2017	Unable to obtain specific outcome data for people with a pulmonary embolism
CONKO-011 2015	Unable to obtain specific outcome data for people with a pulmonary embolism
de Athayde Soares 2019	People with a pulmonary embolism were excluded from the study
DIVERSITY trial 2021	Unable to obtain specific outcome data for people with a pulmonary embolism
Einstein DVT 2013	People with a pulmonary embolism were excluded from the study
EINSTEIN Extension 2007	Extended study testing prophylaxis rather than treatment
EINSTEIN-CHOICE trial 2017	Comparator was aspirin
Einstein-DVT Dose 2008	People with a pulmonary embolism were excluded from the study
EINSTEIN-Jr Trial 2020	Unable to obtain specific outcome data for people with a pulmonary embolism
Farhan 2019	People with a pulmonary embolism were excluded from the study
IRIVASC-Trial 2022	Unable to obtain specific outcome data for people with a pulmonary embolism
Mokadem 2021	People with a pulmonary embolism were excluded from the study
ODIXa-DVT 2007	People with a pulmonary embolism were excluded from the study
Ohmori 2018	People with a pulmonary embolism were excluded from the study
Piazza 2014	People with a pulmonary embolism were excluded from the study
PRAIS trial 2019	People with a pulmonary embolism were excluded from the study

Study	Reason for exclusion
PRIORITY 2022	Unable to obtain specific outcome data for people with a pulmonary embolism
RE-SONATE 2013	People were already included in the RE-COVER I and RE-COVER II studies
REMEDY 2013	Extended study testing prophylaxis rather than treatment
SELECT-D 2018	Unable to obtain specific outcome data for people with a pulmonary embolism
Sukovatykh 2017	People with a pulmonary embolism were excluded from the study
THRIVE 2005	Unable to obtain specific outcome data for people with a pulmonary embolism
THRIVE I 2003	Treatment was for fewer than 3 months
THRIVE III 2003	Participants in control group were given a placebo

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 a day for 7 days followed by 5 mg twice a day for 23 weeks **Intervention 2:** UFH, dose adjustment based on APTT 1.5 to 2.5 times the control value, and until INR ≥ 1.5 for 5 days or more plus warfarin for 24 weeks at a dose to target INR range between 1.5 to 2.5
Outcomes	**Primary:** major bleeding and clinically relevant non-major bleeding **Secondary:** symptomatic VTE or VTE-related death, major bleeding and all bleeding
Notes	

APTT: activated partial thromboplastin time
BP: blood pressure
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**: hospitals **Country**: Austria, Canada, Germany, Italy, Russian Federation, Ukraine, USA **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. CNS 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 > 2x ULN) at randomisation. 7. At the time of randomisation, inadequate renal function as defined in Section 7.2.2 Estimated Glomerular Filtration Rate Assessment of the protocol. 8. Platelet count < 50×10^9 per L at randomisation. 9. At the time of randomisation, uncontrolled severe hypertension as defined in Section 7.1 Physical Examination of the protocol. 10. At the time of randomisation, use of prohibited concomitant medication as listed for apixaban in Section 5.5 Concomitant Medication of the protocol. 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 (BMS) 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 specified
Outcomes	**Primary**: the composite of major and clinically relevant non-major 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 **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

EudraCT 2014-002606-20 *(Continued)*

Starting date	April 2015
Contact information	Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Notes	

NCT02464969

Study name	Apixaban for the acute treatment of VTE in children
Methods	**Study design**: random, open-label, parallel, active controlled study
Participants	**Setting**: hospital, clinic, research centre **Country**: USA, 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 enrolments. 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 - subjects between birth to < 18 years will be dosed on a body weight tiered regimen. Subjects ≥ 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 sub analysis, 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 subjects under 2 years of age, SOC will be limited to UFH or LMWH"
Outcomes	**Primary**: the composite of major and clinically relevant non-major bleeding; a composite of all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE- and VTE-related mortality

NCT02464969 *(Continued)*

	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	VTE 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 creatinine clearance between 30 mL to 50 mL/min (Cockcroft and Gault formulae) or a severe renal insufficiency (between 15 mL 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; life expectancy more 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 blood pressure of more than 180 mm Hg or a diastolic blood pressure of more than 110 mm Hg; anticoagulation for more than 72 hours prior to randomisation; chronic liver disease or chronic hepatitis; people at high risk of bleeding; creatinine clearance < 15 mL/min or end stage renal disease or indication for extra-renal dialysis; need for concomitant anti-platelet therapy other than aspirin 75 mg to 325 mg per day. However concomitant treatment with aspirin is discouraged in this population at bleeding risk; concomitant use of a strong inhibitor of 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 fewer 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**: the control group receiving the SOC, i.e. heparins/VKA regimen. Participants will receive the current recommended therapy: subcutaneous or intravenous UFH/VKA in case of severe renal insufficiency and subcutaneous 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	DOACs versus LMWH with or without warfarin for VTE in cancer
Methods	**Study design**: randomised, open-label, parallel study
Participants	**Setting**: hospital **Country**: USA **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 3 months; age ≥ 18 years; platelet count is ≥ 50,000/mm^3 (≤ 7 days prior to enrolment); CrCL (creatinine clearance) is ≥ 15 mL/min (≤ 7 days prior to enrolment) **Exclusion criteria**: diagnosis of acute leukaemia; has ever received or is scheduled to receive an allogeneic haematopoietic stem cell transplantation; people who have ever received an autologous haematopoietic stem cell transplantation are eligible; people who are scheduled to receive an autologous haematopoietic stem cell transplantation (autoHSCT) are not eligible; ongoing, clinically significant bleeding (Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4); ongoing therapy with a P-gp 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 4 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 3 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 Short Form (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 paediatric patients with confirmed venous thromboembolism
Methods	**Study design**: randomised, open-label, parallel, multicentre study
Participants	**Setting**: hospital **Country**: USA, Argentina, Brazil, Bulgaria, Canada, Chile, Croatia, Czechia, Denmark, El Salvador, France, Germany, Guatemala, Hungary, India, Israel, Kenya, Korea, Lebanon, Malaysia, 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; subjects 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, subjects initially treated with VKA are recommended to have an INR < 2.0; subject 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; subjects 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; subjects 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 the ULN or total bilirubin > 2 × ULN with direct bilirubin > 20% of the total at screening visit; subjects with GFR < 30% of normal for age and size as determined by the Schwartz formula; subjects with stage 2 hypertension defined as blood pressure systolic and/or diastolic confirmed > 99th percentile + 5 mmHg; subject 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); subjects who are known to be pregnant or breastfeeding; subjects 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; subjects 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 years, 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; clinically relevant non-major bleeding; symptomatic recurrent VTE, death as a result of VTE and major and clinically relevant non-major bleeding; peak plasma concentration; area under the plasma concentration versus time curve (AUC); apparent systemic clearance (CL/F); apparent volume of distribution (V/F); prothrombin time (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	

NCT03129555

Study name	The Danish non-vitamin K antagonist oral anticoagulation study in patients with VTE (DAN-NOAC-VTE)
Methods	**Study design**: cluster-randomised cross-over study
Participants	**Setting**: hospital **Country**: Denmark **Inclusion criteria**: 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. After cluster randomisation, dabigatran will be given to all participants with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months one at the time. **Intervention 2**: rivaroxaban oral tablet. After cluster randomisation, rivaroxaban will be given to all participants with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months one at the time. **Intervention 3**: edoxaban oral tablet. After cluster randomisation, edoxaban will be given to all participants with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months one at the time. **Intervention 4**: apixaban oral tablet. After cluster randomisation, apixaban will be given to all participants with VTE when possible for 6 months. Hereafter the cluster will use the other 3 NOACs for 6 months one at the time.
Outcomes	**Primary**: a composite endpoint of new VTE or all-cause death **Secondary**: new VTE; all-cause death; bleeding requiring hospitalisation **Other outcome measures**: 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 VTE
Methods	**Study design:** randomised, open-label, parallel study
Participants	**Setting**: hospital **Country**: Canada

NCT03266783 *(Continued)*

	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; creatinine clearance < 3 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 (note below) or breastfeeding (Note: as reported by the patient or a pregnancy test will be ordered at the discretion of the treating physician for women of childbearing potential as per standard of care).
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 Veronica Bates, BSc, CCRP 613-737-8899 ext, 71068 vebates@ohri.ca
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
Participants	**Setting**: hospital **Country**: USA **Inclusion criteria**: male or female participants ≥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

NCT05171049 *(Continued)*

	(e.g. atrial fibrillation, mechanical heart valve, prior VTE); platelet count <50,000/mm^3; PE leading to haemodynamic instability (blood pressure < 90 mmHg or shock); acute ischaemic or hemorrhagic 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; Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4 at screening; life expectancy < 3 months at randomisation; calculated creatinine clearance < 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 breastfeeding women; people 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; people with any condition that in the investigator's judgement would place them 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 intravenous administration followed by monthly administration of the same dose subcutaneously
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 clinically relevant non-major bleeding events; net clinical benefit defined as survival without VTE recurrence, or major or clinically relevant non-major bleeding
Starting date	May 2022
Contact information	Nancy Widener 239-284-3741,Nancy.w@anthostherapeutics.com Deb Freedholm 609-439-8246, Deb.f@anthostherapeutics.com
Notes	

Pettit 2018

Study name	High treatment failure rates with rivaroxaban and apixaban in a randomised controlled trial of young women with VTE
Methods	**Study design:** randomised, parallel, open-label study
Participants	**Setting**: hospital **Country**: USA **Inclusion criteria**: non-pregnant women, aged 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 menstrua-

Pettit 2018 *(Continued)*

	tion (does not apply to women who were recently pregnant); clinical plan and patient 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 Xarelto or Eliquis (e.g. anaphylactic reactions); plan to become pregnant in the next 3 months; concomitant prescribed use of aspirin or thienopyridines 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 intravenous 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 cross-over to another anticoagulant; rate of clinically relevant non-major bleeding; haemoglobin concentration; physical component summary of standard from 36 [sic].
Starting date	September 2016
Contact information	Patti Hogan, 317-962-1190, hoganpr@iu.edu Kate Pettit, 317-880-3870, klpettit@iu.edu
Notes	

UMIN000020069

Study name	Comparison of efficacy and safety between warfarin, rivaroxaban and edoxaban in patients with acute PE in Showa University
Methods	**Study design**: randomised, parallel, open-label study (assessor(s) blinded)
Participants	**Setting**: hospital **Country**: Japan **Inclusion criteria**: people with acute PE who are hospitalised in Showa University Hospital, Showa University Fujigaoka Hospital and Showa University Koto Toyosu Hospital and needed intensive care, 20 to 90 years old **Exclusion criteria**: creatinine clearance less than 30 mL/min; people with acute bleeding; people with active malignancy; people needing PCPS, IABP, and aortic sheathes; contraindication for each drug
Interventions	**Intervention 1**: rivaroxaban administration at the dose of 15 mg twice a day in the first 3 weeks. Subsequently, rivaroxaban administration at the dose of 15 mg once a day for 6 months. **Intervention 2**: warfarin administration for 6 months with prothrombin time INR between 2.00 and 3.00. **Intervention 3**: edoxaban administration at the dose of 60 mg (30 mg if participants meet the reduced criteria of edoxaban) once a day for 6 months
Outcomes	**Primary**: central disease score and thrombus volume in pulmonary vein measured by CT (if possible)

UMIN000020069 *(Continued)*	**Secondary**: CT index score; coagulation test; change in UCG*; length of hospital stay and coronary care unit; length of disappearance of PE from an initial day *We are unsure what UCG is and have requested information from study authors
Starting date	December 2015
Contact information	Norikazu Watanabe, Division of Cardiology, Department of Medicine, Showa University, Shina-gawaku Tokyo, Email: n-watanabe@med.showa-u.ac.jp
Notes	

ALT: alanine transaminase
APTT: activated partial thromboplastin time
CNS: central nervous system
CYP3A4: cytochrome P-450 3A4
DOACs: direct oral anticoagulantsDVT: deep vein thrombosis
GFR: glomerular filtration rate
IABP: intra-aortic balloon pumping
INR: international normalised ratio
LMWH: low molecular weight heparin
NOAC: non-vitamin K antagonist oral anticoagulation
PBAC: pictorial blood loss assessment chart
PCPS: percutaneous cardiopulmonary support
PE: pulmonary embolism
PK: pharmacokinetics
QALYs: quality-adjusted life years
SOC: standard of care
UFH: unfractionated heparin
ULN: upper limit of normal
VKA: vitamin K antagonist
VTE: venous thromboembolism

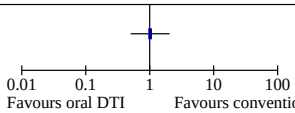
DATA AND ANALYSES

Comparison 1. Oral DTIs versus conventional anticoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Recurrent pulmonary embolism	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Recurrent venous thromboembolism	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Deep vein thrombosis	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.4 Major bleeding	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Oral DTIs versus conventional anticoagulation, Outcome 1: Recurrent pulmonary embolism

Study or Subgroup	Oral DTI Events	Oral DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
RE-COVER 2009 (1)	16	795	16	807	1.02 [0.50 , 2.04]		+	+	+	+	+	+	+

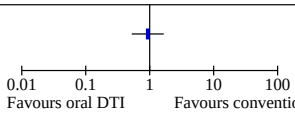


Footnotes
(1) Data was taken from pooled analysis of RE-COVER and RE-COVER II studies

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Oral DTIs versus conventional anticoagulation, Outcome 2: Recurrent venous thromboembolism

Study or Subgroup	Oral DTI Events	Oral DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
RE-COVER 2009 (1)	23	795	25	807	0.93 [0.52 , 1.66]		+	+	+	+	+	+	+

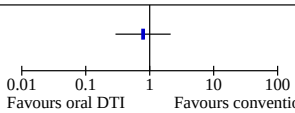


Footnotes
(1) Data was taken from pooled analysis of RE-COVER and RE-COVER II studies

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Oral DTIs versus conventional anticoagulation, Outcome 3: Deep vein thrombosis

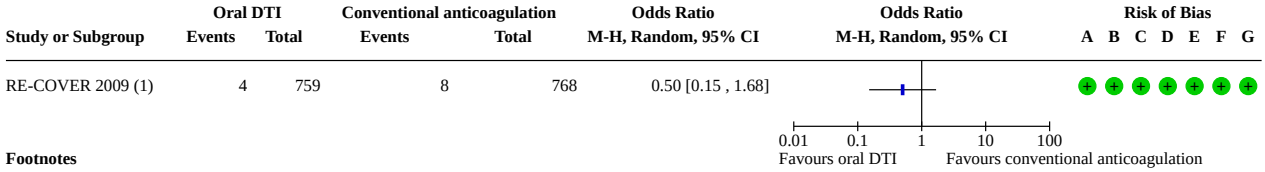
Study or Subgroup	Oral DTI Events	Oral DTI Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
RE-COVER 2009 (1)	7	795	9	807	0.79 [0.29 , 2.13]		+	+	+	+	+	+	+



Footnotes
(1) Data was taken from pooled analysis of RE-COVER and RE-COVER II studies

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Oral DTIs versus conventional anticoagulation, Outcome 4: Major bleeding



Footnotes
(1) Data was taken from pooled analysis of RE-COVER and RE-COVER II studies

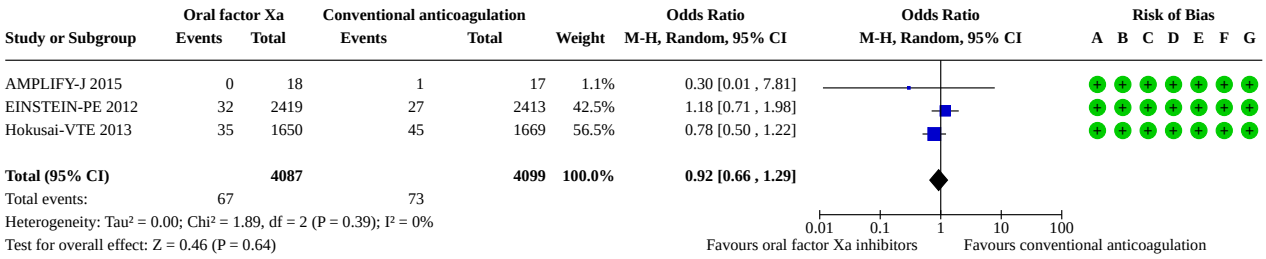
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Oral factor Xa inhibitors versus conventional anticoagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Recurrent pulmonary embolism	3	8186	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.29]
2.2 Recurrent venous thromboembolism	8	11416	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.03]
2.2.1 Non-cancer associated pulmonary embolism	6	9898	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.17]
2.2.2 Cancer associated pulmonary embolism	3	1518	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.42, 1.01]
2.3 Deep vein thrombosis	2	8151	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.25]
2.4 All-cause mortality	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
2.5 Major bleeding	8	11447	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.36, 1.41]
2.5.1 Non-cancer associated pulmonary embolism	6	10152	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.19, 1.06]
2.5.2 Cancer associated pulmonary embolism	2	1295	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.84, 2.71]
2.6 Recurrent venous thromboembolism (subgroup analysis based on different types of factor Xa inhibitors)	8	11416	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.04]
2.6.1 Apixaban	3	2459	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.54, 1.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.2 Rivaroxaban	3	4981	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.71]
2.6.3 Edoxaban	2	3976	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.48, 0.92]
2.7 Major bleeding (subgroup analysis based on different types of factor Xa inhibitors)	8	11447	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.36, 1.41]
2.7.1 Apixaban	3	2503	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.07, 1.91]
2.7.2 Rivaroxaban	3	4968	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.31, 0.79]
2.7.3 Edoxaban	2	3976	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.80, 2.58]
2.8 Recurrent venous thromboembolism (sensitivity analysis by including only studies at low risk of bias)	6	8992	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.54, 1.14]
2.9 Major bleeding (sensitivity analysis by including only studies at low risk of bias)	6	8979	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.42, 1.97]

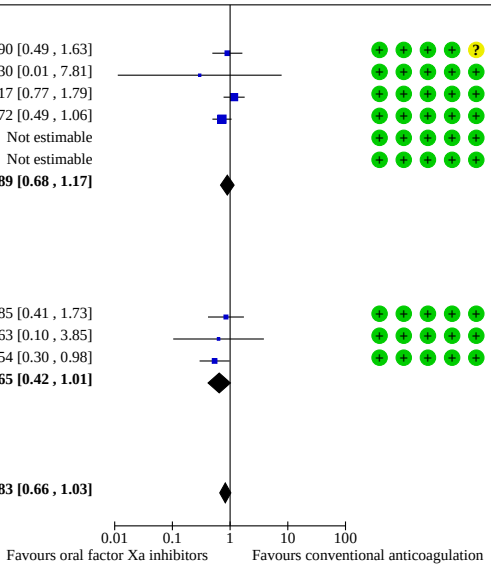
Analysis 2.1. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 1: Recurrent pulmonary embolism



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 2: Recurrent venous thromboembolism

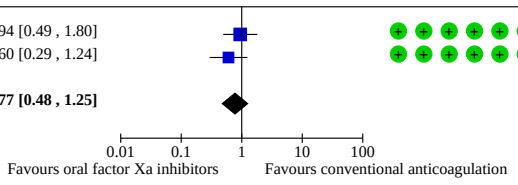
Study or Subgroup	Oral factor Xa Events	Oral factor Xa Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
2.2.1 Non-cancer associated pulmonary embolism						
AMPLIFY 2013	21	900	23	886	13.6%	0.90 [0.49 , 1.63]
AMPLIFY-J 2015	0	18	1	17	0.5%	0.30 [0.01 , 7.81]
EINSTEIN-PE 2012	48	2305	41	2304	27.6%	1.17 [0.77 , 1.79]
Hokusai-VTE 2013	47	1650	65	1669	33.6%	0.72 [0.49 , 1.06]
J-EINSTEIN DVT and PE 2015	0	28	0	7		Not estimable
MERCURY PE 2018	0	51	0	63		Not estimable
Subtotal (95% CI)		**4952**		**4946**	**75.3%**	**0.89 [0.68 , 1.17]**
Total events:	116		130			
Heterogeneity: Tau² = 0.01; Chi² = 3.23, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 0.81 (P = 0.42)						
2.2.2 Cancer associated pulmonary embolism						
Caravaggio 2020	14	304	18	334	9.5%	0.85 [0.41 , 1.73]
EINSTEIN-PE 2012	2	114	3	109	1.5%	0.63 [0.10 , 3.85]
Hokusai VTE Cancer 2018	18	328	32	329	13.6%	0.54 [0.30 , 0.98]
Subtotal (95% CI)		**746**		**772**	**24.7%**	**0.65 [0.42 , 1.01]**
Total events:	34		53			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.91 (P = 0.06)						
Total (95% CI)		**5698**		**5718**	**100.0%**	**0.83 [0.66 , 1.03]**
Total events:	150		183			
Heterogeneity: Tau² = 0.00; Chi² = 5.63, df = 6 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: Chi² = 1.47, df = 1 (P = 0.23), I² = 31.9%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 3: Deep vein thrombosis

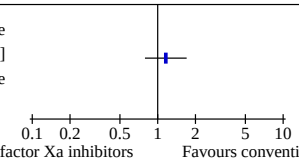
Study or Subgroup	Oral factor Xa Events	Oral factor Xa Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
EINSTEIN-PE 2012	18	2419	19	2413	55.2%	0.94 [0.49 , 1.80]
Hokusai-VTE 2013	12	1650	20	1669	44.8%	0.60 [0.29 , 1.24]
Total (95% CI)		**4069**		**4082**	**100.0%**	**0.77 [0.48 , 1.25]**
Total events:	30		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: Not applicable						

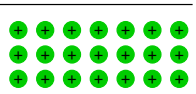


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 4: All-cause mortality

Study or Subgroup	Oral factor Xa Events	Oral factor Xa Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Odds Ratio M-H, Random, 95% CI
AMPLIFY-J 2015	0	18	0	17	Not estimable
EINSTEIN-PE 2012	58	2412	50	2405	1.16 [0.79 , 1.70]
MERCURY PE 2018	0	51	0	63	Not estimable

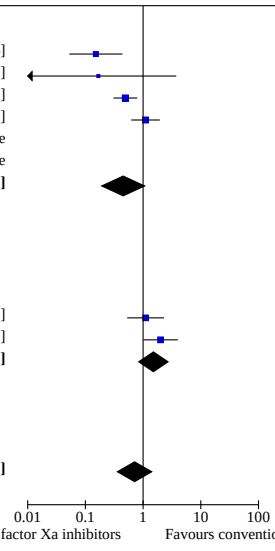




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

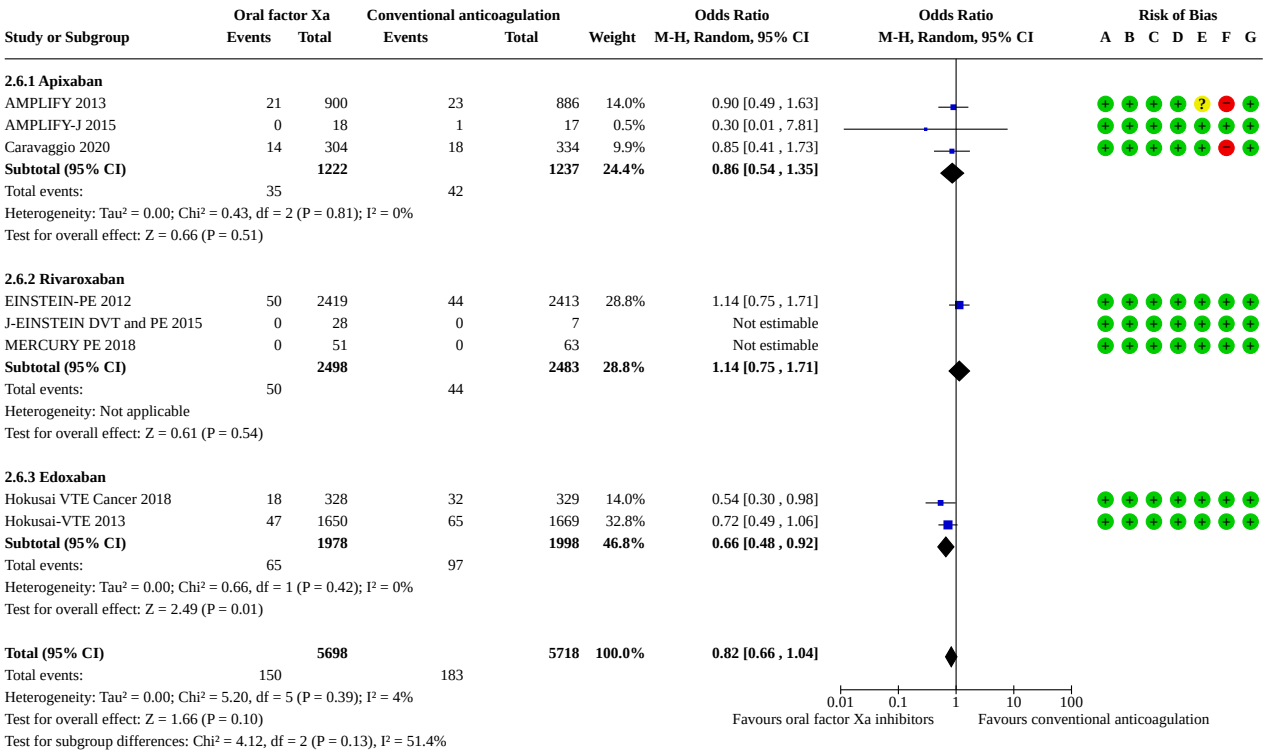
Analysis 2.5. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 5: Major bleeding

Study or Subgroup	Oral factor Xa Events	Oral factor Xa Total	Conventional anticoagulation Events	Conventional anticoagulation Total	Weight	Odds Ratio M-H, Random, 95% CI
2.5.1 Non-cancer associated pulmonary embolism						
AMPLIFY 2013	4	928	25	902	15.3%	0.15 [0.05 , 0.44]
AMPLIFY-J 2015	0	18	2	17	4.0%	0.17 [0.01 , 3.76]
EINSTEIN-PE 2012	26	2412	52	2405	21.6%	0.49 [0.31 , 0.79]
Hokusai-VTE 2013	25	1650	23	1669	20.7%	1.10 [0.62 , 1.95]
J-EINSTEIN DVT and PE 2015	0	30	0	7		Not estimable
MERCURY PE 2018	0	51	0	63		Not estimable
Subtotal (95% CI)		**5089**		**5063**	**61.7%**	**0.45 [0.19 , 1.06]**
Total events:	55		102			
Heterogeneity: Tau² = 0.48; Chi² = 12.23, df = 3 (P = 0.007); I² = 75%						
Test for overall effect: Z = 1.82 (P = 0.07)						
2.5.2 Cancer associated pulmonary embolism						
Caravaggio 2020	15	304	15	334	18.9%	1.10 [0.53 , 2.30]
Hokusai VTE Cancer 2018	25	328	13	329	19.4%	2.01 [1.01 , 3.99]
Subtotal (95% CI)		**632**		**663**	**38.3%**	**1.51 [0.84 , 2.71]**
Total events:	40		28			
Heterogeneity: Tau² = 0.05; Chi² = 1.36, df = 1 (P = 0.24); I² = 26%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)		**5721**		**5726**	**100.0%**	**0.71 [0.36 , 1.41]**
Total events:	95		130			
Heterogeneity: Tau² = 0.51; Chi² = 23.38, df = 5 (P = 0.0003); I² = 79%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 5.21, df = 1 (P = 0.02), I² = 80.8%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

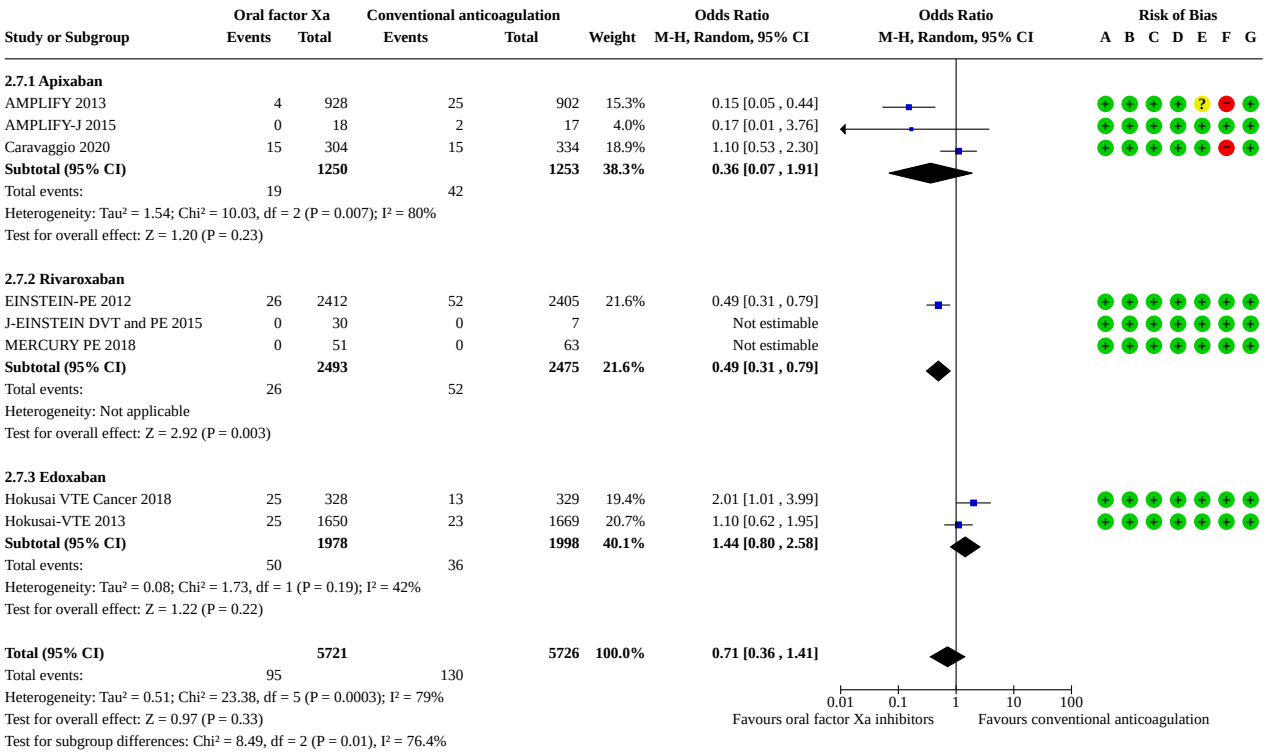
Analysis 2.6. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 6: Recurrent venous thromboembolism (subgroup analysis based on different types of factor Xa inhibitors)



Risk of bias legend

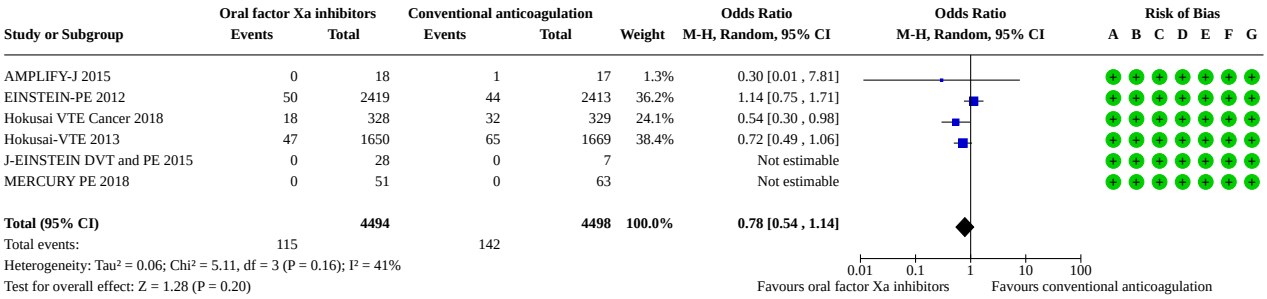
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 7: Major bleeding (subgroup analysis based on different types of factor Xa inhibitors)



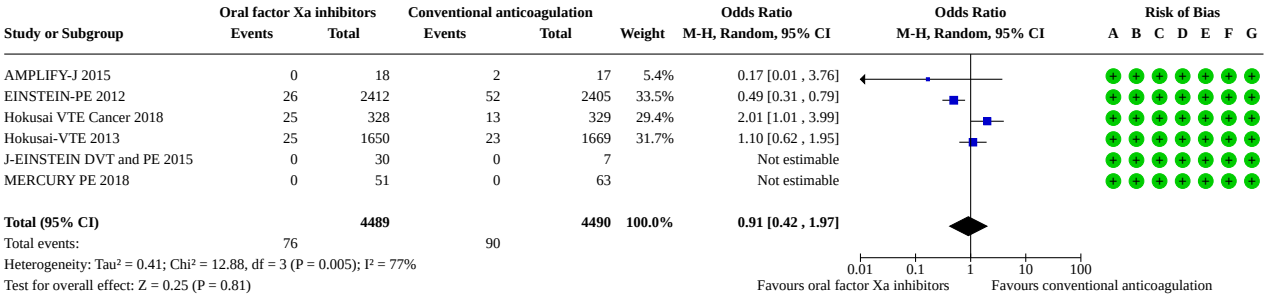
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.8. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 8: Recurrent venous thromboembolism (sensitivity analysis by including only studies at low risk of bias)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.9. Comparison 2: Oral factor Xa inhibitors versus conventional anticoagulation, Outcome 9: Major bleeding (sensitivity analysis by including only studies at low risk of bias)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. 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: 2 March 2022)	1 exp Pulmonary Embolism/ 2 exp THROMBOEMBOLISM/ 3 (emboli* adj4 pulmonary).ti,ab. 4 thromboemboli*.ti,ab. 5 (PE or VTE).ti,ab. 6 (Pulmonary adj4 clot).ti,ab. 7 (lung adj4 clot).ti,ab. 8 or/1-7 9 exp ANTITHROMBINS/ 10 Hirudin Therapy/ 11 (thrombin adj3 inhib*).ti,ab. 12 hirudin*.ti,ab. 13 (dabigatran or Pradaxa or Rendix).ti,ab. 14 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab. 15 (ximelagatran or Exanta or Exarta or melagatran).ti,ab. 16 (AZD0837 or AZD-0837).ti,ab. 17 (S35972 or S-35972).ti,ab.	March 2022: 2641

(Continued)

	18 Factor Xa Inhibitors/	
	19 (Factor X* adj4 (antag* or inhib* or block*)).ti,ab.	
	20 (FX* adj4 (antag* or inhib* or block*)).ti,ab.	
	21 (FX* adj4 (antag* or inhib* or block*)).ti,ab.	
	22 (10* adj4 (antag* or inhib* or block*)).ti,ab.	
	23 (rivaroxaban or Xarelto).ti,ab.	
	24 (Bay-597939 or Bay597939).ti,ab.	
	25 (betrixaban or PRT054021).ti,ab.	
	26 apixaban.ti,ab.	
	27 (BMS-562247 or BMS-562247 or ELIQUIS).ti,ab.	
	28 (DU-176b or DU176b).ti,ab.	
	29 (PRT-054021 or PRT054021).ti,ab.	
	30 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*).ti,ab.	
	31 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893).ti,ab.	
	32 (edoxaban or lixiana).ti,ab.	
	33 or/9-32	
	34 8 and 33	
	35 randomized controlled trial.pt.	
	36 controlled clinical trial.pt.	
	37 randomized.ab.	
	38 placebo.ab.	
	39 drug therapy.fs.	
	40 randomly.ab.	
	41 trial.ab.	
	42 groups.ab.	
	43 or/35-42	
	44 exp animals/ not humans.sh.	
	45 43 not 44	
	46 34 and 45	
2. EMBASE via Ovid (Date of most recent search: 2 March 2022)	1 exp lung embolism/ 2 exp thromboembolism/ 3 (emboli* adj4 pulmonary).ti,ab. 4 thromboemboli*.ti,ab.	March 2022: 7892

(Continued)

5 (PE or VTE).ti,ab.

6 (Pulmonary adj4 clot).ti,ab.

7 (lung adj4 clot).ti,ab.

8 or/1-7

9 exp antithrombin/

10 anticoagulant therapy/

11 (thrombin adj3 inhib*).ti,ab.

12 hirudin*.ti,ab.

13 (dabigatran or Pradaxa or Rendix).ti,ab.

14 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048).ti,ab.

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

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

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

18 blood clotting factor 10a inhibitor/

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

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

21 (10* adj4 (antag* or inhib* or block*)).ti,ab.

22 (rivaroxaban or Xarelto).ti,ab.

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

24 (betrixaban or PRT054021).ti,ab.

25 apixaban.ti,ab.

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

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

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

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

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

31 (edoxaban or lixiana).ti,ab.

32 or/9-31

33 8 and 32

34 randomized controlled trial/

35 controlled clinical trial/

36 random$.ti,ab.

37 randomization/

38 intermethod comparison/

(Continued)

	39 placebo.ti,ab. 40 (compare or compared or comparison).ti. 41 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 42 (open adj label).ti,ab. 43 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 44 double blind procedure/ 45 parallel group$1.ti,ab. 46 (crossover or cross over).ti,ab. 47 ((assign$ 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. 48 (assigned or allocated).ti,ab. 49 (controlled adj7 (study or design or trial)).ti,ab. 50 (volunteer or volunteers).ti,ab. 51 trial.ti. 52 or/34-51 53 33 and 52	
3. CINAHL via Ebsco (Date of most recent search: 2 March 2022)	S47 S31 AND S46 S46 S32 OR S33 OR 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 "Triple-Blind Studies" S43 MH "Double-Blind Studies" S42 MH "Single-Blind Studies" S41 MH "Crossover Design" S40 MH "Factorial Design" S39 MH "Placebos" S38 MH "Clinical Trials" S37 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" S36 TX crossover OR "cross-over" S35 AB placebo* S34 TX random* S33 TX trial* S32 TX "latin square" S31 S8 AND S30	March 2022: 473

(Continued)

	S30 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 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	
	S29 TX apixaban	
	S28 TX edoxaban or lixiana	
	S27 TX GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893	
	S26 TX YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*	
	S25 TX PRT-054021 or PRT054021	
	S24 TX DU-176b or DU176b	
	S23 TX BMS-562247 or BMS-562247 or ELIQUIS	
	S22 TX betrixaban or PRT054021	
	S21 TX Bay-597939 or Bay597939	
	S20 TX rivaroxaban or Xarelto	
	S19 TX (10* n4 (antag* or inhib* or block*))	
	S18 TX (FX* n4 (antag* or inhib* or block*))	
	S17 TX (Factor X* n4 (antag* or inhib* or block*))	
	S16 TX S35972 or S-35972	
	S15 TX AZD0837 or AZD-0837	
	S14 TX ximelagatran or Exanta or Exarta or melagatran	
	S13 TX BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048	
	S12 TX Antithrombins	
	S11 TX dabigatran or Pradaxa or Rendix	
	S10 TX hirudin*	
	S9 TX thrombin n3 inhib*	
	S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	
	S7 TX PE or VTE	
	S6 TX lung N4 clot	
	S5 TX Pulmonary N4 clot	
	S4 TX thromboemboli*	
	S3 TX emboli* N4 pulmonary	
	S2 (MH "Thromboembolism+")	
	S1 (MH "Pulmonary Embolism")	
4. VASCULAR REGISTER IN CRSW	rivaroxaban OR apixaban OR dabigatran OR ximelagatran OR betrixaban OR edoxaban	March 2022: 1568

(Continued)

(Date of most recent search: 2 March 2022)		
5. CENTRAL via CRSO (Date of most recent search: 2 March 2022)	#1 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES 1057 #2 MESH DESCRIPTOR THROMBOEMBOLISM EXPLODE ALL TREES 2166 #3 (emboli* adj4 pulmonary):TI,AB,KY 345 #4 thromboemboli*:TI,AB,KY 10025 #5 (PE or VTE):TI,AB,KY 7326 #6 (Pulmonary adj4 clot):TI,AB,KY 14 #7 (lung adj4 clot):TI,AB,KY 1 #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 15873 #9 MESH DESCRIPTOR ANTITHROMBINS EXPLODE ALL TREES 2289 #10 MESH DESCRIPTOR Hirudin Therapy EXPLODE ALL TREES 75 #11 (thrombin adj3 inhib*):TI,AB,KY 698 #12 hirudin*:TI,AB,KY 483 #13 (dabigatran or Pradaxa or Rendix):TI,AB,KY 1068 #14 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI,AB,KY 48 #15 (ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY 182 #16 (AZD0837 or AZD-0837):TI,AB,KY 22 #17 (S35972 or S-35972):TI,AB,KY 0 #18 MESH DESCRIPTOR Factor Xa Inhibitors EXPLODE ALL TREES 1091 #19 (Factor X* adj4 (antag* or inhib* or block*)):TI,AB,KY 1113 #20 (FX* adj4 (antag* or inhib* or block*)):TI,AB,KY 107 #21 (FX* adj4 (antag* or inhib* or block*)):TI,AB,KY 107 #22 (10* adj4 (antag* or inhib* or block*)):TI,AB,KY 1677 #23 (rivaroxaban or Xarelto):TI,AB,KY 1898 #24 (Bay-597939 or Bay597939):TI,AB,KY 0 #25 (betrixaban or PRT054021):TI,AB,KY 93 #26 apixaban:TI,AB,KY 1030 #27 (BMS-562247 or BMS-562247 or ELIQUIS):TI,AB,KY 48 #28 (DU-176b or DU176b):TI,AB,KY 53 #29 (PRT-054021 or PRT054021):TI,AB,KY 3 #30 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*):TI,AB,KY 108 #31 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893):TI,AB,KY 7	March 2022: 533

(Continued)

	#32 (edoxaban or lixiana):TI,AB,KY 620 #33 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 7475 #34 #8 AND #33 2079	
6. Clinicaltrials.gov (Date of most recent search: 2 March 2022)	Pulmonary Embolism OR thromboembolism | rivaroxaban OR apixaban OR dabigatran OR ximelagatran OR betrixaban OR edoxaban	March 2022: 146
7. ICTRP Search Portal (Date of most recent search: 2 March 2022)	Pulmonary Embolism OR thromboembolism | rivaroxaban OR apixaban OR dabigatran OR ximelagatran OR betrixaban OR edoxaban	March 2022: 159
TOTAL before de-duplication		March 2022: 13412
TOTAL after de-duplication		March 2022: 10797

Appendix 2. CRS search strategy 2015

Search run on Wednesday 28 January 2015		
#1	MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES	790
#2	MESH DESCRIPTOR Hirudin Therapy	75
#3	(thrombin near3 inhib*):TI,AB,KY	444
#4	hirudin*:TI,AB,KY	327
#5	(dabigatran or Pradaxa or Rendix):TI,AB,KY	199
#6	(BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI,AB,KY	9
#7	(ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY	147
#8	(AZD0837 or AZD-0837):TI,AB,KY	12
#9	(S35972 or S-35972):TI,AB,KY	0
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	1387
#11	MESH DESCRIPTOR Factor Xa Inhibitors	1
#12	(Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY	415
#13	(FX* near4 (antag* or inhib* or block*)):TI,AB,KY	33

(Continued)

#14	(10* near4 (antag* or inhib* or block*)):TI,AB,KY	842
#15	#11 OR #12 OR #13 OR #14	1237
#16	(rivaroxaban or Xarelto):TI,AB,KY	251
#17	(Bay-597939 or Bay597939):TI,AB,KY	0
#18	(betrixaban or PRT054021):TI,AB,KY	14
#19	apixaban:TI,AB,KY	134
#20	(BMS-562247 or BMS-562247 or ELIQUIS):TI,AB,KY	0
#21	(DU-176b or DU176b):TI,AB,KY	11
#22	(PRT-054021 or PRT054021):TI,AB,KY	1
#23	(YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*):TI,AB,KY	38
#24	(GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893):TI,AB,KY	3
#25	edoxaban or lixiana	51
#26	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	456
#27	#10 OR #15 OR #26	2793
#28	MESH DESCRIPTOR Thrombosis	1133
#29	MESH DESCRIPTOR Thromboembolism	841
#30	MESH DESCRIPTOR Venous Thromboembolism	159
#31	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	1857
#32	(thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):TI,AB,KY	13382
#33	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	676
#34	(PE or DVT or VTE):TI,AB,KY	3057
#35	((vein* or ven*) near thromb*):TI,AB,KY	5003
#36	(blood near3 clot*):TI,AB,KY	1305
#37	(pulmonary near3 clot*):TI,AB,KY	5
#38	(lung near3 clot*):TI,AB,KY	3
#39	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	16505
#40	#27 AND #39	1026

FEEDBACK

Feedback February 2016,

Summary

Email received from Dr Lynda Ware.

1. The Hokusai-VTE study.
In both the narrative paragraph describing the study (page 11) and in the "characteristics of included studies" section (page 31) you describe a 'dabigatran-like placebo'. This study was looking at edoxaban and the original paper speaks of an edoxaban placebo. I think therefore that there is a possible transcription error and I suggest that you actually meant "edoxaban-like placebo" on pages 11 and 31.

Authors' response: Thank you for pointing this out. This is a transcription error and has now been changed.

2. Recurrent pulmonary embolism.
In the summary of main results in the main body text you conclude that 'for Factor Xa inhibitors, there was substantial heterogeneity when we combined data from the two studies in a meta-analysis. Therefore no meaningful conclusions can be drawn from this analysis'.
The heterogeneity is measured as 58% using the I2 statistic and I can understand why you therefore decided not to combine the studies. When you say "no meaningful conclusions can be drawn from this analysis" do you mean the pooled analysis? Or the individual studies? Do you in fact draw some conclusions from those individual studies (see below)?

Authors' response: We meant to say "no meaningful conclusions can be drawn from the pooled analysis" and this has been been amended.

However, in the authors' conclusions in the abstract it states that 'moderate to high quality evidence suggests that there are no differences between DOACs and standard anticoagulation for the long-term treatment of pulmonary embolism for the outcome(s) recurrent pulmonary embolism ....'. Your use of the term 'DOACs' implies both DTIs (represented in the data by dabigatran) and the Factor Xa inhibitors. In other words, you appear to be saying that
(a) there is "moderate to high quality evidence that there is no difference between DTIs and standard anticoagulation for the long-term treatment etc…", and
(b) there is "moderate to high quality evidence that there is no difference between the Factor Xa inhibitors and standard anticoagulation for the long-term treatment etc…'

There are two problems I believe with this. A specific one is that for the Factor Xa inhibitors you have stated that "no meaningful conclusions can be drawn from this analysis". How can you reconcile this with the above?

Authors' response: We agree with your point and have reworded the paragraph drawing conclusions for the separate drug classes rather than grouping them together.

Secondly, "the absence of evidence is not evidence of absence". Can you really say that there is "moderate to high quality evidence that there is no difference between" the alternatives? Based on three trials? Or do you mean that "there is no evidence of a difference between the two treatments. Using the GRADE criteria, the quality of evidence supporting that statement is moderate to high" or "there is no evidence of a difference between the two treatments. The studies assessing this were at low risk of bias".

Authors' response: Despite there being few studies for any of the comparisons, there is a relatively large number of patients. However, we can see your point and have amended accordingly.

Reply

The authors of the review have responded to this feedback giving a point by point response to the comments above.

Contributors

Feedback: Dr Lynda Ware, Cochrane UK
Response: Dr Lindsay Robertson on behalf of the review authors

WHAT'S NEW

Date	Event	Description
14 April 2023	New search has been performed	New search run. Five new studies included, 17 new studies excluded and 14 ongoing studies identified.

Date	Event	Description
14 April 2023	New citation required but conclusions have not changed	New search run. Five new studies included, 17 new studies excluded and 14 ongoing studies identified. New author team involved. Text has been revised to reflect current Cochrane standards. No change to conclusions.

HISTORY

Protocol first published: Issue 2, 2014
Review first published: Issue 12, 2015

Date	Event	Description
16 December 2016	Feedback has been incorporated	Review amended following comments received

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

ML: none known.
JL: none known.
XW: none known.
XH: none known.
QW: none known.
SX: none known.
PY: none known.
JT: 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

2023 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 conventional 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. In response to peer reviewer comments, we carried out an additional subgroup analysis based on the different types of factor Xa inhibitors.

2015 version
In a change from the protocol (Robertson 2014b), we excluded studies where treatment lasted fewer than three months. This was because a meta-analysis of venous thromboembolism treatment strategies demonstrated an increased rate of recurrence after fewer than three months of anticoagulation but no significant difference with various longer periods of treatment (Boutitie 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

*Anticoagulants [therapeutic use]; *Antithrombins [therapeutic use]; *Factor Xa Inhibitors [therapeutic use]; Hemorrhage [chemically induced]; Neoplasm Recurrence, Local [drug therapy]; *Pulmonary Embolism [drug therapy] [prevention & control]; *Venous Thromboembolism [prevention & control]

MeSH check words

Humans