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Pentasaccharides for the treatment of deep vein thrombosis (Review)

Brandao GMS, Junqueira DR, Rollo HA, Sobreira ML

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Pentasaccharides for the treatment of deep vein thrombosis.
Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD011782.
DOI: [10.1002/14651858.CD011782.pub2](https://doi.org/10.1002/14651858.CD011782.pub2).

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[Intervention Review]

Pentasaccharides for the treatment of deep vein thrombosis

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Editorial group: Cochrane Vascular Group.

Publication status and date: New, published in Issue 12, 2017.

Citation: Brandao GMS, Junqueira DR, Rollo HA, Sobreira ML. Pentasaccharides for the treatment of deep vein thrombosis. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD011782. DOI: [10.1002/14651858.CD011782.pub2](https://doi.org/10.1002/14651858.CD011782.pub2).

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ABSTRACT

Background

Standard treatment of deep vein thrombosis (DVT) is based on antithrombotic therapy, initially with parenteral administration of unfractionated heparin or low molecular weight heparins (LMWH) for five to seven days, then subsequent long-term therapy with oral vitamin K antagonists (e.g. warfarin). Pentasaccharides are novel anticoagulants that may be favourable over standard therapy due to their predictable effect, no need for frequent monitoring or re-dosing, and few known drug interactions. Heparin-induced thrombocytopenia, a harmful effect of heparins, appears to be rare during treatment with pentasaccharides.

Objectives

To assess the efficacy and harms of pentasaccharides for the treatment of deep vein thrombosis.

Search methods

The Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (22 March 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 2) (searched 22 March 2017). We searched clinical trials databases for details of ongoing or unpublished studies and the reference lists of relevant articles for additional citations.

Selection criteria

We included randomised controlled trials in which people 18 years of age or older with a DVT confirmed by standard imaging techniques were allocated to receive a pentasaccharide (fondaparinux, idraparinux, or idrabiotaparinux) for the treatment of DVT in comparison with standard therapy or other treatments.

Data collection and analysis

We extracted data characterising the included trials according to the methods, participants, interventions, and outcomes. We assessed risk of bias using Cochrane's 'Risk of bias' tool and employed the GRADE methodology to evaluate the quality of the evidence.

The main primary outcome for efficacy was recurrent venous thromboembolism (VTE), and the main primary outcome for harm was major and clinically relevant bleeding. Since our outcomes were dichotomous, we calculated the risk ratio (RR) with a 95% confidence interval (CI). We combined the effects of different comparisons through a meta-analysis using a fixed-effect model.

Main results

We included five randomised controlled trials of 6981 participants comparing pentasaccharides with standard therapy or other pentasaccharides. The quality of the evidence varied depending on the outcome and was judged as of moderate to very low quality. We downgraded the quality of the evidence due to risk of bias or imprecision, or both.

Two studies evaluated fondaparinux, at doses of 5.0 mg, 7.5 mg, and 10.0 mg, plus vitamin K antagonist in comparison with standard therapy. A meta-analysis of these two studies showed no clear difference in the risk of recurrent VTE (RR 0.80, 95% CI 0.43 to 1.47; 2658 participants); moderate-quality evidence. The frequencies of major bleeding were similar between interventions in the initial period of treatment (approximately five days) (RR 1.15, 95% CI 0.39 to 3.44; 2645 participants) and at three months' follow-up (RR 1.05, 95% CI 0.64 to 1.71; 2645 participants). We judged the quality of the evidence as moderate.

One study (757 participants) compared idrabiotaparinux (3.0 mg) with idraparinix (2.5 mg) and demonstrated no clear difference in the risk of recurrent VTE at six months' follow-up (RR 0.72, 95% CI 0.31 to 1.69); low-quality evidence. Major bleeding during the initial treatment period was not reported. Major bleeding at six-month follow-up was less frequent in participants receiving idrabiotaparinux versus participants treated with idraparinix (RR 0.21, 95% CI 0.06 to 0.71); low-quality evidence.

The effect of an initial treatment with LMWH followed by three months of idraparinix (10 mg) showed no clear difference from standard therapy for risk of recurrent VTE (RR 1.51, 95% CI 0.26 to 8.90; 263 participants); very low-quality evidence; one study. Major bleeding during the initial treatment period was not reported. The frequency of major and other clinically relevant bleeding at three months' follow-up ranged from 2% to 15% in participants receiving LMWH and increasing doses of idraparinix of 2.5 mg, 5 mg, 7.5 mg, or 10 mg. When dosage groups were combined, there was no clear difference in major plus other clinically relevant bleeding or in major bleeding alone between the idraparinix treatment group and the standard therapy group (RR 1.30, 95% CI 0.70 to 2.40; 659 participants; RR 3.76, 95% CI 0.50 to 28.19; 659 participants, respectively); very low-quality evidence.

One study (2904 participants) compared idraparinix (2.5 mg) to standard therapy. There was no clear difference in the risk of recurrent VTE at three months' follow-up (RR 0.98, 95% CI 0.64 to 1.48); low-quality evidence. Major bleeding during the initial treatment period was not reported. Major bleeding at three months of follow-up appeared to be similar in the idraparinix group and the standard therapy group (RR 0.71, 95% CI 0.34 to 1.47); very low-quality evidence.

Authors' conclusions

We found moderate-quality evidence that the effects of fondaparinux at doses of 5.0 mg, 7.5 mg, and 10.0 mg plus vitamin K antagonist are similar in terms of recurrent VTE and risk of major bleeding compared with standard treatment for DVT.

Low-quality evidence suggests equal efficacy of idraparinix at 2.5 mg and the equimolar dose of 3.0 mg of idrabiotaparinux with regard to recurrent VTE, but a higher frequency of major bleeding was observed in participants treated with idraparinix.

We judged evidence on the effectiveness of idraparinix compared with standard therapy, with or without initial treatment with LMWH, and on associated bleeding risk to be low to very low quality, therefore we have very limited confidence in the estimated effects.

The observed similar effectiveness in terms of recurrent DVT and harmful effects in terms of bleeding risk with fondaparinux plus vitamin K antagonist compared to standard treatment for DVT suggest that it may be an alternative to conventional anticoagulants for the treatment of DVT in certain circumstances.

PLAIN LANGUAGE SUMMARY

Pentasaccharides for the treatment of deep vein thrombosis

Review question

Are fondaparinux, idraparinix, and idrabiotaparinux, new anticoagulants (blood-thinning medications) of the class of the pentasaccharides, a safe and effective alternative to conventional anticoagulants used to treat deep vein thrombosis?

Background

Deep vein thrombosis is a severe and life-threatening disease caused by the formation of a blood clot in the deep veins, usually in the legs. The conventional treatment consists of injections of the anticoagulant heparins for five to seven days, followed by long-term therapy with oral anticoagulants (vitamin K antagonists, e.g. warfarin). However, the high risk of bleeding and need for frequent laboratory control are important limitations to conventional therapy.

The pentasaccharides fondaparinux, idraparinix, and idrabiotaparinux have a more predictable effect and a more convenient dosing regimen in comparison with the conventional treatment. Pentasaccharides also do not require laboratory control and have few known interactions with other medicines and foods. They may be more cost-effective in many settings, and a harmful effect known as heparin-induced thrombocytopenia (heparin injections causing an increase in the risk of clotting (thromboembolic) complications) appears to be rare during treatment with pentasaccharides. Possible limitations of pentasaccharides are that they may be harmful in people with severe renal insufficiency and the need for intravenous or subcutaneous injections to administer these medications.

Study characteristics and key results

After searching the literature for relevant studies, current until 22 March 2017, we included five studies with a total of 6981 participants. The included studies compared fondaparinux, idraparinux, and idrabiotaparinux versus conventional therapy or each another. Our main outcome to judge the effectiveness of the treatments was the occurrence of a recurrent venous thromboembolism (an episode of deep vein thrombosis or pulmonary embolism), and our main outcome to evaluate the harmful effects of the treatments was major and clinically relevant bleeding.

Our review showed that the pentasaccharide fondaparinux (at doses of 5.0 mg, 7.5 mg, and 10.0 mg) plus vitamin K antagonist may show similar effectiveness and harmful effects compared to the conventional treatment for deep vein thrombosis. Idraparinux at the dose of 2.5 mg and idrabiotaparinux at the dose of 3.0 mg resulted in relatively high numbers of bleeding.

Quality of the evidence

We judged our main results on the effectiveness and harms of fondaparinux plus vitamin K antagonist compared with conventional treatment as of moderate quality. This means that we are confident that these results may be correct, though additional studies could possibly change the estimates. Additional evidence was largely imprecise and deemed of low to very low quality depending on the outcome. We downgraded the quality of the evidence for risk of bias or imprecision, or both.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fondaparinux plus vitamin K antagonist compared to standard therapy for the treatment of deep vein thrombosis

Fondaparinux plus vitamin K antagonist compared to standard therapy for the treatment of deep vein thrombosis

Patient or population: people > 18 years of age with a diagnosed deep vein thrombosis

Setting: hospitalised and non-hospitalised patients

Intervention: fondaparinux plus vitamin K antagonist

Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with fondaparinux plus vitamin K antagonist				
Recurrent venous thromboembolism Follow-up: 3 months	Study population		RR 0.80 (0.43 to 1.47)	2658 (2 RCTs)	⊕⊕⊕⊖ MODERATE ¹	
	42 per 1000	33 per 1000 (18 to 61)				
Major bleeding during the initial treatment Follow-up: 5 days	Study population		RR 1.15 (0.39 to 3.44)	2645 (2 RCTs)	⊕⊕⊕⊖ MODERATE ²	In contrast with other harm outcomes, bleeding was not subjected to detection bias.
	11 per 1000	12 per 1000 (4 to 37)				
Major bleeding Follow-up: 3 months	Study population		RR 1.05 (0.64 to 1.71)	2645 (2 RCTs)	⊕⊕⊕⊖ MODERATE ²	In contrast with other harm outcomes, bleeding was not subjected to detection bias.
	24 per 1000	25 per 1000 (15 to 41)				
All-cause mortality Follow-up: 3 months	Study population		RR 0.93 (0.45 to 1.91)	2645 (2 RCTs)	⊕⊕⊕⊖ MODERATE ¹	
	34 per 1000	32 per 1000 (15 to 65)				
Heparin-induced thrombocytopenia - not measured	7 participants in each treatment group of the MATISSE-DVT trial developed thrombocytopenia. This represents a frequency of thrombocytopenia approximately equal to 0.64% in both groups. None of the thrombocytopenic participants were reported as having developed heparin-induced thrombo-		-	-	-	The MATISSE-DVT trial reported no definition of thrombocytopenia and a non-standard definition of heparin-induced thrombocytopenia. It was stated that laboratory tests were used in the

diagnosis of heparin-induced thrombocytopenia, but the report related to these tests was incomplete.

	cytopenia antibodies, and none of the cases were associated with thromboembolism events.				
All harmful effects Follow-up: 3 months	Study population		RR 0.84 (0.76 to 0.93)	2192 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{3, 4}
	447 per 1000	375 per 1000 (340 to 416)			

*We calculated the assumed risk of the standard therapy group from the average risk in the standard therapy group (i.e. the number of participants with events divided by total number of participants of the standard therapy group included in the meta-analysis). **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; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect,

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

¹Downgraded due to unclear risk of bias in multiple criteria (selection bias, performance bias, and attrition bias related to efficacy outcomes) and high risk of attrition bias related to efficacy outcomes in one study.

²Downgraded for high risk of detection bias related to harm outcomes.

³Downgraded twice for high risk of detection and attrition bias related to harm outcomes.

⁴Downgraded for imprecision caused by single study and small number of events.

Summary of findings 2. Idrabiotaparinux compared to idraparinux for the treatment of deep vein thrombosis

Idrabiotaparinux compared to idraparinux for the treatment of deep vein thrombosis

Patient or population: people > 18 years of age with a diagnosed deep vein thrombosis

Setting: hospitalised and non-hospitalised patients

Intervention: idrabiotaparinux

Comparison: idraparinux

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with idraparinux	Risk with idrabiotaparinux				

Recurrent venous thromboembolism Follow-up: 6 months	Study population		RR 0.72 (0.31 to 1.69)	757 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	
	32 per 1000	23 per 1000 (10 to 55)				
Major bleeding during the initial treatment - not reported	See comment	See comment	-	-	-	Major bleeding during the initial treatment period was not reported in the single included study in this comparison.
Major bleeding Follow-up: 6 months	Study population		RR 0.21 (0.06 to 0.71)	755 (1 RCT)	⊕⊕⊕⊕ LOW 2, 3	While bleeding was considered a main harm outcome, it was diagnosed by a committee unaware of treatment assignment and was therefore judged as not influenced by detection bias.
	38 per 1000	8 per 1000 (2 to 27)				
All-cause mortality Follow-up: 6 months	Study population		RR 0.48 (0.18 to 1.27)	757 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	
	32 per 1000	16 per 1000 (6 to 41)				
Heparin-induced thrombocytopenia - not reported	See comment		-	-	-	No definition for or data on thrombocytopenia or heparin-induced thrombocytopenia
All harmful effects Follow-up: 6 months	Study population		RR 0.92 (0.83 to 1.02)	757 (1 RCT)	⊕⊕⊕⊕ VERY LOW 2, 4	
	685 per 1000	630 per 1000 (568 to 698)				

*We calculated the assumed risk of the idraparinux group from the average risk in the idraparinux group (i.e. the number of participants with events divided by total number of participants of the idraparinux group included in the meta-analysis). **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; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

¹Downgraded due to high risk of attrition bias related to efficacy outcome.

²Downgraded due to imprecision caused by single study and small number of events.

³Downgraded due to high risk of attrition bias related to harm outcome.

⁴Downgraded twice due to high risk of detection and attrition bias related to harm outcome.

Summary of findings 3. Low molecular weight heparin and idraparinux compared to standard therapy for the treatment of deep vein thrombosis

Low molecular weight heparin (LMWH) and idraparinux compared to standard therapy for the treatment of deep vein thrombosis

Patient or population: people > 18 years of age with a diagnosed deep vein thrombosis

Setting: hospitalised and non-hospitalised patients

Intervention: LMWH and idraparinux

Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with LMWH and idraparinux				
Recurrent venous thromboembolism assessed with: idraparinux 10 mg Follow-up: 3 months	Study population		RR 1.51 (0.26 to 8.90)	263 (1 RCT)	⊕○○○ VERY LOW 1, 2	
	15 per 1000	23 per 1000 (4 to 135)				
Major bleeding during the initial treatment Follow-up: 5 days	Study population		-	-	-	Major bleeding during the initial treatment period was not reported in the single included study in this comparison.
	See comment	See comment				
Major bleeding assessed with: all doses Follow-up: 3 months	Study population		RR 3.76 (0.50 to 28.19)	659 (1 RCT)	⊕○○○ VERY LOW 2, 3	
	8 per 1000	28 per 1000 (4 to 214)				
All-cause mortality Follow-up: 3 months	A total of 7 cases (of 527 participants) were reported in the group receiving idraparinux after LMWH and zero deaths (of 132 participants) in the group receiving standard therapy. Zero events in the group receiving standard therapy prevented us from conducting a pooled analysis.		-	-	-	The study providing data for this comparison was deemed at high risk of bias for incomplete outcome data.
Heparin-induced thrombocytopenia Follow-up: 3 months	Study population		-	-	-	The published report stated that no events of heparin-induced thrombocytopenia were observed, although
	See comment	See comment				

					without providing any details on how it was assessed and diagnosed.
All harmful effects Follow-up: 3 months	Data on harmful effects were not provided for any of the treatment groups.	-	-	-	The published report stated that "adverse effects were distributed similarly between the groups", but reported an increase in the alanine aminotransferase levels in 15% of participants during the initial LMWH phase.

*We calculated the assumed risk of the standard group from the average risk in the standard therapy group (i.e. the number of participants with events divided by total number of participants of the standard therapy group included in the meta-analysis). **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; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

¹Downgraded twice due to unclear risk of selection bias and high risk of performance and attrition bias related to efficacy outcomes.

²Downgraded due to imprecision caused by single study and small number of participants and events.

³Downgraded twice due to high risk of detection and attrition bias related to harm outcomes.

Summary of findings 4. Idraparinux compared to standard therapy for the treatment of deep vein thrombosis

Idraparinux compared to standard therapy for the treatment of deep vein thrombosis

Patient or population: people > 18 years of age with a diagnosed deep vein thrombosis

Setting: hospitalised and non-hospitalised patients

Intervention: idraparinux

Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with idraparinux				
Recurrent venous thromboembolism	Study population		RR 0.98 (0.64 to 1.48)	2904 (1 RCT)	⊕⊕⊕⊖ LOW 1, 2, 3	

Follow-up: 3 months	30 per 1000	29 per 1000 (19 to 44)				
Major bleeding during the initial treatment	Study population		-	-	-	Major bleeding during the initial treatment period was not reported in the single included study in this comparison.
Follow-up: 5 days	See comment	See comment				
Major bleeding	Study population		RR 0.71 (0.34 to 1.47)	2904 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2, 3	
Follow-up: 3 months	12 per 1000	8 per 1000 (4 to 17)				
All-cause mortality	Study population		RR 1.14 (0.69 to 1.86)	2904 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	
Follow-up: 3 months	20 per 1000	23 per 1000 (14 to 37)				
Heparin-induced thrombocytopenia	Study population		-	-	-	No definition for or data on thrombocytopenia and heparin-induced thrombocytopenia were reported.
Follow-up: 3 months	See comment	See comment				
All harmful effects	Study population		RR 1.03 (1.00 to 1.06)	2904 (1 RCT)	⊕⊕⊕⊕ VERY LOW 1, 2, 3	
Follow-up: 3 months	874 per 1000	900 per 1000 (874 to 926)				

*We calculated the assumed risk of the standard therapy group from the average risk in the standard therapy group (i.e. the number of participants with events divided by total number of participants of the standard therapy group included in the meta-analysis). **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; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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 quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

¹Downgraded due to high risk of performance bias.

- ²Downgraded due to imprecision caused by single study and small number of events.
³Downgraded due to high risk of attrition bias related to harm outcomes.

BACKGROUND

Description of the condition

Deep vein thrombosis (DVT) is a severe disorder caused by acute formation of a clot or thrombus in the deep vein system, typically in the lower extremities of the body. It results in impaired venous blood flow, which may in turn lead to leg swelling, pain, and with propagation of the clot, to pulmonary embolism and death. Clots that form in the deep veins of the lower extremities are more likely to dislodge from the limbs and reach the pulmonary vasculature.

Together, DVT and pulmonary embolism constitute venous thromboembolism (VTE). Between 2007 and 2009, an average 547,596 adults aged 18 years or older were hospitalised with VTE annually in the United States, with confirmed DVT in an estimated annual average of 348,558 hospitalisations (Centers for Disease Control and Prevention 2012). As noted in Goldhaber 2012, recurrence is common after a first episode of DVT or pulmonary embolism. Fowkes 2003 described a steep increase in the incidence of DVT with age, from 2 to 3 per 10,000 in adults aged 30 to 49 years to 20 per 10,000 in adults aged 70 to 79 years.

Deep vein thrombosis may be diagnosed by one of three objective tests: bilateral ascending contrast venography, duplex ultrasound, or colour duplex ultrasound (EMA 2007b). Standard treatment is based on antithrombotic therapy (Kearon 2012), initially with parenteral administration (administration through intravenous or subcutaneous injections) of unfractionated heparin or low molecular weight heparins (LMWH) for five to seven days, then subsequent long-term oral vitamin K antagonists (e.g. warfarin) therapy (Erkens 2010). To manage the ideal dose of vitamin K antagonists, it is necessary to reach a therapeutic international normalised ratio (INR) range of 2.0 to 3.0 before the end of heparin treatment (McRae 2004). In the first three months of therapy, the goal of DVT treatment is to prevent the extension and embolisation of the thrombus so as to minimise late local effects of venous thrombosis. In people with pulmonary embolism, the goal is to prevent potentially fatal recurrence. After the third month, the use of continuous anticoagulation therapy is used as a prophylactic measure to prevent late recurrence. However, therapy with warfarin may be problematic and requires monitoring, since individual response to the medicine may vary. In addition, haemorrhagic complications (major and clinically relevant) are a major concern associated with warfarin treatment, and may occur at virtually any site. Indeed, the haemorrhagic risk of warfarin and the required laboratory control remain the Achilles' heel of vitamin K antagonist management.

Description of the intervention

New anticoagulants have recently been developed aiming to improve the profile of harms and efficacy outcomes of DVT treatment. Among them, synthetic pentasaccharides have been modelled on the sequence of the heparin responsible for the binding of a particular coagulation protein, which leads to inhibition of the coagulation cascade and to clot formation and growth (van Boeckel 1993). Pentasaccharides are, therefore, synthetic and selective anticoagulant drugs, in contrast with heparins, which are obtained from animal sources. More specifically, pentasaccharides act indirectly, inhibiting the activated factor X (Xa), thus interrupting the blood coagulation cascade and inhibiting both thrombin formation and thrombus

development (EMA 2007a; EMA 2010). Factor X is located at the starting point of the common pathway of the extrinsic and intrinsic coagulation systems and therefore plays a central role in thrombin generation (Bauer 2003).

The advantages attributed to pentasaccharides include a more convenient dosing regimen, a more predictable anticoagulant response, and no need for laboratory monitoring (Bauer 2003; Nutescu 2005; Weitz 2004). In addition, because pentasaccharides are not metabolised in the liver, drug interactions may be reduced. Similarly, adverse reactions that often occur with heparins and vitamin K antagonists, such as bleeding and heparin-induced thrombocytopenia, are expected to be reduced (Nutescu 2005). However, other limitations stand for pentasaccharides:

- currently, there is no antidote to reverse the effect of pentasaccharides (except for idrabiotaparinux) if the patient presents any adverse bleeding to treatment or requires an invasive procedure (Gerotziakas 2004);
- the risk-benefit balance of this class of medicines is still under question; and
- financial costs may have significant impact on treatment.

How the intervention might work

The first synthetic pentasaccharide compound granted approval for commercialisation was fondaparinux (approved in 2001 in the United States and 2002 in Europe). Preliminary data have shown that fondaparinux was at least as efficacious as enoxaparin, a LMWH, with similar rates of death or clinically relevant bleeding for VTE prophylaxis following orthopaedic surgery (Eriksson 2001; Lassen 2002). Fondaparinux is currently widely recommended for VTE prophylaxis (Kearon 2012; Reynolds 2004), having been approved for VTE prophylaxis in a number of different medical interventions. However, questions remain regarding its effectiveness and harms in comparison with LMWHs. Furthermore, concerns regarding serious adverse drug reactions with fondaparinux, including bleeding, have prompted pharmacovigilance alerts and labelling changes since its approval (FDA 2009; Prescrire 2006; Prescrire 2012).

Fondaparinux binds selectively to antithrombin, catalysing factor Xa inhibition. It expresses an elevated affinity for antithrombin, and this specific activity leads to lack of variability in anticoagulation action (Garcia 2012). Even though the administration route is still a limitation – pentasaccharides can only be administered parenterally – fondaparinux exhibits a longer half-life (17 hours) in comparison with heparins, which determines a more convenient dosage once a day (Donat 2002). Fondaparinux does not bind to platelets, and so does not cause heparin-induced thrombocytopenia (Reynolds 2004), but renal clearance remains a limitation, contraindicating its use in people with severe renal insufficiency (creatinine clearance less than 20 mL/min).

In addition to fondaparinux, other pentasaccharides include idraparinux and idrabiotaparinux, forms of pentasaccharides that have longer half-lives (80 to 130 hours). The pharmacokinetic properties of idraparinux were designed to allow weekly dosing by subcutaneous injection without coagulation monitoring (The PERSIST Investigators 2004). Idrabiotaparinux is identical to idraparinux but has biotin incorporated to its molecule, so that anticoagulant action can be reversed by avidin injection (Paty 2010; Trellu 2013). However, the development of both idraparinux

and idrabiotaparinux was discontinued during phase III trials. A higher risk of bleeding after treatment of VTE and lower efficacy in the treatment of pulmonary embolism compared to standard treatment (enoxaparin followed by warfarin) appear to be the major problems justifying the pharmaceutical industry statement that these compounds do not appear to be able to bring significant improvement in the care of patients (Harenberg 2008; Sanofi-Aventis 2009; van Gogh Investigators 2007). Nevertheless, a recent non-Cochrane Review noted that the available evidence is still not sufficient to clarify whether or not idraparin and idrabiotaparinux are as effective and safe as the standard warfarin treatment for VTE treatment (Song 2013).

Why it is important to do this review

The traditional forms of anticoagulation therapy may be associated with major limitations in terms of laboratory monitoring, complications induced by adverse reactions, drug interactions, and even dietary aspects (e.g. vitamin K antagonists' interaction with food containing elevated levels of vitamin K). Unfractionated heparin is administered exclusively via parenteral route and requires laboratory monitoring of activated partial thromboplastin time and platelet count due to the risk of heparin-induced thrombocytopenia (Junqueira 2017). Since heparins are produced from biological sources, they are also sensitive to contamination (Blossom 2008).

While Vitamin K antagonists can be administered orally, these agents also require strict laboratory monitoring to ensure that the desired anticoagulation effect occurs during the therapeutic interval. Additional limitations of vitamin K antagonists include interactions with drugs and food, adverse reactions such as skin necrosis, and teratogenic potential (Bauer 2010; Benmira 2010; Garcia 2009; Haas 2008; Laux 2009; Spyropoulos 2008).

Even though monitoring is not required for dose adjustment of LMWH, making home treatment possible (Buller 2004), some clinically relevant aspects have not been fully elucidated. For instance, different types of LMWH (enoxaparin, tinzaparin, etc.) present with different pharmacokinetics properties and thus cannot be readily interchanged, and whether one or another type of heparin is available during the course of a treatment may not be a clinical decision. In countries where public health systems have financial limitations, the type of heparin available depends on costs and may vary on monthly, or sometimes weekly, basis. Weight adjustment doses required for LMWHs may also be a limitation in areas with limited resources and in trauma settings. There is conflicting evidence regarding the advantage of one or two daily applications given that the anticoagulant effect of LMWHs may not always be anticipated (Breddin 2001; Merli 2001), and the best dose for people with renal failure has not yet been fully defined (Collet 2001; Sanderink 2002). These limitations, together with the motivation for the development of more efficacious and convenient anticoagulants drugs, have driven the search for new agents.

Determining the efficacy and harms of pentasaccharides is therefore important to provide useful information to improve the treatment of people with DVT.

OBJECTIVES

To assess the efficacy and harms of pentasaccharides for the treatment of deep vein thrombosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included studies reporting on participants older than 18 years of age with DVT involving popliteal, femoral, iliac veins, or calf veins. Diagnosis of DVT should be confirmed by at least one standard imaging technique (venography or duplex venous ultrasonography).

Types of interventions

The treatment of interest was pentasaccharide anticoagulant therapy for DVT.

Despite the development of idraparin and idrabiotaparinux having been discontinued in 2009 due to safety issues, a non-Cochrane Review has noted that the available evidence is still insufficient to clarify whether or not these two medications are as effective and safe as warfarin for the treatment of VTE (Song 2013). We have therefore included idraparin and idrabiotaparinux in the review to ensure the results are as comprehensive as possible.

We planned to compare our treatment intervention of interest to standard therapy (LMWHs, unfractionated heparin, or vitamin K antagonists, e.g. warfarin) or other treatments identified in the RCTs (e.g. placebo, other anticoagulants).

We excluded studies assessing pentasaccharide anticoagulant therapy for the prevention of VTE, as they form part of another Cochrane Review (Dong 2016). We also did not consider studies investigating the efficacy and harms of pentasaccharide for the treatment of pulmonary embolism to adhere to our review title and protocol.

In order to differentiate treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), we considered trials evaluating participants with DVT and PE only if data concerning participants with DVT could be extracted separately. This was important to assure that the results were not mixing outcomes of participants treated for DVT and those treated for PE.

Types of outcome measures

Primary outcomes

- Main efficacy outcome:
  - * Any VTE: incidence of symptomatic, recurrent VTE during a six-month study period. We defined symptomatic, recurrent VTE as objectively documented DVT or pulmonary embolism.
- Main harm outcome:
  - * Major and clinically relevant bleeding. Major bleeding (as defined by the International Society on Thrombosis and Haemostasis) (Schulman 2005):
    - i. fatal bleeding;
    - ii. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal,

- intra-articular or pericardial bleeding, or intramuscular bleeding progressing to compartment syndrome;
- iii. bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells;
- iv. any combination of points 1 to 3.

Secondary outcomes

- Efficacy outcomes:
  - * All-cause mortality.
  - * Recurrent DVT: symptomatic DVT confirmed by standard imaging techniques including a new non-compressible venous segment or a substantial increase (4 mm or more) in thrombus diameter during full compression in a previously abnormal segment on ultrasonography (Prandoni 1993; Prandoni 2002), or a new intraluminal filling defect found on venography.
  - * Pulmonary embolism (fatal and non-fatal): symptomatic pulmonary embolism confirmed by an intraluminal filling defect on computed tomography or pulmonary angiography; a cut-off vessel of more than 2.5 mm in diameter on pulmonary angiography; a perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan); non-diagnostic lung scan associated with new DVT documented by ultrasonography or venography; or pulmonary embolism confirmed by autopsy (Buller 2004).
- Harm outcomes:
  - * Thrombocytopenia (reduction in platelet count above $150 \times 10^9/L$).
  - * Heparin-induced thrombocytopenia syndrome defined as a relative reduction in platelet count of about 50% (even if the platelet count at its lowest remains above $150 \times 10^9/L$) occurring within 5 to 14 days after the start of heparin therapy (Warkentin 2003). Clinically suspected cases of heparin-induced thrombocytopenia syndrome should have diagnosis confirmed through functional or immunological laboratory tests to detect platelet activation induced by anti-platelet factor 4 antibodies (Keeling 2006).
  - * All other adverse effects induced by the treatments, including those leading to drop out from the trial including but not limited to anaemia, insomnia, increased wound drainage, hypokalaemia, dizziness, hypotension, confusion, bullous eruption, haematoma, increase in transaminases, or dermatological reactions.

Search methods for identification of studies

We performed the electronic searches with no restrictions on language.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials:

- the Cochrane Vascular Specialised Register (22 March 2017);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 2) (searched 22 March 2017) via the Cochrane Register of Studies Online.

See [Appendix 1](#) for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL (Cumulative Index to Nursing and Allied Health Literature), AMED (Allied and Complementary Medicine Database), and through handsearching relevant journals. The full list of the databases, journals, and conference proceedings that have been searched, as well as the search strategies used, are described in the [Specialised Register](#) section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

In addition, the CIS searched the following trial registries (22 March 2017) for details of ongoing or unpublished studies:

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/);
- ISRCTN registry (www.isrctn.com/).

See [Appendix 2](#) for details of the trials registries searches.

Searching other resources

We checked citations of included studies to identify additional studies not retrieved in the electronic search. We also searched the website of the pharmaceutical company GlaxoSmithKline for non-reported trials of fondaparinux.

Data collection and analysis

Selection of studies

Two review authors (GB and DJ) independently screened titles and abstracts of the identified citations for potential eligibility. We excluded studies clearly not relevant (e.g. studies investigating the addition of vena cava filter to anticoagulation with fondaparinux) at this stage, although we retained studies that could have included relevant data or information on other studies. We retrieved the full texts of articles judged to be potentially eligible by at least one review author, and then independently screened the full-text articles for eligibility using a standardised study selection form. Disagreement were resolved by consensus.

Where there was insufficient information available to decide whether a study met the eligibility criteria, we attempted to contact the study authors.

Data extraction and management

Three review authors (GB, MS, and DJ) performed data extraction using a standardised data extraction form. Where we identified more than one report of a study, we extracted data from the primary report and checked discrepancies against reports. Data for reports of subgroup populations were extracted separately but linked to the primary study report. We considered trials evaluating people with DVT and PE if data concerning participants with DVT could be extracted separately. Disagreements were resolved by consensus.

Assessment of risk of bias in included studies

We planned to assess the risk of bias in included studies using Cochrane's 'Risk of bias' tool (Higgins 2011), which contains the following domains:

- sequence generation (selection bias);
- allocation sequence concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias);
- other bias.

At the review stage, we judged it appropriate to assess the risk of bias for some domains separately for different groups/outcomes in accordance with the Cochrane's 'Risk of bias' tool (Higgins 2011). We therefore assessed:

- blinding of participants and personnel (performance bias) separately for (i) participants and (ii) personnel;
- blinding of outcome assessment (detection bias) separately for (i) efficacy outcomes and (ii) harm outcomes;
- incomplete outcome data (attrition bias) separately for (i) primary efficacy outcome and (ii) harm outcomes.

We judged risk of bias in each domain as high, low, or unclear, and provided a statement to support each of our judgements in accordance with the referenced tool.

Measures of treatment effect

Our primary and secondary outcomes were dichotomous variables. For primary efficacy outcomes, we calculated the risk ratio (RR) with 95% confidence intervals (CIs). For harm outcomes, we reported absolute risks (AR, or incidence) and RR with 95% CIs. Groups with zero outcomes were reported but not considered in the analyses of the measures of the treatment effect because most of the estimates of effect may be problematic in a situation of zero events, and analysis of relative effect in these situations could bias the study estimates (Higgins 2011).

In our protocol, we planned to calculate risk differences, but since relative effect measures are considered to be more consistent than absolute measures (Deeks 2002; Engels 2000), we only calculated the RR.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

We based our data analysis on intention-to-treat data from the individual clinical trials thereby accounting for dropout data. We attempted to obtain information regarding dropouts, withdrawals, and other missing data from the study authors. In the event that we were unable to obtain these data from the study authors, we analysed the available data and took the missing information into consideration in the 'Risk of bias' analysis.

Regarding the analysis of harm outcomes in particular, the included studies analysed only the data of those participants who received at least one dose of the study medication. Although this could

be considered a non-randomised comparison (Higgins 2011), we judged it reasonable to measure adverse effects only in those participants who received the intervention (CRD's Guidance 2009). To investigate the potential impact of the missing data on the results, we performed a sensitivity analysis based on the 'worst-case scenario', that is assuming missing participants had experienced the negative outcome. This was a post hoc analysis.

Assessment of heterogeneity

We assessed methodological heterogeneity between studies using the I^2 statistic for quantification of variability. We also used the χ^2 test by setting statistical significance at a level of 0.1 to improve power. We undertook a sensitivity analysis whenever a result demonstrated significant heterogeneity ($P < 0.10$ or an I^2 statistic greater than 50%) (Higgins 2011).

We planned to assess clinical heterogeneity among the studies qualitatively in order to balance the strength of the evidence gathered (internal validity) with the extent to which the results can be generalised to the clinical practice (external validity). We planned to consider the following categories of external validity information (Steckler 2008):

- study participants and delivering settings;
- intervention and treatment consistency across settings, staff, and time;
- impact of the outcomes at population, practitioner, and decision makers level.

Assessment of reporting biases

For each analysis, we planned to use funnel plots to investigate the presence of publication bias (the selective publication of trials with positive findings) among the included studies (Higgins 2011). We would perform this analysis only if a sufficient number of trials (10 or more) were included in the meta-analysis, since a funnel plot with fewer than 10 studies has insufficient test power to distinguish chance from real asymmetry.

Data synthesis

We entered data into Review Manager 5 software (Review Manager 2014), and one review author (DJ) performed data analysis. We combined the efficacy and harmful effects through a meta-analysis using a random-effects model, which we undertook to take into account the between-study variance.

We used a fixed-effect model to present estimates from single studies, that is analysis performed with data from only one study.

Subgroup analysis and investigation of heterogeneity

We were able to explore the following sources of heterogeneity through stratifying participants by:

- body weight;
- cancer;
- outpatient treatment.

Data were not available on the following subgroup characteristics specified in our protocol:

- age and sex;
- different types of heparins and pentasaccharides;

- different treatment duration;
- previous VTE;
- provoked and unprovoked VTE;
- calf vein DVT;
- pregnancy;
- major surgery or trauma in the previous 12 weeks;
- oestrogen therapy; and
- thrombophilia (genetic or acquired).

Sensitivity analysis

If there were an adequate number of studies, we planned to perform a sensitivity analysis to explore causes of heterogeneity and the robustness of the results. We would perform the reanalysis by excluding studies judged to be at high risk of bias and those in which more than 20% of participants were lost to follow-up.

'Summary of findings' table

We presented the main findings of the review concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes in a 'Summary of findings' table according to [Higgins 2011](#).

We described the following outcomes in the 'Summary of findings' table:

- recurrent VTE (at three months' follow-up);

- major bleeding (at five days' and three months' follow-up);
- all-cause mortality (at three months' follow-up);
- thrombocytopenia (at three months' follow-up).
- all harmful effects (at three months' follow-up).

We planned to include thrombocytopenia in the 'Summary of findings' table, however this outcome was not reported in the majority of the included trials. We included the available information on thrombocytopenia and also included our findings on all harmful outcomes in the 'Summary of findings' table to ensure a complete overview of the evidence.

Some studies did not report data on the outcomes at the predefined follow-up cut-off. In such cases, we described the follow-up period closest to the predefined one in the 'Summary of findings' table.

We assessed different interventions and comparators and created a 'Summary of findings' table for each comparison included in the [Results](#) section. We used GRADEpro GDT software to assist in the preparation of the 'Summary of findings' tables ([GRADEpro GDT 2015](#)).

RESULTS

Description of studies

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram.

We identified a total of 734 titles from our electronic searches and one additional title through manually searching the reference lists of relevant studies. Five studies met our inclusion criteria, the results of which were reported in a 18 published titles.

Included studies

The five included studies were multicentric parallel RCTs conducted in South America, North America, Europe, Africa, Asia, and Oceania. The 6981 participants included in the studies were mostly adults,

within the mean age range of 57 to 62 years, presenting with acute symptomatic DVT. The setting where the participants were recruited was unclear for most of the studies, though due to the nature of DVT, participants were probably identified during hospitalisation. The profile of risk factors for DVT was very heterogeneous among studies but was balanced at baseline.

The trials investigated several comparisons between pentasaccharides and standard or alternative therapies. Details of

the study methods, participants, interventions, and outcomes are shown in the [Characteristics of included studies](#) table and in [Table 1](#); [Table 2](#); [Table 3](#).

Fondaparinux plus vitamin K antagonist versus standard therapy

Two studies, [MATISSE-DVT](#) and [Rembrandt Trial](#), compared fondaparinux plus vitamin K antagonist to standard therapy consisting of LMWH, enoxaparin and dalteparin respectively, and vitamin K antagonists. In both trials, fondaparinux was administered once a day for five days. Vitamin K antagonists were started within 72 hours in both trials, and treatment was continued for 3 months. In both trials, the initial treatment with the intervention medications (fondaparinux or LMWH) was discontinued when the international normalised ratio (INR) was maintained greater than 2.0 for two or more consecutive days. These trials randomised a total of 2658 participants.

The [MATISSE-DVT](#) study adjusted doses according to body weight: 5.0 mg if weight was less than 50 kg, 7.5 mg if weight was greater than 50 kg but less than 100 kg, or 10 mg if weight was greater than 100 kg. Data on secondary harmful outcomes from this trial were available from the manufacturer's clinical trial register (presented as a summary of the results), and we extracted data on these outcomes from this source.

The [Rembrandt Trial](#) randomised participants to one of three doses of fondaparinux without weight adjustment (5.0 mg, 7.5 mg, or 10 mg).

The [MATISSE-DVT](#) study reported an intention-to-treat analysis, but three participants were excluded after randomisation because they did not receive treatment. Additional participants were excluded due to suspected inefficacy and harmful effects, and the report did not explain how outcome data for missing participants were analysed. The [Rembrandt Trial](#) states that no participants were lost to follow-up.

Idrabiotaparinux versus idraparinux

One study compared idrabiotaparinux 3.0 mg once a week with idraparinux 2.5 mg once a week ([EQUINOX](#)). Both interventions were administered for six months. An additional follow-up measurement was undertaken three months after the end of treatment and included participants who did not receive avidin (the antidote for idrabiotaparinux) (total follow-up of nine months). Although the study report refers to an intention-to-treat analysis, 88 participants were missing due to withdrawals or lost to follow-up, and it is unclear how outcome data for missing participants were handled. Contact with the study authors indicated that these data were considered missing ("censored"). The study reports that 741 participants completed the six-month clinical follow-up, and 700 participants completed the additional follow-up.

The trial randomised 757 participants. Data regarding the two follow-up periods were analysed cumulatively and according to the total number of participants randomised.

LMWH and idraparinux versus standard therapy

The [PERSIST Trial](#) investigated the effects of initial treatment with LMWH (enoxaparin) followed by three months of idraparinux compared to standard therapy consisting of an initial treatment with LMWH followed by warfarin. The LMWH (enoxaparin) was

administered for five to seven days (1 mg/kg), after which participants were randomised to receive one of four doses of idraparinux (2.5 mg, 5 mg, 7.5 mg, or 10 mg) or warfarin target to an INR rate between 2.0 to 3.0. The doses of idraparinux were administered without weight adjustment.

Treatment with idraparinux and warfarin continued for three months. A total of 701 participants were enrolled and received initial treatment with LMWH. Thirty-five patients were excluded, after which 659 participants were randomised. The trial reports two consent withdrawals, 45 missing data due to lost to follow-up, and 66 premature discontinuation of treatment. The analysis considered all randomised participants as the denominator, although the study report indicates that efficacy analysis only included participants who received treatment and for whom the primary outcome data were available.

Idraparinux versus standard therapy

One trial compared therapy with idraparinux to standard therapy consisting of initial therapy with LMWH (tinzaparin or enoxaparin) or unfractionated heparin followed by warfarin or acenocoumarol ([Van Gogh Trial-DVT](#)). The treatment was administered for three or six months depending on the judgement of the treating physician. The intervention group received a dose of 2.5 mg of idraparinux administered once a week. The comparison group received heparin for at least five days, with doses adjusted for the activated partial-thromboplastin time (ratio: 1.5 to 2.5), and had warfarin or acenocoumarol administered within 24 hours and target to INR 2.0 to 3.0. The majority of the participants in the comparison arm received LMWH as initial treatment (1408, 98.3%), and heparin was discontinued when the INR was 2.0 or more for two consecutive days.

The [Van Gogh Trial-DVT](#) was designed as two separated RCTs, one in which participants were diagnosed with DVT and the other those diagnosed with pulmonary embolism. The DVT study followed a total of 2904 participants. Based on the judgement of the treating physician, 637 participants had treatment planned for three months (idraparinux: n = 321; standard therapy: n = 316), and the remaining participants received treatment for 6 months (idraparinux: n = 1131; standard therapy: n = 1136). The data analysed comprise 2904 participants receiving treatment for 3 months and 2267 participants receiving treatment for 6 months. We did not use cumulative data for the second follow-up period since only a proportion of participants entered this part of the study.

Excluded studies

We excluded 17 reports referring to six studies. We excluded trials enrolling participants with pulmonary embolism ([Cassiopea Investigators](#); [MATISSE-PE](#)), including narrative reviews summarising the results of the DVT study and the pulmonary embolism study of the [MATISSE-PE](#) trial; and trials investigating pentasaccharides for extended prophylaxis of DVT ([The Van Gogh Extension](#)). One study was interested in the potential of avidin to reverse the anti-factor Xa activity of idrabiotaparinux and in the bioequipotency of idrabiotaparinux and idraparinux ([EQUINOXa](#)). One trial did not diagnose DVT in accordance with standard methods ([Nakamura 2011](#)), and one potentially relevant study did not include a control group ([Young 2011](#)).

Risk of bias in included studies

We assessed risk of bias in individual studies using Cochrane's 'Risk of bias' tool (Higgins 2011). Three domains were assessed taking

into consideration different groups (participants and personnel) or outcomes (efficacy and harm outcomes). Summaries of the 'Risk of bias' assessment are shown in 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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Participants	Blinding of participants and personnel (performance bias): Personnel	Blinding of outcome assessment (detection bias): Efficacy outcomes	Blinding of outcome assessment (detection bias): Harmful outcomes	Incomplete outcome data (attrition bias): Primary efficacy outcome	Incomplete outcome data (attrition bias): Harmful outcomes	Selective reporting (reporting bias)	Other bias
EQUINOX	+	+	+	+	+	-	-	-	+	-
MATISSE-DVT	+	+	+	+	+	-	?	+	?	-
PERSIST Trial	?	?	-	-	+	-	-	-	?	-
Rembrandt Trial	+	?	+	?	+	-	-	-	?	-
Van Gogh Trial-DVT	+	+	-	-	+	+	+	-	+	-

Allocation

We considered random sequence generation as at low risk of bias in most of the included studies ([EQUINOX](#); [MATISSE-DVT](#); [Rembrandt Trial](#); [Van Gogh Trial-DVT](#)). One study was reported as randomised but no information on the methods to achieve an adequate randomisation was provided, therefore the random

sequence generation was judged as unclear for this trial ([PERSIST Trial](#)).

We deemed allocation concealment as at low risk of bias in three studies ([EQUINOX](#); [MATISSE-DVT](#); [Van Gogh Trial-DVT](#)). Two studies failed to report methods to guarantee allocation concealment and

were judged as at unclear risk of bias in this domain ([PERSIST Trial](#); [Rembrandt Trial](#)).

Blinding

We assessed blinding (performance bias) separately for participants and personnel in order to better judge the risk of bias of studies reporting complete and incomplete methods applied to ensure blinding of both participants and personnel.

We considered blinding of participants as low risk in three studies ([EQUINOX](#); [MATISSE-DVT](#); [Rembrandt Trial](#)). One study blinded participants to different doses administered of the intervention, but the type of drug of the treatment groups was open, therefore we considered this study as at high risk of bias ([PERSIST Trial](#)). We judged one trial that was reported as open label as at high risk of bias ([Van Gogh Trial-DVT](#)).

We judged blinding of personnel as at low risk of bias in two studies ([EQUINOX](#); [MATISSE-DVT](#)). In one study, the different doses administered of the intervention were blinded, but the type of drug of the treatment groups was open to the investigators ([PERSIST Trial](#)). We deemed this study as at high risk of bias ([PERSIST Trial](#)). One study did not report measures to blind personnel and was judged as at unclear risk of bias with regard to blinding of personnel ([Rembrandt Trial](#)). We judged one trial that was reported as open label as at high risk of bias ([Van Gogh Trial-DVT](#)).

We determined blinding of outcome assessment (detection bias) separately for efficacy and harm outcomes. We assessed all the included studies as at low risk of bias regarding blinding of efficacy outcome assessment, but only one study was at low risk of bias for blinding of harm outcome assessment ([Van Gogh Trial-DVT](#)). We judged the remaining four studies as at high risk of bias:

- in the [EQUINOX](#) and [MATISSE-DVT](#) trials, the efficacy outcomes were classified by an independent central adjudication committee whose members were unaware of treatment assignment, however of the harmful effects, only bleeding was reported as being diagnosed by a committee unaware of treatment assignment;
- in the [PERSIST Trial](#), a central adjudication committee, blinded to treatment allocation, reviewed the diagnosis of the efficacy outcomes, however harmful outcomes were monitored by a committee only partially blinded to treatment groups;
- in the [Rembrandt Trial](#), efficacy outcomes were interpreted by a central committee unaware of treatment allocation. No information was provided on how data of harmful outcomes were collected, interpreted, or diagnosed.

Incomplete outcome data

We assessed incomplete outcome data (attrition bias) separately for primary efficacy and harm outcomes. We chose this methodological option to account for differences in the methods relating specifically to these types of outcomes.

We judged one study, [Van Gogh Trial-DVT](#), as at low risk of bias for incomplete outcome data of efficacy outcomes and three studies as at high risk of bias ([EQUINOX](#); [PERSIST Trial](#); [Rembrandt Trial](#)). The [Rembrandt Trial](#) excluded participants after randomisation and also reported treatment discontinuation due to suspected inefficacy and harmful effects. The [EQUINOX](#) trial reported reasons for withdrawals and loss to follow-up related to efficacy, prognosis,

and adverse effects. The [PERSIST Trial](#) reported a relevant number of participants (113/659) as lost to follow-up or discontinued prematurely after randomisation with reasons potentially related to prognosis. The efficacy analysis is also described as including only participants who received treatment and for whom the primary outcome was available.

We judged risk of bias for incomplete outcome data of the primary efficacy outcome as unclear in one study since reasons for withdrawals and loss to follow-up were not clearly detailed, and there was no explanation for how outcome data for 15 missing participants were handled ([MATISSE-DVT](#)).

We judged one study as at low risk of bias for incomplete outcome data of harm outcomes ([MATISSE-DVT](#)). We considered all the remaining trials as at high risk of bias ([EQUINOX](#); [PERSIST Trial](#); [Rembrandt Trial](#); [Van Gogh Trial-DVT](#)):

- in the [EQUINOX](#) trial, the main harmful effects were reported (bleeding and death), but other harmful effects were reported only if incidence was higher than 2%;
- in the [PERSIST Trial](#), a relevant number of participants withdrew enrolment in the studies due to harm outcomes. Moreover, definitions and descriptions of other harm outcomes besides bleeding were missing;
- in the [Rembrandt Trial](#), only major bleeding was reported;
- the [Van Gogh Trial-DVT](#) reported harm outcomes among the reasons for treatment discontinuation, and only adverse effects with incidence higher than 1% were detailed.

We contacted authors seeking additional information regarding incomplete outcome data. However, it was explained to us that data needed to be sought from the pharmaceutical company that sponsored the trials. Unfortunately, we lacked resources to seek and analyse data from this type of non-published source for this version of the review.

Selective reporting

We considered selective reporting (reporting bias) as at low risk of bias in two studies ([EQUINOX](#); [Van Gogh Trial-DVT](#)). We judged the remaining four studies as at unclear risk of bias ([MATISSE-DVT](#); [PERSIST Trial](#); [Rembrandt Trial](#)), as:

- results about bleeding were included in the trial report ([MATISSE-DVT](#)), but results on additional harmful effects were presented only in a summary report of the results available in the clinical study register of the manufacturer of fondaparinux. We were unsure whether or not this would critically impact the validity of the study's results;
- we could not identify the study trial protocol and were therefore unable to judge selective reporting bias ([PERSIST Trial](#); [Rembrandt Trial](#)).

Other potential sources of bias

All included studies disclosed that the investigators responsible for the study or members of the executive committee acted as advisors or employees of the pharmaceutical company that sponsored the trials. We therefore deemed the studies as at high risk of bias related to conflicts of interest.

Effects of interventions

See: [Summary of findings for the main comparison Fondaparinux plus vitamin K antagonist compared to standard therapy for the treatment of deep vein thrombosis](#); [Summary of findings 2](#) Idaraparin compared to idraparin for the treatment of deep vein thrombosis; [Summary of findings 3](#) Low molecular weight heparin and idraparin compared to standard therapy for the treatment of deep vein thrombosis; [Summary of findings 4](#) Idraparin compared to standard therapy for the treatment of deep vein thrombosis

The main findings of the review results are described in [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#).

We grouped included studies according to comparisons of anticoagulant therapies:

- fondaparinux plus vitamin K antagonist versus standard therapy;
- idraparin compared to idraparin;
- LMWH and idraparin versus standard therapy;
- idraparin versus standard therapy.

In our protocol, we planned to assess our primary efficacy outcome, recurrent venous thromboembolism (VTE), during a six-month study period. However, only two studies followed participants for six months ([EQUINOX](#); [Van Gogh Trial-DVT](#)). The remaining studies assessed the outcomes at three months' follow-up. We therefore analysed data according to the time points measured in the included trials.

We planned to assess reporting bias using a funnel plot, but the insufficient number of studies included in each analysis did not provide appropriate visual inspection for asymmetry on the scatter plot, and therefore the funnel plot was not used.

Primary efficacy outcome: any VTE

Fondaparinux plus vitamin K antagonist versus standard therapy

There was no clear difference in the risk of recurrent VTE at three months' follow-up comparing participants treated with fondaparinux plus vitamin K antagonist and those treated with standard therapy (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.43 to 1.47; [Analysis 1.1](#); [Figure 4](#)); moderate-quality evidence. The results were consistent across studies and independent of the risk of bias of the individual studies. Heterogeneity was detected at 35% ($P = 0.21$) as assessed by the I^2 statistic.

Figure 4. Forest plot of comparison: 1 Fondaparinux plus vitamin K antagonist versus standard therapy, outcome: 1.1 Recurrent VTE at 3 months' follow-up.

Two studies ($n = 2658$) contributed data to this analysis ([MATISSE-DVT](#); [Rembrandt Trial](#)). Data were only extracted from the study reports.

Idraparin compared to idraparin

There was no clear difference in the risk of recurrent VTE at six months' follow-up between idraparin and idraparin (RR 0.72, 95% CI 0.31 to 1.69; [Analysis 2.1](#)); low-quality evidence.

At nine months' follow-up, the estimated risk of VTE again did not show a clear difference between intervention groups (RR 0.60, 95% CI 0.28 to 1.31; [Analysis 2.2](#)).

One study contributed data to this analysis ($n = 757$) ([EQUINOX](#)).

LMWH and idraparin versus standard therapy

The [PERSIST Trial](#) compared the effects of an initial treatment with LMWH followed by three months of idraparin (2.5 mg, 5 mg, 7.5 mg, or 10 mg) versus standard therapy. The trial reports performed an analysis considering as denominator randomised participants who received randomised treatment ($n = 659$), not considering in the analysis two participants who withdrew consent after randomisation. Primary outcome data were available for only 614 participants, the authors acknowledging a significant amount

of missing data due to exclusions, withdrawals, and loss to follow-up. However, details were not provided according to treatment groups. We analysed data as available accounting for a high risk of bias in this analysis, which was reflected in the quality of evidence evaluated in the 'Summary of findings' table. Since we do not know the amount of missing data according to the allocated treatment, we could not evaluate the possible direction of the bias.

No events of recurrent VTE were reported in the groups of participants receiving LMWH followed by idraparin 2.5 mg, 5 mg, or 7.5 mg. Three events of recurrent VTE occurred in participants receiving 10.0 mg of idraparin, and two events were reported in the group receiving standard therapy. However, two participants receiving 2.5 mg of idraparin and one receiving 5.0 mg of idraparin discontinued treatment due to a suspected VTE. Two participants in the standard therapy group were also excluded due to a suspected VTE. Comparing the cases considered as confirmed by the trialists, and excluding the groups with zero outcomes reported, we were able to compare quantitatively the risk of VTE of LMWH followed by 10.0 mg of idraparin with standard therapy. This analysis did not demonstrate a clear difference in the risk of recurrent VTE comparing these two treatment groups (RR 1.51, 95% CI 0.26 to 8.90; [Analysis 3.1](#)); very low-quality evidence.

Idraparinus versus standard therapy

There was no evidence of a difference in the risk of recurrent VTE at three months' follow-up when idraparinus was compared to standard therapy (RR 0.98, 95% CI 0.64 to 1.48; [Analysis 4.1](#)); low-quality evidence. We found what appeared to be a similar result in people receiving treatment for six months (RR 1.00, 95% CI 0.66 to 1.53; [Analysis 4.2](#)). Only one study contributed data for this analysis (n = 2904 and n = 2267, at three and six months' follow-up, respectively) ([Van Gogh Trial-DVT](#)).

Primary harm outcome: major and clinically relevant bleeding**Fondaparinux plus vitamin K antagonist versus standard therapy**

Events of bleeding were analysed during the initial treatment period with fondaparinux (approximately five days), and for the entire study (three months).

Figure 5. Forest plot of comparison: 1 Fondaparinux plus vitamin K antagonist versus standard therapy, outcome: 1.2 Bleeding [initial treatment].

Participants receiving fondaparinux presented an absolute risk of major bleeding equal to 1.26% (95% CI 0.80 to 1.99) (18 out of 1425 participants), and this risk was equal to 1.07% (95% CI 0.62 to 1.82) (13 out of 1220 participants) in participants receiving standard therapy. There was no clear difference in major bleeding between the two interventions (RR 1.15, 95% CI 0.39 to 3.44; [Analysis 1.3](#);

Initial period of treatment (approximately five days)

Major and clinically relevant bleeding occurred in 63 of 1425 participants treated with fondaparinux plus vitamin K antagonist (AR 4.42%, 95% CI 3.47 to 5.62) and in 59 of 1220 participants receiving treatment with standard therapy (AR 4.84%, 95% CI 3.77 to 6.19). There was no clear difference in bleeding between intervention groups (RR 0.80, 95% CI 0.56 to 1.13; [Analysis 1.2](#); [Figure 5](#)). Heterogeneity was not significant in this pooled analysis ($I^2 = 0\%$, $P = 0.40$). The total number of participants included in this analysis was 2645 (considering the safety population defined by the trials as all participants receiving at least one injection of the study treatment in both trials contributing data, [MATISSE-DVT](#) and [Rembrandt Trial](#)).

[Figure 6](#)); moderate-quality evidence. Heterogeneity was estimated as equal to 15% in this pooled analysis by the I^2 statistic ($P = 0.28$). Two studies contributed data to this analysis ([MATISSE-DVT](#); [Rembrandt Trial](#)). The total number of participants included in the analysis was 2645.

Figure 6. Forest plot of comparison: 1 Fondaparinux plus vitamin K antagonist versus standard therapy, outcome: 1.3 Major bleeding [initial treatment].

Separate data were reported for clinically relevant bleeding in one trial ([MATISSE-DVT](#)). The absolute risk of clinically relevant bleeding was estimated as equal to 2.57% (95% CI 1.78 to 3.68) (28 out of 1091 participants) in the fondaparinux plus vitamin K antagonist group and as equal to 2.30% (95% CI 2.36 to 4.59) (33 out of 1101 participants) in the standard therapy group. There was no clear difference in risk of clinically relevant bleeding (RR 0.86, 95% CI 0.52 to 1.41; [Analysis 1.4](#)). The total number of participants included in the analysis was 2192 (data reported only in [MATISSE-DVT](#)).

Three months' follow-up

Bleeding was a very common outcome at three months' follow-up in [MATISSE-DVT](#) and [Rembrandt Trial](#) (n = 2645).

At three months' follow-up in the [MATISSE-DVT](#) and [Rembrandt Trials](#) (n = 2645), the incidence of bleeding in the fondaparinux arm was as high as 8.56% (95% CI 7.22 to 10.13) (122 out of 1425 participants), and in the standard therapy group it was similarly high and equal to 8.93% (95% CI 7.46 to 10.67) (109 out of 1220 participants). There was no clear difference in bleeding between groups (RR 0.81, 95% CI 0.50 to 1.32) ([Analysis 1.5](#)). Heterogeneity

was moderate and estimated as equal to 65% in this pooled analysis by the I^2 statistic ($P = 0.09$).

Major bleeding occurred in 35 of 1425 participants receiving fondaparinux plus vitamin K antagonist (AR 2.46%, 95% CI 1.77 to 3.40) and in 29 of 1220 participants receiving standard therapy (AR 2.38%, 95% CI 1.66 to 3.39). The risk of major bleeding was similar between treatments (RR 1.05, 95% CI 0.64 to 1.71; [Analysis 1.6](#)); moderate-quality evidence. Heterogeneity was estimated as equal to 0% in this pooled analysis by the I^2 statistic ($P = 0.71$).

One trial reported clinically relevant bleeding at three months' follow-up ([MATISSE-DVT](#)). The absolute risk of clinically relevant bleeding was equal to 5.50% (95% CI 4.30 to 7.02) (60 out of 1091 participants) in the fondaparinux plus vitamin K antagonist group and 5.72% (95% CI 4.50 to 7.25) (63 out of 1101 participants) in the standard therapy group. The risk of clinically relevant bleeding was similar between treatment arms (RR 0.96, 95% CI 0.68 to 1.36; [Analysis 1.7](#)). The total number of participants included in the analysis was 2192 ([MATISSE-DVT](#)).

Idrabiotaparinux versus idraparinux

Six months' follow-up

Major and clinically relevant bleeding occurred in a total of 23 of the 385 participants receiving idrabiotaparinux (AR 5.97%, 95% CI 4.01 to 8.80) and in 41 of 370 participants receiving idraparinux (AR 11.08%, 95% CI 8.27 to 14.69). The risk of bleeding was higher in participants receiving idrabiotaparinux (RR 0.54, 95% CI 0.33 to 0.88; [Analysis 2.3](#)).

Major bleeding occurred in 3 out of 385 participants receiving idrabiotaparinux (AR 0.78%, 95% CI 0.26 to 2.27) and in 14 of 370 participants receiving idraparinux (AR 3.78%, 95% CI 2.27 to 6.25). The risk of major bleeding appeared to be lower in participants receiving idrabiotaparinux in comparison with participants treated with idraparinux (RR 0.21, 95% CI 0.06 to 0.71; [Analysis 2.4](#)); low-quality evidence.

Clinically relevant bleeding occurred with incidences of 5.19% (95% CI 3.39 to 7.89) (20 out of 385 participants) in participants receiving idrabiotaparinux, and of 7.30% (95% CI 5.06 to 10.41) (27 out of 370 participants) in participants receiving idraparinux. There was no clear difference in bleeding between intervention groups (RR 0.71, 95% CI 0.41 to 1.25; [Analysis 2.5](#)).

One study provided data for these analyses ($n = 755$ participants; safety population defined as all patients receiving at least one injection of the study treatment) ([EQUINOX](#)).

Nine months' follow-up

Major and clinically relevant bleeding occurred in 32 of 385 participants receiving idrabiotaparinux (AR 8.31%, 95% CI 5.95 to 11.5) and in 52 of 370 participants receiving idraparinux (AR 14.05%, 95% CI 10.88 to 17.97). The risk of bleeding at nine months was higher in participants receiving idrabiotaparinux (RR 0.59, 95% CI 0.39 to 0.90; [Analysis 2.6](#)).

Major bleeding occurred in 5 of 385 participants in the idrabiotaparinux group (AR 1.30%, 95% CI 0.56 to 3.00) and in 17 of 370 participants in the idraparinux group (AR 4.60%, 95% CI 2.89 to 7.23). The risk of major bleeding was higher in participants treated with idrabiotaparinux (RR 0.28, 95% CI 0.11 to 0.76; [Analysis 2.7](#)).

Clinically relevant bleeding occurred in 27 out of 385 participants receiving idrabiotaparinux (AR 7.01%, 95% CI 4.86 to 10.01) and in 35 out of 370 participants receiving idraparinux (AR 9.46%, 95% CI 6.88 to 12.87). Relative analysis did not demonstrate a clear difference in the risk of major bleeding between intervention groups (RR 0.74, 95% CI 0.46 to 1.20; [Analysis 2.8](#)).

Data for these analysis were extracted from one study ($n = 755$ participants; safety population defined as all patients receiving at least one injection of the study treatment) ([EQUINOX](#)).

LMWH and idraparinux versus standard therapy

Bleeding was reported as a reason for discontinuation of treatment in 17 participants receiving idraparinux after LMWH (all doses combined). We took into consideration the exclusion of participants based on prognosis in the 'Risk of bias' assessment and in the evaluation of the quality of the body of the evidence in the 'Summary of findings' table.

The total number of participants contributing data to these analyses was 659 ([PERSIST Trial](#)). Bleeding was reported at three months. No data were available after five days of initial treatment.

Major and other clinically relevant bleeding occurred in participants receiving LMWH followed by idraparinux, especially in higher doses. Absolute frequencies were:

- LMWH + idraparinux 2.5 mg (3/131): 2.29% (95% CI 0.78 to 6.52);
- LMWH + idraparinux 5.0 mg (16/135): 11.85% (95% CI 7.43 to 18.39);
- LMWH + idraparinux 7.5 mg (18/130): 13.85% (95% CI 8.94 to 20.83);
- LMWH + idraparinux 10.0 mg (20/131): 15.27% (95% CI 10.11 to 22.41).

The RRs of bleeding for the various doses of idraparinux in comparison with standard therapy were:

- LMWH + idraparinux 2.5 mg: 0.27 (95% CI 0.08 to 0.96; [Analysis 3.2](#));
- LMWH + idraparinux 5.0 mg: 1.42 (95% CI 0.69 to 2.95; [Analysis 3.3](#));
- LMWH + idraparinux 7.5 mg: 1.66 (95% CI 0.82 to 3.38; [Analysis 3.4](#));
- LMWH + idraparinux 10.0 mg: 1.83 (95% CI 0.91 to 3.67; [Analysis 3.5](#)).

Combining participants receiving LMWH and any dose of idraparinux, 57 out of 527 participants had a major or other clinically relevant bleeding event (10.82%, 95% CI 8.44 to 13.76). In comparison, of the 132 participants treated with standard therapy, 11 had a major or other clinically relevant bleeding event (8.33, 95% CI 4.72 to 14.31). Overall, there was no clear difference in major and other clinically relevant bleeding between treatment groups (RR 1.30, 95% CI 0.70 to 2.40; [Analysis 3.6](#)).

Major bleeding occurred in 4, 2, and 9 of the participants receiving 5.0 mg, 7.5 mg, and 10.0 mg of idraparinux, respectively. No major bleeding was reported in participants treated with 2.5 mg of idraparinux. Absolute frequencies were:

- LMWH + idraparinux 5.0 mg (4/135): 2.96% (95% CI 1.16 to 7.37);

- LMWH + idraparinux 7.5 mg (2/130): 1.54% (95% CI 0.42 to 5.44);
- LMWH + idraparinux 10.0 mg (9/131): 6.87% (95% CI 3.66 to 12.54).

One event of major bleeding occurred in participants allocated to receive standard therapy (1/132; 0.76%, 95% CI 0.14 to 4.16).

When participants receiving LMWH and any dose of idraparinux were combined, there was no clear difference in major bleeding between the idraparinux group and the standard therapy group (RR 3.76, 95% CI 0.50 to 28.18; [Analysis 3.7](#)); very low-quality evidence.

Clinically relevant bleeding was not reported separately.

Idraparinux versus standard therapy

Only one study contributed data to this analysis (n = 2904 and n = 2267, three and six months' follow-up, respectively) ([Van Gogh Trial-DVT](#)).

Three months' follow-up

Major and clinically relevant bleeding occurred in 65 participants receiving idraparinux, a frequency of bleeding of 4.48% (95% CI 3.53 to 5.67). A total of 101 participants receiving standard therapy had major and clinically relevant bleeding, a frequency of 6.96% (95% CI 5.76 to 8.38). Participants receiving idraparinux appeared to be at a reduced risk of bleeding in comparison to standard therapy (RR 0.64, 95% CI 0.48 to 0.87; [Analysis 4.3](#)).

The reduced frequency of bleeding in the idraparinux group was more significant in the number of events of clinically relevant bleeding:

- major bleeding showed no clear difference when comparing the idraparinux group with standard therapy (RR 0.71, 95% CI 0.34 to 1.47; [Analysis 4.4](#)); very low-quality evidence;
- clinically relevant bleeding was slightly reduced in the idraparinux group compared with the standard therapy group (RR 0.63, 95% CI 0.45 to 0.88; [Analysis 4.5](#)).

Six months' follow-up

Major and clinically relevant bleeding were a common harmful event in both groups. Major and clinically relevant bleeding occurred in 94 participants receiving idraparinux, a frequency equal to 8.31% (95% CI 6.84 to 10.06). There were 92 events of major and clinically relevant bleeding in participants receiving standard therapy, a frequency equal to 8.10% (95% CI 6.65 to 9.83). The risk of bleeding appears to be similar in people receiving idraparinux in comparison to standard therapy (RR 1.03, 95% CI 0.78 to 1.35; [Analysis 4.6](#)).

These results were consistent among events of major and clinically relevant bleeding. The RR for major bleeding comparing idraparinux with standard therapy was 1.24, 95% CI 0.66 to 2.34 ([Analysis 4.7](#)), and the RR for clinically relevant bleeding comparing idraparinux with standard therapy was 0.98, 95% CI 0.72 to 1.34 ([Analysis 4.8](#)).

Secondary efficacy outcomes

All-cause mortality

Fondaparinux plus vitamin K antagonist versus standard therapy

All-cause mortality at three months' follow-up was similar in participants treated with fondaparinux and vitamin K antagonist in comparison with participants receiving standard therapy (RR 0.93, 95% CI 0.45 to 1.91; [Analysis 1.8](#)); moderate-quality evidence. The estimated heterogeneity was significant in this pooled analysis ($I^2 = 61%$, $P = 0.11$). Two studies contributed data to this analysis ([MATISSE-DVT](#); [Rembrandt Trial](#)). The total number of participants analysed was 2658.

Idrabiotaparinux versus idraparinux

There was no clear difference in all-cause mortality in participants treated with idrabiotaparinux in comparison with participants receiving idraparinux at six months' follow-up: RR 0.48 (95% CI 0.18 to 1.27; [Analysis 2.9](#)); low-quality evidence. We found similar results at nine months' follow-up (RR 0.59, 95% CI 0.28 to 1.23; [Analysis 2.10](#)).

These analyses were based on one trial and data on 757 participants ([EQUINOX](#)).

LMWH and idraparinux versus standard therapy

A total of seven fatal cases were reported in the group receiving idraparinux after LMWH (7/527; AR 1.33%, 95% CI 0.64 to 2.72), and no events in the group receiving standard therapy.

We could not estimate the risk of all-cause mortality due to the low number of cases.

This analysis was based on one trial with 659 randomised participants ([PERSIST Trial](#)).

Idraparinux versus standard therapy

There was no clear difference in the risk of all-cause mortality between participants treated with idraparinux in comparison with those treated with standard therapy, regardless of the follow-up duration:

- three months' follow-up: RR 1.14 (95% CI 0.69 to 1.86; [Analysis 4.9](#)); low-quality evidence;
- six months' follow-up: RR 1.26 (95% CI 0.85 to 1.85; [Analysis 4.10](#)).

These analyses were based on one trial involving 2904 randomised participants followed for three months, and 2267 randomised participants followed for six months ([Van Gogh Trial-DVT](#)).

Recurrent DVT

Fondaparinux plus vitamin K antagonist versus standard therapy

Only one study included in this comparison reported recurrent DVT at three months' follow-up ([MATISSE-DVT](#)). Data from 2205 participants did not demonstrate a clear difference in the risk of recurrent DVT between intervention groups (RR 0.65, 95% CI 0.36 to 1.16; [Analysis 1.9](#)).

Idrabiotaparinux versus idraparinux

There was no clear difference in the risk of recurrent DVT between intervention groups at six months' follow-up (RR 0.58, 95% CI 0.14 to 2.40; [Analysis 2.11](#)). Data on these outcomes were not reported at nine months' follow-up.

This analysis was based on one trial and data on 757 participants ([EQUINOX](#)).

LMWH and idraparinux versus standard therapy

The [PERSIST Trial](#) (659 randomised participants) reported one event of recurrent DVT in participants receiving 10.0 mg of idraparinux and another one in participants receiving standard therapy. We could not estimate the risk of recurrent DVT due to the low number of cases.

Idraparinux versus standard therapy

There was no clear difference in the risk of recurrent DVT between participants treated with idraparinux in comparison with those receiving standard therapy, regardless of the follow-up duration:

- three months' follow-up: RR 0.94 (95% CI 0.49 to 1.83; [Analysis 4.11](#));
- six months' follow-up: RR 1.00 (95% CI 0.53 to 1.92; [Analysis 4.12](#)).

These analyses were based on one trial involving 2904 randomised participants followed for three months, and 2267 randomised participants followed for six months ([Van Gogh Trial-DVT](#)).

Pulmonary embolism

Fondaparinux plus vitamin K antagonist versus standard therapy

There was no clear difference in the risk of pulmonary embolism at three months' follow-up comparing treatment with fondaparinux plus vitamin K antagonist versus standard therapy (RR 0.88, 95% CI 0.23 to 3.39; [Analysis 1.10](#)). Heterogeneity was evident in this pooled analysis ($I^2 = 63%$, $P = 0.10$). Two studies evaluated this outcome and contributed data to this comparison ($n = 2658$) ([MATISSE-DVT](#); [Rembrandt Trial](#)).

Idrabiotaparinux versus idraparinux

There was no clear difference in the risk of pulmonary embolism between intervention groups at six months' follow-up (RR 0.82, 95% CI 0.28 to 2.43; [Analysis 2.12](#)). Data on this outcome were not reported at nine months' follow-up.

This analysis was based on one trial and data on 757 participants ([EQUINOX](#)).

LMWH and idraparinux versus standard therapy

The [PERSIST Trial](#) (659 participants) reported two events of pulmonary embolism in participants receiving 10.0 mg of idraparinux. We could not estimate the risk of pulmonary embolism due to the low number of cases.

Idraparinux versus standard therapy

There was no clear difference in the risk of recurrent pulmonary embolism between participants treated with idraparinux in comparison with those receiving standard therapy, regardless of the follow-up duration:

- three months' follow-up: RR 0.63 (95% CI 0.38 to 1.02; [Analysis 4.13](#));
- six months' follow-up: RR 1.00 (95% CI 0.57 to 1.76; [Analysis 4.14](#)).

These analyses were based on one trial involving 2904 randomised participants followed for three months, and 2267 randomised participants followed for six months ([Van Gogh Trial-DVT](#)).

Secondary harm outcomes

Secondary harmful outcomes were inconsistently reported by the included studies. Data were mostly detailed only according to the number of participants experiencing a certain type of event. None of the included studies reported number of events.

Thrombocytopenia and heparin-induced thrombocytopenia

The standard definition of thrombocytopenia is platelet count less than $150 \times 10^9/L$, and heparin-induced thrombocytopenia (HIT) is defined as a relative reduction in platelet count of about 50% (even if the platelet count at its lowest remains above $150 \times 10^9/L$) occurring within 5 to 14 days after the start of heparin therapy ([Warkentin 2003](#)), and should be confirmed through functional or immunological laboratory tests to detect platelet activation induced by anti-platelet factor 4 antibodies ([Keeling 2006](#)).

Fondaparinux plus vitamin K antagonist versus standard therapy

One trial measured platelet counts at baseline, day 4, and at the end of the trial ([MATISSE-DVT](#)). The definition used to classify thrombocytopenia was not documented. Heparin-induced thrombocytopenia was defined as platelet count less than $100 \times 10^9/L$ or decreased more than 40% from the baseline. Laboratory tests were used to detect HIT antibodies, but were not described in detail. Seven participants in each treatment group developed thrombocytopenia. This represents a frequency of thrombocytopenia equal to approximately 0.64% in both groups. None of the thrombocytopenic participants were reported as having developed HIT antibodies, and none of the cases were associated with thromboembolism events.

Other comparisons

Three trials did not report a definition for or data on thrombocytopenia and HIT ([EQUINOX](#); [Rembrandt Trial](#); [Van Gogh Trial-DVT](#)). The [PERSIST Trial](#) stated that no events of HIT were observed, although no details on how HIT was assessed and diagnosed were provided in the trial report.

Other harmful effects: adverse effects leading to withdrawals or premature discontinuation of treatment

Fondaparinux plus vitamin K antagonist versus standard therapy

A total of 46 out of 2658 participants recruited to the [MATISSE-DVT](#) and [Rembrandt Trial](#) prematurely discontinued treatment due to harmful effects (1.73%, 95% CI 1.3 to 2.30). However, the data were reported inconsistently, and were not detailed according to type of adverse effect and treatment harm.

The [MATISSE-DVT](#) trial reported data according to treatment group, although without detailing the types of adverse effects ($n = 2205$). These additional data were available only in non-published reports ([GSK Trial Register](#)). We identified no clear difference in withdrawals

due to harmful effects between treatment groups (RR 0.73, 95% CI 0.40 to 1.32; [Analysis 1.11](#)).

[Rembrandt Trial](#) reported that three participants withdrew from the trial due to harmful effects, but did not categorise these data.

Idrabiotaparinux versus idraparinux

A total of 47 participants enrolled in the [EQUINOX](#) trial discontinued treatment prematurely due to harmful effects. Withdrawals due to harmful effects appeared to occur with similar frequency in both treatment groups (RR 0.71, 95% CI 0.41 to 1.25; [Analysis 2.13](#)). The number of participants analysed was 757.

LMWH and idraparinux versus standard therapy

A total of 58 participants treated with LMWH and idraparinux discontinued treatment due to bleeding and other harmful effects ([PERSIST Trial](#)). The occurrence of all harmful effects leading to withdrawal appeared to follow a dose-related curve:

- LMWH + idraparinux 2.5 mg (8/131): 6.11% (95% CI 3.13 to 11.60);
- LMWH + idraparinux 5.0 mg (15/135): 11.11% (95% CI 6.85 to 17.52);
- LMWH + idraparinux 7.5 mg (7/130): 5.38% (95% CI 2.63 to 10.70);
- LMWH + idraparinux 10.0 mg (28/131): 21.37% (95% CI 15.22 to 29.57).

Eight of 132 participants receiving standard therapy discontinued treatment due to harmful effects (AR 6.06, 95% CI 3.10 to 11.5). There was no clear difference in withdrawals due to harmful effects between treatment groups (RR 1.82, 95% CI 0.89 to 3.71; [Analysis 3.8](#)).

The number of participants analysed was 659.

Idraparinux versus standard therapy

A total of 331 participants discontinued treatment prematurely in the trial providing data for this analysis ([Van Gogh Trial-DVT](#)).

The frequency of participants discontinuing treatment for any reason, including suspected lack of efficacy and adverse effects, was:

- total of 177 participants receiving idraparinux for three and six months, an estimated frequency of 12.19% (95% CI 10.61 to 13.97);
- total of 154 participants receiving standard therapy for three and six months, an estimated frequency of 10.60% (95% CI 9.13 to 12.3).

The frequency of participants discontinuing treatment specifically due to harmful effects was:

- total of 103 participants receiving idraparinux for three and six months, an estimated frequency of 7.09% (95% CI 5.88 to 8.53);
- total of 65 participants receiving standard therapy for three and six months, an estimated frequency of 4.48% (95% CI 3.53 to 5.67).

There was a greater occurrence of adverse effects leading to withdrawal in the idraparinux group (RR 1.58, 95% CI 1.17 to 2.14; [Analysis 4.15](#)).

The number of participants for which data were analysed was 2904.

Other harmful effects: other harmful effects during follow-up

Fondaparinux plus vitamin K antagonist versus standard therapy

Considering the 10 most frequently reported harmful effects in the [MATISSE-DVT](#) trial, the initial treatment of DVT with fondaparinux plus vitamin K antagonist appears to present with a similar safety profile to an initial treatment with LMWH ([Table 4](#)). The risk of a harmful effect was increased in the standard therapy group for two types of adverse effects: bruise (RR 0.38, 95% CI 0.18 to 0.81), and increased levels of hepatic enzymes (RR 0.08, 95% CI 0.03 to 0.21). The number of participants analysed was 2192.

Pooling all the harmful effects reported to have occurred in the [MATISSE-DVT](#) trial (including adverse effects leading to premature discontinuation of the study medication), the profile of harmful effects favoured fondaparinux plus vitamin K antagonist (RR 0.84, 95% CI 0.76 to 0.93; [Analysis 1.12](#)); very low-quality evidence. The [MATISSE-DVT](#) trial also reported serious adverse effects, including bleeding, and showed no clear difference between treatment groups (RR 1.24, 95% CI 0.84 to 1.84; [Analysis 1.13](#)).

The number of participants analysed was 2205 ([MATISSE-DVT](#)). [Rembrandt Trial](#) did not report data on harmful effects.

Idrabiotaparinux versus idraparinux

Treatment with idrabiotaparinux and idraparinux appears to be comparable in terms of harmful effects ([Table 5](#)). Pooled analysis of all harmful effects (leading to premature discontinuation or occurring during follow-up) did not show a clear difference in the incidence of harmful effects when comparing both interventions (RR 0.92, 95% CI 0.83 to 1.02; [Analysis 2.14](#)); very low-quality evidence.

The number of participants analysed was 757 ([EQUINOX](#)).

LMWH and idraparinux versus standard therapy

Data on harmful effects were not provided for any of the treatment groups. The published report stated that "adverse effects were distributed similarly between the groups" ([PERSIST Trial](#)). Nevertheless, the trial reports an increase in the alanine aminotransferase during treatment with LMWH (15%, only relative frequency reported), and in participants later allocated to receive idraparinux (0.8%, one participant).

Idraparinux versus standard therapy

Apart from bleeding, the following data on harmful effects were reported: cancer, cardiac failure, rash, dermatitis or urticaria, infection, and other events. The risk of cardiac failure was elevated in participants receiving standard therapy in comparison with those treated with idraparinux (RR 0.33, 95% CI 0.13 to 0.84) ([Table 6](#)). Grouping all harmful effects except bleeding, there was no clear difference in the risk of harmful effects among participants treated with standard therapy in comparison with those receiving idraparinux (RR 1.03, 95% CI 1.00 to 1.06; [Analysis 4.16](#)); very low-quality evidence.

The number of participants contributing data was 2904 ([Van Gogh Trial-DVT](#)).

Assessment of reporting bias

We could not assess reporting bias due to the insufficient number of trials (fewer than 10).

Subgroup analysis

Two studies presented data permitting us to perform subgroup analysis for two treatment comparisons:

- fondaparinux plus vitamin K antagonist versus standard therapy ([MATISSE-DVT](#));
- idraparinux versus standard therapy ([Van Gogh Trial-DVT](#)).

Fondaparinux plus vitamin K antagonist versus standard therapy

The [MATISSE-DVT](#) study published data on participants of different weight categories as well as on participants with active cancer and undergoing outpatient treatment. We were able to perform subgroup analyses comparing the following categories:

- participants weighing less than 50 kg versus participants weighing between 50 kg and 100 kg and participants weighing more than 100 kg;

- participants receiving inpatient versus outpatient treatment; and
- participants with no cancer versus participants with active cancer.

Obese participants

The [MATISSE-DVT](#) trial included 2205 participants, who were categorised according to body weight as follows:

- 55 participants (2.5%) had body weight less than 50 kg;
- 1922 participants (87.2%) had body weight between 50 kg and 100 kg; and
- 228 participants (10.3%) had body weight greater than 100 kg.

Data on recurrent VTE and on major bleeding were reported according to the body weight subgroups.

The pooled analysis was relatively imprecise: the risk of VTE between intervention groups did not show a clear variation according to body weight (RR 0.26, 95% CI 0.03 to 2.33 for participants with body weight less than 50 kg; RR 0.97, 95% CI 0.63 to 1.51 for participants with body weight between 50 kg and 100 kg; and RR 1.53, 95% CI 0.37 to 6.24 for participants with body weight greater than 100 kg; $I^2 = 0\%$, test for subgroup differences: $P = 0.41$; [Analysis 1.14](#); [Figure 7](#)).

Figure 7. Forest plot of comparison: 1 Fondaparinux plus vitamin K antagonist versus standard therapy, outcome: 1.12 Recurrent VTE at 3 months' follow-up [body weight].

Major bleeding occurred in one participant with body weight less than 50 kg in the fondaparinux plus vitamin K antagonist group, and in one participant with body weight greater than 100 kg in the standard therapy group. We could not estimate the comparative risk due to the sparse number of cases.

Outpatient treatment

In the [MATISSE-DVT](#) study, 345 of the participants randomised to the fondaparinux plus vitamin K antagonist group and 374 of the participants randomised to the standard therapy group received

outpatient treatment. We detected no clear difference in the risk of recurrent VTE at three months' follow-up between participants receiving outpatient treatment in comparison with participants receiving inpatient treatment (RR 1.21, 95% CI 0.75 to 1.95; and RR 0.47, 95% CI 0.20 to 1.14, respectively; test for subgroup differences: $I^2 = 70.4\%$, $P = 0.07$; [Analysis 1.15](#)).

People receiving outpatient treatment appeared to experience more major bleeding events than people receiving inpatient treatment, comparing treatment with fondaparinux plus vitamin

K antagonist to standard therapy. We detected a difference in the risk of major bleeding at three months' follow-up between participants receiving inpatient treatment in comparison with participants receiving outpatient treatment (RR 0.68, 95% CI 0.26 to 1.78; and RR 4.34, 95% CI 1.23 to 15.24, respectively; test for subgroup differences: $I^2 = 81\%$, $P = 0.02$; [Analysis 1.16](#)).

Cancer patients

In the [MATISSE-DVT](#) study, a subgroup of 126 participants randomised to fondaparinux plus vitamin K antagonist and 111 participants randomised to standard therapy had active cancer. We detected a difference in the risk of recurrent VTE at three months' follow-up between participants with no cancer (RR 0.71, 95% CI 0.44 to 1.14) in comparison with participants with active cancer (RR 2.35, 95% CI 0.95 to 5.79) (test for subgroup differences: $I^2 = 81.2\%$, $P = 0.02$; [Analysis 1.17](#)). People with active cancer appeared to experience an inferior beneficial effect when treated with fondaparinux plus vitamin K antagonist in comparison with treatment with standard therapy.

Major and clinically relevant bleeding did not appear to differ in participants with no cancer (RR 0.94, 95% CI 0.68 to 1.31) in comparison with participants with active cancer (RR 1.06, 95% CI 0.62 to 1.81) (test for subgroup difference: $I^2 = 0\%$, $P = 0.73$; [Analysis 1.18](#)). The results were slightly inconsistent when analysing the categories of major bleeding and clinically relevant bleeding. The risk of major bleeding in people receiving fondaparinux plus vitamin K antagonist and those receiving standard therapy for three months did not appear to vary between people with no cancer (RR 1.08, 95% CI 0.57 to 2.04) and people with active cancer (RR 0.99, 95% CI 0.40 to 2.48) (test for subgroup differences: $I^2 = 0\%$, $P = 0.89$; [Analysis 1.19](#)), while the risk of clinically relevant bleeding in people receiving fondaparinux plus vitamin K antagonist and those receiving standard therapy for three months varied between people with no cancer (RR 3.82, 95% CI 2.03 to 7.18) and people with active cancer (RR 1.10, 95% CI 0.54 to 2.25) (test for subgroup difference: $I^2 = 84.7\%$, $P = 0.01$; [Analysis 1.20](#)).

Idraparinus versus standard therapy

The [Van Gogh Trial-DVT](#) trial presented data on the group of participants with active cancer. We extracted these data as reported by [Van Gogh Trial-DVT](#) and were able to calculate the comparative data on the group of participants without active cancer. A total of 146 participants treated with idraparinus and 138 participants treated with standard therapy had active cancer ($n = 284$). Clinicians allocated a subgroup of 140 participants treated with LMWH and idraparinus and 130 participants treated with standard therapy to receive treatment for six months; the others were treated for three months.

The specific publication detailing these data had several inconsistencies. For instance, data reported in the text differed from data reported in the tables for the primary efficacy outcome (VTE), and it was stated that data for some major and clinically relevant bleeding were not shown, when the data were clearly presented in a table. We therefore only analysed data for the primary efficacy outcome to avoid major data mistakes.

Cancer patients

The risk of recurrent VTE in people receiving idraparinus and those receiving standard therapy for three months did not appear to

be modified by the presence of active cancer (RR 1.20, 95% CI 0.75 to 1.92 for participants without cancer; and RR 0.43, 95% CI 0.15 to 1.20 for participants with active cancer; test for subgroup differences: $P = 0.08$; [Analysis 4.17](#)).

The risk of recurrent VTE in people receiving idraparinus and those receiving standard therapy for six months appeared to be modified by the presence of active cancer (RR 1.25, 95% CI 0.78 to 2.01 for participants without cancer; and RR 0.39, 95% CI 0.14 to 1.07 for participants with active cancer; test for subgroup difference: $P = 0.04$; [Analysis 4.18](#)). If these results are proven to be accurate in a larger sample of participants receiving treatment after controlling for confounding, then one could expect participants with active cancer to experience a larger benefit from treatment with idraparinus ($I^2 = 76.3\%$).

The results at both three and six months were uncertain due to inconsistencies in the trial report for the subgroup of participants with active cancer.

Sensitivity analysis

We did not perform a sensitivity analysis for most of the comparisons only one study contributed data. One comparison was supported by data from two studies: fondaparinux plus vitamin K antagonist versus standard therapy ([MATISSE-DVT](#); [Rembrandt Trial](#)). We observed similar results after excluding one of the studies from the analysis (data not shown).

We performed an additional sensitivity analysis to investigate the potential impact of missing data on harmful effects on the results. We confirmed that imputing a 'worst-case scenario' did not change the results.

DISCUSSION

Summary of main results

The use of the pentasaccharide fondaparinux is currently an option for the prevention of DVT and pulmonary embolism in non-surgical and surgical patients ([Gould 2012](#); [Kahn 2012](#)), including orthopaedic surgical patients ([Falck-Ytter 2012](#)). In this review, we have complemented this information with the evidence on the usefulness of pentasaccharides to treat DVT by analysing a group of studies investigating the effects of the pentasaccharides fondaparinux, idraparinus, and idrabiotaparinus. We found moderate-quality evidence that the effectiveness/risk balance of fondaparinux is similar to standard therapy. This means that fondaparinux is as effective as the standard treatment in reducing the recurrence of VTE in people treated for DVT, and shows similar rates of major bleeding, the main harmful effect associated with anticoagulant treatment. Moderate-quality evidence means that this estimate is likely to be true, though it remains possible that new research could demonstrate it to be different.

Nevertheless, we were disappointed with the paucity of evidence comparing pentasaccharides and the standard treatment with LMWH or unfractionated heparin followed by vitamin K antagonists for DVT. We identified only five studies, which comprised four direct comparisons between one of these new anticoagulants and the typical therapy. Remarkably, the biotinylated molecule of idraparinus, idrabiotaparinus, the only pentasaccharide with a currently available antidote to reverse its anticoagulant effect, has never been directly compared to the standard treatment.

The five studies included in this review encompassed a parallel design and were reported in 18 different publications. Data of 6981 participants were available from these studies. We assessed recurrent VTE as our primary efficacy outcome and bleeding as our primary harm outcome according to the reported comparisons between the pentasaccharides and standard or alternative therapies. We had planned to assess recurrent VTE after six months of treatment. However, some studies only reported data at three months' follow-up, therefore in each case we considered the follow-up reported by the studies. Our secondary outcomes for efficacy and harms included: all-cause mortality, recurrent DVT, pulmonary embolism, thrombocytopenia and heparin-induced thrombocytopenia, and other harmful effects.

Primary outcomes

Recurrent VTE

Results from the meta-analyses demonstrated no clear difference between the risk of recurrent VTE in participants receiving fondaparinux or lower doses of the long-action pentasaccharides in comparison with those receiving standard therapy. Nevertheless, our confidence in these estimates was ranged from moderate to very low. The treatment duration in the included studies varied from three months, in [MATISSE-DVT](#) and [Rembrandt Trial](#), to six months ([EQUINOX](#); [PERSIST Trial](#); [Van Gogh Trial-DVT](#)). The [EQUINOX](#) trial included three months of additional follow-up after the six months of treatment (total follow-up of nine months).

Fondaparinux

Our analysis demonstrated that fondaparinux followed by vitamin K antagonists offers similar benefits of the standard therapy in the treatment of DVT. Participants were followed up to three months. We judged the quality of the evidence as moderate, which means that we are confident in the results, though the possibility remains that new research could change the estimates. The studies included in this analysis enrolled participants with similar demographic characteristics at baseline, and pooled analysis showed no important heterogeneity ([MATISSE-DVT](#); [Rembrandt Trial](#)).

Idraparinux and idrabiotaparinux

The studies analysing the effect of idraparinux and its biotinylated molecule, idrabiotaparinux, included diverse comparisons and could not be pooled in one meta-analysis.

Idraparinux (2.5 mg) showed no clear difference with an equimolar dose of idrabiotaparinux (3.0 mg) in preventing recurrence of VTE at six and nine months' follow-up. We judged the evidence as low quality, which means that we have limited confidence in the results.

Two trials, [PERSIST Trial](#) and [Van Gogh Trial-DVT](#), appeared to have included two similar intervention groups, which could have allowed us to pursue a pooled analysis comparing treatment with 2.5 mg of idraparinux with the standard therapy. However, the treatments actually tested in these studies differed from one another ([Table 3](#)). Participants assigned to the intervention group in the [PERSIST Trial](#) received five to seven days of enoxaparin before being randomised to receive one of three different doses of idraparinux. Participants enrolled in the intervention group of the [Van Gogh Trial-DVT](#) trial were treated with idraparinux from day one until the end of the follow-up. For this reason, we did not perform a pooled analysis with the data available from these studies.

We found no clear difference between treatment with LMWH followed by 10 mg of idraparinux versus standard therapy in the prevention of recurrent VTE at three months' follow-up. We considered the quality of the evidence to be very low, meaning that we have limited confidence in the validity of the evidence. The results from the single trial providing data for this analysis were influenced by the significant amount of missing outcome data due to exclusions, withdrawals, and loss to follow-up ([PERSIST Trial](#)). Moreover, participants were excluded due to presumed lack of efficacy (suspected VTE). The low number of accumulated cases of recurrent VTE in the group receiving doses of 2.5 mg, 5.0 mg, and 7.5 mg of idraparinux prevented any quantitative analysis.

Treatment with idraparinux from day one demonstrated similar efficacy to the standard treatment in the prevention of recurrent VTE at three and six months' follow-up. We assessed the quality of the evidence at three months' follow-up as low, which limits our confidence in the validity of the evidence.

Bleeding

Fondaparinux

Moderate-quality evidence showed no clear difference in major bleeding between the two intervention groups for the initial five days of treatment and at three months' follow-up. The estimated heterogeneity for the analysis of major bleeding was not important. Only one trial reported clinically relevant bleeding, showing similar frequencies comparing participants treated with fondaparinux to participants receiving standard therapy for the initial five days of treatment and at three months' follow-up.

Overall, the absolute risk of bleeding exceeded 1% in both treatment groups for the initial five days of treatment and at three months' follow-up. An adverse effect occurring in more than 1% of those exposed to the treatment is considered a common and frequent event ([WHO 2011](#)), therefore although we can be moderately confident that bleeding rates associated with fondaparinux are similar to those associated with standard therapy, the frequency of this harmful effect continues to be a concern in people receiving anticoagulant therapy.

Idraparinux and idrabiotaparinux

Overall, we found that participants treated with idrabiotaparinux showed a higher risk of bleeding in comparison with those treated with idraparinux. We judged the quality of the evidence as low, which limits our conclusions. Data on the use of avidin were not reported. The higher frequency of major and clinically relevant bleeding in participants receiving idrabiotaparinux remained three months after participants stopped treatment (nine months of follow-up).

The incidence of major and clinically relevant bleeding in participants receiving LMWH followed by idraparinux at three months' follow-up demonstrated a clear dose-response relationship when compared to participants receiving standard therapy. The risk of bleeding in participants receiving doses of 10 mg of idraparinux was six times the risk of bleeding in those treated with 2.5 mg of idraparinux. Overall, when participants receiving LMWH and any dose of idraparinux were combined, there was no clear difference in bleeding between the idraparinux group and the standard therapy group. The absolute risk (incidence) of bleeding was superior to the expected incidence in both groups (expected

incidence of bleeding range from 0.9% to 2.2%) (Hutten 1999). The high frequency of bleeding was responsible for the withdrawal of 17 participants (PERSIST Trial). Only participants receiving the lower dose of 2.5 mg of idraparinus presented with an absolute risk of bleeding comparable to the standard therapy. We considered the quality of the evidence related to the outcome of major bleeding to be very low, which means that the estimates are largely imprecise.

Participants receiving 2.5 mg of idraparinus from day one in comparison with those receiving standard therapy showed a slightly lower overall risk of major and clinically relevant bleeding at three months' follow-up. We found very low-quality evidence showing no clear difference in major bleeding between participants receiving 2.5 mg of idraparinus and those receiving standard treatment, so we cannot draw any precise conclusions. There was also no clear difference in major bleeding between interventions at six months' follow-up.

Secondary outcomes

All-cause mortality

The analyses of all-cause mortality were expected to complement the results of the primary outcome 'recurrence of VTE'. In this regard, the results for all-cause mortality were consistent with those of the primary efficacy outcome recurrent VTE for all of the following comparisons, that is there was no clear difference in the frequency of mortality between the compared interventions:

- fondaparinux plus vitamin K antagonist versus standard therapy (three months of follow-up, two trials);
- idrabiotaparinus versus idraparinus (six and nine months of follow-up, one trial); and
- idraparinus versus standard therapy (three and six months of follow-up, one trial).

The comparison of LMWH and idraparinus versus standard therapy did not allow further analyses due to sparse number of cases.

We considered the evidence on all-cause mortality to be of moderate quality for the comparison of fondaparinux plus vitamin K antagonist versus standard therapy. We found substantial statistical heterogeneity in this analysis, which could be explained by differences in participants between studies and missing data across studies. We judged the quality of the evidence as low for the comparisons of idrabiotaparinus versus idraparinus (six months' follow-up) and idraparinus versus standard therapy (three months' follow-up).

Recurrent DVT

The risk of recurrent DVT appears to be similar in the following groups:

- participants receiving fondaparinux plus vitamin K antagonist compared to those receiving standard therapy at three months' follow-up;
- participants receiving idrabiotaparinus compared to those receiving idraparinus at six months' follow-up; and
- participants treated with idraparinus compared to those receiving standard treatment at three and six months' follow-up.

Data for these analyses were extracted from single studies and no meta-analysis was performed. The confidence intervals for all

comparisons were wide, thus highlighting the imprecision of these estimates. No data were available to compare the risk of recurrent DVT in people receiving LMWH and idraparinus in comparison with standard therapy.

Pulmonary embolism

There was a similarity between the results for the risk of pulmonary embolism and those for the risk of DVT. There was no clear difference in the risk of pulmonary embolism when considering (i) fondaparinux plus vitamin K antagonist compared to standard treatment (three months of follow-up), (ii) idrabiotaparinus versus idraparinus (six months of follow-up), and (iii) idraparinus versus standard therapy (three and six months of follow-up). Data for these analyses were extracted from single studies and no meta-analysis was performed. The confidence intervals for all comparisons were wide, thus highlighting imprecision of these estimates. No data were available to compare the risk of recurrent pulmonary embolism in people receiving LMWH and idraparinus in comparison with standard treatment.

Secondary harm outcomes

Thrombocytopenia and heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a life-threatening condition and a relatively common harmful effect induced by heparin (Junqueira 2017). It is defined as a relative reduction in platelet count of about 50% (even if the platelet count at its lowest remains above $150 \times 10^9/L$) occurring within 5 to 14 days after the start of heparin therapy (Warkentin 2003). It is an immune-mediated reaction induced by the heparin and frequently followed by venous or arterial thrombosis (Junqueira 2013). In postoperative patients, the incidence of HIT is estimated to be 2.3% in patients exposed to unfractionated heparin and equal to 0.4% in patients treated with LMWH (Junqueira 2017).

Fondaparinux binds with platelet factor 4 forming the fondaparinux-platelet factor 4, which is similar to the heparin-platelet factor 4 responsible for inducing the formation of HIT antibodies (Warkentin 2013). However, it appears that fondaparinux is unable to induce platelet activation in the presence of HIT antibodies (Savi 2005), and only a few cases of HIT associated with fondaparinux have been reported (Bhatt 2013).

We identified only one study reporting outcomes concerning the effect of pentasaccharides on platelets counts (MATISSE-DVT). This is very disappointing since there is a need for further studies evaluating the role of fondaparinux in the treatment of HIT (Linkins 2012). The incidence of thrombocytopenia defined as platelet count less than $100 \times 10^9/L$ or decreased by more than 40% from the baseline was equal to 0.64% in the group receiving fondaparinux plus vitamin K antagonist and in the group receiving LMWH. When the above definition for thrombocytopenia was associated with HIT antibodies detected by laboratory tests, no case of HIT was identified in 1098 participants exposed to fondaparinux plus vitamin K antagonist. Nevertheless, the laboratory test used was not reported. These results are in partial agreement with the commercial package insert of fondaparinux, which does not mention HIT but describes the occurrence of moderate thrombocytopenia (reduction of platelet counts between $100 \times 10^9/L$ and $50 \times 10^9/L$) in 0.5% of participants receiving fondaparinux for the treatment of DVT (GlaxoSmithKline 2011). Severe thrombocytopenia (platelet count lower than $50 \times 10^9/L$) is

also reported as occurring in 0.04% of these participants, though this was not reported in the published trials.

It is unfortunate that underreporting and biased evidence prevent us from drawing definitive conclusions. The occurrence of thrombocytopenia and HIT appears to be rare in patients treated with fondaparinux. However, had we been able to extract and analyse unbiased evidence, this could have significantly reinforced the potential of fondaparinux not just as a treatment option for HIT (Badger 2010; Kang 2015), but also as a safer alternative to heparins.

All harmful effects

Notably, the reporting of harmful effects was inconsistent and incomplete. We could perform meta-analysis only by combining data on all harmful effects. Participants withdrawing from treatment were mostly not detailed according to the randomised treatment and reasons leading to withdrawal.

The available data showed that the proportion of participants withdrawing due to harmful effects from the fondaparinux plus vitamin K antagonist group and the standard treatment group was comparable. However, a higher risk of bruising and increased levels of hepatic enzymes were observed in the group treated with standard therapy. The overall risk of all harmful effects was similar in the fondaparinux plus vitamin K antagonist group in comparison to the standard therapy group. We deemed the quality of the evidence as very low, so our confidence in the validity of these estimates is limited.

The proportion of participants withdrawing due to harmful effects from the idrabiotaparinux group and the idraparinix group was comparable. The overall risk of any harmful effect was also similar in both groups. We judged the quality of the evidence as very low, which limits our conclusions.

Comparing the frequency of harmful effects leading to withdrawal in participants receiving LMWH and idraparinix with those receiving standard treatment demonstrated a clear dose-response relationship, with the lower dose of 2.5 mg idraparinix inducing an almost seven-fold reduced frequency of harms. Withdrawals due to harmful effects appeared to occur with similar frequencies when comparing participants receiving all doses of idraparinix with participants receiving standard therapy. Data on all harmful effects were not reported for this comparison.

Treatment with idraparinix from the first day was associated with higher frequencies of dropouts when compared to standard therapy. Data of very low quality from one single study contrasting idraparinix with standard therapy did not identify a clear difference in the occurrence of all harms in participants treated with idraparinix in comparison with those treated with standard therapy followed for three months. For this analysis, although the confidence interval could suggest a difference between the treatment groups, the limitations of inconsistency and incompleteness regarding the data on harmful outcomes combined with the low point estimate for the risk ratio means that any difference could have been detected by chance.

Subgroup analysis

Data evaluating the benefits and harmful effects of anticoagulant treatment in obese and cancer patients are frequently scarce.

In our review, two studies reported extractable data on obese participants, participants with cancer, and also on participants treated as outpatients/inpatients (MATISSE-DVT; Van Gogh Trial-DVT). Nevertheless, these studies addressed different comparisons and thus could not be pooled.

Fondaparinux plus vitamin K antagonist versus standard therapy

Our analyses suggest that participants with body weight greater than 100 kg appear to experience a reduced beneficial effect of the treatment with fondaparinux plus vitamin K antagonist in comparison with standard therapy when compared to participants weighing less than 50 kg and those weighing between 50 kg and 100 kg. The frequency of bleeding in participants with body weight greater than 100 kg in relation to participants weighing less than 100 kg could not be estimated due to sparse number of cases. Despite the limitations of any subgroup analysis, this evidence suggests that the anticoagulation effect of fondaparinux may vary with body weight and that reduced efficacy could be expected in obese patients.

The beneficial and harmful effects of treatment with fondaparinux plus vitamin K antagonist in comparison with standard therapy appear to differ between people receiving outpatient care and those receiving inpatient treatment. There was no clear difference in beneficial effect between fondaparinux and standard therapy in participants receiving outpatient treatment in comparison to participants receiving inpatient treatment. However, participants receiving outpatient treatment appeared to experience more major bleeding events when treated with fondaparinux versus standard therapy than people receiving inpatient treatment. Fondaparinux may therefore present a poor effectiveness/risk balance in the treatment of people receiving outpatient care.

There were reduced benefits in the treatment of DVT in participants with cancer treated with fondaparinux plus vitamin K antagonist for three months in comparison with participants who did not have cancer. The risk of major bleeding appeared to be similar in participants with and without cancer independent of the treatment, while clinically relevant bleeding appeared to be greater in people with cancer treated with fondaparinux plus vitamin K antagonist than in people without cancer.

Idraparinix versus standard therapy

The risk of recurrent VTE in people receiving idraparinix and standard therapy for three and six months appeared to be similar in people with and without cancer. However, we had several concerns regarding the data reported for the subgroup of participants with active cancer due to inconsistencies in the trial report, which prevented us from analysing additional data regarding the primary harm outcome.

Overall completeness and applicability of evidence

Based on the data gathered in this review we have concluded that the pentasaccharide fondaparinux may present with a similar effectiveness/risk balance to what is currently considered to be standard treatment. We found no clear difference in the recurrence of VTE and the frequency of the main harmful effect of the anticoagulant therapy, that is bleeding, in people treated for DVT with fondaparinux plus vitamin K antagonist compared with standard therapy. All-cause mortality, an important outcome

to support the results of the primary efficacy outcome, was also equivalent among participants receiving pentasaccharides and those receiving standard treatment. Finally, the rates of all harmful outcomes also appeared to be comparable between the intervention and the control treatment, though risk of bias and incomplete reporting for this outcome reduces our confidence in this finding.

Two of the included studies investigated the effects of fondaparinux, and three evaluated the effects of idraparinux (one of them comparing idraparinux to idrabiotaparinux). Overall, the trials included participants with similar demographic characteristics at baseline. In addition, we believe that the evidence gathered from the primary studies can be considered at a reasonable level of external validity. Most of the participants were between 57 and 62 years old, which is the expected population presenting with higher risk of DVT and the most common population expected to seek treatment for DVT.

We found idraparinux to be as efficacious as idrabiotaparinux, and idraparinux as efficacious as standard therapy. Nevertheless, the absolute risk of bleeding was increased in participants receiving higher doses of idraparinux and idrabiotaparinux. The observed similar efficacy of idraparinux when compared to standard treatment appears to have occurred at a cost of an increased risk of harmful effects related to higher doses of idraparinux. Harmful outcomes associated with idraparinux showed a clear dose-response relationship and a high rate of bleeding. These results reveal that doses of idraparinux of 5.0 mg, 7.5 mg, and 10.0 mg may not be safe despite the demonstrated efficacy in the treatment of DVT.

Our results showing the lack of acceptable safety of idraparinux are in agreement with previous observations. In fact, idraparinux and idrabiotaparinux were withdrawn from the market due to a high risk of bleeding after treatment of VTE (Harenberg 2008; van Gogh Investigators 2007). Our results did not identify this safety problem with doses of 2.5 mg of idraparinux and equimolar doses of 3.0 mg of idrabiotaparinux, but this result could have occurred by chance.

The incidence of HIT, a dangerous harmful outcome relatively common with standard treatment of DVT, was not reported. This can be regarded as a major limitation in the available data.

Quality of the evidence

See [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#)

We judged five studies, comprising 6981 participants, as providing overall moderate- to very low-quality evidence. As assessed by the GRADE approach, the quality of the evidence provided by the included randomised controlled trials was downgraded mostly due to risk of performance bias, detection bias related to harmful outcomes, and attrition bias related to efficacy and harmful outcomes. In general, only the main harm outcome, bleeding, was consistently measured and reported by the included trials. Key methodological limitations were missing data, withdrawals, and loss to follow-up not clearly detailed, and data analysis not consistent with an intention-to-treat approach. The quality of the evidence for some outcomes was also downgraded due to the inclusion of relatively few events (imprecision).

One comparison was particularly problematic: LMWH and idraparinux versus standard therapy. We judged the study providing data for this analysis as potentially flawed since a relevant number of participants were lost to follow-up or discontinued treatment prematurely after randomisation (PERSIST Trial), and many participants were excluded based on the suspected occurrence of the efficacy outcome (VTE). The study authors described using an intention-to-treat approach in their analysis, though this was carried out considering only participants who received treatment. We also downgraded the evidence for this comparison due to unclear risk of selection bias, high risk of performance and attrition bias related to efficacy outcomes, high risk of detection and attrition bias concerning harmful outcomes, and due to the relatively few participants and few events available.

Potential biases in the review process

We planned and implemented our review methods following Cochrane guidance to avoid biases in the review process (Higgins 2011). We carried out a comprehensive search strategy of the Cochrane Vascular Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL). We applied no language restrictions and considered conference abstracts as well as complete articles, which minimises the risk of missing potentially eligible studies.

We used a dual selection and data extraction process, with consensus supported by a third review author. A third review author also independently checked data extraction for agreement. These processes were guided by the eligibility criteria established in our review protocol to avoid any subjectivity (Brandao 2015).

We adjusted our analysis plan to consider the more consistent measurement of the effect of the interventions. Reports of zero events could not be considered in the analyses, though we attempted to judge whether reports of zero events could be a result of bias.

Consequently, we believe that there have been no obvious biases within the review process.

Agreements and disagreements with other studies or reviews

This is the first systematic review evaluating the efficacy and harms of treatment with pentasaccharides in people with DVT. Our results are important to corroborate international guidelines recommending fondaparinux as a treatment option comparable to LMWH and unfractionated heparin followed by vitamin K antagonists for DVT and acute pulmonary embolism (Kearon 2012). To our knowledge, only one non-Cochrane review has investigated the effects of the pentasaccharides with longer half-lives, idraparinux and idrabiotaparinux (Song 2013). Song 2013 included two studies not included in our review: Cassiopea, Cassiopea Investigators, and van Gogh-PE, MATISSE-PE. We did not include these studies because they investigated people treated for DVT and pulmonary embolism, and did not report data separately to permit the extraction of data only for participants treated for DVT. Song 2013 did not find convincing evidence that idraparinux and idrabiotaparinux had a profile of efficacy and harm outcome comparable to standard treatment. This is in agreement with our results.

AUTHORS' CONCLUSIONS

Implications for practice

We found moderate-quality evidence that fondaparinux at doses of 5.0 mg, 7.5 mg, and 10.0 mg, with or without weight adjustment, plus vitamin K antagonist, has similar effectiveness in terms of recurrent venous thromboembolism and a similar risk of major bleeding compared with standard treatment for deep vein thrombosis (DVT). The frequency of all harmful outcomes appeared to be comparable between fondaparinux plus vitamin K antagonist and standard treatment, though the quality of the evidence was very low. Evidence from subgroup analysis suggests there could be a reduced efficacy of fondaparinux in obese patients with body weight greater than 100 kg and in people with cancer, and also a poor effectiveness/risk balance in people receiving outpatient care, needs to be interpreted with caution.

Treatment with fondaparinux is more convenient since it requires only one subcutaneous administration per day, while low molecular weight heparins (LMWH) require two subcutaneous injections per day. This convenient dosage facilitates outpatient treatment and early discharge from hospital. Fondaparinux also has a more predictable anticoagulant response, therefore with no need for laboratory monitoring of the anticoagulant effect, and its profile of drug interactions is more favourable since it is not metabolised in the liver. Additionally, fondaparinux appears to be more cost-effective in different settings (Capri 2010; Sullivan 2006). Considering only the price of the medicines, in low- and middle-income countries such as Brazil treatment with fondaparinux for DVT may be almost 75% less expensive than treatment with the LMWH enoxaparin (Anvisa 2016).

In this context, the drawback of fondaparinux would be the lack of an antidote capable to reverse its anticoagulant effect. Nevertheless, in 2016, the US Food and Drug Administration (FDA) accepted the Biologics License Application for a reversal agent to direct and indirect factor Xa inhibitors. Andexanet alfa is a recombinant human factor Xa protein that is catalytically inactive but that retains the ability to bind factor inhibitors in the active site with high affinity and a 1:1 stoichiometric ratio (Siegal 2015). Andexanet alfa has been proven to be effective in reversing the anti-factor activity of apixaban and rivaroxaban (Siegal 2015), and is therefore a promising antidote to fondaparinux.

Together, this evidence could change practice worldwide. Fondaparinux appears to present a more favourable balance of efficacy and harms. Unfortunately, the incidence of heparin-induced thrombocytopenia, a dangerous harm outcome relatively

common with the standard treatment of DVT, was not reported, which prevents us from making any further conclusions. Given the combined more convenient dosage and economical advantages, our review supports the development of further research exploring fondaparinux as an alternative to heparins.

Implications for research

Our review showed that the pentasaccharide fondaparinux appears to be an alternative to conventional anticoagulants for the treatment of DVT. Evidence regarding obese patients, people with cancer, and people receiving outpatient care were derived from subgroup analysis with inherited limitations, thus demanding further and more robust research.

The pharmaceutical industry suspended research on the pentasaccharides idraparinux and idrabiotaparinux during the development of the phase III trials in 2009. Prior to the conclusion of this review, we wondered whether this could have been an early decision or whether further data on harmful outcomes have been unpublished. Nevertheless, our results confirm the lack of treatment benefits of these agents in comparison to standard treatment, and no further research is encouraged.

Treatment with fondaparinux does not have an antidote to reverse the anticoagulant effect, which is a matter of concern to clinicians and patients. A recombinant human factor Xa protein, andexanet, is under review by the FDA and is a promising agent to reverse the anti-factor activity of fondaparinux (Siegal 2015). An injection of 90 mcg of recombinant factor VIIa has also shown potential in reversing the anticoagulant effect in volunteers who used 10 mg of fondaparinux in emergency situations (Bijsterveld 2002). The expectation of near availability of an antidote to the anticoagulation effect of fondaparinux is likely to change research and practice of thromboembolic disease.

Thromboembolic disease is a severe and potentially fatal condition. Its aetiology is multifactorial, its clinical presentation has a myriad of peculiarities that still deserve continuing improvements, and the search continues for an ideal anticoagulant agent. Further randomised studies are encouraged to devote special attention to (i) collecting high-quality data to validate fondaparinux as a treatment option to heparin-induced thrombocytopenia and (ii) investigating the benefits and harms of the treatment of DVT in people at higher risk of thromboembolic disease, such as people with cancer.

ACKNOWLEDGEMENTS

We are grateful to Cochrane Vascular for their invaluable assistance.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

EQUINOX

Methods	- Study design: parallel RCT - Duration of follow-up: 6 months after randomisation, plus an additional visit 3 months after the end of treatment - Outcome monitoring: symptoms and signs of thromboembolism and bleeding were monitored using a checklist and instructing participants to report symptoms to the study centre
Participants	- Countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Israel, Italy, Mexico, the Netherlands, New Zealand, Poland, Russia, South Africa, Spain, USA - Inclusion criteria: patients who presented with acute symptomatic deep venous thrombosis of the leg - Setting: unclear - Total number of participants randomised: 757 - Mean age: 57 years - Sex: 441 (58%) male; 316 (42%) female
Interventions	Intervention group: Idrabiotaparinux - Participants randomised: 386 - Dosage: subcutaneous injections with 3.0 mg idrabiotaparinux in 0.5 mL isotonic sodium chloride once weekly for 6 months - Follow-up completion at 6 months: 381 participants (99%) - Follow-up completion at 3 months after the end of the study treatment period: 361 (of whom 80 received vitamin K antagonists) out of 381 participants (95%) Comparison group: Idraparinux

EQUINOX (Continued)

- Participants randomised: 371
- Dosage: subcutaneous injections with equimolar dose of 2.5 mg idraparinix in 0.5 mL isotonic sodium chloride once weekly for 6 months
- Follow-up completion at 6 months: 360 participants (97%)
- Follow-up completion at 3 months after the end of the study treatment period: 339 (of whom 76 received vitamin K antagonists) out of 360 participants (94%)

Staff training: nurse student under direct supervision of the physician investigator; subsequently, the investigator determined if participants would self inject the medication or continue to receive assistance. Participants were contacted by telephone to ensure the second and third injections were administered according to the protocol. Scheduled visits on the second and third days completed the protocol.

Avidin was provided to all centres to be used at the discretion of the investigator in cases of bleeding or the need to reverse the anticoagulant effect of idrabiotaparinix prior to surgery or other invasive procedures. In such cases, the investigator contacted the computerised voice-response system for unblinding. The avidin regimen was 100 mg diluted in 100 mL of isotonic saline infused over 30 min.

Outcomes	• Primary outcome: symptomatic recurrent venous thromboembolism • Main safety outcome: clinically relevant bleeding (either major or clinically relevant non-major) • Death
Notes	Major bleeding: • Bleeding associated with a fall in haemoglobin of 2 g/dL or more • Bleeding that led to a transfusion of 2 or more units of packed red cells or whole blood • Bleeding that involved a critical organ (intracranial, intraocular, intraspinal, retroperitoneal, or pericardial) • Bleeding that contributed to death Clinically relevant bleeding: • Any bleeding compromising haemodynamics • Any bleeding leading to hospitalisation • Subcutaneous haematoma larger than 25 cm², or 100 cm² if there was a traumatic cause • Intramuscular haematoma documented by ultrasonography • Epistaxis that lasted for more than 5 minutes, was repetitive (i.e. 2 or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g. packing or electrocoagulation) • Gingival bleeding occurring spontaneously (i.e. unrelated to eating or toothbrushing) or lasting for more than 5 minutes • Haematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract • Macroscopic gastrointestinal haemorrhage, including at least 1 episode of melena or haematemesis, if clinically apparent with positive results on a faecal occult-blood test • Rectal blood loss, if more than a few spots on toilet paper • Haemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism • Any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug or associated with pain or impairment of activities of daily life Death was classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses. Pulmonary embolism was considered as the cause of death if objectively documented or if the cause of death was unexplained and pulmonary embolism could not be confidently excluded.

Risk of bias

EQUINOX (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved with the use of a computerised voice-response system. The process was also stratified by centre.
Allocation concealment (selection bias)	Low risk	A computerised voice-response system was used to randomise participants and ensure concealment of allocation.
Blinding of participants and personnel (performance bias) Participants	Low risk	Identically appearing syringes in isotonic sodium chloride were used.
Blinding of participants and personnel (performance bias) Personnel	Low risk	The computerised voice-response system used ensured blinding of personnel.
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	Outcomes were classified by an independent central adjudication committee whose members were unaware of treatment assignment.
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	Only bleeding was reported to be diagnosed by a committee unaware of treatment assignment.
Incomplete outcome data (attrition bias) Primary efficacy outcome	High risk	Reasons for withdrawals and loss to follow-up may be related to efficacy, prognosis, and adverse effects. Outcome data for 1 period of the study follow-up were incompletely reported.
Incomplete outcome data (attrition bias) Harmful outcomes	High risk	Main harmful effects were reported (bleeding and death), but other harmful effects were reported only if incidence was higher than 2%, and supplemental data were not available. Reasons for withdrawals also included adverse effects.
Selective reporting (reporting bias)	Low risk	Comparison between the trial register and the full report does not indicate selective reporting bias.
Other bias	High risk	The sponsor, Sanofi-Aventis, had a role in the study design, protocol, study oversight, verification of the data, and statistical analysis, since 2 sponsor-based scientists were part of the executive advisory board. Also, the data were gathered and maintained by the sponsor.

MATISSE-DVT

Methods	- Study design: parallel RCT - Duration of follow-up: 3 months - Outcome monitoring: symptoms of thromboembolism and bleeding were monitored daily during initial treatment through contact with participant, and at 1 and 3 months. Participants received instructions to immediately report symptoms to the study centre.
Participants	- Countries: Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, New Zealand, Norway, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, UK, USA - Inclusion criteria: patients who presented with acute symptomatic deep venous thrombosis of the popliteal, femoral, or iliac veins or the trifurcation of the calf veins

MATISSE-DVT (Continued)

- Setting: unclear
- Total number of participants randomised: 2205
- Mean age (standard deviation): fondaparinux group 61.1 (16.7); enoxaparin group 61.5 (16.5)
- Female: fondaparinux group 517 (47%); enoxaparin group 529 (47.8%)

Interventions	Intervention group: Fondaparinux • Participants randomised: 1098 • Dosage: 5 days of once-daily subcutaneous injection of fondaparinux 5.0 mg if participant weighed less than 50 kg, 7.5 mg if weighed between 50 and 100 kg, or 10.0 mg weighed more than 100 kg, plus vitamin K antagonist started within 72 hours and continued until 3 months • Follow-up completion at 3 months: 1094 participants (99.6%) Comparison group: Enoxaparin • Participants randomised: 1107 • Dosage: 5 days of twice-daily subcutaneous dose of enoxaparin 1 mg/kg of body weight plus vitamin K antagonist started within 72 hours and continued until 3 months • Follow-up completion at 3 months: 1096 participants (99%) Staff training: unclear for hospitalised participants. Home treatment was described as administered by a home care service.
Outcomes	• Primary efficacy outcome: symptomatic recurrent venous thromboembolism • Primary harm outcome: bleeding
Notes	• Death: classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses, or classified as unexplained • Major bleeding: clinically overt and associated with a decrease in the haemoglobin level of 20 g/L or more, associated with transfusion of 2 or more units of red blood cells or whole blood cells, retroperitoneal or intracranial, occurring in a critical organ, or contributing to death • Clinically relevant bleeding: clinically relevant but not major (e.g. epistaxis that required intervention or spontaneous macroscopic haematuria)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was achieved using a computerised interactive voice-response system. Randomisation was stratified by centre in balanced blocks of 4 participants.
Allocation concealment (selection bias)	Low risk	A computerised voice-response system was used to randomise participants and ensure concealment of allocation.
Blinding of participants and personnel (performance bias) Participants	Low risk	Participants treated with fondaparinux received twice-daily subcutaneous injections of placebo that appeared to be identical to enoxaparin. Participants treated with enoxaparin received once-daily subcutaneous injection of placebo that appeared to be identical to fondaparinux.
Blinding of participants and personnel (performance bias) Personnel	Low risk	The computerised voice-response system used ensured blinding of personnel.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were classified by an independent central adjudication committee whose members were unaware of treatment assignment.

MATISSE-DVT (Continued)

Efficacy outcomes

Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	Only bleeding was reported to be diagnosed by a committee unaware of treatment assignment.
Incomplete outcome data (attrition bias) Primary efficacy outcome	Unclear risk	Reasons for withdrawals and loss to follow-up are not clearly detailed. The authors do not explain how outcome data for 15 missing participants were handled.
Incomplete outcome data (attrition bias) Harmful outcomes	Low risk	Analyses were performed in all participants who received at least 1 dose of the intervention.
Selective reporting (reporting bias)	Unclear risk	We could not find a protocol for the study in a clinical trial register, but a summary of the protocol was available in the clinical study register of GSK, the manufacturer of fondaparinux. We did not judge this domain as high risk of bias because the registry of clinical trials became mandatory only after the study development and completion. Results regarding bleeding were included in the trial report, but results on additional harmful effects were presented only in a summary report of the results available in the clinical study register of GSK. We are unsure whether this would critically impact the validity of the study's results or not.
Other bias	High risk	Investigators responsible for the study and members of the executive committee, are advisors or employees of the pharmaceutical industry that sponsored the trial.

PERSIST Trial

Methods	- Study design: parallel RCT - Duration of follow-up: 3 months - Outcome monitoring: participants were asked to report symptoms of thromboembolism and bleeding. Ultrasonography and lung scan were performed at the end of follow-up,
Participants	- Countries: Austria, Denmark, Italy, the Netherlands, Poland, Spain, Sweden, UK - Inclusion criteria: patients with acute symptomatic proximal DVT confirmed by compression ultrasonography (not compressible) or venography (had an intraluminal filling defect on venography) were potentially eligible for the study - Setting: unclear - Total number of participants randomised: 659 - Mean age (standard deviation): 2.5 mg idraparinux 58.8 (17.2); 5 mg idraparinux 59.5 (16.3); 7.5 mg idraparinux 60.0 (13.5); 10 mg idraparinux 59.1 (14.7); warfarin, 60.0 (14.8) - Male: group 1, 69 (52.7%); group 2, 73 (54.1%); group 3, 85 (65.4%); group 4, 65 (49.6%); warfarin, 71 (53.8%)
Interventions	Intervention group: Idraparinux divided into 4 groups according to dosages received: 2.5 mg; 5 mg; 7.5 mg; 10 mg - Participants randomised: 2.5 mg, 131; 5 mg, 135; 7.5 mg, 130; 10 mg, 131 - Dosage: 5 to 7 days of enoxaparin (1 mg/kg) followed by 1 of 4 doses of idraparinux once a week (2.5 mg, 5.0 mg, 7.5 mg, 10 mg) via subcutaneous injection and without weight adjustment - Follow-up completion at 3 months: 614 (93%) of the participants were available for analysis of the primary efficacy outcome

PERSIST Trial (Continued)

Comparison group: Warfarin

- Participants randomised: 132
- Dosage: 5 to 7 days of enoxaparin (1 mg/kg) followed by warfarin with a target INR rate between 2.0 to 3.0
- Follow-up completion at 3 months: 614 (93%) of the participants were available for analysis of the primary efficacy outcome

Staff training: reported as trained

Outcomes	• Primary efficacy outcome: symptomatic recurrent venous thromboembolism • Primary harm outcome: major bleeding
Notes	The use of clopidogrel and glycoprotein IIb/IIIa antagonist was prohibited during the trial period, and the use of aspirin and non-steroidal anti-inflammatory drugs was discouraged. • Death: the outcome was evaluated to assess the likelihood of pulmonary embolism or bleeding as the cause of death • Major bleeding: clinically overt bleeding that was fatal, retroperitoneal, intracranial, within a critical organ, leading to a decrease in haemoglobin of > 2 g/dL, or required a transfusion of ≥ 2 U of packed cells • Thrombocytopenia: defined as platelet count < 100 × 10⁹ /L or a drop of > 40%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the randomisation method was incomplete.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Participants	High risk	The dose of idraparinux was blinded, but the type of drug administered was open.
Blinding of participants and personnel (performance bias) Personnel	High risk	Investigators were blinded to the dose of idraparinux, but the type of drug administered was open.
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	A central adjudication committee, blinded to treatment allocation, reviewed the diagnosis of the efficacy outcomes.
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	The safety monitoring committee was only partially blinded to the treatment groups.
Incomplete outcome data (attrition bias) Primary efficacy outcome	High risk	A relevant number of participants were lost to follow-up or discontinued prematurely after randomisation (n = 113/659). Also, participants were excluded on the basis of a suspected occurrence of the efficacy outcome (venous thromboembolism), therefore reasons for withdrawals are potentially related to prognosis. Efficacy analysis included only participants who received treatment and for whom the primary outcome was available.

PERSIST Trial (Continued)

Incomplete outcome data (attrition bias) Harmful outcomes	High risk	A significant number of participants withdrew enrolment in the study due to harm outcomes, including the main harmful outcome of anticoagulant treatment, bleeding. Appropriate definition and description of other harmful outcomes besides bleeding were not given. Data collection of harm outcomes apart from bleeding was not detailed.
Selective reporting (reporting bias)	Unclear risk	We could not identify the study trial protocol and were therefore unable to judge selective reporting bias.
Other bias	High risk	Employees of the pharmaceutical industry sponsor were members of the steering committee whose took responsibility for the design, analysis, and publication of the trial. Other members of the steering committee have received an honorarium for their activities, and a writing committee was also paid by the sponsor for their role in the study report.

Rembrandt Trial

Methods	- Study design: parallel RCT - Duration of follow-up: 3 months - Outcome monitoring: symptoms of thromboembolism and bleeding were monitored daily during initial treatment through contact with participant and at 2 and 3 months. Participants received instructions to immediately report symptoms to the study centre.
Participants	- Countries: Australia, Belgium, Canada, France, Italy, New Zealand, Switzerland - Inclusion criteria: patients with acute, symptomatic, proximal deep vein thrombosis, who were older than 18 years old - Setting: consecutive patients referred to hospitals - Total number of participants randomised: 456, but 3 participants did not receive the study drug and were excluded from further analysis (participants analysed = 453) - Mean age (standard deviation): fondaparinux 5 mg, 61.0 (17.6); fondaparinux 7.5 mg, 57.8 (18.9); fondaparinux 10 mg, 59.6 (16.4); dalteparin, 69.4 (16.0) - Sex: 233 (51.1) males; 220 (48.9) females
Interventions	Intervention group: Fondaparinux - Participants randomised: 334 - Dosage: $\pm$ 5 days of once-daily subcutaneous injection of 1 of 3 dosages of fondaparinux (5.0 mg, 7.5 mg, 10 mg) without body weight adjustment. Treatment with vitamin K antagonists was started on day 1 or 2 and continued for $\pm$ 90 days. The study drug was discontinued when the INR was maintained at $\pm$ 2.0 for 2 consecutive days. - Follow-up completion at 3 months: 323 (96.7%) of all 3 dosages completed the follow-up Comparison group: Dalteparin - Participants randomised: 119 - Dosage: $\pm$ 5 days of twice-daily subcutaneous injection of dalteparin 100 IU/kg. Treatment with vitamin K antagonists was started on day 1 or 2 and continued for $\pm$ 90 days. The study drug was discontinued when the INR was maintained at $\pm$ 2.0 for 2 consecutive days. - Follow-up completion at 3 months: 114 (95.8%) received the study intervention in accordance with the protocol Staff training: not reported

Rembrandt Trial (Continued)

Participants were allowed to have received therapeutic dosages of unfractionated heparin or LMWH for 24 hours prior to randomisation, provided that it was stopped 2 or 6 hours before randomisation, respectively, and given for < 24 hours.

Outcomes	- Primary efficacy outcome: symptomatic recurrent venous thromboembolism - Primary harm outcome: major bleeding
Notes	- Major bleeding: clinically overt and associated with a fall in haemoglobin level > 2 g/dL or leading to a transfusion of more than 2 units of red cells; if it was intracranial, retroperitoneal, or in a critical organ; or when it was fatal - Minor bleeding: clinically unusual overt bleeding not meeting the criteria for major bleeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer algorithm through a central 24-hour telephone service.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) Participants	Low risk	Participants treated with fondaparinux received twice-daily subcutaneous injection of a placebo matching dalteparin. Participants treated with dalteparin received a once-daily subcutaneous injection of a placebo matching pentasaccharide. The volumes of the syringes were adjusted to obtain the correct dose of the active treatment or its matching placebo.
Blinding of participants and personnel (performance bias) Personnel	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	Efficacy outcomes were interpreted by a central committee unaware of treatment allocation.
Blinding of outcome assessment (detection bias) Harmful outcomes	High risk	Data collection of harmful outcomes was not detailed.
Incomplete outcome data (attrition bias) Primary efficacy outcome	High risk	The trial report documents the exclusion of 3 randomised participants who did not receive treatment, although the subsequent analysis was considered to have employed an intention-to treat approach. Additional participants were excluded due to suspected inefficacy and harmful effects.
Incomplete outcome data (attrition bias) Harmful outcomes	High risk	Among the harmful outcomes, only major bleeding was reported.
Selective reporting (reporting bias)	Unclear risk	We could not identify the study trial protocol and were therefore unable to assess selective reporting bias.
Other bias	High risk	Investigators responsible for the study and members of the executive committee, are advisors or employees of the pharmaceutical industry that sponsored the trial.

Van Gogh Trial-DVT

Methods	- Study design: parallel RCT - Duration of follow-up: 3 or 6 months. Randomisation was stratified according to intended treatment duration judged on the basis of the perceived risk of recurrence, as assessed by the treating physician. - Outcome monitoring: a checklist was used in scheduled contacts with participants to collect information on symptoms and signs of thromboembolism and bleeding. Participants were instructed to contact the study centre if they experienced any symptoms.
Participants	- Countries: Australia, Canada, France, Italy, the Netherlands, UK, USA - Inclusion criteria: patients over 18 years of age who presented with an acute symptomatic deep vein thrombosis of lower extremities - Setting: unclear - Total number of participants randomised: 2904 (only participants of the DVT study) - Mean age (standard deviation): 58 years - Male: 1568 (54%)
Interventions	Intervention group: Idraparinux - Participants randomised: 1452 (3 months' follow-up: 321; 6 months' follow-up: 1131) - Dosage: once-weekly subcutaneous dose of 2.5 mg. For participants with a creatinine clearance of less than 30 mL per minute (as calculated with the Cockcroft–Gault formula), the second and subsequent doses were 1.5 mg. - Follow-up completion: treatment duration of 3 months was planned for 22% of the participants and 6 months for the remaining participants. Follow-up was completed for the primary efficacy outcome in 99.3% of participants. Comparison group: Standard therapy (LMWH or heparin followed by warfarin or acenocoumarol) - Participants randomised: 1452 (3 months' follow-up: 316; 6 months' follow-up: 1136) - Dosage: tinzaparin, enoxaparin, or intravenous heparin adjusted for the activated partial-thromboplastin time (ratio 1.5 to 2.5), followed by warfarin or acenocoumarol (INR 2.0 to 3.0), which was started within 24 hours after randomisation. Heparin was discontinued when the INR was 2.0 or more for 2 consecutive days and the participant had received at least 5 days of initial treatment. - Follow-up completion: treatment duration of 3 months was planned for 22% of the participants and 6 months for the remaining participants. Follow-up was completed for the primary efficacy outcome in 99.3% of participants. Staff training: not reported
Outcomes	- Primary efficacy outcome: symptomatic recurrent venous thromboembolism - Primary harm outcome: clinically relevant bleeding and death from any cause
Notes	Major bleeding: - Bleeding associated with a fall in haemoglobin of 2 g per decilitre or more - Bleeding that led to a transfusion of 2 or more units of packed red cells or whole blood - Bleeding that involved a critical organ (intracranial, intraocular, intraspinal, retroperitoneal, or pericardial) - Bleeding that contributed to death Clinically relevant bleeding: - Any bleeding compromising haemodynamics - Any bleeding leading to hospitalisation - Subcutaneous haematoma larger than 25 cm², or 100 cm² if there was a traumatic cause - Intramuscular haematoma documented by ultrasonography

Van Gogh Trial-DVT (Continued)

- Epistaxis that lasted for more than 5 minutes, was repetitive (i.e. 2 or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g. packing or electrocoagulation)
- Gingival bleeding occurring spontaneously (i.e. unrelated to eating or toothbrushing) or lasting for more than 5 minutes
- Haematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal haemorrhage, including at least 1 episode of melena or haematemesis, if clinically apparent with positive results on a faecal occult-blood test
- Rectal blood loss, if more than a few spots on toilet paper
- Haemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism
- Any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug or associated with pain or impairment of activities of daily life

Death: classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses

Pulmonary embolism: considered the cause of death if there was objective documentation or if the cause of death was unexplained and pulmonary embolism could not be confidently ruled out

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computerised voice-response system, and stratified according to centre and intended treatment duration.
Allocation concealment (selection bias)	Low risk	A computerised voice-response system was used to randomise participants and ensure concealment of allocation.
Blinding of participants and personnel (performance bias) Participants	High risk	Open-label trial
Blinding of participants and personnel (performance bias) Personnel	High risk	Open-label trial
Blinding of outcome assessment (detection bias) Efficacy outcomes	Low risk	A central adjudication committee unaware of treatment assignments classified all outcomes.
Blinding of outcome assessment (detection bias) Harmful outcomes	Low risk	A central adjudication committee unaware of treatment assignments classified all outcomes. An independent data and safety monitoring board periodically reviewed the outcomes of the study and advised the steering committee.
Incomplete outcome data (attrition bias) Primary efficacy outcome	Low risk	The study report states that all analyses included all randomised participants, and follow-up was successful in 99.1%. Missing data may not have impacted the study results.
Incomplete outcome data (attrition bias) Harmful outcomes	High risk	Harmful outcome was a reason for treatment discontinuation, and only adverse effects with incidence > 1% were reported.

Van Gogh Trial-DVT (Continued)

Selective reporting (reporting bias)	Low risk	The study reports on all the outcomes planned in the study registry (NCT00067093).
Other bias	High risk	Investigators responsible for the study disclosed financial conflict of interest with the pharmaceutical industry that sponsored the trial. The sponsor also had a role in the preparation of the trial report.

DVT: deep vein thrombosis

INR: international normalised ratio

LMWH: low molecular weight heparins

RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cassiopea Investigators	The trial evaluated the treatment of acute symptomatic pulmonary embolism, not deep vein thrombosis
EQUINOXa	These trials from the EQUINOX study aimed to assess the reversibility of the anti-factor X activated activity of idrabiotaparinux by intravenous avidin infusion and the bioequipotency of idrabiotaparinux and idraparinux
MATISSE-PE	These reports from the MATISSE trial evaluated the efficacy of pentasaccharides for pulmonary embolism
Nakamura 2011	The diagnosis of deep vein thrombosis was performed by contrast-enhanced multidetector-row computed tomography, which is not in accordance with our eligibility criteria
The Van Gogh Extension	These reports from the Van Gogh trial evaluated the efficacy of pentasaccharides (idraparinux) for extended prophylaxis of deep vein thrombosis
Young 2011	The study did not have a control group

DATA AND ANALYSES

Comparison 1. Fondaparinux plus vitamin K antagonist versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent VTE [3-months follow-up]	2	2658	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.43, 1.47]
2 Bleeding [initial treatment]	2	2645	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.13]
3 Major bleeding [initial treatment]	2	2645	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.39, 3.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Clinically relevant bleeding [initial treatment]	1	2192	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.52, 1.41]
5 Bleeding [3-months follow-up]	2	2645	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.50, 1.32]
6 Major bleeding [3-months follow-up]	2	2645	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.64, 1.71]
7 Clinically relevant bleeding [3-months follow-up]	1	2192	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.68, 1.36]
8 All-cause mortality [3-months follow-up]	2	2658	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.45, 1.91]
9 Recurrent DVT [3-months follow-up]	1	2205	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.36, 1.16]
10 Pulmonary embolism [3-months follow-up]	2	2658	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.23, 3.39]
11 Harmful effects leading to premature discontinuation	1	2205	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.32]
12 All harmful effects [3-months follow-up]	1	2192	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.76, 0.93]
13 Serious adverse effects [3-months follow-up]	1	2192	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.84, 1.84]
14 Recurrent VTE [3-months follow-up] [body weight]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Recurrent VTE [body weight < 50 kg]	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.33]
14.2 Recurrent VTE [body weight 50-100 kg]	1	1922	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.63, 1.51]
14.3 Recurrent VTE [body weight > 100 kg]	1	228	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.37, 6.24]
15 Recurrent VTE [3-months follow-up] [outpatient treatment]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Recurrent VTE [inpatient treatment]	1	1486	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.75, 1.95]
15.2 Recurrent VTE [outpatient treatment]	1	719	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.14]
16 Major bleeding [3-months follow-up] [outpatient treatment]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Major bleeding [inpatient treatment]	1	1486	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.26, 1.78]
16.2 Major bleeding [outpatient treatment]	1	719	Risk Ratio (M-H, Fixed, 95% CI)	4.34 [1.23, 15.24]
17 Recurrent VTE [3-months follow-up] [participants with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Recurrent VTE [participants with no cancer]	1	1962	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.44, 1.14]
17.2 Recurrent VTE [participants with active cancer]	1	237	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.95, 5.79]
18 Bleeding [3-months follow-up] [participants with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Major bleeding [participants with no cancer]	1	1962	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.31]
18.2 Major bleeding [participants with active cancer]	1	237	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.62, 1.81]
19 Major bleeding [3-months follow-up] [participants with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Major bleeding [participants with no cancer]	1	1962	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.57, 2.04]
19.2 Major bleeding [participants with active cancer]	1	237	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.40, 2.48]
20 Clinically relevant bleeding [3-months follow-up] [participants with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Clinically relevant bleeding [participants with no active cancer]	1	1962	Risk Ratio (M-H, Fixed, 95% CI)	3.82 [2.03, 7.18]
20.2 Clinically relevant bleeding [participants with active cancer]	1	237	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.54, 2.25]

Analysis 1.1. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 1 Recurrent VTE [3-months follow-up].

Study or subgroup	Fondaparinux	Standard therapy	Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI			
MATISSE-DVT	43/1098	45/1107			73.64%	0.96[0.64,1.45]
Rembrandt Trial	8/334	6/119			26.36%	0.48[0.17,1.34]
			Favours fondaparinux		Favours standard therapy	

Analysis 1.2. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 2 Bleeding [initial treatment].

Analysis 1.3. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 3 Major bleeding [initial treatment].

Analysis 1.4. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 4 Clinically relevant bleeding [initial treatment].

Analysis 1.5. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 5 Bleeding [3-months follow-up].

Analysis 1.6. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 6 Major bleeding [3-months follow-up].

Analysis 1.7. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 7 Clinically relevant bleeding [3-months follow-up].

Analysis 1.8. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 8 All-cause mortality [3-months follow-up].

Analysis 1.9. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 9 Recurrent DVT [3-months follow-up].

Analysis 1.10. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 10 Pulmonary embolism [3-months follow-up].

Analysis 1.11. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 11 Harmful effects leading to premature discontinuation.

Analysis 1.12. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 12 All harmful effects [3-months follow-up].

Analysis 1.13. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 13 Serious adverse effects [3-months follow-up].

Analysis 1.14. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 14 Recurrent VTE [3-months follow-up] [body weight].

Analysis 1.15. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 15 Recurrent VTE [3-months follow-up] [outpatient treatment].

Analysis 1.16. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 16 Major bleeding [3-months follow-up] [outpatient treatment].

Analysis 1.17. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 17 Recurrent VTE [3-months follow-up] [participants with active cancer].

Analysis 1.18. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 18 Bleeding [3-months follow-up] [participants with active cancer].

Analysis 1.19. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 19 Major bleeding [3-months follow-up] [participants with active cancer].

Analysis 1.20. Comparison 1 Fondaparinux plus vitamin K antagonist versus standard therapy, Outcome 20 Clinically relevant bleeding [3-months follow-up] [participants with active cancer].

Comparison 2. Idaraparin versus idraparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent VTE [6-months follow-up]	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.31, 1.69]
2 Recurrent VTE [9-months follow-up]	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.28, 1.31]
3 Bleeding [6-months follow-up]	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.33, 0.88]
4 Major bleeding [6-months follow-up]	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.06, 0.71]
5 Clinically relevant bleeding [6-months follow-up]	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Bleeding [9-months follow-up]	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.90]
7 Major bleeding [9-months follow-up]	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.11, 0.76]
8 Clinically relevant bleeding [9-months follow-up]	1	755	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.46, 1.20]
9 All-cause mortality [6-months follow-up]	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.18, 1.27]
10 All-cause mortality [9-months follow-up]	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.28, 1.23]
11 Recurrent DVT [6-months follow-up]	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.40]
12 Pulmonary embolism [6-months follow-up]	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.28, 2.43]
13 Harmful effects leading to premature discontinuation	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.25]
14 All harmful effects	1	757	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]

Analysis 2.1. Comparison 2 Idrabiota-parinux versus idraparinux, Outcome 1 Recurrent VTE [6-months follow-up].

Analysis 2.2. Comparison 2 Idrabiota-parinux versus idraparinux, Outcome 2 Recurrent VTE [9-months follow-up].

Analysis 2.3. Comparison 2 Idrabiota- parinux versus idraparinux, Outcome 3 Bleeding [6-months follow-up].

Analysis 2.4. Comparison 2 Idrabiota- parinux versus idraparinux, Outcome 4 Major bleeding [6-months follow-up].

Analysis 2.5. Comparison 2 Idrabiota- parinux versus idraparinux, Outcome 5 Clinically relevant bleeding [6-months follow-up].

Analysis 2.6. Comparison 2 Idrabiota-parinux versus idraparinux, Outcome 6 Bleeding [9-months follow-up].

Analysis 2.7. Comparison 2 Idrabiota-parinux versus idraparinux, Outcome 7 Major bleeding [9-months follow-up].

Analysis 2.8. Comparison 2 Idrabiota-parinux versus idraparinux, Outcome 8 Clinically relevant bleeding [9-months follow-up].

Analysis 2.9. Comparison 2 Idrabiotaparinux versus idraparinux, Outcome 9 All-cause mortality [6-months follow-up].

Analysis 2.10. Comparison 2 Idrabiotaparinux versus idraparinux, Outcome 10 All-cause mortality [9-months follow-up].

Analysis 2.11. Comparison 2 Idrabiotaparinux versus idraparinux, Outcome 11 Recurrent DVT [6-months follow-up].

Analysis 2.12. Comparison 2 Idrabiotaparinux versus idraparinux, Outcome 12 Pulmonary embolism [6-months follow-up].

Analysis 2.13. Comparison 2 Idrabiotaparinux versus idraparinux, Outcome 13 Harmful effects leading to premature discontinuation.

Analysis 2.14. Comparison 2 Idrabiotaparinux versus idraparinux, Outcome 14 All harmful effects.

Comparison 3. LMWH and idraparinux versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent VTE [idraparinux 10 mg]	1	263	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.26, 8.90]
2 Bleeding [idraparinux 2.5 mg]	1	263	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.08, 0.96]
3 Bleeding [idraparinux 5.0 mg]	1	267	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.69, 2.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Bleeding [idraparinux 7.5 mg]	1	262	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.82, 3.38]
5 Bleeding [idraparinux 10 mg]	1	263	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.91, 3.67]
6 Bleeding [all doses]	1	659	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.70, 2.40]
7 Major bleeding [all doses]	1	659	Risk Ratio (M-H, Fixed, 95% CI)	3.76 [0.50, 28.19]
8 Harmful effects leading to premature discontinuation	1	659	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.89, 3.71]

Analysis 3.1. Comparison 3 LMWH and idraparinux versus standard therapy, Outcome 1 Recurrent VTE [idraparinux 10 mg].

Analysis 3.2. Comparison 3 LMWH and idraparinux versus standard therapy, Outcome 2 Bleeding [idraparinux 2.5 mg].

Analysis 3.3. Comparison 3 LMWH and idraparinix versus standard therapy, Outcome 3 Bleeding [idraparinix 5.0 mg].

Analysis 3.4. Comparison 3 LMWH and idraparinix versus standard therapy, Outcome 4 Bleeding [idraparinix 7.5 mg].

Analysis 3.5. Comparison 3 LMWH and idraparinix versus standard therapy, Outcome 5 Bleeding [idraparinix 10 mg].

Analysis 3.6. Comparison 3 LMWH and idraparinix versus standard therapy, Outcome 6 Bleeding [all doses].

Analysis 3.7. Comparison 3 LMWH and idraparinux versus standard therapy, Outcome 7 Major bleeding [all doses].

Analysis 3.8. Comparison 3 LMWH and idraparinux versus standard therapy, Outcome 8 Harmful effects leading to premature discontinuation.

Comparison 4. Idraparinux versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent VTE [3-months follow-up]	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.64, 1.48]
2 Recurrent VTE [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Bleeding [3-months follow-up]	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.87]
4 Major bleeding [3-months follow-up]	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.34, 1.47]
5 Clinically relevant bleeding [3-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.88]
6 Bleeding [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.35]
7 Major bleeding [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.66, 2.34]
8 Clinically relevant bleeding [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.34]
9 All-cause mortality [3-months follow-up]	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.86]
10 All-cause mortality [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.85, 1.85]
11 Recurrent DVT [3-months follow-up]	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.49, 1.83]
12 Recurrent DVT [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.53, 1.92]
13 Recurrent PE [3-months follow-up]	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.38, 1.02]
14 Recurrent PE [6-months follow-up]	1	2267	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.57, 1.76]
15 Harmful effects leading to premature discontinuation	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.17, 2.14]
16 All harmful effects	1	2904	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [1.00, 1.06]
17 Recurrent VTE [3-months follow-up] [participants with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Recurrent VTE [3-months follow-up] [participants with no cancer]	1	2620	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.75, 1.92]
17.2 Recurrent VTE [3-months follow-up] [participants with active cancer]	1	284	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.20]
18 Recurrent VTE [6-months follow-up] [participants with active cancer]	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Recurrent VTE [6-months follow-up] [participants with no cancer]	1	1997	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.78, 2.01]
18.2 Recurrent VTE [6-months follow-up] [participants with active cancer]	1	270	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.14, 1.07]

Analysis 4.1. Comparison 4 Idraparinux versus standard therapy, Outcome 1 Recurrent VTE [3-months follow-up].

Analysis 4.2. Comparison 4 Idraparinux versus standard therapy, Outcome 2 Recurrent VTE [6-months follow-up].

Analysis 4.3. Comparison 4 Idraparinux versus standard therapy, Outcome 3 Bleeding [3-months follow-up].

Analysis 4.4. Comparison 4 Idraparinux versus standard therapy, Outcome 4 Major bleeding [3-months follow-up].

Analysis 4.5. Comparison 4 Idraparinux versus standard therapy, Outcome 5 Clinically relevant bleeding [3-months follow-up].

Analysis 4.6. Comparison 4 Idraparinux versus standard therapy, Outcome 6 Bleeding [6-months follow-up].

Analysis 4.7. Comparison 4 Idraparinux versus standard therapy, Outcome 7 Major bleeding [6-months follow-up].

Analysis 4.8. Comparison 4 Idraparinux versus standard therapy, Outcome 8 Clinically relevant bleeding [6-months follow-up].

Analysis 4.9. Comparison 4 Idraparinux versus standard therapy, Outcome 9 All-cause mortality [3-months follow-up].

Analysis 4.10. Comparison 4 Idraparinux versus standard therapy, Outcome 10 All-cause mortality [6-months follow-up].

Analysis 4.11. Comparison 4 Idraparinux versus standard therapy, Outcome 11 Recurrent DVT [3-months follow-up].

Analysis 4.12. Comparison 4 Idraparinux versus standard therapy, Outcome 12 Recurrent DVT [6-months follow-up].

Analysis 4.13. Comparison 4 Idraparinux versus standard therapy, Outcome 13 Recurrent PE [3-months follow-up].

Analysis 4.14. Comparison 4 Idraparinux versus standard therapy, Outcome 14 Recurrent PE [6-months follow-up].

Analysis 4.15. Comparison 4 Idraparinux versus standard therapy, Outcome 15 Harmful effects leading to premature discontinuation.

Analysis 4.16. Comparison 4 Idraparinux versus standard therapy, Outcome 16 All harmful effects.

Analysis 4.17. Comparison 4 Idraparinux versus standard therapy, Outcome 17 Recurrent VTE [3-months follow-up] [participants with active cancer].

Analysis 4.18. Comparison 4 Idraparinux versus standard therapy, Outcome 18 Recurrent VTE [6-months follow-up] [participants with active cancer].

ADDITIONAL TABLES

Table 1. Characteristics of included studies: Methods

Study	Year	Countries	Funding sources
EQUINOX	2006/2007	Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Israel, Italy, Mexico, the Netherlands, New Zealand, Poland, Russia, South Africa, Spain, USA	Sanofi
MATISSE-DVT	2000/2001	Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, New Zealand, Norway, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, UK, USA	Sanofi and NV Organon
PERSIST Trial	1999/2001	Austria, Denmark, Italy, the Netherlands, Poland, Spain, Sweden, UK	Sanofi and NV Organon
The Rembrandt Trial	1997/1998	Australia, Belgium, Canada, France, Italy, New Zealand, Switzerland	Sanofi and NV Organon
The Van Gogh Trial-DVT	2003/2004	Australia, Canada, France, Italy, the Netherlands, UK, USA	Sanofi

Table 2. Characteristics of included studies: Participants

Study	Number of randomised participants	Age (mean)	Exclusion criteria
EQUINOX	757	57 years	Patients who had presented with or documented: • symptomatic pulmonary embolism; • active bleeding or high risk of bleeding; • creatinine clearance < 30 mL per min; • severe hepatic disease; • bacterial endocarditis; • uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg); • known allergy to idraparin, idrabiotaparin, or egg proteins; • therapeutic doses of LMWH, unfractionated heparin, or fondaparinux given for more than 36 hours before randomisation; • initiation of vitamin K antagonist treatment or treatment with thrombolysis, thrombectomy, or a vena cava filter for the current episode of deep vein thrombosis; • another indication for prolonged anticoagulant therapy; • life expectancy of < 6 months; • participation in another pharmacotherapeutic study within the prior 30 days; • pregnant women, breastfeeding or premenopausal and not using effective contraceptive measures.
MATISSE-DVT	2205	61 years	Patients who had presented with or documented: • symptomatic pulmonary embolism; • received therapeutic doses of LMWH or oral anticoagulants for more than 24 hours;

Table 2. Characteristics of included studies: Participants (Continued)

			• required thrombolysis, thrombectomy, or a vena cava filter; • anticoagulant therapy contraindication (e.g. active bleeding, thrombocytopenia (platelet count $100,000 \times 10^9/L$)); • elevated serum creatinine levels above $177 \mu\text{mol/L}$ (2 mg/dL); • uncontrolled hypertension (systolic blood pressure $> 180 \text{ mmHg}$ or diastolic blood pressure $> 110 \text{ mmHg}$); • pregnancy; • had a life expectancy < 3 months.
PERSIST Trial	659	59 years	Patients who had presented with or documented: • symptoms for more than 14 days; • symptomatic pulmonary embolism; • documented DVT within the last 2 years; • surgery within the past 10 days; • more than 32 hours of therapeutic anticoagulant treatment; • contraindications for anticoagulants; • life expectancy < 3 months; • pregnancy; • serum creatinine $> 200 \mu\text{mol/L}$; • platelet count $< 100 \times 10^9/L$.
The Rembrandt Trial	456	62 years	Patients who had presented with or documented: • symptomatic pulmonary embolism; • previously documented thrombosis in the same leg, unless complete ultrasound normalisation had been documented; • known bleeding tendency; • surgery within the previous 5 days; • body weight of $< 50 \text{ kg}$ or $> 100 \text{ kg}$; • any contraindication for anticoagulant treatment; • treatment with therapeutic dosages of anticoagulants for > 24 hours before randomisation; • pregnant women, breastfeeding or premenopausal and not using effective contraceptive measures; • drug-addictive disorder or alcoholism; • known renal insufficiency; • life expectancy of < 6 months; • participation in another clinical drug study within the previous 90 days.
The Van Gogh Trial-DVT	2904	58 years	Patients who had presented with or documented: • treatment with a therapeutic dose of LMWH or unfractionated heparin for more than 36 hours before randomisation; • treatment with thrombolysis, embolectomy, or a vena cava filter required for the current episode; • another indication for a vitamin K antagonist; • pregnancy or breastfeeding; • creatinine clearance of less than 10 mL per minute; • uncontrolled hypertension (systolic blood pressure $> 180 \text{ mmHg}$ or diastolic blood pressure $> 110 \text{ mmHg}$); • life expectancy of < 3 months.

DVT: deep vein thrombosis
LMWH: low molecular weight heparin

Table 3. Characteristics of included studies: Outcomes

Study	Intervention	Comparison	Primary efficacy outcome	Primary harm outcome	Time points measured of outcomes
EQUINOX	Idrabiotaparinux: 3.0 mg once a week for 6 months	Idraparinux: 2.5 mg once a week for 6 months	Symptomatic recurrent venous thromboembolism	Clinically relevant bleeding	6 and 9 months
MATISSE-DVT	(1) fondaparinux: 5.0 mg (weight < 50 kg) or 7.5 mg (50 kg > weight < 100 kg) or 10 mg (weight > 100 kg) once daily for 5 days; (2) vitamin K antagonist started within 72 hours and continued for 3 months	Standard therapy: (1) enoxaparin: 1 mg/kg twice daily for 5 days; (2) vitamin K antagonist started within 72 hours and continued for 3 months	Symptomatic recurrent venous thromboembolism	Bleeding	3 months
PERSIST Trial	(1) 5 to 7 days of LMWH (enoxaparin, 1 mg/kg); (2) idraparinux: 2.5 mg, 5 mg, 7.5 mg, or 10 mg once a week without weight adjustment continued for 3 months	Standard therapy: (1) 5 to 7 days of enoxaparin (1 mg/kg); (2) warfarin target to an INR rate between 2.0 to 3.0 continued for 3 months	Symptomatic recurrent venous thromboembolism	Major bleeding	3 months
The Rembrandt Trial	(1) fondaparinux: 5.0 mg, 7.5 mg, or 10 mg once daily without weight adjustment for $\pm$ 5 days; (2) vitamin K antagonist started on day 1 or 2 and continued for $\pm$ 90 days	Standard therapy: (1) dalteparin: 100 IU/kg twice daily for $\pm$ 5 days; (2) vitamin K antagonist started on day 1 or 2 and continued for $\pm$ 90 days	Symptomatic recurrent venous thromboembolism	Major bleeding	3 months
The Van Gogh Trial-DVT	Idraparinux: 2.5 mg once a week for 3 or 6 months, as assessed by the treating physician	Standard therapy: (1) tinzaparin, enoxaparin, or intravenous heparin: dose adjusted for the activated partial thromboplastin time (ratio 1.5 to 2.5); (2) warfarin or acenocoumarol started within 24 hours and target to INR 2.0 to 3.0 for 3 or 6 months, as assessed by the treating physician	Symptomatic recurrent venous thromboembolism	Clinically relevant bleeding and all-cause mortality	3 or 6 months

INR: international normalised ratio
LMWH: low molecular weight heparin

Table 4. Relative risks of the 10 most frequent harmful effects during the initial treatment with fondaparinux versus standard treatment (LMWH, enoxaparin, for 5 days)

Harmful effect, n (%)	Fondaparinux (n = 1091)	Enoxaparin (n = 1101)	Risk ratio (95% CI)
Nausea	27 (2.5)	29 (2.6)	0.94 (0.56 to 1.58)
Constipation	21 (1.9)	32 (2.9)	0.66 (0.38 to 1.14)
Diarrhoea	15 (1.4)	22 (2.0)	0.69 (0.36 to 1.32)
Vomiting	13 (1.2)	14 (1.3)	0.94 (0.44 to 1.98)
Bruise	9 (0.8)	24 (2.2)	0.38 (0.18 to 0.81)
Haematoma	13 (1.2)	17 (1.5)	0.77 (0.38 to 1.58)
Fever	25 (2.3)	32 (2.9)	0.79 (0.47 to 1.32)
Hepatic enzymes increased	4 (0.4)	52 (4.7)	0.08 (0.03 to 0.21)
SGPT increased	2 (0.2)	47 (4.3)	0.04 (0.01 to 0.18)
SGOT increased	1 (0.1)	31 (2.8)	0.03 (0.00 to 0.24)
Headache	35 (3.2)	37 (3.4)	0.95 (0.61 to 1.50)
Coughing	14 (1.3)	7 (0.6)	2.02 (0.82 to 4.98)
Pneumonia	13 (1.2)	5 (0.5)	2.62 (0.94 to 7.33)
Insomnia	25 (2.3)	19 (1.7)	1.33 (0.74 to 2.40)
Urinary tract infection	23 (2.1)	29 (1.8)	0.80 (0.47 to 1.37)

CI: confidence interval

LMWH: low molecular weight heparin

SGOT: serum glutamic oxaloacetic transaminase

SGPT: serum glutamic pyruvic transaminase

Table 5. Relative risks of harmful effects induced by idrabiotaparinux versus idraparinux

Harmful effects, n (%)	Idrabiotaparinux (n = 385)	Idraparinux (n = 370)	Risk ratio (95% CI)
All	223 (57.9)	227 (61.4)	0.94 (0.84 to 1.06)
Infections and infestations	68 (17.7)	83 (22.4)	0.79 (0.59 to 1.05)
Nasopharyngitis	12 (3.1)	7 (1.9)	1.65 (0.66 to 4.14)
Urinary tract infection	8 (2.1)	8 (2.2)	0.96 (0.36 to 2.53)
Bronchitis	7 (1.8)	10 (2.7)	0.67 (0.26 to 1.75)

Table 5. Relative risks of harmful effects induced by idrabiotaparinux versus idraparinux (Continued)

Influenza	6 (1.6)	8 (2.2)	0.72 (0.25 to 2.06)
Musculoskeletal and connective tissue disorders	49 (12.7)	44 (11.9)	1.07 (0.73 to 1.57)
Pain in extremity	14 (3.6)	10 (2.7)	1.35 (0.61 to 2.99)
Arthralgia	8 (2.1)	10 (2.7)	0.77 (0.31 to 1.93)
Gastrointestinal disorders	40 (10.4)	48 (13.0)	0.80 (0.54 to 1.19)
Diarrhoea	9 (2.3)	8 (2.2)	1.08 (0.42 to 2.77)
Vascular disorders	40 (10.4)	35 (9.5)	1.10 (0.71 to 1.69)
Haematoma	15 (3.9)	20 (5.4)	0.72 (0.37 to 1.39)
Hypertension	9 (2.3)	8 (2.2)	0.80 (0.54 to 1.19)
Injury, poisoning, and procedural complications	38 (9.9)	44 (11.9)	0.83 (0.55 to 1.25)
Accidental overdose*	21 (5.5)	13 (3.5)	1.55 (0.79 to 3.05)
Fall	5 (1.3)	12 (3.2)	0.40 (0.14 to 1.13)
Nervous system disorders	38 (9.9)	32 (8.6)	1.14 (0.73 to 1.79)
Headache	19 (4.9)	15 (4.1)	1.22 (0.63 to 2.36)
General disorders and administration site conditions	34 (8.8)	42 (11.4)	0.78 (0.51 to 1.19)
Oedema peripheral	7 (1.8)	13 (3.5)	0.52 (0.21 to 1.28)
Respiratory, thoracic, and mediastinal disorders	32 (8.3)	29 (7.8)	1.06 (0.66 to 1.72)
Epistaxis	12 (3.1)	7 (1.9)	1.65 (0.66 to 4.14)

*Overdose is defined as two or more injections of the study drug in five days or fewer.

CI: confidence interval

Table 6. Relative risks of harmful effects induced by idraparinux versus standard therapy

Adverse effects, n (%)	Idraparinux (n = 1452)	Standard therapy (n = 1452)	Risk ratio (95% CI)
Cancer	97 (6.68)	91 (6.27)	1.07 (0.81 to 1.41)
Cardiac failure	6 (0.41)	18 (1.24)	0.33 (0.13 to 0.84)
Rash, dermatitis, or urticaria	62 (4.27)	46 (3.17)	1.35 (0.93 to 1.96)

Table 6. Relative risks of harmful effects induced by idraparinix versus standard therapy *(Continued)*

Infection	262 (18.0)	295 (20.31)	0.89 (0.76 to 1.03)
Other event	778 (53.58)	754 (51.92)	1.03 (0.96 to 1.11)

CI: confidence interval

APPENDICES

Appendix 1. CENTRAL search strategy

Search run on Wed Mar 22 2017		
#1	MESH DESCRIPTOR Thrombosis	1267
#2	MESH DESCRIPTOR Thromboembolism	921
#3	MESH DESCRIPTOR Venous Thromboembolism	258
#4	MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES	2041
#5	(thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*):TI,AB,KY	18896
#6	MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES	748
#7	(PE or DVT or VTE):TI,AB,KY	4988
#8	((vein* or ven*) near thromb*):TI,AB,KY	6717
#9	(blood near3 clot*):TI,AB,KY	2966
#10	(pulmonary near3 clot*):TI,AB,KY	5
#11	(lung near3 clot*):TI,AB,KY	4
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	24541
#13	MESH DESCRIPTOR Anticoagulants	3362
#14	MESH DESCRIPTOR Polysaccharides EXPLODE ALL TREES WITH QUALIFIERS TU	4734
#15	(fondapar* or Arixtra):TI,AB,KY	282
#16	(Sanorg-34006 or Sanorg34006):TI,AB,KY	2
#17	(SSR-126517* or SSR126517*):TI,AB,KY	3
#18	pentasac*:TI,AB,KY	39
#19	MESH DESCRIPTOR Factor X EXPLODE ALL TREES WITH QUALIFIERS AI	23

(Continued)

#20	(Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY	634
#21	(FX* near4 (antag* or inhib* or block*)):TI,AB,KY	50
#22	(Factor 10* near4 (antag* or inhib* or block*)):TI,AB,KY	111
#23	*arinux:TI,AB,KY	316
#24	ORG31540*:TI,AB,KY	17
#25	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	7763
#26	#12 AND #25	2976

Appendix 2. Trials registries searches

Clinicaltrials.gov

85 studies found for: fondaparinux

7 studies found for: idraparinux

3 studies found for: idrabiotaparinux

WHO trials registry

130 records for 91 trials found for: fondaparinux

41 records for 5 trials found for: idraparinux

1 trial found for: idrabiotaparinux

ISRCTN registry

4 results found for "fondaparinux"

No results found for "idraparinux"

No results found for "idrabiotaparinux"

CONTRIBUTIONS OF AUTHORS

Gustavo MS Brandão conceived the review, conducted the screening of search results, extracted data from the included studies, and appraised the quality of studies together with Daniela R Junqueira. Gustavo interpreted the data and wrote the review.

Daniela R Junqueira designed the review methods and co-ordinated the review development. She participated in the screening of search results and data extraction from the included studies, entered data into Review Manager 5, appraised the quality of studies, and analysed the review results. Together with Gustavo MS Brandão, Daniela interpreted the data and wrote the review.

Hamilton A Rollo made an intellectual contribution to the review and approved the final version of the review.

Marcone L Sobreira participated in the screening of search results and data extraction from the included studies and revised and approved the final text of the review.

Gustavo Brandão and Daniela Junqueira take the responsibility to update the review.

DECLARATIONS OF INTEREST

Gustavo MS Brandão: none known

Daniela R Junqueira: none known

Hamilton A Rollo: none known

Marcone L Sobreira: I have received payment from Sanofi for the development of educational lectures regarding the issue 'venous thromboembolism prophylaxis and treatment'.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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.

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

This project was supported by the NIHR, via a Cochrane Programme Grant funding (13/89/23) to Cochrane Vascular. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS), or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In order to differentiate treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), we only considered trials evaluating people with DVT and PE if data concerning people with DVT could be extracted separately. This was important to ensure that the results were not mixing outcomes of people treated for DVT and those treated for PE.

In our protocol, we planned to assess our primary efficacy outcome, recurrent venous thromboembolism, at six months' follow-up. However, only two studies followed participants for six months, the remaining studies assessing outcomes at three months' follow-up. We therefore analysed data according to the time points at which the outcomes were measured in the included studies.

In our protocol, we planned to calculate risk differences, but since relative effect measures are considered to be more consistent than absolute measures ([Deeks 2002](#); [Engels 2000](#)), we calculated only the risk ratio.

We planned to "combine the efficacy and harmful effects through a meta-analysis using a fixed-effect model, unless significant heterogeneity (Chi² test P value < 0.10 or an I² statistic greater than 50%) is detected, in which case we will use a random-effects model". However, in order to take into account the between-study variance, we chose to use a random-effects model when combining two or more studies in a meta-analysis. We used a fixed-effect model to present estimates from single studies, that is analysis performed with data from only one study.

We planned to calculate the number needed to treat statistics for statistically significant results. However, given that the assessment of the quality of the evidence and the results of the 'Summary of findings' tables are highly informative to support the interpretation of the data, we did not include estimates for the number needed to treat statistics in the final version of the review.

We planned to include thrombocytopenia in the 'Summary of findings' table. However, thrombocytopenia was not reported in the majority of trials, therefore we instead described our findings on all harmful outcomes.

We assessed risk of bias for detection bias and attrition bias for efficacy and harmful outcomes separately. We chose this methodological option to account for differences in the methods relating specifically to these types of outcomes. We also assessed risk of performance bias separately for participants and personnel. This allowed us to better judge the risk of bias of studies reporting complete and incomplete methods applied to ensure blinding of both participants and personnel.

We could perform subgroup analysis only according to participant body weight, cancer, and outpatient treatment, as data on the other subgroup characteristics we planned in our protocol were not available.

We noted during the review stage that the included studies analysed data on harmful outcomes only for those participants who received at least one dose of the study medication. We judged it reasonable to measure adverse effects only in those participants who received the intervention ([CRD's Guidance 2009](#)). To investigate the potential impact of the missing data on the results, we decided to perform a post hoc analysis based on the 'worst-case scenario', that is assuming that missing participants had experienced the negative outcome. This was not planned in our protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [administration & dosage] [adverse effects] [*therapeutic use]; Biotin [administration & dosage] [adverse effects] [*analogs & derivatives] [therapeutic use]; Fondaparinux; Hemorrhage [chemically induced]; Heparin, Low-Molecular-Weight

[therapeutic use]; Oligosaccharides [administration & dosage] [adverse effects] [*therapeutic use]; Polysaccharides [administration & dosage] [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Time Factors; Venous Thrombosis [*drug therapy]

MeSH check words

Humans