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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, Yosuico 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) and vitamin K antagonists (VKAs) for the long-term treatment of venous thromboembolism (VTE) in people with cancer.

Search methods

We conducted a literature search including a major electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1), MEDLINE (Ovid), and Embase (Ovid); handsearching conference proceedings; checking references of included studies; use of the 'related citation' feature in PubMed 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 2018.

Selection criteria

Randomized controlled trials (RCTs) assessing the benefits and harms of long-term treatment with LMWHs, DOACs or VKAs 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).

Main results

Of 15,785 citations, including 7602 unique citations, 16 RCTs fulfilled the eligibility criteria. These trials enrolled 5167 people with cancer and VTE.

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 2018.

Key results

We found 16 trials enrolling 5167 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 for the main comparison. Low molecular weight heparin secondary prophylaxis compared to vitamin K antagonist secondary prophylaxis in people with cancer with venous thromboembolism

LMWH 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: LMWH prophylaxis

Control: VKA prophylaxis

Outcomes	№ of participants (studies)	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 follow-up: 12 months	1747 (5 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	**RR 1.00** (0.88 to 1.13)	Study population	
				373 per 1000	0 fewer per 1000 (45 fewer to 48 more)
Recurrent VTE follow-up: 12 months	1781 (5 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	**RR 0.58** (0.43 to 0.77)	Study population	
				127 per 1000	53 fewer per 1000 (72 fewer to 29 fewer)
Major bleeding follow-up: range 6-12 months	1712 (4 RCTs)	⊕⊕⊕⊖ **Moderate**[c]	**RR 1.09** (0.55 to 2.12)	Study population	
				43 per 1000	4 more per 1000 (19 fewer to 48 more)
Minor bleeding follow-up: range 6 months to 12 months	1712 (4 RCTs)	⊕⊕⊖⊖ **Low**[d,e]	**RR 0.78** (0.47 to 1.27)	Study population	
				174 per 1000	38 fewer per 1000 (92 fewer to 47 more)
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; **LMWH:** low molecular weight heparin; **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.

[a]Downgraded one level due to concerns about both imprecision, 95% CI was consistent with the possibility for important benefit (45 per 1000 absolute reduction) and possibility of important harm (48 per 1000 absolute increase), including 651 events in total, and concerns about 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 five out of five studies.
[b]Downgraded 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 five out of five studies).
[c]Downgraded one level due to concerns about both imprecision, 95% CI was consistent with the possibility for important benefit (19 per 1000 absolute reduction) and possibility of important harm (48 per 1000 absolute increase), including 78 events in total, and concerns about risk of bias, allocation concealment unclear in one study, high risk of selective reporting and high risk of incomplete outcome data in one study, and lack of blinding of participants and personnel in four out of four studies.
[d]Downgraded one level due to serious inconsistency (I^2 = 78%).
[e]Downgraded one level due to concerns about both imprecision, 95% CI was consistent with the possibility for important benefit (92 per 1000 absolute reduction) and possibility of important harm (47 per 1000 absolute increase), including 267 events in total, and concerns about risk of bias, allocation concealment unclear in one study, high risk of selective reporting and high risk of incomplete outcome data in one study, and lack of blinding of participants and personnel in four out of four studies.

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

DOAC secondary prophylaxis compared to VKA secondary prophylaxis in people with active cancer with VTE

Population: people with cancer with VTE receiving secondary prophylaxis

Setting: outpatient

Intervention: DOAC prophylaxis

Control: VKA prophylaxis

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with VKA secondary prophylaxis	Risk difference with DOAC secondary prophylaxis

All-cause mortality up to 12 months	1031 (4 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	**RR 0.93** (0.71 to 1.21)	Study population	
				176 per 1000	12 fewer per 1000 (51 fewer to 37 more)
Recurrent VTE up to 12 months	1022 (4 RCTs)	⊕⊕⊖⊖ **Low**[a,c]	**RR 0.66** (0.33 to 1.31)	Study population	
				40 per 1000	14 fewer per 1000 (27 fewer to 12 more)
Major bleeding follow-up: range 3-12 months	1030 (4 RCTs)	⊕⊕⊖⊖ **Low**[a,d]	**RR 0.77** (0.38 to 1.57)	Study population	
				36 per 1000	8 fewer per 1000 (22 fewer to 20 more)
Minor bleeding follow-up: range 3-12 months	1030 (4 RCTs)	⊕⊕⊖⊖ **Low**[a,e]	**RR 0.84** (0.58 to 1.22)	Study population	
				128 per 1000	21 fewer per 1000 (54 fewer to 28 more)
Health-related quality of life follow-up: range 3-12 months	8485 (1 RCT)	⊕⊕⊕⊖ **Moderate**[f]	—	Prins 2014 (EINSTEIN DVT-PE; 8485 participants): "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 people 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; **DOAC:** direct oral anticoagulant; **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.

[a]Downgraded one level due to serious indirectness. Two studies (RECOVER I-II and RE-MEDY) included people with a diagnosis of cancer within five years before enrolment.
[b]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility of important benefit (51 fewer per 1000) and possibility of important harm (37 more per 1000); included 174 events.

[c]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility of important benefit (27 fewer per 1000) and possibility of important harm (12 more per 1000); included 34 events.
[d]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility for important benefit (22 per 1000 absolute reduction) and possibility of important harm (20 per 1000 absolute increase), included 32 events.
[e]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility for important benefit (54 per 1000 absolute reduction) and possibility of important harm (28 per 1000 absolute increase), included 122 events.
[f]Downgraded one level for serious indirectness. The study by Prins and colleagues (Prins 2014 (EINSTEIN, 8485 participants)) reports health-related quality of life for the whole study population, without providing data for the cancer subgroup.

Summary of findings 3. Direct oral anticoagulant secondary prophylaxis compared to low molecular weight heparin secondary prophylaxis in people with cancer with venous thromboembolism

DOAC secondary prophylaxis compared to LMWH secondary prophylaxis in people with cancer with VTE

Patient: people with cancer with VTE receiving secondary prophylaxis

Setting: outpatient

Intervention: DOAC prophylaxis

Control: LMWH prophylaxis

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with LMWH secondary prophylaxis	Risk difference with DOAC secondary prophylaxis
All-cause mortality up to 12 months	1016 (1 RCT)	⊕⊕⊖⊖ **Low**[a,b]	**RR 1.07** (0.92 to 1.25)	Study population	
				379 per 1000	27 more per 1000 (30 fewer to 95 more)
Recurrent VTE up to 12 months	1016 (1 RCT)	⊕⊕⊖⊖ **Low**[a,c]	**RR 0.69** (0.47 to 1.01)	Study population	
				116 per 1000	36 fewer per 1000 (62 fewer to 1 more)
Major bleeding up to 12 months	1016 (1 RCT)	⊕⊕⊖⊖ **Low**[a,d]	**RR 1.71** (1.01 to 2.88)	Study population	
				41 per 1000	29 more per 1000 (0 fewer to 78 more)
Minor bleeding up to 12 months	1016 (1 RCT)	⊕⊕⊖⊖ **Low**[a,e]	**RR 1.31** (0.95 to 1.80)	Study population	

				114 per 1000	35 more per 1000 (6 fewer to 92 more)
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; **DOAC:** direct oral anticoagulant; **LMWH:** low molecular weight heparin; **RCT:** randomized controlled trial; **RR:** risk ratio; **VTE:** venous thromboembolism.

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

[a]Downgraded one level for serious risk of bias due to lack of blinding of participants and personnel and whether allocation was concealed was not reported.
[b]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for important benefit (30 per 1000 absolute reduction) and possibility of important harm (95 per 1000 absolute increase); included 398 events.
[c]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for important benefit (62 per 1000 absolute reduction) and possibility of harm not exceeding a minimal important difference (1 per 1000 absolute increase); including a total of 100 events.
[d]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for no effect and possibility of important harm (78 per 1000 absolute increase); included 57 events.
[e]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for important benefit (6 per 1000 absolute reduction) and possibility of important harm (92 per 1000 absolute increase); included 134 events.

Summary of findings 4. 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	№ of participants	Certainty of the evidence	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)

	(studies)	(GRADE)		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.

[a]Downgraded 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.
[b]Downgraded 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.
[c]Downgraded 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 (Levitan 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. The last update of this Cochrane systematic review, published in 2014, identified 10 trials enrolling 1981 participants (Cesarone 2003; Deitcher 2006 (ONCENOX); Hull 2006; Lee 2003 (CLOT); Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Romera 2009; Schulman 2003 (extended vs limited); Schulman 2009; van Doormaal 2010 (Van Gogh DVT trial)). It concluded that the existing evidence suggested a reduction in VTE events in people with cancer but not in mortality (Akl 2014a). We excluded two of the previously included trials (Schulman 2003 (extended vs limited); Schulman 2009) taking into consideration that there treatment duration does not apply to the definition of ling term treatment. Since 2014, we have identified eight eligible trials addressing this question (Agnelli 2015 (AMPLIFY); Lee 2015 (CATCH); Mazilu 2014 (OVIDIUS); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Raskob 2018 (HOKUSAI); Schulman 2015 (RECOVER I-II); Young 2017 (SELECT-D)).

Living review approach: following the publication of this current 2018 update of the review, we plan to maintain 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 being piloted by Cochrane, 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 eight ongoing eligible trials that will be important to incorporate in a timely manner. Fourth, we are planning to use this living systematic review as the basis of a living recommendation in a clinical practice guideline with the American Society of Hematology (Akl 2017). For more information about the living systematic review approach being piloted by Cochrane, see Appendix 2.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People with 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.

Types of interventions

Intervention arms consisted of long-term treatment with:

- LMWHs;
- DOACs;
- VKAs.

We included any comparison of the three management options listed above (LMWHs versus VKAs, DOACs versus VKAs, DOACs versus LMWHs). 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, ^{125}I-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.
- Major bleeding: we accepted the authors' definitions of major bleeding.
- Minor bleeding: we accepted the authors' definitions of minor bleeding.
- Thrombocytopenia.
- Health-related quality of life measured using a validated tool.
- Postphlebitic 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 used no language restrictions. We conducted comprehensive searches on 14 May 2018, following the original electronic searches performed in January 2007, February 2010, February 2013 and February 2016 (last major search). We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1), MEDLINE (starting 1946, via Ovid), and Embase (starting 1980, via Ovid). The search strategies combined terms for anticoagulants, terms for cancer and a search filter for RCTs. We used no language restrictions. We list the full search strategies for each of the electronic databases in Appendix 3, Appendix 4, and Appendix 5.

Living review approach: since the last major search in February 2016, we have been running searches monthly, using auto-alerts to deliver the monthly yield by email. We will incorporate new evidence rapidly after it is identified. This update of the systematic review is based on the findings of a literature search conducted on 14 May 2018. 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 2018) and of the American Society of Hematology (ASH, starting with its 2003 issue up to May 2018). 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. We used the 'related citation' feature in PubMed to identify additional articles and 'citation tracking' of included studies in Web of Science Core Collection. In addition, we contacted experts in the field for information about unpublished work and ongoing trials.

Living review approach: we will search on a monthly basis the conference proceedings of ASCO and ASH soon after their publications and ClinicalTrials.gov and WHO International Clinical Trials Registry Platform. As an additional step, 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 on unpublished data. We will continue to review the reference lists for any prospectively identified studies, with running the 'related citation' for all included studies on a monthly basis. Also, we will contact the corresponding authors of any newly included studies for advice as to other relevant studies. Using citation alerts, we will conduct citation tracking of included studies in Web of Science Core Collection on an ongoing basis.

Data collection and analysis

Selection of studies

Two review authors independently screened the title and abstract of identified article citations for potential eligibility. We retrieved the full text of articles judged potentially eligible by at least one review author. Two review authors then 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 any 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% (James Thomas, personal communication). 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

Two review authors 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 (age, gender, co morbidities, co interventions).
- Type of cancer (site and histology).
- Stage of cancer.
- Time since cancer diagnosis.

Interventions

- Type and dosage schedule of LMWHs.
- Type and dosage schedule of DOACs.
- Type and dosage schedule of VKAs.
- Type (e.g. unfractionated heparin (UFH) versus LMWHs versus fondaparinux) and duration of initial anticoagulation.
- 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 extracted data necessary to conduct complete-case analysis as the primary analysis.

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.

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. Two review authors independently assessed the methodologic quality of each included study and resolved any disagreements by discussion. Methodologic criteria included:

- adequate randomization sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- percentage followed up and whether incomplete outcome data were addressed;
- whether the study was free of selective outcome reporting;
- 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 collected and analyzed hazard ratios (HRs) for time-to-event data and risk ratios (RRs) 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

Determining participants with missing data

It was not clear whether certain participant categories (e.g. those described as 'withdrew consent' or 'experienced adverse events') were actually followed up by the trial authors (versus had missing participant data) (Akl 2016). To deal with this issue, we made the following considerations:

- 'ineligible participants,' and 'did not receive the first dose' participant categories, which were defined prior to the initiation of the study intervention, most likely had missing participant data;
- 'withdrew consent,' 'lost to follow-up' and 'outcome not assessable' participant categories, and other category explicitly reported as not being followed up, which were defined after the initiation of the study intervention, most likely had missing participant data;
- 'dead,' 'experienced adverse events,' 'non-compliant' and 'discontinued prematurely' (and similarly described) participant categories, less likely had missing participant data.

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

In the primary meta-analysis, we used a complete-case analysis approach, that is, we excluded participants considered to have missing data (Guyatt 2017).

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

- denominator: (number of participants randomized) – (number of participants most likely with missing data, both pre- and postintervention initiation);
- 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).

For continuous data, we used for each study arm, the reported mean and standard deviation (SD) for participants actually followed up by the trial authors.

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 participant 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; Ebrahim 2013).

For categorical data and for an RR showing a reduction in effect (RR < 1), we used the following increasingly stringent but plausible assumptions (Akl 2013):

- 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) – (number of participants most likely with missing data, preintervention initiation);
- numerator: (number of participants with observed events) + (number of participants most likely with missing data postintervention initiation, with assumed events).

Assumed events are calculated by applying the a priori plausible assumptions to the participants considered most likely with missing data postintervention initiation.

For continuous data, we planned to use the four strategies suggested by Ebrahim and colleagues (Ebrahim 2013). The strategies imputed the means for participants with missing data based on the means of participants actually followed up in the individual trials included in the systematic review. To impute SDs, we used the median SD from the control arms of all included trials (Ebrahim 2013).

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 Subgroup analysis and investigation of heterogeneity section).

Assessment of reporting biases

We assessed selective outcome reporting by trying to identify whether the study was included in a trial registry, whether a protocol was available and whether the methods section provided a list of outcomes (to assess selective outcome reporting bias). We compared the list of outcomes from those sources to the outcomes reported in the published paper. We did not create funnel plots due to the low number of included trials for each outcome.

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 (Review Manager 2014). 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; outcomes included: mortality, recurrent VTE, major bleeding, minor bleeding, health-related quality of life;
- DOAC versus VKA; outcomes included: mortality, recurrent VTE, major bleeding, minor bleeding, health-related quality of life;
- DOAC versus LMWH; outcomes included: mortality, recurrent VTE, major bleeding, minor bleeding, health-related quality of life;
- idraparinux versus VKA; outcomes included: mortality, recurrent VTE, major bleeding, health-related quality of life.

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

We planned subgroup analyses based on the participants characteristics but did not conduct them as the data were not available.

Sensitivity analysis

We conducted sensitivity analyses including the studies published as abstracts (Cesarone 2003; Mazilu 2014 (OVIDIUS)), and the studies that used a different initial anticoagulant in the two study arms (post hoc analysis) (Hull 2006).

In addition, we planned for sensitivity meta-analyses to assess the risk of bias associated with missing participant data when the primary meta-analysis of a specific outcome found a statistically significant effect.

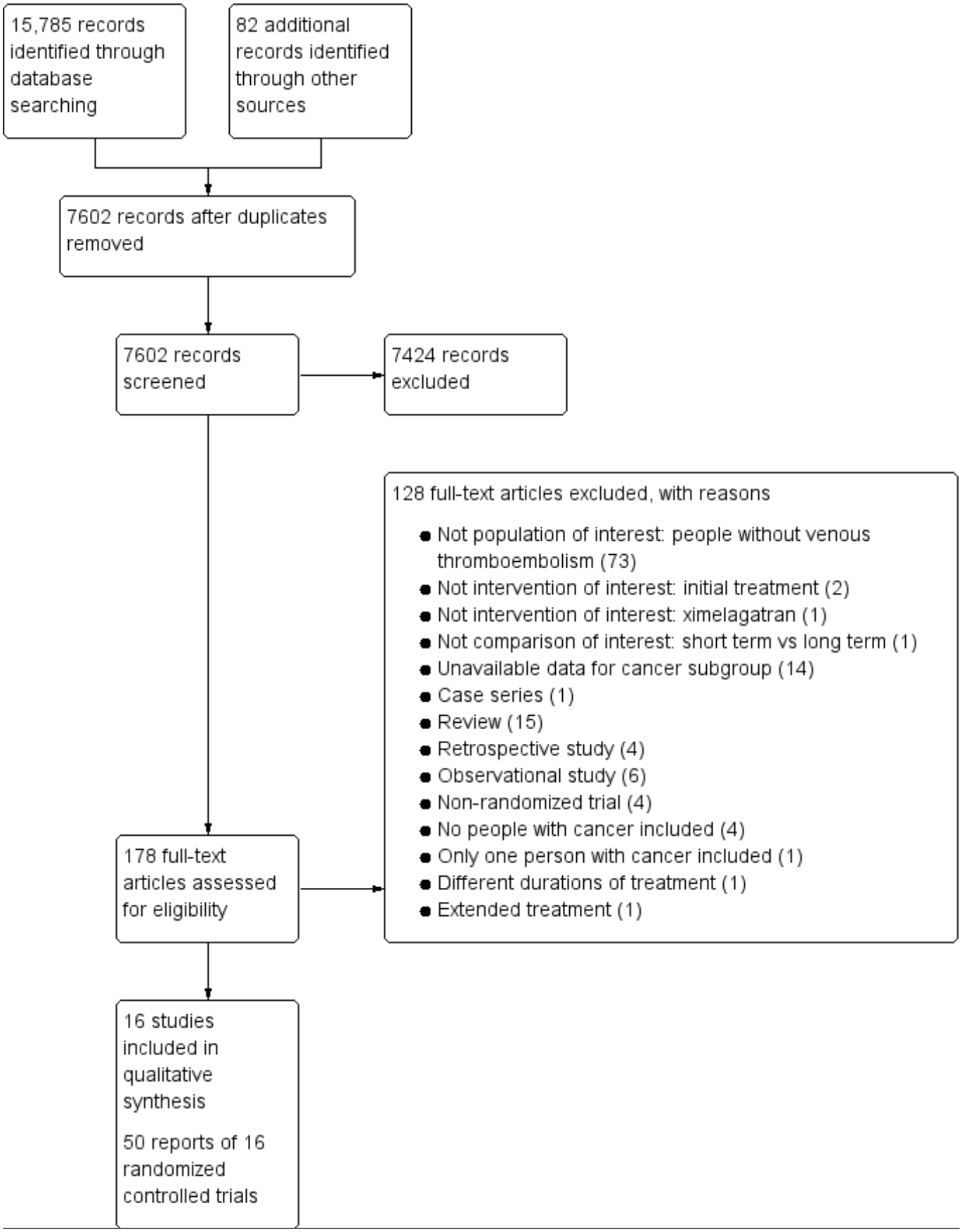
RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow diagram. As of May 2018, the search strategy identified 7602 unique citations. The title and abstract screening identified 178 potentially eligible citations. The full-text screening of the full texts of these 178 citations identified 13 eligible RCTs published as full reports (Agnelli 2015 (AMPLIFY); Deitcher 2006 (ONCENOX); Hull 2006; 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)), and three studies published as abstracts (Cesarone 2003; Mazilu 2014 (OVIDIUS); Young 2017 (SELECT-D)). We identified seven registered but unpublished trials: one terminated (Kamphuisen 2010 (Longheva)), and seven ongoing (Agnelli 2017 (CARAVAGGIO); Kamphuisen 2010 (Longheva); Karatas 2015; McBane 2017 (ADAM VTE); Meyer 2016; Ryun Park 2017 (PRIORITY); Schrag 2016 (CANVAS)). The May 2018 search identified two new reports of a previously identified study (Lee 2015 (CATCH))

Figure 1. Study flow diagram.



Included studies

We included 16 RCTs (50 reports) with 5167 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; 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). Five RCTs compared DOACs to VKAs (Agnelli 2015 (AMPLIFY); Mazilu 2014 (OVIDIUS); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Schulman 2015 (RECOVER I-II)). 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)). Two studies compared DOACs to LMWHs (Raskob 2018 (HOKUSAI); Young 2017 (SELECT-D)). We also identified seven ongoing studies comparing DOACs to LMWHs (Agnelli 2017 (CARAVAGGIO); Kamphuisen 2010 (Longheva); Karatas 2015; McBane 2017 (ADAM VTE); Meyer 2016; 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. No information about follow-up in the cancer subgroup was reported.

Cesarone and colleagues recruited 199 participants with cancer and DVT (Cesarone 2003). Participants were randomized to receive enoxaparin 100 Ul/kg twice daily or coumadin (dose adjusted to keep INR close to 3) for three months. Assessed outcomes were mortality, major bleeding and recurrent VTE in the three-month period. The authors reported that 17 participants dropped out and a 92% follow-up rate.

Deitcher and colleagues recruited 102 participants with 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. The study authors reported complete follow-up.

Hull and colleagues recruited 200 participants with cancer with acute symptomatic proximal vein thrombosis (Hull 2006). 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. The study authors reported complete follow-up.

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. The study authors reported complete follow-up.

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. The authors reported 98% follow-up.

Lopez-Beret and colleagues recruited 35 participants with cancer and symptomatic DVT of the lower limb, a subgroup of 158 participants recruited (Lopez-Beret 2001). 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. The study provided no information on follow-up in the cancer subgroup.

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. The study provided no information on follow-up in the cancer subgroup.

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. The study authors reported 94.5% follow-up.

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 adjust-

ed 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. The study provided no information on follow-up in the cancer subgroup.

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. The study authors reported complete follow-up.

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. The study authors reported 97% follow-up.

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. The study provided no information on follow-up in the cancer subgroup.

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. The study provided no information on follow-up in the cancer subgroup.

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. Participants were followed up for six months. The study authors reported complete follow-up.

Excluded studies

We excluded 91 studies (128 reports) from this review for the following reasons: not population of interest: participants without VTE (73 studies), participants without cancer (four studies), only one participant with cancer was included (one study); not intervention of interest: ximelagatran (one study), initial VTE treatment (two studies), different duration of interventional drugs (one study); not comparison of interest: short-term versus long-term treatment (one study), participants with cancer constituted study subgroups but their outcome data were not available (14 studies) ; not design of interest: case series (one study), review (15 studies), retrospective study (four studies), observational study (six studies), trial but not randomized and controlled (four studies); and extended treatment (one study). 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.

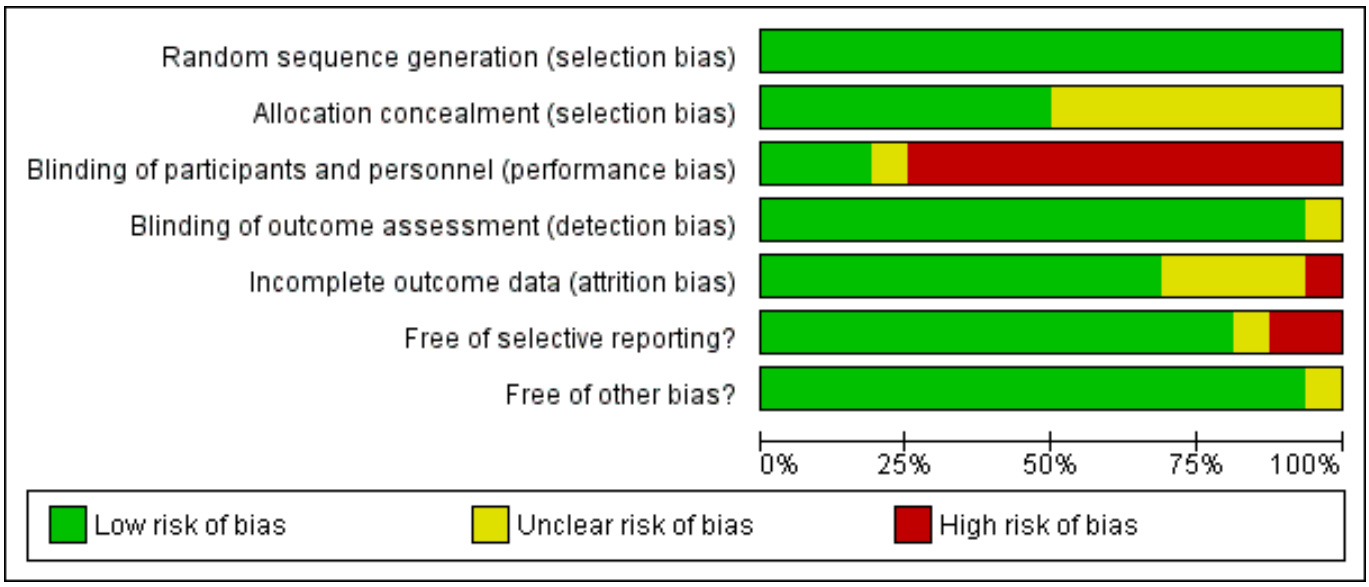
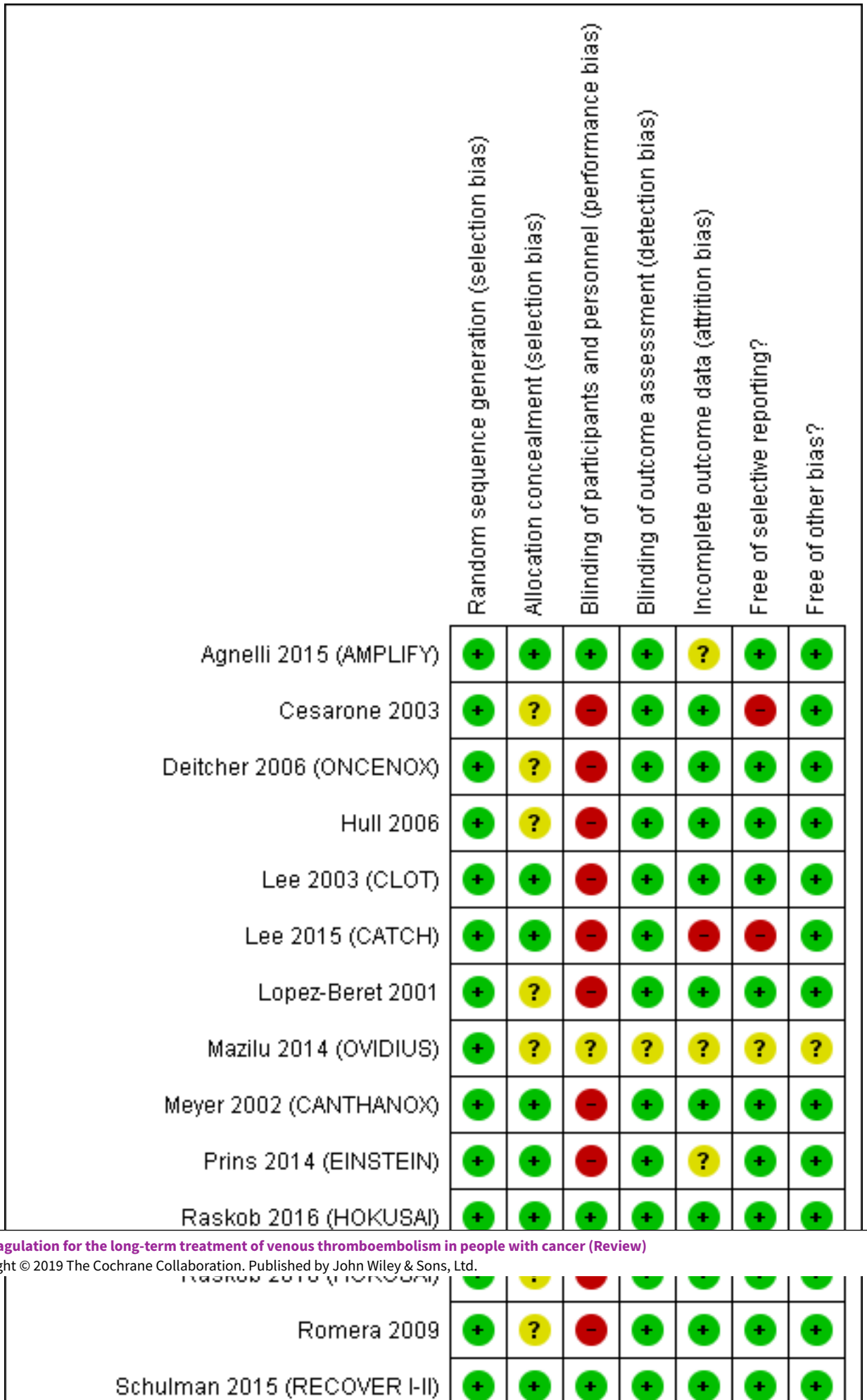


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

We judged allocation to be adequately concealed in eight of the 16 studies (Agnelli 2015 (AMPLIFY); ; ; Lee 2003 (CLOT); Lee 2015 (CATCH); ; Meyer 2002 (CANTHANOX); Prins 2014 (EINSTEIN); Raskob 2016 (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); Hull 2006; Lopez-Beret 2001; Mazilu 2014 (OVIDIUS); Raskob 2018 (HOKUSAI); Romera 2009; Young 2017 (SELECT-D)).

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be definitely blinded in three studies (Agnelli 2015 (AMPLIFY); Raskob 2016 (HOKUSAI); Schulman 2015 (RECOVER I-II)), and definitely not blinded in 12 studies (Cesarone 2003; Deitcher 2006 (ONCENOX); Hull 2006; 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 2017 (SELECT-D)). One study did not report on blinding of participants and personnel (unclear risk of bias; Mazilu 2014 (OVIDIUS)).

Blinding of outcome assessment (detection bias)

Random sequence was definitely generated in 11 studies (Agnelli 2015 (AMPLIFY); Hull 2006; Lee 2003 (CLOT); Lee 2015 (CATCH); 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)). Five studies were judged to be at low risk of selection bias because minimal information about random sequence generation was provided and random sequence was probably generated randomly. (Cesarone 2003; Deitcher 2006 (ONCENOX); Lopez-Beret 2001; Mazilu 2014 (OVIDIUS); Young 2017 (SELECT-D)).

We judged outcome assessors to be definitely blinded in 10 studies (Agnelli 2015 (AMPLIFY); Lee 2003 (CLOT); Lee 2015 (CATCH); Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Romera 2009; Schulman 2015 (RECOVER I-II); van Doormaal 2010 (Van Gogh DVT trial)), and probably not blinded in four studies (Cesarone 2003; Deitcher 2006 (ONCENOX); Hull 2006; Young 2017 (SELECT-D)). Two studies were not clear about the blinding of outcome assessors (Mazilu 2014 (OVIDIUS);Raskob 2018 (HOKUSAI)).

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). Six studies reported complete follow-up (Deitcher 2006 (ONCENOX); Hull 2006; Lee 2003 (CLOT); Raskob 2016 (HOKUSAI); Schulman 2015 (RECOVER I-II); Young 2017 (SELECT-D)). Two studies did not report follow-up data for the cancer subgroup, but we assumed complete follow-up taking into consideration the small sample size (Lopez-Beret 2001; Romera 2009).Three studies were judged to be at low risk of incomplete outcome data because the rates of missing outcome data were lower that the event rate in the studies (Cesarone 2003; Meyer 2002 (CANTHANOX); Raskob 2018 (HOKUSAI)), whereas one study was judged to be at high risk of incomplete outcome data because the rate of missing outcome data was higher that the event rate in the study (Lee 2015 (CATCH))). The risk of incomplete outcome data was not clear in four studies (Agnelli 2015 (AMPLIFY); Mazilu 2014 (OVIDIUS); Prins 2014 (EINSTEIN); van Doormaal 2010 (Van Gogh DVT trial)).

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 of the 16 included studies (Lopez-Beret 2001; Meyer 2002 (CANTHANOX); Romera 2009).

Effects of interventions

See: **Summary of findings for the main comparison** 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 people with active cancer with venous thromboembolism; **Summary of findings 3** Direct oral anticoagulant secondary prophylaxis compared to low molecular weight heparin secondary prophylaxis in people with cancer with venous thromboembolism; **Summary of findings 4** 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

All-cause mortality

Mortality up to 12 months: we pooled data from all five studies reporting on mortality irrespective of the timing of outcome assessment based on the assumption that relative effect was constant over time. For studies reporting relative effect for more than one period of time, we included data for the longest period reported. Meta-analysis of five RCTs including 1747 participants and comparing LMWHs to VKAs did not rule out a clinically significant increase or decrease in mortality up to 12 months (RR 1.00, 95% CI 0.88 to 1.13; RD 0 fewer per 1000, 95% CI 45 fewer to 48 more; moderate-certainty evidence; Analysis 1.1) (Deitcher 2006 (ONCENOX); Lee 2003 (CLOT); Lee 2015 (CATCH); Lopez-Beret 2001; Meyer 2002 (CANTHANOX)). The I^2 value indicated no heterogeneity (I^2 = 0%). 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), 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).

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 LMWHs compared to VKAs has no effect on reduction in the risk of death ((HR 0.94, 95% CI 0.74 to 1.20)). The I^2 value indicated low heterogeneity (I^2 = 16%). 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).

Recurrent venous thromboembolism

None of the studies reported DVT and PE as separate outcomes. Meta-analysis of five studies including 1781 participants found that LMWHs probably reduced the risk of recurrent VTE up to six months compared to VKAs (RR 0.58, 95% CI 0.43 to 0.77; RD 53 fewer per 1000, 95% CI 72 fewer to 29 fewer; moderate-certainty evidence; Analysis 1.3) (Deitcher 2006 (ONCENOX); Lee 2003 (CLOT); Lee 2015 (CATCH); Meyer 2002 (CANTHANOX); Romera 2009). The I^2 value indicated no heterogeneity (I^2 = 0%). The results were consistent 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). 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 10).

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 LMWHs reduced the risk of recurrent VTE ((HR 0.49, 95% CI 0.31 to 0.78)).The I^2 value indicated no heterogeneity (I^2 = 0%) 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 0.47, 95% CI 0.32 to 0.71) (Hull 2006).

Major and minor bleeding

Meta-analysis of four studies including 1712 participants did not rule out a beneficial or harmful effect of LMWHs compared with 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; Analysis 1.5) 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; Analysis 1.6) (Deitcher 2006 (ONCENOX); Lee 2003 (CLOT); Lee 2015 (CATCH); Meyer 2002 (CANTHANOX)). The I^2 value indicated moderate heterogeneity for major bleeding (I^2 = 46%) and serious inconsistency for minor bleeding (I^2 = 78%). The results were consistent in a sensitivity analysis including the study that 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) and minor bleeding (RR 0.84, 95% CI 0.56 to 1.27) (Hull 2006).

Thrombocytopenia

One study including 146 participants assessed thrombocytopenia (Meyer 2002 (CANTHANOX)). The study did not rule out a beneficial or harmful effect of LMWHs compared with VKAs (RR 0.94, 95% CI 0.52 to 1.69). The results were consistent in a sensitivity analysis including the study that used a different initial anticoagulant in the two study arms (RR 1.03, 95% CI 0.60 to 1.74) (Hull 2006).

Health-related quality of life

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

Postphlebitic syndrome

None of the studies reported postphlebitic syndrome.

Direct oral anticoagulants versus vitamin K antagonists

All-cause mortality up to 12 months

Meta-analysis of four RCTs, including 1031 participants did not rule out a beneficial or harmful effect of DOACs on mortality up to 12 months compared to VKAs (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; Analysis 2.1) (Agnelli 2015 (AMPLIFY); Prins 2014 (EINSTEIN); Raskob 2016 (HOKUSAI); Schulman 2015 (RECOVER I-II)). The I^2 value indicated no heterogeneity (I^2 = 0%). The results were consistent in a sensitivity analysis including the study published as an abstract (RR 0.92, 95% CI 0.71 to 1.19) (Mazilu 2014 (OVIDIUS)).

Recurrent venous thromboembolism up to 12 months

None of the studies reported DVT and PE as separate outcomes. Meta-analysis of four studies including 1022 participants did not rule out a beneficial or harmful effect of DOACs on recurrent VTE up to 12 months compared to VKAs (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; Analysis 2.2). The I^2 value indicated no heterogeneity (I^2 = 0%).

Major and minor bleeding

Meta-analysis of four studies including 1030 participants did not rule out a beneficial or harmful effect of DOACs on major bleeding compared to VKAs (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; Analysis 2.3) 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; Analysis 2.4). The I^2 value indicated no heterogeneity for major bleeding (I^2 = 0%) and low heterogeneity for minor bleeding (I^2 = 14%).

Thrombocytopenia

None of the studies reported thrombocytopenia.

Health-related quality of life

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 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)).

Postphlebitic syndrome

None of the studies reported postphlebitic syndrome.

Direct oral anticoagulants versus low molecular weight heparins

Two studies enrolling 1455 participants compared DOAC with LMWH (Raskob 2018 (HOKUSAI); Young 2017 (SELECT-D)). The study by Young and colleagues was published as abstract and was only included in the sensitivity analysis.

We identified seven ongoing studies comparing DOACs to LMWHs for the long-term treatment of cancer participants with VTE (Agnelli 2017 (CARAVAGGIO); Kamphuisen 2010 (Longheva); Karatas 2015; McBane 2017 (ADAM VTE); Meyer 2016; Ryun Park 2017 (PRIORITY); Schrag 2016 (CANVAS)).

All-cause mortality up to 12 months

The study by Raskob and colleagues did not rule out a beneficial or harmful effect of DOACs on all-cause mortality at 12 months of follow-up compared to LMWH (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) (Raskob 2018 (HOKUSAI)). The results were consistent with a sensitivity analysis including the study that was published as abstract (RR 1.01, 95% CI 0.84 to 1.21) (Young 2017 (SELECT-D)). The I^2 value in the sensitivity analysis indicated low heterogeneity between the studies for all-cause mortality (I^2 = 27%).

Recurrent venous thromboembolism up to 12 months

The study by Raskob and colleagues showed that DOACs likely reduced the recurrence of VTE compared to LMWH up to 12 months of follow-up (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; Analysis 3.2). The results were consistent in a sensitivity analysis including the study published as an abstract (RR 0.55, 95% CI 0.30 to 1.01) (Young 2017 (SELECT-D)). The I^2 value in the sensitivity analysis indicated moderate heterogeneity between the studies for VTE recurrence (I^2 = 52%). With such limited number of included trials, we could not explain the heterogeneity by conducting subgroup analysis.

Major bleeding up to 12 months

The study by Raskob and colleagues showed that DOAC increased major bleeding up to 12 months 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; Analysis 3.3) (Raskob 2018 (HOKUSAI)). The results were consistent in a sensitivity analysis including the study published as an abstract (RR 1.62, 95% CI 1.02 to 2.59) (Young 2017 (SELECT-D)). The I^2 value in the sensitivity analysis indicated no heterogeneity between the studies for major bleeding (I^2 = 0%). 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 lost statistical significance for all plausible assumptions (see Appendix 10).

Minor bleeding up to 12 months

The study by Raskob and colleagues showed that DOAC likely increased minor bleeding up to 12 months 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) (Raskob 2018 (HOKUSAI)). The results were consistent in a sensitivity analysis including the study published as an abstract (RR 2.48, 95% CI 0.61 to 10.10) (Young 2017 (SELECT-D)) The I^2 value in the sensitivity analysis indicated large heterogeneity between the studies for all-cause mortality (I^2 = 88%). With such limited number of included trials, we could not explain the heterogeneity by conducting subgroup analysis.

Thrombocytopenia

None of the studies reported thrombocytopenia.

Health-related quality of life

None of the studies reported HRQoL.

Postphlebitic syndrome

None of the studies reported postphlebitic syndrome.

Once-weekly 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 (van Doormaal 2010 (Van Gogh DVT trial)).

All-cause mortality

The trial 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).

Recurrent venous thromboembolism up to six months

The trial did not rule out a beneficial or harmful effect of idraparinux compared to VKAs on 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).

Major bleeding

The trial did not rule out a beneficial or harmful effect of idraparinux compared to VKAs on 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).

Minor bleeding

The study did not report minor bleeding.

Thrombocytopenia

The study did not report thrombocytopenia.

Health-related quality of life

The study did not report HRQoL.

Postphlebitic syndrome

The study did not report postphlebitic syndrome.

DISCUSSION

Summary of main results

For the long-term treatment of VTE in people with cancer, LMWHs compared with VKAs probably showed an important reduction in VTE but the analysis did not rule out beneficial or harmful effect for the outcomes of mortality and bleeding. The analysis comparing DOACs to VKAs may not have ruled out beneficial or harmful effect for all studied outcomes. DOACs compared to LMWHs may have shown a likely reduction in VTE recurrence and may have shown an increase in major bleeding. For once-weekly subcutaneous injection of idraparinux compared with standard treatment, the findings probably did not rule out a beneficial or harmful effect of idraparinux on recurrent VTE, mortality and bleeding.

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).

We were unable to conduct subgroup analyses based on histologic type or stage of cancer because of the lack of data. In the absence of evidence for the contrary, we assumed that the results of this study applied to people with any type or stage of cancer.

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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Akl EA, Labedi N, Barba M, Terrenato I, Sperati F, Muti P, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD006650.pub3]

Akl 2014b

Akl EA, Kahale LA, Barba M, Neumann I, Labedi N, Terrenato I, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD006650.pub4]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agnelli 2015 (AMPLIFY)

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
Outcomes	Duration of follow-up for the following outcomes: 6 months • All-cause mortality (at 3 months) • Recurrent VTE • Major bleeding • 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	• Study details obtained from original AMPLIFY report published in *New England Journal of Medicine* 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: AMPILIFY study. G Agnelli, HR Buller, A Cohen, AS Gallus, GE Raskob and JI Weitz received honoraria as Steering Committee members of the AMPLIFY trial, and all were paid consultants to Bristol-Myers Squibb and Pfizer in connection with the development of this manuscript.

Agnelli 2015 (AMPLIFY) *(Continued)*

- ITT: "All efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented."

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" Definitely blinded
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	Unclear risk	No information about follow-up in the cancer subgroup reported
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

Cesarone 2003

Methods	Randomized trial
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: not reported
Outcomes	Duration of follow-up for the following outcomes: 3 months • 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	• Funding: not reported

Cesarone 2003 *(Continued)*

- 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)	Unclear risk	Not reported
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 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	Low risk	Comment: judgment based on comparison between MPD rate (17/199 (8.5%)) and event rate (oral anticoagulant group: 16.3%; LMWHs group: 5.2%)
Free of selective reporting?	High risk	Outcomes mentioned in the methods section (DVT, PE, major bleeding) not reported in the results section 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"
Free of other bias?	Low risk	Study not reported as stopped early for benefit

Deitcher 2006 (ONCENOX)

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: 52/102 participants overall

Deitcher 2006 (ONCENOX) *(Continued)*

Outcomes	Duration of follow-up for the following outcomes: 1 year • Mortality • Symptomatic recurrent VTE • Major bleeding • Minor bleeding **Diagnostic test for DVT/PE**: not reported
Notes	• 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"

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)	Unclear risk	Not reported
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	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 were reported on in the results section.
Free of other bias?	Low risk	Study not reported as stopped early for benefit

Hull 2006

Methods	Randomized clinical trial
Participants	200 participants with cancer (solid or hematologic) with proximal DVT with or without PE Minimum age 18 years, minimum life expectancy 3 months, 50% men, 19% had previous VTE

Hull 2006 *(Continued)*

Interventions	Interventions: tinzaparin 175 anti-Xa/kg SC daily for 12 weeks Control: UFH either 5000 U or 80 U/kg for 5 days followed by VKAs (target INR 2-3) for 12 weeks Discontinued treatment: none
Outcomes	Duration of follow-up for the following outcomes: 12 months • Mortality at 3 and 12 months • Recurrent VTE evaluated at 3 and 12 months • Bleeding (major and minor) evaluated at 3 months • Thtombocytopenia evaluated at 3 months **Screening test for DVT/PE**: not reported **Diagnostic test for recurrent VTE**: venography or compression ultrasonography
Notes	• 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)	Unclear risk	Not reported
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	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." Comment: probably yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
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 No other bias suspected

Lee 2003 (CLOT)

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: none
Outcomes	Duration of follow-up for the following outcomes: 6 months • 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	• Funding: Pharmacia • Ethical approval: the study protocol was reviewed and approved by the institutional review boards of each participating center • Conflict of interest: Dr Lee is the recipient of a New Investigator Award from the Canadian Institutes of Health Research, Drug Research and Development Program; Dr Levine is the Buffett Taylor Chair in Breast Cancer Research, McMaster University, Hamilton, ON, Canada; and Dr Kovacs is an Internal Scholar of the Department of Medicine, University of Western Ontario, London, ON, Canada. • 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 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)	Low risk	Complete follow-up

Lee 2003 (CLOT) *(Continued)*

All outcomes

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)

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)
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: 84 participants in the tinzaparin group and 108 participants in the warfarin group discontinued treatment
Outcomes	Duration of follow-up for the following outcomes: every 30 days until day 180 • 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 • 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 **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: "All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest." • ITT: "patients were randomised and included in intention-to-treat efficacy and safety analysis."

Risk of bias

Bias	Authors' judgement	Support for judgement

Lee 2015 (CATCH) *(Continued)*

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 between MPD rate (tinazapin group 33/449 (7.3%), warfarin group 50/451 (11%)) and event rate (recurrent VTE: tinzaparin group 6.9%, warfarin group 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

Methods	Randomized clinical trial
Participants	35 participants with known malignancy; treated for symptomatic DVT of the lower limbs Minimum age 18 years, mean age 65.7 years
Interventions	Intervention: nadroparin 1.025 anti-Xa IU/10 kg twice daily for 3 days then randomized to nadroparin 1.025 anti-Xa IU/10 kg twice daily After the 3rd month, nadroparin was switched to once daily Control: nadroparin 1.025 anti-Xa IU/10 kg twice daily for 3 days then randomized 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 • Mortality • Symptomatic recurrence or progression of VTE • Bleeding **Screening test for DVT/PE**: not reported **Diagnostic test for DVT**: duplex scan examination
Notes	• Funding: not reported • Ethical approval: "The study protocol was approved by the Hospital Ethics Committee."

Lopez-Beret 2001 *(Continued)*

- 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)	Unclear risk	Not reported
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 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 final allocation of all potential outcome events, including deaths, was made by an independent panel of physicians." 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	Low risk	No information about follow-up in the cancer subgroup 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 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

Mazilu 2014 (OVIDIUS)

Methods	Randomized controlled trial
Participants	46 participants with paraneoplastic DVT
Interventions	Fixed-dose dabigatran (according to individual creatinine clearance) Adjusted-dose acenocoumarol (according to individual INR determined monthly) Discontinued treatment: not reported
Outcomes	Duration of follow-up for the following outcomes: 6 months • Mortality • Combined outcome major bleeding or recurrent thrombosis **Screening test for DVT/PE**: not reported

Mazilu 2014 (OVIDIUS) *(Continued)*

	Diagnostic test for DVT/PE: not reported
Notes	• 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
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

Meyer 2002 (CANTHANOX)

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. Cointervention: not reported

Meyer 2002 (CANTHANOX) *(Continued)*

	Discontinued treatment: not reported
Outcomes	Duration of follow-up for the following outcomes: 3 and 6 months • 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 between MPD rate (8/146 (5.5%)) and event rate (mortality warfarin group 22.7%, enoxaparin group 11.3%)
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)

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 Quote: "Active cancer at baseline, defined as a diagnosis of cancer that occurred within 6 months before enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer."
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: • 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: "MHP has received research support and honoraria, and has participated in advisory boards for Bayer HealthCare, Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, Daiichi Sankyo, LEO Pharma, ThromboGenics, and Pfizer." • 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 interactive voice response system for Einstein-DVT and Einstein-PE, separately."
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Prins 2014 (EINSTEIN) *(Continued)*

All outcomes		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	Unclear 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)

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 • 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 **Screening test for DVT/PE**: not reported **Diagnostic test for DVT/PE**: not reported

Raskob 2016 (HOKUSAI) *(Continued)*

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: "GER has served as a consultant and received honoraria from Daiichi Sankyo, Bayer Healthcare, Bristol-Myers Squibb, Eli Lilly, Janssen Pharmaceuticals, Johnson & Johnson, Portola, and Pfizer." • 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	Complete follow-up
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)

Methods	Randomized, open-label, non-inferiority, multicenter clinical trial
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."

Raskob 2018 (HOKUSAI) *(Continued)*

Interventions	Duration of treatment: 6-12 months Intervention: LMWH for ≥ 5 days followed by oral edoxaban 60 mg once daily Control: dalteparin 200 IU per kilogram bodyweight SC once daily for 1 month followed by dalteparin 150 IU per kilogram once daily Cointervention: initial therapy with LMWH for ≥ 5 days
Outcomes	Duration of follow-up for the following outcomes: 12 months (on day 31 after randomization and months 3, 6, 9 and 12) • Recurrent VTE • Death from any cause • Major bleeding • Clinically relevant non-major bleeding • Recurrent DVT • Recurrent PE • Event-free survival **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." **Diagnosis test for DVT/PE**: "Appropriate diagnostic tests, laboratory tests, or both were required in people with suspected outcome events...aminotransferase and bilirubin levels."
Notes	• Study rationale and design of the HOKUSAI VTE-cancer study published in Journal of Thrombosis and Haemostasis August 2015. • Study registered at ClinicalTrials.gov, number: NCT02073682 • 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: "Dr. Buller reports personal fees from Daiichi-Sankyo, during the conduct of the study; personal fees from Bayer Healthcare, personal fees from BMS/Pfizer, personal fees from Boehringer-Ingelheim, personal fees from Portola, personal fees from Medscape, personal fees from Eli Lilly, personal fees from Sanofi Aventis, and personal fees from Ionis outside the submitted work. Dr. Carrier reports personal fees from Daiichi Sankyo during the conduct of the study; grants and personal fees from BMS, grants and personal fees from LEO Pharma, personal fees from Pfizer, personal fees from Sanofi, and personal fees from Bayer outside the submitted work. Dr. Di Nisio reports personal fees from Daiichi Sankyo outside the submitted work. Dr. Garcia reports grants and personal fees from Daiichi Sankyo during the conduct of the study; personal fees from BMS, personal fees from Boehringer-Ingelheim, grants and personal fees from Janssen, personal fees from Pfizer, personal fees from Medscape, and grants and personal fees from Incyte outside the submitted work. Dr. Grosso reports personal fees from Daiichi Sankyo outside the submitted work. Dr. Kakkar reports personal fees from Daiichi Sankyo during the conduct of the study; grants and personal fees from Bayer AG, personal fees from Boehringer-Ingelheim, personal fees from Janssen Pharma, personal fees from Sanofi SA, and personal fees from Verseon outside the submitted work. Dr. Kovacs reports grants and personal fees from Pfizer, grants and personal fees from Bayer, grants from Daiichi Sankyo Pharma, and grants from Bristol Meyers Squibb outside the submitted work. Dr. Mercuri reports personal fees from Daiichi-Sankyo, outside the submitted work. Dr. Meyer reports non-financial support from Leo Pharma, grants and non-financial support from BMS-Pfizer, non-financial support from Stago, and non-financial support from Bayer Healthcare outside the submitted work. Dr. Raskob reports personal fees from Daiichi Sankyo during the conduct of the study; personal fees from Bayer Healthcare, personal fees from BMS, personal fees from Boehringer-Ingelheim, personal fees from Eli Lilly, personal fees from Janssen, personal fees from Johnson and Johnson, personal fees from Pfizer, personal fees from Portola, personal fees from Merck, and personal fees from Medscape outside the submitted work. Dr. Segers reports grants from Daiichi Sankyo during the conduct of the study; grants from IONIS Pharmaceuticals, grants from Daiichi Sankyo, and grants from Janssen Pharmaceuticals outside the sub-

Raskob 2018 (HOKUSAI) *(Continued)*

mitted work. Dr. Shi reports personal fees from Daiichi Sankyo outside the submitted work. Dr. van Es reports personal fees from Daiichi Sankyo during the conduct of the study; personal fees from Pfizer outside the submitted work. Dr. Verhamme reports grants and personal fees from Daiichi Sankyo, during the conduct of the study; grants and personal fees from Bayer Healthcare, personal fees from BMS, grants and personal fees from Boehringer-Ingelheim, personal fees from Portola, personal fees from Medscape, grants and personal fees from LeoPharma, grants from Sanofi, personal fees from Medtronic, personal fees from Pfizer, outside the submitted work. Dr. Wang reports non-financial support from Daiichi Sankyo during the conduct of the study. Dr. Weitz reports personal fees from Daiichi-Sankyo, during the conduct of the study; personal fees from Bayer Healthcare, personal fees from BMS, personal fees from Boehringer-Ingelheim, personal fees from Ionis Pharmaceuticals, personal fees from Janssen, personal fees from Johnson and Johnson, personal fees from Pfizer, personal fees from Portola, personal fees from Medscape, personal fees from Novartis outside the submitted work. Dr. Yeo reports grants and personal fees from Daiichi Sankyo during the conduct of the study; personal fees from Bayer Healthcare, personal fees from Pfizer, personal fees from Boehringer Ingelheim, personal fees from Sanofi, and personal fees from Leo Pharma outside the submitted work. Dr. Zhang reports personal fees from Daiichi Sankyo outside the submitted work. Dr. Zwicker reports personal fees from Daiichi Sankyo during the conduct of the study; grants from Quercegen Pharma and personal fees from Parexel outside the submitted work."

- 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."
Allocation concealment (selection bias)	Unclear risk	Not reported
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	Low risk	Comment: judgment based on comparison between MPD rate (16/525 (3.04%) in intervention arm, 18/525 (3.40%) in control arm) and event rate (Recurrent VTE 41/525 (7.8%) in intervention arm, 59/525 (11.2%) in control arm).
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

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) **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: "Esteve Colome works in Laboratorios LEO Pharma, SA, and participated in the writing of the manuscript. None of the other authors had any financial interest or arrangements of concern with the medications that might pose a conflict of interest. • 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)	Unclear risk	Not reported
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)	Low risk	No information about follow-up in the cancer subgroup reported

Romera 2009 *(Continued)*

All outcomes		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)

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 Randomized, double-blind, double-dummy, multicenter trials
Participants	221 participants with active cancer at baseline and acute symptomatic proximal DVT or PE, from 228 clinical centers in 29 countries Mean age 63.5 years, 61% male, 8% with metastatic cancer
Interventions	All participants received parenteral anticoagulant (UFH, LMWH or fondaparinux) until the INR or sham INR became ≥ 2 for 2 consecutive days. Intervention: dabigatran fixed-dose 150 mg twice daily and warfarin-placebo Control: dose-adjusted warfarin therapy, after initial parenteral anticoagulation and dabigatran-placebo 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." Discontinued treatment: not reported
Outcomes	Duration of follow-up for the following outcomes: 6 months (assessed at 7 days and monthly thereafter) • All-cause mortality • Recurrent VTE • Major bleeding • Non-major clinically relevant bleeding **Screening test for DVT/PE**: not reported **Diagnosis test for DVT/PE**: not reported
Notes	• 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: "Sam Schulman reports receiving consulting fees from Boehringer Ingelheim and grant support from Bayer Healthcare." • ITT: not reported

Risk of bias

Schulman 2015 (RECOVER I-II) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used a computer generated randomisation scheme with variable block sizes" (from main study RECOVER-I). "Patients were randomised by use of an interactive voice response system and a computer-generated randomisation scheme in blocks of 4" (from main Studi RECOVER-II).
Allocation concealment (selection bias)	Low risk	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."
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)

Methods	Post hoc analysis in the subgroup of participants with cancer included in the Van Gogh DVT clinical 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

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

	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
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) • All-cause mortality (follow-up at 6 and 9 months) • 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	• NCT00067093 • 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: "Drs. Buller, Cohen, and Piovella report receiving consulting and lecture fees and grant support from Sanofi-Aventis..." • 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, *New England Journal of Medicine* 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, *New England Journal of Medicine* 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.).

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

Incomplete outcome data (attrition bias) All outcomes	Unclear 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 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

Young 2017 (SELECT-D)

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 Cointervention: not reported Discontinued treatment: not reported
Outcomes	Duration of follow-up for the following outcomes: 6 months • Recurrent VTE • Mortality • Major bleeding • Clinically relevant non-major bleeding • Acceptability • Health economics **Screening test for DVT/PE**: not reported **Diagnosis test for DVT/PE**: not reported
Notes	• ISRCTN86712308 • Funding: Bayer PLC • Ethical approval: not reported • Conflict of interest: Young: Leo Pharma: Honoraria; Bayer: Honoraria, Research Funding; Helsinn: Honoraria. Kakkar: Daiichi Sankyo: Consultancy, Honoraria; Bayer Healthcare: Consultancy, Research Funding; Boehringer Ingelheim: Consultancy, Honoraria; Janssen: Consultancy, Honoraria; Sanofi SA: Consultancy, Honoraria; Verseon: Consultancy, Honoraria. • ITT: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Young 2017 (SELECT-D) *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "203 patients randomised to each arm" Comment: probably generated sequence randomly
Allocation concealment (selection bias)	Unclear risk	Not reported
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: "Open label trial" 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	Complete follow-up
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; DOAC: direct oral anticoagulant; DVT: deep venous thrombosis; ECOG: Eastern Co-operative 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 1998	Not population of interest (people with cancer without VTE)
Agnelli 2005	Not population of interest (surgical setting)
Alikhan 2003 (MEDENOX)	Not population of interest (people with cancer without VTE); included 2 reports
Altschuler 1990	Not an RCT (no control group)
Andrea 2003	Review
Astermark 1998	Observational study
Auer 2011	Not population of interest (people with cancer without VTE)
Beckman 2003	Study included people with cancer as a subgroup for whom outcome data were not available.

Study	Reason for exclusion
Bigg 1992	Not population of interest (people with cancer without VTE)
Bona 1997	Not an RCT (no control group)
Browse 1974	Review
Burgos 1999	Not population of interest (people with cancer without VTE)
Cahan 2000	Not population of interest (people with cancer without VTE)
Clarke-Pearson 1983	Retrospective study
Clarke-Pearson 1993	Not population of interest (people with cancer without VTE)
Clenney 2003	Review
Cohen 1997	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); included 3 reports
Couban 2005	Not population of interest (people with cancer with CVC without VTE); included 3 reports
Das 1996	Study included people with cancer as a subgroup for whom outcome data were not available.
Daskalopoulos 2005	Study included people with cancer as a subgroup for whom outcome data were not available.
Dickinson 1998	Not population of interest (people with cancer without VTE)
Eriksson 2005	Too few participants with cancer (1 in LMWH group)
Farred 2004	Not an RCT
Ferretti 2005	Review
Ferretti 2006	Review of another study
Fiessinger 2005	Study included people with cancer as a subgroup for whom outcome data were not available.
Goldhaber 2002	Not population of interest (people with cancer without VTE)
Gonzalez-Fajardo 1999	Study included people with cancer as a subgroup for whom outcome data were not available.
Haas 2011	Not population of interest (people with cancer without VTE); included 3 reports
Harenberg 1996	Not population of interest (people with cancer without VTE); included 2 reports
Hata 2016	Not population of interest (people with cancer without VTE)
Hull 2007	Study included people with cancer as a subgroup for whom outcome data were not available.
Hull 2009	Study included people with cancer as a subgroup for whom outcome data were not available.
Hyers 2005	Review

Study	Reason for exclusion
Iorio 2003	Review
Kakkar 2003	Not population of interest (none of participants had cancer)
Kakkar 2010 (CANBESURE)	Not population of interest (people with cancer without VTE); included 2 reports
Kakkar 2014 (SAVE-ABDO)	Not population of interest (people with cancer without VTE); included 2 reports
Khorana 2017 (PHACS)	Not population of interest (people with cancer without VTE); included 2 reports
King 2005	Retrospective study
Koppenhagen 1992	Not population of interest (people with cancer without VTE)
Kovacs 2005	Observational study
Kucher 2005	Study included people with cancer as a subgroup for whom outcome data were not available.
Larocca 2012	Not comparison of interest (LMWH vs aspirin)
Lee 2005	Review
Lee 2006	Review
Levine 1995	Study included people with cancer as a subgroup for whom outcome data were not available.
Levine 2003	Review
Lopaciuk 1999	Study included people with cancer as a subgroup for whom outcome data were not available.
Loprinzi 1999	Not population of interest (people with cancer without VTE)
Macbeth 2016 (FRAGMATIC)	Not population of interest (people with cancer without VTE); included 4 reports
Massicotte 2003	Study included people with cancer as a subgroup for whom outcome data were not available.
Maxwell 2001	Not population of interest (people with cancer without VTE)
McCan 2000	Review
Murakami 2002	Not population of interest (people with cancer without VTE)
Nagata 2015	Not population of interest (people with cancer without VTE)
Nurmohamed 1996	Not population of interest (people with cancer without VTE)
Olin 1987	Retrospective study
Palareti 2000	Observational study
Palumbo 2011	Not population of interest (people with cancer without VTE); included 6 reports
Partsch 2001	Observational study
Pelzer 2015 (CONKO-004)	Not population of interest (people with cancer without VTE); included 10 reports

Study	Reason for exclusion
Pinede 2001	Not population of interest (none of participants had cancer)
Pini 1994	Study included people with cancer as a subgroup for whom outcome data were not available.
Pérez-de-Llano 2010	Study included people with cancer as a subgroup for whom outcome data were not available.
Sakon 2010	Not population of interest (people with cancer without VTE)
Schulman 2003 (extended vs limited)	Not intervention of interest
Schulman 2006	Not population of interest (none of participants had cancer)
Schulman 2013 (RE-MEDY)	Extended treatment
Schwartz 2005	Case series
Scott 2003	Review
Shattil 1984	Review
Siragusa 2010	Not intervention of interest: different duration of interventional drugs
Solymoss 1999	Review
Song 2014	Not population of interest (people with cancer without VTE)
Stine 2004	Retrospective study
Streiff 2006	Review
Suarez Alvarez 2003	Not an RCT (no control group)
Taliani 2003	Observational study
Tedoldi 1993	Not population of interest (none of participants had cancer)
Vedovati 2014	Not population of interest (people with cancer without VTE); included 4 reports
Veiga 2000	Study included people with cancer as a subgroup for whom outcome data were not available.
Verso 2008	Not population of interest (people with cancer without VTE); included 4 reports
Vucic 2002	Observational study
Ward 1998	Not population of interest (people with cancer without VTE)
Wester 1996	Not population of interest (people with cancer with VTE) or not comparison of interest (LMWH vs DOAC); included 2 reports
Zheng 2014	Not population of interest (people with cancer without VTE)
Zwicker 2013 (MICROTEC)	Not population of interest (people with cancer without VTE); included 2 reports

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

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

Agnelli 2017 (CARAVAGGIO)

Trial name or title	Apixaban for the treatment of venous thromboembolism in patients with cancer (CARAVAGGIO)
Methods	Randomized open-label trial
Participants	People with cancer aged > 18 years and newly diagnosed, objectively confirmed symptomatic or unsuspected, proximal lower-limb DVT or symptomatic PE or unsuspected PE
Interventions	Intervention: apixaban orally 10 mg twice daily for 7 days, followed by 5 mg twice daily (total period of treatment: 6 months) Control: dalteparin 200 IU/kg SC once daily for 1 month. Thereafter, dalteparin will be administered at 150 IU/kg once daily for 5 months
Outcomes	Primary outcome: objectively confirmed recurrent VTE occurring during the study period
Starting date	April 2017
Contact information	Giancarlo Agnelli, MD, email: giancarlo.agnelli@unipg.it
Notes	Status as of May 2018: recruiting Funding: Fadoi Foundation, Italy

Kamphuisen 2010 (Longheva)

Trial name or title	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 2018: terminated Funding: University Medical Center Groningen

Karatas 2015

Trial name or title	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 × 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 2018: recruiting Funding: AIO-Studien-gGmbH

McBane 2017 (ADAM VTE)

Trial name or title	Apixaban or dalteparin in reducing blood clots in patients with cancer related venous thromboembolism
Methods	Randomized, open-label trial
Participants	People with cancer aged ≥ 18 years with confirmed acute lower extremity or upper extremity DVT
Interventions	Intervention 1: apixaban 10 mg oral twice daily on days 1-7 and lower-dose apixaban 5 mg oral twice daily on days 8-180 Intervention 2: dalteparin 200 IU/kg/day SC daily on days 1-30 and lower-dose dalteparin 150 IU/kg/day SC daily on days 31-180
Outcomes	Primary outcome: major bleeding including fatal bleeding up to 7 days after treatment termination Secondary outcome: bleeding event defined as a major bleed or a clinically relevant non-major bleed, time to the first event of the composite DVT/PE
Starting date	November 2015
Contact information	Robert D McBane, email: mcbane.robert@mayo.edu
Notes	Status as of May 2018: active but not recruiting participants Funding: Academic and Community Cancer Research United

Meyer 2016

Trial name or title	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 2018: recruiting Funding: Assistance Publique – Hôpitaux de Paris

Ryun Park 2017 (PRIORITY)

Trial name or title	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 2018: recruiting Fending: Asan Medical Center

Schrag 2016 (CANVAS)

Trial name or title	Direct oral anticoagulants (DOACs) versus LMWH ± 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 2018: recruiting Funding: Patient-Centered Outcomes Research Institute (PCORI)

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

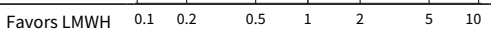
DATA AND ANALYSES

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 All-cause mortality (up to 12 months)	5	1747	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.13]
2 All-cause mortality (up to 12 months) (time-to-event)	2	810	HR (Random, 95% CI)	0.94 [0.74, 1.20]
3 Recurrent venous thromboembolism (up to 6 months)	5	1781	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.43, 0.77]
4 Recurrent venous thromboembolism (time-to-event)	2	810	HR (Random, 95% CI)	0.49 [0.31, 0.78]
5 Major bleeding (6-12 months)	4	1712	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.55, 2.12]
6 Minor bleeding (6-12 months)	4	1712	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.27]
7 Thrombocytopenia (6-12 months)	1	138	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.52, 1.69]

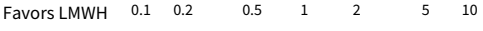
Analysis 1.1. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 1 All-cause mortality (up to 12 months).

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Deitcher 2006 (ONCENOX)	22/53	11/32		4.51%	1.21[0.68,2.15]
Lee 2003 (CLOT)	130/336	136/336		42.75%	0.96[0.79,1.15]
Lee 2015 (CATCH)	150/416	138/401		43.12%	1.05[0.87,1.26]
Lopez-Beret 2001	7/17	6/18		1.99%	1.24[0.52,2.94]
Meyer 2002 (CANTHANOX)	22/67	29/71		7.63%	0.8[0.52,1.25]
Total (95% CI)	**889**	**858**		**100%**	**1[0.88,1.13]**
Total events: 331 (LMWH), 320 (VKA)					
Heterogeneity: Tau²=0; Chi²=2.04, df=4(P=0.73); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					



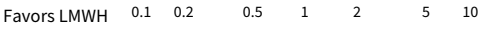
Analysis 1.2. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 2 All-cause mortality (up to 12 months) (time-to-event).

Study or subgroup	LMWH N	VKA N	log[HR] (SE)	HR IV, Random, 95% CI	Weight	HR IV, Random, 95% CI
Lee 2003 (CLOT)	336	336	-0 (0.1)		82.48%	1[0.82,1.21]
Meyer 2002 (CANTHANOX)	67	71	-0.3 (0.28)		17.52%	0.72[0.42,1.25]
Total (95% CI)					**100%**	**0.94[0.74,1.2]**
Heterogeneity: Tau²=0.01; Chi²=1.19, df=1(P=0.28); I²=16.05%						
Test for overall effect: Z=0.49(P=0.62)						



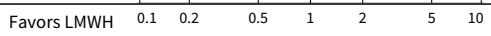
Analysis 1.3. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 3 Recurrent venous thromboembolism (up to 6 months).

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Deitcher 2006 (ONCENOX)	4/53	3/32		4.17%	0.81[0.19,3.37]
Lee 2003 (CLOT)	27/336	53/336		44.47%	0.51[0.33,0.79]
Lee 2015 (CATCH)	31/416	45/401		44.8%	0.66[0.43,1.03]
Meyer 2002 (CANTHANOX)	2/67	3/71		2.76%	0.71[0.12,4.1]
Romera 2009	2/36	7/33		3.8%	0.26[0.06,1.17]
Total (95% CI)	**908**	**873**		**100%**	**0.58[0.43,0.77]**
Total events: 66 (LMWH), 111 (VKA)					
Heterogeneity: Tau²=0; Chi²=2.04, df=4(P=0.73); I²=0%					
Test for overall effect: Z=3.71(P=0)					



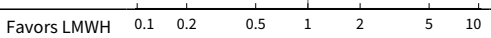
Analysis 1.4. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 4 Recurrent venous thromboembolism (time-to-event).

Study or subgroup	LMWH N	VKA N	log[HR] (SE)	HR IV, Random, 95% CI	Weight	HR IV, Random, 95% CI
Lee 2003 (CLOT)	336	336	-0.7 (0.24)		93.36%	0.48[0.3,0.77]
Meyer 2002 (CANTHANOX)	67	71	-0.4 (0.9)		6.64%	0.7[0.12,4.08]
Total (95% CI)					**100%**	**0.49[0.31,0.78]**
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%						
Test for overall effect: Z=3.06(P=0)						



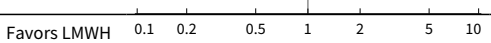
Analysis 1.5. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 5 Major bleeding (6-12 months).

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Deitcher 2006 (ONCENOX)	6/53	1/32		8.85%	3.62[0.46,28.74]
Lee 2003 (CLOT)	19/336	12/336		34.7%	1.58[0.78,3.21]
Lee 2015 (CATCH)	12/416	11/401		31.08%	1.05[0.47,2.36]
Meyer 2002 (CANTHANOX)	5/67	12/71		25.37%	0.44[0.16,1.19]
Total (95% CI)	**872**	**840**		**100%**	**1.09[0.55,2.12]**
Total events: 42 (LMWH), 36 (VKA)					
Heterogeneity: Tau²=0.21; Chi²=5.59, df=3(P=0.13); I²=46.3%					
Test for overall effect: Z=0.24(P=0.81)					



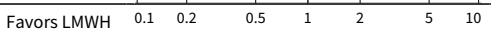
Analysis 1.6. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 6 Minor bleeding (6-12 months).

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Deitcher 2006 (ONCENOX)	39/53	17/32		29.19%	1.39[0.96,1.99]
Lee 2003 (CLOT)	28/336	51/336		27.32%	0.55[0.36,0.85]
Lee 2015 (CATCH)	49/416	69/401		29.78%	0.68[0.49,0.96]
Meyer 2002 (CANTHANOX)	5/67	9/71		13.71%	0.59[0.21,1.67]
Total (95% CI)	**872**	**840**		**100%**	**0.78[0.47,1.27]**
Total events: 121 (LMWH), 146 (VKA)					
Heterogeneity: Tau²=0.19; Chi²=13.85, df=3(P=0); I²=78.34%					
Test for overall effect: Z=1(P=0.32)					



Analysis 1.7. Comparison 1 Low molecular weight heparins (LMWH) versus vitamin K antagonists (VKA), Outcome 7 Thrombocytopenia (6-12 months).

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Meyer 2002 (CANTHANOX)	16/67	18/71		100%	0.94[0.52,1.69]
Total (95% CI)	**67**	**71**		**100%**	**0.94[0.52,1.69]**
Total events: 16 (LMWH), 18 (VKA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.2(P=0.84)					

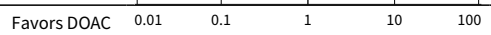


Comparison 2. Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 All-cause mortality (up to 12 months)	4	1031	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.71, 1.21]
2 Recurrent venous thromboembolism (up to 12 months)	4	1022	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.31]
3 Major bleeding (up to 12 months)	4	1030	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.38, 1.57]
4 Minor bleeding (up to 12 months)	4	1030	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.58, 1.22]

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

Study or subgroup	DOAC n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2015 (AMPLIFY)	5/74	6/69		5.48%	0.78[0.25,2.43]
Prins 2014 (EINSTEIN)	38/257	36/202		41.04%	0.83[0.55,1.26]
Raskob 2016 (HOKUSAI)	31/109	26/99		36.1%	1.08[0.69,1.69]
Schulman 2015 (RECOVER I-II)	16/114	16/107		17.38%	0.94[0.49,1.78]
Total (95% CI)	**554**	**477**		**100%**	**0.93[0.71,1.21]**
Total events: 90 (DOAC), 84 (VKA)					
Heterogeneity: Tau^2=0; Chi^2=0.84, df=3(P=0.84); I^2=0%					
Test for overall effect: Z=0.53(P=0.59)					

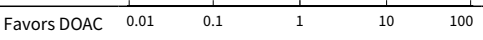


Analysis 2.2. Comparison 2 Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA), Outcome 2 Recurrent venous thromboembolism (up to 12 months).

Study or subgroup	DOAC n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2015 (AMPLIFY)	3/68	1/66		9.35%	2.91[0.31,27.29]
Prins 2014 (EINSTEIN)	6/257	8/202		43.09%	0.59[0.21,1.67]
Raskob 2016 (HOKUSAI)	4/109	7/99		32.62%	0.52[0.16,1.72]
Schulman 2015 (RECOVER I-II)	2/114	3/107		14.95%	0.63[0.11,3.67]
Total (95% CI)	**548**	**474**		**100%**	**0.66[0.33,1.31]**
Total events: 15 (DOAC), 19 (VKA)					
Heterogeneity: Tau^2=0; Chi^2=1.9, df=3(P=0.59); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					

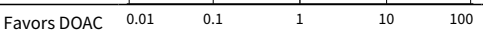
Analysis 2.3. Comparison 2 Direct oral anticoagulants (DOAC) versus vitamin K antagonists (VKA), Outcome 3 Major bleeding (up to 12 months).

Study or subgroup	DOAC n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2015 (AMPLIFY)	1/74	3/68		10.02%	0.31[0.03,2.87]
Prins 2014 (EINSTEIN)	5/257	8/202		41.38%	0.49[0.16,1.48]
Raskob 2016 (HOKUSAI)	5/109	3/99		25.45%	1.51[0.37,6.17]
Schulman 2015 (RECOVER I-II)	4/114	3/107		23.15%	1.25[0.29,5.46]
Total (95% CI)	**554**	**476**		**100%**	**0.77[0.38,1.57]**
Total events: 15 (DOAC), 17 (VKA)					
Heterogeneity: Tau^2=0; Chi^2=2.6, df=3(P=0.46); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					



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

Study or subgroup	DOAC n/N	VKA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2015 (AMPLIFY)	9/74	13/68		19.7%	0.64[0.29,1.39]
Prins 2014 (EINSTEIN)	25/257	19/202		34.01%	1.03[0.59,1.82]
Raskob 2016 (HOKUSAI)	16/109	23/99		33.09%	0.63[0.35,1.13]
Schulman 2015 (RECOVER I-II)	10/114	6/107		13.21%	1.56[0.59,4.16]
Total (95% CI)	**554**	**476**		**100%**	**0.84[0.58,1.22]**
Total events: 60 (DOAC), 61 (VKA)					
Heterogeneity: Tau^2=0.02; Chi^2=3.5, df=3(P=0.32); I^2=14.27%					
Test for overall effect: Z=0.9(P=0.37)					



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
1 All-cause mortality (up to 12 months)	1	1016	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.25]
2 Recurrent venous thromboembolism (up to 12 months)	1	1016	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.47, 1.01]
3 Major bleeding (up to 12 months)	1	1016	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.01, 2.88]
4 Minor bleeding (up to 12 months)	1	1016	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.95, 1.80]

Analysis 3.1. Comparison 3 Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 1 All-cause mortality (up to 12 months).

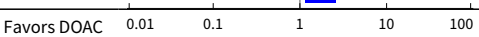
Study or subgroup	DOAC n/N	LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Raskob 2018 (HOKUSAI)	206/509	192/507		100%	1.07[0.92,1.25]
Total (95% CI)	**509**	**507**		**100%**	**1.07[0.92,1.25]**
Total events: 206 (DOAC), 192 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.4)					

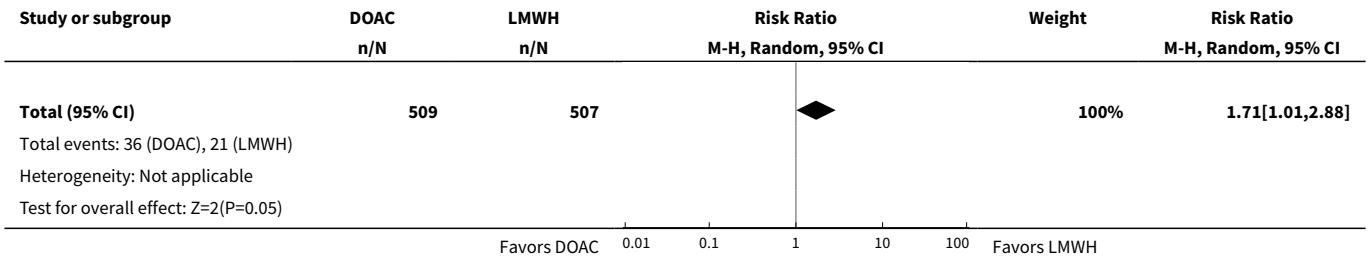
Analysis 3.2. Comparison 3 Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 2 Recurrent venous thromboembolism (up to 12 months).

Study or subgroup	DOAC n/N	LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Raskob 2018 (HOKUSAI)	41/509	59/507		100%	0.69[0.47,1.01]
Total (95% CI)	**509**	**507**		**100%**	**0.69[0.47,1.01]**
Total events: 41 (DOAC), 59 (LMWH)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.9(P=0.06)					

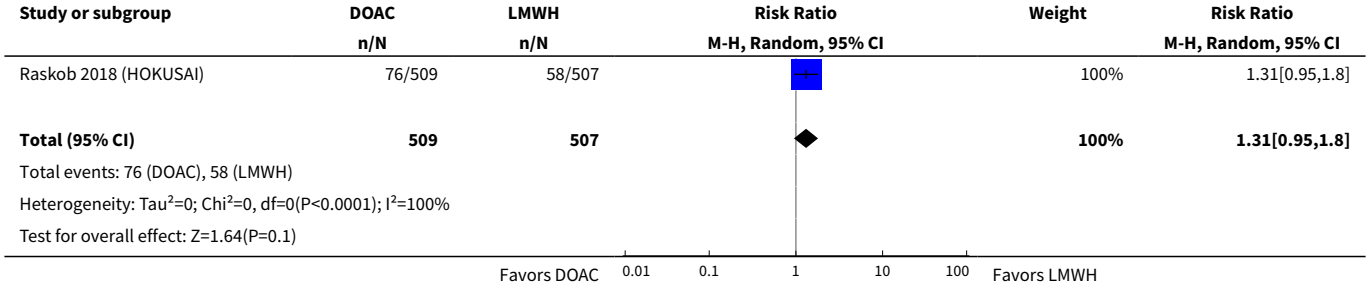
Analysis 3.3. Comparison 3 Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 3 Major bleeding (up to 12 months).

Study or subgroup	DOAC n/N	LMWH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Raskob 2018 (HOKUSAI)	36/509	21/507		100%	1.71[1.01,2.88]





Analysis 3.4. Comparison 3 Direct oral anticoagulants (DOAC) versus low molecular weight heparins (LMWH), Outcome 4 Minor bleeding (up to 12 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).

Table 1. Glossary *(Continued)*

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.
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 conduct citation tracking of included studies in Web of Science Core Collection on an ongoing basis. For that purpose, we have set up citation alerts in Web of Science Core Collection. We will manually screen the reference list of any newly included studies, and identified relevant guidelines and systematic reviews. Also, we will use the 'related citation' feature in PubMed to identify additional articles.

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% (James Thomas, personal communication). 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. Cochrane's living systematic review pilots

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 (Elliott 2017). Cochrane is exploring the feasibility of preparing and publishing living systematic reviews in a series of pilots (which includes this review). For the Cochrane pilots, searching is being conducted monthly, and new relevant evidence (studies, data or other information) will be incorporated into the review in a timely manner, so that the findings of the review remain current.

For the most up-to-date information about the review, the results of the searches and any new evidence being incorporated, readers are encouraged to check the update status information. The update status information will be updated whenever the searches are rerun. The review will be updated with a new citation whenever a new study is found.

Appendix 3. Full search strategies for the electronic databases: update 2010

Database	Strategy
CENTRAL (the Cochrane Library, latest issue)	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane 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 orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocoumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor #8 6 AND 7
MEDLINE	#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane 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 orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocoumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 (fondaparinux OR Arixtra).tw #11 (ximelagatran OR Exanta).tw #12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw. #13 5 OR 9 OR 10 OR 11 OR 12 #14 Neoplasms/ #15 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw

(Continued)

	#16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19
Embase	#1 Heparin/ #2 heparin.tw #3 Low Molecular Weight Heparin/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane 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 orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarin derivative/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocoumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 fondaparinux/ #11 (fondaparinux OR Arixtra).tw #12 ximelagatran/ #13 (ximelagatran OR Exanta).tw #14 (Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban).tw. #15 5 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 #16 Neoplasm/ #17 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #18 16 OR 17 #19 Random:.tw. OR clinical trial:.mp. OR exp health care quality #20 animals/ NOT human/ #21 19 NOT 20 #22 15 AND 18 AND 21
ISI (International Scientific Information) the Web of Science	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane 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 orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocoumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor #8 random$ OR placebo$ OR versus OR vs OR double blind OR double-blind OR compar$ OR controlled #9 6 AND 7 AND 8

Appendix 4. Full search strategies for the electronic databases: update 2013

Database	Strategy

(Continued)

CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Heparin] explode all trees #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane 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 orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum) #3 MeSH descriptor: [Coumarins] explode all trees #4 (warfarin or coumadin or acenocoumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA) #5 (fondaparinux or arixtra) #6 (ximelagatran or exanta) #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Neoplasms] explode all trees #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) #11 #9 or #10 #12 #8 and #10
MEDLINE	#1 exp Heparin/ #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane 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 orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.; #4 (warfarin or coumadin or acenocoumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw. #5 (fondaparinux or arixtra).tw. #6 (ximelagatran or exanta).tw. #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw. #8 1 or 2 or 3 or 4 or 5 or 6 or 7 #9 exp Neoplasms/ #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw. #11 9 or 10 #12 8 and 11 #13 randomised controlled trial.pt. #14 controlled clinical trial.pt. #15 randomized.ab. #16 placebo.ab. #17 drug therapy.fs.

(Continued)

	#18 randomly.ab. #19 trial.ab. #20 groups.ab. #21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 #22 12 and 21 #23 exp animals/ not humans.sh. #24 22 not 23
Embase	#1 heparin/ #2 exp low molecular weight heparin/ #3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane 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 orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw. #4 exp coumarin derivative/ #5 (warfarin or coumadin or acenocoumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw. #6 (fondaparinux or arixtra).tw. #7 (ximelagatran or exanta).tw. #8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw. #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 #10 exp neoplasm/ #11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw. #12 10 or 11 #13 9 and 12 #14 crossover procedure/ #15 double-blind procedure/ #16 randomised controlled trial/ #17 single-blind procedure/ #18 random*.mp. #19 factorial*.mp. #20 (crossover* or cross over* or cross-over*).mp. #21 placebo*.mp. #22 (double* adj blind*).mp. #23 (singl* adj blind*).mp. #24 assign*.mp.

(Continued)

	#25 allocat*.mp.
	#26 volunteer*.mp.
	#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
	#28 13 and 27
	#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
	#30 28 not 29

Appendix 5. Full search strategies for the electronic databases: update 2017

Database	Strategy
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Anticoagulants] explode all trees
	#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 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 Hepalean or Calcilean or Calciparine or Liquaemin 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-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl)
	#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 argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b
	#10 TSOAC* or NOAC* or DOAC*
	#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
	#12 MeSH descriptor: [Neoplasms] explode all trees

(Continued)

	#13 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* #14 #13 or #14 #15 #11 and #14
MEDLINE	**RCT search strategy**: 1. exp Anticoagulants/ 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 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 Hepalean or Calcilean or Calciparine or Liquaemin 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/ 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 Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).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 BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. 10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw. 11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12. exp Neoplasms/ 13. (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. 14. 12 or 13 15. 11 and 14 16. randomised controlled trial.pt. 17. controlled clinical trial.pt. 18. randomized.ab.

(Continued)

19. placebo.ab.

20. clinical trials as topic.sh.

21. randomly.ab.

22. trial.ti.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. (animals not (humans and animals)).sh.

25. 23 not 24

26. 15 and 25

Systematic Review search strategy:

1. exp Anticoagulants/

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 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 Hepalean or Calcilean or Calciparine or Liquaemin 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/

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 Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).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 BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp Neoplasms/

13. (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.

14. 12 or 13

(Continued)

	15. 11 and 14 16. (review or review,tutorial or review, academic).pt. 17. (medline or medlars or embase or pubmed or cochrane).tw,sh. 18. (scisearch or psychinfo or psycinfo).tw,sh. 19. (psychlit or psyclit).tw,sh. 20. cinahl.tw,sh. 21. ((hand adj2 search*) or (manual* adj2 search*)).tw,sh. 22. (electronic database* or bibliographic database* or computeri?ed database* or online database*).tw,sh. 23. (pooling or pooled or mantel haenszel).tw,sh. 24. (peto or dersimonian or der simonian or fixed effect).tw,sh. 25. (retraction of publication or retracted publication).pt. 26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27. 16 and 26 28. meta-analysis.pt. 29. meta-analysis.sh. 30. (meta-analys* or meta analys* or metaanalys*).tw,sh. 31. (systematic* adj5 review*).tw,sh. 32. (systematic* adj5 overview*).tw,sh. 33. (quantitativ* adj5 review*).tw,sh. 34. (quantitativ* adj5 overview*).tw,sh. 35. (methodologic* adj5 review*).tw,sh. 36. (methodologic* adj5 overview*).tw,sh. 37. (integrative research review* or research integration).tw. 38. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 39. 27 or 38 41. 15 and 39
Embase	**RCT search strategy:** 1. exp anticoagulant agent/ 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 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 Hepalean or Calcilean or Calciparine or Liquaemin 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.

(Continued)

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 coumarin derivative/

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 Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).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 BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp neoplasm/

13. (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.

14. 12 or 13

15. 11 and 14

16. crossover procedure/

17. double-blind procedure/

18. randomised controlled trial/

19. single-blind procedure/

20. random*.mp.

21. factorial*.mp.

22. (crossover* or cross over* or cross-over*).mp.

23. placebo*.mp.

24. (double* adj blind*).mp.

25. (singl* adj blind*).mp.

26. assign*.mp.

27. allocat*.mp.

28. volunteer*.mp.

29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

(Continued)

30. 15 and 29

Systematic Review search strategy:

1. exp anticoagulant agent/

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 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 Hepalean or Calcilean or Calciparine or Liquaemin 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 coumarin derivative/

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 Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).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 BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp neoplasm/

13. (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.

14. 12 or 13

15. 11 and 14

16. exp review/

17. (literature adj3 review*).ti,ab.

18. exp meta analysis/

19. exp "Systematic Review"/

20. 16 or 17 or 18 or 19

(Continued)

	21. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab. 22. RETRACTED ARTICLE/ 23. 21 or 22 24. 20 and 23 25. (systematic* adj2 (review* or overview)).ti,ab. 26. (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*).ti,ab. 27. 24 or 25 or 26 28. 15 and 27
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Anticoagulants] explode all trees #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 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 Hepalean or Calcilean or Calciparine or Liquaemin 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-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl) #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 argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b #10 TSOAC* or NOAC* or DOAC* #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 #12 MeSH descriptor: [Neoplasms] explode all trees #13 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* #14 #13 or #14

(Continued)

	#15 #11 and #14

Appendix 6. GRADE evidence profile low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Certainty assessment							№ of participants		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH secondary prophylaxis	VKA secondary prophylaxis	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: 12 months)												
5	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	331/889 (37.2%)	320/858 (37.3%)	**RR 1.00** (0.88 to 1.13)	**0 fewer per 1000** (from 45 fewer to 48 more)	⊕⊕⊕⊖ **Moderate**	Critical
Recurrent venous thromboembolism (follow-up: 12 months)												
5	Randomized trials	Serious[b]	Not serious	Not serious	Not serious	None	66/908 (7.3%)	111/873 (12.7%)	**RR 0.58** (0.43 to 0.77)	**53 fewer per 1000** (from 29 fewer to 72 fewer)	⊕⊕⊕⊖ **Moderate**	Critical
Major bleeding (follow-up: range 6-12 months)												
4	Randomized trials	Not serious	Not serious	Not serious	Serious[c]	None	42/872 (4.8%)	36/840 (4.3%)	**RR 1.09** (0.55 to 2.12)	**4 more per 1000** (from 19 fewer to 48 more)	⊕⊕⊕⊖ **Moderate**	Critical
Minor bleeding (follow-up: range 6-12 months)												
4	Randomized trials	Not serious	Serious[d]	Not serious	Serious[e]	None	121/872 (13.9%)	146/840 (17.4%)	**RR 0.78** (0.47 to 1.27)	**38 fewer per 1000** (from 47 more to 92 fewer)	⊕⊕⊖⊖ **Low**	Critical
Health-related quality of life – not reported												
—	—	—	—	—	—	—	—	—	—	—	—	Critical

CI: confidence interval; **LMWH:** low molecular weight heparin; **RR:** risk ratio; **VKA:** vitamin K antagonist.

Explanations

[a]Downgraded one level due to concerns about both imprecision, 95% CI was consistent with the possibility for important benefit (45 per 1000 absolute reduction) and possibility of important harm (48 per 1000 absolute increase), included 651 events in total, and concerns about 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 five out of five studies.

[b]Downgraded 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 five out of five studies).

[c]Downgraded one level due to concerns about both imprecision, 95% CI was consistent with the possibility for important benefit (19 per 1000 absolute reduction) and possibility of important harm (48 per 1000 absolute increase), included 78 events in total, and concerns about risk of bias, allocation concealment unclear in one study, high risk of selective reporting and high risk of incomplete outcome data in one study and lack of blinding of participants and personnel in four out of four studies.

[d]Downgraded one level due to serious inconsistency (I^2 = 78%).

[e]Downgraded one level due to concerns about both imprecision, 95% CI was consistent with the possibility for important benefit (92 per 1000 absolute reduction) and possibility of important harm (47 per 1000 absolute increase), included 267 events in total, and concerns about risk of bias, allocation concealment unclear in one study, high risk of selective reporting and high risk of incomplete outcome data in one study and lack of blinding of participants and personnel in four out of four studies.

Appendix 7. GRADE evidence profile direct oral anticoagulant (DOAC) versus vitamin K antagonist (VKA)

Certainty assessment						№ of participants		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOAC secondary prophylaxis	VKA secondary prophylaxis	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality up to 12 months												
4	Randomized trials	Not serious	Not serious	Serious[a]	Serious[b]	None	90/554 (16.2%)	84/477 (17.6%)	**RR 0.93** (0.71 to 1.21)	**12 fewer per 1000** (from 37 more to 51 fewer)	⊕⊕⊖⊖ **Low**	Critical
Recurrent venous thromboembolism up to 12 months												
4	Randomized trials	Not serious	Not serious	Serious[a]	Serious[c]	None	15/548 (2.7%)	19/474 (4.0%)	**RR 0.66** (0.33 to 1.31)	**14 fewer per 1000** (from 12 more to 27 fewer)	⊕⊕⊖⊖ **Low**	Critical
Major bleeding (follow-up: range 3-12 months)												
4	Randomized trials	Not serious	Not serious	Serious[a]	Serious[d]	None	15/554 (2.7%)	17/476 (3.6%)	**RR 0.77** (0.38 to 1.57)	**8 fewer per 1000** (from 20 more to 22 fewer)	⊕⊕⊖⊖ **Low**	Critical
Minor bleeding (follow-up: range 3-12 months)												
4	Randomized trials	Not serious	Not serious	Serious[a]	Serious[e]	None	60/554 (10.8%)	61/476 (12.8%)	**RR 0.84** (0.58 to 1.22)	**21 fewer per 1000** (from 28 more to 54 fewer)	⊕⊕⊖⊖ **Low**	Critical
Health-related quality of life (follow-up: range 3-12 months)												
1	Randomized trials	Not serious	Not serious	Serious[f]	Not serious	None	Prins 2014 (EINSTEIN DVT-PE; 8485 participants): "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				⊕⊕⊕⊖ **Moderate**	Critical

injected low molecular-weight heparin." The tool used was validated measure of treatment satisfaction – the Anti-Clot Treatment Scale (ACTS))

(Continued)

CI: confidence interval; **DOAC:** direct oral anticoagulant; **RR:** risk ratio; **VTA:** vitamin K antagonist.

Explanations

[a]Downgraded one level due to serious indirectness. Two studies (RECOVER I-II and RE-MEDY) included people with a diagnosis of cancer within five years before enrolment.

[b]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility of important benefit (51 fewer per 1000) and possibility of important harm (37 more per 1000); included 174 events.

[c]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility of important benefit (27 fewer per 1000) and possibility of important harm (12 more per 1000); included 34 events.

[d]Downgraded one level due to serious imprecision, 95% CI was consistent with the possibility for important benefit (22 per 1000 absolute reduction) and possibility of important harm (20 per 1000 absolute increase), included 32 events.

[e]Downgraded by one level due to serious imprecision, 95% CI was consistent with the possibility for important benefit (54 per 1000 absolute reduction) and possibility of important harm (28 per 1000 absolute increase), included 122 events.

[f]Downgraded by one level for serious indirectness. The study by Prins and colleagues (Prins 2014 (EINSTEIN); 8485 participants) reported health-related quality of life for the whole study population, without providing data for the cancer subgroup.

Appendix 8. GRADE Evidence profile direct oral anticoagulant versus low molecular weight heparin

Certainty assessment							№ of participants		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOAC secondary prophylaxis	LMWH secondary prophylaxis	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality up to 12 months												
1	Randomized trials	Serious [a]	Not serious	Not serious	Serious[b]	None	206/509 (40.5%)	192/507 (37.9%)	**RR 1.07** (0.92 to 1.25)	**27 more per 1000** (from 30 fewer to 95 more)	⊕⊕⊖⊖ **Low**	Critical
Recurrent venous thromboembolism up to 12 months												
1	Randomized trials	Serious [a]	Not serious	Not serious	Serious[c]	None	41/509 (8.1%)	59/507 (11.6%)	**RR 0.69** (0.47 to 1.01)	**36 fewer per 1000** (from 1 more to 62 fewer)	⊕⊕⊖⊖ **Low**	Critical
Major bleeding up to 12 months												
1	Randomized trials	Serious [a]	Not serious	Not serious	Serious[d]	None	36/509 (7.1%)	21/507 (4.1%)	**RR 1.71** (1.01 to 2.88)	**29 more per 1000** (from 0 fewer to 78 more)	⊕⊕⊖⊖ **Low**	Critical
Minor bleeding up to 12 months												
1	Randomized trials	Serious [a]	Not serious	Not serious	Serious[e]	None	76/509 (14.9%)	58/507 (11.4%)	**RR 1.31** (0.95 to 1.80)	**35 more per 1000** (from 6 fewer to 92 more)	⊕⊕⊖⊖ **Low**	Important
Health-related quality of life – not reported												
—	—	—	—	—	—	—	—	—	—	—	—	

CI: confidence interval; **DOAC:** direct oral anticoagulant; **LMWH:** low molecular weight heparin; **RR:** risk ratio.

Explanations

[a]Downgraded one level for serious risk of bias due to lack of blinding of patients and personnel and whether allocation was concealed was not reported.

[b]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for important benefit (30 per 1000 absolute reduction) and possibility of important harm (95 per 1000 absolute increase); included 398 events.

[c]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for important benefit (62 per 1000 absolute reduction) and possibility of harm not exceeding a minimal important difference (1 per 1000 absolute increase); included 100 events.

[d]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for no effect and possibility of important harm (78 per 1000 absolute increase); included 57 events.

[e]Downgraded one level for serious imprecision, 95% CI was consistent with the possibility for important benefit (6 per 1000 absolute reduction) and possibility of important harm (92 per 1000 absolute increase); included 134 events.

Appendix 9. GRADE Evidence profile idraparinux versus vitamin K antagonist

Certainty assessment							№ of participants		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Idraparinux secondary prophylaxis**	**VKA secondary prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause mortality (follow-up: mean 6 months)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	46/146 (31.5%)	39/138 (28.3%)	**RR 1.11** (0.78 to 1.59)	**31 more per 1000** (from 62 fewer to 167 more)	⊕⊕⊕⊖ **Moderate**	Critical
Recurrent venous thromboembolism (follow-up: mean 6 months)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	5/140 (3.6%)	10/130 (7.7%)	**RR 0.46** (0.16 to 1.32)	**42 fewer per 1000** (from 25 more to 65 fewer)	⊕⊕⊖⊖ **Low**	Critical
Major bleeding (follow-up: mean 6 months)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	6/140 (4.3%)	5/130 (3.8%)	**RR 1.11** (0.35 to 3.56)	**4 more per 1000** (from 25 fewer to 98 more)	⊕⊕⊖⊖ **Low**	Critical
Minor bleeding – not reported												
—	—	—	—	—	—	—	—	—	—	—	—	Critical
Health-related quality of life – not reported												
—	—	—	—	—	—	—	—	—	—	—	—	Critical

CI: confidence interval; **RR:** risk ratio; VKA: vitamin K antagonist.

Explanations

[a]Downgraded 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.

[b]Downgraded two levels 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.

[c]Downgraded 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.

Appendix 10. Detailed results of sensitivity analyses

Comparison	**LMWH vs VKA**
Outcome	**Recurrent VTE**
CCA effect estimate	RR 0.58 (95% CI 0.43 to 0.77)
Sensitivity analysis	—
RI $1.5_{intervention}$ $1_{control}$	RR 0.59 (95% CI 0.44 to 0.79)
RI $2_{intervention}$ $1_{control}$	RR 0.60 (95% CI 0.45 to 0.80)
RI $3_{intervention}$ $1_{control}$	RR 0.62 (95% CI 0.46 to 0.83)
RI $5_{intervention}$ $1_{control}$	RR 0.65 (95% CI 0.47 to 0.90)

Comparison	**DOAC vs LMWH**
Outcome	**Major bleeding**
CCA effect estimate	RR 1.70 (95% CI 1.01 to 2.88)
Sensitivity analysis	—
RI $1.5_{intervention}$ $1_{control}$	RR 1.68 (95% CI 0.99 to 2.83)
RI $2_{intervention}$ $1_{control}$	RR 1.65 (95% CI 0.98 to 2.79)
RI $3_{intervention}$ $1_{control}$	RR 1.61 (95% CI 0.95 to 2.71)
RI $5_{intervention}$ $1_{control}$	RR 1.53 (95% CI 0.91 to 2.58)

CCA: complete case analysis; CI: confidence interval; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; RI: relative incidence; RR: risk ratio; VKA: vitamin K antagonist; VTE: venous thromboembolism.

WHAT'S NEW

Date	Event	Description
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.

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 2, 2008

Date	Event	Description
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.
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

Date	Event	Description
		been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
28 June 2018	Amended	Declaration of interest updated.
28 June 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2018. 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.
14 May 2018	New citation required but conclusions have not changed	Updated author list.
14 May 2018	New search has been performed	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2018. 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.
25 June 2014	Amended	Table format update
4 June 2014	New citation required but conclusions have not changed	Data abstraction verified and detailed statistical data included as appendix Data reanalyzed by using a complete case analysis approach for the primary meta-analysis
9 February 2013	New search has been performed	Search Updated
28 November 2012	Amended	Author contact details amended
9 May 2011	New search has been performed	Search updated 7 February 2010. One new RCT was identified.
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.

CONTRIBUTIONS OF AUTHORS

LAK: searching for trials, screening, full-text retrieval, data extraction, data analysis, data interpretation, manuscript drafting, review coordination.
MBH: screening, full-text retrieval, data extraction, manuscript drafting.
IGT: screening, data extraction, manuscript drafting.
CFM: screening.
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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update included new sections relevant to living systematic reviews, that are included in the Methods and also described in Appendix 1 and Appendix 2.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anticoagulants [adverse effects] [*therapeutic use]; Azetidines [therapeutic use]; Benzimidazoles [therapeutic use]; Benzylamines [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]; beta-Alanine [analogs & derivatives] [therapeutic use]

MeSH check words

Humans