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Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer (Review)

Kahale LA, Hakoum MB, Tsolakian IG, Alturki F, Matar CF, Terrenato I, Sperati F, Barba M, Yosunico VED, Schünemann H, Akl EA

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[Intervention Review]

Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer

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ABSTRACT

Background

Cancer increases the risk of thromboembolic events, especially in people receiving anticoagulation treatments.

Objectives

To compare the efficacy and safety of low molecular weight heparins (LMWHs), direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs), and other anticoagulants for the long-term treatment of venous thromboembolism (VTE) in people with cancer.

Search methods

We conducted a literature search including a comprehensive electronic search of the Cochrane Central Register of Controlled Trials (), MEDLINE (Ovid), and Embase (Ovid); handsearching conference proceedings; checking references of included studies; and a search for ongoing studies in trial registries. As part of the living systematic review approach, we run searches continually, incorporating new evidence after it is identified. Last search date 14 May 2021.

Selection criteria

Randomized controlled trials (RCTs) assessing the benefits and harms of long-term treatment with LMWHs, DOACs, VKAs, or other anticoagulants in people with cancer and symptomatic VTE.

Data collection and analysis

We extracted data in duplicate on study characteristics and risk of bias. Outcomes included: all-cause mortality, recurrent VTE, major bleeding, minor bleeding, thrombocytopenia, and health-related quality of life (QoL). We assessed the certainty of the evidence at the outcome level following the GRADE approach (GRADE handbook [GRADE handbook]).

Main results

Of 3583 citations, 19 RCTs fulfilled the eligibility criteria.

Low molecular weight heparins versus vitamin K antagonists

Eight studies enrolling 2327 participants compared LMWHs with VKAs. Meta-analysis of five studies probably did not rule out a beneficial or harmful effect of LMWHs compared to VKAs on mortality up to 12 months of follow-up (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.88 to 1.13; risk difference (RD) 0 fewer per 1000, 95% CI 45 fewer to 48 more; moderate-certainty evidence). Meta-analysis of four studies did not rule out a beneficial or harmful effect of LMWHs compared to VKAs on major bleeding (RR 1.09, 95% CI 0.55 to 2.12; RD 4 more per 1000, 95% CI 19 fewer to 48 more, moderate-certainty evidence) or minor bleeding (RR 0.78, 95% CI 0.47 to 1.27; RD 38 fewer per 1000, 95% CI 92 fewer to 47 more; low-certainty evidence), or thrombocytopenia (RR 0.94, 95% CI 0.52 to 1.69). Meta-analysis of five studies showed that LMWHs probably reduced the recurrence of VTE compared to VKAs (RR 0.58, 95% CI 0.43 to 0.77; RD 53 fewer per 1000, 95% CI 29 fewer to 72 fewer, moderate-certainty evidence).

Direct oral anticoagulants versus vitamin K antagonists

Five studies enrolling 982 participants compared DOACs with VKAs. Meta-analysis of four studies may not rule out a beneficial or harmful effect of DOACs compared to VKAs on mortality (RR 0.93, 95% CI 0.71 to 1.21; RD 12 fewer per 1000, 95% CI 51 fewer to 37 more; low-certainty evidence), recurrent VTE (RR 0.66, 95% CI 0.33 to 1.31; RD 14 fewer per 1000, 95% CI 27 fewer to 12 more; low-certainty evidence), major bleeding (RR 0.77, 95% CI 0.38 to 1.57, RD 8 fewer per 1000, 95% CI 22 fewer to 20 more; low-certainty evidence), or minor bleeding (RR 0.84, 95% CI 0.58 to 1.22; RD 21 fewer per 1000, 95% CI 54 fewer to 28 more; low-certainty evidence). One study reporting on DOAC versus VKA was published as abstract so is not included in the main analysis.

Direct oral anticoagulants versus low molecular weight heparins

Two studies enrolling 1455 participants compared DOAC with LMWH. The study by Raskob did not rule out a beneficial or harmful effect of DOACs compared to LMWH on mortality up to 12 months of follow-up (RR 1.07, 95% CI 0.92 to 1.25; RD 27 more per 1000, 95% CI 30 fewer to 95 more; low-certainty evidence). The data also showed that DOACs may have shown a likely reduction in VTE recurrence up to 12 months of follow-up compared to LMWH (RR 0.69, 95% CI 0.47 to 1.01; RD 36 fewer per 1000, 95% CI 62 fewer to 1 more; low-certainty evidence). DOAC may have increased major bleeding at 12 months of follow-up compared to LMWH (RR 1.71, 95% CI 1.01 to 2.88; RD 29 more per 1000, 95% CI 0 fewer to 78 more; low-certainty evidence) and likely increased minor bleeding up to 12 months of follow-up compared to LMWH (RR 1.31, 95% CI 0.95 to 1.80; RD 35 more per 1000, 95% CI 6 fewer to 92 more; low-certainty evidence). The second study on DOAC versus LMWH was published as an abstract and is not included in the main analysis.

Idraparinux versus vitamin K antagonists

One RCT with 284 participants compared once-weekly subcutaneous injection of idraparinux versus standard treatment (parenteral anticoagulation followed by warfarin or acenocoumarol) for three or six months. The data probably did not rule out a beneficial or harmful effect of idraparinux compared to VKAs on mortality at six months (RR 1.11, 95% CI 0.78 to 1.59; RD 31 more per 1000, 95% CI 62 fewer to 167 more; moderate-certainty evidence), VTE recurrence at six months (RR 0.46, 95% CI 0.16 to 1.32; RD 42 fewer per 1000, 95% CI 65 fewer to 25 more; low-certainty evidence) or major bleeding (RR 1.11, 95% CI 0.35 to 3.56; RD 4 more per 1000, 95% CI 25 fewer to 98 more; low-certainty evidence).

Authors' conclusions

For the long-term treatment of VTE in people with cancer, evidence shows that LMWHs compared to VKAs probably produces an important reduction in VTE and DOACs compared to LMWH, may likely reduce VTE but may increase risk of major bleeding. Decisions for a person with cancer and VTE to start long-term LMWHs versus oral anticoagulation should balance benefits and harms and integrate the person's values and preferences for the important outcomes and alternative management strategies.

Editorial note: this is a living systematic review (LSR). LSRs offer new approaches to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

PLAIN LANGUAGE SUMMARY

Blood thinners for the long-term treatment of blood clots in people with cancer

Background

People with cancer are at an increased risk of developing blood clots and might respond differently to different types of blood thinners (anticoagulants).

Study characteristics

We searched scientific databases for clinical trials looking at the effects of long-term treatment with different blood thinners on blood clot recurrence in people with cancer with a confirmed diagnosis of deep venous thrombosis (a blood clot in the limbs) or pulmonary embolism (a blood clot in the lungs). We included trials with any type of cancer, and irrespective of the type of cancer treatment. The trials looked at survival, recurrent blood clot, bleeding and blood platelet levels (which are involved in blood clotting). The evidence was current to May 2021.

Key results

We found 18 trials enrolling participants with cancer and blood clots. The studies found that low molecular weight heparins (LMWHs; a type of blood thinner that is injected into a vein) were superior to vitamin K antagonists (VKAs; a type of blood thinner taken by mouth (oral)) in reducing the recurrence of blood clots. The available data did not provide a clear answer about the effects of these drugs on death and the side effect of bleeding. The studies also found that direct oral anticoagulants (DOACs; another type of blood thinner taken by mouth) might decrease the recurrence of blood clots compared to LMWH while increasing the risk of bleeding. There was no clear answer when comparing DOACs (a newer type of oral blood thinner) and VKAs (an older type of oral blood thinner) for death, blood clot recurrence and bleeding.

Reliability of the evidence

When comparing LMWHs to VKAs, we judged the certainty of the evidence to be moderate for recurrent blood clots, death at one year and major bleeding, and low for minor bleeding.

When comparing DOACs to VKAs, we judged the certainty of the evidence to be low for death, recurrent blood clots and bleeding complications.

Editorial note: this is a living systematic review. Living systematic reviews offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

SUMMARY OF FINDINGS

Summary of findings 1. Low molecular weight heparin secondary prophylaxis compared to vitamin K antagonist secondary prophylaxis in people with cancer with venous thromboembolism

Low molecular weight heparin secondary prophylaxis compared to vitamin K antagonist secondary prophylaxis in patients with cancer with venous thromboembolism

Population: People with cancer with venous thromboembolism

Setting: Outpatient

Intervention: LMWH secondary prophylaxis

Comparison: VKA secondary prophylaxis

Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with VKA secondary prophylaxis	Risk difference with LMWH secondary prophylaxis
All-cause mortality (main analysis - active cancer) follow up: 6 months	1712 (4 RCTs)	⊕⊕⊕⊖ LOW ^{1 2}	RR 0.99 (0.88 to 1.12)	Study population 374 per 1,000	 4 fewer per 1,000 (45 fewer to 45 more)
All-cause mortality (time-to-event)	1243 (2 RCTs)	⊕⊕⊕⊖ LOW ^{2 3}	HR 0.94 (0.74 to 1.20)	Study population 374 per 1,000	 18 fewer per 1,000 (81 fewer to 56 more)
Recurrent venous thromboembolism (main analysis - active cancer) follow up: 6 months	1712 (4 RCTs)	⊕⊕⊕⊖ MODERATE ¹	RR 0.59 (0.44 to 0.80)	Study population 124 per 1,000	 51 fewer per 1,000 (69 fewer to 25 fewer)
Recurrent venous thromboembolism (time-to-event)	1243 (2 RCTs)	⊕⊕⊕⊖ MODERATE ³	HR 0.49 (0.31 to 0.78)	Study population 124 per 1,000	 61 fewer per 1,000 (84 fewer to 26 fewer)
Major bleeding (main analysis - active cancer) follow up: 6 months	1712 (4 RCTs)	⊕⊕⊕⊖ LOW ^{1 2 4}	RR 1.09 (0.55 to 2.12)	Study population 43 per 1,000	 4 more per 1,000 (19 fewer to 48 more)

Minor bleeding (main analysis - active cancer) follow up: 6 months	1712 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 2 5}	RR 0.78 (0.47 to 1.27)	Study population	
				174 per 1,000	38 fewer per 1,000 (92 fewer to 47 more)
Thrombocytopenia (main analysis- active cancer) follow up: 6 months	138 (1 RCT)	⊕⊕⊕⊕ LOW ^{3 6}	RR 0.94 (0.52 to 1.69)	Study population	
				254 per 1,000	15 fewer per 1,000 (122 fewer to 175 more)

***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; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

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

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Downgraded by one level due to serious risk of bias (allocation concealment unclear in one study, lack of blinding of participants and personnel in all the four studies, high risk of incomplete outcome data in one study, and high risk of selective reporting in one study).

² Downgraded by one level due to serious imprecision. Confidence interval includes suggests both potential harm and potential benefit.

³ Some concern with lack of blinding of patients and personnel.

⁴ Some concern with inconsistency. I²= 46%

⁵ Downgraded by one level due to serious inconsistency (I²= 78%)

⁶ Downgraded by two levels due to very serious imprecision. Confidence interval includes suggests both potential harm and potential benefit. Low number of events.

Summary of findings 2. Direct oral anticoagulant secondary prophylaxis compared to Vitamin K antagonist secondary prophylaxis in patients with active cancer with venous thromboembolism

Direct oral anticoagulant secondary prophylaxis compared to Vitamin K antagonist secondary prophylaxis in patients with active cancer with venous thromboembolism

Population: patients with active cancer with venous thromboembolism

Setting: Outpatient

Intervention: DOAC secondary prophylaxis

Comparison: VKA secondary prophylaxis

Outcomes	Nº of participants (studies)	Certainty of the evidence	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)
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	Follow up	(GRADE)		Risk with Vitamin K antagonist (VKA) secondary prophylaxis	Risk difference with Direct oral anti-coagulant (DOAC) secondary prophylaxis
All-cause mortality follow up: range 6 months to 12 months	1060 (4 RCTs)	⊕⊕⊕⊕ LOW ^{1 2}	RR 0.94 (0.72 to 1.23)	Study population 171 per 1,000	 10 fewer per 1,000 (48 fewer to 39 more)
Recurrent venous thromboembolism follow up: range 6 months to 12 months	1050 (4 RCTs)	⊕⊕⊕⊕ LOW ^{1 3}	RR 0.63 (0.34 to 1.15)	Study population 49 per 1,000	 18 fewer per 1,000 (32 fewer to 7 more)
Major bleeding follow up: range 6 months to 12 months	1055 (4 RCTs)	⊕⊕⊕⊕ LOW ^{1 2}	RR 0.77 (0.39 to 1.53)	Study population 37 per 1,000	 8 fewer per 1,000 (23 fewer to 20 more)
Minor bleeding follow up: range 6 months to 12 months	1055 (4 RCTs)	⊕⊕⊕⊕ LOW ^{1 2}	RR 0.83 (0.57 to 1.23)	Study population 127 per 1,000	 22 fewer per 1,000 (55 fewer to 29 more)
Thrombocytopenia - not reported	-	-	-	-	-
Health related quality of life follow up: range 3 months to 12 months	8485 (1 RCT)	⊕⊕⊕⊕ MODERATE ⁴	-	Prins 2014 (EINSTEIN DVT-PE; n=8485): "in the general population of the EINSTEIN studies, patient-reported satisfaction and quality of life was better in the rivaroxaban-treated patients than in the group treated with enoxaparin and vitamin K antagonist, although we have not yet examined whether this is the same in patients with active cancer. Hence, it can be expected that quality of life will also be improved with rivaroxaban compared with long-term injected low molecular-weight heparin." The tool used was validated measure of treatment satisfaction – the Anti-Clot Treatment Scale (ACTS))	

***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; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

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

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

1 Some concern with indirectness (study by Schulman et al (RECOVER I-II) included patients with a diagnosis of cancer within five years before enrollment), however the weight of these studies was low and heterogeneity was very low.

2 Downgraded by two levels due to very serious imprecision. Confidence interval suggests both potential benefit and potential harm.

3 Downgraded by two levels due to very serious imprecision. Confidence interval suggests both potential benefit and potential no effect. Low number of events.

4 Downgraded by one level for serious indirectness. The study by Prins and colleagues (Prins 2014 (EINSTEIN n=8485)) reports health related quality of life for the whole study population, without providing data for the cancer subgroup

Summary of findings 4. Direct oral anticoagulant secondary prophylaxis compared to Low molecular weight heparin secondary prophylaxis in patients with cancer with venous thromboembolism

Direct oral anticoagulant secondary prophylaxis compared to Low molecular weight heparin secondary prophylaxis in patients with cancer with venous thromboembolism

Patient or population: patients with cancer with venous thromboembolism

Setting: Outpatient

Intervention: DOAC secondary prophylaxis

Comparison: LMWH secondary prophylaxis

Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Low molecular weight heparin (LMWH) secondary prophylaxis	Risk difference with Direct oral anticoagulant (DOAC) secondary prophylaxis
All-cause mortality follow up: mean 6 months	2854 (5 RCTs)	⊕⊕⊕⊕ LOW 12	RR 0.97 (0.83 to 1.14)	Study population 248 per 1,000	 7 fewer per 1,000 (42 fewer to 35 more)
Recurrent VTE follow up: mean 6 months	2854 (5 RCTs)	⊕⊕⊕⊕ LOW 13	RR 0.63 (0.45 to 0.88)	Study population 87 per 1,000	 32 fewer per 1,000 (48 fewer to 10 fewer)
Major bleeding follow up: mean 6 months	2994 (5 RCTs)	⊕⊕⊕⊕ LOW 14	RR 1.20 (0.83 to 1.73)	Study population 35 per 1,000	 7 more per 1,000

				(6 fewer to 25 more)	
Major GI bleeding follow up: mean 6 months	1838 (4 RCTs)	⊕⊕⊕⊕ LOW ^{1 4}	RR 1.16 (0.62 to 2.17)	Study population	
				20 per 1,000	3 more per 1,000 (8 fewer to 23 more)
Major upper GI bleeding follow up: mean 6 months	1838 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 5}	RR 1.18 (0.51 to 2.76)	Study population	
				11 per 1,000	2 more per 1,000 (5 fewer to 19 more)
Major lower GI bleeding follow up: mean 6 months	1838 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 5}	RR 1.10 (0.43 to 2.80)	Study population	
				9 per 1,000	1 more per 1,000 (5 fewer to 16 more)
Major non-GI bleeding follow up: mean 6 months	1838 (4 RCTs)	⊕⊕⊕⊕ VERY LOW ^{1 6}	RR 0.84 (0.42 to 1.68)	Study population	
				19 per 1,000	3 fewer per 1,000 (11 fewer to 13 more)
Minor bleeding follow up: mean 6 months	2854 (5 RCTs)	⊕⊕⊕⊕ MODERATE ¹	RR 1.58 (1.15 to 2.16)	Study population	
				67 per 1,000	39 more per 1,000 (10 more to 78 more)
Minor GI bleeding follow up: mean 6 months	1495 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{6 7 8}	RR 1.37 (0.41 to 4.64)	Study population	
				25 per 1,000	9 more per 1,000 (15 fewer to 92 more)
Minor upper GI bleeding follow up: mean 6 months	1495 (2 RCTs)	⊕⊕⊕⊕ VERY LOW ^{6 7 9}	RR 1.03 (0.04 to 25.97)	Study population	
				11 per 1,000	0 fewer per 1,000 (10 fewer to 267 more)
Minor lower GI bleeding follow up: mean 6 months	1495 (2 RCTs)	⊕⊕⊕⊕ LOW ^{5 7}	RR 1.54 (0.72 to 3.27)	Study population	
				15 per 1,000	8 more per 1,000 (4 fewer to 33 more)
Minor non-GI bleeding follow up: mean 6 months	1495 (2 RCTs)	⊕⊕⊕⊕ MODERATE ^{7 10}	RR 2.37 (1.44 to 3.89)	Study population	

31 per 1,000

42 more per 1,000
(14 more to 89 more)

***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; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

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

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Downgraded by one level due to serious risk of bias. Allocation concealment was not reported in one study, lack of blinding of patients and personnel in all studies, and high risk of bias related to incomplete outcome data.

² Downgraded by one level due to serious imprecision. Confidence interval suggests both potential benefit and potential harm.

³ Downgraded by one level due to serious imprecision. Confidence interval suggests both potential benefit and potential no effect.

⁴ Downgraded by one level due to serious imprecision. Confidence interval suggests both potential harm and potential no effect.

⁵ Downgraded by two levels due to very serious imprecision. Confidence interval suggests both potential harm and potential no effect. Low number of events.

⁶ Downgraded by two levels due to very serious imprecision. Confidence interval suggests both potential harm and potential benefit. Low number of events.

⁷ Some concern with risk of bias. Lack of blinding of patients and personnel in both studies.

⁸ Downgraded by one level due to serious inconsistency (unexplained heterogeneity I²=64%) and due to some concern with risk of bias.

⁹ Downgraded by two levels due to very serious inconsistency (unexplained heterogeneity I²=74%.) and due to some concern with risk of bias.

¹⁰ Downgraded by one level due to serious imprecision. Low number of events.

Summary of findings 5. Idraparinux secondary prophylaxis compared to vitamin K antagonist secondary prophylaxis in people with cancer with venous thromboembolism

Idraparinux secondary prophylaxis compared to VKA secondary prophylaxis in people with cancer with VTE

Population: people with cancer with VTE receiving secondary prophylaxis

Setting: outpatient

Intervention: idraparinux prophylaxis

Control: VKA prophylaxis

Outcomes	N° of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)
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			Risk with VKA secondary prophylaxis	Risk difference with idraparinux secondary prophylaxis
All-cause mortality follow-up: mean 6 months	284 (1 RCT)	⊕⊕⊕⊖ Moderate ^a	RR 1.11 (0.78 to 1.59)	Study population 283 per 1000 31 more per 1000 (62 fewer to 167 more)
Recurrent VTE follow-up: mean 6 months	270 (1 RCT)	⊕⊕⊕⊖ Low ^b	RR 0.46 (0.16 to 1.32)	Study population 77 per 1000 42 fewer per 1000 (65 fewer to 25 more)
Major bleeding follow-up: mean 6 months	270 (1 RCT)	⊕⊕⊕⊖ Low ^c	RR 1.11 (0.35 to 3.56)	Study population 38 per 1000 4 more per 1000 (25 fewer to 98 more)
Minor bleeding – not reported	—	—	—	—
Health-related quality of life – not reported	—	—	—	—

***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:** randomized controlled trial; **RR:** risk ratio; **VKA:** vitamin K antagonist; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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

^aDowngraded one level due to serious imprecision, 95% CI was consistent with the possibility for important benefit (62 per 1000 absolute reduction) and possibility of important harm (167 per 1000 absolute increase), included 85 events.

^bDowngraded two level due to very serious imprecision, 95% CI was consistent with the possibility of important benefit (65 fewer per 1000) and possibility of important harm (25 more per 1000); included 15 events.

^cDowngraded two levels due to very serious imprecision, 95% CI was consistent with the possibility for important benefit (25 per 1000 absolute reduction) and possibility of important harm (98 per 1000 absolute increase), included 11 events.

BACKGROUND

Please refer to the glossary for the definitions of technical terms (Table 1).

Description of the condition

Cancer is associated with an increased risk of venous thromboembolism (VTE) of four- to six-fold (Heit 2000). Cancer-related interventions such as chemotherapy, hormonal therapy and indwelling central venous catheters also increase the risk of VTE (Heit 2000). Similarly, people undergoing surgery for cancer have a higher risk of VTE than people undergoing surgery for diseases other than cancer (Gallus 1997; Kakkar 1970). Furthermore, people with cancer and VTE have a higher risk of death than people with cancer alone or with VTE alone (Leviton 1999; Sorensen 2000).

People with cancer also have different benefits and risks from anticoagulant treatment than people without cancer. For instance, during oral anticoagulation therapy for VTE, people with cancer, compared with people without cancer, have a higher incidence of recurrent VTE (27.1 events per 100 participant-years with cancer versus 9.0 events per 100 participant-years without cancer; $P = 0.003$) and of major bleeding (13.3 events per 100 participant-years with cancer versus 2.2 events per 100 participant-years without cancer; $P = 0.002$) (Hutten 2000).

Description of the intervention

Low molecular weight heparins (LMWHs) do not have intrinsic anticoagulant activity but potentiate the activity of antithrombin III in inhibiting activated coagulation factors. These agents constitute indirect anticoagulants as their activity is mediated by plasma cofactors. LMWHs are not absorbed orally and must be administered parenterally by subcutaneous injections (Hirsh 1993).

Direct oral anticoagulant (DOACs) are a new generation of medications with a rapid onset of action that allows a fixed-dose treatment, and may simplify treatment of VTE by eliminating the need for an initial parenteral anticoagulation (Agnelli 2013).

Vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant therapy since the 1950s. Well-designed clinical trials have shown the effectiveness of VKAs for the primary and secondary prevention of several venous and arterial thrombotic diseases (Ansell 2008).

How the intervention might work

Several systematic reviews have compared LMWHs, DOACs and VKAs in the long-term treatment of VTE, but in populations not representative of people with cancer (Conti 2003; Iorio 2003; van der Heijden 2007). The review by van der Heijden and colleagues did not complete a preplanned subgroup analysis in people with cancer as the required data were not specifically reported (van der Heijden 2007). The review by Conti and colleagues did not conduct a meta-analysis in the subgroup of people with cancer (Conti 2003). In the review by Iorio and colleagues, one meta-analysis in the subgroup of people with cancer found no significant difference in mortality (odds ratio 1.13, 95% confidence interval (CI) 0.54 to 2.38).

Why it is important to do this review

We initially conducted this and other reviews on this topic and their updates to directly and better inform clinical practice guidelines. This is fourth versions of this review (previous version published respectively in 2007, 2011, 2016 and cite them). The last major update of this Cochrane systematic review, published in 2018, identified 16 trials. It concluded that the LMWHs compared to VKAs probably produces an important reduction in VTE, and DOACs compared to LMWH may likely reduce VTE but may increase risk of major bleeding (Kahale 2018). Since 2018, we have identified three new eligible trials and one full-text publication of a previously identified abstract) addressing this question.

Living review approach: since the publication of the 2018 update of the review, we are maintaining it as a living systematic review. This means we will be continually running the searches and rapidly incorporating any newly identified evidence (for more information about the living systematic review approach, see Appendix 1). We believe a living systematic review approach is appropriate for this review for four reasons. First, the review addresses an important topic for clinical practice; people with cancer being treated for VTE have a relatively high rate of VTE recurrence. For instance, during oral anticoagulation therapy for VTE, people with cancer, compared with people without cancer, have a higher incidence of recurrent VTE (27.1 events per 100 participant-years with cancer versus 9.0 events per 100 participant-years without cancer; $P = 0.003$) (Hutten 2000). Second, there remains uncertainty in the existing evidence in relation to the outcomes of mortality and bleeding. Third, we are aware of five ongoing eligible trials that will be important to incorporate in a timely manner. Fourth, this living systematic review may be used as part of a living guideline project (Akl 2017).

OBJECTIVES

- To compare the efficacy and safety of antithrombotics including low molecular weight heparins (LMWHs), direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs), and Idaraparinux for the long-term treatment of venous thromboembolism (VTE) in people with cancer.
- To maintain this review as a living systematic review by continually running the searches and incorporating newly identified studies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People with active cancer with a confirmed diagnosis of VTE (deep venous thrombosis (DVT) or pulmonary embolism (PE)). Participants could have been of any age group (including children), with either solid or hematologic cancer, at any cancer stage and irrespective of the type of cancer therapy. VTE should have been diagnosed using an objective diagnostic test.

Cancer should have been diagnosed by the time of inclusion in the study.

We included studies with at least 75% of participants with a cancer status being active (i.e., we excluded studies with more than 25% of participants with non-active cancer). If between 25% and 75% of the population had active cancer and outcome data for this subgroup of people were not reported, we excluded such studies from the main analysis and included them in the sensitivity analysis.

Types of interventions

Intervention arms consisted of long-term treatment with antithrombotics including (beyond 3 months of initial treatment) :

- LMWHs;
- DOACs;
- VKAs;
- Idraparinux

We included any comparison of the three management options listed above (LMWHs versus VKAs, DOACs versus VKAs, DOACs versus LMWHs; idra). Cointerventions, if any, should have been balanced across the groups compared.

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Symptomatic recurrent DVT: DVT events suspected clinically, and confirmed using an objective diagnostic test such as: venography, ¹²⁵I-fibrinogen-uptake test, impedance plethysmography or compression ultrasound.
- Symptomatic recurrent PE: PE events suspected clinically, and confirmed using an objective diagnostic test such as: pulmonary ventilation/perfusion scans, computed tomography, pulmonary angiography or autopsy.
- Symptomatic VTE:
- Major bleeding: we accepted the authors' definitions of major bleeding.
- Minor bleeding: we accepted the authors' definitions of minor bleeding.
- Thrombocytopenia: we accepted the authors' definitions of thrombocytopenia.
- Health-related quality of life measured using a validated tool.
- Postphlebotic syndrome.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in people with cancer. We conducted a comprehensive search on 14 May 2021, following the a major search in February 2016. We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (starting 1946, via Ovid), and Embase (starting 1980, via Ovid). We used no language restrictions. The search strategies combined terms for anticoagulants, terms for cancer and a search filter for RCTs. We used no language restrictions. The search strategy was revised by an information specialist (JP). We

list the full search strategy for each of the electronic databases in [Appendix 2](#).

Living systematic review approach: We will be updating the searches using auto-alerts on a monthly basis. We will publish an update every six months to incorporate any new identified evidence. This update of the systematic review is based on the findings of a literature search conducted on 14 May 2021. We will review search methods and strategies approximately yearly, to ensure they reflect any terminology changes in the topic area, or in the databases.

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982 up to May 2021) and of the American Society of Hematology (ASH, starting with its 2003 issue up to May 2021). We also searched [ClinicalTrials.gov](#) and [World Health Organization \(WHO\) International Clinical Trials Registry Platform](#) for ongoing studies. We reviewed the reference lists of papers included in this review and of other relevant systematic reviews.. In addition, we contacted experts in the field for information about unpublished work and ongoing trials.

Living review approach: we will search the conference proceedings of ASCO and ASH soon after their publications and [ClinicalTrials.gov](#) and [WHO International Clinical Trials Registry Platform](#). . We will continue to review the reference lists for any prospectively identified studies specify in differences between protocol

Data collection and analysis

Selection of studies

Four pairs of review authors (LAK, FA, MBK, CFM, VEDY, IT, FS, MB, IGT) independently screened the title and abstract of identified articles for potential eligibility. We retrieved the full text of articles judged potentially eligible by at least one review author. Then, the pairs of authors independently screened the full-text article for eligibility using a standardized form piloted on 500 RCTs with explicit inclusion and exclusion criteria (as detailed in the [Criteria for considering studies for this review](#) section) and resolved any disagreements by discussion or by consulting a third review author.

Living systematic review approach: for the monthly searches, we will immediately screen the new citations retrieved each month. As the first step of monthly screening, we will apply the machine learning classifier (RCT model) available in the Cochrane Register of Studies ([CSR-web](#); [Wallace 2017](#)). The classifier assigns a probability (from 0 to 100) to each citation for being a true RCT. For citations that are assigned a probability score of less than 10, the machine learning classifier currently has a specificity/recall of 99.987% ([Thomas 2017](#); [Wallace 2017](#)). For citations assigned a score from 10 to 100, we will screen them in duplicate and independently. Citations that score 9 or less will be screened by Cochrane Crowd ([Cochrane Crowd](#)). Any citations that are deemed to be potential RCTs by Cochrane Crowd will be returned to the authors for screening.

Data extraction and management

Four pairs of review authors (LAK, FA, IT, IGT) independently extracted the data from each study and resolved any disagreements

by discussion or by consulting a third review author. We aimed to collect data related to the following.

Participants

- Number of participants randomized to each study arm.
- Number of participants followed up in each study arm.
- Number of participants who discontinued treatment in each arm.
- Population characteristics (e.g., age, gender, co morbidities).
- Type of cancer (site, histology).
- Stage of cancer.

We defined active cancer as (1) non-squamous cell or basal cell invasive cancer diagnosed within 6 months before enrollment, (2) cancer treated within the previous 6 months, (3) recurrent or metastatic cancer, or (4) reported as active cancer during the study.

We extracted outcome data for people with active cancer. If the study included both people with active cancer and people with non-active cancer, we sought outcome data for the subgroup of people with active cancer.

Interventions

- Type of anticoagulant. (LMWH, VKA, or DOAC)
- Dosage or intensity of anticoagulation
- Duration of long-term and initial treatment
- Cointerventions including chemotherapy, target therapy, immunotherapy, radiation therapy, or a combination of these (type and duration).

Outcomes

We extracted both time-to-event data (for the mortality and recurrence of VTE outcomes) and dichotomous data (for all outcomes).

For time-to-event data, we abstracted the log (hazard ratio (HR)) and its variance from trial reports; if these were not reported, we digitized the published Kaplan-Meier survival curves and estimated the log (HR) and its variance using the method of Parmar (Parmar 1998). We also noted the minimum and maximum duration of follow-up, which were required to make these estimates. We performed these calculations in [Stata 9](#) using a specially written program, which yielded the reported log (HR) and variance when used on the data presented in Table V of [Parmar 1998](#).

For dichotomous data, we collected for each outcome and per arm number of events, number of participants randomized, and number of participants with incomplete data.

For the outcome major bleeding, we extracted events among people with gastrointestinal (GI) tract cancer and people without GI tract cancer. We further extracted major GI bleeding, major upper GI bleeding, major lower GI bleeding, and major non-GI bleeding.

We attempted to contact study authors for incompletely reported data. We decided a priori to consider abstracts in the main analysis only if authors supplied us with full reports of their methods and results, otherwise we included abstracts in the sensitivity analysis

None of the outcomes of interest were continuous variables.

Other

We extracted from each included trial any information on the following:

- Ethical approval;
- Source of funding;
- Conflict of interest.

Assessment of risk of bias in included studies

We assessed risk of bias at the study level using Cochrane's 'Risk of bias' tool ([Higgins 2011](#)). Four pairs of review authors ((LAK, FA, IT, IGT) independently assessed the methodologic quality of each included study and resolved any disagreements by discussion. Methodologic criteria included:

- Adequate sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data ;
- Selective outcome reporting;
- Other bias (e.g., whether the study was stopped early for benefit).

See the [Dealing with missing data](#) section about assessing risk of bias associated with participants with missing data per outcome and across studies.

We attempted to contact the authors for any study domain that was unclear. We re-evaluated our judgment when authors provided clarification.

Measures of treatment effect

We analyzed hazard ratio (HR) for time-to-event data and relative risk (RR) for dichotomous data, with 95% confidence intervals (CI). None of the outcomes of interest was meta-analyzed as a continuous variable.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Identifying participants with missing data

It was not clear whether certain categories of participants (e.g. those described as 'withdrew consent' or 'experienced adverse events') were actually followed up by the trial authors (versus had missing data) ([Akl 2016](#)). To identify participants with missing data, we followed the guidance suggested by Kahale et al ([Kahale 2019](#)) :

- Definitely not missing data: (1) participants explicitly reported as followed-up; (2) participants who died during the trial; (3) participants belonging to centres that were excluded.
- Definitely missing data: (1) participants explicitly reported as not followed up; (2) participants with unclear follow-up status and (a) excluded from the denominator of the analysis (i.e., complete case analysis); or (b) included in the denominator of the analysis and their outcomes were explicitly stated to be imputed. However, we did not treat them as missing data unless

it is possible to obtain the number of observed/actual events (i.e., excluding imputed events) to avoid double counting.

- Potentially missing data: Participants with unclear follow-up status (e.g., included in the denominator of the analysis and their outcomes were not explicitly stated to be imputed).

Dealing with participants with missing data in the primary meta-analysis

In the primary meta-analysis, we used a complete-case analysis approach, i.e., we excluded participants considered to have missing data (Guyatt 2017; Kahale 2020).

For categorical data, we used the following calculations for each study arm:

- denominator: (number of participants randomized) – (number of participants definitely with missing data);
- numerator: number of participants with observed events (i.e. participants who experienced at least one event for the outcome of interest during their available follow-up time).

Assessing the risk of bias associated with participants with missing data

When the primary meta-analysis of a specific outcome found a statistically significant effect, we conducted sensitivity meta-analyses to assess the risk of bias associated with missing outcome data. Those sensitivity meta-analyses used a priori plausible assumptions about the outcomes of participants considered to have missing data. The assumptions we used in the sensitivity meta-analyses were increasingly stringent in order to challenge the statistical significance of the results of the primary analysis progressively (Akl 2013; Kahale 2020).

For categorical data and for an RR showing a reduction in effect ($RR < 1$), we used the following increasingly stringent but plausible assumptions:

- For the control arm, relative incidence (RI) among those with missing data (lost to follow-up (LTFU)) compared with those with available data (followed up, FU) in the same arm ($RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 1.5$;
- For the control arm, $RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 2$;
- For the control arm, $RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 3$;
- For the control arm, $RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 5$.

For RR showing an increase in effect ($RR > 1$), we switched the above assumptions between the control and interventions arms (i.e. used $RI_{LTFU/FU} = 1$ for the intervention arm).

Specifically, we used the following calculations for each study arm:

- denominator: (number of participants randomized)
- numerator: (number of participants with observed events) + (number of participants definitely with missing data with assumed events).

Assumed events are calculated by applying the a priori plausible assumptions to the participants definitely with missing data.

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (I^2 test; Higgins 2011), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this (see section on Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We planned to create funnel plots for outcomes including 10 or more trials.

Data synthesis

For time-to-event data, we pooled the log(HRs) using a random-effects model (DerSimonian 1986), and the generic inverse variance facility of Review Manager 5.4.1 (Review Manager 2020). For dichotomous data, we calculated the RR separately for each study. When analyzing data related to participants who were reported as non-compliant, we attempted to adhere to the principles of intention-to-treat (ITT) analysis. We approached the issue of non-compliance independently from that of missing data (Alshurafa 2012). We then pooled the results of the different studies using a random-effects model. We assessed the certainty evidence at the outcome level using the GRADE approach for each of the following comparisons and outcomes (GRADE Handbook):

- LMWH versus VKA
- DOAC versus VKA
- DOAC versus LMWH
- Idaraparinux versus VKA

We included in the primary analysis all studies that provided outcome data for participants with active cancer, and in the sensitivity analysis all studies that included between 25% and 75% of their study sample participants with active cancer and did not provide outcome data for this subgroup of people.

Living systematic review approach: whenever new evidence (studies, data or information) that meets the review inclusion criteria is identified, we will immediately assess risk of bias and extract the data and incorporate it in the synthesis, as appropriate. We will not adjust the meta-analyses to account for multiple testing given the methods related to frequent updating of meta-analyses are under development (Simmonds 2017).

Subgroup analysis and investigation of heterogeneity

Since anticoagulants might perform differently in participants with GI tract cancer (CITATION), we planned to do a subgroup analysis for the outcome major bleeding among participants with GI tract cancer and those without GI tract cancer. We included studies that

- Recruited only patients with GI tract cancer and studies that recruited only participants with non-GI tract cancer;

- Recruited both GI and non-GI tract cancer if they provided outcome data for subgroups of participants with GI tract cancer and data for subgroups of participants with non-GI tract cancer;
- Recruited both GI tract and non-GI tract cancer but did not provide subgroup data only if more than 75% of participants had GI tract cancer or more than 75% of participants had non-GI tract cancer.

If the proportion of participants with GI tract cancer ranged between 25% and 75% and outcome data for this subgroup was not provided, we did not include such a study in the subgroup analysis.

For this subgroup analysis, we did not conduct complete case analysis for the primary analysis as noted under Dealing with missing data section. Instead we used the denominator reported in the analysis of each study report in order to balance numbers of participants with GI tract cancer and those without GI tract cancer.

Sensitivity analysis

We decided a priori to consider abstracts and completed studies published exclusively on [ClinicalTrials.gov](https://clinicaltrials.gov) in the main analysis only if study authors supplied us with full reports of their methods and results; otherwise abstracts were included only in the sensitivity analysis.

As described earlier under Dealing with missing data section, we also planned for sensitivity meta-analyses to assess the risk of bias associated with missing outcome data when the primary meta-analysis of a specific outcome found a statistically significant effect.

In addition, we planned a sensitivity analysis including studies that included between 25% and 75% of their study sample participants with active cancer and did not provide outcome data for this subgroup of people.

RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow diagram. As of May 2021, the search strategy identified 3583 unique citations. The title and abstract screening identified 102 potentially eligible citations. The full-text screening of the full texts of these 102 citations identified 19 eligible RCTs published as full reports ([Agnelli 2015 \(AMPLIFY\)](#); [Agnelli 2020 \(Caravaggio\)](#); [Deitcher 2006 \(ONCENOX\)](#); [El Mokadem 2020](#); [Hull 2006 \(LITE\)](#); [Lee 2003 \(CLOT\)](#); [Lee 2015 \(CATCH\)](#); [Lopez-Beret 2001](#); [McBane 2019 \(ADAM-VTE\)](#); [Meyer 2002 \(CANTHANOX\)](#); [Prins 2014 \(EINSTEIN\)](#); [Raskob 2016 \(HOKUSAI\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Romera 2009](#); [Schulman 2015 \(RECOVER I-II\)](#); [van Doormaal 2010 \(Van Gogh DVT trial\)](#); [Young 2018 \(SELECT-D\)](#)), and two studies published as abstracts ([Cesarone 2003](#); [Mazilu 2014 \(OVIDIUS\)](#)). Since the last major update in May 2018, we included the full text of two previously identified ongoing studies ([Agnelli 2020 \(Caravaggio\)](#); [McBane 2019 \(ADAM-VTE\)](#)), included the full text of a previously previously identified abstract ([Young 2018 \(SELECT-D\)](#)), included the full text of a new study ([El Mokadem 2020](#)). We identified five registered but unpublished trials: one terminated ([Kamphuisen 2010 \(Longheva\)](#)) and four ongoing ([Kamphuisen 2010 \(Longheva\)](#); [Karatas 2015](#); [Meyer 2016 \(CASTA-DIVA\)](#); [Ryun Park 2017 \(PRIORITY\)](#); [Schrage 2016 \(CANVAS\)](#)).

Figure 1. Study flow diagram.

Included studies

We included 19 RCTs (55 reports) with participants with cancer for which outcome data were available (see [Characteristics of included studies](#) table).

Eight RCTs compared LMWHs to VKAs for the long-term treatment of VTE (Cesarone 2003; Deitcher 2006 (ONCENOX); Hull 2006 (LITE); Lee 2003 (CLOT); Lee 2015 (CATCH); Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Romera 2009); only one of these studies used a different initial anticoagulant in the two study arms (LMWH in the

LMWH group and UFH in the VKA group) (Hull 2006 (LITE)). Four studies did not explicitly specify whether patients had active cancer or did not provide outcome data for subgroups of patients with active cancer (Cesarone 2003; Hull 2006 (LITE); Lopez-Beret 2001; Romera 2009).

Five RCTs compared DOACs to VKAs (Agnelli 2015 (AMPLIFY); Mazilu 2014 (OVIDIUS); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Schulman 2015 (RECOVER I-II)). One study did not explicitly specify whether patients had active cancer (Mazilu 2014 (OVIDIUS)). One RCT compared a once-weekly subcutaneous injection of

idraparinux for three or six months versus standard treatment (tinzaparin, enoxaparin or dose-adjusted intravenous heparin followed by warfarin or acenocoumarol; [van Doormaal 2010](#) (Van Gogh DVT trial)).

Five studies compared DOACs to LMWHs ([Agnelli 2020](#) (Caravaggio); [El Mokadem 2020](#); [McBane 2019](#) (ADAM-VTE); [Raskob 2018](#) (HOKUSAI); [Young 2018](#) (SELECT-D)). We also identified five ongoing studies comparing DOACs to LMWHs ([Kamphuisen 2010](#) (Longheva); [Karatas 2015](#); [Meyer 2016](#) (CASTA-DIVA); [Ryun Park 2017](#) (PRIORITY); [Schrag 2016](#) (CANVAS))).

Agnelli and colleagues recruited 169 participants with active cancer and VTE, a subgroup in the AMPLIFY trial, and followed them up for six months ([Agnelli 2015](#) (AMPLIFY)). Participants were randomized to receive apixaban (10 mg twice daily for seven days followed by 5 mg twice daily) or enoxaparin (1 mg/kg twice daily for at least five days) followed by dose-adjusted warfarin (target international normalized ratio (INR) of 2 to 3). Assessed outcomes were mortality, recurrent VTE and major bleeding. It is of note that 25 participants (13 in the apixaban group and 12 in the enoxaparin/warfarin group) without cancer or a history of cancer at baseline were diagnosed with cancer after treatment assignment.

Agnelli and colleagues recruited and analyzed 1155 participants with active cancer from 119 centers in 9 European countries, Israel and The U.S.A. ([Agnelli 2020](#) (Caravaggio)). Participants were randomized to receive apixaban 10 mg twice daily for seven days then 5 mg twice daily for a total of six months or dalteparin 200 IU/kg once daily for the first month and then 150 IU/kg daily for a total of six months. Assessed outcomes were all cause mortality, recurrent VTE, recurrent DVT, PE, major and minor bleeding. Gastrointestinal bleeding was also reported. Participants were followed up for six months.

Cesarone and colleagues recruited 199 participants with cancer and DVT ([Cesarone 2003](#)). The authors did not report whether the participants had active cancer or not. Participants were randomized to receive enoxaparin 100 IU/kg twice daily or coumadin (dose adjusted to keep INR close to 3) for three months. Assessed outcomes were mortality and major outcome event in the three-month period.

Deitcher and colleagues recruited 102 participants with active cancer with acute symptomatic VTE ([Deitcher 2006](#) (ONCENOX)). Participants were randomized to receive enoxaparin subcutaneous twice daily (1.0 mg/kg) for five days followed by once daily enoxaparin for 175 days or enoxaparin subcutaneous twice daily (1.0 mg/kg) for five days then warfarin starting day two of enoxaparin for 180 days. Assessed outcomes were mortality, recurrent VTE, and major and minor bleeding.

El Mokadem and colleagues recruited and analyzed 138 participants with active cancer and acute DVT ([El Mokadem 2020](#)). Participants were randomized to receive apixaban 10 mg twice daily for seven days then 5 mg twice daily for a total of six months or enoxaparin 1 mg/kg/sc every 12 h for a total of six months. Assessed outcomes were mortality, recurrence of DVT and PE, major bleeding, and minor bleeding. Participants were followed up for six months.

Hull and colleagues recruited 200 participants with cancer with acute symptomatic proximal vein thrombosis ([Hull 2006](#) (LITE)).

Participants were randomized to receive tinzaparin 175 anti-Xa/kg subcutaneously daily for 12 weeks or UFH either 5000 U or 80 U/kg for five days followed by VKAs (target INR 2 to 3) for 12 weeks. Assessed outcomes were mortality, recurrent VTE, major and minor bleeding, and thrombocytopenia. Participants were followed up for one year.

Lee and colleagues recruited 676 participants with cancer and proximal DVT, PE or both in the CLOT study ([Lee 2003](#) (CLOT)). Participants were randomized to receive dalteparin 200 IU per kilogram once daily for five to seven days and a coumarin derivative for six months (target INR 2.5) or dalteparin alone for six months (200 IU per kilogram once daily for one month, followed by a daily dose of approximately 150 IU per kilogram for five months). Assessed outcomes were mortality, recurrent VTE, and major and minor bleeding. Participants were followed up for six months.

Lee and colleagues recruited 900 participants with active cancer and objectively documented proximal DVT or PE in the CATCH study ([Lee 2015](#) (CATCH)). Participants were randomized to receive tinzaparin 175 IU/kg once daily for six months or conventional therapy with tinzaparin 175 IU/kg once daily for five to 10 days followed by warfarin at a dose adjusted to maintain the INR within the therapeutic range (2 to 3) for six months. Assessed outcomes were mortality, recurrent VTE, and major and non-major bleeding. Participants were followed up for six months.

Lopez-Beret and colleagues recruited 35 participants with cancer and symptomatic DVT of the lower limb, a subgroup of 158 participants recruited (Lopez-Beret 2001a). Participants were randomized to receive nadroparin 1.025 anti-Xa IU/10 kg twice daily for three days then 1.025 anti-Xa IU/10 kg twice daily, after the third month, nadroparin was switched to once daily, or nadroparin 1.025 anti-Xa IU/10 kg twice daily for three days then acenocoumarol (target INR 2 to 3) for three to six months. Assessed outcome available for the cancer subgroup was mortality. Participants were followed up for 12 months.

Mazilu and colleagues recruited 46 participants with paraneoplastic DVT ([Mazilu 2014](#) (OVIDIUS)). Participants were randomized to receive either fixed-dose dabigatran or adjusted-dose acenocoumarol. Assessed outcomes were mortality, recurrent VTE and bleeding.

McBane and colleagues recruited 300 participants with active cancer from 28 centers the U.S.A. (McBane 2019 (ADAM-VTE)). Participants were randomized to receive apixaban 10 mg twice daily for seven days then 5 mg twice daily for a total of six months or dalteparin 200 IU/kg for the first month and then 150 IU/kg once daily for a total of six months. Assessed outcomes were major bleeding, clinically-relevant non-major bleeding, any recurrence of DVT, PE, fatal PE, arterial thromboembolism and mortality. Gastrointestinal bleeding was also reported. Participants were followed up for six months.

Meyer and colleagues recruited 146 participants with cancer and VTE ([Meyer 2002](#) (CANTHANOX)). Participants were randomized to receive enoxaparin 1.5 mg/kg daily for three months or enoxaparin 1.5 mg/kg daily for four days followed by warfarin (target INR 2 to 3) for three months. Outcomes assessed were mortality, recurrent VTE and major bleeding. Participants were followed up for three months. The study noted that 52% of participants had

ongoing cancer treatment in the warfarin group versus 76% in the enoxaparin group.

Prins and colleagues recruited 459 participants with active cancer at baseline and DVT or PE, a subgroup of the EINSTEIN-DVT and EINSTEIN-PE studies (Prins 2014 (EINSTEIN)). Participants were randomized to receive rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily. Participants assigned to the enoxaparin and VKA group received enoxaparin subcutaneously 1.0 mg/kg bodyweight twice daily and either oral warfarin or acenocoumarol (target INR 2 to 3), started within 48 hours of randomization. Enoxaparin was discontinued when the INR was 2 or more for two days consecutively and the participant had received at least five days of enoxaparin treatment. The dose of the VKA was adjusted to maintain an INR of 2 to 3. Assessed outcomes were mortality, recurrent VTE, major bleeding and clinically relevant bleeding. Participants were followed up for 12 months.

Raskob and colleagues recruited 208 participants with active cancer and DVT or PE (Raskob 2016 (HOKUSAI)). Participants were randomized to receive LMWH for at least five days followed by oral edoxaban 60 mg once daily (edoxaban group) or warfarin (or placebo) started concurrently with the study regimen of heparin. Assessed outcomes were recurrent VTE, major and non-major bleeding, and mortality. Participants were followed up for one year.

Raskob and colleagues recruited 1050 participants with active cancer and VTE (Raskob 2018 (HOKUSAI)). Participants were randomized to receive LMWH for at least five days followed by oral edoxaban 60 mg once daily (edoxaban group) or subcutaneous dalteparin 200 IU per kilogram bodyweight once daily for one month followed by dalteparin 150 IU per kilogram once daily (dalteparin group). Assessed outcomes were recurrent VTE, major and non-major bleeding, and mortality. Participants were followed up for one year.

Romera and colleagues recruited 69 participants with cancer with symptomatic proximal DVT, a subgroup of 241 recruited participants (Romera 2009). All participants were given tinzaparin fixed dose 175 IU anti-Xa per kg bodyweight once daily. The participants randomized to tinzaparin received this regimen for six months without dosage adjustments. The participants randomized to oral anticoagulants were given acenocoumarol 3 mg orally, which was subsequently adjusted to achieve a regular INR between

2 and 3 for six months. This group received tinzaparin until the INR reached at least 2 on two consecutive measurements. The assessed outcome for the cancer subgroup was recurrent VTE. Participants were followed up for one year.

Schulman and colleagues recruited 221 participants with active cancer and VTE, a subgroup of the RECOVER and RECOVER-II trials (Schulman 2015 (RECOVER I-II)). Participants were randomized to receive warfarin adjusted to achieve an INR of 2 to 3 or dabigatran fixed-dose 150 mg twice daily. In both randomization arms, initial treatment was with a parenteral anticoagulant (UFH, LMWH or fondaparinux) until the INR or sham INR became at least 2 for two consecutive days. Assessed outcomes were symptomatic recurrent VTE and VTE-related death, major bleeding and clinically relevant non-major bleeding. Participants were followed up for six months. The study authors reported complete follow-up.

Van Doormaal and colleagues recruited 284 participants with active cancer and DVT, a subgroup of the Van Gogh DVT trial (van Doormaal 2010 (Van Gogh DVT trial)). Participants were randomized to receive idraparinux for three or six months or VKA. The study noted that 66% of the idraparinux group and 69% of the VKAs group had active cancer. Assessed outcomes were mortality, recurrent VTE and bleeding. Participants were followed up for six months.

Young and colleagues recruited 406 participants with active cancer and VTE (Young 2017 (SELECT-D)). Participants were randomized to receive rivaroxaban 15 mg twice daily for three weeks then 20 mg once daily for a total of six months or dalteparin 200 IU/kg daily for one month and 150 IU/kg daily for a total of six months. Assessed outcomes were recurrent VTE, mortality, and major and clinically non-major bleeding. Gastrointestinal bleeding was also reported. Participants were followed up for six months.

Excluded studies

We excluded 46 reports from this review for the following reasons: not population of interest (26); not intervention of interest (3); not design of interest (10) and outcome data for cancer subgroup not reported (7). See [Characteristics of excluded studies](#) table.

Risk of bias in included studies

The judgments for the risk of bias are summarized in [Figure 2](#) and [Figure 3](#).

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

Figure 3. Risk of bias summary: review authors' judgments 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): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Free of selective reporting?	Free of other bias?
Agnelli 2015 (AMPLIFY)	+	+	+	+	+	+	+
Agnelli 2020 (Caravaggio)	+	+	-	+	+	+	+
Cesarone 2003	+	-	-	+	-	-	-
Deitcher 2006 (ONCENOX)	+	-	-	+	+	+	+
El Mokadem 2020	+	-	-	+	-	+	+
Hull 2006 (LITE)	+	-	-	+	+	+	+
Lee 2003 (CLOT)	+	+	-	+	+	+	+
Lee 2015 (CATCH)	+	+	-	+	-	-	+
Lopez-Beret 2001	+	-	-	+	+	+	+
Mazilu 2014 (OVIDIUS)	+	?	?	?	?	?	?
McBane 2019 (ADAM-VTE)	+	+	-	+	-	+	+
Meyer 2002 (CANTHANOX)	+	+	-	+	+	+	+
Prins 2014 (EINSTEIN)	+	+	-	+	+	+	+
Raskob 2016 (HOKUSAI)	+	+	+	+	+	+	+
Raskob 2018 (HOKUSAI)	+	+	-	+	-	+	+
Romera 2009	+	-	-	+	+	+	+
Schulman 2015 (RECOVER I-II)	+	+	+	+	+	+	+

Figure 3. (Continued)

Schulman 2015 (RECOVER I-II)	+	+	+	+	+	+	+
van Doormaal 2010 (Van Gogh DVT trial)	+	+	+	+	+	+	+
Young 2018 (SELECT-D)	+	+	+	+	+	+	+

Allocation

Random sequence was definitely generated in 14 studies (Agnelli 2015 (AMPLIFY); Agnelli 2020 (Caravaggio); El Mokadem 2020; Hull 2006 (LITE); Lee 2003 (CLOT); Lee 2015 (CATCH); McBane 2019 (ADAM-VTE); Meyer 2002 (CANTHANOX); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Raskob 2018 (HOKUSAI); Schulman 2015 (RECOVER I-II); van Doormaal 2010 (Van Gogh DVT trial); Young 2018 (SELECT-D)).

Five studies were judged to be at low risk of selection bias because minimal information about random sequence generation was provided (Cesarone 2003; Deitcher 2006 (ONCENOX); Lopez-Beret 2001; Mazilu 2014 (OVIDIUS); Romera 2009).

We judged allocation to be adequately concealed in 12 studies (Agnelli 2015 (AMPLIFY); Agnelli 2020 (Caravaggio); Lee 2003 (CLOT); Lee 2015 (CATCH); McBane 2019 (ADAM-VTE); Meyer 2002 (CANTHANOX); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Raskob 2018 (HOKUSAI); Schulman 2015 (RECOVER I-II); van Doormaal 2010 (Van Gogh DVT trial)). Eight studies did not report allocation concealment (Cesarone 2003; Deitcher 2006 (ONCENOX); El Mokadem 2020; Hull 2006 (LITE); Lopez-Beret 2001; Mazilu 2014 (OVIDIUS); Raskob 2018 (HOKUSAI); Romera 2009).

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be definitely blinded in four studies (Agnelli 2015 (AMPLIFY); Deitcher 2006 (ONCENOX); Raskob 2016 (HOKUSAI); Schulman 2015 (RECOVER I-II)), definitely not blinded in 11 studies (Agnelli 2020 (Caravaggio); Hull 2006 (LITE); Lee 2003 (CLOT); Lee 2015 (CATCH); Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Prins 2014 (EINSTEIN); Raskob 2018 (HOKUSAI); Romera 2009; van Doormaal 2010 (Van Gogh DVT trial); Young 2018 (SELECT-D)), and probably not blinded in three studies (Cesarone 2003; El Mokadem 2020; McBane 2019 (ADAM-VTE)). One study did not report on blinding of participants and personnel (unclear risk of bias; Mazilu 2014 (OVIDIUS)).

Blinding of outcome assessment (detection bias)

We judged outcome assessors to be definitely blinded in 10 studies (Agnelli 2015 (AMPLIFY); Agnelli 2020 (Caravaggio); Hull 2006 (LITE); Lee 2003 (CLOT); Lee 2015 (CATCH); Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Raskob 2018 (HOKUSAI); Romera 2009; Schulman 2015 (RECOVER I-II); van Doormaal 2010 (Van Gogh DVT trial)), definitely not blinded in one study (Young 2018 (SELECT-D)), and probably not blinded in four studies (Cesarone 2003; Deitcher 2006 (ONCENOX); El

Mokadem 2020; McBane 2019 (ADAM-VTE)). One study was not clear about the blinding of outcome assessors (Mazilu 2014 (OVIDIUS)).

Incomplete outcome data

We assessed the risk of bias associated with missing data for each outcome with a significant effect (please see [Effects of interventions](#) section). Seven studies did not report follow-up data for the cancer subgroup, but we assumed complete follow-up taking into consideration the small sample size (Agnelli 2015 (AMPLIFY); Lopez-Beret 2001; Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Romera 2009; van Doormaal 2010 (Van Gogh DVT trial)). Six studies were judged to be at low risk of incomplete outcome data because the rates of missing outcome data were lower than the event rate in the studies (Agnelli 2020 (Caravaggio); Deitcher 2006 (ONCENOX); Hull 2006 (LITE); Lee 2003 (CLOT); Meyer 2002 (CANTHANOX); Young 2018 (SELECT-D)), whereas five studies were judged to be at high risk of incomplete outcome data because the rate of missing outcome data was higher than the event rate in the study (Cesarone 2003; El Mokadem 2020; Lee 2015 (CATCH); McBane 2019 (ADAM-VTE); Raskob 2018 (HOKUSAI)). One study reported complete follow-up based on communication with author (Schulman 2015 (RECOVER I-II)). The risk of incomplete outcome data was not clear in one study (Mazilu 2014 (OVIDIUS)).

Selective reporting

We did not suspect selective reporting of outcomes for any of the studies except for Cesarone 2003 where results for outcomes of interest were not reported individually, and all results were reported under the term "major outcome," in addition we suspected selective reporting in Lee 2015 (CATCH) where authors failed to report on some of the outcomes mentioned in the study protocol. The cancer subgroup data were missing for a large number of studies. Reporting bias was not clear in one study (Mazilu 2014 (OVIDIUS)).

Other potential sources of bias

Another potential source of bias was the screening for asymptomatic VTE in three studies (Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Romera 2009). The full-text of the abstract Cesarone 2003 was never published.

Effects of interventions

See: [Summary of findings 1](#) Low molecular weight heparin secondary prophylaxis compared to vitamin K antagonist secondary prophylaxis in people with cancer with venous thromboembolism; [Summary of findings 2](#) Direct oral anticoagulant secondary prophylaxis compared to Vitamin K antagonist secondary prophylaxis in patients with active cancer with venous thromboembolism; [Summary of findings 4](#) Direct oral anticoagulant secondary prophylaxis compared to Low

molecular weight heparin secondary prophylaxis in patients with cancer with venous thromboembolism; **Summary of findings 5** Idraparinux secondary prophylaxis compared to vitamin K antagonist secondary prophylaxis in people with cancer with venous thromboembolism

Low molecular weight heparin versus vitamin K antagonist

Seven RCTs compared LMWH to VKA for the long-term treatment of VTE in patients with cancer (Cesarone 2003; Deitcher 2006 (ONCENOX); Hull 2006 (LITE); Lee 2003 (CLOT); Lee 2015 (CATCH); Meyer 2002 (CANTHANOX); Romera 2009). The initial treatment was heparin in both arms for all the seven studies.

We identified one ongoing study comparing LMWH to VKA for the long-term treatment of cancer participants with VTE that was terminated due to slow inclusion of patients (Kamphuisen 2010 (Longheva)).

All-cause mortality up to six months

Meta-analysis of four RCTs including 1712 participants, found that LMWH may result in little to no difference on mortality up to six months when compared to VKA (Relative Risk (RR) 0.99, 95% CI 0.88 to 1.13; Risk Difference (RD) 4 fewer per 1000, 95% CI 45 fewer to 45 more; I^2 0%; low certainty evidence; **Analysis 1.1**) (Deitcher 2006 (ONCENOX); Lee 2003 (CLOT); Lee 2015 (CATCH); Meyer 2002 (CANTHANOX)). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision (**Summary of findings 1**).

The results were consistent in a sensitivity analysis including the study published as an abstract (RR 0.99, 95% CI 0.88 to 1.12) (Cesarone 2003), in a sensitivity analysis including the studies that did not specify whether the cancer was active in the included patients (RR 1.00, 95% CI 0.89 to 1.13) (Hull 2006 (LITE); Lopez-Beret 2001), and in a sensitivity analysis including the study that used a different initial anticoagulant in the two study arms (RR 1.00, 95% CI 0.89 to 1.12) (Hull 2006 (LITE)).

We did not create a funnel plot for the outcome of mortality due to the low number of included trials.

All-cause mortality: time-to-event analysis

Two studies including 810 participants reported data allowing their inclusion in the time-to-event analysis (Lee 2003 (CLOT); Meyer 2002 (CANTHANOX)). Meta-analysis indicated that LMWH may reduce mortality slightly compared to VKA (HR 0.94, 95% CI 0.74 to 1.20; RD 18 fewer per 1000, 95% CI 81 fewer to 56 more; I^2 16%; low certainty evidence **Analysis 1.2**). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision (**Summary of findings 1**). The results were consistent in a sensitivity analysis including data provided by the author for the study that used a different initial anticoagulant in the two study arms (HR 0.96, 95% CI 0.81 to 1.14) (Hull 2006 (LITE)).

Recurrent venous thromboembolism up to six months

None of the studies reported DVT and PE as separate outcomes. Meta-analysis of four studies including 956 participants found that LMWH probably reduces recurrent VTE up to six months compared to VKA (RR 0.59, 95% CI 0.44 to 0.80; RD 51 fewer per 1000, 95% CI 69 fewer to 25 fewer; I^2 0%; moderate certainty evidence; **Analysis 1.3**) (Deitcher 2006 (ONCENOX); Lee 2003 (CLOT); Lee 2015 (CATCH);

Meyer 2002 (CANTHANOX)). The certainty of evidence was rated down to moderate due to serious risk of bias (**Summary of findings 1**).

The results were consistent in a sensitivity analysis including the studies that did not specify whether the cancer was active in the included patients (RR 0.59, 95% CI 0.45 to 0.79) (Hull 2006 (LITE); Romera 2009) and in a sensitivity analysis including the study that used a different initial anticoagulant in the two study arms (RR 0.56, 95% CI 0.42 to 0.74) (Hull 2006 (LITE)).

Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the **Methods** section. The effect estimate remained significant across all four stringent assumptions (**Appendix 3**).

We did not create a funnel plot for the outcome of recurrent VTE due to the low number of included trials.

Recurrent venous thromboembolism: time-to-event analysis

Two studies including 810 participants reported data allowing their inclusion in the time-to-event meta-analyses. We used time-to-event data reported by two studies (Lee 2003 (CLOT); Meyer 2002 (CANTHANOX)). Meta-analysis showed that LMWH probably reduces recurrent VTE (HR 0.49, 95% CI 0.31 to 0.78; RD 61 fewer per 1000, 95% CI 84 fewer to 26 fewer; I^2 0%; moderate certainty evidence; **Analysis 1.4**). The certainty of evidence was rated down to moderate due to serious risk of bias (**Summary of findings 1**).

The results were consistent in a sensitivity analysis (Hull 2006 (LITE); Romera 2009) including data provided by the author for the study that used a different initial anticoagulant in the two study arms (HR 0.47, 95% CI 0.32 to 0.71) (Hull 2006 (LITE)).

We did not create a funnel plot for the outcome of recurrent VTE due to the low number of included trials.

Major bleeding up to six months

Meta-analysis of four studies including 1712 participants found that LMWH may result in little to no difference in major bleeding up to six months compared to VKA (RR 1.09, 95% CI 0.55 to 2.12; RD 4 more per 1000, 95% CI 19 fewer to 48 more; I^2 = 46%; low certainty evidence; **Analysis 1.5**) (Deitcher 2006 (ONCENOX); Lee 2003 (CLOT); Lee 2015 (CATCH); Meyer 2002 (CANTHANOX)). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision (**Summary of findings 1**).

The results were different in a sensitivity analysis including the study published as an abstract (RR 0.85, 95% CI 0.41 to 1.74) (Cesarone 2003) and in a sensitivity analysis including the study that did not specify whether the cancer was active in the included patient and used a different initial anticoagulant in the two study arms for the outcome of major bleeding (RR 1.07, 95% CI 0.64 to 1.78) (Hull 2006 (LITE)).

We did not create a funnel plot for the outcome of major bleeding due to the low number of included trials.

Minor bleeding up to six months

Meta-analysis of four studies including 1712 participants found that LMWH may reduce minor bleeding up to six months compared to VKA but the evidence is very uncertain (RR 0.78, 95% CI 0.47 to 1.27; RD 38 fewer per 1000, 95% CI 92 fewer to 47 more; $I^2 = 78\%$; very low certainty evidence; [Analysis 1.6](#)) ([Deitcher 2006 \(ONCENOX\)](#); [Lee 2003 \(CLOT\)](#); [Lee 2015 \(CATCH\)](#); [Meyer 2002 \(CANTHANOX\)](#)). The certainty of evidence was rated down to very low due to serious risk of bias, serious inconsistency, and serious imprecision ([Summary of findings 1](#)).

The results were consistent in a sensitivity analysis including the study that did not specify whether the cancer was active in the included patient and used a different initial anticoagulant in the two study arms (RR 0.84, 95% CI 0.56 to 1.27) ([Hull 2006 \(LITE\)](#)).

We did not create a funnel plot for the outcome of minor bleeding due to the low number of included trials.

Thrombocytopenia up to six months

One study including 138 participants assessed thrombocytopenia ([Meyer 2002 \(CANTHANOX\)](#)). The study found that LMWH may reduce thrombocytopenia up to six months slightly compared to VKA (RR 0.94, 95% CI 0.52 to 1.69; RD 15 fewer per 1000, 95% CI 122 fewer to 175 more; low certainty evidence; [Analysis 1.7](#)). The certainty of evidence was rated down to low due to very serious imprecision ([Summary of findings 1](#)).

The results were consistent in a sensitivity analysis including the study that did not specify whether the cancer was active in the included patient and used a different initial anticoagulant in the two study arms (RR 1.10, 95% CI 0.67 to 1.79) ([Hull 2006 \(LITE\)](#)).

We did not create a funnel plot for the outcome of thrombocytopenia due to the low number of included trials.

Health-related quality of life up to six months

None of the studies reported health-related quality of life.

Postphlebotic syndrome up to six months

None of the studies reported postphlebotic syndrome.

Direct oral anticoagulants versus vitamin K antagonists

Five RCTs compared DOAC to VKA for the long-term treatment of VTE in patients with cancer ([Agnelli 2015 \(AMPLIFY\)](#); [Mazilu 2014 \(OVIDIUS\)](#); [Prins 2014 \(EINSTEIN\)](#); [Raskob 2016 \(HOKUSAI\)](#); [Schulman 2015 \(RECOVER I-II\)](#)). The initial treatment was heparin in both arms for two studies ([Raskob 2016 \(HOKUSAI\)](#); [Schulman 2015 \(RECOVER I-II\)](#)), DOAC vs LMWH for two other studies ([Agnelli 2015 \(AMPLIFY\)](#); [Prins 2014 \(EINSTEIN\)](#)), and DOAC vs VKA in one study ([Mazilu 2014 \(OVIDIUS\)](#)).

All-cause mortality six to 12 months

Meta-analysis of five RCTs, including 1060 participants found that DOAC may reduce mortality from six to 12 months slightly compared to VKA (RR 0.94, 95% CI 0.72 to 1.23; RD 10 fewer per 1000, 95% CI 48 fewer to 39 more; $I^2 = 0\%$; low certainty evidence; [Analysis 2.1](#)) ([Agnelli 2015 \(AMPLIFY\)](#); [Prins 2014 \(EINSTEIN\)](#); [Raskob 2016 \(HOKUSAI\)](#); [Schulman 2015 \(RECOVER I-II\)](#)). The certainty of

evidence was rated down to low due to very serious imprecision ([Summary of findings 2](#)).

The results were consistent in a sensitivity analysis including the study published as an abstract and that did not specify whether the cancer was active in the included patients (RR 0.92, 95% CI 0.71 to 1.19) ([Mazilu 2014 \(OVIDIUS\)](#)).

We did not create a funnel plot for the outcome of all-cause mortality due to the low number of included trials.

Recurrent venous thromboembolism six to 12 months

None of the studies reported DVT and PE as separate outcomes. Meta-analysis of four studies including 1050 participants found that DOAC may reduce recurrent VTE from six to 12 months slightly compared to VKA (RR 0.63, 95% CI 0.34 to 1.15; RD 18 fewer per 1000, 95% CI 32 fewer to 7 more; $I^2 = 0\%$, low certainty evidence; [Analysis 2.2](#)) ([Agnelli 2015 \(AMPLIFY\)](#); [Prins 2014 \(EINSTEIN\)](#); [Raskob 2016 \(HOKUSAI\)](#); [Schulman 2015 \(RECOVER I-II\)](#)). The certainty of evidence was rated down to low due to very serious imprecision ([Summary of findings 2](#)).

We did not create a funnel plot for the outcome of recurrent VTE due to the low number of included trials.

Major bleeding six to 12 months

Meta-analysis of four studies including 1055 participants found that DOACs may result in little to no difference in major bleeding compared to VKA (RR 0.77, 95% CI 0.39 to 1.53; RD 8 fewer per 1000, 95% CI 23 fewer to 20 more; low certainty evidence; $I^2 = 0\%$; [Analysis 2.3](#)) ([Agnelli 2015 \(AMPLIFY\)](#); [Prins 2014 \(EINSTEIN\)](#); [Raskob 2016 \(HOKUSAI\)](#); [Schulman 2015 \(RECOVER I-II\)](#)). The certainty of evidence was rated down to low due to very serious imprecision ([Summary of findings 2](#)).

We did not create a funnel plot for the outcome of major bleeding due to the low number of included trials.

Minor bleeding six to 12 months

Meta-analysis of four studies including 1055 participants found that DOACs may reduce minor bleeding from six to 12 months slightly compared to VKA (RR 0.83, 95% CI 0.57 to 1.23; RD 22 fewer per 1000, 95% CI 55 fewer to 29 more; low-certainty evidence; [Analysis 2.4](#)) ([Agnelli 2015 \(AMPLIFY\)](#); [Prins 2014 \(EINSTEIN\)](#); [Raskob 2016 \(HOKUSAI\)](#); [Schulman 2015 \(RECOVER I-II\)](#)). The certainty of evidence was rated down to low due to very serious imprecision ([Summary of findings 2](#)).

We did not create a funnel plot for the outcome of minor bleeding due to the low number of included trials.

Thrombocytopenia six to 12 months

None of the studies reported thrombocytopenia.

Health-related quality of life six to 12 months

Two studies assessed health-related quality of life; the first used the Anti-Clot Treatment Scale (ACTS) ([Prins 2014 \(EINSTEIN\)](#)), while the other did not report the tool used for assessment ([Mazilu 2014 \(OVIDIUS\)](#)). Prins and colleagues assessed the outcome for the study population (8485 participants) without reporting on the cancer subgroup (655 participants). They reported that HRQoL

was better in the rivaroxaban-treated participants than in the group treated with enoxaparin and VKAs (no further statistical data reported). The certainty of evidence was rated down to low due to very serious imprecision ([Summary of findings 2](#)).

The study by Mazilu and colleagues, published as an abstract, reported that HRQoL was better in the dabigatran group due to the fact that there was no need for monthly blood tests as in the acenocoumarol group ([Mazilu 2014 \(OVIDIUS\)](#)).

Postphlebotic syndrome

None of the studies reported postphlebotic syndrome.

Direct oral anticoagulants versus low molecular weight heparins

Five RCTs compared DOAC to LMWH for the long-term treatment of VTE in patients with cancer ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)). The initial treatment was DOAC vs LMWH for four studies ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Young 2018 \(SELECT-D\)](#)) and heparin in both arms for one study ([Raskob 2018 \(HOKUSAI\)](#)).

We identified four ongoing studies comparing DOACs to LMWHs for the long-term treatment of cancer participants with VTE; two are completed and not published yet ([Meyer 2016 \(CASTA-DIVA\)](#); [Schrage 2016 \(CANVAS\)](#)); one is still recruiting ([Ryun Park 2017 \(PRIORITY\)](#)); and one ongoing study that was terminated since recruitment was not as expected ([Karatas 2015](#)).

All-cause mortality up to six months

Meta-analysis of five RCTs, including 2854 participants found that DOAC may result in little to no difference in mortality up to six months compared to LMWH (RR 0.97, 95% CI 0.84 to 1.14; RD 7 fewer per 1000, 95% CI 42 fewer to 35 more; $I^2 = 25\%$; low certainty evidence; [Analysis 3.1](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision ([Summary of findings 4](#)).

We did not create a funnel plot for the outcome of all cause mortality due to the low number of included trials.

Recurrent venous thromboembolism up to six months

Meta-analysis of five RCTs, including 2854 participants found that DOAC may reduce recurrent VTE up to six months compared to LMWH (RR 0.63, 95% CI 0.45 to 0.88; RD 32 fewer per 1000, 95% CI 48 fewer to 10 more; $I^2 = 18\%$; low certainty evidence; [Analysis 3.2](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision ([Summary of findings 4](#)).

We did not create a funnel plot for the outcome of recurrent VTE due to the low number of included trials.

Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the [Methods](#) section.

The effect estimate remained significant across all four stringent assumptions ([Appendix 3](#)).

Major bleeding up to six months

Meta-analysis of five RCTs, including 2854 participants found that DOAC may result in little to no difference in major bleeding up to six months compared to LMWH (RR 1.20, 95% CI 0.83 to 1.73; RD 7 more per 1000, 95% CI 6 fewer to 25 more; $I^2 = 18\%$; low certainty evidence; [Analysis 3.3](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision ([Summary of findings 4](#)). A subgroup analysis of participants with GI tract cancer versus participants without GI tract cancer found no subgroup difference (among people with GI tract cancer RR 1.47, 95% CI 0.76 to 2.84; among people without GI tract cancer RR 1.05, 95% CI 0.63 to 1.73) ([Analysis 3.3](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)).

Meta-analysis of four RCTs, including 1838 participants found that DOAC may result in little to no difference in major GI tract bleeding up to six months compared to LMWH (RR 1.16, 95% CI 0.62 to 2.17; RD 3 more per 1000, 95% CI 8 fewer to 23 more; $I^2 = 0\%$; low certainty evidence; [Analysis 3.4](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to low due to serious risk of bias and serious imprecision ([Summary of findings 4](#)).

Meta-analysis of four RCTs, including 1838 participants found that DOAC may have little to no difference in major upper GI tract bleeding up to six months compared to LMWH but the evidence is very uncertain (RR 1.18, 95% CI 0.51 to 2.76; RD 2 more per 1000, 95% CI 5 fewer to 19 more; $I^2 = 0\%$; very low certainty evidence; [Analysis 3.5](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to very low due to serious risk of bias and very serious imprecision ([Summary of findings 4](#)).

Meta-analysis of four RCTs, including 1838 participants found that DOAC may have little to no difference in major lower GI tract bleeding up to six months compared to LMWH but the evidence is very uncertain (RR 1.10, 95% CI 0.43 to 2.80; RD 1 more per 1000, 95% CI 5 fewer to 16 more; $I^2 = 0\%$; very low certainty evidence; [Analysis 3.6](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to very low due to serious risk of bias and very serious imprecision ([Summary of findings 4](#)).

Meta-analysis of four RCTs, including 1838 participants found that DOAC may have little to no difference in major non-GI tract bleeding up to six months compared to LMWH but the evidence is very uncertain (RR 0.84, 95% CI 0.62 to 1.68; RD 3 fewer per 1000, 95% CI 11 fewer to 13 more; $I^2 = 0\%$; very low certainty evidence; [Analysis 3.7](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to very low due to serious risk of bias and very serious imprecision ([Summary of findings 4](#)).

We did not create a funnel plot for the outcome of recurrent VTE due to the low number of included trials.

Minor bleeding up to six months

Meta-analysis of five RCTs, including 2854 participants found that DOAC probably reduces minor bleeding up to six months compared to LMWH (RR 1.58, 95% CI 1.15 to 2.16; RD 39 more per 1000, 95% CI 10 more to 78 more; $I^2 = 23\%$; moderate certainty evidence; [Analysis 3.8](#)) ([Agnelli 2020 \(Caravaggio\)](#); [El Mokadem 2020](#); [McBane 2019 \(ADAM-VTE\)](#); [Raskob 2018 \(HOKUSAI\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to moderate due to serious risk of bias ([Summary of findings 4](#)).

Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the [Methods](#) section. The effect estimate lost significance with RI 3 and RI 5, indicating high risk of bias associated with missing data ([Appendix 3](#)).

Meta-analysis of two RCTs, including 1495 participants found that DOAC may have little to no difference in minor GI tract bleeding up to six months compared to LMWH but the evidence is very uncertain (RR 1.37, 95% CI 0.41 to 4.64; RD 9 more per 1000, 95% CI 15 fewer to 92 more; $I^2 = 64\%$; very low certainty evidence; [Analysis 3.9](#)) ([Agnelli 2020 \(Caravaggio\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to very low due to serious inconsistency and very serious imprecision ([Summary of findings 4](#)).

Meta-analysis of two RCTs, including 1495 participants found that DOAC may have little to no difference in minor upper GI tract bleeding up to six months compared to LMWH but the evidence is very uncertain (RR 1.03, 95% CI 0.04 to 25.97; RD 0 more per 1000, 95% CI 10 fewer to 267 more; $I^2 = 74\%$; very low certainty evidence; [Analysis 3.10](#)) ([Agnelli 2020 \(Caravaggio\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to very low due to very serious inconsistency and very serious imprecision ([Summary of findings 4](#)).

Meta-analysis of two RCTs, including 1495 participants found that DOAC may have little to no difference in minor lower GI tract bleeding up to six months compared to LMWH (RR 1.54, 95% CI 0.72 to 3.27; RD 8 more per 1000, 95% CI 4 fewer to 33 more; $I^2 = 0\%$; low certainty evidence; [Analysis 3.11](#)) ([Agnelli 2020 \(Caravaggio\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to low due to very serious imprecision ([Summary of findings 4](#)).

Meta-analysis of two RCTs, including 1495 participants found that DOAC probably increases minor non- GI tract bleeding up to six months compared to LMWH (RR 2.37, 95% CI 1.44 to 3.89; RD 42 more per 1000, 95% CI 18 fewer to 89 more; $I^2 = 3\%$; moderate certainty evidence; [Analysis 3.12](#)) ([Agnelli 2020 \(Caravaggio\)](#); [Young 2018 \(SELECT-D\)](#)). The certainty of evidence was rated down to moderate due to serious imprecision ([Summary of findings 4](#)).

Thrombocytopenia up to six months

None of the studies reported thrombocytopenia.

Health-related quality of life up to six months

None of the studies reported HRQoL.

Postphlebotic syndrome up to six months

None of the studies reported postphlebotic syndrome.

Once-weekly idraparin versus vitamin K antagonists

One RCT with 284 participants compared once-weekly subcutaneous injection of idraparin versus standard treatment (parenteral anticoagulation followed by warfarin or acenocoumarol) for three or six months ([van Doormaal 2010 \(Van Gogh DVT trial\)](#)).

All-cause mortality up to six months

The trial found that idraparin may reduce all-cause mortality up to six months slightly compared to VKAs on mortality at six months (RR 1.11, 95% CI 0.78 to 1.59; RD 31 more per 1000, 95% CI 62 fewer to 167 more; low-certainty evidence).

Recurrent venous thromboembolism up to six months

The trial found that idraparin may reduce recurrent VTE up to six months slightly compared to VKA (RR 0.46, 95% CI 0.16 to 1.32; RD 42 fewer per 1000, 95% CI 65 fewer to 25 more; low-certainty evidence).

Major bleeding up to six months

The trial found that idraparin may result in little to no difference in major bleeding up to six months slightly compared to VKA (RR 1.11, 95% CI 0.35 to 3.56; RD 4 more per 1000, 95% CI 25 fewer to 98 more; low-certainty evidence).

Minor bleeding up to six months

The study did not report minor bleeding.

Thrombocytopenia up to six months

The study did not report thrombocytopenia.

Health-related quality of life up to six months

The study did not report HRQoL.

Postphlebotic syndrome

The study did not report postphlebotic syndrome.

We did not create funnel plots due to the low number of included trials for each outcome.

DISCUSSION

Summary of main results

For the long-term treatment of VTE in people with cancer, LMWH compared to VKA may result in little to no difference on mortality and major bleeding up to six months, probably reduces recurrent VTE up to six months, may reduce minor bleeding up to six months but the evidence is very uncertain, and may reduce thrombocytopenia up to six months slightly.

Direct oral anticoagulants compared to VKA may reduce mortality, recurrent VTE from six to 12 months slightly and may result in little to no difference in major bleeding compared to VKA.

Direct oral anticoagulants compared to LMWH may result in little to no difference in mortality, major bleeding, major GI tract bleeding, up to six months, may reduce recurrent VTE up to six months, may have little to no difference in major upper GI tract bleeding, major lower GI tract bleeding, major non-GI tract bleeding, minor GI tract

bleeding, minor upper GI tract bleeding, but the evidence is very uncertain, probably reduces minor bleeding up to six months, may have little to no difference in minor lower GI tract bleeding, and probably increases minor non-GI tract bleeding up to six months

Idraparinux compared to VKA may reduce all-cause mortality, recurrent VTE, up to six months slightly, and may result in little to no difference in major bleeding up to six months slightly.

Overall completeness and applicability of evidence

While the reduction in VTE with LMWHs was expected to reduce thrombosis-related mortality, this did not translate into an observed reduction in all-cause mortality. This finding was not apparently explained by an increase in any specific-cause mortality (e.g. fatal bleeding), but might have been due to the lack of power to detect a reduction in all-cause mortality. Similarly, the size of the available evidence was not large enough to rule out beneficial or harmful effects for many comparisons (e.g. effects of LMWHs versus VKAs on bleeding, effects of DOACs vs VKA on bleeding, effects of DOACs vs LMWH on mortality, bleeding).

Stratifying bleeding outcomes based on type of cancer (GI tract vs non-GI tract) did not find any subgroup effect when comparing DOAC to LMWH. When adding patients with non-active cancer (or unclear whether active cancer) to patients with active cancer, the results of the meta-analyses for all studied outcomes remained unchanged. We were unable to conduct subgroup analyses based on histologic type (GI tract) or stage of cancer (active) because of the lack of data DELETE ONCE CONFIRMED BY EA. In the absence of evidence for the contrary, we assumed that the results of this review applied to people with any type or stage of cancer.

For comparisons including DOACs, four RCTs used Apixaban (Agnelli 2015 (AMPLIFY); Agnelli 2020 (Caravaggio); El Mokadem 2020; McBane 2019 (ADAM-VTE)); three RCTs used Rivaroxaban (Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Raskob 2018 (HOKUSAI)); two RCTs used Edoxaban (Raskob 2016 (HOKUSAI); Raskob 2018 (HOKUSAI)); Raskob 2016 2018; dabigatran mazilu schulman we were unable to conduct subgroup analyses based on different agents and hence we cannot make any judgment in related to class effect. The majority of studies used Apixaban CHARBEL, SOME LITERATURE ON CLASS EFFECT

majority of studies used apixaban - unclear evidence regarding edoxaban or other classes of DPAC

Quality of the evidence

Our systematic approach to searching, study selection and data extraction should have minimized the likelihood of missing relevant studies.

When comparing LMWHs to VKAs, we judged the certainty of evidence to be moderate for recurrent VTE due to serious risk of bias, and moderate for mortality at one year, and major bleeding due to both imprecision and risk of bias and low for minor bleeding due to imprecision, risk of bias and inconsistency.

We downgraded recurrent VTE by one level due to serious risk of bias, allocation concealment unclear in two studies, high risk of selective reporting and high risk of incomplete outcome data in

one study, and lack of blinding of participants and personnel in all included studies. We downgraded the outcomes of mortality and major bleeding by one level due to both risk of bias and imprecision, in addition we downgraded the outcome of minor bleed by two levels, one for inconsistency and one for risk of bias and imprecision combined. The lack of allocation concealment in two of the studies did not affect the results when conducting a sensitivity analysis after removing those studies that had a combined weight of 6.5%, but we were concerned about the lack of blinding of participants and personnel in all included studies in addition to high risk of bias in the CATCH trial that represented 43.1% of the weight, so we decided to downgrade by one level due to both concerns about imprecision and risk of bias.

When comparing DOACs to VKAs, we judged the certainty of evidence to be moderate for HRQoL due to serious indirectness, low for mortality, recurrent VTE, and major and minor bleeding due to serious imprecision and serious indirectness.

When comparing DOACs to LMWHs, we judged the certainty of evidence to be low for mortality, VTE recurrence, and major and minor bleeding due to serious risk of bias and serious imprecision.

When comparing idraparinux to VKAs, we judged the certainty of evidence to be moderate for mortality due to serious imprecision and low for recurrent VTE and major bleeding due to very serious imprecision. Taking into consideration the wide CIs, the low number of events and the fact that only one study is providing data for this comparison.

Potential biases in the review process

The inclusion of different types of cancer in the same study precluded us from conducting the subgroup analyses to explore effect modifiers such as type and stage of cancer. The interpretation of findings was also limited by not including data from the trials published as abstracts only. A potential bias of our review might be the limitation of the electronic search strategy to participants with cancer, while the data needed for this review came from studies not restricted to this subgroup. Also, there might be potential bias associated with multiple testing in the planned meta-analyses and currently there are no plans to adjust meta-analyses for multiple testing. A major limitation of this review was that we were unable to include in the meta-analyses 11 eligible RCTs with subgroups of participants with cancer because relevant data were not reported and not obtainable from the authors.

Agreements and disagreements with other studies or reviews

We identified seven published systematic reviews comparing LMWHs or DOACs to VKAs in the long-term treatment of VTE (Conti 2003; Iorio 2003; Laporte 2011; Noble 2008; Posch 2015; Romera-Villegas 2010; Vedovati 2015). We review below the findings of the two most recent reviews.

Posch and colleagues compared LMWHs or DOACs to VKAs for the long-term treatment of VTE in participants with cancer including six RCTs comparing LMWHs to VKAs and four RCTs comparing DOACs to VKAs (Posch 2015). The meta-analysis found a significant reduction of recurrent VTE in favor of LMWHs (RR 0.6, 95% CI 0.45 to 0.79) and a non-significant difference in major bleeding episodes (RR 1.07, 95% CI 0.66 to 1.73; $p = 0.80$). There was no significant difference in recurrent VTE and major bleeding when comparing DOACs to VKAs

(recurrent VTE: RR 0.65, 95% CI 0.38 to 1.09; major bleeding: RR 0.72, 95% CI 0.39 to 1.35). These results were in agreement with our study.

Vedovati and colleagues compared DOACs to VKAs in the long-term treatment of VTE in participants with cancer (Vedovati 2015). Meta-analysis of five RCTs showed no significant difference in VTE recurrence when comparing DOACs to VKAs (RR 0.63, 95% CI 0.37 to 1.1). These results were in agreement with our study.

AUTHORS' CONCLUSIONS

Implications for practice

The decision for a person with cancer and venous thromboembolism (VTE) to start long-term low molecular weight heparin (LMWHs) treatment or oral anticoagulation treatment should balance the benefits and harms and integrate people's values and preferences for outcomes and management options (Haynes 2002). While DOACs compared to LMWHs may show a likely reduction in VTE recurrence, it may show an increase in major bleeding.

Implications for research

There is a need for research assessing patients' values and preferences regarding long-term anticoagulant agents for treating VTE. Researchers should consider making the raw data from randomized controlled trials (RCTs) available for individual participant data meta-analysis. Further RCTs including subgroups of people with cancer should report separate results for these subgroups.

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For our update of these reviews, we followed Cochrane methods using the same eligibility criteria and outcomes used previously. The ASH guidelines group used slightly different methods that generated slightly different results. For example, the ASH guideline panel agreed to prioritize different outcomes; include unpublished data; include abstracts; use different definitions for duration of treatment; and rate certainty of evidence slightly differently for some outcomes, for instance because of imprecision or indirectness. These differences are not described in this publication. Instead, they will be described in the ASH guideline publication.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agnelli 2015 (AMPLIFY)

Study characteristics

Methods	Multicenter randomized double-blind trial
Participants	169 (3.1%) participants with active cancer at baseline with objectively confirmed symptomatic proximal DVT or PE, or both from 358 centers in 28 countries Mean age 65.3 years, 58.5% male, 1/3 had metastatic disease. Most common cancer sites were prostate, breast, colon, bladder and lung
Interventions	Intervention: apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) for a total of 6 months Control: enoxaparin (1 mg/kg twice daily for at least 5 days) and warfarin (target INR 2-3) starting day 2 of enoxaparin for a total of 6 months Discontinued treatment: not reported for subgroup of participants with active cancer
Outcomes	Duration of follow-up for the following outcomes: 6 months <ul style="list-style-type: none">• All-cause mortality• Recurrent VTE• Major bleeding

Agnelli 2015 (AMPLIFY) (Continued)

- Clinically relevant non-major bleeding

Screening test for DVT/PE: not reported

Diagnostic test for DVT/PE: echo-doppler for DVT and spiral CT scan for PE

Notes	<ul style="list-style-type: none"> Study details obtained from original AMPLIFY report published in <i>New England Journal of Medicine</i> August 2013. Participants with cancer history at baseline and without active cancer at baseline and participants with no cancer history and no active cancer at baseline were excluded from this meta-analysis. Funded by Bristol-Myers Squibb and Pfizer Inc. Ethical approval: not reported Conflict of interest: more than one author reported financial COI ITT: "All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented."
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with the use of an interactive voice-response system"
Allocation concealment (selection bias)	Low risk	Quote: "interactive voice-response system" Comment: Definitely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "AMPLIFY was a randomised, double-blind trial." Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All efficacy and safety outcomes were adjudicated by an independent committee blinded to treatment assignment." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information about follow-up in the cancer subgroup reported comment: probably complete follow-up
Free of selective reporting?	Low risk	Study not registered. All outcomes listed in the protocol and methods section of this study were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit

Agnelli 2020 (Caravaggio)

Study characteristics

Methods	Multinational, randomized, investigator-initiated, open-label, non-inferiority trial.
Participants	1155 patients with active cancer from 119 centers in 9 European countries, Israel and the United States. Mean age 67.2 years, 49.2% male, 68% had metastatic disease, 9.2% had previous VTE.

Agnelli 2020 (Caravaggio) (Continued)

Both solid and hematological malignancy. The most frequent solid tumours were: colorectal (about 20%), lung (about 17%) and breast (about 13%).

Interventions	<p>Intervention: Apixaban (10 mg twice daily for 7 days and 5 mg twice daily) for a total of 6 months</p> <p>Control: Dalteparin (200IU per kilogram of body weight once daily for the first months, after which the dose was reduced to 150IU per kilogram daily).</p> <p>Discontinued treatment: 38/ 576 (6.6%) in the intervention arm and 48/579 (8.3%)</p>
Outcomes	<p>Duration of follow-up for the following outcomes: 6 months</p> <ul style="list-style-type: none"> All-cause mortality (at 7 months) Recurrent VTE, DVT, PE Major bleeding (gastrointestinal and nongastrointestinal) Clinically relevant non-major bleeding <p>Screening test for DVT/PE: CT pulmonary angiography.</p> <p>Diagnostic test for DVT/PE: For DVT ultrasonography, venography, CT venography, or MR venography. For PE CT pulmonary angiography/angiogram or VQ scan.</p>
Notes	<ul style="list-style-type: none"> Funded by Bristol-Myers Squibb and Pfizer Inc. The Bristol-Myers Squibb–Pfizer Alliance played no role in the design or conduct of the trial, the collection or analysis of the data, or the review or editing of the manuscript. Ethical approval: The protocol and its amendments were approved by the ethics committee at each trial center. Conflict of interest: More than one author reported reported financial conflict of interest ITT: No formal interim analysis was planned. The primary efficacy data set (modified intention-to-treat population) and safety data set consisted of all the patients who had undergone randomization and received at least one dose of a trial drug. The secondary efficacy data set consisted of all the patients who had undergone randomization (intention-to-treat population) along with the per-protocol population; the latter consisted of all the patients in the intention-to-treat population who completed the trial in full compliance with the protocol and without any major deviation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was centrally performed through an interactive online system and stratified according to..."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was centrally performed through an interactive online system and stratified according to..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "This trial was a multinational, randomized, controlled, investigator-initiated, open-label, noninferiority trial with blinded adjudication of the outcomes"</p> <p>Comment: probably not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions)</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This trial was a multinational, randomized, controlled, investigator-initiated, open-label, noninferiority trial with blinded adjudication of the outcomes"
Incomplete outcome data (attrition bias)	Low risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (24/585 (4.1%)) and event rate (135/585)

Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer (Review)

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Agnelli 2020 (Caravaggio) (Continued)

All outcomes		(24%)) for the main outcome-mortality. Similar for the control arm: rate of participants with missing data (17/585 (3%)) and event rate (153/568 (27%)).
Free of selective reporting?	Low risk	All outcomes listed in the methods section of this study were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit.

Cesarone 2003
Study characteristics

Methods	Randomized trial (abstract)
Participants	199 participants with cancer with DVT 17 dropouts, 182 participants completed study
Interventions	Intervention: enoxaparin 100 IU/kg twice daily × 3 months Control: coumadin (target INR 3) × 3 months Discontinued treatment: 17/199 (8.5%) in both arms
Outcomes	Duration of follow-up for the following outcomes: 3 months <ul style="list-style-type: none">• Mortality• Major bleeding• Recurrent DVT or PE but no data available Screening test for DVT/PE: not reported Diagnostic test for DVT/PE: ultrasound
Notes	<ul style="list-style-type: none">• Funding: not reported• Ethical approval: not reported• Conflict of interest: not reported• ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised outpatient trial" Comment: probably generated sequence randomly
Allocation concealment (selection bias)	High risk	Not reported Comment: probably not done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported (oral vs SC intervention) Comment: probably not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential

Cesarone 2003 (Continued)

		dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported Comment: probably not blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison between rate of participants with missing data (17/199 (8.5%)) and event rate for mortality 1/185 (0.5%) and for major outcome 19/185 (10%) across both arms
Free of selective reporting?	High risk	Quote: "in the OC [oral coumadin] group 14 subjects (16.3%) experienced one major outcome event compared with 5 patients (5.2%) out of 96 in the LMWH" Outcomes mentioned in the methods section (DVT, PE, major bleeding) not reported in the results section
Free of other bias?	High risk	Study not reported as stopped early for benefit. The full-text of the study was never published.

Deitcher 2006 (ONCENOX)

Study characteristics

Methods	Randomized clinical trial
Participants	102 participants with active cancer with DVT, PE, or both 85% Caucasian, mean age 64 years, 46% male, 8.7% had previous VTE
Interventions	Intervention: enoxaparin 1 mg/kg twice daily × 5 days followed by 1.0-1.5 mg/kg daily × 175 days (group 1a); enoxaparin 1.5 mg/kg daily × 175 days (group 1b) Control: enoxaparin for a minimum of 5 days and until achievement of a stable INR 2-3 on oral warfarin begun on day 2 of enoxaparin and continued for a total of 180 days of anticoagulation Cointervention: chemotherapy, radiation therapy, or both (not better specified) Discontinued treatment: 43/98 (63%) in the intervention arm and 21/34 (61%) in the control arm
Outcomes	Duration of follow-up for the following outcomes: 1 year <ul style="list-style-type: none"> • Mortality • Symptomatic recurrent VTE • Major bleeding • Minor bleeding Diagnostic test for DVT/PE: not reported
Notes	<ul style="list-style-type: none"> • Funding: Aventis Pharmaceutical • Ethical approval: "The appropriate institutional review board at each investigative site approved this study." • Conflict of interest: not reported • ITT: "patients in the intent-to-treat population"

Deitcher 2006 (ONCENOX) (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated" Comment: probably generated sequence randomly
Allocation concealment (selection bias)	High risk	Not reported Comment: probably not done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label trial Comment: probably not blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (15/68 (22%)) and event rate (22/53 (41%)) for the main outcome-mortality. Similar for the control arm: rate of participants with missing data (2/34 (6%)) and event rate (11/32 (34%)).
Free of selective reporting?	Low risk	Study not registered and no published protocol identified. All relevant outcomes listed in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit

El Mokadem 2020
Study characteristics

Methods	Randomized clinical study.
Participants	138 participants with active cancer and acute VTE from the oncology outpatient clinic of Beni-Suef University hospital Egypt. Mean age 60 years; 42% men, 84% had metastatic disease, 100% solid malignancy, 42% had colon cancer
Interventions	Intervention: Apixaban 10 mg twice daily dose for seven days followed by apixaban 5mg twice daily. Apixaban dose was adjusted to be 2.5mg twice daily in patients with serum creatinine 1.5 mg/dL, elderly patients 80 years or those with body weight 60 kg. Apixaban 10 mg twice daily for seven days followed by 5 mg twice daily for six months. Control: Enoxaparin (1 mg/kg/SC every 12 h). Discontinued treatment: 4/69 (5.8%) in the intervention arm and 8/69 (11.6%) in the control arm
Outcomes	Duration of follow-up for the following outcomes: 6 months • Mortality

El Mokadem 2020 (Continued)

- Recurrence DVT
- Recurrence PE
- Major bleeding
- Minor bleeding

Screening test for DVT/PE: venous doppler ultrasound.

Diagnostic test for DVT/PE: venous doppler ultrasound.

Notes

- Not funded.
- Ethical approval: The protocol was approved by the ethics committee.
- Conflict of interest: The authors declare no competing financial interest.
- ITT: The intention-to-treat analysis defined included all the patients who had undergone randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer based program (Random number generators) using Math.random".
Allocation concealment (selection bias)	High risk	Not reported. Comment: probably not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Comment: probably not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Comment: probably not blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (4/69 (5.7%)) and event rate (3/50 (6%)) for the outcome recurrent VTE. Similar for the control arm: rate of participants with missing data (8/68 (11.6%)) and event rate (5/50 (10%)).
Free of selective reporting?	Low risk	All outcomes listed in the methods section of this study were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit. Monocentric study.

Hull 2006 (LITE)

Study characteristics

Methods	Randomized clinical trial
Participants	200 participants with cancer (solid or hematologic) with proximal DVT with or without PE

Hull 2006 (LITE) (Continued)

Minimum age 18 years, minimum life expectancy 3 months, 50% men, 19% had previous VTE

Interventions	<p>Interventions: tinzaparin 175 anti-Xa/kg SC daily for 12 weeks</p> <p>Control: UFH either 5000 U or 80 U/kg for 5 days followed by VKAs (target INR 2-3) for 12 weeks</p> <p>Discontinued treatment: 1/100 (1%) in the intervention arm and 1/100 (1%) in the control arm</p>
Outcomes	<p>Duration of follow-up for the following outcomes: 12 months</p> <ul style="list-style-type: none"> • Mortality at 3 and 12 months • Recurrent VTE evaluated at 3 and 12 months • Bleeding (major and minor) evaluated at 3 months • Thrombocytopenia evaluated at 3 months <p>Screening test for DVT/PE: not reported</p> <p>Diagnostic test for recurrent VTE: venography or compression ultrasonography</p>
Notes	<ul style="list-style-type: none"> • Funding: Canadian Institute for Health Research, industry grant, Leo Pharmaceutical, Pharmion Pharmaceutical and DuPont Pharmaceutical • Ethical approval: "The protocol was approved by the institutional review board at each center." • Conflict of interest: not reported • ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer-derived randomised treatment schedule was used; within the each stratum, the randomised schedule was balanced in blocks of 2 and 4."
Allocation concealment (selection bias)	High risk	<p>Not reported</p> <p>Comment: probably not concealed</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Open-label trial</p> <p>Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Adjudication was made by 2 committee members not involved in the patient's care, and disputes were resolved independently by a third. Members of the committee were unaware of the patients' treatment assignments."</p> <p>Comment: probably yes</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (1/100 (1%)) and event rate (20/99 (20%)) for the outcome mortality. Similar for the control arm: rate of participants with missing data (1/100 (1%)) and event rate 19/99 (19%).
Free of selective reporting?	Low risk	Study not registered. No published protocol identified but a protocol was clearly mentioned in the discussion. All relevant outcomes listed in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit

Hull 2006 (LITE) (Continued)

No other bias suspected

Lee 2003 (CLOT)
Study characteristics

Methods	Randomized clinical trial
Participants	676 participants with active cancer and with DVT, PE, or both; ECOG 1 or 2 Mean age 63 years, 49% male, 11% had history of DVT/PE
Interventions	Intervention: dalteparin 200 IU/kg daily × 1 month followed by 150 IU/kg daily × 5 months Control: dalteparin 200 IU/kg daily × 5-7 days followed by warfarin or acenocoumarol (target INR 2-3) × 6 months; 46% of time on target Discontinued treatment: 2/338 (0.5%) in the intervention arm and 2/338 (0.5%) in the control arm
Outcomes	Duration of follow-up for the following outcomes: 6 months <ul style="list-style-type: none"> • Mortality • Symptomatic recurrent DVT and PE • Clinically overt bleeding (both major bleeding and any bleeding) Screening test for DVT/PE: not reported Diagnostic test for DVT: ultrasonography, venography Diagnostic test for PE: lung scan, angiography, autopsy
Notes	<ul style="list-style-type: none"> • Funding: Pharmacia • Ethical approval: the study protocol was reviewed and approved by the institutional review boards of each participating center • Conflict of interest: More than one author reported financial conflict of interest. • ITT: "analysis was performed according to intention to treat principle."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomizations was stratified according to the clinical center and centralized at the coordinating and methods center."
Allocation concealment (selection bias)	Low risk	Quote: "randomizations was stratified according to the clinical center and centralized at the coordinating and methods center."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential

Lee 2003 (CLOT) (Continued)

		dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all suspected events were reviewed by a central adjudication committee whose members were unaware of the patient's treatment assignments." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (2/338 (0.5%)) and event rate (120/336 (38.7%)) for the outcome mortality. Similary for the control arm: rate of participants with missing data 2/338 (0.5%)) and event rate 136/336 (40.4%)).
Free of selective reporting?	Low risk	Study not registered and no published protocol identified. All relevant outcomes listed in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Lee 2015 (CATCH)

Study characteristics

Methods	Phase III, multinational, concealed, randomized, active-controlled, open-label trial with blinded adjudication
Participants	900 randomized participants (adults with active cancer and acute proximal DVT, PE, or both) Mean age 59%, 40% men, 22% gynecologic cancer
Interventions	Intervention: LMWH (tinzaparin) 175 IU/kg SC once daily for 180 days (almost 6 months) Control: VKA (warfarin) for 6 months, overlapping with tinzaparin 175 IU/kg once daily (first 5-10 days and until INR > 2 for 2 consecutive days) Discontinued treatment: 140/449 (%) in the intervention arm and 172/451 (%) in the control arm
Outcomes	Duration of follow-up for the following outcomes: every 30 days until day 180 <ul style="list-style-type: none"> • Symptomatic DVT • Symptomatic non-fatal PE • Fatal PE • Incidental proximal DVT (popliteal vein or higher) • Incidental proximal PE (segmental arteries or larger) Duration of follow-up for the following outcomes: until 1 month following last dose of study treatment <ul style="list-style-type: none"> • All-cause mortality • Major bleeding • Clinically relevant non-major bleeding • Heparin-induced thrombocytopenia Screening test for DVT/PE: not reported Diagnostic test for DVT: ultrasonography, venography, CT venography or magnetic resonance venography

Lee 2015 (CATCH) (Continued)

Diagnostic test for PE: ventilation/perfusion scintigraphy, standard pulmonary angiography or CT

Notes

- NCT01130025
- Funding: LEO Pharma
- Ethical approval: "Institutional ethics approval was obtained at each participating center."
- Conflict of interest: More than one author reported financial COI
- ITT: "patients were randomised and included in intention-to-treat efficacy and safety analysis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "treatment assignment was planned according to a computer-generated randomisation schedule 1:1 in a ratio."
Allocation concealment (selection bias)	Low risk	Quote: "concealed until individual randomisation using an interactive voice-response system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Members of a central, independent adjudication committee, who were unaware of the study treatment assignments, reviewed and adjudicated all suspected cases of recurrent VTE, heparin-induced thrombocytopenia (HIT), bleeding events, and causes of death."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (33/449 (7.3%)) and event rate (6.9%)) for the outcome recurrent VTE. Similary for the control arm: rate of participants with missing data (50/451 (11%)) and event rate 136/336 (10%))
Free of selective reporting?	High risk	Protocol available. Not all outcomes listed in the protocol were reported on (such as other assessments: post-thrombotic syndrome, HRQoL, VTE risk factors, healthcare resource utilization).
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Lopez-Beret 2001

Study characteristics

Methods	Randomized clinical trial
Participants	35 participants with known malignancy; treated for symptomatic DVT of the lower limbs

Lopez-Beret 2001 (Continued)

Minimum age 18 years, mean age 65.7 years

Interventions	Intervention: nadroparin 1.025 AXa IU/10 kg twice daily for 3 days then randomised to nadroparin 1.025 antiXa IU/10 kg twice daily After the 3rd month, nadroparin was switched to once daily Control: nadroparin 1.025 AXa IU/10 kg twice daily for 3 days then randomised to acenocoumarol (target INR 2-3) for 3-6 months. . 68% of INR values were on target Discontinued treatment: not reported	
Outcomes	Duration of follow-up for the following outcomes: 12 months <ul style="list-style-type: none">• Mortality• Symptomatic recurrence or progression of VTE• Bleeding Screening test for DVT/PE: not reported Diagnostic test for DVT: duplex scan examination	
Notes	<ul style="list-style-type: none">• Funding: not reported• Ethical approval: "The study protocol was approved by the Hospital Ethics Committee"• Conflict of interest: "Competition of interest: nil."• ITT: not reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were allocated at random on third day to receive a LMWH or an OA [oral anticoagulant]" Comment: Probably generated sequence randomly
Allocation concealment (selection bias)	High risk	Not reported Comment: probably not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "It was not possible to use a double design for the study" Comment: definitely not blinded; knowledge of the assigned intervention may lead to differential behaviours across intervention groups (for example, differential drop-out, differential cross-over to an alternative intervention, or differential administration of co-interventions)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the final allocation of all potential outcome events, including deaths, was made by an independent panel of physicians" Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information about follow-up in the cancer subgroup was reported Comment: assumed complete follow-up
Free of selective reporting?	Low risk	Study not registered and no published protocol identified. All relevant outcomes listed in the methods section are reported on in the results section

Lopez-Beret 2001 (Continued)

Free of other bias?	Low risk	Study not reported as stopped early for benefit
		No other bias suspected

Mazilu 2014 (OVIDIUS)
Study characteristics

Methods	Randomized controlled trial (abstract)
Participants	46 participants with paraneoplastic DVT
Interventions	Intervention: Fixed-dose dabigatran (according to individual creatinine clearance) Control: Adjusted-dose acenocoumarol (according to individual INR determined monthly) Discontinued treatment: not reported
Outcomes	Duration of follow-up for the following outcomes: 6 months <ul style="list-style-type: none"> Mortality Combined outcome major bleeding or recurrent thrombosis Screening test for DVT/PE: not reported Diagnostic test for DVT/PE: not reported
Notes	<ul style="list-style-type: none"> Funding: not reported Ethical approval: not reported Conflict of interest: not reported ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "we randomised" Comment: probably generated sequence randomly
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Mazilu 2014 (OVIDIUS) (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Free of selective reporting?	Unclear risk	Study not registered and no published protocol identified
Free of other bias?	Unclear risk	Study not reported as stopped early for benefit No other bias suspected

McBane 2019 (ADAM-VTE)
Study characteristics

Methods	Randomized, open-label, investigator-initiated, IV phase, multicenter, superiority trial.
Participants	300 patients from 28 center in the United States. Mean age 64 years; 48% men, 65% had metastatic disease, 36% had DVT at baseline, 40% had PE at baseline, 6,5% had previous VTE. Both solid and hematological malignancy. The most frequent solid tumours were: colorectal (about 16%), lung (about 17%) and pancreatic (about 16%).
Interventions	Intervention: Apixaban 10 mg twice daily for seven days followed by 5 mg twice daily for six months. Control: Dalteparin (200 IU/kg for one month followed by 150 IU/kg once daily) for six months. Discontinued treatment: 20/150 (13.3%) in the intervention arm and 37/150 (24.7%)
Outcomes	Duration of follow-up for the following outcomes: 6 months <ul style="list-style-type: none">Major bleedingClinically relevant non-major bleedingAny recurrence of: DVT, PE, fatal PE and arterial thromboembolismMortality Screening test for DVT/PE: surveillance related imaging Diagnostic test for DVT: duplex ultrasonography and venography and CT or MRI. Diagnostic test for PE: CT, MR, pulmonary angiography or VQ imaging.

Notes

- Funded by a grant from Bristol-Myers Squibb and Pfizer Inc.
- Ethical approval: The protocol and its amendments were approved by the ethics committee at each trial center.
- Conflict of interest: The authors declare no competing financial interest.
- ITT: The intention-to-treat analysis defined included all the patients who had undergone randomization and received at least one dose of the assigned treatment.

Risk of bias

McBane 2019 (ADAM-VTE) (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using an established interactive Web-based system that is used for all clinical trials conducted through the Mayo Clinic Cancer Center and through the ACCRU infrastructure."
Allocation concealment (selection bias)	Low risk	Not reported Comment: probably not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Comment: probably not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Comment: probably not blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (20/150 (13.3%)) and event rate (23/130 (17.7%)) for the outcome mortality. Similar for the control arm: rate of participants with missing data 37/150 (24.6%) and event rate 15/113 (13.2%)
Free of selective reporting?	Low risk	All outcomes listed in the methods section of this study were reported on in the results section.
Free of other bias?	Low risk	Quote: "Study not reported as stopped early for benefit".

Meyer 2002 (CANTHANOX)
Study characteristics

Methods	Randomized clinical trial
Participants	146 participants with cancer (solid or hematologic; active or in remission but on treatment); with PE, DVT, or both Minimum age 18 years, minimum life expectancy 3 months, mean age 65.5 years; 45% men
Interventions	Intervention: enoxaparin 1.5 mg/kg daily × 3 months Control: enoxaparin 1.5 mg/kg daily × 4 days followed by warfarin (target INR 2-3) × 3 months; 41% of time on target The continuation and nature of anticoagulant treatment after 3 months were left to the attending physician. Discontinued treatment: 4/71 (5.6%) in the intervention arm and 4/75 (5.3%) in the control arm
Outcomes	Duration of follow-up for the following outcomes: 3 and 6 months

Meyer 2002 (CANTHANOX) (Continued)

- Mortality
- Asymptomatic VTE
- Symptomatic and objectively confirmed recurrent VTE
- Major bleeding
- Minor bleeding
- Thrombocytopenia

Screening test for VTE: radiologic surveillance

Diagnostic test for DVT: venography or compression ultrasonography

Diagnostic test for PE: pulmonary angiography or ventilation/perfusion scanning

Notes

- Funding: Aventis, Assistance Publique, Hospitaux de Paris
- Ethical approval: "the ethics committee of Saint-Louis Hospital in Paris approved the study protocol."
- Conflict of interest: not reported
- ITT: "analysis was performed on an intention to treat basis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocation was balanced at each center in blocks of 4."
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was performed using pre-sealed treatment boxes."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all potential outcome events were assessed by an independent adjudication committee whose members were unaware of the treatment assignment." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (4/71 (5.6%)) and event rate (11.3%) for the outcome mortality. Similar for the control arm: rate of participants with missing data (4/75 (5.3%)) and event rate (22.7%)
Free of selective reporting?	Low risk	Study not registered and no published protocol identified. All relevant outcomes listed in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Prins 2014 (EINSTEIN)

Study characteristics

Methods	Subgroup analysis of participants with active cancer in the EINSTEIN-DVT and EINSTEIN-PE phase 3 open-label multicenter trials
Participants	459 participants with active cancer, symptomatic DVT and PE enrolled from 314 centers in 38 countries Median age 65-75 years, 56% males, 22% had metastatic disease, 26% received chemotherapy
Interventions	Intervention: rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily for 3, 6 or 12 months Control: enoxaparin 1 mg/kg twice daily started within 48 hours after randomization and discontinued when the INR was ≥ 2 for 2 days consecutively and the participant had received ≥ 5 days and warfarin or acenocoumarol (adjusted to maintain INR 2-3) for 3, 6 or 12 months Discontinued treatment: not reported for cancer subgroup
Outcomes	Duration of follow-up was for the intended treatment period (3, 6 or 12 months) at 1 week, 2 weeks, 1 month and monthly thereafter for the following outcomes: <ul style="list-style-type: none"> All-cause mortality Symptomatic recurrent VTE Major bleeding Clinically relevant non-major bleeding (using validated measure of treatment satisfaction – the Anti-Clot Treatment Scale (ACTS)) Screening test for DVT/PE: not reported Diagnostic test for DVT/PE: echo-doppler for DVT and spiral CT scan for PE

Notes

- The EINSTEIN-DVT and EINSTEIN-PE studies registered at ClinicalTrials.gov, numbers NCT00440193 and NCT00439777
- Funding: Bayer HealthCare Pharmaceuticals and Janssen Research & Development
- Ethical approval: "The study protocols were reviewed and approved by the institutional review boards of each participating centre."
- Conflict of interest: More than one author reported financial COI
- ITT: "we did efficacy and mortality analyses on an intention-to-treat basis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done separately for participants with deep-vein thrombosis and pulmonary embolism (with or without deep-vein thrombosis), with a computerised voice-response system, and was stratified according to country and the intended treatment duration (3, 6, or 12 months), as decided locally before randomisation."
Allocation concealment (selection bias)	Low risk	Quote from protocol: "Allocation to treatment will be done centrally by inter-active voice response system for Einstein-DVT and Einstein-PE, separately."

Prins 2014 (EINSTEIN) (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected outcomes were classified by an independent blinded adjudication committee." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information about follow-up in the cancer subgroup was reported.
Free of selective reporting?	Low risk	Study registered and published protocol identified. All outcomes listed in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Raskob 2016 (HOKUSAI)

Study characteristics

Methods	Subgroup analysis of participants with cancer or history of cancer in the HOKUSAI trial Randomized, double-blind, double-dummy, multicenter trial
Participants	208 participants with active cancer at baseline from 439 centers in 37 countries (208 with active cancer prespecified categorization made by study physician at enrolment; 162 with active cancer post-hoc classification) Mean age 66 years, 50% male, 6% with metastatic disease, 10% receiving systemic cancer-drug therapy, excludes 77 participants with non-melanoma skin cancer
Interventions	All participants received initial therapy with open-label enoxaparin or UFH for ≥ 5 days Intervention: edoxaban 60 mg once per day or 30 mg once per day + dummy warfarin for ≥ 3 months Control: warfarin concurrently started with the study regimen of heparin (adjusted to maintain INR 2-3) + dummy edoxaban for ≥ 3 months. Enoxaparin was discontinued when the INR was ≥ 2 for 2 days consecutively and the participant had received ≥ 5 days of enoxaparin treatment Initial therapy with open-label enoxaparin or UFH for ≥ 5 days Discontinued treatment: not reported for the active cancer subgroup
Outcomes	Duration of follow-up for the following outcomes: 12 months <ul style="list-style-type: none"> • Mortality • Adjudicated symptomatic recurrent VTE (defined as the composite of DVT or non-fatal or fatal PE) • First occurrence of symptomatic recurrent VTE • Major bleeding • Clinically relevant non-major bleeding

Raskob 2016 (HOKUSAI) (Continued)

Screening test for DVT/PE: not reported

Diagnostic test for DVT/PE: not reported

Notes

- Study details obtained from original HOKUSAI methodology report published in Journal of Thrombosis and Haemostasis July 2013
- Study registered at ClinicalTrials.gov, number: NCT00986154
- Funding: Daiichi Sankyo
- Ethical approval: "The institutional review board at each centre approved the protocol."
- Conflict of interest: More than one author reported financial COI
- ITT: "use of a modified intention-to-treat analysis"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "local site study physician or study coordinator did the randomisation using an interactive web-based system, with stratification according to the qualifying diagnosis (deep-vein thrombosis or pulmonary embolism), presence or absence of temporary risk factors, and the dose of edoxaban."
Allocation concealment (selection bias)	Low risk	Quote: "The investigator provides this information to an interactive telephone and web-based management system (IXRS; Almac, Yardley, PA, USA), which randomly assigns the participant to the LMWH/edoxaban or standard therapy group, and allocates the appropriate drug supply. The day of randomisation is day 1 of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "central independent adjudication of all suspected outcomes" Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information about follow-up in the cancer subgroup was reported.
Free of selective reporting?	Low risk	Study registered and published protocol identified. All outcomes reported in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Raskob 2018 (HOKUSAI)
Study characteristics

Methods	Randomized, open-label, non-inferiority, multicenter clinical trial
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Raskob 2018 (HOKUSAI) (Continued)

Participants	1050 people with active cancer from 114 centers in 13 countries with acute symptomatic or incidentally detected DVT or PE Median age 64 years, 51.7% males, 53% had metastatic disease, 72.4% received cancer treatment within previous 4 weeks "anticancer drug therapy (cytotoxic, hormonal, targeted, or immunomodulatory), radiation therapy, surgery, or a combination of these therapies."	
Interventions	<p>All patients received initial therapy with LMWH for ≥ 5 days. Duration of treatment: 6-12 months</p> <p>Intervention: LMWH for ≥ 5 days followed by oral edoxaban 60 mg once daily</p> <p>Control: dalteparin 200 IU per kilogram bodyweight SC once daily for 1 month followed by dalteparin 150 IU per kilogram once daily</p> <p>Discontinued treatment: 48/525 (9.1%) in the intervention arm and 34/525 (6.4%)</p>	
Outcomes	<p>Duration of follow-up for the following outcomes: 12 months (on day 31 after randomization and months 3, 6, 9 and 12)</p> <ul style="list-style-type: none">• Recurrent VTE• Death from any cause• Major bleeding• Clinically relevant non-major bleeding• Recurrent DVT• Recurrent PE• Event-free survival <p>Screening test for DVT/PE: "Incidental venous thromboembolism was defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thromboembolism."</p> <p>Diagnosis test for DVT/PE: "Appropriate diagnostic tests, laboratory tests, or both were required in people with suspected outcome events...aminotransferase and bilirubin levels."</p>	
Notes	<ul style="list-style-type: none">• Study rationale and design of the HOKUSAI VTE-cancer study published in Journal of Thrombosis and Haemostasis August 2015.• Funding: Daiichi Sankyo• Ethical approval: "The institutional review board at each participating center approved the protocol." and "All the patients provided written informed consent."• Conflict of interest: More than one author reported financial conflict of interest.• ITT: "The analysis of the primary outcome was performed in the modified intention-to-treat population, which included all the patients who had undergone randomisation and received at least one dose of the assigned treatment."	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with the use of an interactive Web-based system, with stratification according to whether risk factors for bleeding were present and whether the patient met the criteria to receive a lower dose of edoxaban."

Raskob 2018 (HOKUSAI) (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with the use of an interactive Web-based system, with stratification according to whether risk factors for bleeding were present and whether the patient met the criteria to receive a lower dose of edoxaban." Comment: probably concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label trial" Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all events were adjudicated by a committee whose members were unaware of the treatment assignments." Comment: probably blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (16/525 (3.04%)) and event rate (34/509 (6.7%)) for the outcome recurrent VTE. Similar for the control arm: rate of participants with missing data (59/525 (11.2%)) and event rate (46/507 (9.07%))
Free of selective reporting?	Low risk	Study registered and published protocol identified. All outcomes reported in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Romera 2009
Study characteristics

Methods	Randomized trial
Participants	69 participants with cancer (study subgroup) and symptomatic proximal DVT Minimum age 18 years, mean age 61 years
Interventions	Intervention: tinzaparin SC fixed-dose 175 IU anti-Xa per kg once daily for 6 months Control: acenocoumarol 3 mg orally, which was subsequently adjusted to achieve an INR of 2-3, tinzaparin was given until the INR reached ≥ 2 on 2 consecutive measurements. All participants received tinzaparin SC in a fixed dose of 175 IU anti-Xa per kg once daily Discontinued treatment: not reported for cancer subgroup
Outcomes	Duration of follow-up for the following outcomes: 12 months • VTE (no data available for other outcomes in participants with cancer)

Romera 2009 (Continued)

Screening test for DVT/PE: not reported

Diagnostic test for DVT: duplex ultrasonography

Notes

- Funding: Hospital Universitari de Bellvitge, LEO Pharma
- Ethical approval: "The protocol was approved by the institutional review board at each centre and by the regulatory authorities."
- Conflict of interest: At least one author reported financial COI.
- ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to either LMWH group SQ [subcutaneous] or LMWH followed by acenocoumarol" Comment: probably generated sequence randomly
Allocation concealment (selection bias)	High risk	Not reported Comment: probably not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study Comment: probably not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the ultrasonic evaluations were performed blindly;" "All objective diagnostic tests were interpreted by specialists who were not involved in the study." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information about follow-up in the cancer subgroup reported Comment: assumed complete follow-up
Free of selective reporting?	Low risk	Study was registered (NCT00689520). All relevant outcomes listed on the registration page and the methods section of the published manuscript were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

Schulman 2015 (RECOVER I-II)
Study characteristics

Methods	Subgroup analysis of participants with cancer at baseline, diagnosed with cancer during the study, or history of cancer pooled from the RE-COVER and RE-COVER II trials
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Schulman 2015 (RECOVER I-II) (Continued)

Randomized, double-blind, double-dummy, multicenter trials

Participants	<p>221 participants with active cancer at baseline and acute symptomatic proximal DVT or PE, from 228 clinical centers in 29 countries</p> <p>Mean age 63.5 years, 61% male, 8% with metastatic cancer</p>
Interventions	<p>All participants received parenteral anticoagulant (UFH, LMWH or fondaparinux) until the INR or sham INR became ≥ 2 for 2 consecutive days.</p> <p>Intervention: dabigatran fixed-dose 150 mg twice daily and warfarin-placebo</p> <p>Control: dose-adjusted warfarin therapy, after initial parenteral anticoagulation and dabigatran-placebo</p> <p>Cointervention: "initial treatment was with a parenteral anticoagulant (UFH, LMWH, or fondaparinux) until INR or sham INR became at least 2.0 for two consecutive days."</p> <p>Discontinued treatment: not reported</p>
Outcomes	<p>Duration of follow-up for the following outcomes: 6 months (assessed at 7 days and monthly thereafter)</p> <ul style="list-style-type: none"> All-cause mortality Recurrent VTE Major bleeding Non-major clinically relevant bleeding <p>Screening test for DVT/PE: not reported</p> <p>Diagnosis test for DVT/PE: not reported</p>
Notes	<ul style="list-style-type: none"> RECOVER and RECOVER II trials registered at ClinicalTrials.gov, numbers NCT00291330 and NCT00680186 Funding Sources: Boehringer Ingelheim Ethical approval: "The institutional review board at each participating clinical centre approved the original studies" Conflict of interest: At least one author reported financial COI ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "We used a computer generated randomisation scheme with variable block sizes" (from main study RECOVER-I).</p> <p>"Patients were randomised by use of an interactive voice response system and a computer-generated randomisation scheme in blocks of 4" (from main Study RECOVER-II).</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "If the patient was enrolled from the RE-COVER study or the RE-COVER II study, a point-of-care coagulometer with encrypted INR results was used to guide the transition so that the patients and investigators would remain unaware of the initial treatment."</p>

Schulman 2015 (RECOVER I-II) (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "central adjudication committee" Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up (correspondence with author)
Free of selective reporting?	Low risk	Study registered and published protocol identified. All outcomes reported in the methods section were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

van Doormaal 2010 (Van Gogh DVT trial)

Study characteristics

Methods	Post hoc analysis in the subgroup of participants with cancer included in the Van Gogh DVT clinical trial randomized, open-label noninferiority trial
Participants	284 participants with active cancer having acute symptomatic and objectively confirmed DVT involving the popliteal, femoral, iliac veins or the trifurcation of the calf veins, without symptomatic PE Quote: "no detailed information on cancer type and stage or co-medication was collected."
Interventions	Intervention: idraparinux 2.5 mg SC once-weekly × 3 or 6 months according to the decision of treating physician Control: standard treatment: tinzaparin, enoxaparin or intravenous heparin adjusted for the activated partial thromboplastin time ratio (ratio 1.5-2.5), followed by warfarin or acenocoumarol (INR 2-3), which was started within 24 hours after randomization. Cointervention: not reported Quote: "A total of 8% of all patients were randomised in the 3-month arm, and 92% in the 6-month treatment arm." Quote: "The duration of treatment was similar with a median of 183 days in both groups." 75% of participants completed the study medication Quote: "Of idraparinux recipients 48 patients (22%) stopped the study medication before the end of the study compared to 56 (28%) patients in the standard treatment arm." Discontinued treatment: not reported for subgroup of patients with active cancer
Outcomes	Duration of follow-up for the following outcomes: 6-month treatment period plus additional 3-month follow-up period (median 183 days in both groups) <ul style="list-style-type: none"> All-cause mortality (follow-up at 6 and 9 months)

van Doormaal 2010 (Van Gogh DVT trial) (Continued)

- Symptomatic objectively confirmed recurrent VTE: DVT (follow-up at 3 and 6 months), non-fatal or fatal PE (follow-up at 6 and 9 months)
- Clinically relevant major bleeding (follow-up at 3 and 6 months)
- Clinically relevant non-major bleeding (follow-up at 3 and 6 months)

Screening test for DVT/PE: not reported

Diagnostic test for DVT/PE: none reported in this manuscript, but available from Buller HR, *New England Journal of Medicine* 2007;357:1094-104

Diagnostic testing for PE: spiral computed tomography, pulmonary angiography

Diagnostic testing for DVT: ultrasonography, venography

Notes

- Funding: "The original trial was sponsored by Sanofi-Aventis. Their biostatisticians extracted the data of the present study."
- Ethical approval: "The protocols were approved by the institutional review board at each center."
- Conflict of interest: More than one author reported financial COI
- ITT: "The analyses were calculated in the intention to treat population."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After giving written informed consent, patients were randomly assigned to receive either idraparinux or standard therapy with the use of a computerized voice-response system" (from Buller HR, <i>New England Journal of Medicine</i> 2007;357:1094-104).
Allocation concealment (selection bias)	Low risk	Quote: "After giving written informed consent, patients were randomly assigned to receive either idraparinux or standard therapy with the use of a computerized voice-response system" (from Buller HR, <i>New England Journal of Medicine</i> 2007;357:1094-104).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All suspected outcomes were classified by an independent blinded adjudication committee." Comment: definitely blinded; knowledge of the assigned intervention may not have impacted the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information about follow-up in the cancer subgroup reported Comment: assumed complete follow-up
Free of selective reporting?	Low risk	Post-hoc analysis. Study registered and no published protocol identified. All relevant outcomes listed in the methods section were reported on in the results section.

van Doormaal 2010 (Van Gogh DVT trial) (Continued)

Free of other bias?	Low risk	Study not reported as stopped early for benefit
		No other bias suspected

Young 2018 (SELECT-D)
Study characteristics

Methods	Prospective, randomized, open-label, multicenter pilot trial
Participants	406 people with active cancer at baseline with VTE from 58 centers across the UK Mean age 67 years, 53% males, 38% early or locally advanced disease, 59% metastatic disease, 57% receiving chemotherapy, 10% receiving targeted therapy
Interventions	Duration of treatment: 6 months Intervention: rivaroxaban 15 mg twice daily for 3 weeks then 20 mg once daily, for 6 months in total Control: dalteparin 200 IU/kg daily, month 1 and 150 IU/kg, months 2-6 Discontinued treatment: not reported
Outcomes	Duration of follow-up for the following outcomes: 6 months <ul style="list-style-type: none">• Recurrent VTE• Mortality• Major bleeding• Clinically relevant non-major bleeding• Acceptability• Health economics Screening test for DVT/PE: compression ultrasound Diagnosis test for DVT/PE: compression ultrasound
Notes	<ul style="list-style-type: none">• Funding: Bayer PLC• Ethical approval: not reported• Conflict of interest: More than one author reported financial COI.• ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned centrally by telephoning Warwick Clinical Trials Unit. Consenting patients were randomly assigned at a one-to-one ratio using a computer-based minimization algorithm with..."

Young 2018 (SELECT-D) (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned centrally by telephoning Warwick Clinical Trials Unit. Consenting patients were randomly assigned at a one-to-one ratio using a computer-based minimization algorithm with..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Trial staff, participants, and investigators were not blinded to treatment allocation" Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of cointerventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Trial staff, participants, and investigators were not blinded to treatment allocation" Comment: probably not blinded; however, knowledge of the assigned intervention may not have impacted the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison in the intervention arm between rate of participants with missing data (17/203 (8.03%)) and event rate (48/186 (25.8%)) for the outcome mortality. Similar for the control arm: rate of participants with missing data (23/203 (11.3%)) and event rate (56/180 (31.1%))
Free of selective reporting?	Low risk	Study registered. All relevant outcomes listed in the methods section were reported on in the results section
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected

CT: computer tomography; COI: conflict of interest; DOAC: direct oral anticoagulant; DVT: deep venous thrombosis; ECOG: Eastern Cooperative Oncology Group; HRQoL: health-related quality of life; INR: international normalized ratio; ITT: intention to treat; IU: international unit; LMWH: low molecular weight heparin; MPD: missing participants data; PE: pulmonary embolism; SC: subcutaneous; U: unit; UFH: unfractionated heparin; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agnelli 2005	Not population of interest (surgical setting)
Alikhan 2003 (MEDENOX)	Not population of interest (people with cancer without VTE)
Auer 2011	Not population of interest (people with cancer without VTE)
Cohen 2006	Not population of interest (people with cancer without VTE)
Cohen 2007 (PREVENT)	Not population of interest (people with cancer without VTE)
Couban 2005	Not population of interest (people with cancer with CVC without VTE)
Eriksson 2005	Not population of interest (people without cancer)
Farred 2004	Not design of interest (review)

Study	Reason for exclusion
Ferretti 2005	Not design of interest (review)
Ferretti 2006	Not design of interest (review)
Fiessinger 2005	Outcome data for cancer subgroup not reported
Haas 2011	Not population of interest (people with cancer without VTE)
Hata 2016	Not population of interest (people with cancer without VTE)
Hull 2007	Outcome data for cancer subgroup not reported
Hull 2009	Outcome data for cancer subgroup not reported
Hyers 2005	Not design of interest (review)
Kakkar 2003	Not population of interest (patients without cancer)
Kakkar 2010 (CANBESURE)	Not population of interest (people with cancer without VTE)
Kakkar 2014 (SAVE-ABDO)	Not population of interest (people with cancer without VTE)
Khorana 2017 (PHACS)	Not population of interest (people with cancer without VTE)
King 2005	Not design of interest (retrospective)
Kovacs 2005	Not design of interest (observational)
Kucher 2005	Outcome data for cancer subgroup not reported
Larocca 2012	Not population of interest (people with cancer without VTE)
Lee 2005	Not design of interest (review)
Lee 2006	Not design of interest (review)
Levine 2003	Not design of interest (review)
Macbeth 2016 (FRAGMATIC)	Not population of interest (people with cancer without VTE)
Massicotte 2003	Outcome data for cancer subgroup not reported
Murakami 2002	Not population of interest (people with cancer without VTE)
Nagata 2015	Not population of interest (people with cancer without VTE)
Palumbo 2011	Not population of interest (people with cancer without VTE)
Pelzer 2015 (CONKO-004)	Not population of interest (people with cancer without VTE)
Pérez-de-Llano 2010	Outcome data for cancer subgroup not reported
Sakon 2010	Not population of interest (people with cancer without VTE)
Schulman 2003	Not intervention of interest (extended treatment)

Study	Reason for exclusion
Schulman 2006	Not population of interest (none of participants had cancer)
Schulman 2013 (RE-MEDY)	Not intervention of interest (extended treatment)
Siragusa 2010	Not intervention of interest: different duration of interventional drugs
Song 2014	Not population of interest (people with cancer without VTE)
Suarez Alvarez 2003	Not design of interest (not an RCT)
Vedovati 2014	Not population of interest (people with cancer without VTE)
Veiga 2000	Outcome data for cancer subgroup not reported
Verso 2008	Not population of interest (people with cancer without VTE)
Zheng 2014	Not population of interest (people with cancer without VTE)
Zwicker 2013 (MICROTEC)	Not population of interest (people with cancer without VTE)

DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; RCT: randomized controlled trial; VTE: venous thromboembolism.

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

[Kamphuisen 2010 \(Longheva\)](#)

Study name	PO-67 Long-term treatment for cancer patients with deep vein thrombosis or pulmonary embolism – a randomised controlled trial
Methods	Multicenter, multinational, randomized, open-label trial
Participants	Participants with malignancy (all types, solid and hematologic) who had received 6-12 months of anticoagulation for VTE and had an indication for continuing anticoagulation
Interventions	Intervention: weight-adjusted scheme of LMWH for 6 additional months, 65-75% of full therapeutic dose Control: VKA for 6 additional months
Outcomes	Symptomatic recurrent VTE (DVT and PE), all clinically relevant bleeding (i.e. major bleeding and other clinically relevant non-major bleeding), all-cause mortality
Starting date	August 2010
Contact information	Professor Pieter W Kamphuisen, telephone: 0031503612943, email: p.w.kamphuisen@umcg.nl
Notes	Status as of May 2021: Terminated (Due to slow inclusion of patients) Funding: University Medical Center Groningen NCT: NCT01164046

Karatas 2015

Study name	Rivaroxaban in the treatment of venous thromboembolism (VTE) in cancer patients
Methods	Randomized open-label phase III trial
Participants	Aged ≥ 18 years with active malignancy and newly diagnosed and objectively confirmed acute VTE
Interventions	Drug: rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily over 3 months Drug: LMWH in therapeutic dosage ($1-2 \times$ daily SC) according to standards of the individual study center, using licensed dosages
Outcomes	Primary outcome: participant-reported treatment satisfaction (convenience) with rivaroxaban in the treatment of acute VTE in people with cancer in comparison with the standard treatment with LMWH Secondary outcome: rate of VTE
Starting date	March 2016
Contact information	Dr Aysun Karatas, email: aysun.karatas@aio-studien-ggmbh.de
Notes	Status as of May 2021: Terminated (Recruitment was not as expected). Funding: AIO-Studien-gGmbH NCT02583191

Meyer 2016 (CASTA-DIVA)

Study name	Cancer associated thrombosis, a pilot treatment study using rivaroxaban (CASTA-DIVA)
Methods	Randomized, open-label trial
Participants	People with cancer aged > 18 years with objectively confirmed symptomatic VTE
Interventions	Intervention 1: dalteparin 200 IU/kg SC once daily for 1 month followed by 150 IU/kg SC once daily for 2 months Intervention 2: rivaroxaban 15 mg orally twice daily for 3 weeks followed by 20 mg once daily for 9 weeks
Outcomes	Primary outcome: symptomatic DVT, PE at 3 months Secondary outcome: major and clinically significant bleedings during the 3-month treatment period
Starting date	September 2016
Contact information	Guy Meyer, MD, email: guy.meyer@aphp.fr
Notes	Status as of May 2021: completed Funding: Assistance Publique – Hôpitaux de Paris NCT02746185

Ryun Park 2017 (PRIORITY)

Study name	A randomized phase II study to compare the safety and efficacy of dalteparin vs. rivaroxaban for cancer-associated venous thromboembolism (PRIORITY)
Methods	Multicenter, randomized, open-label phase II trial
Participants	Aged ≥ 18 years with confirmed locally advanced unresectable or metastatic active cancer and newly diagnosed DVT or PE
Interventions	Intervention 1: dalteparin 200 IU/kg SC once daily for 4 weeks followed by 150 IU/kg once daily for 20 weeks Intervention 2: rivaroxaban 15 mg orally twice daily for 3 weeks followed by 20 mg once daily for 21 weeks
Outcomes	Primary outcome: rate of clinical relevant bleeding Secondary outcome: total event of bleeding, time to event of bleeding, recurrent VTE
Starting date	May 2017
Contact information	Sook Ryun Park, MD, PhD, email: srpark@amc.seoul.kr
Notes	Status as of May 2021: recruiting Funding: Asan Medical Center NCT03139487

Schrag 2016 (CANVAS)

Study name	Direct oral anticoagulants (DOACs) versus LMWH $\pm$ warfarin for VTE in cancer (CANVAS)
Methods	Randomized, open-label trial
Participants	Aged ≥ 21 years with solid tumor cancer, lymphoma or myeloma, diagnosed with VTE < 30 days prior to study enrolment
Interventions	Intervention 1: DOAC Intervention 2: LMWH with or without transition to warfarin
Outcomes	Primary outcome: cumulative VTE recurrence Secondary outcome: major bleeding, burden of anticoagulation therapy, mortality
Starting date	December 2016
Contact information	Deborah Schrag, MD MPH, telephone: 617-582-8301, email: deb_schrag@dfci.harvard.edu
Notes	Status as of May 2021: completed Funding: Patient-Centered Outcomes Research Institute (PCORI) NCT NCT02744092

DOAC: direct oral anticoagulant; DVT: deep venous thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; SC: subcutaneous; VTE: venous thromboembolism.

DATA AND ANALYSES

Comparison 1. Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality (up to 6 months) (main analysis - active cancer)	4	1712	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.12]
1.2 All-cause mortality (time-to-event)	2	810	HR (IV, Random, 95% CI)	0.94 [0.74, 1.20]
1.3 Recurrent venous thromboembolism (up to 6 months) (main analysis - active cancer)	4	1712	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.44, 0.80]
1.4 Recurrent venous thromboembolism (time-to-event)	2	810	HR (IV, Random, 95% CI)	0.49 [0.31, 0.78]
1.5 Major bleeding (up to 6 months) (main analysis - active cancer)	4	1712	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.55, 2.12]
1.6 Minor bleeding (up to 6 months) (main analysis - active cancer)	4	1712	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.27]
1.7 Thrombocytopenia (up to 6 months) (main analysis - active cancer)	1	138	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.52, 1.69]

Analysis 1.1. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 1: All-cause mortality (up to 6 months) (main analysis - active cancer)

Analysis 1.2. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 2: All-cause mortality (time-to-event)

Analysis 1.3. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 3: Recurrent venous thromboembolism (up to 6 months) (main analysis - active cancer)

Analysis 1.4. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 4: Recurrent venous thromboembolism (time-to-event)

Analysis 1.5. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 5: Major bleeding (up to 6 months) (main analysis - active cancer) **Analysis 1.6. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 6: Minor bleeding (up to 6 months) (main analysis - active cancer)** **Analysis 1.7. Comparison 1: Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 7: Thrombocytopenia (up to 6 months) (main analysis- active cancer)** **Comparison 2. Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality (6-12 months)	4	1060	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Recurrent venous thromboembolism (6-12 months)	4	1050	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.34, 1.15]
2.3 Major bleeding (6-12 months)	4	1055	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.39, 1.53]
2.4 Minor bleeding (6-12 months)	4	1055	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.57, 1.23]

Analysis 2.1. Comparison 2: Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA), Outcome 1: All-cause mortality (6-12 months)

Analysis 2.2. Comparison 2: Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA), Outcome 2: Recurrent venous thromboembolism (6-12 months)

Analysis 2.3. Comparison 2: Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA), Outcome 3: Major bleeding (6-12 months)

Analysis 2.4. Comparison 2: Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA), Outcome 4: Minor bleeding (6-12 months)

Comparison 3. Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality (6 months)	5	2854	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.14]
3.2 Recurrent VTE (6 months)	5	2854	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.88]
3.3 Major bleeding (6 months)	5	2994	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.83, 1.73]
3.3.1 GI tract cancer	4	854	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.76, 2.84]
3.3.2 Non-GI tract cancer	4	1853	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.63, 1.73]
3.3.3 GI tract cancer not specified	1	287	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Major GI bleeding (6 months)	4	1838	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.62, 2.17]
3.5 Major upper GI bleeding (6 months)	4	1838	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.51, 2.76]
3.6 Major lower GI bleeding (6 months)	4	1838	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.43, 2.80]
3.7 Major non-GI bleeding (6 months)	4	1838	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.68]
3.8 Minor bleeding (6 months)	5	2854	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.15, 2.16]
3.9 Minor GI bleeding (6 months)	2	1495	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.41, 4.64]
3.10 Minor upper GI bleeding (6 months)	2	1495	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.04, 25.97]
3.11 Minor lower GI bleeding (6 months)	2	1495	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.72, 3.27]
3.12 Minor non-GI bleeding (6 months)	2	1495	Risk Ratio (M-H, Random, 95% CI)	2.37 [1.44, 3.89]

Analysis 3.1. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 1: All-cause mortality (6 months)

Study or Subgroup	DOAC		LMWH		Weight	Risk Ratio		Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI		M-H, Random, 95% CI	
Agnelli 2020 (Caravaggio)	135	561	153	568	38.1%	0.89 [0.73 , 1.09]			
El Mokadem 2020	0	50	0	50		Not estimable			
McBane 2019 (ADAM-VTE)	23	130	15	113	6.4%	1.33 [0.73 , 2.43]			
Raskob 2018 (HOKUSAI)	140	509	127	507	36.6%	1.10 [0.89 , 1.35]			
Young 2018 (SELECT-D)	48	186	56	180	18.8%	0.83 [0.60 , 1.15]			
Total (95% CI)		1436		1418	100.0%	0.97 [0.83 , 1.14]			
Total events:	346		351						
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 4.00$, $df = 3$ ($P = 0.26$); $I^2 = 25\%$									
Test for overall effect: $Z = 0.32$ ($P = 0.75$)									
Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 2: Recurrent VTE (6 months)

Analysis 3.3. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 3: Major bleeding (6 months)

Analysis 3.4. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 4: Major GI bleeding (6 months) **Analysis 3.5. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 5: Major upper GI bleeding (6 months)** **Analysis 3.6. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 6: Major lower GI bleeding (6 months)**

Analysis 3.7. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 7: Major non-GI bleeding (6 months)

Analysis 3.8. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 8: Minor bleeding (6 months)

Analysis 3.9. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 9: Minor GI bleeding (6 months)

Analysis 3.10. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 10: Minor upper GI bleeding (6 months)

Analysis 3.11. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 11: Minor lower GI bleeding (6 months)

Analysis 3.12. Comparison 3: Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 12: Minor non-GI bleeding (6 months)

Comparison 4. Idraparinux versus vitamin K antagonists (VKA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality (up to 6 months)	1	284	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.78, 1.59]
4.2 Recurrent VTE (up to 6 months)	1	270	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.16, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Major bleeding (up to 6 months)	1	270	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.35, 3.56]
4.4 Minor bleeding (up to 6 months)	1	270	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.30, 1.60]

Analysis 4.1. Comparison 4: Idraparinux versus vitamin K antagonists (VKA), Outcome 1: All-cause mortality (up to 6 months)

Analysis 4.2. Comparison 4: Idraparinux versus vitamin K antagonists (VKA), Outcome 2: Recurrent VTE (up to 6 months)

Analysis 4.3. Comparison 4: Idraparinux versus vitamin K antagonists (VKA), Outcome 3: Major bleeding (up to 6 months)

Analysis 4.4. Comparison 4: Idraparinux versus vitamin K antagonists (VKA), Outcome 4: Minor bleeding (up to 6 months)

ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Adjuvant therapy	A therapy given in addition to the primary treatment to decrease the risk of the cancer recurrence or to assist in the cure.
Anticoagulation	The process of hindering the clotting of blood especially by treatment with an anticoagulant.
Antithrombotic	Used against or tending to prevent thrombosis (clotting)
Coagulation	Clotting
Direct oral anticoagulants (DOAC)	Also known as NOACs are anticoagulant medications that require less monitoring compared to the traditional anticoagulants.
Deep vein thrombosis (DVT)	A condition marked by the formation of a thrombus within a deep vein (as of the leg or pelvis) that may be asymptomatic or be accompanied by symptoms (as swelling and pain) and that is potentially life-threatening if dislodgment of the thrombus results in pulmonary embolism.
Fondaparinux	An anticoagulant medication
Hemostatic system	The system that shortens the clotting time of blood and stops bleeding.
Heparin	An enzyme occurring especially in the liver and lungs that prolongs the clotting time of blood by preventing the formation of fibrin. 2 forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low molecular weight heparins (LMWH).
Impedance plethysmography	A technique that measures the change in blood volume (venous blood volume as well as the pulsation of the arteries) for a specific body segment
Kappa statistic	A measure of degree of nonrandom agreement between observers, measurements of a specific categorical variable, or both.
Metastasis	The spread of a cancer cells from the initial or primary site of disease to another part of the body.
Parenteral nutrition	The practice of feeding a person intravenously, circumventing the gastrointestinal tract.
Pulmonary embolism (PE)	Embolism of a pulmonary artery or one of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock and sometimes death.

Table 1. Glossary *(Continued)*

Thrombocytopenia	Persistent decrease in the number of blood platelets that is often associated with hemorrhagic conditions.
Thrombosis	The formation or presence of a blood clot within a blood vessel.
Vitamin K antagonists	Anticoagulant medications. Warfarin is a vitamin K antagonist.
Warfarin	An anticoagulant medication that is a vitamin K antagonist that is used for anticoagulation.

APPENDICES

Appendix 1. Living systematic review protocol

The methods outlined below are specific to maintaining the review as a living systematic review in the Cochrane Library ([Synnot 2017](#)). They will be implemented immediately upon publication of this update. Core review methods, such as the criteria for considering studies in the review and assessment of risk of bias, are unchanged. As such, below we outline only those areas of the methods for which additional or different activities are planned or rules apply.

Search methods for identification of studies

We will rerun the majority of searches monthly. For electronic databases and other electronic sources (CENTRAL, MEDLINE, Embase), we have set up auto-alerts to deliver a monthly search yield by email. We will search the remaining resources (conference proceedings of the American Society of Clinical Oncology (ASCO); the American Society of Haematology (ASH); and [clinicaltrials.gov](#)) on a bi-yearly basis. For that purpose, we will note when these conference proceedings are published.

As additional steps to inform the living systematic review, we will contact corresponding authors of ongoing studies as they are identified and ask them to advise when results are available, and to share early or unpublished data. We will contact the corresponding authors of any newly included studies for advice as to other relevant studies. We will manually screen the reference list of any newly included studies, and identified relevant guidelines and systematic reviews. .

We will review search methods and strategies approximately yearly, to ensure they reflect any terminology changes in the topic area, or in the databases.

Selection of studies

We will immediately screen any new citations retrieved by the monthly searches. As the first step of monthly screening, we will apply the machine learning classifier (RCT model) available in the Cochrane Register of Studies ([CSR-web](#); [Wallace 2017](#)). The classifier assigns a probability (from 0 to 100) to each citation for being a true RCT. For citations that are assigned a probability score of less than 10, the machine learning classifier currently has a specificity/recall of 99.987% ([Thomas 2017](#)). For citations assigned a score from 10 to 100, we will screen them in duplicate and independently. Citations that score 9 or less will be screened by [Cochrane Crowd](#). Any citations that are deemed to be potential RCTs by [Cochrane Crowd](#) will be returned to the authors for screening.

Data synthesis

Whenever new evidence (studies, data or information) that meets the review inclusion criteria is identified, we will immediately assess risk of bias and extract the data and incorporate it in the synthesis, as appropriate. We will not adjust the meta-analyses to account for multiple testing given the methods related to frequent updating of meta-analyses are under development ([Simmonds 2017](#)).

Other

We will review the review scope and methods approximately yearly, or more frequently if appropriate, in light of potential changes in the topic area, or the evidence being included in the review (e.g. additional comparisons, interventions or outcomes, or new review methods available).

Appendix 2. Full search strategies for the electronic databases: update December 2020

Database	Strategy
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Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer (Review)

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(Continued)

CENTRAL (the Cochrane Library, latest issue)

RCTsearch strategy:

1. exp Anticoagulants/

(anticoagulant* or anti-coagulant*).tw.

(Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organon or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organon or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.

2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or organon or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liqueamin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

4. exp Coumarins/

(coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.

5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldoumar).mp.

6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

7. (thrombin adj inhibitor*).mp.

8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. RIVAROXABAN/

(Continued)

11. DABIGATRAN/ (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC)
12. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp Neoplasms/
15. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adeno-ma*).tw.
16. 14 or 15
17. 13 and 16
18. randomised controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. clinical trials as topic.sh.
23. randomly.ab.
24. trial.ti.
25. 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (animals not (humans and animals)).sh.
27. 25 not 26
28. 17 and 27

Systematic Review search strategy:

1. exp Anticoagulants/
2. (anticoagulant* or anti-coagulant*).tw.
3. (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organan or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organan or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organan or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organan or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or cer-

(Continued)

toparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or organon or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liguaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

6. exp Coumarins/

7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.

8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldoumar).mp.

9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

10. (thrombin adj inhibitor*).mp.

11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

13. RIVAROXABAN/

14. DABIGATRAN/

15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp.
[mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.

17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18. exp Neoplasms/

19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

20. 18 or 19

21. 17 and 20

22. Meta-Analysis as Topic/

23. meta analy\$.tw.

(Continued)

24. metaanaly\$.tw.
25. Meta-Analysis/
26. (systematic adj (review\$1 or overview\$1)).tw.
27. exp Review Literature as Topic/
28. 22 or 23 or 24 or 25 or 26 or 27
29. cochrane.ab.
30. embase.ab.
31. (psychlit or psyclit).ab.
32. (psychinfo or psycinfo).ab.
33. (cinahl or cinhal).ab.
34. science citation index.ab.
35. bids.ab.
36. cancerlit.ab.
37. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. reference list\$.ab.
39. bibliograph\$.ab.
40. hand-search\$.ab.
41. relevant journals.ab.
42. manual search\$.ab.
43. 38 or 39 or 40 or 41 or 42
44. selection criteria.ab.
45. data extraction.ab.
46. 44 or 45
47. Review/
48. 46 and 47
49. Comment/
50. Letter/
51. Editorial/
52. animal/
53. human/
54. 52 not (52 and 53)
55. 49 or 50 or 51 or 54
56. 28 or 37 or 43 or 48
57. 56 not 55

(Continued)

58. 21 and 57

MEDLINE

RCT search strategy:

1. exp anticoagulant agent/
2. (anticoagulant* or anti-coagulant*).tw.
3. (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organon or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organon or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or klexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or cer-toparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or organon or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liqueamin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.
5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
6. exp coumarin derivative/
7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.
8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumac-etate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetra-lyl or coumadin* or warfant or marevan or aldoumar).mp.
9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
10. (thrombin adj inhibitor*).mp.
11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or arga-trovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
13. rivaroxaban/

(Continued)

14. dabigatran/
15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp.
16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp neoplasm/
19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adeno-
ma*).tw.
20. 18 or 19
21. 17 and 20
22. crossover procedure/
23. double-blind procedure/
24. randomised controlled trial/
25. single-blind procedure/
26. random*.mp.
27. factorial*.mp.
28. (crossover* or cross over* or cross-over*).mp.
29. placebo*.mp.
30. (double* adj blind*).mp.
31. (singl* adj blind*).mp.
32. assign*.mp.
33. allocat*.mp.
34. volunteer*.mp.
35. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 21 and 35

Systematic Review search strategy:

1. exp anticoagulant agent/
2. (anticoagulant* or anti-coagulant*).tw.
3. (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or organan or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or organan or sulodexide or zivor or embolex or xaparin or fondaparinux

(Continued)

or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.

4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or cer-toparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or He-palean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Epa-rina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or He-parin Lock).mp.

5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

6. exp coumarin derivative/

7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyra-nocoumarins or umbelliferones).tw.

8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumac-etate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetra-lyl or coumadin* or warfant or marevan or aldoumar).mp.

9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

10. (thrombin adj inhibitor*).mp.

11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or arga-trovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

13. rivaroxaban/

14. dabigatran/

15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp.

16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.

17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18. exp neoplasm/

19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adeno-ma*).tw.

20. 18 or 19

21. 17 and 20

(Continued)

22. exp Meta Analysis/
23. ((meta adj analy\$) or metaanalys\$).tw.
24. (systematic adj (review\$1 or overview\$1)).tw.
25. 22 or 23 or 24
26. cancerlit.ab.
27. cochrane.ab.
28. embase.ab.
29. (psychinfo or psycinfo).ab.
30. (cinahl or cinhal).ab.
31. science citation index.ab.
32. bids.ab.
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. reference lists.ab.
35. bibliograph\$.ab.
36. hand-search\$.ab.
37. manual search\$.ab.
38. relevant journals.ab.
39. 34 or 35 or 36 or 37 or 38
40. data extraction.ab.
41. selection criteria.ab.
42. 40 or 41
43. review.pt.
44. 42 and 43
45. letter.pt.
46. editorial.pt.
47. animal/
48. human/
49. 47 not (47 and 48)
50. 45 or 46 or 49
51. 25 or 33 or 39 or 44
52. 51 not 50
53. 21 and 52

Embase

#1 MeSH descriptor: [Anticoagulants] explode all trees

(Continued)

#2 (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or organon or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedel-parin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or organon or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquetaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock)

#3 FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216

#4 MeSH descriptor: [Coumarins] explode all trees

#5 (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-bis-coumacetate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcum-ar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or cou-matetralyl)

#6 (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix)

#7 thrombin near inhibitor*

#8 factor Xa inhibitor* or antithrombin* or anticoagul*

#9 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or arga-trovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

#10 MeSH descriptor: [Rivaroxaban] this term only

#11 MeSH descriptor: [Dabigatran] this term only

#12 target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Neoplasms] explode all trees

#15 malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*

#16 #14 or #15

#17 #13 and #16

Appendix 3. Detailed results of sensitivity analyses

Comparison	LMWH vs VKA
Outcome	Recurrent VTE

(Continued)

CCA effect estimate RR 0.59 (95% CI 0.43 to 0.80)

Sensitivity analysis

RI 1.5 intervention 1 control RR 0.61 (95% CI 0.45 to 0.82)

RI 2 intervention 1 control RR 0.62 (95% CI 0.46 to 0.83)

RI 3 intervention 1 control RR 0.64 (95% CI 0.48 to 0.86)

RI 5 intervention 1 control RR 0.68 (95% CI 0.50 to 0.91)

Comparison DOAC vs LMWH

Outcome Recurrent VTE

CCA effect estimate RR 0.63 (95% CI 0.45 to 0.88)

Sensitivity analysis

RI 1.5 intervention 1 control RR 0.65 (95% CI 0.48 to 0.89)

RI 2 intervention 1 control RR 0.67 (95% CI 0.50 to 0.90)

RI 3 intervention 1 control RR 0.71 (95% CI 0.54 to 0.93)

RI 5 intervention 1 control RR 0.75 (95% CI 0.57 to 0.99)

Comparison DOAC vs LMWH

Outcome Minor bleeding

CCA effect estimate RR 1.58 (95% CI 1.15 to 2.16)

Sensitivity analysis

RI 1.5 intervention 1 control RR 1.53 (95% CI 1.11 to 2.11)

RI 2 intervention 1 control RR 1.48 (95% CI 1.07 to 2.07)

RI 3 intervention 1 control RR 1.41 (95% CI 0.99 to 2.00)

RI 5 intervention 1 control RR 1.28 (95% CI 0.87 to 1.88)

WHAT'S NEW

Date	Event	Description
21 December 2022	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 December 2022 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date. [Enter text here]

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2008

Date	Event	Description
26 October 2022	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 October 2022 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
13 June 2022	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2022 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
29 December 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 December 2021 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
14 April 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2021. We have identified and incorporated four new studies (Agnelli 2020 (Caravaggio) ; El Mokadem 2020 ; McBane 2019 (ADAM-VTE) ; Young 2018 (SELECT-D)). Conclusion has changed accordingly. xxxx The conclusions of this Cochrane Review are therefore considered up to date.
29 October 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 October 2020. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
17 June 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2020. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated.

Date	Event	Description
		porated. The conclusions of this Cochrane Review are therefore considered up to date.
12 March 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2020. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
2 January 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 November 2019. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
7 October 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 August 2019. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
25 July 2019	Amended	Typographical error corrected.
9 July 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 June 2019. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
9 May 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 24 April 2019. We have identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
25 February 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2019 when we identified the full-text of a previously identified abstract. As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
29 November 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 November 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
1 October 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 September 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.

Date	Event	Description
9 August 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 July 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
28 June 2018	Amended	<p>This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2018.</p> <p>New comparison added (direct oral anticoagulant (DOAC) versus low molecular weight heparin (LMWH)). Two new studies found for the comparison DOAC versus LMWH (one published as full text and the other as an abstract). As such, results of all included studies identified were incorporated. The conclusions of this Cochrane Review are therefore considered up to date.</p>
28 June 2018	Amended	Declaration of interest updated.
14 May 2018	New citation required but conclusions have not changed	Updated author list.
14 May 2018	New search has been performed	<p>This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2018.</p> <p>New comparison added (direct oral anticoagulant (DOAC) versus low molecular weight heparin (LMWH)). Two new studies found for the comparison DOAC versus LMWH (one published as full text and the other as an abstract). As such, results of all included studies identified were incorporated. The conclusions of this Cochrane Review are therefore considered up to date.</p>
25 June 2014	Amended	Table format update
4 June 2014	New citation required but conclusions have not changed	<p>Data abstraction verified and detailed statistical data included as appendix</p> <p>Data reanalyzed by using a complete case analysis approach for the primary meta-analysis</p>
9 February 2013	New search has been performed	Search Updated
28 November 2012	Amended	Author contact details amended
9 May 2011	New citation required but conclusions have not changed	One new randomized controlled trial (RCT) identified and added to review. New authors also added.
9 May 2011	New search has been performed	Search updated 7 February 2010. One new RCT was identified.

CONTRIBUTIONS OF AUTHORS

LAK: searching, screening, full-text retrieval, data extraction, data analysis, data interpretation, manuscript drafting, review co-ordination.

MBH: screening, full-text retrieval, data extraction, manuscript drafting.

IGT: screening, data extraction, manuscript drafting.

CFM: screening.

FA: data extraction.

IT: screening, data extraction.

FS: screening.

MB: screening.

VEDY: screening.

HJS: protocol development, data interpretation, methodological expertise.

EAA: protocol development, data analysis, data interpretation, manuscript drafting, methodological expertise, review co-ordination.

DECLARATIONS OF INTEREST

LAK: no conflicts of interest

MBH: no conflicts of interests

IGT: no conflicts of interests

CFM: no conflicts of interests

IT: no conflicts of interests

FS: no conflicts of interests.

MB: no conflicts of interests

VEDY: no conflicts of interests

HJS: panel member of the ASH VTE in Cancer patients, Vice-Chair of the ASH VTE guidelines and played various leadership roles from 1999 until 2014 with ACCP VTE guidelines.

EAA: served on the executive committee the ACCP Antithrombotic Therapy Guidelines published in 2016

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research Cochrane Review Incentive Scheme 2016. Award reference Number 16/72/24, UK

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- American Society of Hematology, USA

This project was supported by the American Society of Hematology

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We previously reported using the 'related citation' feature in PubMed and 'citation tracking' of included studies in Web of Science Core Collection to identify additional articles. We stopped applying this method since February 2018, as over two years (February 2016 till February 2018), this method did not retrieve any additional reference compared to the findings of the database automated search.
- We have updated our search strategy ([Appendix 2](#)).
- For feasibility reasons, we will be updating the status of this systematic review every six months instead of every month.
- We focused in the primary analysis on participants with active cancer.
- We stratified major and minor bleeding for the comparison DOAC versus LMWH as follows:
 - GastroIntestinal (GI) tract bleeding
 - Upper GI bleeding
 - Lower GI bleeding
 - non-GI bleeding

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anticoagulants [adverse effects] [*therapeutic use]; Azetidines [therapeutic use]; Benzimidazoles [therapeutic use]; Benzylamines [therapeutic use]; beta-Alanine [analogs & derivatives] [therapeutic use]; Dabigatran [therapeutic use]; Hemorrhage [chemically induced]; Heparin, Low-Molecular-Weight [therapeutic use]; Neoplasms [*complications]; Oligosaccharides [therapeutic use]; Randomized Controlled Trials as Topic; Venous Thromboembolism [*drug therapy] [etiology] [mortality]; Vitamin K [antagonists & inhibitors]

MeSH check words

Humans