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Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy (Review)

Rutjes AWS, Porreca E, Candeloro M, Valeriani E, Di Nisio M

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[Intervention Review]

Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

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ABSTRACT

Background

Venous thromboembolism (VTE) often complicates the clinical course of cancer. The risk is further increased by chemotherapy, but the trade-off between safety and efficacy of primary thromboprophylaxis in cancer patients treated with chemotherapy is uncertain. This is the third update of a review first published in February 2012.

Objectives

To assess the efficacy and safety of primary thromboprophylaxis for VTE in ambulatory cancer patients receiving chemotherapy compared with placebo or no thromboprophylaxis, or an active control intervention.

Search methods

For this update, the Cochrane Vascular Information Specialist searched the Cochrane Vascular, CENTRAL, MEDLINE, Embase and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 3 August 2020. We also searched the reference lists of identified studies and contacted content experts and trialists for relevant references.

Selection criteria

Randomised controlled trials comparing any oral or parenteral anticoagulant or mechanical intervention to no thromboprophylaxis or placebo, or comparing two different anticoagulants.

Data collection and analysis

We extracted data on risk of bias, participant characteristics, interventions, and outcomes including symptomatic VTE and major bleeding as the primary effectiveness and safety outcomes, respectively. We applied GRADE to assess the certainty of evidence.

Main results

We identified six additional randomised controlled trials (3326 participants) for this update, bringing the included study total to 32 (15,678 participants), all evaluating pharmacological interventions and performed mainly in people with locally advanced or metastatic cancer. The certainty of the evidence ranged from high to very low across the different outcomes and comparisons. The main limiting factors were imprecision and risk of bias.

Thromboprophylaxis with direct oral anticoagulants (direct factor Xa inhibitors apixaban and rivaroxaban) may decrease the incidence of symptomatic VTE (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.18 to 1.06; 3 studies, 1526 participants; low-certainty evidence); and probably increases the risk of major bleeding compared with placebo (RR 1.74, 95% CI 0.82 to 3.68; 3 studies, 1494 participants; moderate-certainty evidence).

When compared with no thromboprophylaxis, low-molecular-weight heparin (LMWH) reduced the incidence of symptomatic VTE (RR 0.62, 95% CI 0.46 to 0.83; 11 studies, 3931 participants; high-certainty evidence); and probably increased the risk of major bleeding events (RR 1.63, 95% CI 1.12 to 2.35; 15 studies, 7282 participants; moderate-certainty evidence).

In participants with multiple myeloma, LMWH resulted in lower symptomatic VTE compared with the vitamin K antagonist warfarin (RR 0.33, 95% CI 0.14 to 0.83; 1 study, 439 participants; high-certainty evidence), while LMWH probably lowers symptomatic VTE more than aspirin (RR 0.51, 95% CI 0.22 to 1.17; 2 studies, 781 participants; moderate-certainty evidence). Major bleeding was observed in none of the participants with multiple myeloma treated with LMWH or warfarin and in less than 1% of those treated with aspirin.

Only one study evaluated unfractionated heparin against no thromboprophylaxis, but did not report on VTE or major bleeding.

When compared with placebo or no thromboprophylaxis, warfarin may importantly reduce symptomatic VTE (RR 0.15, 95% CI 0.02 to 1.20; 1 study, 311 participants; low-certainty evidence) and may result in a large increase in major bleeding (RR 3.82, 95% CI 0.97 to 15.04; 4 studies, 994 participants; low-certainty evidence).

One study evaluated antithrombin versus no antithrombin in children. This study did not report on symptomatic VTE but did report any VTE (symptomatic and incidental VTE). The effect of antithrombin on any VTE and major bleeding is uncertain (any VTE: RR 0.84, 95% CI 0.41 to 1.73; major bleeding: RR 0.78, 95% CI 0.03 to 18.57; 1 study, 85 participants; very low-certainty evidence).

Authors' conclusions

In ambulatory cancer patients, primary thromboprophylaxis with direct factor Xa inhibitors may reduce the incidence of symptomatic VTE (low-certainty evidence) and probably increases the risk of major bleeding (moderate-certainty evidence) when compared with placebo. LMWH decreases the incidence of symptomatic VTE (high-certainty evidence), but increases the risk of major bleeding (moderate-certainty evidence) when compared with placebo or no thromboprophylaxis. Evidence for the use of thromboprophylaxis with anticoagulants other than direct factor Xa inhibitors and LMWH is limited. More studies are warranted to evaluate the efficacy and safety of primary prophylaxis in specific types of chemotherapeutic agents and types of cancer, such as gastrointestinal or genitourinary cancer.

PLAIN LANGUAGE SUMMARY

Prevention of blood clots in non-hospitalised cancer patients receiving chemotherapy

Background

Cancer patients are more likely than people without cancer to develop venous thromboembolism (blood clots in the veins). Chemotherapy may activate blood coagulation (clotting) and further increase this risk. Anticoagulants are medicines which are used to prevent and treat blood clots. They are sometimes known as blood thinners. This systematic review aimed to look at the effectiveness and safety of anticoagulants and mechanical interventions when used to prevent blood clots in cancer patients receiving chemotherapy.

Key results

We included 32 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) involving 15,678 participants (current search to August 2020). All studies evaluated anticoagulants and were performed mainly in people with locally advanced (unlikely to be cured) or metastatic (where the cancer has spread from the part of the body where it started) cancer. Direct oral anticoagulants (anticoagulants that act by directly binding to and inhibiting specific coagulation factors – thrombin or activated factor X) may reduce the occurrence of blood clots and probably increase the risk of major bleeding in people with cancer. Low-molecular-weight heparins (anticoagulants that increase the activity of the natural anticoagulant antithrombin) were associated with a reduction in symptomatic blood clots, but increased the risk of major bleeding. In people with the blood-related cancer, multiple myeloma, low-molecular-weight heparin reduced the number of symptomatic blood clots when compared with the vitamin K antagonist warfarin, while the difference with aspirin was not clear; there were no major bleeds with low-molecular-weight heparin or warfarin, and in participants treated with aspirin the rate was below 1%. One study evaluated unfractionated heparin and did not report on blood clots or major bleeding. Data for warfarin in comparison with placebo (pretend treatment) were too limited to support the use of warfarin in the prevention of symptomatic blood clots in cancer patients. One study in children evaluated antithrombin, which had no significant effect on any type of blood clots or major bleeding when compared with no antithrombin.

Quality of the evidence

The methodological quality of the included studies ranged from low to high, such that future studies may change our confidence in the results, in particular with regard to the safety of anticoagulants. The reliability of the findings ranged from high to very low across the different outcomes and comparisons. The main limiting factors, which were the reason for a decrease in reliability in some outcomes,

were imprecision and risk of bias. The relatively low number of studies, participants, and clinical events prevented us from providing more definitive conclusions about the risk of bleeding in association with anticoagulants. None of the studies tested intermittent pneumatic compression (a mechanical device using an air pump and inflatable leggings to provide pulsing pressure that pushes blood through the veins) or graduated elastic stockings (special socks that improve blood flow in the leg veins and prevent blood from pooling in the legs) for the prevention of venous thromboembolism.

SUMMARY OF FINDINGS

Summary of findings 1. DOAC versus placebo

DOAC direct factor Xa inhibitors compared with placebo for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: DOAC direct factor Xa inhibitors (apixaban or rivaroxaban)

Comparison: placebo

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With placebo Number of events per 1000 participants	With DOAC (any dosage) Number of events per 1000 participants				
Symptomatic VTE Follow-up: median 6 months	**RR 0.43** (0.18 to 1.06)	**High-risk population[c]**		46 per 1000 fewer events (66 fewer to 5 more)	1526 (3)	⊕⊕⊖⊖ **Low** [d]	DOACs may decrease the incidence of symptomatic VTE across different cancer types.
		80 per 1000	34 per 1000 (14 to 85)				
Major bleeding Follow-up: median 6 months	**RR 1.74** (0.82 to 3.68)	**High-risk population[c]**		13 per 1000 more events (3 fewer to 49 more)	1494 (3)	⊕⊕⊕⊖ **Moderate** [e]	DOACs probably increase the incidence of major bleeding across different cancer types.
		18 per 1000	32 per 1000 (15 to 67)				
Symptomatic PE Follow-up: median 6 months	**RR 0.38** (0.10 to 1.47)	**High-risk population[c]**		21 per 1000 fewer events (31 fewer to 16 more)	1526 (3)	⊕⊕⊖⊖ **Low** [d]	DOACs may decrease the incidence of symptomatic PE across different cancer types.
		34 per 1000	13 per 1000 (3 to 51)				
Symptomatic DVT	**RR 0.51** (0.21 to 1.22)	**High-risk population[c]**			1526 (3)	⊕⊕⊖⊖ **Low** [d]	

Follow-up: median 6 months		45 per 1000	23 per 1000 (9 to 55)	22 per 1000 fewer events (36 fewer to 10 more)			DOACs may decrease the incidence of symptomatic DVT across different cancer types.
Any VTE Follow-up: median 6 months	**RR 0.55** (0.34 to 0.90)	**High-risk population[c]**		43 per 1000 fewer events (9 fewer to 63 fewer events)	1404 (2)	⊕⊕⊕⊖ **Moderate** [e]	DOACs probably decrease the incidence of any VTE across different cancer types.
		95 per 1000	52 per 1000 (32 to 85)				
1-year overall mortality Follow-up: NA	NA[f]	**High-risk population[c]**		NA	0 (0)	NA	We do not know how DOAC affect overall mortality.
		NA	NA				
Clinically relevant bleeding Follow-up: median 4.5 months	**RR 1.61** (0.82 to 3.15)	**High-risk population[c]**		20 per 1000 more events (6 fewer to 69 more)	931 (2)	⊕⊕⊕⊖ **Moderate** [e]	DOACs probably increase the incidence of clinically relevant bleeding across different cancer types.
		32 per 1000	52 per 1000 (26 to 101)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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 anticoagulants; **DVT:** deep vein thrombosis; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the median control group risk across the studies.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]High-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses (71 per 1000). Rates from 7% and higher are considered high risk (Khorana 2008).
[d]Downgraded two levels because of imprecision, inconsistency, and attrition bias, see Characteristics of included studies table.
[e]Downgraded one level because of imprecision and risk of attrition bias, see Characteristics of included studies table.
[f]No trials contributed to this outcome.

Summary of findings 2. Low-molecular-weight heparin versus no thromboprophylaxis

LMWH compared with no thromboprophylaxis for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: LMWH

Comparison: no thromboprophylaxis (placebo or no LMWH)

Outcomes	Relative effect (95% CI)	Illustrative comparative risk (95% CI)*		Difference (95% CI)[b]	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With no thromboprophylaxis Number of events per 1000 participants	With LMWH Number of events per 1000 participants				
Symptomatic VTE Follow-up: median 10 months	**RR 0.62** (0.46 to 0.83)	**High-risk population[c]**		27 per 1000 fewer events (12 fewer to 39 fewer)	3931 (11)	⊕⊕⊕⊕ **High** [d]	LMWH decreases the incidence of symptomatic VTE across different cancer types.
		71 per 1000	44 per 1000 (33 to 59)				
Major bleeding Follow-up: median 10 months	**RR 1.63** (1.12 to 2.35)	**High-risk population[c]**		7 per 1000 more major bleeds (1 more to 15 more)	7282 (15)	⊕⊕⊕⊖ **Moderate** [e]	LMWH probably increases major bleedings across different cancer types.
		11 per 1000	18 per 1000 (12 to 26)				
Symptomatic PE Follow-up: median 8 months	**RR 0.60** (0.42 to 0.88)	**High-risk population[c]**		7 per 1000 fewer events (2 fewer to 11 fewer)	5324 (8)	⊕⊕⊕⊖ **Moderate** [f]	LMWH probably decreases the incidence of symptomatic PE across different cancer types.
		18 per 1000	11 per 1000 (8 to 16)				

Symptomatic DVT Follow-up: median 10 months	**RR 0.48** (0.35 to 0.67)	**High-risk population[c]** 28 per 1000	14 per 1000 (10 to 19)	15 per 1000 fewer events (9 fewer to 18 fewer)	5408 (9)	⊕⊕⊕⊕ **High** [g]	LMWH decreases the incidence of symptomatic DVT across different cancer types.
Any VTE Follow-up: median 8 months	**RR 0.57** (0.46 to 0.71)	**High-risk population[c]** 90 per 1000	52 per 1000 (43 to 64)	38 per 1000 fewer events (26 fewer to 48 fewer)	5743 (10)	⊕⊕⊕⊕ **High** [h]	LMWH decreases the incidence of any VTE across different cancer types.
1-year overall mortality Follow-up: median 12 months	**RR 0.94** (0.83 to 1.07)	**High-risk population[c]** 586 per 1000	551 per 1000 (486 to 627)	35 per 1000 fewer deaths (100 fewer to 41 more)	2681 (9)	⊕⊕⊖⊖ **Low** [i]	LMWH may decrease the incidence of death across different cancer types.
Clinically relevant bleeding Follow-up: median 11 months	**RR 3.40** (1.20 to 9.63)	**High-risk population[c]** 17 per 1000	57 per 1000 (20 to 162)	40 per 1000 more clinically relevant bleeds (3 more to 145 more)	3105 (4)	⊕⊕⊕⊖ **Moderate** [j]	LMWH probably increases the incidence of clinically relevant bleeding across different cancer types.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **LMWH:** low-molecular-weight heparin; **PE:** pulmonary embolism; **RR:** risk ratio; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the median control group risk across the studies.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]High-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses. It corresponds to 71 per 1000 for symptomatic VTE, which is consistent with previous literature, suggesting that rates of 7% or higher identify individuals at high risk of symptomatic VTE (Khorana 2008). The high-risk label for other outcomes is based on the risk profile for symptomatic VTE.
[d]Although 7/11 trials were not double-blind, and 3/11 trials used dosages exceeding typical prophylactic dosages, results were consistent across trials, so we did not downgrade.
[e]Downgraded one level because 10/15 trials contributing to the analyses were not double-blind, and 4/15 trials did not use standard definitions to ascertain major bleeding. Overall, no relevant inconsistency was detected, so that the effects of non-blinding, definitions, and other study characteristics were deemed to be small. One study reported zero events in both the intervention and control arm, and was not considered in the 'Summary of findings' table (Zwicker 2013).

[f]Downgraded one level because risk of selective outcome reporting, with only 8/15 trials reporting symptomatic PE.
[g]Although 5/9 trials were not double-blind, and 2/9 trials used dosages exceeding typical prophylactic dosages, results were very consistent across trials, so we did not downgrade.
[h]Although 7/10 trials were not double-blind, and 4/10 trials used dosages exceeding typical prophylactic dosages, results were very consistent across trials, so we did not downgrade.
[i]Downgraded two levels because the 95% CI included both small and appreciable benefit or harm; with some variability in estimates across trials due to heterogeneity other than sampling error (chance).
[j]Downgraded one level due to unexplained between-trial variation.

Summary of findings 3. Low-molecular-weight heparin versus with active control (1)

LMWH: prophylactic dose compared with intermediate or therapeutic dose for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: prophylactic dose LMWH

Comparison: intermediate or therapeutic dose LMWH

Outcomes	Control type	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
			Assumed risk[a]	Corresponding risk				
			With intermediate/therapeutic dose LMWH Number of events per 1000 participants	With prophylactic dose LMWH Number of events per 1000 participants				
			Intermediate-risk population[c]					
Symptomatic VTE	Intermediate	**RR 2.89** (0.12 to 66.75)	31 per 1000	90 per 1000 (4 to 2086)	59 per 1000 more events (28 fewer	51 (1)	⊕⊕⊖⊖ **Low** [d]	Prophylactic-dose LMWH may be associated with a higher risk of symptomatic VTE when

Follow-up: median 3.5 months					events to 2055 more)			compared to intermediate-dose LMWH in ovarian cancer.
	Therapeutic	**RR 1.00** (0.07 to 15.15)	53 per 1000	53 per 1000 (4 to 805)	0 per 1000 fewer events (49 fewer events to 752 more)	52 (1)	⊕⊕⊖⊖ **Low** [d]	We do not know if prophylactic-dose LMWH is associated with a higher risk of symptomatic VTE when compared to therapeutic-dose LMWH in ovarian cancer.
			Intermediate-risk population[c]					
Major bleeding Follow-up: median 3.5 months	Intermediate	Not estimable[e]	NA	NA	NA	NA	NA	As we have insufficient data to estimate the relative risk, we do not know how prophylactic-dose LMWH affects major bleeding in ovarian cancer.
	Therapeutic	Not estimable[e]	NA	NA	NA	NA	NA	
			Intermediate-risk population[c]					
Symptomatic PE Follow-up: median 3.5 months	Intermediate	**RR 2.89** (0.12 to 66.75)	NA[f]	NA	NA	NA	NA	As we have insufficient data to estimate the assumed risk, we do not know how prophylactic-dose LMWH affects symptomatic PE in ovarian cancer.
	Therapeutic	**RR 3.00** (0.13 to 70.42)	NA[f]	NA	NA	NA	NA	
			Intermediate-risk population[c]					
Symptomatic DVT Follow-up: median 3.5 months	Intermediate	Not estimable[e]	NA	NA	NA	NA	NA	We do not know how prophylactic-dose LMWH affects symptomatic DVT across different cancer types.
	Therapeutic	**RR 0.33** (0.01 to 7.82)	53 per 1000	18 per 1000 (1 to 415)	36 per 1000 fewer DVT (53 fewer to 362 more)	52 (1)	⊕⊕⊖⊖ **Low** [d]	Prophylactic-dose LMWH may reduce the risk of symptomatic DVT when compared to therapeutic-dose LMWH in ovarian cancer, although this seems an implausible finding.
			Intermediate-risk population[c]					

Any VTE Follow-up: NA	Intermediate	**RR 4.81** (0.24 to 95.58)	NA[f]	NA	NA	NA	NA	As we have insufficient data to estimate the assumed risk, we do not know how prophylactic-dose LMWH affects any VTE across different cancer types.
	Therapeutic	**RR 5.00** (0.25 to 99.34)	NA[f]	NA	NA	NA	NA	
			Intermediate-risk population[c]					
1-year overall mortality Follow-up: NA	Intermediate	NA[g]	NA	NA	NA	NA	NA	We do not know how prophylactic-dose LMWH affects overall mortality when compared to intermediate or therapeutic-dose LMWH across different cancer types.
	Therapeutic	NA[g]	NA	NA	NA	NA	NA	
			Intermediate-risk population[c]					
Clinically relevant bleeding Follow-up: median 3.5 months	Intermediate	NA[e]	NA	NA	NA	NA	NA	We do not know how prophylactic-dose LMWH affects clinically relevant bleeding across different cancer types.
	Therapeutic	**RR 0.33** (0.01 to 7.82)	38 per 1000[h]	13 per 1000 (0 to 301)	26 per 1000 fewer clinically relevant bleeding (38 fewer to 262 more)	52 (1)	⊕⊕⊖⊖ **Low** [d]	Prophylactic-dose LMWH may reduce clinically relevant bleeding when compared to therapeutic-dose LMWH in ovarian cancer.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **LMWH:** low-molecular-weight heparin; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk is calculated from the medium observed control group risk in Elit 2012 and Pelzer 2015 for the intermediate-dose estimation, and from Elit 2012 and Maraveyas 2012 for therapeutic-dose LMWH.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]Intermediate-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses (31 per 1000 and 53 per 1000). Rates between 2% and 7% are considered intermediate risk (Khorana 2008).
[d]Downgraded two levels because of imprecision.
[e]Not estimable due to zero event count in both trial arms.
[f]We have insufficient data to estimate the assumed risk due to the zero event rate in both the intermediate-dose and therapeutic-dose LMWH.
[g]No trials contributed to this outcome.
[h]The assumed risk was based on the small trial by Elit 2012 only (the observed event rate in the control group was 1 out of 26).

Summary of findings 4. Low-molecular-weight heparin versus active control (2)

LMWH compared with aspirin for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: LMWH

Comparison: aspirin

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With aspirin Number of events per 1000 participants	With LMWH (any dosage) Number of events per 1000 participants				
Symptomatic VTE Follow-up: median 18.5 months	**RR 0.51** (0.22 to 1.17)	**Intermediate-risk population[c]**		19 per 1000 fewer events (30 fewer to 7 more)	781 (2)	⊕⊕⊕⊖ **Moderate** [d]	LMWH probably decreases the incidence of symptomatic VTE when compared with aspirin in multiple myeloma.
		39 per 1000	20 per 1000 (9 to 45)				

Major bleeding Follow-up: median 18.5 months	**RR 0.14** (0.01 to 2.76)	**Intermediate-risk population[c]**		6 per 1000 fewer events (7 fewer to 12 more)	781 (2)	⊕⊕⊖⊖ **Low** [e]	LMWH may reduce the incidence of major bleeding when compared with aspirin in multiple myeloma.
		7 per 1000	1 per 1000 (0 to 19)				
Symptomatic PE Follow-up: median 18.5 months	**RR 0.13** (0.02 to 1.03)	**Intermediate-risk population[c]**		15 per 1000 fewer events (17 fewer to 1 more)	781 (2)	⊕⊕⊕⊖ **Moderate** [d]	LMWH probably reduces the incidence of symptomatic PE when compared with aspirin in multiple myeloma.
		18 per 1000	2 per 1000 (0 to 18)				
Symptomatic DVT Follow-up: median 18.5 months	**RR 0.81** (0.32 to 2.04)	**Intermediate-risk population[c]**		5 per 1000 fewer events (16 fewer to 25 more)	781 (2)	⊕⊕⊕⊖ **Moderate** [d]	LMWH probably reduces the incidence of symptomatic DVT when compared with aspirin in multiple myeloma.
		24 per 1000	19 per 1000 (8 to 49)				
Any VTE Follow-up: NA	NA[f]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how LMWH affects any VTE when compared with aspirin in multiple myeloma.
		NA	NA				
1-year overall mortality Follow-up: NA	NA[f]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how LMWH affects 1-year overall mortality when compared with aspirin in multiple myeloma.
		NA	NA				
Clinically relevant bleeding Follow-up: NA	NA[f]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how LMWH affects clinically relevant bleeding when compared with aspirin in multiple myeloma.
		NA	NA				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **LMWH:** low-molecular-weight heparin; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the medium observed control group risk across the studies.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.

[c]Intermediate-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses (39 per 1000). Rates between 2% and 7% are considered intermediate risk (Khorana 2008).
[d]Downgraded one level because of imprecision.
[e]Downgraded two levels because of imprecision.
[f]No trials contributed to this outcome.

Summary of findings 5. Low-molecular-weight heparin versus active control (3)

LMWH compared with VKA for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: LMWH

Comparison: VKA

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With VKA Number of events per 1000 participants	With LMWH (any dosage) Number of events per 1000 participants				
Symptomatic VTE Follow-up: median 25 months	**RR 0.33** (0.14 to 0.83)	**High-risk population[c]**		55 per 1000 fewer events (14 fewer to 70 fewer)	439 (1)	⊕⊕⊕⊕ **High** [d]	LMWH reduces the incidence of symptomatic VTE when compared to VKA in multiple myeloma.
		82 per 1000	27 per 1000 (11 to 68)				
Major bleeding Follow-up: median 25 months	Not estimable[e]	**High-risk population[c]**		NA	NA	NA	We do not know how LMWH affects major bleeding when compared to VKA across different cancer types.
		NA	NA				
Symptomatic PE	**RR 0.11** (0.01 to 2.06)	**High-risk population[c]**		16 per 1000 fewer events	439 (1)	⊕⊕⊖⊖ **Low** [f]	

Follow-up: median 25 months		18 per 1000	2 per 1000 (0 to 37)	(18 fewer to 19 more)			LMWH may reduce the incidence of symptomatic PE when compared to VKA in multiple myeloma.
Symptomatic DVT Follow-up: median 25 months	**RR 0.43** (0.17 to 1.10)	**High-risk population[c]**		36 per 1000 fewer events (53 fewer to 6 more)	439 (1)	⊕⊕⊕⊖ **Moderate** [g]	LMWH probably reduces the incidence of symptomatic DVT when compared to VKA in multiple myeloma.
		64 per 1000	27 per 1000 (11 to 70)				
Any VTE Follow-up: NA	NA[h]	**High-risk population[c]**		NA	NA	NA	We do not know how LMWH affects any VTE when compared to VKA across different cancer types.
		NA	NA				
1-year overall mortality Follow-up: NA	NA[h]	**High-risk population[c]**		NA	NA	NA	We do not know how LMWH affects 1-year overall mortality when compared to VKA across different cancer types.
		NA	NA				
Clinically relevant bleeding Follow-up: NA	NA[h]	**High-risk population[c]**		NA	NA	NA	We do not know how LMWH affects clinically relevant bleeding when compared to VKA across different cancer types.
		NA	NA				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **LMWH:** low-molecular-weight heparin; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VKA:** vitamin K antagonist; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the observed control group risk in Palumbo 2011.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]High-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses (82 per 1000). Rates from 7% and higher are considered high risk (Khorana 2008).
[d]Although there was some risk of attrition bias, imputation of the missing data in various ways showed that estimates would not change in a clinically relevant manner (data not shown).
[e]Not estimable due to zero event count in both trial arms.
[f]Downgraded two levels because of imprecision.

[g]Downgraded one level because of imprecision.
[h]No trials contributed to this outcome.

Summary of findings 6. Ultra-low-molecular-weight heparin versus placebo

uLMWH (semuloparin) compared with placebo for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: semuloparin

Comparison: placebo

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With placebo Number of events per 1000 participants	With semuloparin Number of events per 1000 participants				
Symptomatic VTE Follow-up: median 3.5 months	**RR 0.36** (0.22 to 0.60)	**Intermediate-risk population[c]**		22 per 1000 fewer events (14 fewer to 27 fewer)	3212 (1)	⊕⊕⊕⊕ **High**	Semuloparin decreases the incidence of symptomatic VTE across different cancer types.
		34 per 1000	12 per 1000 (8 to 21)				
Major bleeding Follow-up: median 3.5 months	**RR 1.05** (0.55 to 2.0)	**Intermediate-risk population[c]**		1 per 1000 more events (5 fewer to 11 more)	3172 (1)	⊕⊕⊕⊖ **Moderate** [d]	Semuloparin probably has little effect on major bleedings across different cancer types.
		11 per 1000	12 per 1000 (6 to 23)				
Symptomatic PE Follow-up: median 3.5 months	**RR 0.48** (0.22 to 1.01)	**Intermediate-risk population[c]**		7 per 1000 fewer events (0 fewer to 10 fewer)	3212 (1)	⊕⊕⊕⊖ **Moderate** [d]	Semuloparin probably decreases the incidence of symptomatic PE across different cancer types.
		13 per 1000	6 per 1000 (3 to 13)				

Symptomatic DVT Follow-up: median 3.5 months	**RR 0.32** (0.16 to 0.63)	**Intermediate-risk population[c]**		14 per 1000 fewer events (8 fewer to 18 fewer)	3212 (1)	⊕⊕⊕⊕ **High**	Semuloparin decreases the incidence of symptomatic DVT across different cancer types.
		21 per 1000	7 per 1000 (3 to 13)				
Any VTE Follow-up: median 3.5 months	**RR 0.36** (0.22 to 0.60)	**Intermediate-risk population[c]**		22 per 1000 fewer (14 fewer to 27 fewer)	3212 (1)	⊕⊕⊕⊕ **High**	Semuloparin decreases the incidence of any VTE across different cancer type.
		34 per 1000	12 per 1000 (8 to 21)				
1-year overall mortality Follow-up: 1 year	**RR 1.02** (0.96 to 1.08)	**Intermediate-risk population[c]**		11 per 1000 more events (22 fewer to 44 more)	3212 (1)	⊕⊕⊕⊖ **Moderate** [d]	Semuloparin probably has no effect on 1-year overall mortality across different cancer types.
		555 per 1000	566 per 1000 (533 to 599)				
Clinically relevant bleeding Follow-up: median 3.5 months	**RR 1.40** (0.90 to 2.19)	**Intermediate-risk population[c]**		8 per 1000 more events (2 fewer to 24 more)	3172 (1)	⊕⊕⊕⊖ **Moderate** [d]	Semuloparin probably increases the incidence of clinically relevant bleeding across different cancer types.
		20 per 1000	28 per 1000 (18 to 44)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **uLMWH:** ultra-low-molecular-weight heparin; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the medium observed control group risk in the study.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]Intermediate risk population refers to the observed median risk to experience symptomatic VTE in the single trial contributing to the analyses (34 per 1000). Rates between 2% and 7% are considered intermediate risk (Khorana 2008).
[d]Downgraded one level because of imprecision.

Summary of findings 7. Unfractionated heparin versus no thromboprophylaxis

UFH compared with no thromboprophylaxis for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: UFH

Comparison: no thromboprophylaxis

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With no thromboprophylaxis Number of events per 1000 participants	With UFH Number of events per 1000 participants				
Symptomatic VTE Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how UFH affects symptomatic VTE across different cancer types.
		NA	NA				
Major bleeding Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how UFH affects major bleeding across different cancer types.
		NA	NA				
Symptomatic PE Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how UFH affects symptomatic PE across different cancer types.
		NA	NA				
Symptomatic DVT Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how UFH affects symptomatic DVT across different cancer types.
		NA	NA				
Any VTE Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how UFH affects any VTE across different cancer types.

		NA	NA				
1-year overall mortality Follow-up: 1 year	**RR 0.86** (0.72 to 1.03)	**Population at unclear risk[d]**		98 per 1000 fewer events (195 fewer to 21 more)	277 (1)	⊕⊕⊕⊖ **Moderate** [e]	UFH probably decreases the incidence of 1-year overall mortality in small-cell lung cancer.
		698 per 1000	600 per 1000 (502 to 719)				
Clinically relevant bleeding Follow-up: median not reported, maximum of 4.9 years of follow-up	**RR 2.01** (0.18 to 21.96)	**Population at unclear risk[d]**		7 per 1000 more events (6 fewer to 151 more)	277 (1)	⊕⊕⊖⊖ **Low** [f]	UFH may increase the risk of clinically relevant bleeding in small-cell lung cancer.
		7 per 1000	14 per 1000 (1 to 158)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **UFH:** unfractionated heparin; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the observed control group risk in Lebeau 1994.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]No trials contributed to this outcome.
[d]The risk profile refers to the median observed risk to experience symptomatic VTEs. As Lebeau 1994 did not report this outcome, the risk profile remains unclear.
[e]Downgraded one level because of imprecision.
[f]Downgraded two levels because of imprecision.

Summary of findings 8. Vitamin K antagonists versus placebo or no thromboprophylaxis

VKA compared with placebo or no thromboprophylaxis for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: VKA

Comparison: placebo or no thromboprophylaxis

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With placebo or no thromboprophylaxis Number of events per 1000 participants	With VKA Number of events per 1000 participants				
Symptomatic VTE Follow-up: mean 6 months	**RR 0.15** (0.02 to 1.2)	**Intermediate-risk population[c]**		37 per 1000 fewer events (43 fewer to 9 more)	311 (1)	⊕⊕⊖⊖ **Low** [d]	VKA may reduce the incidence of symptomatic VTE in breast cancer.
		44 per 1000	7 per 1000 (1 to 53)				
Major bleeding Follow-up: mean 6 months	**RR 3.82** (0.97 to 15.04)	**Intermediate-risk population[c]**		18 per 1000 more events (0 fewer to 88 more)	994 (4)	⊕⊕⊖⊖ **Low** [e]	VKA may increase the incidence of major bleeding in breast cancer and small-cell lung cancer.
		6 per 1000	24 per 1000 (6 to 95)				
Symptomatic PE Follow-up: mean 6 months	**RR 1.05** (0.07 to 16.58)	**Intermediate-risk population[c]**		0 per 1000 fewer events (6 fewer to 101 more)	311 (1)	⊕⊖⊖⊖ **Very low** [f]	We have very little confidence in the estimated effect of VKA on symptomatic PE in breast cancer.
		6 per 1000	7 per 1000 (0 to 108)				
Symptomatic DVT Follow-up: mean 6 months	**RR 0.08** (0 to 1.42)	**Intermediate-risk population[c]**		35 per 1000 fewer events (38 fewer to 16 more)	311 (1)	⊕⊕⊖⊖ **Low** [d]	VKA may reduce the incidence of symptomatic DVT in breast cancer.
		38 per 1000	3 per 1000 (0 to 54)				
Any VTE Follow-up: NA	NA[g]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how VKA affects any VTE across different cancer types.
		NA	NA				
1-year overall mortality	NA[g]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how VKA affects 1-year overall mortality across different cancer types.
		NA	NA				

Follow-up: NA						
Clinically relevant bleeding Follow-up: NA	NA[g]	**Intermediate-risk population[c]** NA	NA	NA	NA	We do not know how VKA affects clinically relevant bleeding across different cancer types.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VKA:** vitamin K antagonists; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the medium observed control group risk across the trials.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]Intermediate-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses (44 per 1000). Rates between 2% and 7% are considered intermediate risk (Khorana 2008).
[d]Downgraded two levels because of imprecision, risk of publication bias (only 1/4 trials reported on this outcome), and potential risk of attrition bias, see Characteristics of included studies table.
[e]Downgraded two levels because of imprecision and potential attrition bias in 2/4 trials.
[f]Downgraded three levels because of imprecision (two levels), the risk for publication bias, as only 1/4 trials reported on this outcome, and potential attrition bias, see Characteristics of included studies table.
[g]No trials contributed to this outcome.

Summary of findings 9. Vitamin K antagonists versus active control

VKA compared with aspirin for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy

Settings: outpatient clinics

Intervention: VKA

Comparison: aspirin

Outcomes	Relative effect (95% CI)	Illustrative comparative risks* (95% CI)		Difference[b] (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What it means
		Assumed risk[a]	Corresponding risk				
		With aspirin Number of events per 1000 participants	With VKA Number of events per 1000 participants				
Symptomatic VTE Follow-up: median 2.1 years	**RR 1.50** (0.74 to 3.04)	**Intermediate-risk population[c]**		27 per 1000 more events (14 fewer to 211 more)	440 (1)	⊕⊕⊕⊖ **Moderate** [d]	VKA probably increases the incidence of symptomatic VTE when compared to aspirin in multiple myeloma.
		55 per 1000	82 per 1000 (40 to 166)				
Major bleeding Follow-up: median 2.1 years	**RR 0.14** (0.01 to 2.75)	**Intermediate-risk population[c]**		12 per 1000 fewer events (14 fewer to 24 more)	440 (1)	⊕⊕⊖⊖ **Low** [e]	VKA may reduce the incidence of major bleeding when compared to aspirin in multiple myeloma.
		14 per 1000	2 per 1000 (0 to 38)				
Symptomatic PE Follow-up: median 2.1 years	**RR 1.00** (0.25 to 3.95)	**Intermediate-risk population[c]**		0 per 1000 fewer events (14 fewer to 54 more)	440 (1)	⊕⊕⊕⊖ **Moderate** [d]	VKA is probably as effective as aspirin in the prevention of symptomatic PE in multiple myeloma.
		18 per 1000	18 per 1000 (5 to 72)				
Symptomatic DVT Follow-up: median 2.1 years	**RR 1.75** (0.75 to 4.09)	**Intermediate-risk population[c]**		27 per 1000 more events (9 fewer to 112 more)	440 (1)	⊕⊕⊕⊖ **Moderate** [d]	VKA probably increases the incidence of symptomatic DVT when compared to aspirin in multiple myeloma.
		36 per 1000	64 per 1000 (27 to 149)				
Any VTE Follow-up: NA	NA[f]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how VKA affects any VTE when compared to aspirin across different cancer types.
		NA	NA				
1-year overall mortality Follow-up: NA	NA[f]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how VKA affects 1-year overall mortality when compared to aspirin across different cancer types.
		NA	NA				

Clinically relevant bleeding Follow-up: NA	NA[f]	**Intermediate-risk population[c]**		NA	NA	NA	We do not know how VKA affects clinically relevant bleeding when compared to aspirin across different cancer types.
		NA	NA				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VKA:** vitamin K antagonists; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the observed control group risk in Palumbo 2011.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]Intermediate-risk population refers to the median observed risk to experience symptomatic VTE in the trials contributing to the analyses (55 per 1000). Rates between 2% and 7% are considered intermediate risk (Khorana 2008).
[d]Downgraded one level because of imprecision. Although attrition bias may have occurred, it is unlikely to have changed the results in a clinically relevant manner.
[e]Downgraded two levels because of imprecision. Although attrition bias may have occurred, it is unlikely to have changed the results in a clinically relevant manner.
[f]No trials contributed to this outcome.

Summary of findings 10. Antithrombin versus no thromboprophylaxis

Antithrombin compared with placebo for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory paediatric cancer patients newly diagnosed with acute lymphoblastic leukaemia who received chemotherapy

Settings: outpatient clinics

Intervention: antithrombin

Comparison: placebo

Outcomes	**Relative effect (95% CI)**	**Illustrative comparative risks* (95% CI)**		**Difference[b] (95% CI)**	**No of participants (studies)**	**Certainty** of the evidence (GRADE)	**What it means**
		Assumed risk[a]	**Corresponding risk**				

		With placebo Number of events per 1000 participants	With antithrombin (any dosage) Number of events per 1000 participants				
Symptomatic VTE Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how antithrombin affects symptomatic VTE across different cancer types.
		NA	NA				
Major bleeding Follow-up: median 4 months	**RR 0.78** (0.03 to 18.57)	**Population at unclear risk[d]**		4 per 1000 fewer events (16 fewer to 293 more)	85 (1)	⊕⊖⊖⊖ **Very low** [e]	We have very little confidence in the estimated effect of antithrombin on the incidence of major bleeding in acute lymphoblastic leukaemia.
		17 per 1000	13 per 1000 (1 to 310)				
Symptomatic PE Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how antithrombin affects symptomatic PE across different cancer types.
		NA	NA				
Symptomatic DVT Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how antithrombin affects symptomatic DVT across different cancer types.
		NA	NA				
Any VTE Follow-up: median 4 months	**RR 0.84** (0.41 to 1.73)	**Population at unclear risk[d]**		53 per 1000 fewer events (197 fewer to 243 more)	85 (1)	⊕⊖⊖⊖ **Very low** [e]	We have very little confidence in the estimated effect of antithrombin on the incidence of any VTE in acute lymphoblastic leukaemia.
		333 per 1000	280 per 1000 (137 to 577)				
1-year overall mortality Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how antithrombin affects 1-year overall mortality across different cancer types.
		NA	NA				
Clinically relevant bleeding Follow-up: NA	NA[c]	**Population at unclear risk[d]**		NA	NA	NA	We do not know how antithrombin affects clinically relevant bleeding across different cancer types.
		NA	NA				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DVT:** deep vein thrombosis; **NA:** not applicable; **PE:** pulmonary embolism; **RR:** risk ratio; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]The assumed risk was calculated from the observed control group risk in Mitchell 2003.
[b]Difference calculated as the absolute risk difference between the assumed risk and corresponding risk, expressed per 1000.
[c]No trials contributed to this outcome.
[d]The risk profile refers to the median observed risk to experience symptomatic VTEs. As Mitchell 2003 did not report this outcome, the risk profile remains unclear.
[e]Downgraded three levels because of imprecision, indirectness and attrition bias, see Characteristics of included studies table.

BACKGROUND

Cancer is often complicated by venous thromboembolism (VTE), which can present as deep vein thrombosis (DVT) or pulmonary embolism (PE), or both (Ay 2017; Cohen 2017; Khorana 2009a; Timp 2013). Cancer patients with VTE have a two-fold or greater increased mortality compared with cancer patients without thrombosis, which could be explained by the development of fatal PEs or by a more aggressive disease in patients who develop VTE (Sorensen 2000). VTE in cancer patients may be difficult to recognise due to aspecific symptoms, which may overlap and be confused with symptoms caused by the underlying cancer disease process or cancer treatments. VTE carries significant morbidity due to the need for hospitalisation and an increased risk of recurrent VTE or bleeding complications while on anticoagulation (Hutten 2000; Prandoni 2002). The occurrence of symptomatic or incidental VTE may delay the delivery of cancer treatments such as chemotherapy, with a negative impact on morbidity and potentially mortality. In addition, the occurrence of VTE brings further emotional strain for patients and their families, which negatively affects their quality of life. Finally, the costs related to the management of VTE may be considerable, resulting from the expenses related to the drugs and hospitalisation (Heit 2015).

Description of the condition

The incidence of VTE is higher in people with cancer compared with people without cancer, with similar rates of PE and proximal DVT (Heit 2015; Timp 2013). Compared with an incidence of about 0.1% in the general population, the absolute risk of VTE in people with cancer varies between 0.6% and about 8%, depending on patient and cancer characteristics, duration of follow-up, and diagnostic tests used for VTE (Cohen 2017; Khorana 2009a; Timp 2013). In cancer patients with advanced disease, the incidence rate of VTE has been estimated to be as high as 68 per 1000 person-years (Horsted 2012). About one-half of all VTEs in cancer patients are incidentally detected on routine imaging without any clinical suspicion of VTE at the time of diagnosis (incidental VTE; Di Nisio 2017). The clinical relevance of incidental VTE seems to be comparable to that of symptomatic VTE with similar risk of recurrent thrombosis (Di Nisio 2017; Kraaijpoel 2019; van Es 2014). Chemotherapy has been recognised as an independent predictor for symptomatic VTE, with reported rates ranging from 11%, in Otten 2004, up to 75%, in Heit 2015 and Khorana 2009a, depending on the type of chemotherapeutic agent used. The risk of thrombosis in cancer patients receiving chemotherapy seems to vary based on the stage of the disease, ranging from 3% to 5% in patients with early-stage cancer to 30% in those with metastatic or advanced malignancy (Khorana 2009a; Timp 2013). The benefit-risk ratio of primary prophylaxis in ambulatory patients with cancer who are receiving chemotherapy is not well established. Current guidelines do not recommend routine thromboprophylaxis in such patients and suggest risk stratification to identify people with a higher risk of VTE who may have a greater benefit from thromboprophylaxis (Connors 2014; Key 2020).

Description of the intervention

Currently available drugs for the prevention of VTE include parenteral (e.g. unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), and fondaparinux), and oral anticoagulants (e.g. vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs) including the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban). In fact, each one of these agents may present disadvantages for long-term prophylaxis in ambulatory patients with cancer. Heparins and fondaparinux, as well as the ultra-low-molecular-weight heparin (uLMWH) semuloparin, require daily subcutaneous injections, which represent a considerable burden for the patient. Of note is that marketing applications for semuloparin have been withdrawn worldwide, and it is, therefore, unlikely to ever be commercially available (EMEA 2012). Treatment with VKAs requires laboratory monitoring with frequent dose-adjustments and may be complicated by multiple drug and food interactions. Direct thrombin and factor Xa inhibitors offer the potential advantages of an oral route of administration, and in comparison with VKAs do not require routine laboratory monitoring and have fewer pharmacological interactions. VKAs and direct thrombin or factor Xa inhibitors can be difficult to administer in cancer patients with nausea or vomiting.

The use of pharmacological prophylaxis may be more challenging in people with cancer. The efficacy could be reduced by the intrinsic procoagulant state induced by the cancer itself, prothrombotic treatments for cancer (e.g. chemotherapy), as well as the decline in the patient's general condition leading to immobilisation. In contrast, the risk of bleeding events could be high even with prophylactic doses because of a number of predisposing factors such as the bleeding tendency at the site of the cancer, the relative decrease in the number of platelets in the blood (thrombocytopenia) secondary to chemotherapy, and the concomitant use of drugs (e.g. bevacizumab) that affect the vessel wall integrity (Kamphuisen 2014).

Currently available mechanical interventions for the prevention of VTE include intermittent pneumatic compression and graduated elastic stockings. These non-pharmacological interventions may be a valid option in cancer patients who are at risk of bleeding; however, evidence supporting their benefit and assuring no harm is limited.

Why it is important to do this review

The overall burden of VTE in people with cancer is steadily increasing as a result of an ageing population, greater awareness, prothrombotic anticancer treatments, as well as the growing cancer population (Heit 2015). In addition, an increasing number of VTEs in cancer patients are diagnosed incidentally on imaging tests requested for baseline staging, treatment response evaluation, or routine surveillance while off anticancer treatment (Di Nisio 2017). Provision of widespread primary thromboprophylaxis for ambulatory cancer patients who receive chemotherapy may help in preventing VTE. However, the efficacy of thromboprophylaxis needs to be balanced with the associated risks of bleeding complications.

OBJECTIVES

To assess the efficacy and safety of primary thromboprophylaxis for VTE in ambulatory patients with cancer receiving chemotherapy compared with placebo, no thromboprophylaxis, or an active control intervention.

To compare the efficacy and safety of different types of primary thromboprophylaxis by stratifying the main results per type of drug

or mechanical intervention, and by aggregating results from head-to-head comparisons.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-randomised trials (Higgins 2011).

Types of participants

We included participants who were ambulatory outpatients receiving chemotherapy at the time of randomisation or study entry. We included participants of any age (including children) with either a solid or haematological cancer, at any stage. We included any type of chemotherapy as described by the study authors.

We excluded studies of participants receiving anticoagulation for a previous VTE or an indication other than VTE if data could not be extracted separately for participants not receiving anticoagulants. We excluded studies evaluating prophylaxis for catheter-related thrombosis, since this is already the subject of another Cochrane Review (Kahale 2018).

Types of interventions

We included studies that evaluated any oral or parenteral anticoagulant (e.g. UFH, LMWH, uLMWH, fondaparinux, direct thrombin or factor Xa inhibitors and VKAs) or mechanical intervention (intermittent pneumatic compression or graduated elastic stockings), or both, used to prevent VTE in ambulatory patients with cancer who were receiving chemotherapy. Comparison interventions included no thromboprophylaxis in the form of an inactive control intervention (placebo, no treatment, standard care) or an active control intervention (a different scheme or regimen of the same intervention, a different pharmacological type of prophylaxis, a different type of non-pharmacological prophylaxis). We considered any frequency or duration of administration, dosage or intensity, and timing of delivery of pharmacological prophylaxis.

Types of outcome measures

We considered all outcomes as binary outcomes except for quality of life, which we considered a continuous outcome.

Primary outcomes

- Symptomatic VTE: objectively verified by means of Doppler (compression) ultrasonography or venography for DVT, and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE.
- Major bleeding; typically defined as overt bleeding associated with a decrease in haemoglobin of 2 g/dL or more, or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleeding that occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death (Schulman 2005).

Secondary outcomes

- Symptomatic PE.
- Symptomatic DVT.
- Any VTE (symptomatic and incidental).
- One-year overall mortality.
- Clinically relevant bleeding (major and clinically relevant non-major bleeding); typically defined as overt bleeding that does not meet the criteria for major bleeding, but is associated with the need for medical intervention, contact with a physician, or interruption of the study drug or with discomfort or impairment of activities of daily life (Kaatz 2015).
- Incidental VTE.
- Minor bleeding; defined as a bleeding event not matching the criteria for major bleeding or clinically relevant non-major bleeding.
- Arterial thromboembolic events.
- Superficial venous thrombosis.
- Quality of life.
- Any serious adverse event; defined as events resulting in patient hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events. or death. For trials using LMWH as the intervention or control, we recorded heparin-induced thrombocytopenia (HIT) and the incidence of osteoporosis, as defined by the trial authors.

For the 'Summary of findings' tables, we selected the following outcomes as the most patient-relevant.

- Symptomatic VTE.
- Major bleeding.
- Symptomatic PE.
- Symptomatic DVT.
- Any VTE.
- One-year overall mortality.
- Clinically relevant bleeding.

Search methods for identification of studies

Electronic searches

For this update, the Cochrane Vascular Information Specialist conducted systematic searches of the following databases for RCTs and controlled clinical trials without language, publication year, or publication status restrictions:

- the Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched from inception to 3 August 2020);
- the Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Register of Studies Online (CRSO 2020, Issue 7);
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (searched from 1 January 2017 to 3 August 2020);
- Embase Ovid (searched from 1 January 2017 to 3 August 2020);
- CINAHL EBSCO (searched from 1 January 2017 to 3 August 2020);
- AMED Ovid (searched from 1 January 2017 to 3 August 2020).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with adaptations of the highly sensitive search strategy designed by Cochrane for identifying

RCTs and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6, Lefebvre 2011). Search strategies for major databases are provided in Appendix 1.

The Information Specialist searched the following trials registries on 3 August 2020:

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

Searching other resources

The review authors searched the reference lists of identified studies and contacted content experts and trialists for relevant references. One review author (MC) screened the conference proceedings of the American Society of Clinical Oncology (from 2009 to 2018) and the International Society of Thrombosis and Haemostasis (from 2003 to 2019), combining the search terms of 'venous thrombosis', 'vein thrombosis', or 'pulmonary embolism' with 'cancer' or 'tumour'. We included studies if we could obtain adequate information from either the abstract or personal communication.

Data collection and analysis

Selection of studies

Two review authors (EV, MC) independently reviewed the titles and abstracts identified from the database searches to determine whether they met the inclusion criteria. Any disagreements were resolved through discussion between the review authors. The review authors were not blinded to the journal, institution, or results of the study. We applied no language restrictions. We reassessed studies with insufficient information if we were able to obtain additional details from the trial authors. We documented reasons for excluding studies in the Characteristics of excluded studies table. We considered all reports relating to the same trial if there were multiple reports. We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram

Data extraction and management

Two review authors (EV, MC) independently extracted the data from the included studies onto standardised forms, resolving any disagreements by consensus or by involving a third review author (AWSR). We collected information on risk of bias, participant characteristics, characteristics of the intervention and control groups, and outcomes. Whenever possible, we extracted the results from an intention-to-treat analysis. If we could not calculate effect sizes, we contacted the trial authors to request additional data.

Assessment of risk of bias in included studies

Two review authors (EV, MC) independently assessed randomisation, blinding, and adequacy of analyses (Higgins 2011). We resolved disagreements by consensus or by involving a third review author (AWSR).

We assessed two components of randomisation: generation of allocation sequence and concealment of allocation. We considered generation of the allocation sequence to be adequate if it resulted in an unpredictable allocation schedule. Mechanisms considered to be adequate included random number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards, and drawing lots. We considered trials using an unpredictable allocation sequence to be randomised. We considered trials using potentially predictable allocation mechanisms, such as alternation or allocation of participants according to date of birth, date of presentation, or case record number, to be quasi-randomised (Higgins 2011).

We considered concealment of allocation to be adequate if participants and the investigators responsible for participant selection were unable to predict before allocation which treatment was next. Methods considered adequate included central randomisation; pharmacy-controlled randomisation using identical, prenumbered containers; and sequentially numbered, sealed, opaque envelopes. We considered blinding of participants and therapists to be adequate if experimental and control preparations were explicitly described as indistinguishable, or if a study used a double-dummy technique. We considered assessors to be blinded if this was explicitly mentioned by the investigators.

We considered the risk of attrition bias to be low if all randomised participants were included in the analyses according to the intention-to-treat principle. We classified the item 'selective reporting' as at low risk of bias if we had both the protocol and the full report of a given study, where the full report presented results for all outcomes listed in the protocol. We classified a study as at high risk of bias if a report did not present data on all outcomes reported in either the protocol or the methods section. We did not consider the item 'other bias' in this review. We assessed the reporting of primary outcomes and sample size calculations. Finally, we used GRADE to describe the certainty of the overall body of evidence, defined as the extent of our confidence in the estimates of treatment benefits and harms (Guyatt 2008; Higgins 2011).

Measures of treatment effect

We presented results as summary risk ratios (RRs) for dichotomous variables, determining a 95% confidence interval (CI) for each estimate. The unit of analysis was the participant throughout all outcomes. We planned to summarise results on quality of life with the standardised mean difference (SMD), but none of the studies provided quality of life data on the continuous scale. We used inverse-variance random-effects model meta-analysis to combine the trials (DerSimonian 1986). For outcomes considered in the 'Summary of findings' tables, we also calculated clinical effect summary statistics such as the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) to express the final results of the review. NNTB and NNTH were only calculated in the case of statistically significant findings.

Assessment of heterogeneity

We identified between-study variation visually by looking at the overlap of CIs of individual studies. In addition, we measured and described heterogeneity of the treatment effect between trials using the I^2 statistic and the P value from the corresponding Chi^2 test and the variance estimate Tau^2.

Assessment of reporting biases

For the primary outcomes symptomatic VTE and major bleeding, we evaluated publication bias and other biases related to small-

study size using funnel plots, whenever 10 studies contributed. We plotted the RRs on the vertical axis against their standard errors on the horizontal axis (Sterne 2001). Funnel plot symmetry would be expected in the absence of any bias related to small-study size. We used the Harbord–Egger's test to assess symmetry (Harbord 2006). We further explored any anomaly in stratified analyses, in which we investigated the effects of differences in types of LMWH, age, type of cancer, and suboptimal study design choices on the magnitude of the effects.

Data synthesis

In the main analyses, we analysed and presented data by stratifying for the type of thromboprophylaxis used and grouped comparisons according to whether control treatment included placebo/no thromboprophylaxis or active control treatment.

We planned to explore the between-trial heterogeneity by stratifying the primary outcomes for the following trial characteristics: age (65 years or less versus above 65 years); type of cancer; stage of cancer (metastatic versus non-metastatic); type of major bleeding (according to the definition provided by Schulman 2005 versus unclear or different definition); concealment of allocation (adequate versus inadequate or unclear); blinding (adequate versus inadequate or unclear); analysis in accordance with the intention-to-treat principle (yes versus no or unclear); selective outcome reporting (low versus high or unclear risk); and differences in the use of cointerventions in the trial groups. We planned to use univariate random-effects model meta-regression to determine whether treatment effects were affected by these factors and by three continuous variables at trial level: dosage of intervention, treatment duration, and length of follow-up (Thompson 1999). Not all planned analyses could be performed, which is explained in the Differences between protocol and review section.

We performed the data analysis in Review Manager 5 (Review Manager 2014). We performed stratified analyses and funnel plot exploration in STATA release 15.1 (Stata 2019).

'Summary of findings' table

We presented the main findings of the review concerning the certainty of the evidence, magnitude of effect of the interventions examined, and sum of available data in 'Summary of findings' tables, according to the GRADE principles described by Higgins 2011 and Guyatt 2008. We created separate tables for different comparisons of thromboprophylaxis used and reported the findings of the outcomes symptomatic VTE, major bleeding, symptomatic PE, symptomatic DVT, any VTE, one-year overall mortality, and clinically relevant bleeding. For the critical outcome symptomatic VTE, we applied cutoffs to define high- and intermediate-risk groups. We used a cutoff of 7% to define high risk, in line with the cutoff proposed by Khorana 2008, which is between 6.7% and 7.1% over about three months, and with the results of a recent trial (Carrier 2019). We used event rates between 2% and 7% to define groups at intermediate risk for symptomatic VTEs (Khorana 2008).

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

Following title and abstract screening, we considered 52 reports (31 trials) to be potentially eligible for this update. We included 26 reports related to six new trials (Campos-Cabrera 2018; Carrier 2019; Ek 2018; Greiner 2019; Khorana 2019; Meyer 2018), and 15 reports related to previously included trials. We identified five new excluded studies (Groen 2019; NCT04106700; NCT04352439; Storrar 2019; Zwicker 2019). We added five reports to the Characteristics of ongoing studies table (ChiCTR-TRC-08000267; NCT01518465; NCT03090880; NCT03428373; O'Brien 2019). One study previously listed as awaiting classification has now been excluded (Salat 1990). See Figure 1 for the study flow diagram.

Figure 1. Study flow diagram. RCT: randomised controlled trial; VTE: venous thromboembolism.

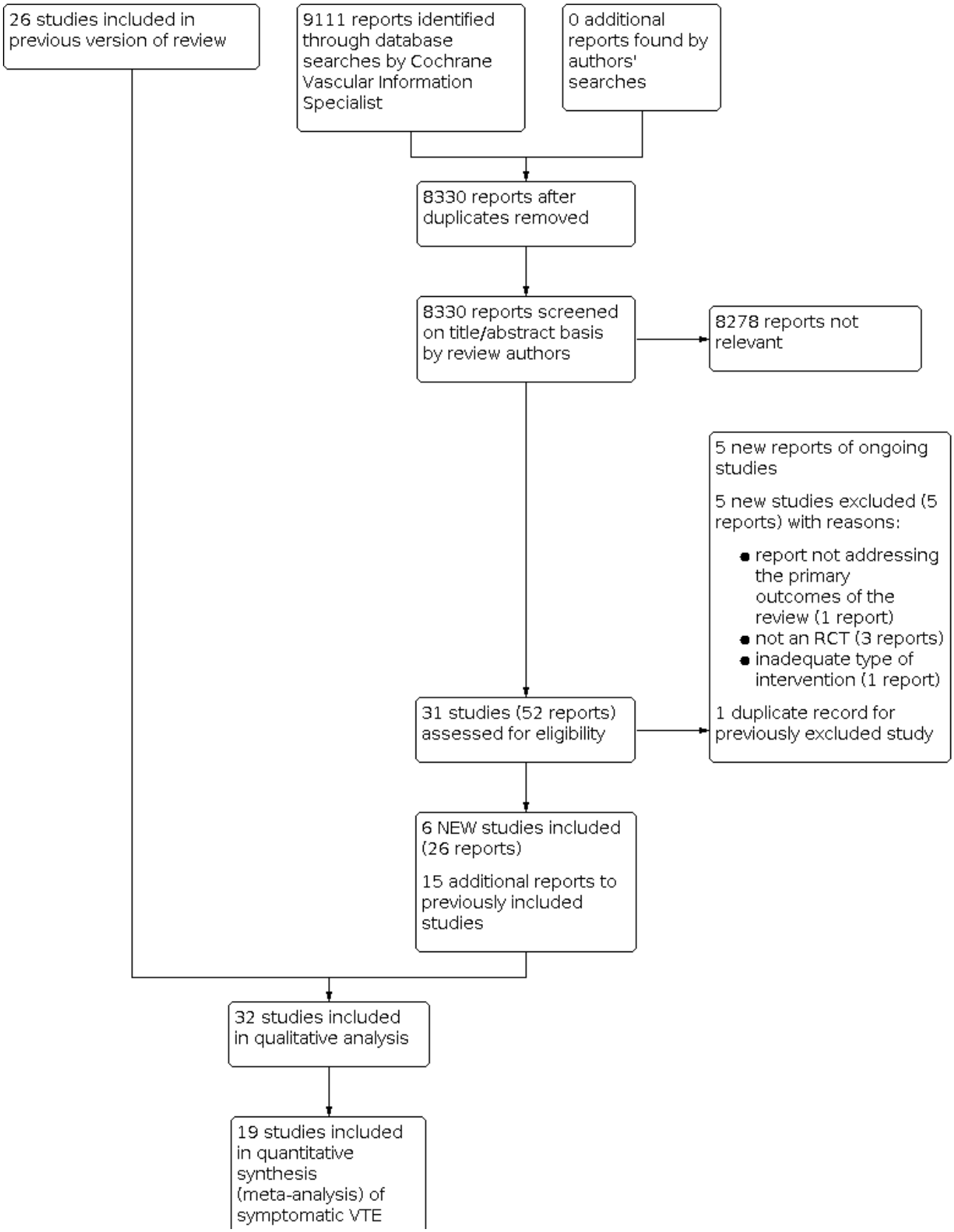
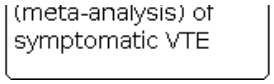


Figure 1. (Continued)



Included studies

For this update, we included six new studies (Campos-Cabrera 2018; Carrier 2019; Ek 2018; Greiner 2019; Khorana 2019; Meyer 2018). Two of these were reported as ongoing studies in the previous version of the review (Carrier 2019; Ek 2018).

The review includes 32 RCTs randomising 15,678 participants. The treatments evaluated consisted of the uLMWH semuloparin (Agnelli 2012), LMWH (Agnelli 2009; Altinbas 2004; Ek 2018; Elit 2012; Greiner 2019; Haas 2012; Kakkar 2004; Khorana 2017; Klerk 2005; Larocca 2012; Lecumberri 2013; Macbeth 2016; Maraveyas 2012; Meyer 2018; Palumbo 2011; Pelzer 2015; Perry 2010; Sideras 2006; Vadhan-Raj 2013; van Doormaal 2011; Zwicker 2013), UFH (Greiner 2019; Lebeau 1994), the VKA warfarin (Chahinian 1989; Levine 1994; Maurer 1997; Palumbo 2011; Zacharski 1981), antithrombin (Greiner 2019; Mitchell 2003), and the oral direct factor Xa inhibitors apixaban (Carrier 2019; Levine 2012) and rivaroxaban (Campos-Cabrera 2018; Khorana 2019). None of the included RCTs used non-pharmacological prophylaxis, or pharmacological thromboprophylaxis with fondaparinux, the direct thrombin inhibitor dabigatran, or the direct factor Xa inhibitor edoxaban. In 17/32 studies, inclusion was restricted to people with locally advanced or metastatic cancer, in three studies limited cancer was included, in six studies both early and advanced disease were included, while in the remaining studies the stage was not clear (see Characteristics of included studies table). Meyer 2018 recruited participants with completely resected stage I, II, or IIIA non-small-cell lung cancer. Greiner 2019 and Mitchell 2003 included children with acute lymphoblastic leukaemia.

Two studies assessed the use of the oral direct factor Xa inhibitors apixaban (Carrier 2019) and rivaroxaban (Khorana 2019) versus placebo in patients with cancer considered at intermediate-to-high risk of VTE (Khorana score 2 or greater).

- Carrier 2019 recruited 574 participants with a Khorana score of 2 or greater and newly diagnosed cancer or progression of known cancer after complete or partial remission and who were initiating a new course of chemotherapy with a minimum treatment intent of three months. Participants were randomised to apixaban 2.5 mg twice daily or placebo for six months.
- Khorana 2019 recruited 841 ambulatory adults with various cancers initiating a new systemic regimen and at increased risk for VTE (defined as Khorana score of 2 or greater) who had no DVT on screening ultrasonography. Participants were randomised 1:1 to rivaroxaban 10 mg once daily or placebo up to day 180.

In a pilot, phase II study, Levine 2012 recruited 125 participants receiving either first- or second-line chemotherapy for advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian, or prostate cancer; cancer of unknown origin; myeloma; or selected lymphomas. Participants were randomised to apixaban 5 mg (32 participants), 10 mg (30 participants), 20 mg (33 participants), and placebo (30 participants). The study treatment was given for 12 weeks, beginning within four weeks of starting chemotherapy.

Campos-Cabrera 2018 recruited 23 participants with multiple myeloma who received thalidomide- and dexamethasone-based triplet induction therapy and maintenance thalidomide. Participants were randomised 5:1 to receive aspirin 100 mg or rivaroxaban 10 mg until relapse and further treatment was needed.

One study assessed the uLMWH semuloparin versus placebo.

- Agnelli 2012 recruited 3212 participants with metastatic or locally advanced solid cancer of the lung, pancreas, stomach, colon or rectum, bladder, or ovary and randomised them to the uLMWH semuloparin 20 mg once daily versus placebo starting on the first day of a first or new regimen of chemotherapy. The intervention was continued for three months unless chemotherapy was stopped earlier.

Twenty-one studies assessed LMWH.

Seventeen studies evaluated LMWH either versus placebo or no thromboprophylaxis (Agnelli 2009; Altinbas 2004; Ek 2018; Haas 2012; Kakkar 2004; Khorana 2017; Klerk 2005; Lecumberri 2013; Macbeth 2016; Maraveyas 2012; Meyer 2018; Pelzer 2015; Perry 2010; Sideras 2006; Vadhan-Raj 2013; van Doormaal 2011; Zwicker 2013). One study compared different doses from prophylactic to full therapeutic of LMWH with each other (Elit 2012). These 18 trials varied in the duration and type of LMWH, including eight weeks to 48 months of subcutaneous (SC) dalteparin, enoxaparin, certoparin, nadroparin, bemiparin, and tinzaparin. The dose of LMWH was prophylactic in most studies, intermediate in three (Ek 2018; Meyer 2018; Pelzer 2015), and therapeutic in one study (Maraveyas 2012). In two studies, initial therapeutic LMWH was followed by intermediate doses (Klerk 2005; van Doormaal 2011). Fifteen of these 18 studies reported a mean age at study entry of 65 years or younger, whereas Ek 2018 and Zwicker 2013 included participants with a mean age above 65 years.

- Agnelli 2009 recruited 1150 participants with metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer and randomised them to nadroparin 3800 IU SC once daily versus placebo. Study treatment started on the same day as chemotherapy and was given for the duration of the chemotherapy or up to a maximum of 120 days (± 10 days).
- Altinbas 2004 recruited 84 participants with histologically confirmed small-cell lung carcinoma and randomised them to standard anticancer treatment with or without dalteparin 5000 IU SC once daily. Dalteparin was stopped with disease progression or at the end of the 18 weeks of chemotherapy.
- Ek 2018 recruited 390 participants with newly diagnosed small-cell lung cancer and randomised them to enoxaparin at a supraprophylactic dose (1 mg/kg) in addition to standard treatment versus standard treatment alone. Enoxaparin was started on the same day as chemotherapy and continued until the 21st day of the last chemotherapy cycle.
- Elit 2012 recruited 77 women with newly diagnosed epithelial ovarian cancer and randomised them to receive standard chemotherapy and one of three SC doses of dalteparin (50 IU/kg,

100 IU/kg, or 150 IU/kg), once daily during the first three of six cycles of three-weekly chemotherapy.

- Haas 2012 recruited 353 participants with metastatic breast cancer or 547 participants with non-small-cell lung carcinoma and receiving first- or second-line chemotherapy. Participants were randomised to six months of certoparin 3000 IU SC, once daily versus placebo.
- Kakkar 2004 recruited 385 participants with histologically confirmed locally advanced or metastatic malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus and randomised them to dalteparin 5000 IU SC, once daily versus placebo. Study treatment was for one year or until the participant died, whichever occurred first.
- Khorana 2017 recruited 98 participants with cancer at high risk for VTE (Khorana score 3 or greater) who initiated a new systemic chemotherapy regimen and randomised them to dalteparin 5000 IU SC once daily for 12 weeks versus no thromboprophylaxis.
- Klerk 2005 recruited 302 participants with metastasised or locally advanced solid tumours and randomised them to nadroparin versus placebo. Study treatment was given using prefilled syringes containing a fixed volume of nadroparin (anti-factor Xa 9500 IU/mL) or placebo according to the participant's weight: 0.4 mL for those weighing less than 50 kg, 0.6 mL for those weighing between 50 kg and 70 kg, and 0.8 mL for those weighing more than 70 kg. Study treatment was to be administered SC twice daily during the initial 14 days of treatment and once daily thereafter for another four weeks.
- Lecumberri 2013 recruited 39 participants with newly diagnosed, limited-stage small-cell lung cancer and randomised them to standard chemoradiotherapy alone or combined with bemiparin 3500 IU SC once daily for a maximum of 26 weeks.
- Macbeth 2016 recruited 2202 participants with histopathological or cytological diagnosis of primary bronchial carcinoma of any stage and histology (small-cell or non-small-cell) and randomised them to standard anticancer treatment (including active supportive or palliative care) with or without dalteparin 5000 IU SC once daily for a maximum of 24 weeks.
- Maraveyas 2012 recruited 123 participants with advanced pancreatic cancer and randomised them to dalteparin (200 IU/kg SC, once daily for four weeks followed by 150 IU/kg for a further eight weeks) in combination with gemcitabine versus gemcitabine alone. Continuing dalteparin prophylaxis after 12 weeks was not recommended, but was left to the discretion of the investigator.
- Meyer 2018 recruited 553 participants with completely resected stage I, II or IIIA non-small-cell lung cancer and randomised them to tinzaparin 100 IU/kg SC once daily for 12 weeks in addition to standard of care versus standard of care alone.
- Pelzer 2015 recruited 312 participants with histologically or cytologically confirmed advanced pancreatic cancer and randomised them to standard anticancer treatment with or without enoxaparin 1 mg/kg SC once daily for three months, started simultaneously with palliative systemic chemotherapy; after 12 weeks of initial chemotherapy, all participants who had not progressed received the standard therapy with or without enoxaparin 40 mg SC once daily for an additional three months.
- Perry 2010 recruited 186 participants with newly diagnosed, pathologically confirmed WHO grade 3 or grade 4 glioma and randomised them to six months of dalteparin 5000 IU SC once daily versus placebo starting within the first month after surgery. Participants were allowed to continue the study medication for 12 months.
- Sideras 2006 recruited 138 participants with advanced breast cancer who did not respond to first-line chemotherapy, advanced prostate cancer resistant to primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer. In the first part of the study, participants were randomised to dalteparin 5000 IU SC once daily versus placebo, while in the second part participants were randomised to dalteparin 5000 IU SC once daily plus standard clinical care versus standard clinical care alone. Dalteparin (or placebo) was given for 18 weeks or until disease progression.
- Vadhan-Raj 2013 recruited 75 participants with advanced stage (unresectable or metastatic) adenocarcinoma of the pancreas planning to initiate systemic chemotherapy and randomised them to chemotherapy with or without dalteparin 5000 IU SC once daily for 16 weeks.
- van Doormaal 2011 recruited 503 participants with non-small-cell lung cancer (stage IIIB), hormone-refractory prostate cancer, or locally advanced pancreatic cancer and randomised them to standard anticancer treatment with or without nadroparin. Sc nadroparin was administered for six weeks (two weeks at therapeutic dose and four weeks at half therapeutic dose). The participants were eligible to receive additional cycles of nadroparin (two weeks at therapeutic dose and four weeks washout period) for a maximum of six cycles.
- Zwicker 2013 recruited 34 participants with histologically confirmed advanced stage malignancy, which included adenocarcinoma of the pancreas (locally advanced or metastatic), colorectal (stage IV), non-small-cell lung cancer (stage III or IV), relapsed or stage IV ovarian, or surgically unresectable or metastatic gastric adenocarcinoma. Participants were randomised to enoxaparin 40 mg SC once daily for two months or observation.

Three additional studies compared LMWH against an active control.

- Greiner 2019 recruited 949 participants aged one to 18 years with newly diagnosed acute lymphoblastic leukaemia and randomised them to low-dose UFH (2 IU/kg body weight/hour), LMWH (enoxaparin 80 IU/kg to 100 IU/kg body weight once daily SC with a target anti-Xa level not exceeding 0.4 U/L) or activity-adapted antithrombin throughout induction therapy. Thromboprophylaxis was started on day eight and ended on day 33 of induction chemotherapy.
- Larocca 2012 recruited 342 participants with newly diagnosed multiple myeloma treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone-lenalidomide consolidation. Participants were randomised to aspirin 100 mg per day or LMWH (enoxaparin 40 mg once daily). Prophylaxis was provided during the four (28-day) cycles of induction and the six (28-day) cycles of consolidation therapy.
- Palumbo 2011 recruited 667 participants with previously untreated myeloma who received thalidomide-containing regimens and randomised them to aspirin 100 mg once daily, low-dose warfarin (1.25 mg once daily) or LMWH (enoxaparin 40 mg once daily). The prophylaxis was administered during the three cycles of induction therapy in participants aged 65 years

or less and during the first six cycles of induction therapy in participants aged over 65 years.

Four studies compared the VKA warfarin against no thromboprophylaxis or placebo.

- Chahinian 1989 recruited 328 participants with extensive carcinoma of the lung and randomised them to warfarin (dose to maintain a prothrombin time 1.5 to twice the control values) versus no warfarin. Warfarin was continued throughout the course of chemotherapy.
- Levine 1994 recruited 311 participants with metastatic stage IV breast carcinoma who had been receiving first- or second-line chemotherapy for four weeks or less and randomised them to warfarin (target of international normalised ratio (INR) 1.3 to 1.9) versus placebo. Study treatment began either at the start of chemotherapy or within the following four weeks and continued until one week after termination of chemotherapy.
- Maurer 1997 recruited 347 participants with limited-stage small-cell lung cancer who were to receive chemotherapy and radiotherapy and randomised them to warfarin or no warfarin. Warfarin (dose of 10 mg once daily for the first three days and then at a dose to maintain the prothrombin time between 1.4 and 1.6 times the local institutional control standards) was continued through the complete course of chemotherapy and radiation therapy and was stopped three weeks after the last cycle of chemotherapy.
- Zacharski 1981 recruited 50 participants with small-cell lung cancer and randomised them to warfarin (dose to prolong the prothrombin time to approximately two times the control value) versus no warfarin.

One study each evaluated UFH and antithrombin against no thromboprophylaxis.

- Lebeau 1994 recruited 277 participants with limited and extensive small-cell lung cancer who had not been previously treated with chemotherapy or radiotherapy. The dose of UFH was initially adapted to weight (500 IU/kg/day), then adjusted by clotting times (different techniques used, and results had to be between two and three times the control value). UFH was administered in two or three daily injections for five weeks and stopped one week after the second course of chemotherapy.
- Mitchell 2003 recruited 85 children newly diagnosed with acute lymphoblastic leukaemia and randomised them to receive, or not, weekly infusions of antithrombin.

Excluded studies

We excluded 30 studies for the following reasons: design other than an RCT (Baz 2005; Bocharov 2011; Kessler 2011; Meister 2008; Minnema 2004; NCT04106700; NCT04352439; Paydas 2008; Storrar 2019; Zangari 2003); studies on perioperative thromboprophylaxis (Bergqvist 1983; Heilmann 1995; Hills 1972; Macintyre 1974; Maxwell 2000; Sideras 2007; Welti 1981); inclusion of hospitalised cancer patients (Eichinger 2008; Haas 2011; Poniewierski 1988; Weber 2008); no relevant outcomes reported (Groen 2019; Rajan 1995; Salat 1990); no eligible intervention (Niesvizky 2007; Zwicker 2019); and prophylaxis was for catheter-related thrombosis (NCT00004875). Three studies were terminated early: NCT00790452 because of a drug supply issue; NCT00662688 due to the lack of eligible patients; NCT00031837 with no reason for study termination reported.

Studies awaiting classification

There are two completed studies awaiting classification, one published in abstract form (Ciftci 2012), one published as trial registration (NCT00771563). Outcome data for these two trials are not yet published but may be available at the time of the next update.

Ongoing studies

Five new ongoing studies were identified for this update (ChiCTR-TRC-08000267; NCT01518465; NCT03090880; NCT03428373; O'Brien 2019), bringing the total to eight ongoing studies (ChiCTR-TRC-08000267; NCT00718354; NCT01518465; NCT02285738; NCT02555878; NCT03090880; NCT03428373; O'Brien 2019).

Risk of bias in included studies

The 'Risk of bias' summary is shown in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

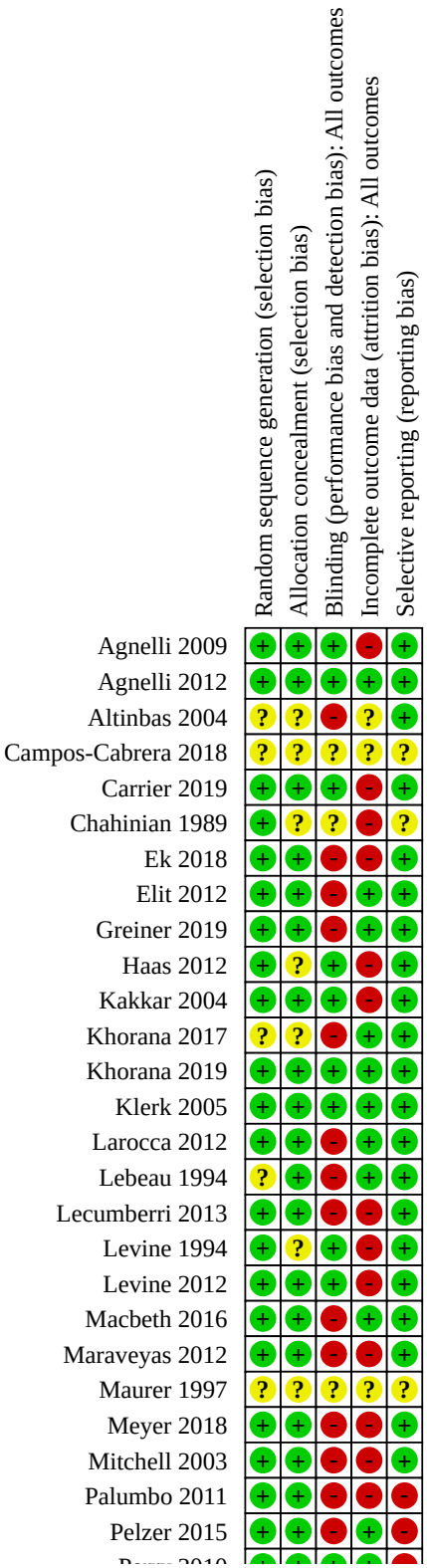
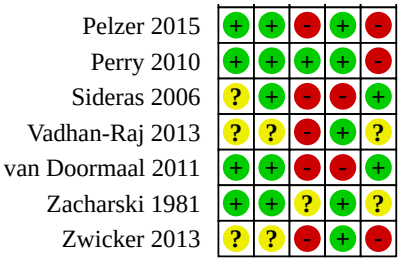


Figure 2. (Continued)



Allocation

The random sequence was adequately generated in 24 studies (Agnelli 2009; Agnelli 2012; Carrier 2019; Chahinian 1989; Ek 2018; Elit 2012; Greiner 2019; Haas 2012; Kakkar 2004; Khorana 2019; Klerk 2005; Larocca 2012; Lecumberri 2013; Levine 1994; Levine 2012; Macbeth 2016; Maraveyas 2012; Meyer 2018; Mitchell 2003; Palumbo 2011; Pelzer 2015; Perry 2010; van Doormaal 2011; Zacharski 1981), but was unclear in the remaining eight studies due to poor reporting (Altinbas 2004; Campos-Cabrera 2018; Khorana 2017; Lebeau 1994; Maurer 1997; Sideras 2006; Vadhan-Raj 2013; Zwicker 2013).

Allocation was adequately concealed in 23 studies (Agnelli 2009; Agnelli 2012; Carrier 2019; Ek 2018; Elit 2012; Greiner 2019; Kakkar 2004; Khorana 2019; Klerk 2005; Larocca 2012; Lebeau 1994; Lecumberri 2013; Levine 2012; Macbeth 2016; Maraveyas 2012; Meyer 2018; Mitchell 2003; Palumbo 2011; Pelzer 2015; Perry 2010; Sideras 2006; van Doormaal 2011; Zwicker 2013), and was unclear in the remaining nine studies due to poor reporting (Altinbas 2004; Campos-Cabrera 2018; Chahinian 1989; Haas 2012; Khorana 2017; Levine 1994; Maurer 1997; Vadhan-Raj 2013; Zwicker 2013).

Blinding

Ten studies had a double-blind design and were at low risk of performance and detection bias (Agnelli 2009; Agnelli 2012; Carrier 2019; Haas 2012; Kakkar 2004; Khorana 2019; Klerk 2005; Levine 1994; Levine 2012; Perry 2010), and 18 were open studies and at high risk of bias (Altinbas 2004; Ek 2018; Elit 2012; Greiner 2019; Khorana 2017; Larocca 2012; Lebeau 1994; Lecumberri 2013; Macbeth 2016; Maraveyas 2012; Meyer 2018; Mitchell 2003; Palumbo 2011; Pelzer 2015; Sideras 2006; Vadhan-Raj 2013; van Doormaal 2011; Zwicker 2013). In four studies blinding was unclear due to poor reporting (Campos-Cabrera 2018; Chahinian 1989; Maurer 1997; Zacharski 1981).

Incomplete outcome data

Fourteen studies performed the analysis according to the intention-to-treat principle and so were at low risk of attrition bias (Agnelli 2012; Elit 2012; Greiner 2019; Khorana 2017; Khorana 2019; Klerk 2005; Larocca 2012; Lebeau 1994; Macbeth 2016; Pelzer 2015; Perry 2010; Vadhan-Raj 2013; Zacharski 1981; Zwicker 2013), while in 14 studies the percentages of participants randomised and subsequently excluded from the analyses ranged from 0.7% to 10%; we considered these at high risk of bias (Agnelli 2009; Carrier 2019; Chahinian 1989; Ek 2018; Haas 2012; Kakkar 2004; Lecumberri 2013; Levine 1994; Levine 2012; Maraveyas 2012; Meyer 2018; Palumbo 2011; Sideras 2006; van Doormaal 2011). The study involving children used a per-protocol analysis and excluded 22% of the participants that were initially enrolled (Mitchell 2003); we considered this study at high risk of attrition bias. Attrition bias was unclear in three studies (Altinbas 2004; Campos-Cabrera 2018; Maurer 1997).

Selective reporting

We judged 23 studies free of selective reporting and thus at low risk of reporting bias (Agnelli 2009; Agnelli 2012; Altinbas 2004; Carrier 2019; Ek 2018; Elit 2012; Greiner 2019; Haas 2012; Kakkar 2004; Khorana 2019; Khorana 2017; Klerk 2005; Larocca 2012; Lebeau 1994; Lecumberri 2013; Levine 1994; Levine 2012; Macbeth 2016; Maraveyas 2012; Meyer 2018; Mitchell 2003; Sideras 2006; van Doormaal 2011). In five studies one or more outcomes that were reported in the results were not anticipated in the methods sections of the publications; we considered these at unclear risk of reporting bias (Campos-Cabrera 2018; Chahinian 1989; Maurer 1997; Vadhan-Raj 2013; Zacharski 1981). In four studies not all outcomes were reported in the results; we considered these at high risk of reporting bias (Palumbo 2011; Pelzer 2015; Perry 2010; Zwicker 2013).

Effects of interventions

See: **Summary of findings 1** DOAC versus placebo; **Summary of findings 2** Low-molecular-weight heparin versus no thromboprophylaxis; **Summary of findings 3** Low-molecular-weight heparin versus with active control (1); **Summary of findings 4** Low-molecular-weight heparin versus active control (2); **Summary of findings 5** Low-molecular-weight heparin versus active control (3); **Summary of findings 6** Ultra-low-molecular-weight heparin versus placebo; **Summary of findings 7** Unfractionated heparin versus no thromboprophylaxis; **Summary of findings 8** Vitamin K antagonists versus placebo or no thromboprophylaxis; **Summary of findings 9** Vitamin K antagonists versus active control; **Summary of findings 10** Antithrombin versus no thromboprophylaxis

The section Data and analyses depicts effects of interventions derived from studies conducted in adults. In this section, we describe outcome data from both paediatric and adult populations.

Direct oral anticoagulant versus placebo

We found no studies on the direct thrombin inhibitor dabigatran. Three RCTs evaluated the use of factor Xa inhibitors versus placebo (Carrier 2019; Khorana 2019; Levine 2012). We found low-certainty evidence that factor Xa inhibitors may be associated with a reduction of symptomatic VTE (RR 0.43, 95% CI 0.18 to 1.06; 3 studies, 1526 participants; high heterogeneity, $Tau^2 = 0.35$, Analysis 1.1). We downgraded the overall body of evidence because of imprecision, inconsistency, and risk of bias (Summary of findings

1). Levine 2012 was a pilot dose-finding study that evaluated three regimens of apixaban prophylaxis that are currently not approved. Exclusion of Levine 2012 reduced between-trial heterogeneity for symptomatic VTE and confirmed that factor Xa inhibitors may be associated with a lower symptomatic VTE (RR 0.57, 95% CI 0.29 to 1.14 for symptomatic VTE).

We found moderate-certainty evidence that factor Xa inhibitors probably increase major bleeding (RR 1.74, 95% CI 0.82 to 3.68; 3 studies, 1494 participants; no heterogeneity, $Tau^2 = 0.00$; Analysis 2.1). We downgraded due to imprecision. After exclusion of Levine 2012, differences in effects compared to placebo remained similar (RR 1.95, 95% CI 0.88 to 4.30).

Factor Xa inhibitors may reduce symptomatic PE but between-study variation was large and the estimate was imprecise (RR 0.38, 95% CI 0.10 to 1.47; 3 studies, 1526 participants; high heterogeneity, $Tau^2 = 0.65$; low-certainty evidence; Analysis 3.1). Similarly, there was low-certainty evidence that factor Xa inhibitors may decrease symptomatic DVT when compared to placebo (RR 0.51, 95% CI 0.21 to 1.22; 3 studies, 1526 participants; high heterogeneity, $Tau^2 = 0.30$; low-certainty evidence; Analysis 5.1). We downgraded to low certainty because of imprecision, inconsistency, and risk of bias. Factor Xa inhibitors halved the risk of any VTE (RR 0.55, 95% CI 0.34 to 0.90; 2 studies, 1404 participants; moderate-certainty evidence; Analysis 6.1). Assuming a background risk of 95 per 1000 participants, this corresponds to an NNTB of 24 (95% CI 16 to 106). Factor Xa inhibitors also halved incidental VTE (RR 0.50, 95% CI 0.25 to 0.98; 2 studies, 1404 participants; Analysis 9.1). Factor Xa inhibitors probably increase clinically relevant bleeding (RR 1.61, 95% CI 0.82 to 3.15; 2 studies, 931 participants; moderate-certainty evidence; Analysis 8.1), probably decrease arterial thromboembolism (RR 0.57, 95% CI 0.17 to 1.94; Analysis 11.1), and probably have little effect on serious adverse events (RR 0.96, 95% CI 0.82 to 1.13; Analysis 13.1). We downgraded to moderate-certainty evidence due to imprecision.

None of the studies reported the remaining outcomes of interest (one-year overall mortality, superficial venous thrombosis, and quality of life).

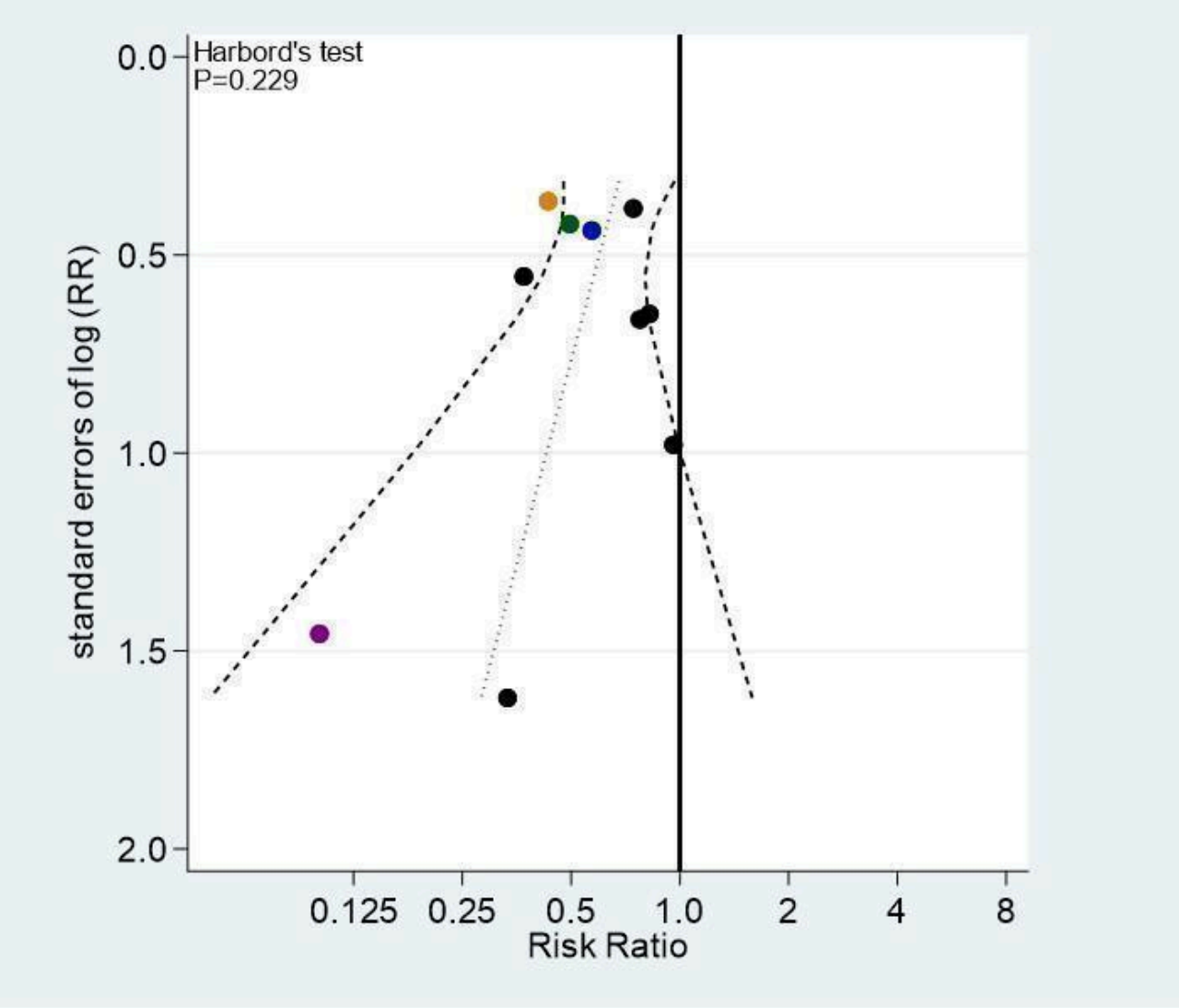
Campos-Cabrera 2018 randomised 23 patients with multiple myeloma 5:1 to receive aspirin or rivaroxaban. There was no VTE in participants who received rivaroxaban and one participant in the aspirin group. There were no cases of major bleeding in either group. The study did not report incidental VTE, clinically relevant bleeding, arterial thromboembolism, or serious adverse events.

Low-molecular-weight heparin versus placebo or no thromboprophylaxis

Seventeen studies evaluated LMWH versus placebo or no thromboprophylaxis (Agnelli 2009; Altinbas 2004; Ek 2018; Haas 2012; Kakkar 2004; Khorana 2017; Klerk 2005; Lecumberri 2013; Macbeth 2016; Maraveyas 2012; Meyer 2018; Pelzer 2015; Perry 2010; Sideras 2006; Vadhan-Raj 2013; van Doormaal 2011; Zwicker 2013).

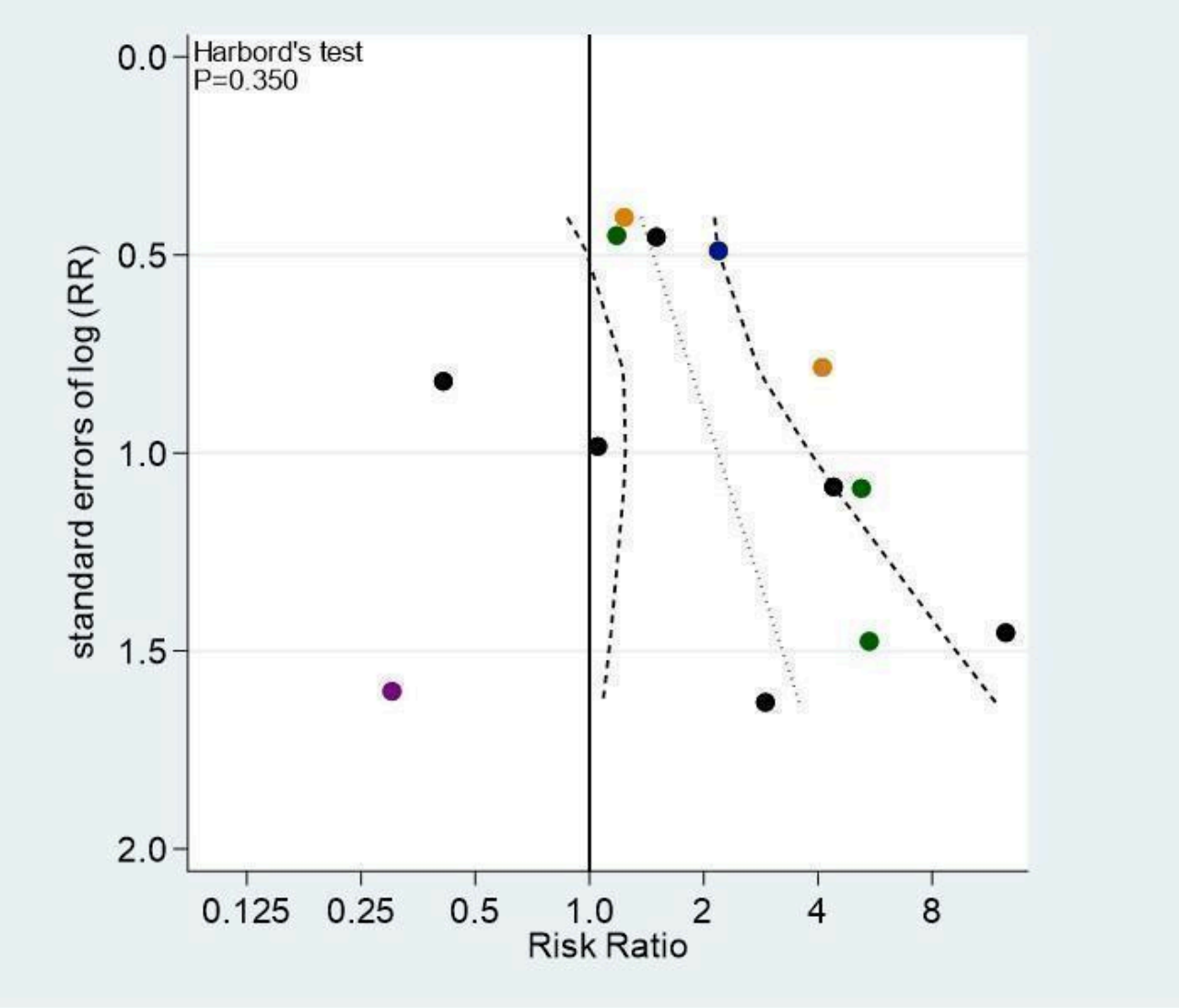
Based on high-certainty evidence from 11 RCTs, there was a reduction in symptomatic VTE with LMWH compared with no thromboprophylaxis in the absence of heterogeneity (RR 0.62, 95% CI 0.46 to 0.83; 3931 participants; $Tau^2 = 0.00$; Analysis 1.2). This corresponded to an NNTB of 37 (95% CI 26 to 83), assuming a background risk of 71 symptomatic VTE events per 1000 participants (Summary of findings 2 and Khorana 2008). Funnel plot exploration found no evidence of biases associated with small studies (Figure 3). Stratified analyses showed no effect of the type of LMWH, dosage, treatment duration, type or stage of cancer, or design characteristics on the relative risk of symptomatic VTE (Table 1). Similarly, we found no evidence for a linear association between treatment duration and the risk of symptomatic VTE using meta-regression analysis (P = 0.643).

Figure 3. Funnel plot of comparison: 1 Anticoagulants versus control: symptomatic venous thromboembolism (VTE), outcome: 1.2 Symptomatic VTE: low-molecular weight heparin versus no thromboprophylaxis.



When compared with no thromboprophylaxis, we found moderate-certainty evidence that LMWH was associated with an increase in major bleeding in the absence of heterogeneity (RR 1.63, 95% CI 1.12 to 2.35; 15 studies, 7282 participants; Tau^2 = 0.00; Analysis 2.2). We downgraded by one level for risk of bias. Assuming a background risk of 11 major bleeding episodes per 1000 participants, this corresponds to an NNTH of 144 (95% CI 67 to 758). Visual examination of the funnel plot and Harbord–Egger's test (P = 0.350) found no asymmetry (Figure 4), so that we detected no publication bias or other biases related to small-study size. The stratified analyses showed no effect of the type of LMWH, dosage, treatment duration, age, type or stage of cancer, definition of major bleeding, or other design characteristics on the relative risk of major bleeding (Table 2). We found no evidence for a linear association between treatment duration and the risk of major bleeding using meta-regression analysis (P = 0.892). In Ek 2018, three (1.6%) participants in the enoxaparin group had a fatal bleeding compared to one (0.5%) in the control group. In Meyer 2018, three participants in both groups had a fatal bleeding and Khorana 2017 reported no fatal bleeds in either group.

Figure 4. Funnel plot of comparison: 2 Anticoagulants versus control: major bleeding, outcome: 2.2 Major bleeding: low-molecular weight heparin versus no thromboprophylaxis.



Pooled estimates of LMWH effects on symptomatic VTE and major bleeding were unchanged after excluding Meyer 2018, which enrolled participants with completely resected cancer (symptomatic VTE: RR 0.55, 95% CI 0.39 to 0.76: major bleeding: RR 1.60, 95% CI 1.10 to 2.32).

LMWH probably reduces symptomatic PE (RR 0.60, 95% CI 0.42 to 0.88; 8 studies, 5324 participants; $Tau^2 = 0.00$; moderate-certainty evidence; Analysis 3.2). We downgraded by one level due to selective outcome reporting. Assuming a background risk of 18 PE per 1000 participants, this corresponds to an NNTB of 138 (95% CI 95 to 458). LMWH may reduce fatal PE but four out of seven studies reporting this outcome did not contribute to the summary estimate as no fatal PE occurred in either trial arm, leading to a very imprecise pooled estimate (RR 0.37, 95% CI 0.11 to 1.21; 7 studies, 4286 participants; $Tau^2 = 0.00$; low-certainty evidence; Analysis 4.1).

The risk of symptomatic DVT was reduced by 52% (RR 0.48, 95% CI 0.35 to 0.67; 9 studies, 5408 participants; $Tau^2 = 0.00$; high-certainty evidence; Analysis 5.2). Assuming a background risk of 28 per 1000 participants, this corresponds to an NNTB of 69 (95% CI 55 to 108).

The incidence of any VTE was reduced by 43% (RR 0.57, 95% CI 0.46 to 0.71; 10 studies, 5743 participants; $Tau^2 = 0.00$; high-certainty evidence; Analysis 6.2), which corresponds to an NNTB of 27 (95% CI 21 to 39), assuming a background risk of 90 per 1000 participants.

There was no clear difference detected for one-year overall mortality (RR 0.94, 95% CI 0.83 to 1.07; 9 studies, 2681 participants; $Tau^2 = 0.02$; low-certainty evidence; Analysis 7.1). We downgraded by two levels because of imprecision and inconsistency. LMWH probably results in a large increase in clinically relevant bleeding (RR 3.40, 95% CI 1.20 to 9.63; 4 studies, 3105 participants; $Tau^2 = 0.73$; moderate-certainty evidence; Analysis 8.2). We downgraded by one level because of inconsistency. With a background risk of 17 per 1000 participants, the NNTH is 24 (95% CI 6 to 298). The incidence of incidental VTE is probably lowered by LMWH (RR 0.63, 95% CI 0.40 to 0.99; 5 studies, 4452 participants; $Tau^2 = 0.00$; Analysis 9.2). LMWH may increase minor bleeding (Analysis 10.1;

low-certainty evidence) and may decrease symptomatic arterial thromboembolism (Analysis 11.2; low-certainty evidence). The effects of LMWH on superficial venous thrombosis (Analysis 12.1; very low-certainty evidence), or serious adverse events (Analysis 13.2; very low-certainty evidence) were uncertain.

Only two studies evaluated quality of life (Macbeth 2016; Sideras 2006). Macbeth 2016 used the Hospital Anxiety and Depression Score and the EuroQol 5 Dimensions (EQ-5D) while Sideras 2006 used the single-item visual analogue Uniscale and a 5-item series of linear analogue self-assessment measures supplemented by a 13-item symptom distress scale. Sideras 2006 reported similar results across groups with respect to decreased quality of life of 10 or more points on the 0- to 100-point visual analogue Uniscale (RR 1.06, 95% CI 0.77 to 1.45; 138 participants). Results on the symptom distress scale were incompletely reported in Sideras 2006, but they did describe that they found similar results in participants randomised to LMWH or no thromboprophylaxis, both at baseline and during the study period. Macbeth 2016 found no difference between LMWH and no thromboprophylaxis with respect to quality-adjusted life years gained in the first year (mean difference (MD) not reported, 95% CI −0.02 to 0.03) and no difference in overall quality of life at six months (EQ-5D: MD 0.11, 95% CI −3.18 to 3.40; 940 participants; P = 0.94) or 12 months (EQ-5D: MD −0.34, 95% CI −5.25 to 4.57; 445 participants; P = 0.89).

Three studies reported no cases of HIT with LMWH use (Haas 2012; Klerk 2005; Pelzer 2015). Haas 2012 reported objectively verified skeletal events (including all fractures, spinal cord compressions, and requirements for surgery to treat fractures or for bone irradiation) in 16/442 participants in the LMWH group and 19/441 participants in the placebo group (RR 0.84, 95% CI 0.44 to 1.61).

Macbeth 2016 reported compliance with LMWH. Of the 977 (89%) participants in whom compliance was evaluated, 180 (18.4%) were considered as fully compliant, whereas 431 (39%) received half of the planned syringes or less. In Ek 2018, approximately 85% of the participants in the enoxaparin group reported full adherence.

Five studies reported symptomatic VTE and six studies on major bleeding in participants with non-small-cell lung cancer (Haas 2012; Meyer 2018), small-cell lung cancer (Altinbas 2004; Lecumberri 2013; Ek 2018), or both (Agnelli 2009; Macbeth 2016). Pooled analysis of these trials showed a probable reduction in symptomatic VTE (RR 0.62, 95% CI 0.38 to 1.02), and possibly a higher risk of major bleeding with LMWH compared with the control treatment (RR 1.79, 95% CI 1.01 to 3.19; no evidence of statistical heterogeneity; $Tau^2 = 0.00$; moderate-certainty evidence; Table 1; Table 2).

Two studies reported symptomatic VTE and major bleeding in participants with advanced pancreatic cancer (Maraveyas 2012; Pelzer 2015). Pooled analysis of these trials showed that LMWH probably substantially reduce symptomatic VTE (RR 0.41, 95% CI 0.23 to 0.75) and may slightly increase major bleeding (RR 1.21, 95% CI 0.58 to 2.51; no evidence of statistical heterogeneity; $Tau^2 = 0.00$) (Table 1; Table 2). Vadhan-Raj 2013 also selectively included participants with advanced pancreatic cancer and reported two DVTs in the dalteparin group and eight VTEs (two PE and six DVT) in 37 participants receiving no thromboprophylaxis. The abstract did not report whether these events were symptomatic, incidental, or both. There were no clinically significant bleeding events with dalteparin, although the definition of bleeding was not provided, and it was not reported if any bleeding occurred in participants of the control group.

Low-molecular-weight heparin versus active control

Elit 2012 compared prophylactic, intermediate and therapeutic doses of dalteparin against each other. There were no symptomatic VTE or major bleeding events during dalteparin administration. Two participants developed symptomatic VTE and one was diagnosed with incidental PE after dalteparin discontinuation (see Analysis 1.3; Analysis 3.3; Analysis 5.3; Analysis 6.3; Analysis 9.3). The certainty of the evidence was low for symptomatic VTE and could not be evaluated for major bleeding as the RR was not estimable due to zero counts in all trial groups (see Summary of findings 3). There were no data on one-year overall mortality, arterial thromboembolism, clinically relevant bleeding, and serious adverse events reported. Two participants had minor bleeding in the highest dose group (150 IU/kg). There were no cases of HIT. Compliance with injections was more than 80% in all three dose groups.

Two studies of participants with multiple myeloma receiving thalidomide- and lenalidomide-based regimens compared LMWH against an active control, which in both studies was aspirin (Larocca 2012; Palumbo 2011), and in one of the studies was a VKA (warfarin) (Palumbo 2011). See Summary of findings 4. When compared with aspirin, pooled analysis showed a possible reduction (49%) in symptomatic VTE (RR 0.51, 95% CI 0.22 to 1.17; 2 studies, 781 participants; moderate-certainty evidence; Analysis 1.4). There were 3/396 (0.75%) major bleeding events with aspirin and 0/385 with LMWH (RR 0.14, 95% CI 0.01 to 2.76; 2 studies, 781 participants; low-certainty evidence; Analysis 2.4). The incidence of symptomatic PE was possibly reduced by 87% (RR 0.13, 95% CI 0.02 to 1.03; 2 studies, 781 participants; moderate-certainty evidence). We downgraded due to imprecision. LMWH probably decreases the incidence of symptomatic DVT when compared to aspirin (RR 0.81, 95% CI 0.32 to 2.04; 2 studies, 781 participants; moderate-certainty evidence; Analysis 5.4). Very low-certainty evidence showed no clear differences between LMWH and aspirin regarding the incidence of minor bleeding (Analysis 10.3), and symptomatic arterial thromboembolism (Analysis 11.3). There were no data on one-year overall mortality, clinically relevant bleeding, and serious adverse events.

In the study of Palumbo 2011, LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR 0.33, 95% CI 0.14 to 0.83; 439 participants; high-certainty evidence; Analysis 1.5), with no major bleeding events in either group. The pooled estimate for the reduction in symptomatic PE was very imprecise (RR 0.11, 95% CI 0.01 to 2.06; low-certainty evidence; Analysis 3.5), whereas LMWH probably reduces symptomatic DVT more than active control (RR 0.43, 95% CI 0.17 to 1.10; moderate-certainty evidence; Analysis 5.5). We downgraded by either one or two levels due to imprecision (see Summary of findings 5). There were no clear differences between LMWH and warfarin regarding the incidence of minor bleeding and symptomatic arterial thromboembolism. There were no data on one-year overall mortality.

In the study of Greiner 2019, conducted in participants aged one to 18 years, the incidence of symptomatic VTE was reduced by both enoxaparin (3.5%) and antithrombin (1.9%) compared with UFH (8.0%; LMWH versus UFH: RR 0.41, 95% CI 0.20 to 0.85; antithrombin versus UFH: RR 0.22, 95% CI 0.09 to 0.54; 949 participants). Major

bleeding occurred in four (1.1%) participants treated with UFU, three (0.9%) with antithrombin, and one (0.5%) with enoxaparin. The study did not report the remaining outcomes of interest.

Ultra-low-molecular-weight heparin versus placebo

In one large trial of 3212 participants, semuloparin was associated with a reduction in symptomatic VTE (RR 0.36, 95% CI 0.22 to 0.60, high-certainty evidence; Analysis 1.6), corresponding to an NNTB of 46 (95% CI 38 to 73) using a control group risk of 34 VTE per 1000 participants (Agnelli 2012). There were 19/1589 major bleeding events in the semuloparin group versus 18/1583 in the placebo group (RR 1.05, 95% CI 0.55 to 2.00; moderate-certainty evidence; Analysis 2.6). We downgraded one level for imprecision (see Summary of findings 6). Semuloparin reduced symptomatic VTE by 64% in participants with lung cancer (9/591 with semuloparin versus 25/589 with placebo; RR 0.36, 95% CI 0.17 to 0.76) and by 78% in participants with pancreatic cancer (3/126 with semuloparin versus 14/128 with placebo; RR 0.22, 95% CI 0.06 to 0.74). The occurrence of major bleeding was not reported separately for these types of cancer.

Semuloparin probably reduced the risk of symptomatic PE by 52% (RR 0.48, 95% CI 0.22 to 1.01; moderate-certainty evidence; Analysis 3.6). We downgraded by one level for imprecision. Both symptomatic DVT (RR 0.32, 95% CI 0.16 to 0.63; high-certainty evidence; Analysis 5.6) and any VTE (RR 0.36, 95% CI 0.22 to 0.60; high-certainty evidence; Analysis 6.4) were reduced by about two-thirds with semuloparin. Fatal PE occurred in 0.4% of participants on semuloparin and 0.6% of participants on placebo. Clinically relevant bleeding was reported in 2.8% of participants on semuloparin and 2.0% of participants on placebo (RR 1.40, 95% CI 0.90 to 2.19; moderate-certainty evidence; Analysis 8.4). We downgraded by one level for imprecision. Semuloparin may reduce incidental VTE but the study was too small to estimate effects precisely (RR 0.14, 95% CI 0.01 to 2.76; Analysis 9.4). We found no evidence that semuloparin had an effect on one-year overall mortality (RR 1.02, 95% CI 0.96 to 1.08; moderate-certainty evidence; Analysis 7.2). The incidence of serious adverse events or thrombocytopenia was similar in the semuloparin and placebo groups (serious adverse effects: 26% with semuloparin versus 25% with placebo; thrombocytopenia: 7.1% with semuloparin versus 7.6% with placebo; Analysis 13.3), with no cases of HIT.

Unfractionated heparin versus no thromboprophylaxis

One study evaluated UFH against no thromboprophylaxis (Lebeau 1994), and did not report on VTE or major bleeding. UFH probably decreases the incidence of one-year overall mortality in small-cell lung cancer, although the CIs of the summary estimate did not conclusively rule out an increase in one-year overall mortality (RR 0.86, 95% CI 0.72 to 1.03; moderate-certainty evidence; Analysis 7.3). Clinically relevant bleeding occurred in 2/138 participants with UFH versus 1/139 participants with no thromboprophylaxis (RR 2.01, 95% CI 0.18 to 21.96; low-certainty evidence; Analysis 8.5). We downgraded by one or two levels due to imprecision. See Summary of findings 7. The study by Lebeau and colleagues was too small to evaluate effects on minor bleeding (RR 3.02, 95% CI 0.12 to 73.54; Analysis 10.5), and they found no cases of HIT. The study did not report the remaining outcomes of interest.

Vitamin K antagonist versus placebo or no thromboprophylaxis

Four studies compared the VKA warfarin against no thromboprophylaxis or placebo, but did not all report our primary outcomes (Chahinian 1989; Levine 1994; Maurer 1997; Zacharski 1981).

Levine 1994 found that warfarin may reduce symptomatic VTE substantially relative to placebo (RR 0.15, 95% CI 0.02 to 1.20; 311 participants; low-certainty evidence; Analysis 1.7). We downgraded by two levels because of imprecision, potential risk of attrition bias, and risk of publication bias. No other study reported on VTE. There was no clear effect on major bleeding (RR 0.52, 95% CI 0.05 to 5.71), symptomatic PE (RR 1.05, 95% CI 0.07 to 16.58; 311 participants; very low-certainty evidence; Analysis 3.7), whereas warfarin may decrease symptomatic DVT substantially (RR 0.08, 95% CI 0.00 to 1.42; 311 participants; low-certainty evidence; Analysis 5.7), and may increase minor bleeding (RR 2.44, 95% CI 0.64 to 9.27; Analysis 10.6). There were no symptomatic arterial thromboembolic events in either group.

The three remaining studies reported major bleeding events, but provided no data on the occurrence of symptomatic or incidental VTE (Chahinian 1989; Maurer 1997; Zacharski 1981). Pooled analysis of all four studies evaluating VKA versus placebo or no thromboprophylaxis showed that major bleeding may substantially increase with VKA, with evidence of a high degree of heterogeneity (RR 3.82, 95% CI 0.97 to 15.04; 4 studies, 994 participants; low-certainty evidence; $Tau^2 = 0.71$; Analysis 2.7).

The certainty of the evidence was low for symptomatic VTE, major bleeding, and symptomatic DVT and very low for symptomatic PE. We downgraded two or three levels due to imprecision and risk of bias concerns (see Summary of findings 8).

Vitamin K antagonist versus active control

Palumbo 2011 reported a possible increased risk of symptomatic VTE with VKA (warfarin) compared to aspirin in patients with multiple myeloma (RR 1.50, 95% CI 0.74 to 3.04; 440 participants; moderate-certainty evidence; Analysis 1.8). There were 3/220 major bleeding events in the aspirin group and none (0/220) in the warfarin group (RR 0.14, 95% CI 0.01 to 2.75; 440 participants; low-certainty evidence; Analysis 2.8). Evidence suggests that VKA and aspirin probably reduce the incidence of symptomatic PE to a similar extent (RR 1.00, 95% CI 0.25 to 3.95; 440 participants; moderate-certainty evidence; Analysis 3.8). VKA is probably less effective than aspirin in reducing symptomatic DVT (RR 1.75, 95% CI 0.75 to 4.09; 440 participants; moderate-certainty evidence; Analysis 5.8). The study by Palumbo and colleagues was too small to precisely estimate effects on other secondary outcomes minor bleeding (Analysis 10.7), and symptomatic arterial thromboembolism (Analysis 11.6). See Summary of findings 9.

Results for the comparison of 'VKA versus LMWH' are presented in the previous section 'LMWH versus active control'.

Antithrombin versus no thromboprophylaxis

One study that recruited 85 children assessed antithrombin (Mitchell 2003). This study did not report on symptomatic VTE but did report any VTE. Effects of antithrombin compared to placebo were uncertain with regard to major bleeding (RR 0.78, 95% CI

0.03 to 18.57; 85 participants; very low-certainty evidence), any VTE (RR 0.84, 95% CI 0.41 to 1.73; 85 participants; very low-certainty evidence), and minor bleeding (RR 11.73, 95% CI 0.58 to 235.96; 85 participants; very low-certainty evidence). We downgraded the certainty of the evidence due to imprecision and risk of bias. The study did not report the remaining outcomes. See Summary of findings 10.

DISCUSSION

Summary of main results

Thromboprophylaxis with direct oral factor Xa inhibitors may decrease the incidence of symptomatic VTE (low-certainty evidence) and probably increases the risk of major bleeding compared with placebo (moderate-certainty evidence). See Summary of findings 1. Factor Xa inhibitors reduced the risk of any VTE by 45% and of incidental VTE by 50% There were no clear differences in symptomatic PE, symptomatic DVT, clinically relevant bleeding, arterial thromboembolism, or serious adverse events.

When compared with placebo or no thromboprophylaxis, LMWH reduced the incidence of symptomatic VTE by 38% (high-certainty evidence; NNTB 37), but probably increased the risk of major bleeding by 63% (moderate-certainty evidence; NNTH 144). LMWH probably reduced the incidence of symptomatic PE (moderate-certainty evidence), reduced symptomatic DVT (high-certainty evidence), any VTE (high-certainty evidence), and incidental VTE and may decrease one-year overall mortality (low-certainty evidence). LMWH was associated with a probable three-fold higher risk of clinically relevant bleeding compared with no thromboprophylaxis (moderate-certainty evidence). See Summary of findings 2.

Evidence for the use of thromboprophylaxis with anticoagulants other than factor Xa inhibitors and LMWH appear to be preliminary.

Marketing applications for the uLMWH semuloparin have been withdrawn worldwide, and it is therefore unlikely to ever be commercially available (EMEA 2012).

In participants with multiple myeloma, LMWH probably reduces symptomatic VTE more than aspirin (moderate-certainty evidence). There was major bleeding in none of the participants treated with LMWH and in less than 1% of those treated with aspirin (low-certainty evidence). See Summary of findings 4. There is a possible increased risk of symptomatic VTE with VKA (warfarin) compared to aspirin (moderate-certainty evidence) while VKA may be associated with a lower risk of major bleeding when compared to aspirin (low-certainty evidence). See Summary of findings 9.

One study in participants with multiple myeloma receiving thalidomide- or lenalidomide-based regimens showed that LMWH was associated with a 67% lower risk of symptomatic VTE compared with warfarin (high-certainty evidence), but this study was underpowered to show differences for major bleeding (Palumbo 2011; Summary of findings 5). Similarly, the evidence was insufficient to precisely estimate the effects in people without myeloma. In the latter, warfarin may reduce symptomatic VTE (Analysis 1.7) and increase major bleeding (see Analysis 2.7), but the magnitude of effects remain uncertain.

The lack of an adequate control group receiving placebo or no thromboprophylaxis in the studies of participants with myeloma hampers definitive recommendations for one specific thromboprophylaxis over another. In addition, these trials focused on specific regimens (thalidomide- and lenalidomide-based combinations), thus findings and conclusions may not apply to people with myeloma receiving other treatments. As renal insufficiency often complicates the course of multiple myeloma, the administration and dosing of drugs such as LMWH with a predominant renal clearance should be taken with great caution.

Only one study evaluated UFH against no thromboprophylaxis, but did not report on VTE or major bleeding. See Summary of findings 7.

When compared with placebo or no thromboprophylaxis, warfarin may reduce symptomatic VTE (low-certainty evidence); and may increase major bleeding (low-certainty evidence). See Summary of findings 8.

While additional studies could help clarify the efficacy and safety of VKAs, the bleeding concerns and the complexity of VKAs management remain significant barriers for VKAs use as primary prophylaxis in ambulatory cancer patients.

Antithrombin, evaluated in one study involving children, had no clear difference in effect on any VTE (very low-certainty evidence) or major bleeding when compared with no antithrombin (very low-certainty evidence). See Summary of findings 10.

Overall completeness and applicability of evidence

No RCTs evaluated fondaparinux, dabigatran, edoxaban, and mechanical interventions. The oral factor Xa inhibitors apixaban and rivaroxaban do not require routine laboratory monitoring and may be easy for patients to use. Results with these agents are encouraging although several issues remain. Levels of apixaban and rivaroxaban can be influenced by the concurrent administration of strong inhibitors and inducers of the P-glycoprotein and CYP3A4. The clinical relevance of drug–drug interactions with chemotherapy and new target therapies interfering with P-glycoprotein and CYP3A4 requires further investigation. In addition, prolonged nausea and vomiting, gastrointestinal toxicity from cancer treatment, or surgery involving the gastrointestinal tract may influence drug absorption and need careful consideration.

Comorbidities predisposing to bleeding, which often represent an exclusion criterion in RCTs on anticoagulants, might result in a greater number of major bleeding complications and limit the use of thromboprophylaxis in routine clinical practice. Additional concerns may be the use of thromboprophylaxis with apixaban or rivaroxaban in some types of cancers, such as those of the gastrointestinal or genitourinary tracts, which were more prone to bleed in the studies with DOAC (Carrier 2019; Khorana 2019).

We performed stratified analyses and there was no evidence to suggest that effects of LMWH versus placebo or no thromboprophylaxis on symptomatic VTE or major bleeding varied by type of cancer, presence of metastatic disease, treatment duration, or dosing. However, we acknowledge that there was an insufficient number of studies to make strong conclusions about the variation by type of cancer. Stratified analyses could not be performed for other comparisons as the number of identified studies was too low. Nevertheless, since this review mainly included participants with locally advanced or metastatic cancer, the results may not be generalisable to patients with earlier stages

of cancer. Estimates may not apply to paediatric populations as the majority of evidence was derived from adult populations. Likewise, the very low-certainty evidence of effects of antithrombin versus placebo on major bleeding and VTE was derived from a single study in a paediatric population, and the described effects may not apply to adult populations.

Quality of the evidence

The risk of bias of the individual studies, as assessed using Cochrane's risk of bias tool, ranged from low to high (Figure 2). Analytical exploration of the effects of design flaws was feasible only for the comparison of LMWH versus no thromboprophylaxis. We found no evidence of design-related biases. An inspection of the funnel plot and formal analysis of asymmetry did not indicate asymmetry for the primary efficacy outcome symptomatic VTE and major bleeding (Figure 3; Figure 4), suggesting the absence of publication bias or other biases related to small-study size.

Across comparisons, the certainty of the evidence for symptomatic VTE ranged from very low to high. While it is very unlikely that new evidence will change our confidence in the estimate of the effects on VTE of LMWH or semuloparin compared to placebo or no thromboprophylaxis or of LMWH compared to VKA (all high-certainty evidence), we are less certain about the estimates of the other comparisons. The certainty of the evidence for major bleeding varied from very low to moderate, indicating that further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate (Guyatt 2008). Overall, the largest concern was imprecision due to the small-study size of the majority of the trials. We could not judge the certainty of the evidence for several outcomes across comparisons due to incomplete reporting or the absence of events in both trial arms so these were downgraded for risk of bias concerns.

See Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8; Summary of findings 9; Summary of findings 10.

Potential biases in the review process

Our systematic approach to searching, study selection, and data extraction followed that described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). It is unlikely that we have missed relevant trials, but frequent updates of this review are warranted given that we identified several new trials since the previous version of this review, which covered published trials up to 2016 (Di Nisio 2016). We minimised data extraction errors by using two independent review authors (EV, MC). Judgements on the certainty of evidence were discussed with a third review author (AWSR). We acknowledge that risk of bias assessment leaves room for different interpretations, especially where the quality of reporting is poor. We applied strict rules regarding the risk of attrition bias, requiring that all randomised participants be analysed according to the intention-to-treat principle. We chose this rather strict approach, as the incidence of symptomatic VTE varies considerably between trials and may be rather low, so that even a small proportion of participants not analysed may impact on the study estimates if the fraction not analysed is associated with the outcome. Other reviews have also applied this approach (Juni 2001; Rutjes 2009; Rutjes 2012). Following Cochrane guidance, we included quotes and the arguments on which we based our risk of bias judgements, allowing the reader to reach their own conclusions. Our systematic approach and the consistency of the results (lack of significant heterogeneity) increase confidence in the internal validity of our findings.

One limitation in the interpretation of this review is the 'no evidence of a difference' findings. The lack of such evidence may be related to the small number of RCTs and small number of participants, events, or both, as well as the absence of a true effect. In this regard, the lack of a clear effect between the DOACs and symptomatic VTE or major bleeding could be the result of the relatively low number of events observed. The three studies comparing DOAC with placebo reported only 30 major bleeds in total, with a point estimate suggesting a 74% higher risk with DOAC and the upper value of the 95% CI not excluding a near four-fold higher risk of major bleeding.

Another limitation related to the small number of RCTs, poor reporting, or both, was our inability to conduct some subgroup analyses (e.g. use of cointerventions) for the primary efficacy outcome symptomatic VTE, whereas other stratified analyses were hampered by the lack of contrast (e.g. age and presence of metastasis). We performed subgroup analysis by type of cancer for the lung and pancreatic cancers, albeit the data for the pooled analysis were derived from only seven (lung) and two (pancreatic) studies. The lack of reporting, as well as the heterogeneity of the cancers treated, prevented us from assessing the importance of background chemotherapy on the response to thromboprophylaxis. Finally, the lack of evidence precluded any inference on the use of mechanical prophylaxis.

Agreements and disagreements with other studies or reviews

The evidence on the use of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy was summarised by the recently updated guidelines of the American Society of Clinical Oncology, the International Initiative on Thrombosis and Cancer (ITAC), and the National Comprehensive Cancer Network (Farge 2019; Key 2020; National Comprehensive Cancer Network 2020). One potential advantage of the current review is that we provided pooled estimates with 95% CIs for both efficacy and safety outcomes, allowing a better estimation of the risks and benefits of thromboprophylaxis in this setting. The use of a larger dataset allowed us to stratify multiple outcomes by type of treatment. Other narrative reviews summarised the evidence on the use of thromboprophylaxis for VTE in ambulatory cancer patients (Aikens 2013; Maxwell 2012). These reviews lacked a systematic search of the literature and, as for Farge 2019, Key 2020, and National Comprehensive Cancer Network 2020, there was no meta-analysis or evaluation of study quality items and assessment of risk of bias performed.

The conclusions of our review are in agreement with those of the American Society of Clinical Oncology (Key 2020), and differ somewhat from the 2012 guidelines of the American College of Chest Physicians (Kahn 2012), which suggested primary thromboprophylaxis with LMWH or UFH in ambulatory patients with solid tumours who have additional risk factors for VTE (that is previous venous thrombosis, immobilisation, angiogenesis inhibitors, thalidomide and lenalidomide) and a low risk of bleeding.

AUTHORS' CONCLUSIONS

Implications for practice

In ambulatory cancer patients, primary thromboprophylaxis with direct factor Xa inhibitors may reduce the incidence of symptomatic venous thromboembolism (VTE) (low-certainty evidence) and probably increases the risk major bleeding (moderate-certainty evidence) when compared with placebo. Low-molecular-weight heparin (LMWH) reduces symptomatic VTE with 37 participants requiring prophylaxis to prevent one event (high-certainty evidence). This benefit comes at the cost of a higher incidence of major bleeding, where for each 144 participants treated, one event is expected to occur when compared against placebo or no thromboprophylaxis (moderate-certainty evidence). When deciding whether to use primary antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy, clinicians need to determine the patient's baseline risk of VTE with the help of risk-stratification models and weigh the magnitude of benefit with antithrombotic prophylaxis, especially on major clinical endpoints, against the risk of major bleeding complications. Evidence for the use of thromboprophylaxis with anticoagulants other than direct factor Xa inhibitors and LMWH is limited.

Implications for research

Further randomised studies are needed to establish the risk–benefit ratio of primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy. Additional studies may be useful to improve VTE risk stratification to identify subgroups of patients who may have larger benefits from thromboprophylaxis.

Although several tools have been proposed to stratify VTE risk in ambulatory cancer patients, the score developed by Khorana and colleagues remains one of the most extensively evaluated (Ay 2010; George 2011; Khorana 2008; Khorana 2009a; Khorana 2009b; Khorana 2018; Verso 2012; Zwicker 2013). A Khorana score of 2 or greater was recently used in Carrier 2019 and Khorana 2019 to identify and include patients with a high-risk of VTE. In the control group, symptomatic VTE occurred at a similar rate as in previous studies which did not use any risk score (Analysis 1.2). According to the results of one recent large meta-analysis of over 34,000 cancer patients, the incidence of thromboembolic complications in patients at low VTE risk according to the Khorana score may be not negligible (Mulder 2019). One potential limitation of current scoring systems is the overall low sensitivity, which may result in the exclusion of over half of patients who ultimately develop cancer-associated VTE from the potential benefits of thromboprophylaxis. These observations suggest that further refinement of risk stratification tools could help to significantly reduce the burden of cancer-associated VTE.

Several additional aspects related to thromboprophylaxis deserve further study, such as the development of bleeding-risk models, optimal doses and duration of thromboprophylaxis, patient preferences, and quality of life.

Cost-analysis data on the use of anticoagulation in people with cancer undergoing chemotherapy would be very valuable and supportive of a broader application of prophylaxis in the future.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agnelli 2009

Study characteristics	
Methods	Trial acronym: PROTECHT Design: multicentre, double-blind, placebo-controlled trial with modified intention-to-treat analysis, including participants who received ≥ 1 dose of study treatment. Median duration of follow-up: 111 days in nadroparin; 113 days in placebo
Participants	Ambulatory patients aged > 18 years who were receiving chemotherapy for metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer Mean age: 62.1 (SD 10.3) years in nadroparin group; 63.7 (SD 9.2) years in placebo group Gender, n (%) males: 372 (48.4%) in nadroparin group; 183 (48%) in placebo group Metastatic disease, n (%): not reported Previous VTE, n (%): 12 (1.6%) in nadroparin group; 6 (1.6%) in placebo group
Interventions	Intervention: LMWH, nadroparin 3800 IU SC, once daily Control: placebo Study treatment started on the same day as chemotherapy (the first cycle or a new course), and was given for the duration of chemotherapy or up to a maximum of 120 days (± 10 days).
Outcomes	Primary outcomes: composite of symptomatic venous or arterial thromboembolic events occurring during study treatment plus 10 days; major bleeding that occurred between randomisation and 48 hours after last injection of study drug Secondary efficacy outcomes: incidental thromboembolic events incidentally diagnosed; survival at end of study treatment and at 12 months; superficial venous thrombosis of lower limbs; response to chemotherapy; central venous catheter-related complications of possible thrombotic origin Secondary safety outcome: minor bleeding
Notes	Antiplatelet agents, oral anticoagulants, fibrinolytic agents, UFH, or LMWH other than nadroparin not allowed during study Funding: Italfarmaco SpA, Milan, Italy Disclosure of potential conflicts of interest: the scientific director of Italfarmaco was involved as an author. Publication format: published as full text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list was generated by an independent statistician who used a standard permuted block of six without stratification. The list was generated with SAS version 8.2." Comment: adequate method of sequence generation.

Agnelli 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was available online to the investigators using the Hypernet web-based system. At the time the investigator accessed the web-based system with personal codes (user ID and password) and requested the treatment allocation for a new patient who fulfilled the eligibility criteria, the system assigned the next free number in accordance with the randomisation sequence" Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Patients and investigators did not know whether study drug or placebo was being given, since pre-filled syringes were used which were identical in appearance. Treatment assignments were masked from all study personnel and participants for the duration of the study." "All study outcomes were assessed by a central independent adjudication committee whose members were unaware of patients' study-group allocation." Comment: double-blind RCT and adequate methods of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "All randomised patients who received at least one dose of the study treatment were included in the efficacy and safety analyses." Comment: 769/779 (98.7%) participants randomised were analysed in the LMWH group, 381/387 (98.4%) randomised were analysed in the placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section.

Agnelli 2012

Study characteristics	
Methods	Trial acronym: SAVE-ONCO study Design: multicentre, double-blind RCT, with intention-to-treat for effectiveness and modified intention-to-treat analysis for safety outcomes, including participants who received ≥ 1 study dose Mean duration of follow-up: not reported
Participants	Patients with metastatic or locally advanced solid cancer of the lung, pancreas, stomach, colon or rectum, bladder, or ovary who were beginning a course of chemotherapy Mean age: 59.8 years in semuloparin group; 59.4 years in placebo group Gender, n (%) males: 974 (60.6%) in semuloparin group; 956 (59.6%) in placebo group Metastatic disease: not reported Previous VTE: 2% in semuloparin group; 2.3% in placebo group
Interventions	Intervention: uLMWH semuloparin 20 mg SC, once daily Control: placebo The first dose of the study drug was administered on the first day of a course of chemotherapy (first regimen or a new regimen), continuing for the duration of chemotherapy (intended to be a minimum of 3 months). Median treatment duration was 3.5 months.

Agnelli 2012 *(Continued)*

Outcomes	Primary efficacy outcome: composite of any symptomatic DVT, any non-fatal PE, and death related to VTE Primary safety outcome: clinically relevant bleeding (major and non-major) Secondary efficacy outcome: 1-year overall survival or at study end date
Notes	Funding, quote: "Supported by Sanofi". "The study was designed by the steering committee members and sponsored by Sanofi. Data were collected through a clinical research organization and analyzed by Sanofi. No Sanofi employees were members of the steering committee or the data and safety monitoring board." Disclosure of potential conflicts of interest: in the section 'The Work Under Consideration for Publication,' some of the authors declared they were employed by Sanofi or had received consulting fee or honorarium and support for travel to meetings by Sanofi-Aventis. Publication format: published as full text Marketing applications for semuloparin have been withdrawn worldwide, and it is, therefore, unlikely to ever be commercially available (EMEA 2012).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally by means of an interactive voice-response system." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally by means of an interactive voice-response system." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Efficacy and bleeding outcomes were assessed by a central independent adjudication committee, whose members were unaware of the study treatment" Comment: double-blind RCT and blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients who underwent randomization were included in the primary efficacy population (intention-to-treat population), and those who underwent randomization and received at least one dose of the study treatment were included in the safety population" Comment: for safety, 1589/1608 (98.8%) participants randomised were analysed in uLMWH group, 1583/1604 (98.7%) participants randomised were analysed in placebo group.
Selective reporting (reporting bias)	Low risk	All outcomes reported in the protocol and in the methods section of the full report were addressed in the results or discussion section, except for 1 outcome mentioned in the protocol only: "Secondary efficacy variables include the initiation of curative treatment by the investigator after VTE," We did not consider this outcome to be relevant for the current review.

Altinbas 2004

Study characteristics	
Methods	Trial acronym: none reported Design: RCT with intention-to-treat analysis for survival outcomes Median duration of follow-up: 10 (range 2–33) months
Participants	Patients aged 18–75 years with histologically confirmed small-cell lung carcinoma with an ECOG performance status < 3 and normal haematological, renal, and hepatic function tests Median age: 58 (range 34–75) years Gender, n: 33 men and 9 women in dalteparin group; 35 men and 7 women in control group Metastatic disease: 19 in dalteparin group; 17 in control group Previous VTE: 0/84
Interventions	Intervention: LMWH, dalteparin 5000 IU SC, once daily Control: no dalteparin Dalteparin was stopped with disease progression or at end of 18 weeks of chemotherapy Median duration of treatment: 18 weeks
Outcomes	Primary outcome: overall survival Secondary outcomes: progression-free survival, adverse effects
Notes	Funding: not reported Disclosure of potential conflicts of interest: not disclosed, no COI forms available Publication format: published as full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive either CT [chemotherapy] or CT plus LMWH." Comment: method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to receive either CT or CT plus LMWH." Comment: method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: trial is reported as a "Chemotherapy-only" vs "Chemotherapy + LMWH" trial, without mentioning the use of placebo LMWH, or any attempt to blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: for effectiveness is not reported. For safety, survival was analysed according to the intention-to-treat principle.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Campos-Cabrera 2018

Study characteristics	
Methods	Trial acronym: none reported Design: randomised study with active control Median duration of follow-up: not reported
Participants	Patients with multiple myeloma who received thalidomide- and dexamethasone-based triplet induction therapy, maintenance with thalidomide and creatinine clearance > 30 mL/minute and had an additional cardiovascular risk factor. Median age: 67.5 years in rivaroxaban group; 66.8 years in aspirin group Gender, n (%) males: 3 (60%) males in rivaroxaban group; 10 (55.6%) males in aspirin group Metastatic disease: not reported Previous VTE: not reported
Interventions	Intervention 1: rivaroxaban 10 mg once daily Intervention 2: aspirin 100 mg once daily Treatment was continued until relapse and need another treatment
Outcomes	VTE including symptomatic or incidental DVT and symptomatic PE; bleeding
Notes	Funding: none reported Disclosure of potential conflicts of interest: "no relevant conflicts to declare." Publication format: published as conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear if all participants included were analysed.
Selective reporting (reporting bias)	Unclear risk	Not clear if all outcomes were reported.

Carrier 2019

Study characteristics	
Methods	Trial acronym: AVERT Design: double-blind (participant, carer, investigator, outcomes assessor), parallel-assignment RCT Median duration of follow-up: 183 days in each group
Participants	Patients with a newly diagnosed cancer site or progression of the malignant disease after complete or partial remission who were initiating a new course of chemotherapy with a minimum intent of 3 months' therapy and who had a VTE risk stratification score of ≥ 2, according to the Khorana scoring method. Mean age: 61 years in whole study population; 61.2 (SD 12.4) years in apixaban group; 61.7 (SD 11.3) years in placebo group Gender, n (%) males: 121 (41.6%) in apixaban group; 119 (42%) in placebo group Metastatic disease, n (%): 73 (25.1%) in apixaban group; 67 (23.7%) in placebo group Previous VTE, n (%): 9 (3.1%) in apixaban group; 8 (2.8%) in placebo group
Interventions	Intervention: apixaban 2.5 mg twice daily for 6 months Control: placebo
Outcomes	Primary outcome: symptomatic or incidental VTE (DVT, PE, or both) at 6 months Secondary outcomes: rate of adverse events, clinical overt bleeding (major and minor bleeding), and death within the study period
Notes	Funded by the Canadian Institutes of Health Research and Bristol-Myers Squibb–Pfizer Alliance; AVERT Disclosure of potential conflicts of interest (extracted for first, second, and last author): • Lead author: Dr Carrier reported grants from Pfizer/Bristol-Myers Squibb and Canadian Institutes of Health Research during the conduct of the study; grants and personal fees from Leo Pharma and Bayer; personal fees from Sanofi Aventis, Pfizer, and Bristol-Myers Squibb outside the submitted work. • Second author: Dr Abou-Nassar reported personal fees from Janssen, Sanofi, Lundbeck, Novartis, Celgene, and Leo Pharma outside the submitted work. • Last author: Dr Wells reported grants from Pfizer/BMS, Canadian Institutes of Health Research, and BMS/Pfizer during the conduct of the study; grants and personal fees from Bayer Healthcare; personal fees from Medscape, Itreas, Pfizer, Janssen Scientific, Daiichi Sankyo, and Sanofi outside the submitted work. Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients underwent randomization by means of a centralized, Web-based randomization system to receive apixaban or placebo in a 1:1 ratio. Randomization was stratified according to age, sex, and participating center and occurred up to 5 days before the administration of the first chemotherapy." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Eligible patients underwent randomization by means of a centralized, Web-based randomization system to receive apixaban or placebo in a 1:1 ra-

Carrier 2019 *(Continued)*

		tio. Randomization was stratified according to age, sex, and participating center and occurred up to 5 days before the administration of the first chemotherapy." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All trial outcomes were adjudicated by an independent adjudication committee whose members were unaware of the treatment assignments." Comment: double-blind RCT and blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 11/574 (1.9%) participants enrolled in the study were not considered for the analysis. Exclusions per trial arm were reported. 24 (4.2%) participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Chahinian 1989

Study characteristics	
Methods	Trial acronym: none reported, is a trial run by Cancer and Leukemia Group B (CALGB) institutions in USA Design: multicentre, 3-arm RCT, type of analyses not reported Median duration of follow-up: 36 months
Participants	Patients with extensive carcinoma of the lung Mean age: not reported. % patients aged ≥ 60 years: 55% in warfarin group; 60% in control group Gender, n (%) males: 70 (68%) in warfarin group; 129 (68%) in control group Metastatic or extensive disease, n (%): 294 (100%) Previous VTE: not reported
Interventions	Intervention: warfarin to maintain a prothrombin 1.5 to twice the control values Control 1: no warfarin[a] Control 2: no warfarin[a] [a]All groups received chemotherapy with methotrexate, doxorubicin, cyclophosphamide, and lomustine (MACC), but control group 2 alternated mitomycin, etoposide, cisplatin, and hexamethylmelamin with MACC. Warfarin was continued throughout the course of chemotherapy, and it was withheld in participants with brain metastases during cranial irradiation and whenever platelet counts < 75,000/µL. The median time on warfarin was 162 (range 2–627) days.
Outcomes	Main outcomes: overall survival, failure-free survival, and cancer response (complete response, partial response, and objective response rate) to therapy Secondary outcomes: toxicity
Notes	Funding: grants from the National Cancer Institute, Department of Health and Human Services, and the T.J. Martell Foundation for Leukemia and Cancer Research

Chahinian 1989 *(Continued)*

	Disclosure of potential conflicts of interest: not disclosed, no COI forms available
	Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "allocation was determined by a Latin square arrangement balancing the sequence within and across institutions." Comment: adequate method of sequence generation; stratified randomisation, use of Latin square design.
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: blinding not reported, use of placebo warfarin not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 34/328 (10%) participants enrolled in the study were not considered for the analysis. Exclusions per trial group were not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section. Toxicity was addressed in the results, but not explicitly reported as an outcome in the methods section.

Ek 2018

Study characteristics

Methods	Trial acronym: none reported Design: international, open-label RCT Median follow-up: 41 (IQR 21–81) months for participants still alive
Participants	Patients with histologically or cytologically verified newly diagnosed small-cell lung cancer of all stages Mean age: 67 (SD 7.9) years in enoxaparin group; 68 (SD 8.5) years in control group Gender, n (%) males: 78 (42%) in enoxaparin group; 82 (43%) in control group Metastatic disease, n (%): extensive disease: 114 (61%) in enoxaparin group; 113 (59%) in control group Previous VTE: not reported
Interventions	Intervention: enoxaparin at a supraprophylactic dose (1 mg/kg) in addition to standard treatment. Enoxaparin was started on day 1 of chemotherapy and continued until the 21st day of the last chemotherapy cycle Control: standard treatment
Outcomes	Primary outcome: overall survival Secondary outcomes were progression-free survival, incidence of VTE and haemorrhagic events

Ek 2018 *(Continued)*

Notes	Funding: Swedish Research Councile (to MB, grant number: 2014-3421); the Swedish Cancer Society (to MB, grant number: 2014/378); the Skane University Hospital donation funds (to MB, no grant number); the Medical Faculty, Lund University (to MB, no grant number); the Governmental funding of clinical research within the national health services (ALF) (to MB and EG, no grant number); the Gunnar Nilsson, Anna Lisa and Sven Eric Lundgren and Kamprad Foundations (to MB, no grant number); a restricted grant support from Sanofi Aventis, Sweden (to LE, no grant number); a donation by Viveca Jeppsson (to MB, no grant number); and received honoraria from Leo Pharma, AstraZeneca and Pfizer (to MB, no grant number) Disclosure of potential conflicts of interest: "the authors have declared no conflicts of interest." Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization procedure was conducted at the Clinical Research Unit at Lund University Hospital, using a computer algorithm." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization procedure was conducted at the Clinical Research Unit at Lund University Hospital, using a computer algorithm." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "international, open-label trial."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 13/574 (3.3%) participants enrolled in the study were not considered for the analysis. Exclusions per trial group were reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section

Elit 2012

Study characteristics

Methods	Trial acronym: none reported, trial run by the Ontario Clinical Oncology Group Design: multicentre, open-label, 4-arm phase II randomised trial. The study was terminated early due to poor recruitment. Median duration of follow-up: not reported, participants were followed until the end of chemotherapy
Participants	Women with newly diagnosed epithelial ovarian cancer stage IIB–IV Age, median: 61 (range 34–74) years Gender, n (%) females: 77 (100%) Metastatic disease: not reported Previous VTE, n (%): 4 (5%)

Elit 2012 *(Continued)*

Interventions	Intervention 1: standard adjuvant chemotherapy (taxane and platinum-based) and dalteparin 50 IU/kg SC once daily during the first 3 of 6 cycles of 3-weekly chemotherapy Intervention 2: standard adjuvant chemotherapy (taxane and platinum-based) and dalteparin 100 IU/kg SC once daily during the first 3 of 6 cycles of 3-weekly chemotherapy Intervention 3: standard adjuvant chemotherapy (taxane and platinum-based) and dalteparin 150 IU/kg SC once daily during the first 3 of 6 cycles of 3-weekly chemotherapy Study medication was started within 7 days prior to the first 21-day cycle of chemotherapy and continued until day 21 of cycle 3. Median duration of LMWH was 67 days.
Outcomes	Primary outcome: tumour response defined by ≥ 50% reduction in serum CA125 from baseline sustained for ≥ 28 days Secondary outcomes: major bleeding up to 24 hours after the last dose of dalteparin; any bleeding up to 24 hours after the last dose of dalteparin; symptomatic VTE up to 7 days after the last dose of dalteparin; death up to the last day of follow-up; and compliance with dalteparin administration
Notes	Funding, quote: "The Steering Committee wishes to acknowledge the financial support from both the Juravinski Cancer Centre Foundation and Pfizer Canada Inc." Disclosure of potential conflicts of interest, quote: "There are no financial disclosures from any of the authors related to this work except for Dr. Lee who has provided educational lectures and received financial reimbursement from Pfizer Canada Inc." Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Concealed randomization was performed centrally … using a computer-generated, permuted-block randomization schedule." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Concealed randomization was performed centrally … using a computer-generated, permuted-block randomization schedule." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Study outcomes were adjudicated by members of a Central Adjudication Committee masked to treatment assignment." Comment: open-label study with blinded adjudication of outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The primary analysis included all patients as randomized." Comment: all participants who were randomised were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes indicated in the methods were presented in the results.

Greiner 2019

Study characteristics	
Methods	Trial acronym: THROMBOTECT Design: open-label, prospective, randomised, multicentre study Median duration of follow-up: not reported
Participants	Patients aged 1–18 years with newly diagnosed acute lymphoblastic leukaemia Mean age: not reported. 54% of participants were aged 1–6 years, 19.8% were 6–10 years, and 26.2% were > 10 years Gender, n (%) males: 537 (56.6%) Metastatic disease: not applicable, haematological cancer Previous VTE: not reported
Interventions	Intervention 1: low-dose UFH 2 IU/kg bodyweight/hour Intervention 2: prophylactic LMWH, enoxaparin (ClexaneTM) at a dose of 80–100 IU/kg bodyweight once daily SC with a target anti-Xa level not exceeding 0.4 U/L, measured 4 hours after the third or fourth injection Intervention 3: activity-adapted antithrombin throughout induction therapy Thromboprophylaxis started on day 8 and ended on day 33 of induction chemotherapy
Outcomes	Primary: symptomatic VTE Secondary: major and minor bleeding, event-free survival, and overall survival
Notes	Funding: both interventional drugs were provided free of charge by the respective pharmaceutical companies: enoxaparin (Clexane) by Sanofi and antithrombin (Kybernin) by CSL Behring. Neither company was acting as a sponsor, they were not involved in the THROMBOTECT study design, neither in the collection and analysis of data nor in the content and wording of the manuscript. Neither of them had access to the THROMBOTECT data sets nor did they have information on unpublished results. Disclosures of potential conflicts of interest: 3/19 authors had disclosures unrelated to the work under consideration: Martin Schrappe: honoraria: prIMEOncology; research funding: Medac, Baxalta, SigmaTau; Speaker's Bureau: Baxalta; Wolfgang Korte: honoraria: Bayer, Boehringer Ingelheim, Pfizer, Daichii, Abbott, Siemens; consulting, medical advisor: Bayer, Boehringer Ingelheim, Pfizer, Daichii; research funding: CSL Behring; travel expenses: Bayer, Pfizer; Johannes Rischewski: honoraria, medical advisor, research funding: CSL Behring International and Switzerland Publication format: full-text publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally by the ALL-BFM study coordination center using computer-generated random number lists." Comment: adequate method of random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally by the ALL-BFM study coordination center using computer-generated random number lists" and "The assigned arm was submitted to the center by fax."

Greiner 2019 *(Continued)*

		Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "No systematic provision was made for blinding the attending physicians or radiologists to the randomization arm." Comment: open study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Haas 2012

Study characteristics	
Methods	Trial acronym: TOPIC-1 and TOPIC-2 Design: multicentre RCTs, intention-to-treat analysis for effectiveness and modified intention-to-treat analysis for safety outcomes. TOPIC-1 was prematurely halted after an interim analysis. Median duration of follow-up: not reported
Participants	Patients with metastatic breast cancer (n = 353) or non-small-cell lung carcinoma (n = 547) receiving first- or second-line chemotherapy. Mean age in TOPIC-1 study (participants with breast cancer): 54.6 (SD 10.3) years in certoparin group; 56.6 (SD 11.0) years in placebo group Mean age in TOPIC-2 study (participants with lung cancer): 60.8 (SD 9.5) years in certoparin group; 60.3 (SD 10.0) years in placebo group Gender, n (%) males: TOPIC-1: 0 (0%); TOPIC-2: 227 (83.2%) overall Metastatic disease: not reported Previous VTE: 0/900
Interventions	Intervention: LMWH, certoparin 3000 IU SC, once daily Control: placebo Study treatment given for 6 months.
Outcomes	Primary outcomes: symptomatic or incidental VTE, major bleeding Secondary outcomes: symptomatic VTE, overall thrombosis rate (to include arterial thrombotic events, superficial venous thrombosis, and central-line thrombosis), minor bleeding, thrombocytopenia, heparin-induced thrombocytopenia, osteoporotic fractures, survival Post hoc: mortality, symptomatic or incidental VTE according to tumour stage
Notes	Funding: grant from Novartis Pharma, Nuremberg, Germany. Quote: "The TOPIC studies were supported by an unrestricted grant from Novartis Pharma GmbH, Germany." Disclosure of potential conflicts of interest, quote: "The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article."

Haas 2012 *(Continued)*

Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a computer-generated randomisation list" and "Randomization was block-stratified according to treatment with hormone-based chemotherapy." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization numbers were allocated sequentially as patients were enrolled at each center." Comment: concealment of allocation was poorly reported. It was not reported if sealed, opaque, and consecutively numbered envelopes, coded syringes, or other methods were used. In addition, it remains unclear what is meant by randomisation number in "Patients were allocated to the lowest available randomisation number available for each study center."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Efficacy outcomes were validated by a blinded, independent Central Thrombosis Evaluation Team; safety end points were validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments." and "Only the external statistician from the Safety Committee had access to the randomization codes." Comment: double-blind, placebo-controlled RCT with blinding of participants, physicians, and outcome assessors#.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness, 442/447 (98.9%) in LMWH group and 441/453 (97.4%) in placebo group were analysed. For safety, 447/447 (100%) in LMWH group and 451/453 (99.6%) in placebo group were analysed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section. However, the outcome osteoporotic fracture was incompletely reported; it remained unclear in which of the TOPIC-2 trial arms the single event occurred. Post hoc analyses were reported transparently.

Kakkar 2004

Study characteristics

Methods	Trial acronym: FAMOUS Design: double-blind, placebo-controlled, multicentre RCT; modified intention-to-treat analysis for both effectiveness and safety analyses, including participants with ≥ 1 study dose and 1 follow-up visit Median duration of follow-up: 10 months in dalteparin group; 9 months in placebo group
Participants	Patients aged 18–80 years with histologically confirmed advanced stage III or IV (locally advanced or metastatic) malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus. Mean age: 62 (IQR 54–68) years in dalteparin group; 60.9 (IQR 52–69) years in placebo group Gender, n (%) males: 77 (40.5%) in dalteparin group; 84 (45.7%) in placebo group

Kakkar 2004 *(Continued)*

	Metastatic disease, n (%): 161 (85%) in dalteparin group; 161 (87.5%) in placebo group Previous VTE: 0/385 (0%)
Interventions	Intervention: LMWH, dalteparin 5000 IU SC, once daily Control: placebo (0.9% normal saline) Study treatment given for 1 year or until the participant died, whichever occurred sooner
Outcomes	Primary outcomes: mortality after 1 year of therapy Secondary outcomes: symptomatic, objectively confirmed VTE disease and bleeding complications
Notes	Funding: Pharmacia Corp, New York, NY Disclosure of potential conflicts of interest: the lead author declared having acted as a consultant for Pfizer. Quote: "The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Ajay K. Kakkar, Pfizer. Received more than $2,000 a year from a company for either of the last 2 years: Ajay K. Kakkar, Pfizer." Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally by computer-generated code." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally by computer-generated code." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "placebo (0.9% normal saline), each supplied in 0.2-mL prefilled syringes." Comment: trial reported as double-blind, with active substance or placebo provided in prefilled syringes. It is not reported whether syringes were identical in appearance or if outcome assessor were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: both for effectiveness and safety, 190/196 (96.9%) participants were analysed in the LMWH group and 184/189 (97.4%) participants were analysed in the placebo group.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Khorana 2017

Study characteristics

Methods	Trial acronym: PHACS Design: multicentre RCT

Khorana 2017 *(Continued)*

	Study terminated early due to poor accrual Median duration of follow-up: not reported
Participants	Cancer patients at high risk for VTE (Khorana score ≥ 3) and initiating a new systemic chemotherapy regimen who had no VTE at initial baseline screening compression ultrasonography of the lower extremities and baseline computed tomography of the chest. Mean age: overall 59 years; 60 (SD 10) years in dalteparin group; 58 (SD 12) years in observation group Gender, n (%) males: 29 (58%) in dalteparin group; 24 (50%) in observation group Metastatic disease: not reported Previous VTE, n (%): 4 (8%) in dalteparin group; 2 (4%) in observation group
Interventions	Intervention: LMWH, dalteparin 5000 IU daily SC for 12 weeks Control: no dalteparin
Outcomes	Primary outcome: any VTE over 12 weeks. VTE included adjudicated symptomatic lower extremity DVT, PE and upper extremity thrombosis as well as all unsuspected DVT and PE diagnosed by screening ultrasonography and computed tomography tests, respectively, occurring during 12 weeks of the study treatment or observation. Participants in both arms were screened with lower extremity ultrasounds every 4 weeks of study. Primary safety endpoint: clinically relevant bleeding events over 13 weeks. Secondary outcomes: symptomatic VTE, all-cause mortality Secondary safety outcomes: major bleeding and all bleeding including major, non-major and minor bleeding events.
Notes	Funding: not reported. Dalteparin was provided free of charge by Eisai, Inc. Disclosure of potential conflicts of interest: all authors reported conflicts of interest. Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized to either dalteparin 5000 units daily subcutaneously or no prophylactic anticoagulation." Comment: method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized to either dalteparin 5000 units daily subcutaneously or no prophylactic anticoagulation." Comment: method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study. Quote: "Thrombotic events were adjudicated by a thrombosis adjudication committee, comprising 2 radiologists who reviewed de-identified imaging studies and were blinded to treatment assignment" and "Bleeding events were adjudicated by a bleeding committee comprising two hematologists who were blinded to treatment assignment."

Khorana 2017 *(Continued)*

		Comment: participants and personnel not blinded. Blinded adjudication of outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 117 enrolled patients, 19 were not randomized due to the presence of VTE on initial screening (N =10, 8.5%) or for other reasons (N = 9)." Comment: all randomised participants were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes indicated in the methods of the abstract are reported in the results.

Khorana 2019

Study characteristics	
Methods	Trial acronym: CASSINI Design: double-blind, randomised, placebo-controlled, parallel-group, multicentre Phase IIIB study Median follow-up duration: not reported
Participants	High-risk ambulatory patients with solid cancer or lymphoma who had a Khorana score of ≥ 2, had a plan to start a new systemic regimen within 1 week before or after initiating the trial regimen and had no DVT on screening ultrasonography. Enrolled patients underwent venous duplex compression ultrasonography of both legs to rule out pre-existing proximal DVT. Median age: 63 (range 23–88) years overall; 63 (range 23–87) years in rivaroxaban group; 62 (range 28–88) years in placebo group Gender, n (%) males: 428 (50.9%) overall; 222 (52.9%) in rivaroxaban group; 206 (48.9%) in placebo group Metastatic disease: 54.5% overall in those with solid tumour Previous VTE, n (%): 15 (1.7%) overall; 13 (3.1%) in rivaroxaban group; 2 (0.5%) in placebo group
Interventions	Intervention: rivaroxaban 10 mg once daily up to day 180 Control: placebo up to day 180 Mean intervention period was 4.3 months
Outcomes	Primary efficacy endpoint: composite of objectively confirmed symptomatic or asymptomatic lower-extremity proximal DVT, symptomatic upper extremity, symptomatic lower-extremity distal DVT, symptomatic or incidental PE, and VTE-related death Secondary efficacy endpoints: included components of the primary endpoint, symptomatic VTE, death from any cause, confirmed arterial thromboembolism, and confirmed visceral thromboembolism
Notes	Funding: by Janssen, Bayer, and the Sondra and Stephen Hardis Chair in Oncology Research (to Dr Khorana), by grants (U01HL143402 and R34 HL127156, to Dr Khorana) from the National Heart, Lung, and Blood Institute, and by the Cleveland Clinic Center of Excellence for Cancer-Associated Thrombosis (to Dr Khorana) and the Porter Family Fund (to Dr Khorana). Disclosure of potential conflicts of interest: all authors reported conflicts of interest Publication format: full-text publication
Risk of bias	

Khorana 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients without thrombosis were randomly assigned in a 1:1 ratio to receive rivaroxaban at a dose of 10 mg or placebo orally once daily for 180 days (with a window of ±3 days) according to a computer generated randomization schedule." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Patients without thrombosis were randomly assigned in a 1:1 ratio to receive rivaroxaban at a dose of 10 mg or placebo orally once daily for 180 days (with a window of ±3 days) according to a computer generated randomization schedule." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "… as adjudicated by an independent clinical end-point committee whose members were unaware of the trial-group assignments." and "Double-blind, randomized, placebo-controlled." Comment: double-blind, randomised, placebo-controlled and all endpoints adjudicated by blinded independent committees.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment; all participants enrolled were analysed as reported in the methods.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Klerk 2005

Study characteristics	
Methods	Trial acronym: MALT Design: multicentre, double-blind, randomised, placebo-controlled study with intention-to-treat analyses for both effectiveness and safety, including participants who received ≥ 1 study dose Mean duration of follow-up: 12 months
Participants	Patients with metastasised or locally advanced solid tumours Median age: 63 (range 36–86) years in nadroparin group; 64 (range 28–83) years in placebo group Gender, n (%) males: 77 (52%) in nadroparin group; 81 (53%) in placebo group Metastatic disease, n (%): 137 (93%) in nadroparin group; 139 (90%) in placebo group Previous VTE: 0/302 (0%) overall
Interventions	Intervention: LMWH, nadroparin Control: placebo Prefilled syringes containing a fixed volume of nadroparin (9500 anti-factor Xa U/mL) or placebo were provided according to participant's weight: 0.4 mL for those weighing < 50 kg, 0.6 mL for those weigh-

Klerk 2005 *(Continued)*

	ing 50–70 kg, and 0.8 mL for those weighing > 70 kg. Administered SC twice daily during the initial 14 days of treatment and once daily thereafter for another 4 weeks.
Outcomes	Primary efficacy outcome: death from any cause Primary safety outcome: major bleeding Secondary safety outcome: clinically relevant non-major bleeding
Notes	Funding: treatment provided by Sanofi-Synthelabo (Paris, France). The authors stated that "protocol design, data collection, and analysis were solely the responsibility of the authors." Disclosure of potential conflicts of interest: the senior author and statistician declared consultancy activities for various pharmaceutical companies, including Sanofi-Synthelabo. Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Sequentially numbered boxes of syringes with nadroparin or placebo were prepared using a central computer-generated randomization schedule, stratified for body weight with blocks of four." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered boxes of syringes with nadroparin or placebo were prepared using a central computer-generated randomization schedule, stratified for body weight with blocks of four." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Prefilled syringes containing a fixed volume of nadroparin (9,500 antifactor Xa U/mL) or placebo were provided according to patient's weight." Comment: trial reported as double-blind, with active substance or placebo provided in prefilled syringes. It was not reported whether syringes were identical in appearance or if outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all enrolled participants were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section. The authors reported reasons for the discontinuation of the study drug in the results section only, but this was for descriptive purposes, so unlikely to introduce bias.

Larocca 2012

Study characteristics

Methods	Trial acronym: substudy of RV-MM-PI209 Design: prospective, multicentre, open-label, randomised substudy of a phase III trial with modified intention-to-treat analyses of both effectiveness and safety outcomes, including participants who received ≥ 1 study dose

Larocca 2012 *(Continued)*

	Median follow-up duration: 20 months
Participants	Patients with newly diagnosed multiple myeloma treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone-lenalidomide consolidation. Median age: 57 (IQR 51–61) years in aspirin group; 58 (IQR 52–62) years in LMWH group Gender, n (%) males: 87 (49%) in aspirin group; 99 (60%) in LMWH group Metastatic disease: not reported Previous VTE: 0/342 (0%) overall
Interventions	Intervention 1: LMWH, enoxaparin 40 mg/day SC Intervention 2: aspirin 100 mg/day Prophylaxis was provided during the 4 (28-day) cycles of lenalidomide and low-dose dexamethasone and the 6 (28-day) cycles of melphalan-prednisone-lenalidomide consolidation. Median treatment duration: 3.6 months in aspirin group; 3.5 months in LMWH group
Outcomes	Primary endpoint: composite of symptomatic DVT, PE, arterial thrombosis, any acute cardiovascular event, or sudden otherwise-unexplained death in the first 6 months after randomisation Secondary outcomes: major and minor bleeding, any complications related to thromboprophylaxis
Notes	Funding: main study (RV-MM-PI209) was supported by Fondazione Neoplasie Sangue Onlus, and Celgene supplied free lenalidomide. The authors declared that Celgene had no role in the study design, data analysis, data interpretation, or writing of the report. Disclosure of potential conflicts of interest: several authors declared having received honoraria or consultancy fees from various pharmaceutical companies, including Celgene. Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomization sequence run by a central computer, which generated an automated assignment procedure that was concealed from the investigators in each study center." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "simple randomization sequence run by a central computer, which generated an automated assignment procedure that was concealed from the investigators in each study center." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Open-label" study Comment: open study with no blinding of participants, physicians, and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were included in the analysis.

Larocca 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Lebeau 1994

Study characteristics	
Methods	Trial acronym: 02 PC 85, run by the "Petites Cellules" group Design: multicentre, open-label, randomised substudy, with intention-to-treat analyses Median duration of follow-up: not reported
Participants	Patients with limited and extensive small-cell lung cancer who had not been previously treated with chemotherapy or radiotherapy Mean age: not reported overall; 42 (15%) < 50 years; 104 (38%) 50–59 years; 88 (32%) 60–69 years, 44 (16%) 70–81 years Gender, n (%) males: 120 (87%) in heparin group; 132 (95%) in control group Metastatic disease, n (%): extensive disease: 74 (54%) in heparin group; 82 (59%) in control group Previous VTE: not reported
Interventions	Intervention: chemotherapy with SC UFH. The dose of UFH was initially adapted to weight (500 IU/kg/day) then adjusted by clotting times. UFH was administered in 2 or 3 daily injections for 5 weeks and stopped 1 week after the second course of chemotherapy. Control: chemotherapy without UFH
Outcomes	Primary outcome: overall survival, response to chemotherapy Secondary outcomes: bleeding, UFH-related thrombocytopenia
Notes	Funding: none reported Disclosure of potential conflicts of interest: not disclosed, no COI forms available Publication format: full-text publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized through a centralized blind telephone assignment procedure." Comment: method of sequence generation not clearly reported.
Allocation concealment (selection bias)	Low risk	Quote: "randomized through a centralized blind telephone assignment procedure." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "No blinding procedure for patients and physicians was used." Comment: open-label study with no blinding of participants or physicians. Not reported if there was blinding of outcome assessors.

Lebeau 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient was lost to follow up." Comment: all participants enrolled in the randomised substudy were analysed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results section.

Lecumberri 2013

Study characteristics	
Methods	Trial acronym: Adjuvant Bemiparin in Small Cell Lung Cancer (ABEL) Design: a multicentre, investigator-initiated, open-label, randomised study Study terminated early due to slow recruitment Median duration of follow-up: not reported
Participants	Patients with newly diagnosed, limited-stage small-cell lung cancer Mean age: 62.7 (SD 8.9) years overall Gender, n (%) males: 33 (87%) males overall Previous VTE: none Metastatic disease: none
Interventions	Intervention: standard chemoradiotherapy plus bemiparin 3500 IU daily for a maximum of 26 weeks Participants received a median of 26 weeks of LMWH. Bemiparin was started on the first day of the first cycle of chemotherapy and stopped at disease progression or at the end of the 26 weeks of treatment. Control: standard first-line platinum-based chemotherapy and radiotherapy
Outcomes	Primary efficacy outcome: progression-free survival Primary safety outcome: major bleeding Secondary outcomes: overall survival, tumour response rate to chemoradiotherapy, incidence of objectively confirmed symptomatic VTE, minor bleeding, thrombocytopenia, death from any cause, and incidence of any other adverse event.
Notes	Funding, quote: "Bemiparin 3,500 IU syringes were provided without charge by Laboratorios Farmacéuticos ROVI. S.A. The company also gave economic support for the expenses of the CRO, but was not directly involved in the design of the study, collection or analysis of the data or in the preparation of the manuscript." Disclosure of potential conflicts of interest: "Drs. Lecumberri and Rocha report receiving investigational grant support and consulting and lecture fees from Rovi. No other potential conflict of interest relevant to this article was reported." Publication format: full-text publication

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lecumberri 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed through an automatic central randomization system." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed through an automatic central randomization system." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "there was no central adjudication committee." Comment: open study with unblinded adjudication of outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 1/39 (2.56%) included participants was excluded from the analysis.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes indicated in the methods were reported in the results.

Levine 1994

Study characteristics	
Methods	Trial acronym: none reported Design: multicentre, double-blind, randomised, placebo-controlled trial; intention-to-treat analysis Mean duration of follow-up: 199 days (SD 126) in warfarin and 188 days (SD 137) in placebo
Participants	Patients with metastatic stage IV breast carcinoma who had been receiving first- or second-line chemotherapy for 4 weeks or less. Mean age: 57.1 (SD 10.2) years in warfarin group; 56.1 (SD 10.9) years in placebo group Gender (%) females: 100% Metastatic disease: not reported Previous VTE: 0 in warfarin group; 2/159 in placebo group
Interventions	Intervention: warfarin 1 mg daily for 6 weeks and then adjusted to maintain the INR at 1.3–1.9 Control: placebo Study treatment began either at the start of chemotherapy or within the next 4 weeks and continued until 1 week after termination of chemotherapy. Median treatment duration: 181 (SD 123) days in warfarin group; 166 (SD 139) days in placebo group
Outcomes	Primary outcomes: VTE and arterial thrombosis; major and minor bleeding Secondary outcome: survival
Notes	Funding: study supported by a grant-in-aid from the National Cancer Institute of Canada Disclosure of potential conflicts of interest: none disclosed, no COI forms available

Levine 1994 *(Continued)*

Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to a computer-generated random arrangement." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "neither patients nor doctors were aware of treatment allocation" and "All outcome events were reviewed by a central adjudicating committee, unaware of treatment allocation" and "placebo patients took an identical inert tablet." Comment: adequate blinding of participants, physicians, and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, 152/154 (98.7%) in warfarin group and 159/161 (98.8%) in placebo group were analysed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results.

Levine 2012

Study characteristics

Methods	Trial acronym: none reported Design: randomised, double-blind, phase II trial; intention-to-treat analyses not reported Trials closed prematurely due to slow accrual rate Median duration of follow-up: not reported, maximum 114–121 days
Participants	Patients receiving either first- or second-line chemotherapy for advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian, or prostate cancer; cancer of unknown origin; myeloma; or selected lymphomas. Median age: 57 (range 41–67) years in apixaban 5 mg group, 60 (range 39–76) years in apixaban 10 mg group, 64 (range 25–86) years in apixaban 20 mg group, and 59 (range 20–82) years in placebo group Gender, n (%) males: 15 (46.9%) in apixaban 5 mg group; 13 (43.3%) in apixaban 10 mg group; 20 (60.6%) in apixaban 20 mg group; 15 (50%) in placebo group Metastatic disease (%): advanced or metastatic: 100% Previous VTE: 0/125 (0%)
Interventions	Intervention: factor Xa inhibitor, apixaban 5 mg, 10 mg, or 20 mg once daily orally Control: placebo Study treatment given for 12 weeks beginning within 4 weeks of starting chemotherapy.

Levine 2012 *(Continued)*

	Median treatment duration: 79.2 (range 29–90) days in apixaban 5 mg group; 76.0 (range 16–90) days in apixaban 10 mg group; 73.6 (range 14–92) days in apixaban 20 mg group; 69.6 (range 7–91) days in placebo group
Outcomes	Primary outcome: major bleeding or clinically relevant non-major bleeding Secondary outcomes: VTE, grade III or higher adverse events related to study drug
Notes	Funding, quote: "The study was sponsored by Bristol-Myers Squibb and Pfizer Inc." Disclosure of potential conflicts of interest: no other COI reported, no COI forms available, but 2 of the authors were employees of the sponsor. Publication format: full-text publication Pilot dose-finding study of 3 apixaban regimens (5 mg, 10 mg, or 20 mg once daily orally)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed centrally by contacting a computerised telephone voice response system provided by Bristol Myers Squibb." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed centrally by contacting a computerised telephone voice response system provided by Bristol Myers Squibb" and "BMS generated and kept the randomization schedules." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind" study, "treatment groups or all placebo tablets for the placebo treatment group such that the study supplies for subjects in all treatment groups were identical in appearance", and "All bleeding and VTE events were adjudicated by a committee unaware of treatment allocation." Comment: participants, physicians, and outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, 32/32 (100%) participants analysed in the 5 mg group; 29/30 (96.7%) analysed in the 10 mg group; 32/33 (97%) analysed in the 20 mg group; and 29/30 (96.7%) analysed in the placebo group. None of these excluded participants received study treatment, and we could not rule out that their exclusion was associated with the outcome. In addition to these 3 excluded participants, it also remains unclear why the 5 participants (4%) enrolled after the protocol amendment were not considered in the analyses.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results section.

Macbeth 2016

Study characteristics

Methods	Trial acronym: FRAGMATIC Design: an open-label, multicentre, parallel-group, superiority, randomised phase III trial.

Macbeth 2016 *(Continued)*

	Median follow-up of 23.1 (IQR 3.6–31.2) months
Participants	Patients with histopathological or cytological diagnosis of primary bronchial carcinoma of any stage and histology (small-cell or non-small-cell) within 6 weeks Median age: 65 (IQR 59–71) years in LMWH group; 64 (IQR 58–71) years in control group Gender, n (%) males: 61 (60.0%) in LMWH group; 656 (59.6%) in control group Metastatic disease, n (%): 670 (60.9%) in LMWH group; 666 (60.5%) in control group Previous VTE: not reported
Interventions	Intervention: standard anticancer treatment (including active supportive or palliative care) plus dalteparin 5000 IU SC once daily for a maximum of 24 weeks Dalteparin was started as soon as possible and before first definitive anticancer treatment Control: standard anticancer treatment (including active supportive or palliative care) Use of prophylactic anticoagulant outside of trial (short-term use, e.g. inpatient thromboprophylaxis, and therapeutic anticoagulation were allowed if clinically indicated according to local guidelines), n (%): 106 (9.7%) in LMWH group; 88 (8.0%) in control group
Outcomes	Primary outcome: overall survival Secondary outcomes: VTE-free survival, bleeding (major and clinically relevant non-major), metastasis-free survival, toxic effects, quality of life, dyspnoea, cost-effectiveness, and cost utility Compliance with dalteparin was assessed by counting empty syringes at follow-up visits and from the local pharmacy logs.
Notes	Funding, quote: "Supported by Cancer Research UK Grant No. CR UK/06/007, an educational grant from Pfizer, and the National Institute for Health Research Cancer Network; sponsored by Velindre National Health Service Trust, Cardiff; and coordinated by the Cancer Research UK core-funded Wales Cancer Trials Unit at Cardiff University." Disclosure of potential conflicts of interest: some of the authors reported COI. Publication format: full-text publication Quote: "The trial did not reach its intended number of events for the primary analysis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned by the Wales Cancer Trials Unit in a 1:1 ratio to receive either LMWH or no LMWH, by use of a computer algorithm using the method of minimization and a random element." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was by research nurses (who recruited patients) telephoning the Wales Cancer Trials Unit, where randomization and treatment allocation was done by a trial/data manager using a computerized system." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias)	High risk	Quote: "The study had an open-label design." Comment: not reported if outcome assessors were blinded.

Macbeth 2016 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All analyses were performed using intention to treat." Comment: for the analysis of the primary outcomes and most of the secondary outcomes, all randomised participants were apparently included in the analysis. For the evaluation of compliance with LMWH, 977/1101 participants were assessed.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes indicated in the methods were reported in the results of the main or related papers.

Maraveyas 2012

Study characteristics	
Methods	Trial acronym: FRAGEM Design: phase IIb RCT; intention-to-treat analyses not reported Median duration of follow-up: 19.3 months
Participants	Patients with non-resectable, recurrent, or metastatic pancreatic adenocarcinoma Median age: 63 (range 40–82) years overall Gender, n (%) males: 72 (59%) overall Metastatic disease (%): 54% overall Previous VTE: 0/123 (0%) overall
Interventions	Intervention: LMWH, dalteparin 200 IU/kg once daily, SC for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks and gemcitabine Continuing dalteparin prophylaxis beyond 12 weeks was not recommended, but was left to the discretion of the investigator. Control: gemcitabine with no dalteparin
Outcomes	Primary outcome: reduction of all-type vascular thromboembolism during the study period. All-type vascular thromboembolism included DVT, PE, all arterial events (e.g. cerebrovascular accident/myocardial infarction), and all visceral thromboembolic events diagnosed on the basis of clinical symptomatology, postmortem, or incidentally. Outcome data kindly provided by the authors: VTE
Notes	Central venous access devices and inferior vena cava filters were not allowed. Funding: the Hull and East Yorkshire Hospitals National Health Service Trust; Pfizer provided a grant covering the cost of dalteparin; Lilly provided a grant covering the cost of biostatistics. Disclosure of potential conflicts of interest: the lead author has received honoraria and participated on advisory boards for Pfizer. Another author received travel expenses from Pfizer. None of the other authors had any conflicting interests. Publication format: full-text publication
Risk of bias	

Maraveyas 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in the facilities of the Postgraduate Medical Institute in Hull with software developed by York University". Allocation and stratification were done through remote telephone "block" randomisation (personal communication). Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Comment: performed centrally at the Medical Institute in Hull for all of the 7 recruiting sites. Allocation and stratification were done through remote telephone "block" randomisation (personal communication).
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: open study (personal communication). Not reported if outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, 59/60 (98.3%) were analysed in the LMWH group, and 62/63 (98.4%) were analysed in the control group.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results section.

Maurer 1997

Study characteristics	
Methods	Trial acronym: CALGB Protocol 8534, run by the Cancer and Leukemia Group B study Design: multicentre RCT; intention-to-treat analyses not reported Median duration of follow-up: 69 months in those still alive
Participants	Patients with limited-stage small-cell lung cancer receiving chemotherapy and radiotherapy Participants aged ≥ 60 years: 57.6% Gender, n (%) males: 225 (64.8%) Metastatic disease: none Previous VTE: not reported
Interventions	Intervention: warfarin 10 mg/day for the first 3 days and then at a dose to maintain the prothrombin time between 1.4 and 1.6 times the local institutional control standards Control: no warfarin Warfarin was continued through the complete course of chemotherapy and radiotherapy and stopped 3 weeks after the last cycle of chemotherapy. Warfarin was administered for a median of 112.5 days.
Outcomes	Primary outcomes: overall survival and cancer response to therapy Secondary outcomes: failure-free survival, disease-free survival, patterns of relapse, toxicity
Notes	Funding: grants from the National Cancer Institute, Bethesda, MD Disclosure of potential conflicts of interest: not reported, no COI forms available

Maurer 1997 *(Continued)*

	Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive warfarin or no warfarin." Comment: method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to receive warfarin or no warfarin." Comment: method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: it is not reported whether participants, physicians, and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Table 6 of the study full-text indicated that not all randomised participants were analysed, but the exact numbers were not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: only the outcomes of overall survival and complete tumour response were specified in the methods section. All other outcomes were addressed in the results section only, including the survival analyses at 8 months, and 2, 3, and 4 years. Only the 8 months' analyses were reported to be exploratory.

Meyer 2018

Study characteristics

Methods	Trial acronym: TILT Design: randomised, multicentre, open, controlled trial with blinded adjudication of outcome Median follow-up: 5.7 years
Participants	Patients with completely resected stage I, II, or IIIA non-small-cell lung cancer Mean age: 61.6 (SD 9.0) years in tinzaparin group; 61.6 (SD 8.8) years in control group Gender, n (%) males: 167 (62.1%) in tinzaparin group; 189 (67.5%) in control group Metastatic disease n (%): 0; 190 (34.6%) participants had stage II–III disease, and 220 (40.1%) participants received adjuvant chemotherapy Previous VTE: not reported
Interventions	Intervention: tinzaparin (Innohep, Leo Pharma France) 100 IU/kg SC once a day for 12 weeks in addition to standard of care Control: standard of care
Outcomes	Primary outcome: overall survival

Meyer 2018 *(Continued)*

	Secondary outcomes: serious bleeding recorded during the 12-week treatment period in tinzaparin group or corresponding period in control group, recurrence-free survival, cancer-related mortality, and symptomatic VTE recorded during the whole follow-up period
Notes	The study was supported by 2 grants issued by the French Ministry of Health (PHRC AOM05185 and PHRC AOM12612). Leo Pharma provided the study drug and a complementary grant. Disclosure of potential conflicts of interest: the first author received research funding and paid travel expenses from Leo Pharma. The last author received honoraria for consultancy and paid travel expenses from Leo Pharma. All other authors declared no relevant COI. Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned in a 1:1 ratio to receive either tinzaparin or no anticoagulants according to a list of randomisation numbers with treatment assignments. This list was computer-generated, used alternate blocks of small size (2,4,6) to make it unpredictable and was stratified according to centre and tumour stage (I *versus* II-III). An Internet application (CleanWeb) allowed central randomisation." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly assigned in a 1:1 ratio to receive either tinzaparin or no anticoagulants according to a list of randomisation numbers with treatment assignments. This list was computer-generated, used alternate blocks of small size (2,4,6) to make it unpredictable and was stratified according to centre and tumour stage (I *versus* II-III). An Internet application (CleanWeb) allowed central randomisation." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The trial was open-label with blinded central adjudication of study outcomes." and "All suspected outcome events and deaths were adjudicated by an independent clinical events committee whose members were unaware of treatment assignment." Comment: open-label study with blinded adjudication of outcomes.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 4/553 (0.7%) participants enrolled in the study were not considered for the analysis. Exclusions per trial arm were reported. 2 (0.4%) participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Mitchell 2003

Study characteristics

Methods	Trial acronym: PARKAA Design: multicentre, open, phase II RCT; per-protocol analysis Median duration of follow-up: not reported

Mitchell 2003 *(Continued)*

Participants	Children newly diagnosed with acute lymphoblastic leukaemia treated with L-asparaginase and a functioning central venous line placed within 2 weeks of initiating induction chemotherapy. Median age: 3.8 (range 1.6–17.2) years in antithrombin group; 5.9 (range 1.9–16.7) years in control group Gender, n (%) males: 15 (60%) in antithrombin group; 37 (61.7%) in control group Metastatic disease: not applicable, haematological cancer Previous VTE: not reported
Interventions	Intervention: Thrombate III, a sterile, lyophilised preparation of purified human antithrombin manufactured and supplied by Bayer Corporation, USA. Antithrombin infused once weekly for 4 weeks to increase plasma concentrations of antithrombin to approximately 3.0 U/mL but no more than 4.0 units/mL Control: standard care
Outcomes	Primary outcomes: clinically symptomatic or incidental thrombotic event in any location; major and minor bleeding Secondary outcome: surrogate outcome for thrombotic events by measuring markers of thrombin generation
Notes	Participants received small amounts of UFH for prophylaxis of central venous line blockage either by continuous infusion (1–3 U/mL) or intermittent flushes (50–100 U/mL up to 4 times per day) according to local standard of care. Funding: study was supported by a grant from the Canadian Institutes of Health Research and Bayer Inc. Disclosure of potential conflicts of interest: not reported, no COI forms available Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by the pharmacist-on-call using a computer generated random number list." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Investigators at participating centres were blinded to the randomisation code and unaware of patient treatment allocation until after patients had been randomised." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The PARKAA study was an open, randomised, multi-centre extended phase II clinical study" and "The thrombotic events outcomes were adjudicated centrally by committees consisting of physicians with appropriate expertise, who were not involved with study patients' care and were blinded to treatment groups." Comment: participants and physicians were not blinded, whereas outcome assessors were.

Mitchell 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, 25/37 (67.6%) participants were analysed in the antithrombin group, and 60/72 (83.3%) participants were analysed in the control group.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results section.

Palumbo 2011

Study characteristics	
Methods	Trial acronym: substudy of GIMEMA MM-BO2005 and GIMEMA-MM-03-05 Design: randomised, open-label, multicentre study; modified intention-to-treat analysis, including participant receiving ≥ 1 study dose The trial sampled participants from 2 distinct RCTs, of which participants who received thalidomide-based regimens were eligible to the substudy randomising antithrombotic prophylaxis treatments Median follow-up time: 24.9 months
Participants	Patients with previously untreated myeloma who received thalidomide-containing regimens and had no clinical indication or contraindication for a specific antiplatelet or anticoagulant therapy Median age: 61 (range 55–66) years in aspirin group; 60 (range 54–66) years in warfarin group; 62 (range 55–66) years in heparin group Gender, n (%) males: 117 (53%) in aspirin group; 115 (52%) in warfarin group; 130 (59%) in heparin group Metastatic disease: not reported Previous VTE: none
Interventions	Intervention 1: aspirin 100 mg/day Intervention 2: low-dose warfarin (1.25 mg/day) Intervention 3: LMWH (enoxaparin 40 mg/day) Prophylaxis was administered during the 3 cycles of induction therapy in participants aged ≤ 65 years and during the first 6 cycles of induction therapy in participants aged > 65 years. Median treatment duration: 2.6 months in aspirin group; 2.4 months in low-dose warfarin group; 2.6 months in LMWH group
Outcomes	Primary outcomes: a composite measure of a first episode of objectively confirmed symptomatic DVT, PE, arterial thrombosis, acute myocardial infarction or stroke, or sudden, otherwise-unexplained death during the first 6 months from random assignment Secondary outcomes: each component of the composite primary endpoint; long-term cumulative incidence of the primary endpoint; major and minor bleeding events; any toxicity that required interruption of study prophylaxis
Notes	Funding: none reported Disclosure of potential conflicts of interest: several authors reported paid consultant or advisory roles, honoraria, and research funds that were relevant to the subject matter under consideration in their trial report.

Palumbo 2011 *(Continued)*

Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A simple random assignment sequence was generated by a centralized computer." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "After registration in a centralized database through the Internet and validation of eligibility, patients were randomly allocated to treatments using an automated assignment procedure concealed to the investigators." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "open-label." Comment: this was an open-label study. It is not reported whether outcomes were assessed blindly.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, 220/224 (98.2%) participants in aspirin group, 220/222 (99.1%) participants in warfarin group, and 219/221 (99.1%) participants in LMWH group were analysed. In addition, 1 participant was not randomised by "clinician mistake."
Selective reporting (reporting bias)	High risk	Comment: the outcome "any toxicity that required interruption of study prophylaxis" was not reported in the final report.

Pelzer 2015

Study characteristics

Methods	Trial acronym: CONKO 004 Design: open-label, multicentre RCT; intention-to-treat and per-protocol analyses Median follow-up: 30.4 weeks
Participants	Outpatients with histologically confirmed advanced pancreatic cancer treated with first-line chemotherapy Median age: 62 (range 32–81) years in enoxaparin group; 63 (range 27–83) years in control group Gender, n (%) males: 91 (57%) in enoxaparin group; 94 (62%) in control group Metastatic disease, n (%): 119 (74%) in enoxaparin group; 118 (78%) in control group Previous VTE: not reported
Interventions	Intervention: LMWH, enoxaparin (1 mg/kg once daily) for 3 months started simultaneously to palliative systemic chemotherapy Control: no enoxaparin Quote: "After 3 months of initial enoxaparin use at half the therapeutic dosage (time point of primary end point), treatment was continued with a fixed dose of 40 mg daily until disease progression."

Pelzer 2015 *(Continued)*

Outcomes	Primary outcome: symptomatic VTE within 3 months after random assignment Secondary outcomes: progression-free survival; overall survival; overall symptomatic VTE after 6, 9, and 12 months; major bleeding Additional outcomes reported in related references: incidental DVT during months 6, 9, and 12; toxicity of the therapeutic regimen; time to cancer progression; remission at 3, 6, 9, and 12 months; quality of life
Notes	Funding, quote: "Supported by Charité–Forschungsförderung, Arbeitsgemeinschaft Internistische Onkologie, Deutsche Krebsgesellschaft, Amgen, Eli Lilly, and sanofi-aventis, which provided enoxaparin free of charge." Disclosure of potential conflicts of interest: quote: "Employment or Leadership Position: None Consultant or Advisory Role: Helmut Oettle, Celgene (C), Eli Lilly (C), Fresenius (C); Hanno Riess, sanofi-aventis (C) Stock Ownership: None Honoraria: Helmut Oettle, Celgene; Hanno Riess, sanofi-aventis, Roche, Amgen, Bayer, Novartis, Eli Lilly Research Funding: Helmut Oettle, Celgene, Eli Lilly Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: Uwe Pelzer, sanofi-aventis, Roche, Eli Lilly, Amgen; Jens M. Stieler, sanofi-aventis, Roche, Eli Lilly, Amgen." Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers generated at the study coordination center at the Charité–Universitätsmedizin Berlin." Comment: adequate method of random sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "computer-generated random numbers generated at the study coordination center at the Charité–Universitätsmedizin Berlin." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "All symptomatic VTEs and major hemorrhages were documented using the serious adverse event form, centrally reviewed and evaluated by an independent, blinded event review board." Comment: open-label study, with blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were included in the analysis.
Selective reporting (reporting bias)	High risk	Comment: some of the outcomes indicated in the related reports or in the main article (quality of life) are not reported.

Perry 2010

Study characteristics

Methods	Trial acronym: PRODIGE Design: phase III, randomised, placebo-controlled trial; intention-to-treat analysis Median duration of follow-up: not reported, planned follow-up up to 12 months

Perry 2010 *(Continued)*

Participants	Patients aged > 18 years with newly diagnosed, pathologically confirmed WHO grade 3 or grade 4 glioma Mean age: 57 (range 30–81) years in dalteparin group; 55 (26–77) years in placebo group Gender, n (%) males: 61 (62%) in dalteparin group; 50 (57%) in placebo group Metastatic disease: not reported Previous VTE: none
Interventions	Intervention: LMWH, dalteparin (5000 IU SC, once daily) Control: placebo Study treatment given for 6 months starting within the first month after surgery. Participants were allowed to continue study medication for 12 months. Median treatment duration: 183 days in LMWH group; 157 days in placebo group
Outcomes	Primary outcomes: objectively documented symptomatic DVT or PE occurring during the 6 months postrandomisation Secondary outcomes: major and all bleeding, quality of life, cognition assessments, and death
Notes	Funding: Pfizer Inc, Ontario Clinical Oncology Group, Crolla Chair in Brain Tumour Research Disclosure of potential conflicts of interest: the lead author disclosed research support (and funding) by Pfizer Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using a computer-generated randomization list." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Consenting patients were randomized by contacting the Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre at the Henderson Research Centre." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "In our study, investigators, patients and outcome assessors were blinded to treatment allocation. In addition, VTE and bleeding outcomes were adjudicated by a central committee unaware of treatment assignment." Comment: participants, physicians, and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were included in the analysis.
Selective reporting (reporting bias)	High risk	Comment: the outcomes quality of life and cognition assessment were mentioned in the methods but not reported in the results.

Sideras 2006

Study characteristics	
Methods	Trial acronym: none reported, trial of the North Central Cancer Treatment Group and Mayo Clinic Design: multicentre, placebo-controlled 2-arm randomised study; type of analyses not reported After 52 accrued participants, the study was modified because of concerns that the low accrual rate was related to the requirements for placebo injections. The saline placebo injections were eliminated, then, unblinded LMWH was compared with standard clinical care (with 89 more participants accrued after that point). Median duration of follow-up: not reported, planned minimum follow-up of 18 months
Participants	Patients with advanced breast cancer who had failed first-line chemotherapy; advanced prostate cancer who had failed primary hormonal therapy; advanced lung cancer; or advanced colorectal cancer. Median age: 64.5 years in for blinded LMWH group; 63.5 years in placebo group; 68.5 years in unblinded LMWH group; 70.5 years in standard care group. SDs not reported Gender, n (%) males: 12 (50%) in blinded LMWH group; 11 (42%) in placebo group; 28 (64%) in unblinded LMWH group; 31 (70%) in standard care group Metastatic disease, n (%): not reported, but all had advanced incurable cancer Previous VTE, n (%): 1 (4%) in blinded LMWH group; 1 (4%) in placebo group; 2 (5%) in unblinded LMWH group; 0 (0%) in standard care group
Interventions	*First part of the study, double-blind (52 participants):* LMWH, dalteparin (5000 IU SC, once daily) plus standard care Control: placebo (saline injections) plus standard care *Second part of the study, open (86 participants):* LMWH, dalteparin (5000 IU SC, once daily) plus standard care Control: standard care alone Duration: 18 weeks or until disease progression
Outcomes	Primary outcome: overall survival Secondary outcomes: toxic effects, incidence of thromboembolic events, changes in quality of life
Notes	Funding: Public Health Services grants from the National Cancer Institute, Department of Health and Human Services Disclosure of potential conflicts of interest: not reported and no COI forms available Publication format: full-text publication

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of random sequence generation not reported.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization processes applied were handled through the North Central Cancer Treatment Group (NCCTG) Randomization Office."

Sideras 2006 *(Continued)*

		Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: the study used a double-blind design in the first part of the trial, and an open-label design in the second part. It is not reported if outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, 68/69 (98.6%) participants were analysed in the LMWH group, and 70/72 (97.2%) were analysed in the placebo group.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion sections.

Vadhan-Raj 2013

Study characteristics	
Methods	Trial acronym: none reported, registry Identifier of NCI CTRP: NCI-2011-01773 Design: randomised, open-label, parallel-group trial Median duration of follow-up: not reported
Participants	Patients aged ≥ 18 years with a diagnosis of advanced stage (unresectable or metastatic) adenocarcinoma of the pancreas planning to initiate systemic chemotherapy within 2 weeks, ECOG performance status 0–2, adequate renal function (creatinine clearance > 50 mL/minute). Mean age: 52 (range 36–77) years overall; 59 (range 36–75) years in dalteparin group; 64 (range 38–77) years in control group Gender, n (%) males: 41 (54.7%) males overall; 20 (52.6%) in dalteparin group; 21 (56.8%) in control group Metastatic disease: not reported Previous VTE: not reported
Interventions	Intervention: LMWH, dalteparin (5000 IU SC, once daily) for 16 weeks during chemotherapy Control: chemotherapy alone
Outcomes	Primary outcome: venous thromboembolic events during 16 weeks of treatment Other outcomes mentioned in the abstract: adverse events, clinically significant bleeding, overall survival
Notes	Funding: not reported; however, Eisai Inc. is listed as collaborator at ClinicalTrials.gov Disclosure of potential conflicts of interest: not reported Publication format: published conference abstract Baseline characteristics and overall VTE outcome data available at clinicaltrials.gov/ct2/show/results/NCT00966277. The trial database was used as source for data extraction.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Vadhan-Raj 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "were randomized 1:1 to dalteparin vs control arms." Comment: method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "were randomized 1:1 to dalteparin vs control arms." Comment: method of allocation concealment not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: open-label study. It is not reported in the abstract if outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 75 patients were evaluable for response in an intent-to-treat analysis." Comment: all randomised participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: study not published as full report yet. The conference abstract did not address all planned outcomes in sufficient detail.

van Doormaal 2011

Study characteristics	
Methods	Trial acronym: INPACT Design: multicentre, open-label RCT; intention-to-treat analyses for mortality Median duration of follow-up: 10.4 months
Participants	Patients with non-small-cell lung cancer (stage IIIB), hormone-refractory prostate cancer, or locally advanced pancreatic cancer Age, mean: 65 (SD 10) years in nadroparin group; 65 (SD 9.8) years in no-nadroparin group Gender, n (%) males: 197 (81%) in nadroparin group; 206 (80%) in no-nadroparin group Metastatic disease in prostate cancer, n (%): 73 (73.7%) in nadroparin group; 85 (87.6%) in no-nadroparin group Previous VTE: none
Interventions	Intervention: LMWH, nadroparin in addition to standard anticancer treatment SC nadroparin was administered for 6 weeks (2 weeks at therapeutic dose and 4 weeks at half therapeutic dose). Participants were eligible to receive additional cycles of nadroparin (2 weeks at therapeutic dose and 4 weeks of washout period) for a maximum of 6 cycles. Mean duration of treatment: 12.6 weeks Control: standard anticancer treatment (no nadroparin)
Outcomes	Primary efficacy outcome: all-cause mortality Primary safety outcome: major bleeding Secondary efficacy outcomes: time to disease progression, clinically relevant non-major bleeding, VTE, arterial thromboembolic events

van Doormaal 2011 *(Continued)*

Notes	Funding: the study was supported by a grant from GlaxoSmithKline (Paris, France). Disclosure of potential conflicts of interest: 2 authors reported consultant or advisory roles, honoraria, and research funds that were relevant to the subject matter under consideration in their trial report. Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation of treatment proceeded centrally by using an interactive-voice response system." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation of treatment proceeded centrally by using an interactive-voice response system." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "all study outcomes were adjudicated by an independent, blinded committee." Comment: open study with blinded outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: for effectiveness and safety, the overall percentage of participants enrolled and subsequently excluded from the analysis was 2.2% (11/503).
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported in the methods section were addressed in the results or discussion section.

Zacharski 1981

Study characteristics

Methods	Trial acronym: Veterans Administration Study No. 75 Design: multicentre RCT, type of analyses not reported Median duration of follow-up: not reported, maximum follow-up was approximately 95 weeks in warfarin group and 94 weeks in control group (approximated from figure)
Participants	Patients with small-cell lung carcinoma treated with chemotherapy and radiotherapy Mean age: 58.9 (SD not reported) in warfarin group: 59.8 (SD not reported) in control group Gender, n (%) males: 50 (100%) Metastatic disease: extensive cancer in 13 (52%) in warfarin group; 12 (48%) in control group Previous VTE: not reported
Interventions	Intervention: warfarin at doses to prolong the prothrombin time to approximately 2 times the control value Control: no warfarin

Zacharski 1981 *(Continued)*

	Median duration of warfarin administration: 27 weeks
Outcomes	Primary efficacy outcomes: survival and cancer response to treatment
Notes	Funding: VA Cooperative Studies Program Disclosure of potential conflicts of interest: not reported, no COI forms available Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjected to computer randomization." Comment: adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "subjected to computer randomization." Comment: adequate method of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: it is not reported whether participants, physicians, and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient has been lost to follow-up." Comment: all enrolled participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: bleeding was addressed in the results section, but not mentioned in the methods section.

Zwicker 2013

Study characteristics

Methods	Trial acronym: MicroTEC Design: 3-arm[a] randomised, multicentre phase II study; use of intention-to-treat analyses reported Median duration of follow-up: 2 months for the primary efficacy endpoint
Participants	Patients with histologically confirmed advanced-stage malignancy for which standard curative therapies did not exist. Eligible malignancies included: adenocarcinoma of the pancreas (locally advanced or metastatic), colorectal (stage IV), non-small-cell lung cancer (stage III or IV), relapsed or stage IV ovarian cancer, or surgically unresectable or metastatic gastric adenocarcinoma. Median age: 68.1 (range 46.6–80.1) years in LMWH group; 67.5 (range 28.8–78.7) years in observation group Gender, n (%) males: 14 (61%) in LMWH group; 5 (46%) in observation group Metastatic disease: 52 (78.8%) overall across 3 trial arms Previous VTE: none
Interventions	Intervention: LMWH, enoxaparin (40 mg SC, once daily)

Zwicker 2013 *(Continued)*

	Control: observation Treatment was given for 2 months
Outcomes	Primary efficacy outcome: cumulative incidence of VTE (i.e. any symptomatic proximal or distal lower extremity DVT, incidental proximal DVT, symptomatic PE, or fatal PE) at 2 months Primary safety outcome: major bleeding Secondary: toxicity and survival
Notes	[a]2/3 trial arms with high tissue factor-bearing microparticles (TFMP) were considered in this review. The trial arm with low TFMP without enoxaparin was excluded. Funding, quote: "the study was supported by grants from the National Institutes of Health, K23 HL84052 (JIZ) and R01 HL095084 (BF), as well as a research grant from Sanofi." Disclosure of potential conflicts of interest: 1 author had served on steering committees for Sanofi, and another had received research funds and served on advisory boards for Sanofi and Eisai Publication format: full-text publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomized (2:1) to enoxaparin 40 mg subcutaneously once daily or observation." Comment: method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "Study coordination, randomization, and monitoring were performed by the Quality Assurance Office for Clinical Trials (QACT) at Dana Farber/Harvard Cancer Center." Comment: method of allocation concealment not clearly specified.
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: both the treating physicians and participants in the observation arms were blinded to microparticle status. However, participants in the control group were only observed; the use of placebo, blinding method, or an independent and blinded adjudication committee was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all randomised participants were included in the analysis. 4/70 participants initially enrolled were excluded prior to randomisation.
Selective reporting (reporting bias)	High risk	Comment: the outcome toxicity was not reported in the results section.

COI: conflict of interest; DVT: deep vein thrombosis; ECOG: Eastern Cooperative Oncology Group; INR: international normalised ratio; IQR: interquartile range; LMWH: low-molecular-weight heparin; n: number of participants; PE: pulmonary embolism; RCT: randomised controlled trial; SC: subcutaneous; SD: standard deviation; UFH: unfractionated heparin; uLMWH: ultra-low-molecular-weight heparin; VTE: venous thromboembolism; WHO: World Health Organization.

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

Study	Reason for exclusion
Baz 2005	Not an RCT.

Study	Reason for exclusion
Bergqvist 1983	Perioperative thromboprophylaxis.
Bocharov 2011	Not an RCT and study included surgical patients.
Eichinger 2008	Inadequate population: hospitalised cancer patients.
Groen 2019	Other: none of the primary outcomes of this review were reported.
Haas 2011	Inadequate population: hospitalised cancer patients.
Heilmann 1995	Perioperative thromboprophylaxis.
Hills 1972	Perioperative thromboprophylaxis.
Kessler 2011	Not an RCT.
Macintyre 1974	Perioperative thromboprophylaxis.
Maxwell 2000	Perioperative thromboprophylaxis.
Meister 2008	Not an RCT.
Minnema 2004	Not an RCT.
NCT00004875	Prophylaxis for catheter-related thrombosis.
NCT00031837	Study was terminated early, and no results were posted on ClinicalTrials.gov (accessed at clinicaltrials.gov/ct2/show/NCT00031837 on 13 June 2013).
NCT00662688	Study terminated. No published data available and results not reported in ClinicalTrials.gov.
NCT00790452	Study was terminated early because of a drug supply issue. Results of a single participant were posted (accessed at clinicaltrials.gov/ct2/show/results/NCT00790452 on 11 December 2012).
NCT04106700	Not an RCT.
NCT04352439	Not an RCT.
Niesvizky 2007	Inadequate type of intervention: antiplatelet agent vs placebo.
Paydas 2008	Not an RCT.
Poniewierski 1988	Inadequate population: hospitalised cancer patients.
Rajan 1995	Inadequate outcomes.
Salat 1990	No outcome data extractable and unlikely that trial will be published as full report in future.
Sideras 2007	Perioperative thromboprophylaxis.
Storrar 2019	Not an RCT.
Weber 2008	Inadequate population: hospitalised cancer patients.
Welti 1981	Perioperative thromboprophylaxis.

Study	Reason for exclusion
Zangari 2003	Not an RCT.
Zwicker 2019	Inadequate type of intervention: flavonoid.

RCT: randomised controlled trial.

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

Ciftci 2012

Methods	Single-centre, randomised study
Participants	Patients with lung cancer
Interventions	Intervention: warfarin in addition to standard anticancer treatment. Warfarin orally for 6 months starting on day 1 of chemotherapy at a dose of 5 mg/day to achieve a target international normalised ratio of 1.5–2.5 Control: standard anticancer treatment
Outcomes	No clear distinction between primary and secondary outcomes. Outcomes reported in the abstract: overall median survival, response rates (complete and partial), bleeding
Notes	Reason to be listed as awaiting classification: no outcome data extractable, trial not yet published as full article.

NCT00771563

Methods	Open-label RCT
Participants	Patients with locally advanced or metastatic non-small-cell lung cancer (stage IIIB or IV) who were not candidates for radical combined-modality treatments or high-dose radiotherapy
Interventions	Intervention: chemotherapy (cisplatin + docetaxel) and enoxaparin 1 mg/kg/day SC Control: chemotherapy (cisplatin + docetaxel)
Outcomes	Primary outcome: progression-free survival Secondary outcomes: symptom control evaluated with the Lung Cancer Symptoms Scale, overall survival, best overall response, incidence of total documented thromboembolic and haemorrhagic events, overall safety, and tolerability
Notes	ClinicalTrials.gov identifier: NCT00771563 Reason to be listed as awaiting classification: no outcome data extractable, trial not yet published as full article.

RCT: randomised controlled trial; SC: subcutaneous.

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

ChiCTR-TRC-08000267

Study name	The role of LMWH combined with TACE in hepatocellular carcinoma
Methods	Randomised parallel controlled trial Phase: postmarket
Participants	Adults with hepatocellular carcinoma that is not amenable to surgical resection, liver transplantation, or local ablative therapy; without metastasis out of liver
Interventions	Intervention: hypodermic injection LMWH 4100 IU each 12 hours in 6 weeks Control: no intervention
Outcomes	Primary outcomes: survival time; survival time with no tumour progression Secondary outcome: response rate
Starting date	1 December 2008
Contact information	Jiamei Yang, yang-jia-mei@163.com
Notes	Recruitment status: completed Primary sponsor: Shanghai Eastern Hepatobiliary Surgery Hospital

NCT00718354

Study name	Randomized, phase III-b, multi-centre, open-label, parallel study of enoxaparin (low molecular weight heparin) given concomitantly with chemotherapy vs chemotherapy alone in patients with inoperable gastric and gastro-oesophageal cancer
Methods	Randomised, open-label, multicentre study. Methods of randomisation and allocation concealment unclear
Participants	Patients with inoperable (locally advanced) or metastatic newly diagnosed gastric or gastro-oesophageal cancer
Interventions	Intervention: LMWH, enoxaparin (1 mg/kg SC once daily) in addition to standard chemotherapy up to 6 months Control: standard chemotherapy (up to 6 cycles)
Outcomes	Primary outcome: event-free survival (composite endpoint of overall survival plus free of symptomatic VTE) Secondary outcomes: incidence of symptomatic VTE, overall survival, major and minor bleeding during chemotherapy or up to 30 days after last dose is provided, serious adverse events, all reported adverse events, HIT
Starting date	July 2008
Contact information	Maganji JM, mmaganji@tri-london.ac.uk
Notes	NCT00718354 Study status in ClinicalTrials.gov is "complete."

NCT01518465

Study name	Dalteparin, lenalidomide, and low-dose dexamethasone in treating patients with previously untreated multiple myeloma
Methods	Randomised, open-label, pilot phase II trial
Participants	Patients with a diagnosis of active multiple myeloma requiring treatment
Interventions	Intervention: dalteparin 5000 IU SC once daily on days 1–28; lenalidomide on days 1–21; and low-dose dexamethasone on days 1, 8, 15, and 22 Control: dalteparin 200 IU/kg SC on days 1–21
Outcomes	Primary outcome: number of participants who experienced grade 4 haemorrhage regardless of attribution, or grade 3 haemorrhage that is possibly, probably, or definitely attributable to dalteparin Secondary outcome: toxicities observed at each dose level
Starting date	January 2012
Contact information	Ann Mohrbacher
Notes	NCT01518465 The study status in ClinicalTrials.gov is "terminated" due to insufficient accrual.

NCT02285738

Study name	Anti-platelet and statin therapy to prevent cancer-associated thrombosis: a pilot study
Methods	Open-label, parallel-assignment RCT
Participants	Patients with a histological diagnosis of malignancy of a solid organ or lymphoma who have a VTE risk score of ≥ 1 and will be initiating a new systemic chemotherapy regimen
Interventions	Intervention 1: aspirin Intervention 2: simvastatin Control: observation
Outcomes	Primary outcome: change in average soluble P-selectin levels Secondary outcomes: major bleeding complications or clinically significant non-bleeding complications; change in circulating biomarkers; thrombotic events including venous thrombosis, PE, visceral vein thrombosis; arterial thromboembolic events including stroke, myocardial infarction, or arterial embolism
Starting date	December 2014
Contact information	
Notes	ClinicalTrials.gov identifier: NCT02285738

NCT02555878

Study name	Efficacy and safety of rivaroxaban prophylaxis compared with placebo in ambulatory cancer patients initiating systemic cancer therapy and at high risk for venous thromboembolism
Methods	Multicentre, randomised, double-blind (participant, carer, investigator), placebo-controlled, parallel-group superiority study
Participants	Patients with histologically confirmed solid malignancy including but not limited to: pancreas, lung, stomach, colon, rectum, bladder, breast, ovary, renal, or lymphoma (haematological), with locally advanced or metastatic disease who have a Khorana thromboembolic risk score ≥ 2
Interventions	Intervention: rivaroxaban 10 mg tablet orally once daily for 180 days Control: placebo
Outcomes	Primary efficacy outcomes: symptomatic and incidental lower extremity proximal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, VTE-related death Primary safety outcome: major bleeding Secondary outcomes: symptomatic VTE and VTE-related deaths, all-cause mortality, clinically relevant non-major bleeding, minor bleeding, any bleeding adverse events, and serious adverse events
Starting date	September 2015
Contact information	Janssen Research & Development, LLC Clinical Trial
Notes	ClinicalTrials.gov identifier: NCT02555878

NCT03090880

Study name	Prophylaxis of venous thromboembolism in advanced lung cancer (PROVE)
Methods	Randomised, phase III, open, multicentre trial with blinded adjudication of endpoints
Participants	Adults aged > 18 years with stage IV non-small-cell lung cancer and elevated D-dimer > 1500 µg/L
Interventions	Intervention: tinzaparin 4500 IU SC once daily for 6 months Control: usual care
Outcomes	Primary outcome: VTE including symptomatic or incidental PE, symptomatic or incidental proximal DVT of the lower extremity, symptomatic DVT of the upper extremity, VTE-related death during the six-month treatment period Secondary outcomes: symptomatic VTE, any VTE, major bleeding, death at 6 and 12 months
Starting date	March 2017
Contact information	Guy Meyer
Notes	ClinicalTrials.gov identifier: NCT03090880

NCT03428373

Study name	ASA vs. rivaroxaban in newly diagnosed or relapsed and refractory multiple myeloma patients treated with Len-Dex combination therapy (RithMM)
Methods	Multicentre, open-label, pilot, RCT. A web-based randomisation system will ensure allocation concealment
Participants	Patients with newly diagnosed or relapsed and refractory multiple myeloma treated with lenalidomide dexamethasone combination therapy
Interventions	Intervention 1: aspirin 81 mg daily Intervention 2: rivaroxaban 10 mg daily for 6 months
Outcomes	Venous or arterial thromboembolism, treatment-related adverse events
Starting date	1 January 2019
Contact information	Martha Louzada, mailto:Martha.Louzada%40lhsc.on.ca?subject=NCT03428373, 10014356, ASA vs. Rivaroxaban in Newly Diagnosed or Relapsed and Refractory Multiple Myeloma Patients Treated With Len-Dex Combination Therapy.
Notes	

O'Brien 2019

Study name	PREVAPIX-ALL: apixaban compared to standard of care for prevention of venous thrombosis in paediatric acute lymphoblastic leukaemia (ALL) – rationale and design
Methods	Multinational, multicentre, randomised, open-label trial
Participants	Children and adolescents with acute lymphoblastic leukaemia and T/B cell lymphoblastic lymphoma receiving standard induction chemotherapy with asparaginase and the presence of a central venous access device
Interventions	Intervention: apixaban. Children 5 years or older randomised to the apixaban arm and weighing ≥ 35 kg may be administered either 2.5 mg tablets, 0.5 mg tablets, or oral solution apixaban twice daily for approximately 28 days, while children < 5 years and < 35 kg may be administered 0.5 mg tablets only. Children weighing ≥ 35 kg will be administered the adult dose of apixaban 2.5 mg twice daily Control: standard of care
Outcomes	Primary efficacy endpoint: composite of symptomatic and asymptomatic VTE that includes DVT, PE, cerebral sinovenous thrombosis, or VTE-related death Primary safety outcome: major bleeding Secondary outcomes: central line-associated infections, patency and line replacement, superficial thrombosis, arterial events, and death
Starting date	Not reported
Contact information	Sarah H O'Brien, sarah.obrien@nationwidechildrens.org
Notes	

DVT: deep vein thrombosis; HIT: heparin-induced thrombocytopenia; IV: intravenous; LMWH: low-molecular-weight heparin; PE: pulmonary embolism; RCT: randomised controlled trial;
SC: subcutaneous; TACE: transarterial chemoembolisation; VTE: venous thromboembolism.

DATA AND ANALYSES

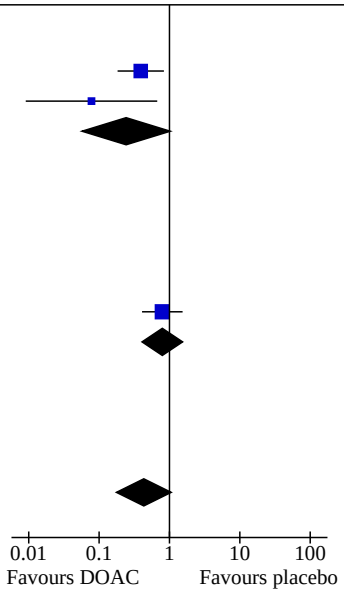
Comparison 1. Anticoagulants versus control: symptomatic venous thromboembolism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Symptomatic VTE: DOAC vs placebo	3	1526	Risk Ratio (IV, Random, 95% CI)	0.43 [0.18, 1.06]
1.1.1 Apixaban	2	685	Risk Ratio (IV, Random, 95% CI)	0.24 [0.06, 1.02]
1.1.2 Rivaroxaban	1	841	Risk Ratio (IV, Random, 95% CI)	0.79 [0.41, 1.54]
1.2 Symptomatic VTE: LMWH vs no thromboprophylaxis	11	3931	Risk Ratio (IV, Random, 95% CI)	0.62 [0.46, 0.83]
1.2.1 Dalteparin	6	999	Risk Ratio (IV, Random, 95% CI)	0.66 [0.40, 1.07]
1.2.2 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.57 [0.24, 1.35]
1.2.3 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.50 [0.22, 1.13]
1.2.4 Enoxaparin	1	312	Risk Ratio (IV, Random, 95% CI)	0.43 [0.21, 0.88]
1.2.5 Bemiparin	1	38	Risk Ratio (IV, Random, 95% CI)	0.10 [0.01, 1.75]
1.2.6 Tinzaparin	1	549	Risk Ratio (IV, Random, 95% CI)	0.94 [0.51, 1.73]
1.3 Symptomatic VTE: prophylactic vs intermediate or therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	2.89 [0.12, 67.75]
1.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.07, 15.15]
1.4 Symptomatic VTE: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.51 [0.22, 1.17]
1.5 Symptomatic VTE: LMWH vs warfarin	1	439	Risk Ratio (IV, Fixed, 95% CI)	0.33 [0.14, 0.83]

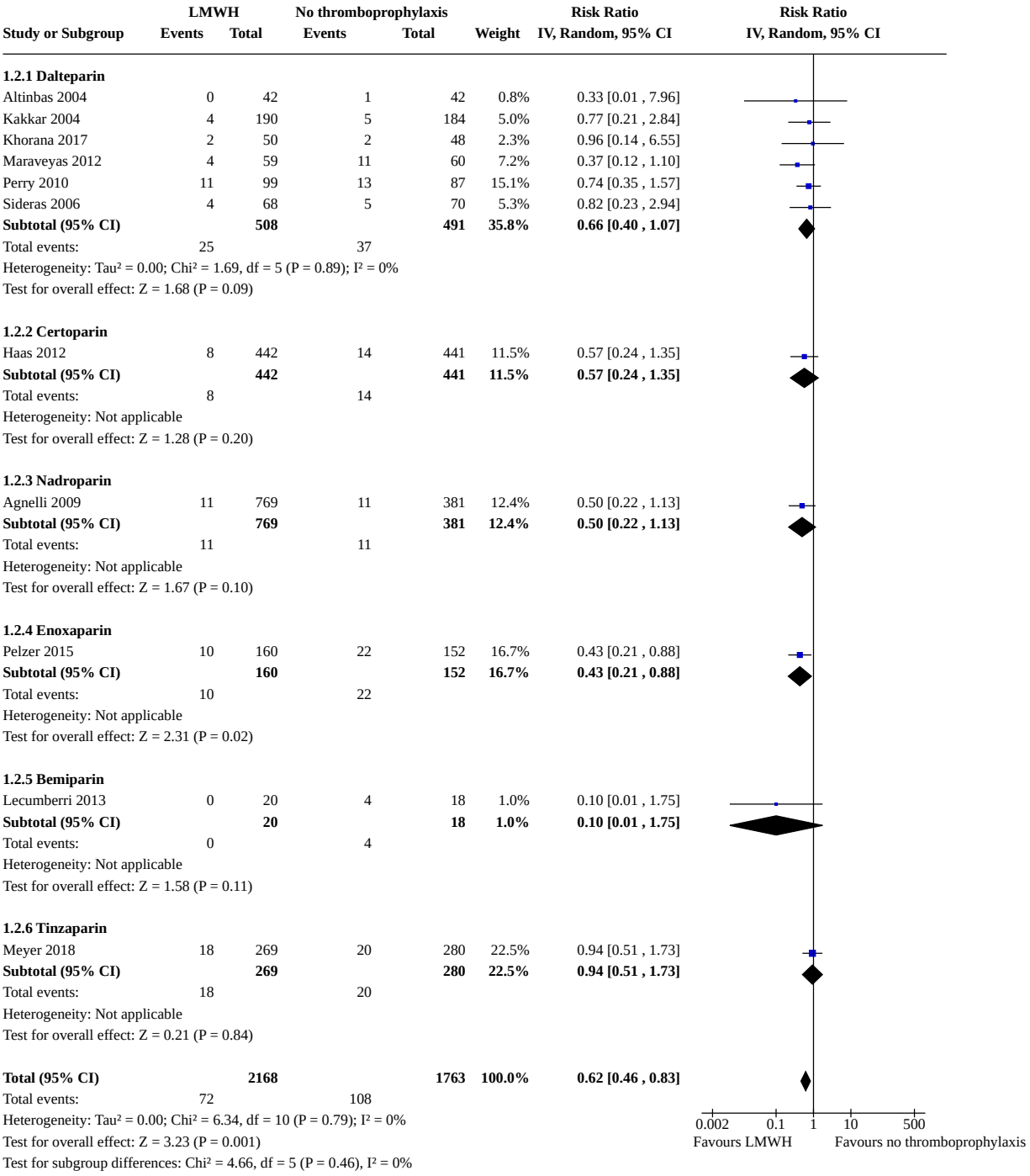
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Symptomatic VTE: semuloparin vs placebo	1	3212	Risk Ratio (IV, Fixed, 95% CI)	0.36 [0.22, 0.60]
1.7 Symptomatic VTE: vitamin K antagonists vs placebo	1	311	Risk Ratio (IV, Fixed, 95% CI)	0.15 [0.02, 1.20]
1.8 Symptomatic VTE: warfarin vs aspirin	1	440	Risk Ratio (IV, Fixed, 95% CI)	1.50 [0.74, 3.04]

Analysis 1.1. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 1: Symptomatic VTE: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Apixaban						
Carrier 2019	9	288	22	275	41.7%	0.39 [0.18 , 0.83]
Levine 2012	1	93	4	29	13.4%	0.08 [0.01 , 0.67]
Subtotal (95% CI)		**381**		**304**	**55.1%**	**0.24 [0.06 , 1.02]**
Total events:	10		26			
Heterogeneity: Tau² = 0.62; Chi² = 1.92, df = 1 (P = 0.17); I² = 48%						
Test for overall effect: Z = 1.93 (P = 0.05)						
1.1.2 Rivaroxaban						
Khorana 2019	15	420	19	421	44.9%	0.79 [0.41 , 1.54]
Subtotal (95% CI)		**420**		**421**	**44.9%**	**0.79 [0.41 , 1.54]**
Total events:	15		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**801**		**725**	**100.0%**	**0.43 [0.18 , 1.06]**
Total events:	25		45			
Heterogeneity: Tau² = 0.35; Chi² = 5.07, df = 2 (P = 0.08); I² = 61%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Chi² = 2.14, df = 1 (P = 0.14), I² = 53.2%						

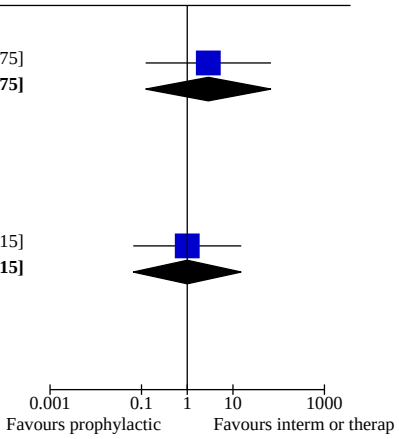


Analysis 1.2. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 2: Symptomatic VTE: LMWH vs no thromboprophylaxis



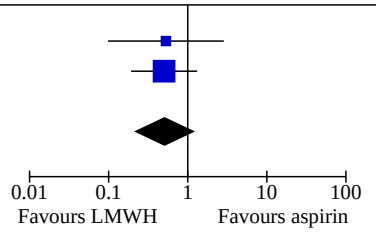
Analysis 1.3. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 3: Symptomatic VTE: prophylactic vs intermediate or therapeutic LMWH

Study or Subgroup	Prophylactic LMWH Events	Total	Interm or therap LMWH Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
1.3.1 Prophylactic vs intermediate						
Elit 2012	1	26	0	25	100.0%	2.89 [0.12 , 67.75]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**2.89 [0.12 , 67.75]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.3.2 Prophylactic vs therapeutic						
Elit 2012	1	26	1	26	100.0%	1.00 [0.07 , 15.15]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**1.00 [0.07 , 15.15]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



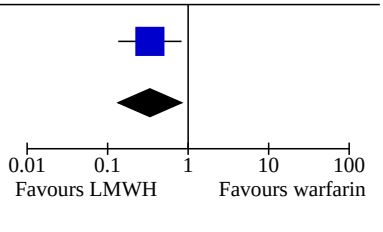
Analysis 1.4. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 4: Symptomatic VTE: LMWH vs aspirin

Study or Subgroup	LMWH Events	Total	Aspirin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Larocca 2012	2	166	4	176	24.6%	0.53 [0.10 , 2.86]
Palumbo 2011	6	219	12	220	75.4%	0.50 [0.19 , 1.31]
Total (95% CI)		**385**		**396**	**100.0%**	**0.51 [0.22 , 1.17]**
Total events:	8		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Not applicable						



Analysis 1.5. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 5: Symptomatic VTE: LMWH vs warfarin

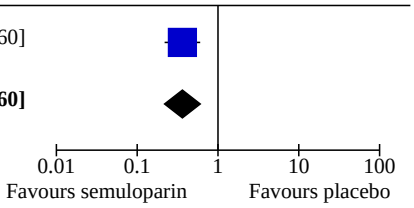
Study or Subgroup	LMWH Events	Total	Warfarin Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	6	219	18	220	100.0%	0.33 [0.14 , 0.83]
Total (95% CI)		**219**		**220**	**100.0%**	**0.33 [0.14 , 0.83]**
Total events:	6		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: Not applicable						



Analysis 1.6. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 6: Symptomatic VTE: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Semuloparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Agnelli 2012	20	1608	55	1604	100.0%	0.36 [0.22 , 0.60]
Total (95% CI)		**1608**		**1604**	**100.0%**	**0.36 [0.22 , 0.60]**
Total events:	20		55			

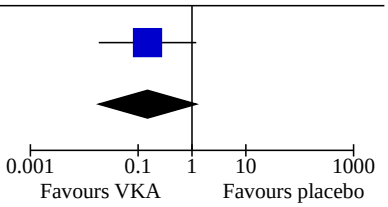
Heterogeneity: Not applicable
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 7: Symptomatic VTE: vitamin K antagonists vs placebo

Study or Subgroup	VKA Events	VKA Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Levine 1994	1	152	7	159	100.0%	0.15 [0.02 , 1.20]
Total (95% CI)		**152**		**159**	**100.0%**	**0.15 [0.02 , 1.20]**
Total events:	1		7			

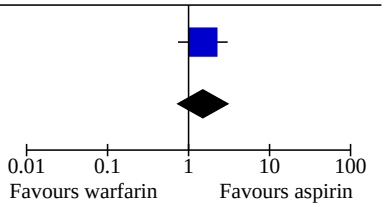
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Anticoagulants versus control: symptomatic venous thromboembolism, Outcome 8: Symptomatic VTE: warfarin vs aspirin

Study or Subgroup	Warfarin Events	Warfarin Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	18	220	12	220	100.0%	1.50 [0.74 , 3.04]
Total (95% CI)		**220**		**220**	**100.0%**	**1.50 [0.74 , 3.04]**
Total events:	18		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



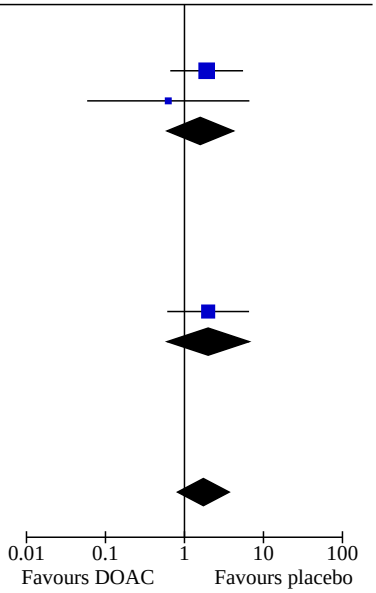
Comparison 2. Anticoagulants versus control: major bleeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Major bleeding: DOAC vs placebo	3	1494	Risk Ratio (IV, Random, 95% CI)	1.74 [0.82, 3.68]
2.1.1 Apixaban	2	685	Risk Ratio (IV, Random, 95% CI)	1.58 [0.60, 4.17]

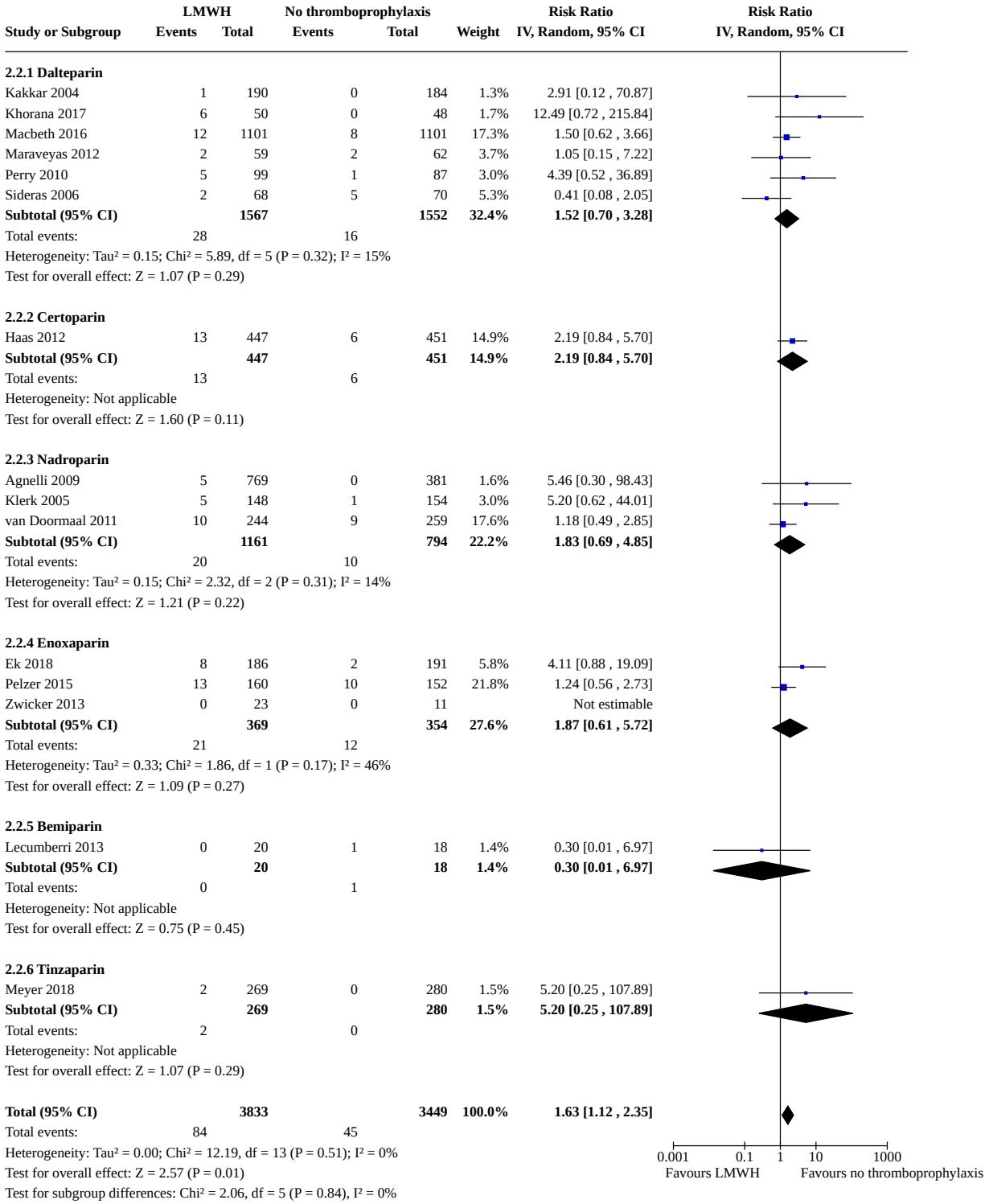
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.2 Rivaroxaban	1	809	Risk Ratio (IV, Random, 95% CI)	2.00 [0.61, 6.57]
2.2 Major bleeding: LMWH vs no thromboprophylaxis	15	7282	Risk Ratio (IV, Random, 95% CI)	1.63 [1.12, 2.35]
2.2.1 Dalteparin	6	3119	Risk Ratio (IV, Random, 95% CI)	1.52 [0.70, 3.28]
2.2.2 Certoparin	1	898	Risk Ratio (IV, Random, 95% CI)	2.19 [0.84, 5.70]
2.2.3 Nadroparin	3	1955	Risk Ratio (IV, Random, 95% CI)	1.83 [0.69, 4.85]
2.2.4 Enoxaparin	3	723	Risk Ratio (IV, Random, 95% CI)	1.87 [0.61, 5.72]
2.2.5 Bemiparin	1	38	Risk Ratio (IV, Random, 95% CI)	0.30 [0.01, 6.97]
2.2.6 Tinzaparin	1	549	Risk Ratio (IV, Random, 95% CI)	5.20 [0.25, 107.89]
2.3 Major bleeding: prophylactic vs intermediate or therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
2.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
2.4 Major bleeding: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.76]
2.5 Major bleeding: LMWH vs warfarin	1	439	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
2.6 Major bleeding: semuloparin vs placebo	1	3172	Risk Ratio (IV, Fixed, 95% CI)	1.05 [0.55, 2.00]
2.7 Major bleeding: vitamin K antagonists vs no thromboprophylaxis	4	994	Risk Ratio (IV, Random, 95% CI)	3.82 [0.97, 15.04]
2.8 Major bleeding: warfarin vs aspirin	1	440	Risk Ratio (IV, Fixed, 95% CI)	0.14 [0.01, 2.75]

Analysis 2.1. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 1: Major bleeding: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Apixaban						
Carrier 2019	10	288	5	275	50.2%	1.91 [0.66 , 5.52]
Levine 2012	2	93	1	29	10.1%	0.62 [0.06 , 6.63]
Subtotal (95% CI)		**381**		**304**	**60.3%**	**1.58 [0.60 , 4.17]**
Total events:	12		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.1.2 Rivaroxaban						
Khorana 2019	8	405	4	404	39.7%	2.00 [0.61 , 6.57]
Subtotal (95% CI)		**405**		**404**	**39.7%**	**2.00 [0.61 , 6.57]**
Total events:	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.26)						
Total (95% CI)		**786**		**708**	**100.0%**	**1.74 [0.82 , 3.68]**
Total events:	20		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						

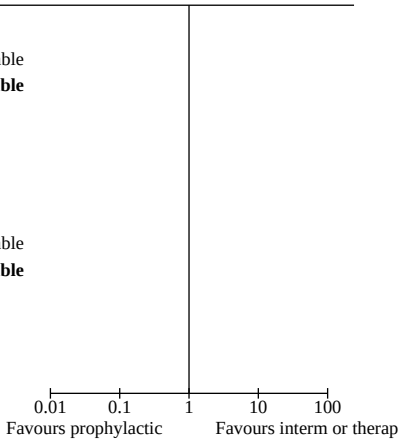


Analysis 2.2. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 2: Major bleeding: LMWH vs no thromboprophylaxis



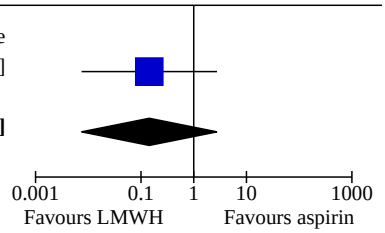
Analysis 2.3. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 3: Major bleeding: prophylactic vs intermediate or therapeutic LMWH

Study or Subgroup	Prophylactic LMWH Events	Total	Interm or therap LMWH Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
2.3.1 Prophylactic vs intermediate						
Elit 2012	0	26	0	25		Not estimable
Subtotal (95% CI)		**26**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.3.2 Prophylactic vs therapeutic						
Elit 2012	0	26	0	26		Not estimable
Subtotal (95% CI)		**26**		**26**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



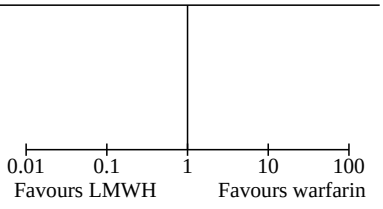
Analysis 2.4. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 4: Major bleeding: LMWH vs aspirin

Study or Subgroup	LMWH Events	Total	Aspirin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Larocca 2012	0	166	0	176		Not estimable
Palumbo 2011	0	219	3	220	100.0%	0.14 [0.01 , 2.76]
Total (95% CI)		**385**		**396**	**100.0%**	**0.14 [0.01 , 2.76]**
Total events:	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
Test for subgroup differences: Not applicable						



Analysis 2.5. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 5: Major bleeding: LMWH vs warfarin

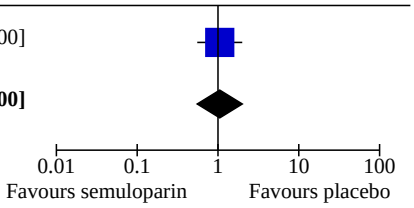
Study or Subgroup	LMWH Events	Total	Warfarin Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	0	219	0	220		Not estimable
Total (95% CI)		**219**		**220**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 2.6. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 6: Major bleeding: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Semuloparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Agnelli 2012	19	1589	18	1583	100.0%	1.05 [0.55 , 2.00]
Total (95% CI)		**1589**		**1583**	**100.0%**	**1.05 [0.55 , 2.00]**
Total events:	19		18			

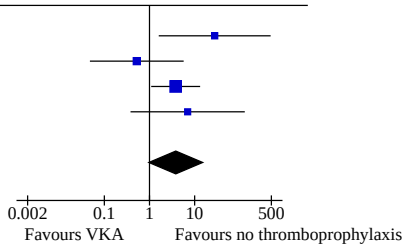
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 7: Major bleeding: vitamin K antagonists vs no thromboprophylaxis

Study or Subgroup	VKA Events	VKA Total	No thromboprophylaxis Events	No thromboprophylaxis Total	Weight	Risk Ratio IV, Random, 95% CI
Chahinian 1989	7	100	0	186	17.3%	27.77 [1.60 , 481.30]
Levine 1994	1	152	2	159	22.2%	0.52 [0.05 , 5.71]
Maurer 1997	12	178	3	169	43.7%	3.80 [1.09 , 13.22]
Zacharski 1981	3	25	0	25	16.7%	7.00 [0.38 , 128.87]
Total (95% CI)		**455**		**539**	**100.0%**	**3.82 [0.97 , 15.04]**
Total events:	23		5			

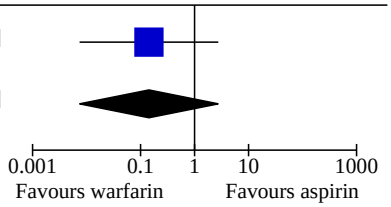
Heterogeneity: Tau² = 0.71; Chi² = 4.68, df = 3 (P = 0.20); I² = 36%
Test for overall effect: Z = 1.92 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Anticoagulants versus control: major bleeding, Outcome 8: Major bleeding: warfarin vs aspirin

Study or Subgroup	Warfarin Events	Warfarin Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	0	220	3	220	100.0%	0.14 [0.01 , 2.75]
Total (95% CI)		**220**		**220**	**100.0%**	**0.14 [0.01 , 2.75]**
Total events:	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable



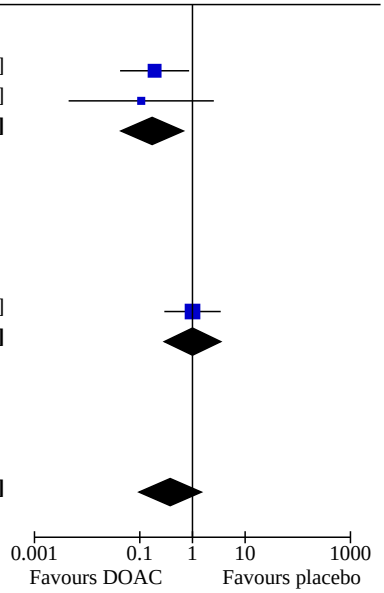
Comparison 3. Anticoagulants versus control: symptomatic pulmonary embolism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Symptomatic PE: DOAC vs placebo	3	1526	Risk Ratio (IV, Random, 95% CI)	0.38 [0.10, 1.47]
3.1.1 Apixaban	2	685	Risk Ratio (IV, Random, 95% CI)	0.17 [0.04, 0.67]

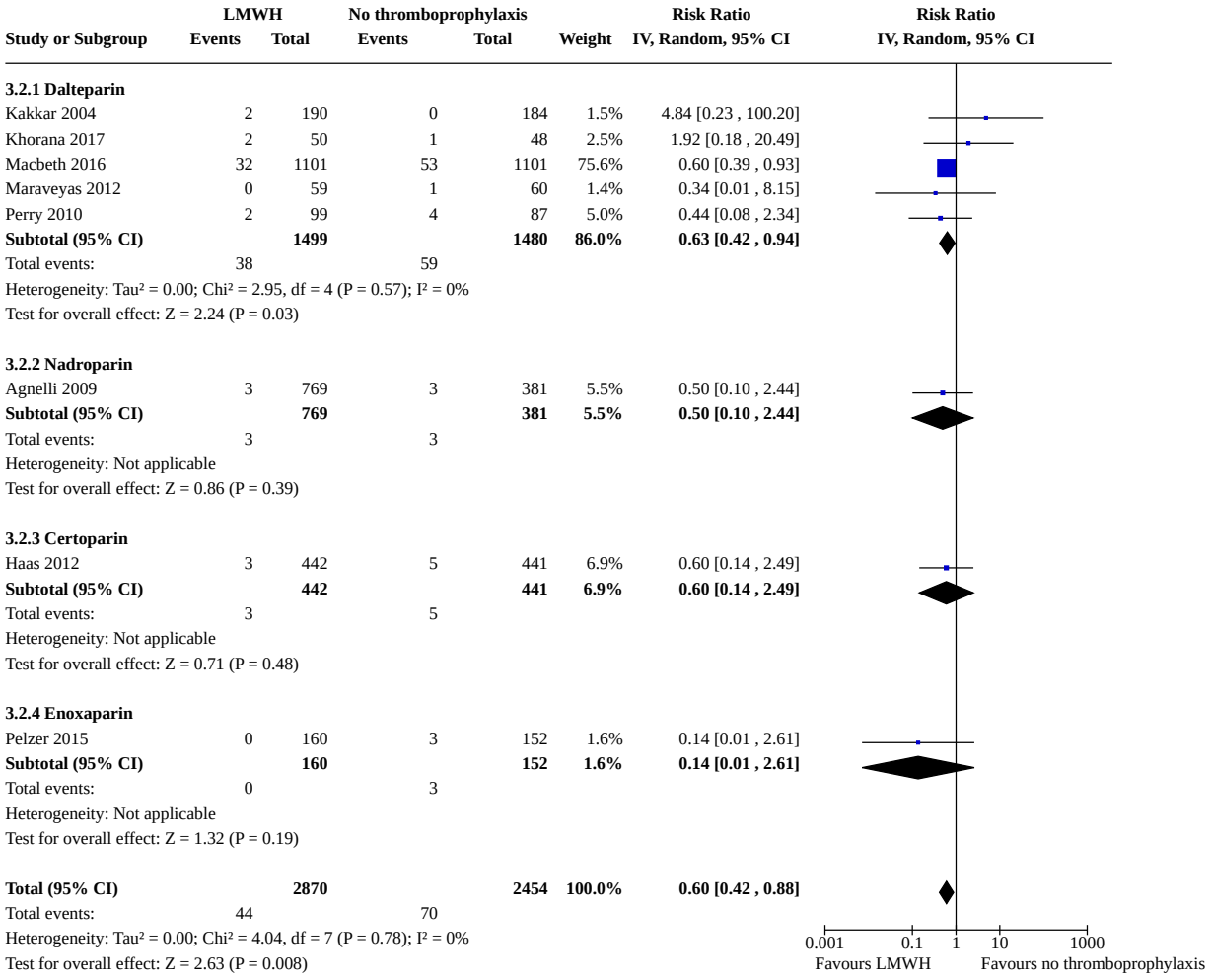
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.2 Rivaroxaban	1	841	Risk Ratio (IV, Random, 95% CI)	1.00 [0.29, 3.44]
3.2 Symptomatic PE: LMWH vs no thromboprophylaxis	8	5324	Risk Ratio (IV, Random, 95% CI)	0.60 [0.42, 0.88]
3.2.1 Dalteparin	5	2979	Risk Ratio (IV, Random, 95% CI)	0.63 [0.42, 0.94]
3.2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.50 [0.10, 2.44]
3.2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.60 [0.14, 2.49]
3.2.4 Enoxaparin	1	312	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.61]
3.3 Symptomatic PE: prophylactic vs intermediate or therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
3.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	2.89 [0.12, 67.75]
3.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	3.00 [0.13, 70.42]
3.4 Symptomatic PE: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.13 [0.02, 1.03]
3.5 Symptomatic PE: LMWH vs warfarin	1	439	Risk Ratio (IV, Fixed, 95% CI)	0.11 [0.01, 2.06]
3.6 Symptomatic PE: semuloparin vs placebo	1	3212	Risk Ratio (IV, Fixed, 95% CI)	0.48 [0.22, 1.01]
3.7 Symptomatic PE: vitamin K antagonists vs placebo	1	311	Risk Ratio (IV, Fixed, 95% CI)	1.05 [0.07, 16.58]
3.8 Symptomatic PE: warfarin vs aspirin	1	440	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.25, 3.95]

Analysis 3.1. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 1: Symptomatic PE: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Apixaban						
Carrier 2019	2	288	10	275	38.9%	0.19 [0.04 , 0.86]
Levine 2012	0	93	1	29	14.8%	0.11 [0.00 , 2.54]
Subtotal (95% CI)		**381**		**304**	**53.7%**	**0.17 [0.04 , 0.67]**
Total events:	2		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.54 (P = 0.01)						
3.1.2 Rivaroxaban						
Khorana 2019	5	420	5	421	46.3%	1.00 [0.29 , 3.44]
Subtotal (95% CI)		**420**		**421**	**46.3%**	**1.00 [0.29 , 3.44]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**801**		**725**	**100.0%**	**0.38 [0.10 , 1.47]**
Total events:	7		16			
Heterogeneity: Tau² = 0.65; Chi² = 3.65, df = 2 (P = 0.16); I² = 45%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 3.55, df = 1 (P = 0.06), I² = 71.8%						

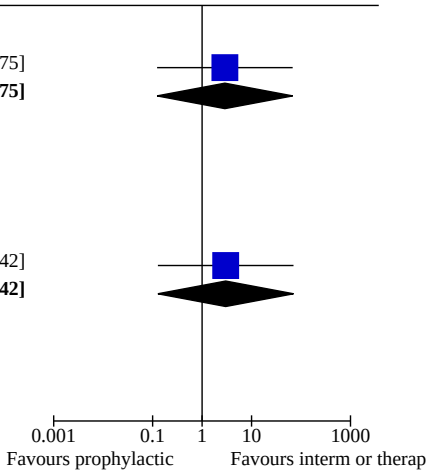


Analysis 3.2. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 2: Symptomatic PE: LMWH vs no thromboprophylaxis



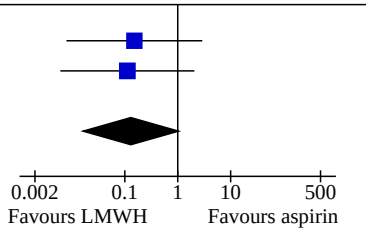
Analysis 3.3. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 3: Symptomatic PE: prophylactic vs intermediate or therapeutic LMWH

Study or Subgroup	Prophylactic Events	Prophylactic Total	Interm or therap Events	Interm or therap Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.3.1 Prophylactic vs intermediate						
Elit 2012	1	26	0	25	100.0%	2.89 [0.12 , 67.75]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**2.89 [0.12 , 67.75]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
3.3.2 Prophylactic vs therapeutic						
Elit 2012	1	26	0	26	100.0%	3.00 [0.13 , 70.42]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**3.00 [0.13 , 70.42]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



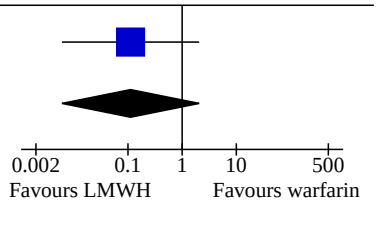
Analysis 3.4. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 4: Symptomatic PE: LMWH vs aspirin

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Random, 95% CI
Larocca 2012	0	166	3	176	49.3%	0.15 [0.01 , 2.91]
Palumbo 2011	0	219	4	220	50.7%	0.11 [0.01 , 2.06]
Total (95% CI)		**385**		**396**	**100.0%**	**0.13 [0.02 , 1.03]**
Total events:	0		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Not applicable						



Analysis 3.5. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 5: Symptomatic PE: LMWH vs warfarin

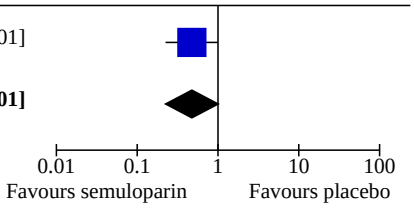
Study or Subgroup	LMWH Events	LMWH Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	0	219	4	220	100.0%	0.11 [0.01 , 2.06]
Total (95% CI)		**219**		**220**	**100.0%**	**0.11 [0.01 , 2.06]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
Test for subgroup differences: Not applicable						



Analysis 3.6. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 6: Symptomatic PE: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Semuloparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Agnelli 2012	10	1608	21	1604	100.0%	0.48 [0.22 , 1.01]
Total (95% CI)		**1608**		**1604**	**100.0%**	**0.48 [0.22 , 1.01]**
Total events:	10		21			

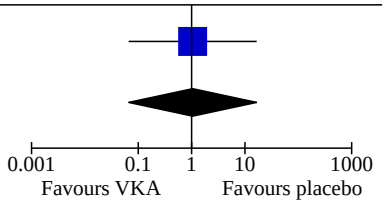
Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 7: Symptomatic PE: vitamin K antagonists vs placebo

Study or Subgroup	VKA Events	VKA Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Levine 1994	1	152	1	159	100.0%	1.05 [0.07 , 16.58]
Total (95% CI)		**152**		**159**	**100.0%**	**1.05 [0.07 , 16.58]**
Total events:	1		1			

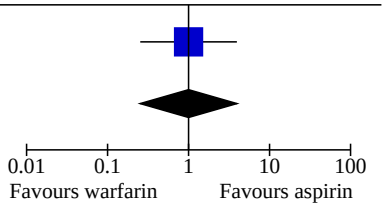
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Anticoagulants versus control: symptomatic pulmonary embolism, Outcome 8: Symptomatic PE: warfarin vs aspirin

Study or Subgroup	Warfarin Events	Warfarin Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	4	220	4	220	100.0%	1.00 [0.25 , 3.95]
Total (95% CI)		**220**		**220**	**100.0%**	**1.00 [0.25 , 3.95]**
Total events:	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



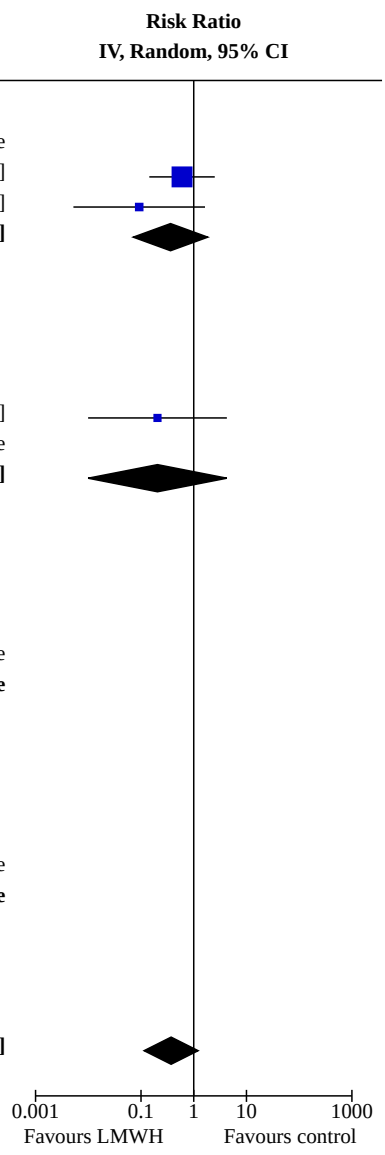
Comparison 4. Anticoagulants versus control: fatal PE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Fatal PE: LMWH vs no thromboprophylaxis	7	4286	Risk Ratio (IV, Random, 95% CI)	0.37 [0.11, 1.21]
4.1.1 Dalteparin	3	2419	Risk Ratio (IV, Random, 95% CI)	0.36 [0.07, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.2 Enoxaparin	2	679	Risk Ratio (IV, Random, 95% CI)	0.21 [0.01, 4.25]
4.1.3 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	Not estimable
4.1.4 Bemiparin	1	38	Risk Ratio (IV, Random, 95% CI)	Not estimable

Analysis 4.1. Comparison 4: Anticoagulants versus control: fatal PE, Outcome 1: Fatal PE: LMWH vs no thromboprophylaxis

Study or Subgroup	LMWH Events	LMWH Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 Dalteparin						
Khorana 2017	0	50	0	48		Not estimable
Macbeth 2016	3	1101	5	1101	68.0%	0.60 [0.14 , 2.50]
Maraveyas 2012	0	59	5	60	16.8%	0.09 [0.01 , 1.64]
Subtotal (95% CI)		**1210**		**1209**	**84.9%**	**0.36 [0.07 , 1.84]**
Total events:	3		10			
Heterogeneity: Tau² = 0.41; Chi² = 1.31, df = 1 (P = 0.25); I² = 23%						
Test for overall effect: Z = 1.22 (P = 0.22)						
4.1.2 Enoxaparin						
Ek 2018	0	186	2	191	15.1%	0.21 [0.01 , 4.25]
Pelzer 2015	0	150	0	152		Not estimable
Subtotal (95% CI)		**336**		**343**	**15.1%**	**0.21 [0.01 , 4.25]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
4.1.3 Nadroparin						
Agnelli 2009	0	769	0	381		Not estimable
Subtotal (95% CI)		**769**		**381**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.1.4 Bemiparin						
Lecumberri 2013	0	20	0	18		Not estimable
Subtotal (95% CI)		**20**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2335**		**1951**	**100.0%**	**0.37 [0.11 , 1.21]**
Total events:	3		12			
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.75), I² = 0%						

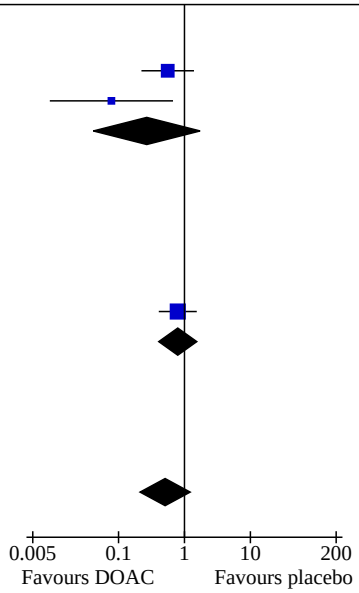


Comparison 5. Anticoagulants versus control: symptomatic deep vein thrombosis

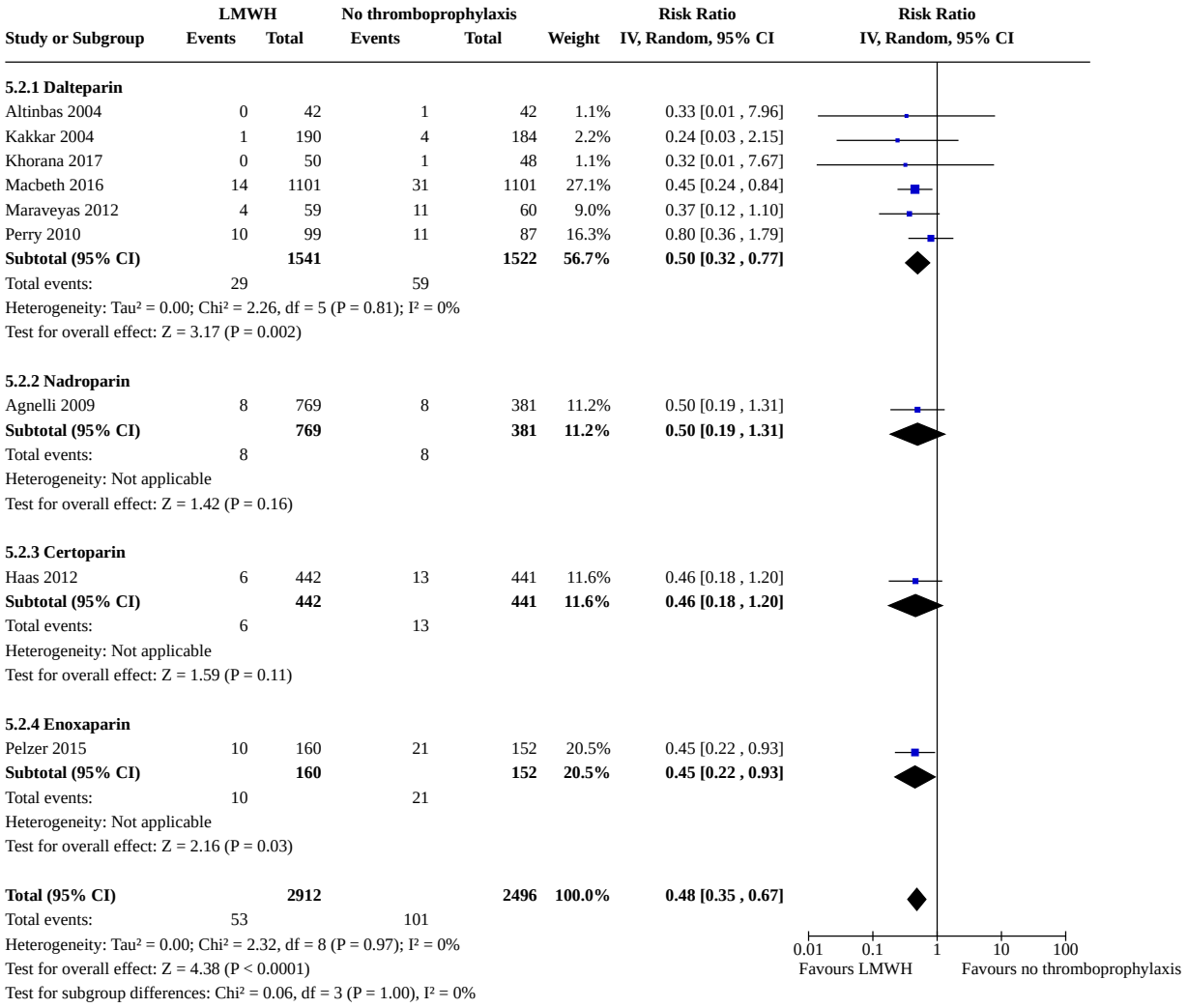
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Symptomatic DVT: DOAC vs placebo	3	1526	Risk Ratio (IV, Random, 95% CI)	0.51 [0.21, 1.22]
5.1.1 Apixaban	2	685	Risk Ratio (IV, Random, 95% CI)	0.27 [0.04, 1.73]
5.1.2 Rivaroxaban	1	841	Risk Ratio (IV, Random, 95% CI)	0.79 [0.41, 1.54]
5.2 Symptomatic DVT: LMWH vs no thromboprophylaxis	9	5408	Risk Ratio (IV, Random, 95% CI)	0.48 [0.35, 0.67]
5.2.1 Dalteparin	6	3063	Risk Ratio (IV, Random, 95% CI)	0.50 [0.32, 0.77]
5.2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.50 [0.19, 1.31]
5.2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.46 [0.18, 1.20]
5.2.4 Enoxaparin	1	312	Risk Ratio (IV, Random, 95% CI)	0.45 [0.22, 0.93]
5.3 Symptomatic DVT: prophylactic vs intermediate or therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
5.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
5.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	0.33 [0.01, 7.82]
5.4 Symptomatic DVT: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.81 [0.32, 2.04]
5.5 Symptomatic DVT: LMWH vs warfarin	1	439	Risk Ratio (IV, Fixed, 95% CI)	0.43 [0.17, 1.10]
5.6 Symptomatic DVT: semuloparin vs placebo	1	3212	Risk Ratio (IV, Fixed, 95% CI)	0.32 [0.16, 0.63]
5.7 Symptomatic DVT: vitamin K antagonists vs placebo	1	311	Risk Ratio (IV, Fixed, 95% CI)	0.08 [0.00, 1.42]
5.8 Symptomatic DVT: warfarin vs aspirin	1	440	Risk Ratio (IV, Fixed, 95% CI)	1.75 [0.75, 4.09]

Analysis 5.1. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 1: Symptomatic DVT: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
5.1.1 Apixaban						
Carrier 2019	7	288	12	275	38.5%	0.56 [0.22 , 1.39]
Levine 2012	1	93	4	29	13.2%	0.08 [0.01 , 0.67]
Subtotal (95% CI)		**381**		**304**	**51.7%**	**0.27 [0.04 , 1.73]**
Total events:	8		16			
Heterogeneity: Tau² = 1.22; Chi² = 2.72, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 1.39 (P = 0.17)						
5.1.2 Rivaroxaban						
Khorana 2019	15	420	19	421	48.3%	0.79 [0.41 , 1.54]
Subtotal (95% CI)		**420**		**421**	**48.3%**	**0.79 [0.41 , 1.54]**
Total events:	15		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**801**		**725**	**100.0%**	**0.51 [0.21 , 1.22]**
Total events:	23		35			
Heterogeneity: Tau² = 0.30; Chi² = 4.14, df = 2 (P = 0.13); I² = 52%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Chi² = 1.15, df = 1 (P = 0.28), I² = 13.3%						

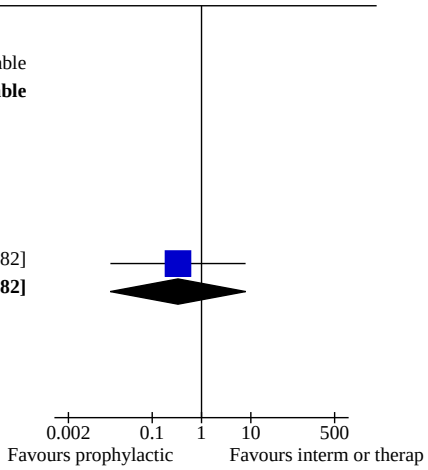


Analysis 5.2. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 2: Symptomatic DVT: LMWH vs no thromboprophylaxis



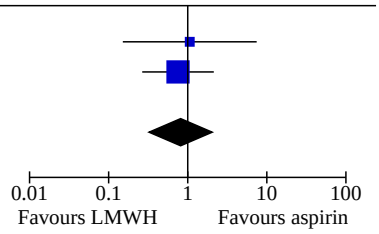
Analysis 5.3. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 3: Symptomatic DVT: prophylactic vs intermediate or therapeutic LMWH

Study or Subgroup	Prophylactic Events	Prophylactic Total	Intermed or therap Events	Intermed or therap Total	Weight	Risk Ratio IV, Fixed, 95% CI
5.3.1 Prophylactic vs intermediate						
Elit 2012	0	26	0	25		Not estimable
Subtotal (95% CI)		**26**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.3.2 Prophylactic vs therapeutic						
Elit 2012	0	26	1	26	100.0%	0.33 [0.01 , 7.82]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**0.33 [0.01 , 7.82]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



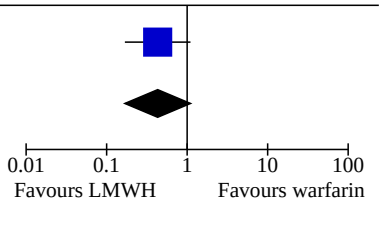
Analysis 5.4. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 4: Symptomatic DVT: LMWH vs aspirin

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Random, 95% CI
Larocca 2012	2	166	2	176	22.2%	1.06 [0.15 , 7.44]
Palumbo 2011	6	219	8	220	77.8%	0.75 [0.27 , 2.14]
Total (95% CI)		**385**		**396**	**100.0%**	**0.81 [0.32 , 2.04]**
Total events:	8		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Not applicable						



Analysis 5.5. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 5: Symptomatic DVT: LMWH vs warfarin

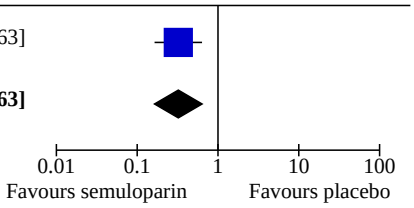
Study or Subgroup	LMWH Events	LMWH Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	6	219	14	220	100.0%	0.43 [0.17 , 1.10]
Total (95% CI)		**219**		**220**	**100.0%**	**0.43 [0.17 , 1.10]**
Total events:	6		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Not applicable						



Analysis 5.6. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 6: Symptomatic DVT: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Semuloparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Agnelli 2012	11	1608	34	1604	100.0%	0.32 [0.16 , 0.63]
Total (95% CI)		**1608**		**1604**	**100.0%**	**0.32 [0.16 , 0.63]**
Total events:	11		34			

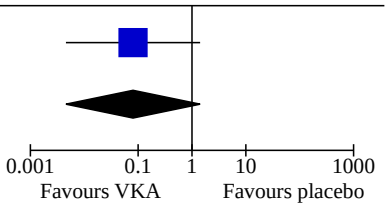
Heterogeneity: Not applicable
Test for overall effect: Z = 3.28 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 5.7. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 7: Symptomatic DVT: vitamin K antagonists vs placebo

Study or Subgroup	VKA Events	VKA Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Levine 1994	0	152	6	159	100.0%	0.08 [0.00 , 1.42]
Total (95% CI)		**152**		**159**	**100.0%**	**0.08 [0.00 , 1.42]**
Total events:	0		6			

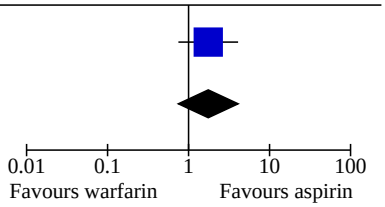
Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 5.8. Comparison 5: Anticoagulants versus control: symptomatic deep vein thrombosis, Outcome 8: Symptomatic DVT: warfarin vs aspirin

Study or Subgroup	Warfarin Events	Warfarin Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	14	220	8	220	100.0%	1.75 [0.75 , 4.09]
Total (95% CI)		**220**		**220**	**100.0%**	**1.75 [0.75 , 4.09]**
Total events:	14		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable

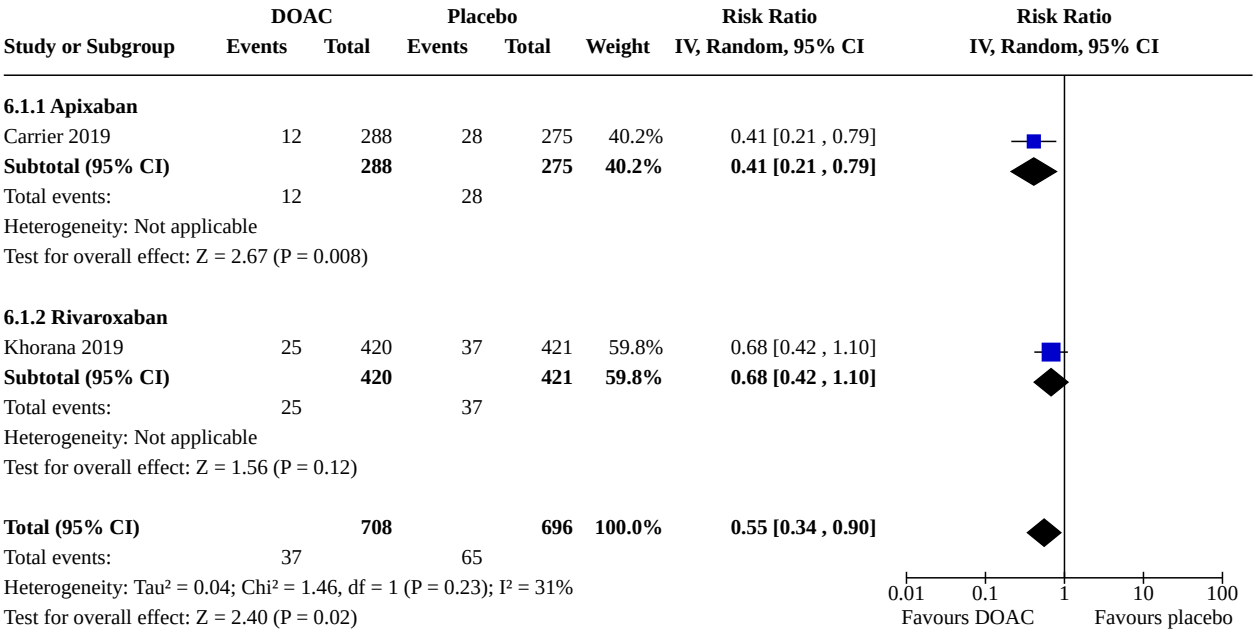


Comparison 6. Anticoagulants versus control: any venous thromboembolism

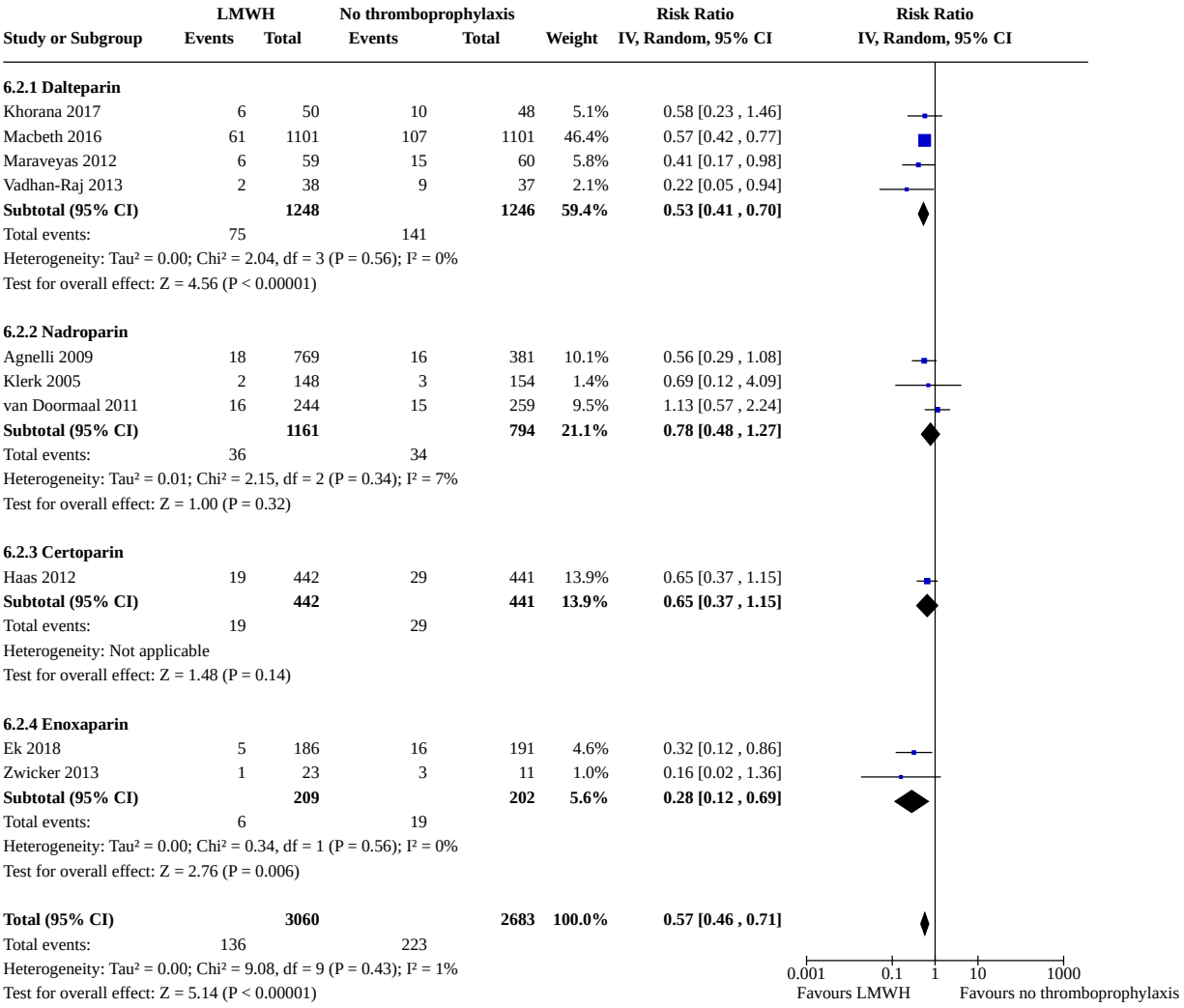
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Any VTE: DOAC vs placebo	2	1404	Risk Ratio (IV, Random, 95% CI)	0.55 [0.34, 0.90]
6.1.1 Apixaban	1	563	Risk Ratio (IV, Random, 95% CI)	0.41 [0.21, 0.79]
6.1.2 Rivaroxaban	1	841	Risk Ratio (IV, Random, 95% CI)	0.68 [0.42, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Any VTE: LMWH vs no thromboprophylaxis	10	5743	Risk Ratio (IV, Random, 95% CI)	0.57 [0.46, 0.71]
6.2.1 Dalteparin	4	2494	Risk Ratio (IV, Random, 95% CI)	0.53 [0.41, 0.70]
6.2.2 Nadroparin	3	1955	Risk Ratio (IV, Random, 95% CI)	0.78 [0.48, 1.27]
6.2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.65 [0.37, 1.15]
6.2.4 Enoxaparin	2	411	Risk Ratio (IV, Random, 95% CI)	0.28 [0.12, 0.69]
6.3 Any VTE: prophylactic vs intermediate vs therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	4.81 [0.24, 95.58]
6.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	5.00 [0.25, 99.34]
6.4 Any VTE: semuloparin vs placebo	1	3212	Risk Ratio (IV, Fixed, 95% CI)	0.36 [0.22, 0.60]

Analysis 6.1. Comparison 6: Anticoagulants versus control: any venous thromboembolism, Outcome 1: Any VTE: DOAC vs placebo

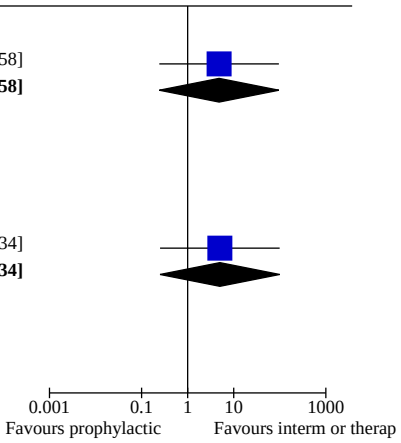


Analysis 6.2. Comparison 6: Anticoagulants versus control: any venous thromboembolism, Outcome 2: Any VTE: LMWH vs no thromboprophylaxis



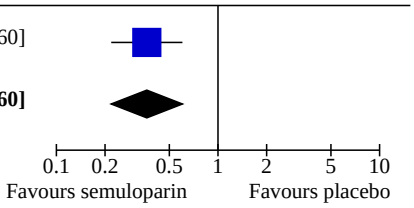
Analysis 6.3. Comparison 6: Anticoagulants versus control: any venous thromboembolism, Outcome 3: Any VTE: prophylactic vs intermediate vs therapeutic LMWH

Study or Subgroup	Favours prophylactic Events	Total	Interm or therapeutic Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
6.3.1 Prophylactic vs intermediate						
Elit 2012	2	26	0	25	100.0%	4.81 [0.24 , 95.58]
Subtotal (95% CI)		**26**		**25**	**100.0%**	**4.81 [0.24 , 95.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
6.3.2 Prophylactic vs therapeutic						
Elit 2012	2	26	0	26	100.0%	5.00 [0.25 , 99.34]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**5.00 [0.25 , 99.34]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



Analysis 6.4. Comparison 6: Anticoagulants versus control: any venous thromboembolism, Outcome 4: Any VTE: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Agnelli 2012	20	1608	55	1604	100.0%	0.36 [0.22 , 0.60]
Total (95% CI)		**1608**		**1604**	**100.0%**	**0.36 [0.22 , 0.60]**
Total events:	20		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.92 (P < 0.0001)						
Test for subgroup differences: Not applicable						



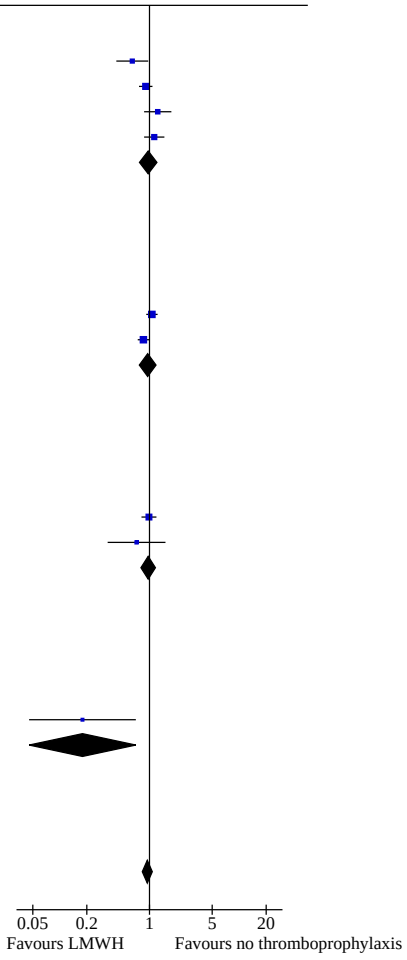
Comparison 7. Anticoagulants versus control: 1-year overall mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 1-year overall mortality: LMWH vs no thromboprophylaxis	9	2681	Risk Ratio (IV, Random, 95% CI)	0.94 [0.83, 1.07]
7.1.1 Dalteparin	4	782	Risk Ratio (IV, Random, 95% CI)	0.97 [0.77, 1.21]
7.1.2 Nadroparin	2	1452	Risk Ratio (IV, Random, 95% CI)	0.95 [0.77, 1.18]
7.1.3 Enoxaparin	2	411	Risk Ratio (IV, Random, 95% CI)	0.97 [0.80, 1.16]
7.1.4 Bemiparin	1	36	Risk Ratio (IV, Random, 95% CI)	0.18 [0.05, 0.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 1-year overall mortality: semuloparin vs placebo	1	3212	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.96, 1.08]
7.3 1-year overall mortality: UFH vs no thromboprophylaxis	1	277	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.72, 1.03]

Analysis 7.1. Comparison 7: Anticoagulants versus control: 1-year overall mortality, Outcome 1: 1-year overall mortality: LMWH vs no thromboprophylaxis

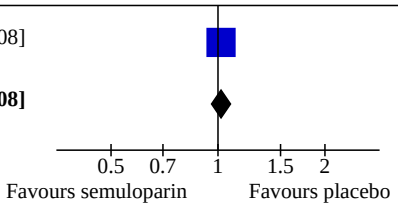
Study or Subgroup	LMWH Events	LMWH Total	No thromboprophylaxis Events	No thromboprophylaxis Total	Weight	Risk Ratio IV, Random, 95% CI
7.1.1 Dalteparin						
Altinbas 2004	18	42	28	42	7.0%	0.64 [0.43 , 0.97]
Kakkar 2004	105	190	112	184	16.7%	0.91 [0.76 , 1.08]
Perry 2010	45	99	32	87	8.6%	1.24 [0.87 , 1.75]
Sideras 2006	45	68	41	70	12.1%	1.13 [0.87 , 1.47]
Subtotal (95% CI)		**399**		**383**	**44.3%**	**0.97 [0.77 , 1.21]**
Total events:	213		213			
Heterogeneity: Tau² = 0.03; Chi² = 7.59, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 0.29 (P = 0.77)						
7.1.2 Nadroparin						
Agnelli 2009	333	769	155	381	18.3%	1.06 [0.92 , 1.23]
Klerk 2005	97	148	118	154	18.3%	0.86 [0.74 , 0.99]
Subtotal (95% CI)		**917**		**535**	**36.6%**	**0.95 [0.77 , 1.18]**
Total events:	430		273			
Heterogeneity: Tau² = 0.02; Chi² = 4.32, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.43 (P = 0.67)						
7.1.3 Enoxaparin						
Ek 2018	97	186	101	191	15.6%	0.99 [0.81 , 1.19]
Zwicker 2013	9	23	6	11	2.7%	0.72 [0.34 , 1.51]
Subtotal (95% CI)		**209**		**202**	**18.2%**	**0.97 [0.80 , 1.16]**
Total events:	106		107			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
7.1.4 Bemiparin						
Lecumberri 2013	2	19	10	17	0.8%	0.18 [0.05 , 0.70]
Subtotal (95% CI)		**19**		**17**	**0.8%**	**0.18 [0.05 , 0.70]**
Total events:	2		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.46 (P = 0.01)						
Total (95% CI)		**1544**		**1137**	**100.0%**	**0.94 [0.83 , 1.07]**
Total events:	751		603			
Heterogeneity: Tau² = 0.02; Chi² = 18.35, df = 8 (P = 0.02); I² = 56%						
Test for overall effect: Z = 0.87 (P = 0.39)						
Test for subgroup differences: Chi² = 5.76, df = 3 (P = 0.12), I² = 48.0%						



Analysis 7.2. Comparison 7: Anticoagulants versus control: 1-year overall mortality, Outcome 2: 1-year overall mortality: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Agnelli 2012	910	1608	890	1604	100.0%	1.02 [0.96 , 1.08]
Total (95% CI)		**1608**		**1604**	**100.0%**	**1.02 [0.96 , 1.08]**
Total events:	910		890			

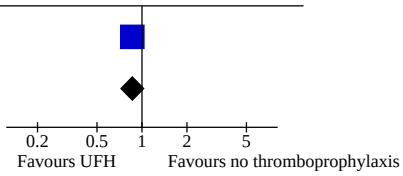
Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Anticoagulants versus control: 1-year overall mortality, Outcome 3: 1-year overall mortality: UFH vs no thromboprophylaxis

Study or Subgroup	UFH Events	Total	No thromboprophylaxis Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Lebeau 1994	83	138	97	139	100.0%	0.86 [0.72 , 1.03]
Total (95% CI)		**138**		**139**	**100.0%**	**0.86 [0.72 , 1.03]**
Total events:	83		97			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



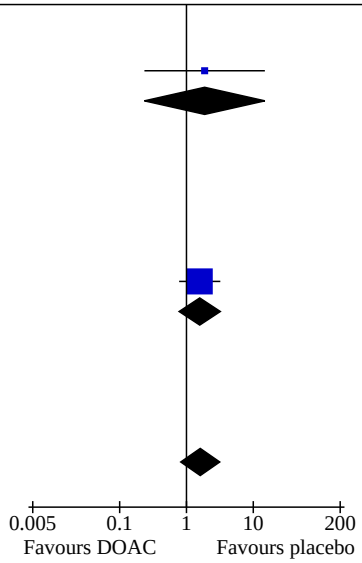
Comparison 8. Anticoagulants versus control: clinically relevant bleeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Clinically relevant bleeding: DOAC vs placebo	2	931	Risk Ratio (IV, Random, 95% CI)	1.61 [0.82, 3.15]
8.1.1 Apixaban	1	122	Risk Ratio (IV, Random, 95% CI)	1.87 [0.23, 14.91]
8.1.2 Rivaroxaban	1	809	Risk Ratio (IV, Random, 95% CI)	1.58 [0.78, 3.21]
8.2 Clinically relevant bleeding: LMWH vs no thromboprophylaxis	4	3105	Risk Ratio (IV, Random, 95% CI)	3.40 [1.20, 9.63]
8.3 Clinically relevant bleeding: prophylactic vs intermediate vs therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
8.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
8.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	0.33 [0.01, 7.82]
8.4 Clinically relevant bleeding: semuloparin vs placebo	1	3172	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.90, 2.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 Clinically relevant bleeding: UFH vs no thromboprophylaxis	1	277	Risk Ratio (IV, Fixed, 95% CI)	2.01 [0.18, 21.96]

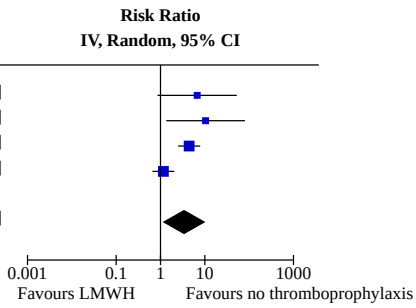
Analysis 8.1. Comparison 8: Anticoagulants versus control: clinically relevant bleeding, Outcome 1: Clinically relevant bleeding: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
8.1.1 Apixaban						
Levine 2012	6	93	1	29	10.5%	1.87 [0.23 , 14.91]
Subtotal (95% CI)		**93**		**29**	**10.5%**	**1.87 [0.23 , 14.91]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
8.1.2 Rivaroxaban						
Khorana 2019	19	405	12	404	89.5%	1.58 [0.78 , 3.21]
Subtotal (95% CI)		**405**		**404**	**89.5%**	**1.58 [0.78 , 3.21]**
Total events:	19		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)		**498**		**433**	**100.0%**	**1.61 [0.82 , 3.15]**
Total events:	25		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.17)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



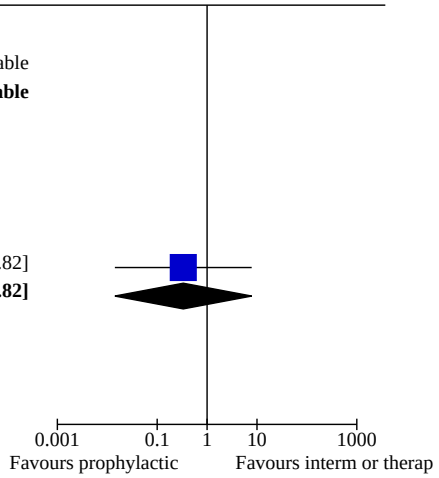
Analysis 8.2. Comparison 8: Anticoagulants versus control: clinically relevant bleeding, Outcome 2: Clinically relevant bleeding: LMWH vs no thromboprophylaxis

Study or Subgroup	LMWH Events	LMWH Total	No thromboprophylaxis Events	No thromboprophylaxis Total	Weight	Risk Ratio IV, Random, 95% CI
Khorana 2017	7	50	1	48	15.4%	6.72 [0.86 , 52.59]
Klerk 2005	10	148	1	154	15.5%	10.41 [1.35 , 80.28]
Macbeth 2016	62	1101	14	1101	34.5%	4.43 [2.49 , 7.86]
van Doormaal 2011	23	244	21	259	34.6%	1.16 [0.66 , 2.05]
Total (95% CI)		**1543**		**1562**	**100.0%**	**3.40 [1.20 , 9.63]**
Total events:	102		37			
Heterogeneity: Tau² = 0.73; Chi² = 13.62, df = 3 (P = 0.003); I² = 78%						
Test for overall effect: Z = 2.30 (P = 0.02)						
Test for subgroup differences: Not applicable						



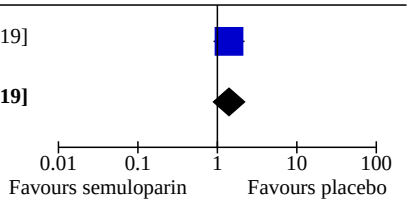
Analysis 8.3. Comparison 8: Anticoagulants versus control: clinically relevant bleeding, Outcome 3: Clinically relevant bleeding: prophylactic vs intermediate vs therapeutic LMWH

Study or Subgroup	Prophylactic Events	Prophylactic Total	Interm or therap Events	Interm or therap Total	Weight	Risk Ratio IV, Fixed, 95% CI
8.3.1 Prophylactic vs intermediate						
Elit 2012	0	26	0	25		Not estimable
Subtotal (95% CI)		**26**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.3.2 Prophylactic vs therapeutic						
Elit 2012	0	26	1	26	100.0%	0.33 [0.01 , 7.82]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**0.33 [0.01 , 7.82]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



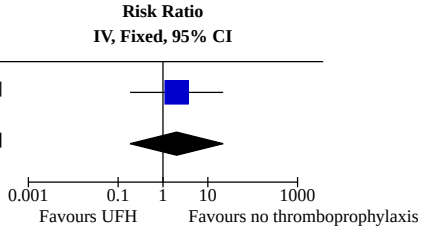
Analysis 8.4. Comparison 8: Anticoagulants versus control: clinically relevant bleeding, Outcome 4: Clinically relevant bleeding: semuloparin vs placebo

Study or Subgroup	Semuloparin Events	Semuloparin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agnelli 2012	45	1589	32	1583	100.0%	1.40 [0.90 , 2.19]
Total (95% CI)		**1589**		**1583**	**100.0%**	**1.40 [0.90 , 2.19]**
Total events:	45		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Not applicable						



Analysis 8.5. Comparison 8: Anticoagulants versus control: clinically relevant bleeding, Outcome 5: Clinically relevant bleeding: UFH vs no thromboprophylaxis

Study or Subgroup	UFH Events	UFH Total	No thromboprophylaxis Events	No thromboprophylaxis Total	Weight	Risk Ratio IV, Fixed, 95% CI
Lebeau 1994	2	138	1	139	100.0%	2.01 [0.18 , 21.96]
Total (95% CI)		**138**		**139**	**100.0%**	**2.01 [0.18 , 21.96]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Not applicable						

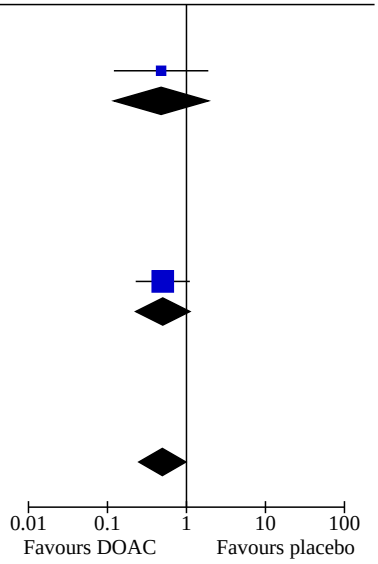


Comparison 9. Anticoagulants versus control: incidental venous thromboembolism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Incidental VTE: DOAC vs placebo	2	1404	Risk Ratio (IV, Random, 95% CI)	0.50 [0.25, 0.98]
9.1.1 Apixaban	1	563	Risk Ratio (IV, Random, 95% CI)	0.48 [0.12, 1.89]
9.1.2 Rivaroxaban	1	841	Risk Ratio (IV, Random, 95% CI)	0.50 [0.23, 1.10]
9.2 Incidental VTE: LMWH vs no thromboprophylaxis	5	4452	Risk Ratio (IV, Random, 95% CI)	0.63 [0.40, 0.99]
9.2.1 Dalteparin	3	2419	Risk Ratio (IV, Random, 95% CI)	0.58 [0.34, 1.00]
9.2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.74 [0.21, 2.62]
9.2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.75 [0.26, 2.14]
9.3 Incidental VTE: prophylactic vs intermediate or therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
9.3.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	2.89 [0.12, 67.75]
9.3.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	3.00 [0.13, 70.42]
9.4 Incidental VTE: semuloparin vs placebo	1	3212	Risk Ratio (IV, Fixed, 95% CI)	0.14 [0.01, 2.76]

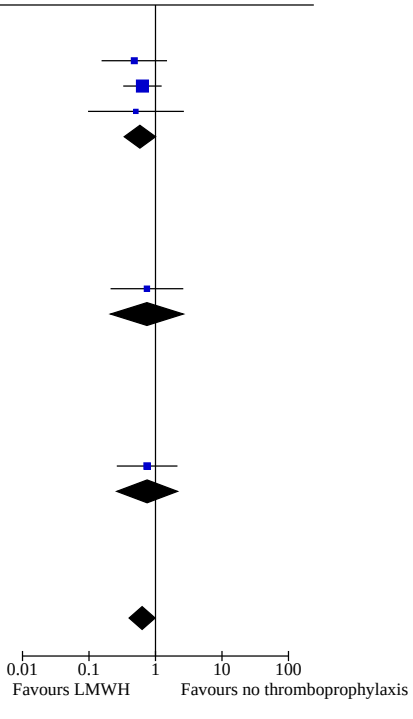
Analysis 9.1. Comparison 9: Anticoagulants versus control: incidental venous thromboembolism, Outcome 1: Incidental VTE: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.1.1 Apixaban						
Carrier 2019	3	288	6	275	24.7%	0.48 [0.12 , 1.89]
Subtotal (95% CI)		**288**		**275**	**24.7%**	**0.48 [0.12 , 1.89]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
9.1.2 Rivaroxaban						
Khorana 2019	9	420	18	421	75.3%	0.50 [0.23 , 1.10]
Subtotal (95% CI)		**420**		**421**	**75.3%**	**0.50 [0.23 , 1.10]**
Total events:	9		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
Total (95% CI)		**708**		**696**	**100.0%**	**0.50 [0.25 , 0.98]**
Total events:	12		24			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						

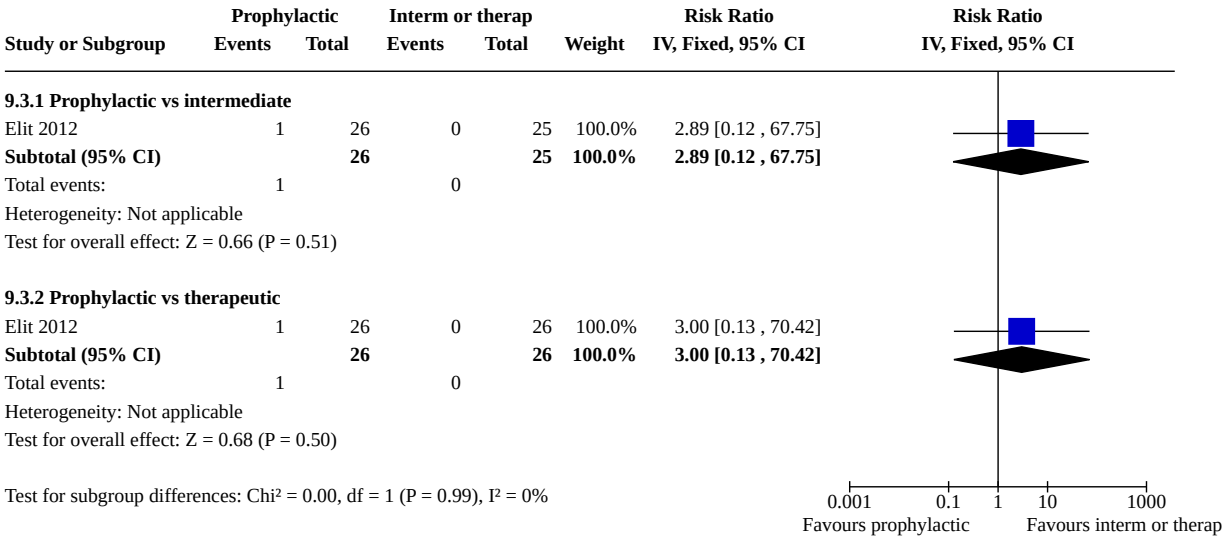


Analysis 9.2. Comparison 9: Anticoagulants versus control: incidental venous thromboembolism, Outcome 2: Incidental VTE: LMWH vs no thromboprophylaxis

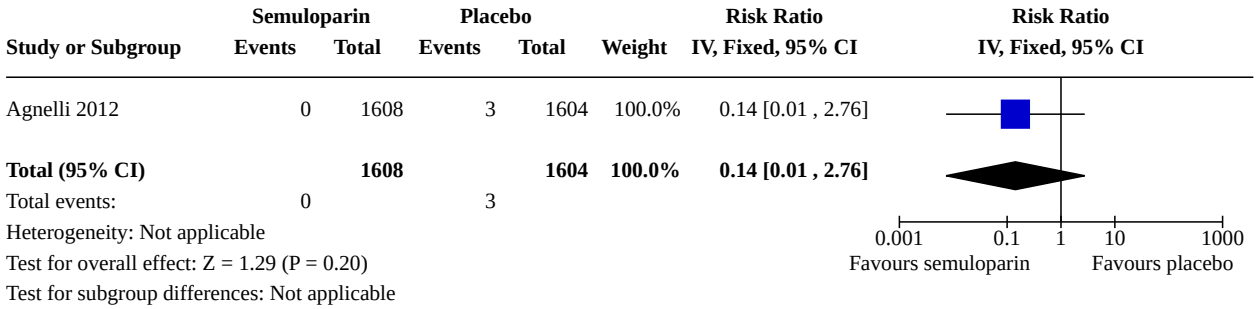
Study or Subgroup	LMWH Events	LMWH Total	No thromboprophylaxis Events	No thromboprophylaxis Total	Weight	Risk Ratio IV, Random, 95% CI
9.2.1 Dalteparin						
Khorana 2017	4	50	8	48	15.8%	0.48 [0.15 , 1.49]
Macbeth 2016	14	1101	22	1101	45.8%	0.64 [0.33 , 1.24]
Maraveyas 2012	2	59	4	60	7.4%	0.51 [0.10 , 2.67]
Subtotal (95% CI)		**1210**		**1209**	**68.9%**	**0.58 [0.34 , 1.00]**
Total events:	20		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.95 (P = 0.05)						
9.2.2 Nadroparin						
Agnelli 2009	6	769	4	381	12.8%	0.74 [0.21 , 2.62]
Subtotal (95% CI)		**769**		**381**	**12.8%**	**0.74 [0.21 , 2.62]**
Total events:	6		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
9.2.3 Certoparin						
Haas 2012	6	442	8	441	18.3%	0.75 [0.26 , 2.14]
Subtotal (95% CI)		**442**		**441**	**18.3%**	**0.75 [0.26 , 2.14]**
Total events:	6		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**2421**		**2031**	**100.0%**	**0.63 [0.40 , 0.99]**
Total events:	32		46			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 0.25, df = 2 (P = 0.88), I² = 0%						



Analysis 9.3. Comparison 9: Anticoagulants versus control: incidental venous thromboembolism, Outcome 3: Incidental VTE: prophylactic vs intermediate or therapeutic LMWH



Analysis 9.4. Comparison 9: Anticoagulants versus control: incidental venous thromboembolism, Outcome 4: Incidental VTE: semuloparin vs placebo

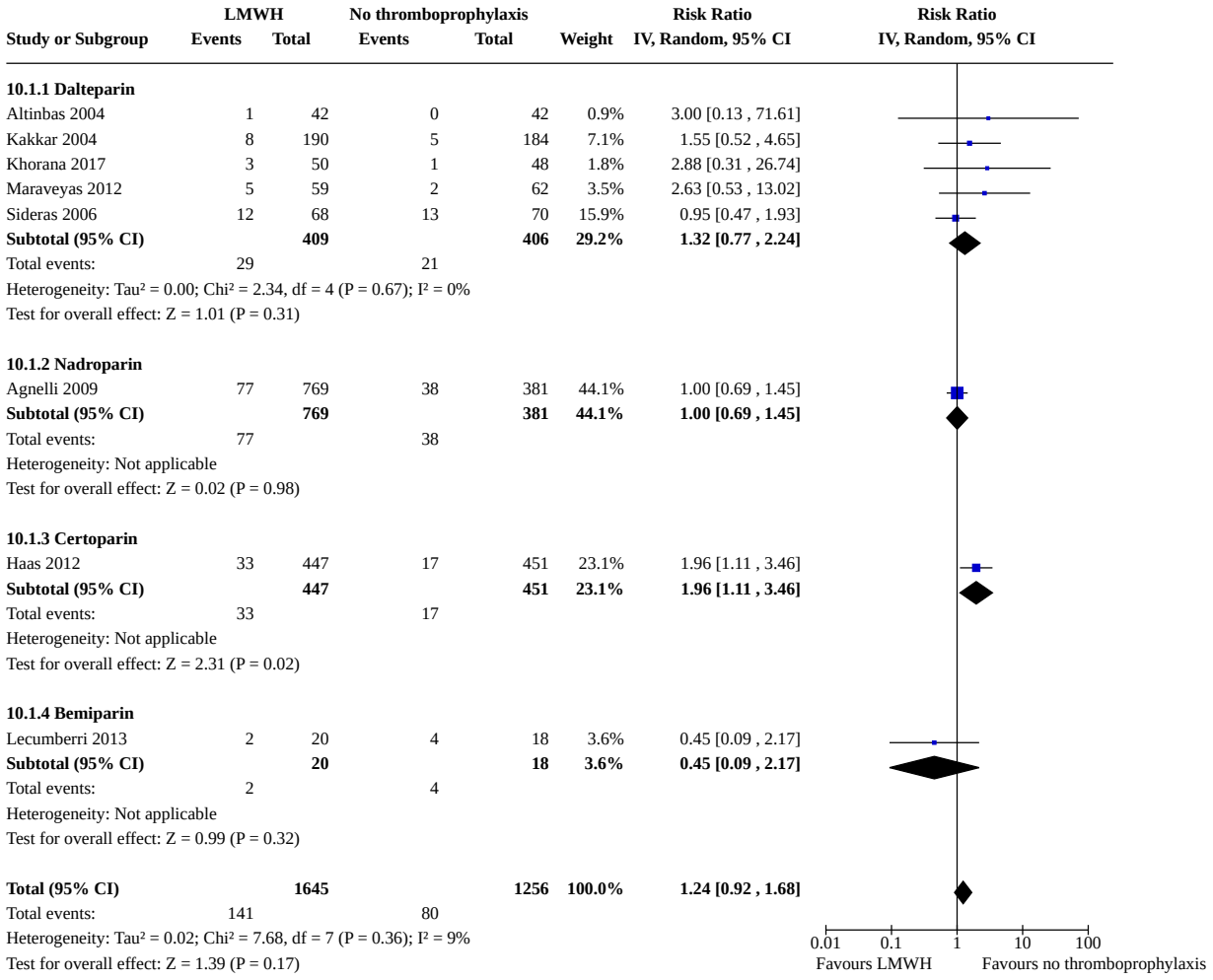


Comparison 10. Anticoagulants versus control: minor bleeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Minor bleeding: LMWH vs no thromboprophylaxis	8	2901	Risk Ratio (IV, Random, 95% CI)	1.24 [0.92, 1.68]
10.1.1 Dalteparin	5	815	Risk Ratio (IV, Random, 95% CI)	1.32 [0.77, 2.24]
10.1.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	1.00 [0.69, 1.45]
10.1.3 Certoparin	1	898	Risk Ratio (IV, Random, 95% CI)	1.96 [1.11, 3.46]

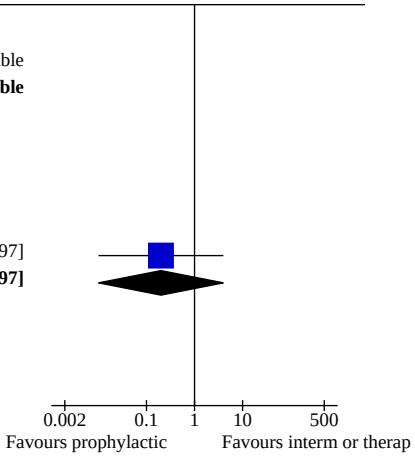
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1.4 Bemiparin	1	38	Risk Ratio (IV, Random, 95% CI)	0.45 [0.09, 2.17]
10.2 Minor bleeding: prophylactic vs intermediate or therapeutic LMWH	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
10.2.1 Prophylactic vs intermediate	1	51	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
10.2.2 Prophylactic vs therapeutic	1	52	Risk Ratio (IV, Fixed, 95% CI)	0.20 [0.01, 3.97]
10.3 Minor bleeding: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.70 [0.17, 2.84]
10.4 Minor bleeding: LMWH vs warfarin	1	439	Risk Ratio (IV, Fixed, 95% CI)	3.01 [0.32, 28.75]
10.5 Minor bleeding: UFH vs no thromboprophylaxis	1	277	Risk Ratio (IV, Fixed, 95% CI)	3.02 [0.12, 73.54]
10.6 Minor bleeding: vitamin K antagonists vs placebo	1	311	Risk Ratio (IV, Fixed, 95% CI)	2.44 [0.64, 9.27]
10.7 Minor bleeding: warfarin vs aspirin	1	440	Risk Ratio (IV, Fixed, 95% CI)	0.17 [0.02, 1.37]

Analysis 10.1. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 1: Minor bleeding: LMWH vs no thromboprophylaxis



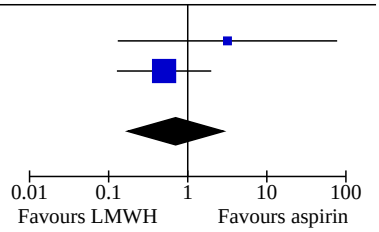
Analysis 10.2. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 2: Minor bleeding: prophylactic vs intermediate or therapeutic LMWH

Study or Subgroup	Prophylactic Events	Prophylactic Total	Intermediate or therap Events	Intermediate or therap Total	Weight	Risk Ratio IV, Fixed, 95% CI
10.2.1 Prophylactic vs intermediate						
Elit 2012	0	26	0	25		Not estimable
Subtotal (95% CI)		**26**		**25**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.2.2 Prophylactic vs therapeutic						
Elit 2012	0	26	2	26	100.0%	0.20 [0.01 , 3.97]
Subtotal (95% CI)		**26**		**26**	**100.0%**	**0.20 [0.01 , 3.97]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						



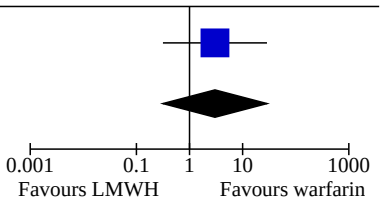
Analysis 10.3. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 3: Minor bleeding: LMWH vs aspirin

Study or Subgroup	LMWH Events	LMWH Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Random, 95% CI
Larocca 2012	1	166	0	176	18.2%	3.18 [0.13 , 77.51]
Palumbo 2011	3	219	6	220	81.8%	0.50 [0.13 , 1.98]
Total (95% CI)		**385**		**396**	**100.0%**	**0.70 [0.17 , 2.84]**
Total events:	4		6			
Heterogeneity: Tau² = 0.13; Chi² = 1.08, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Not applicable						

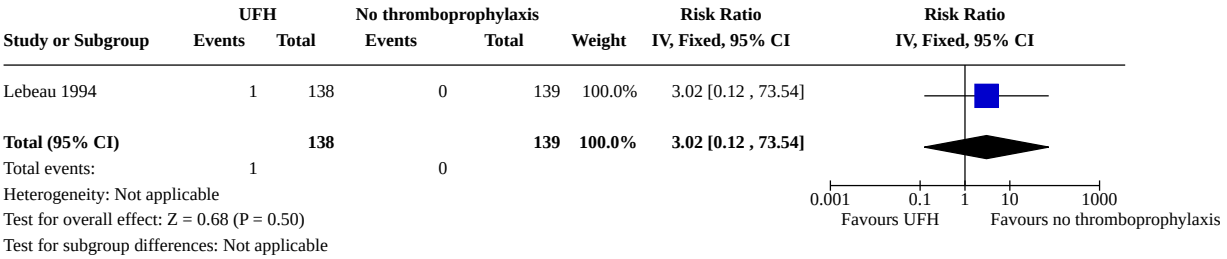


Analysis 10.4. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 4: Minor bleeding: LMWH vs warfarin

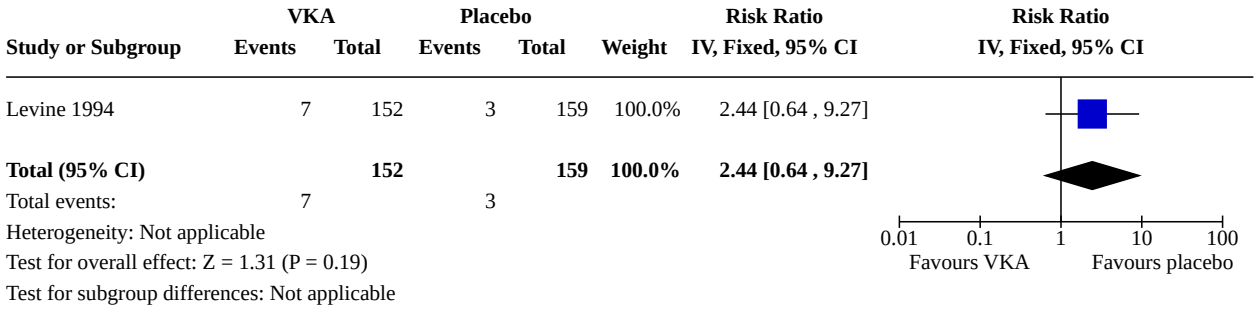
Study or Subgroup	LMWH Events	LMWH Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	3	219	1	220	100.0%	3.01 [0.32 , 28.75]
Total (95% CI)		**219**		**220**	**100.0%**	**3.01 [0.32 , 28.75]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Not applicable						



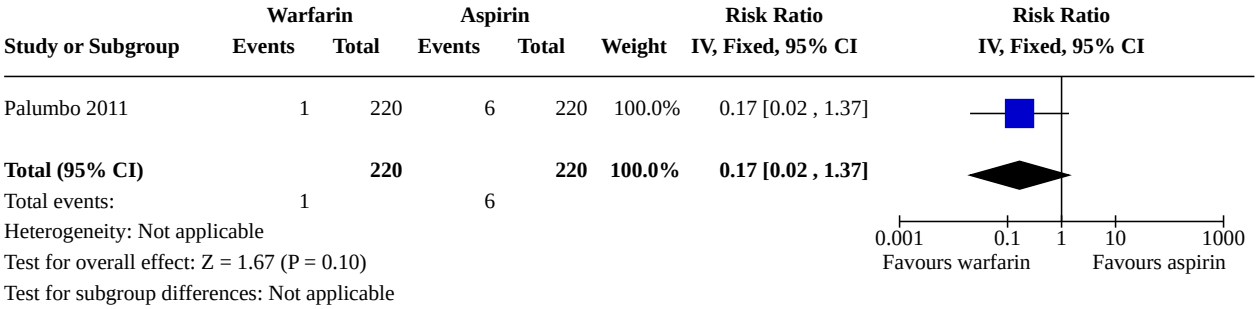
Analysis 10.5. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 5: Minor bleeding: UFH vs no thromboprophylaxis



Analysis 10.6. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 6: Minor bleeding: vitamin K antagonists vs placebo



Analysis 10.7. Comparison 10: Anticoagulants versus control: minor bleeding, Outcome 7: Minor bleeding: warfarin vs aspirin



Comparison 11. Anticoagulants versus control: symptomatic arterial thromboembolism

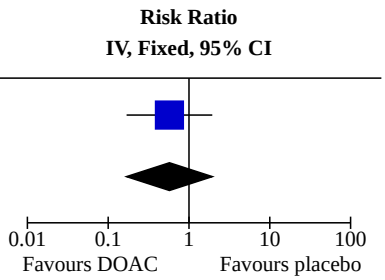
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Symptomatic arterial thromboembolism: DOAC vs placebo	1	841	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.17, 1.94]
11.2 Symptomatic arterial thromboembolism: LMWH vs no thromboprophylaxis	5	4351	Risk Ratio (IV, Random, 95% CI)	0.78 [0.49, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2.1 Dalteparin	2	2321	Risk Ratio (IV, Random, 95% CI)	0.90 [0.52, 1.53]
11.2.2 Nadroparin	2	1653	Risk Ratio (IV, Random, 95% CI)	0.38 [0.14, 1.03]
11.2.3 Enoxaparin	1	377	Risk Ratio (IV, Random, 95% CI)	1.54 [0.26, 9.11]
11.3 Symptomatic arterial thromboembolism: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	2.01 [0.37, 10.86]
11.4 Symptomatic arterial thromboembolism: LMWH vs warfarin	1	439	Risk Ratio (IV, Fixed, 95% CI)	9.04 [0.49, 166.92]
11.5 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo	1	311	Risk Ratio (IV, Fixed, 95% CI)	Not estimable
11.6 Symptomatic arterial thromboembolism: warfarin vs aspirin	1	440	Risk Ratio (IV, Fixed, 95% CI)	0.20 [0.01, 4.14]

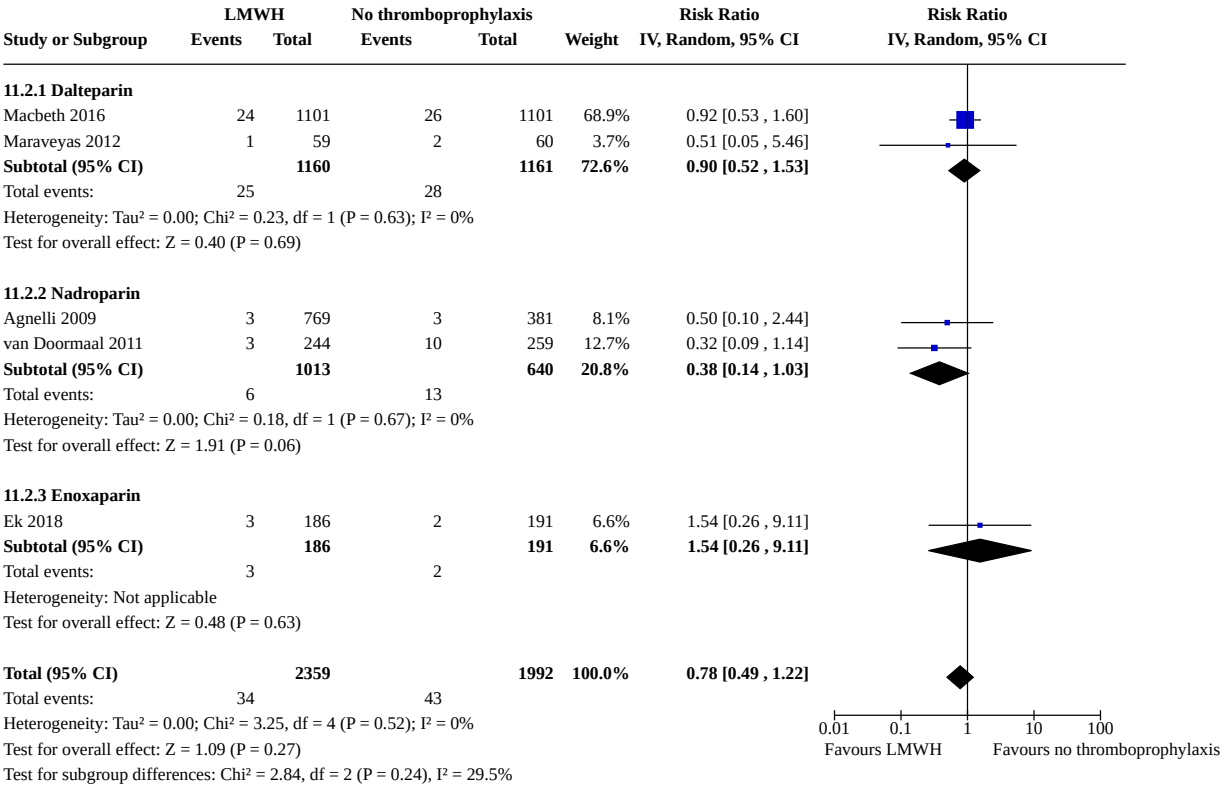
Analysis 11.1. Comparison 11: Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 1: Symptomatic arterial thromboembolism: DOAC vs placebo

Study or Subgroup	DOAC Events	DOAC Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Khorana 2019	4	420	7	421	100.0%	0.57 [0.17 , 1.94]
Total (95% CI)		**420**		**421**	**100.0%**	**0.57 [0.17 , 1.94]**
Total events:	4		7			

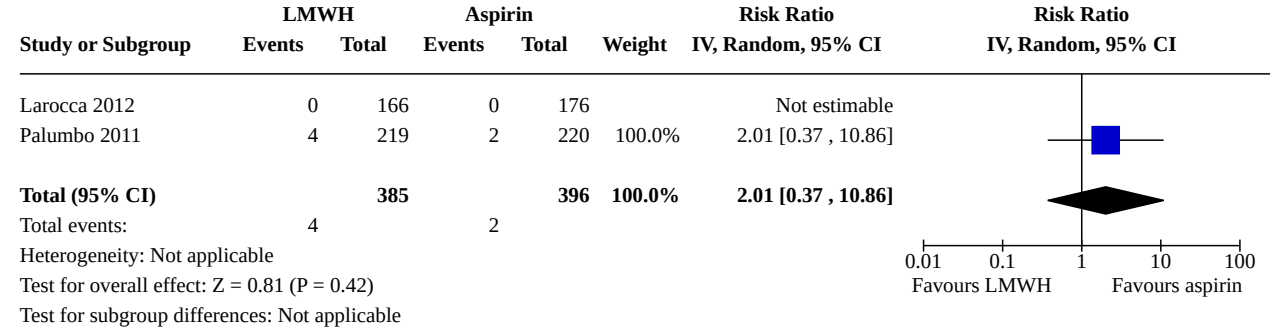
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable



Analysis 11.2. Comparison 11: Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 2: Symptomatic arterial thromboembolism: LMWH vs no thromboprophylaxis



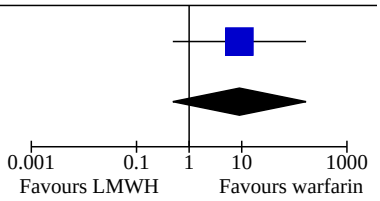
Analysis 11.3. Comparison 11: Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 3: Symptomatic arterial thromboembolism: LMWH vs aspirin



Analysis 11.4. Comparison 11: Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 4: Symptomatic arterial thromboembolism: LMWH vs warfarin

Study or Subgroup	LMWH Events	LMWH Total	Warfarin Events	Warfarin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	4	219	0	220	100.0%	9.04 [0.49 , 166.92]
Total (95% CI)		**219**		**220**	**100.0%**	**9.04 [0.49 , 166.92]**
Total events:	4		0			

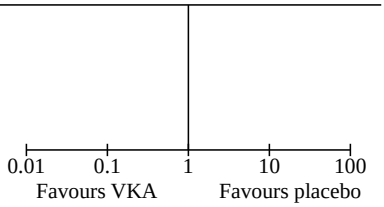
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 11.5. Comparison 11: Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 5: Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo

Study or Subgroup	VKA Events	VKA Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Levine 1994	0	152	0	159		Not estimable
Total (95% CI)		**152**		**159**		**Not estimable**
Total events:	0		0			

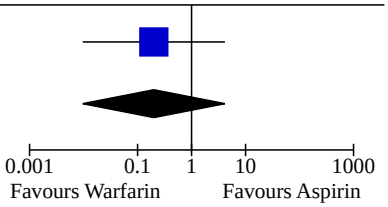
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 11.6. Comparison 11: Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 6: Symptomatic arterial thromboembolism: warfarin vs aspirin

Study or Subgroup	Warfarin Events	Warfarin Total	Aspirin Events	Aspirin Total	Weight	Risk Ratio IV, Fixed, 95% CI
Palumbo 2011	0	220	2	220	100.0%	0.20 [0.01 , 4.14]
Total (95% CI)		**220**		**220**	**100.0%**	**0.20 [0.01 , 4.14]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable

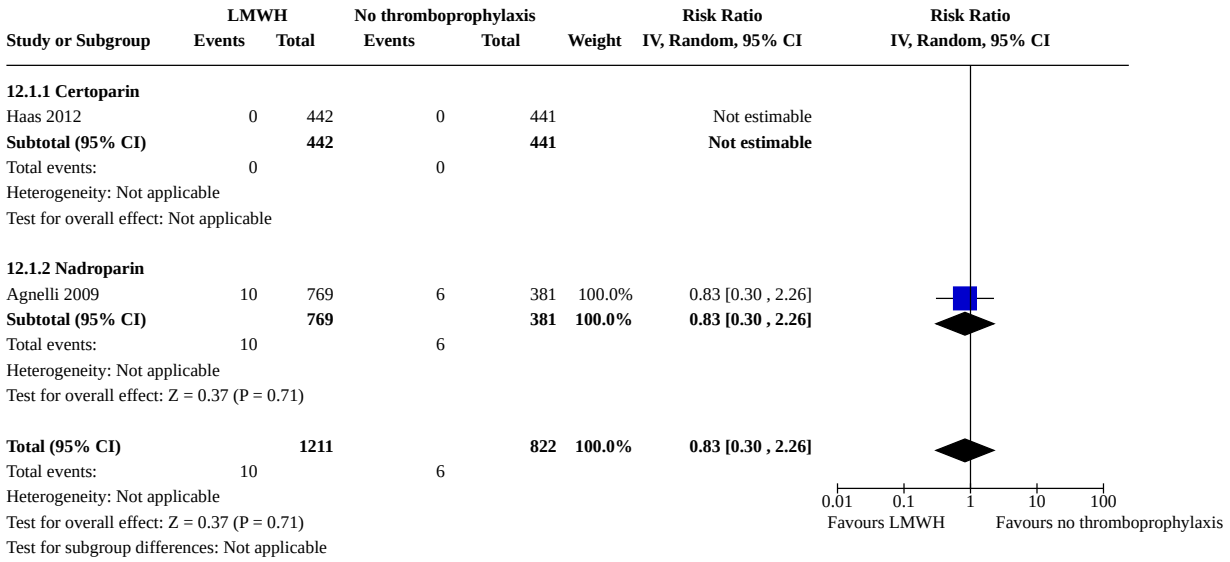


Comparison 12. Anticoagulants versus control: superficial venous thrombosis

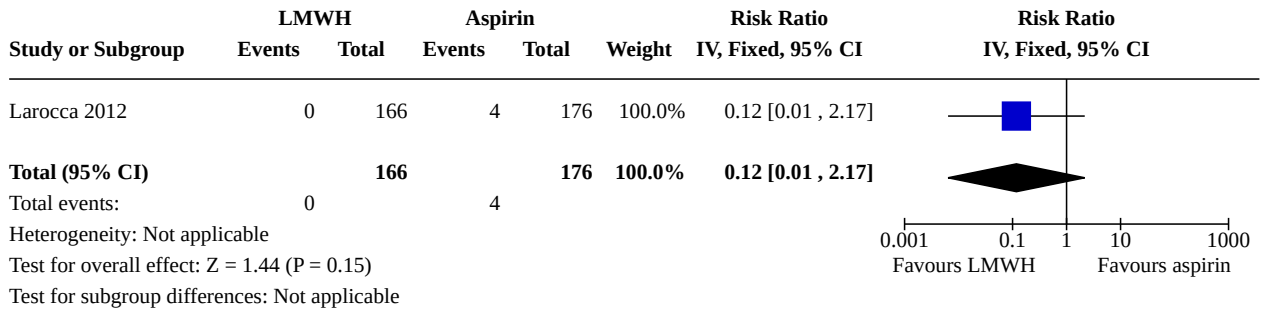
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Superficial venous thrombosis: LMWH vs no thromboprophylaxis	2	2033	Risk Ratio (IV, Random, 95% CI)	0.83 [0.30, 2.26]
12.1.1 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.83 [0.30, 2.26]
12.2 Superficial venous thrombosis: LMWH vs aspirin	1	342	Risk Ratio (IV, Fixed, 95% CI)	0.12 [0.01, 2.17]

Analysis 12.1. Comparison 12: Anticoagulants versus control: superficial venous thrombosis, Outcome 1: Superficial venous thrombosis: LMWH vs no thromboprophylaxis



Analysis 12.2. Comparison 12: Anticoagulants versus control: superficial venous thrombosis, Outcome 2: Superficial venous thrombosis: LMWH vs aspirin



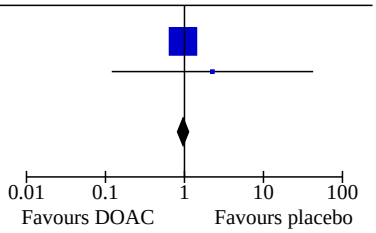
Comparison 13. Anticoagulants versus control: serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Serious adverse events: DOAC vs placebo	2	934	Risk Ratio (IV, Random, 95% CI)	0.96 [0.82, 1.13]
13.2 Serious adverse events: LMWH vs no thromboprophylaxis	5	1531	Risk Ratio (IV, Random, 95% CI)	0.86 [0.70, 1.07]
13.2.1 Dalteparin	3	343	Risk Ratio (IV, Random, 95% CI)	1.22 [0.45, 3.34]
13.2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.89 [0.68, 1.17]
13.2.3 Bemiparin	1	38	Risk Ratio (IV, Random, 95% CI)	0.75 [0.43, 1.30]
13.3 Serious adverse events: semuloparin vs placebo	1	3172	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.92, 1.16]

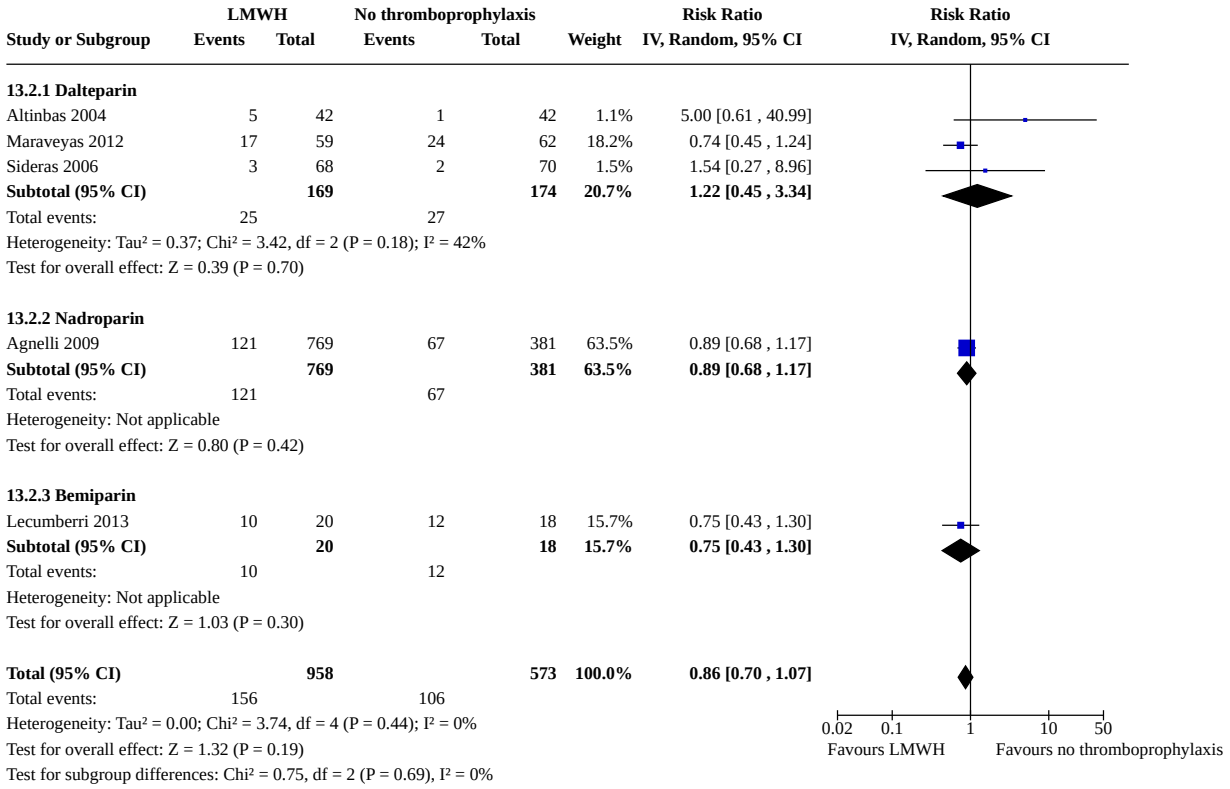
Analysis 13.1. Comparison 13: Anticoagulants versus control: serious adverse events, Outcome 1: Serious adverse events: DOAC vs placebo

	DOAC		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Khorana 2019	168	405	175	404	99.7%	0.96 [0.82 , 1.12]	
Levine 2012	3	95	0	30	0.3%	2.26 [0.12 , 42.56]	
Total (95% CI)		**500**		**434**	**100.0%**	**0.96 [0.82 , 1.13]**	
Total events:	171		175				

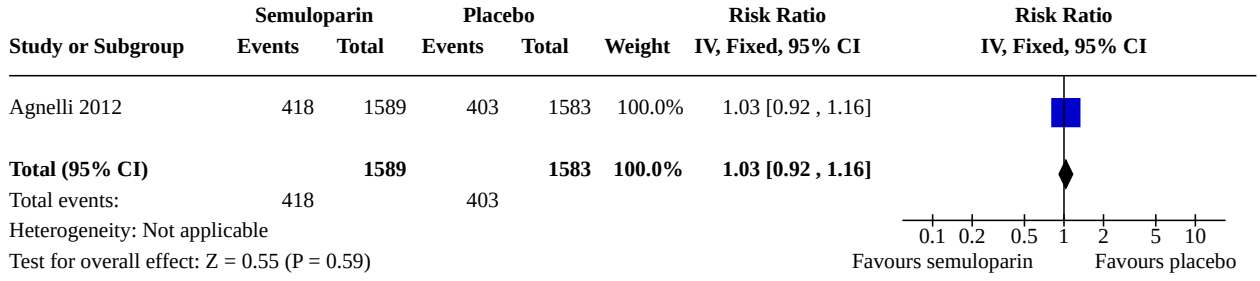
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: Anticoagulants versus control: serious adverse events, Outcome 2: Serious adverse events: LMWH vs no thromboprophylaxis



Analysis 13.3. Comparison 13: Anticoagulants versus control: serious adverse events, Outcome 3: Serious adverse events: semuloparin vs placebo



ADDITIONAL TABLES

Table 1. Results of stratified analyses on symptomatic venous thromboembolism for LMWH versus no thromboprophylaxis

Variable	No of trials	No of participants (LMWH)	No of participants (control)	RR (95% CI)	Heterogeneity I^2 statistic/Tau^2	P for interaction

Table 1. Results of stratified analyses on symptomatic venous thromboembolism for LMWH versus no thromboprophylaxis *(Continued)*

All trials	11	2168	1763	0.62 (0.46 to 0.83)	0.0/0.00	—
Type of LMWH						0.530
Dalteparin	6	508	491	0.66 (0.40 to 1.07)	0.0/0.00	—
Certoparin	1	442	441	0.57 (0.24 to 1.35)	NA	
Nadroparin	1	769	381	0.50 (0.22 to 1.13)	NA	
Enoxaparin	1	160	152	0.43 (0.21 to 0.88)	NA	
Bemiparin	1	20	18	0.10 (0.01 to 1.75)	NA	
Tinzaparin	1	269	280	0.94 (0.51 to 1.73)	NA	
Type of dosage						0.965
Prophylactic	8	1680	1271	0.62 (0.42 to 0.93)	0.0/0.00	—
Higher than prophylactic	3	488	492	0.58 (0.32 to 1.05)	44.2/0.12	
Treatment duration						0.646
< 12 weeks	3	378	388	0.74 (0.42 to 1.31)	8.7/0.03	—
12–24 weeks	3	879	493	0.56 (0.29 to 1.11)	0.0/0.00	
> 24 weeks	5	911	882	0.56 (0.37 to 0.85)	0.0/0.00	
Type of cancer [a]						0.683
Mixed	4	878	603	0.74 (0.36 to 1.49)	0.0/0.00	—
Lung	5	798	684	0.62 (0.38 to 1.02)	6.9/0.03	
Pancreatic	2	219	212	0.41 (0.23 to 0.75)	0.0/0.00	
Glioma	1	99	87	0.74 (0.35 to 1.57)	NA	
Breast cancer	1	174	177	0.76 (0.17 to 3.36)	NA	
Presence of metastatic disease [b]						0.237
Yes, mixed population	5	519	508	0.50 (0.30 to 0.82)	0.0/0.00	—
No	2	289	298	0.48 (0.07 to 3.56)	55.4/1.38	
Allocation concealment						0.935
Adequate	8	1634	1232	0.62 (0.45 to 0.85)	0.0/0.00	—

Table 1. Results of stratified analyses on symptomatic venous thromboembolism for LMWH versus no thromboprophylaxis *(Continued)*

Inadequate or unclear	3	534	531	0.60 (0.28 to 1.28)	0.0/0.00	
Blinding of participants						0.975
Double-blind	4	1500	1093	0.62 (0.40 to 0.96)	0.0/0.00	—
Inadequate or unclear blinding	7	668	670	0.62 (0.42 to 0.91)	0.0/0.00	
Intention-to-treat analysis						0.317
Yes	5	388	365	0.51 (0.33 to 0.81)	0.0/0.00	—
No or unclear	6	1780	1398	0.71 (0.48 to 1.04)	0.0/0.00	
Selective outcome reporting						0.655
Adequate	9	1909	1524	0.65 (0.46 to 0.92)	0.0/0.00	—
Incomplete or unclear	2	259	239	0.56 (0.33 to 0.95)	5.6/0.01	

CI: confidence interval; LMWH: low-molecular-weight heparin; NA: not applicable, only one trial contributing to this stratum; RR: risk ratio. Analyses performed in STATA.

[a] Haas 2012 contributed to both the breast cancer and lung cancer strata; Agnelli 2009 contributed both to the lung cancer and mixed cancer strata

[b]Studies that did not report the selection criteria for metastatic disease were omitted from this analyses (Agnelli 2009; Haas 2012; Khorana 2017; Perry 2010).

Table 2. Results of stratified analyses on major bleeding for LMWH versus no thromboprophylaxis

Variable	No of trials	No of participants (LMWH)	No of participants (control)	RR (95% CI)	Heterogeneity I^2 statistic/Tau^2	P for interaction
All trials	14[a]	3833	3449	1.63 (1.12 to 2.35)	0.0/0.00	—
Type of LMWH						0.860
Dalteparin	6	1567	1552	1.52 (0.70 to 3.28)	15.1/0.15	—
Certoparin	1	447	451	2.19 (0.84 to 5.70)	NA	
Nadroparin	3	1161	794	1.83 (0.69 to 4.85)	13.8/0.15	
Enoxaparin	2[a]	346	343	1.87 (0.61 to 5.72)	46.1/0.33	
Bemiparin	1	20	18	0.30 (0.01 to 6.97)	NA	
Tinzaparin	1	269	280	5.20 (0.25 to 107.89)	NA	

Table 2. Results of stratified analyses on major bleeding for LMWH versus no thromboprophylaxis *(Continued)*

Type of dosage						0.797
Prophylactic	8	2744	2340	1.73 (0.94 to 3.21)	11.2/0.09	—
Higher than prophylactic	6	1066	1098	1.55 (0.93 to 2.57)	0.0/0.00	
Treatment duration [b]						0.348
Up to 12 weeks	4	526	544	3.32 (1.02 to 10.80)	0.0/0.00	—
12 to 24 weeks	4	2182	1811	1.21 (0.68 to 2.15)	0.0/0.00	
more than 24 weeks	5	916	892	1.62 (0.92 to 2.86)	0.0/0.00	
Age						0.246
up to 65 years	13	3624	3247	1.54 (1.05 to 2.25)	0.0/0.00	—
66 years or older	1	186	191	4.11 (0.88 to 19.09)	NA	
Type of cancer						0.626
Mixed	6	1293	1027	1.67 (0.68 to 4.12)	25.4/0.32	—
Lung	6	2048	1943	1.79 (1.01 to 3.19)	0.0/0.00	
Pancreatic	2	219	214	1.21 (0.58 to 2.51)	0.0/0.00	
Glioma	1	99	87	4.39 (0.52 to 36.89)	NA	
Breast cancer	1	174	178	7.16 (0.37 to 137.60)	NA	
Presence of metastatic disease [c]						0.967
Yes, mixed population	8	2156	2173	1.38 (0.90 to 2.12)	0.0/0.00	—
No	2	289	298	1.29 (0.08 to 21.04)	38.9/1.58	
Definition of major bleeding						0.505
Standard[d]	10	3127	2745	1.79 (1.13 to 2.82)	0.0/0.00	—
Alternative or unclear	4	683	693	1.45 (0.56 to 3.77)	39.1/0.37	
Allocation concealment						0.285
Adequate	12	3313	2939	1.48 (0.99 to 2.22)	0.0/0.00	—
Inadequate or unclear	2	497	499	3.05 (0.80 to 11.70)	22.5/0.34	
Blinding of participants						0.403

Table 2. Results of stratified analyses on major bleeding for LMWH versus no thromboprophylaxis *(Continued)*

Double-blind	6	1897	1516	1.97 (1.11 to 3.51)	0.0/0.00	—
Inadequate or unclear blinding	8	1913	1922	1.44 (0.82 to 2.54)	14.9/0.10	
Intention-to-treat analysis						0.895
Yes	7	1637	1622	1.58 (0.95 to 2.65)	0.0/0.00	—
No or unclear	7	2173	1816	1.69 (0.95 to 3.00)	6.8/0.04	
Selective outcome reporting						0.726
Adequate	12	3551	3199	1.69 (1.10 to 2.59)	0.0/0.00	—
Incomplete or unclear	2	259	239	1.56 (0.59 to 4.11)	16.7/0.13	

CI: confidence interval; LMWH: low-molecular-weight heparin; NA: not applicable, only one trial contributing to this stratum; RR: risk ratio. Analyses performed in STATA.

[a] Zwicker 2013, who reported zero events in both the LMWH and control group, was excluded from all analyses.

[b] Ek 2018 was excluded in the stratified analyses by treatment duration, as the duration of anticoagulation was unclear.

[c]The definition of major bleeding was considered 'standard' when it matched the definition of the International Society of Thrombosis and Haemostasis (Schulman 2005).

[d]Studies that did not report the selection criteria for metastatic disease were omitted from this analyses (Agnelli 2009; Haas 2012; Khorana 2017; Perry 2010).

APPENDICES

Appendix 1. Database searches

Source	Search strategy	Hits retrieved
CENTRAL via CRSO	#1 MESH DESCRIPTOR Thrombosis 1690	8 January 2019 – 3626
	#2 MESH DESCRIPTOR Thromboembolism 1159	9 July 2019 – 581
	#3 MESH DESCRIPTOR Venous Thromboembolism 500	14 October 19 – 43
	#4 MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES 2453	3 August 2020 – 450
	#5 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboembolic* or thrombos* or embol* or microembol*):TI,AB,KY 29547	
	#6 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES 899	
	#7 (DVT or VTE):TI,AB,KY 3100	
	#8 (((vein* or ven*) near thromb*)):TI,AB,KY 10154	
	#9 (blood near3 clot*):TI,AB,KY 4945	
	#10 (pulmonary near3 clot*):TI,AB,KY 13	
	#11 (lung near3 clot*):TI,AB,KY 11	

(Continued)

#12 MESH DESCRIPTOR Antineoplastic Protocols EXPLODE ALL TREES 12850

#13 MESH DESCRIPTOR Survival EXPLODE ALL TREES 129

#14 surviv*:TI,AB,KY 102184

#15 chemotherap*:TI,AB,KY 67936

#16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 165162

#17 MESH DESCRIPTOR Anticoagulants EXPLODE ALL TREES 10046

#18 (anticoagul* or anti-coagu*):TI,AB,KY 12207

#19 MESH DESCRIPTOR Heparin EXPLODE ALL TREES 4448

#20 heparin*:TI,AB,KY 11287

#21 UFH:TI,AB,KY 667

#22 LMWH:TI,AB,KY 1267

#23 LMH:TI,AB,KY 9

#24 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren):TI,AB,KY 14

#25 (Clexane or klexane or lovenox):TI,AB,KY 157

#26 Fragmin:TI,AB,KY 215

#27 Innohep:TI,AB,KY 25

#28 clivarin*:TI,AB,KY 22

#29 (danaproid or danaparoid):TI,AB,KY 55

#30 antixarin:TI,AB,KY 2

#31 (Zibor or cy 222 or embolex or monoembolex):TI,AB,KY 38

#32 (rd 11885 or RD1185):TI,AB,KY 0

#33 (Kabi-2165 or Kabi 2165):TI,AB,KY 39

#34 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169):TI,AB,KY 8

#35 (fr-860 or fr860 or cy-216 or cy216):TI,AB,KY 53

#36 (kb101 or lomoparan or orgaran):TI,AB,KY 32

#37 (fluxum or lohepa or lowhepa):TI,AB,KY 13

#38 (op 2123 or op2123):TI,AB,KY 1

#39 (ave 5026 or ave5026):TI,AB,KY 12

#40 (M118 or RO-1):TI,AB,KY 10

#41 coumar*:TI,AB,KY 385

#42 (warfarin or (vitamin near/3 antagonist*)):TI,AB,KY 4427

(Continued)

#43 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin):TI,AB,KY 692

#44 MESH DESCRIPTOR Antithrombins EXPLODE ALL TREES 1745

#45 MESH DESCRIPTOR Hirudin Therapy EXPLODE ALL TREES 75

#46 (thrombin near3 inhib*):TI,AB,KY 675

#47 (BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048):TI,AB,KY 48

#48 (ximelagatran or Exanta or Exarta or melagatran):TI,AB,KY 189

#49 (AZD0837 or AZD-0837):TI,AB,KY 23

#50 (S35972 or S-35972):TI,AB,KY 0

#51 MESH DESCRIPTOR Factor Xa Inhibitors 457

#52 (Factor X* near4 (antag* or inhib* or block*)):TI,AB,KY 914

#53 (FX* near4 (antag* or inhib* or block*)):TI,AB,KY 84

#54 (10* near4 (antag* or inhib* or block*)):TI,AB,KY 1473

#55 (rivaroxaban or Xarelto):TI,AB,KY 1282

#56 (Bay-597939 or Bay597939):TI,AB,KY 0

#57 (betrixaban or PRT054021):TI,AB,KY 79

#58 apixaban:TI,AB,KY 745

#59 (BMS-562247 or BMS-562247 or ELIQUIS):TI,AB,KY 36

#60 (DU-176b or DU176b):TI,AB,KY 48

#61 (PRT-054021 or PRT054021):TI,AB,KY 3

#62 (YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*):TI,AB,KY 101

#63 (GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893):TI,AB,KY 7

#64 (edoxaban or lixiana):TI,AB,KY 462

#65 etexilate:TI,AB,KY 273

#66 agatroban:TI,AB,KY 1

#67 MESH DESCRIPTOR Bandages EXPLODE ALL TREES 2603

#68 (stocking* or hosier* or tight* or sock* or bandag*):TI,AB,KY 8039

#69 (jobst or surepress or activa or kendall or elbeo or levante or lloveras or cette or sigvaris or solidea or medilast or VenoTrain* or Ulcertec or ComfortPro or Comfort-Pro or "Ulcer Kit"):TI,AB,KY 462

#70 MESH DESCRIPTOR Intermittent Pneumatic Compression Devices EXPLODE ALL TREES 125

#71 compres*:TI,AB,KY 9404

(Continued)

#72 (foot near3 impulse):TI,AB,KY 9

#73 MESH DESCRIPTOR Platelet Aggregation Inhibitors EXPLODE ALL TREES 10232

#74 MESH DESCRIPTOR Phosphodiesterase Inhibitors EXPLODE ALL TREES 6703

#75 MESH DESCRIPTOR Tetrazoles EXPLODE ALL TREES 3304

#76 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*):TI,AB,KY 5733

#77 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) near3 (antagonist or inhibitor)):TI,AB,KY 2854

#78 (((gp* or glycoprotein* or protease or P2Y12 or TXA2) near3 inhibit*)):TI,AB,KY 4468

#79 thienopyridine:TI,AB,KY 374

#80 (ticlopidine or Ticlid):TI,AB,KY 2311

#81 (clopidogrel or Plavix):TI,AB,KY 4952

#82 (Prasugrel or Effient or Efient or Prasita):TI,AB,KY 975

#83 (ticagrelor or AZD6140 or Brilinta):TI,AB,KY 1288

#84 (elinogrel or PRT060128 or PRT-060128):TI,AB,KY 10

#85 (cangrelor or AR-C6993* or ARC6993*):TI,AB,KY 119

#86 (SCH530348 or SCH-530348):TI,AB,KY 25

#87 E5555:TI,AB,KY 12

#88 (terutroban or Triplion):TI,AB,KY 26

#89 (aspirin* or nitroaspirin):TI,AB,KY 12416

#90 (acetylsalicylic acid):TI,AB,KY 5301

#91 (acetyl salicylic acid*):TI,AB,KY 150

#92 (triflusal or disgren):TI,AB,KY 111

#93 (Cilostazol or Pletal or Pletaal):TI,AB,KY 738

#94 (dipyridamol* or Persantine):TI,AB,KY 1359

#95 (OPC-13013 or OPC13013):TI,AB,KY 6

#96 (picotamide or picotinamide):TI,AB,KY 46

#97 satigrel:TI,AB,KY 3

#98 vorapaxar:TI,AB,KY 120

#99 indobufen:TI,AB,KY 92

#100 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR

(Continued)

	#68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 73572 #101 #16 AND #100 18481 #102 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 69579 #103 (malignan* or neoplas* or cancer*):TI,AB,KY 169102 #104 (carcinoma* or adenocarcinoma*):TI,AB,KY 43590 #105 (tumour* or tumor*):TI,AB,KY 64990 #106 (glio* or leukemia):TI,AB,KY 15433 #107 chemotherapy:TI,AB,KY 67159 #108 chemoanticoagul*:TI,AB,KY 0 #109 myeloma:TI,AB,KY 4924 #110 oncolog*:TI,AB,KY 22997 #111 metastas*:TI,AB,KY 22284 #112 MESH DESCRIPTOR Antineoplastic Agents EXPLODE ALL TREES 52113 #113 MESH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES 4722 #114 #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 238167 #115 #101 AND #114 3106 #116 01/01/2019 TO 09/07/2019:CD 243198 #117 #115 AND #116 581	
Clinicaltrials.gov	chemotherapy OR malignancy OR neoplasm OR cancer OR tumour OR tumor OR carcinoma OR adenocarcinoma | Thrombosis OR Thromboembolism OR "venous thromboembolism" OR "venous thrombosi"s OR "pulmonary embolism" OR DVT OR VTE OR "deep vein thrombosis" | Anticoagulants OR Heparin OR Antithrombins OR Hirudin Therapy OR "Factor Xa Inhibitors" OR Bandages OR "Intermittent Pneumatic Compression Device"s OR "Platelet Aggregation Inhibitors" OR "Phosphodiesterase Inhibitors" OR Tetrazoles OR aspirin	8 January 2019 – 35 9 July 2019 – 4 14 October 2019 – 2 3 August 2020 – 151
ICTRP Search Portal	chemotherapy OR malignancy OR neoplasm OR cancer OR tumour OR tumor OR carcinoma OR adenocarcinoma | Thrombosis OR Thromboembolism OR "venous thromboembolism" OR "venous thrombosi"s OR "pulmonary embolism" OR DVT OR VTE OR "deep vein thrombosis" | Anticoagulants OR Heparin OR Antithrombins OR Hirudin Therapy OR "Factor Xa Inhibitors" OR Bandages OR "Intermittent Pneumatic Compression Device" OR "Platelet Aggregation Inhibitors" OR "Phosphodiesterase Inhibitors" OR Tetrazoles OR aspirin	8 January 2019 – 6 9 July 2019 – 0 14 October 2019 – 0 3 August 2020 – portal not available
Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present	1 THROMBOSIS/ 2 THROMBOEMBOLISM/ 3 exp Venous Thromboembolism/ 4 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*).ti,ab.	8 January 2019 – 644 9 July 2019 – 161 14 October 19 – 101 3 August 2020 – 539

(Continued)

2017, 2018, 2019 AND 2020 only	5 exp Pulmonary Embolism/ 6 (PE or DVT or VTE).ti,ab. 7 ((vein* or ven*) adj thromb*).ti,ab. 8 (blood adj3 clot*).ti,ab. 9 (pulmonary adj3 clot*).ti,ab. 10 (lung adj3 clot*).ti,ab. 11 or/1-10 12 exp ANTICOAGULANTS/ 13 exp HEPARIN/ 14 exp ANTITHROMBINS/ 15 exp Hirudin Therapy/ 16 exp BANDAGES/ 17 exp Factor Xa Inhibitors/ 18 exp Intermittent Pneumatic Compression Devices/ 19 exp Platelet Aggregation Inhibitors/ 20 exp Phosphodiesterase Inhibitors/ 21 exp TETRAZOLES/ 22 (anticoagul* or anti-coagu*).ti,ab. 23 heparin*.ti,ab. 24 UFH.ti,ab. 25 LMWH.ti,ab. 26 LMH.ti,ab. 27 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren).ti,ab. 28 (Clexane or klexane or lovenox).ti,ab. 29 Fragmin.ti,ab. 30 Innohep.ti,ab. 31 clivarin*.ti,ab. 32 (danaproid or danaparoid).ti,ab. 33 antixarin.ti,ab. 34 (Zibor or cy 222 or embolex or monoembolex).ti,ab. 35 (Kabi-2165 or Kabi 2165).ti,ab. 36 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169).ti,ab. 37 (fr-860 or fr860 or cy-216 or cy216).ti,ab.

(Continued)

38 (kb101 or lomoparan or orgaran).ti,ab.

39 (fluxum or lohepa or lowhepa).ti,ab.

40 (ave 5026 or ave5026).ti,ab.

41 (M118 or RO-1).ti,ab.

42 coumar*.ti,ab.

43 ((warfarin or vitamin) adj3 antagonist*).ti,ab.

44 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or al-documar or carfin or jantoven or kumatox or lawarin or marevan or prothro-madin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab.

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

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

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

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

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

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

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

52 (rivaroxaban or Xarelto).ti,ab.

53 (betrixaban or PRT054021).ti,ab.

54 apixaban.ti,ab.

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

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

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

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

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

60 (edoxaban or lixiana).ti,ab.

61 etexilate.ti,ab.

62 agatroban.ti,ab.

63 (stocking* or hosier* or tight* or sock* or bandag*).ti,ab.

64 (jobst or surepress or activa or kendall or elbeo or levante or lloveras or cette or sigvaris or solidea or medilast or VenoTrain* or Ulcertec or ComfortPro or Comfort-Pro or "Ulcer Kit").ti,ab.

65 (compres* or ICD).ti,ab.

66 (foot adj3 impulse).ti,ab.

67 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).ti,ab.

(Continued)

68 ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj2 inhibit*).ti,ab.

69 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) adj2 (antagonist or inhibitor)).ti,ab.

70 thienopyridine.ti,ab.

71 (ticlopidine or Ticlid).ti,ab.

72 (clopidogrel or Plavix).ti,ab.

73 (Prasugrel or Effient or Efient or Prasita).ti,ab.

74 (ticagrelor or AZD6140 or Brilinta).ti,ab.

75 (elinogrel or PRT060128 or PRT-060128).ti,ab.

76 (cangrelor or AR-C6993* or ARC6993*).ti,ab.

77 (SCH530348 or SCH-530348).ti,ab.

78 E5555.ti,ab.

79 (terutroban or Triplion).ti,ab.

80 (aspirin* or nitroaspirin or ASA).ti,ab.

81 acetylsalicylic acid.ti,ab.

82 acetyl salicylic acid*.ti,ab.

83 (triflusal or disgren).ti,ab.

84 (Cilostazol or Pletal or Pletaal).ti,ab.

85 (dipyridamol* or Persantine).ti,ab.

86 (OPC-13013 or OPC13013).ti,ab.

87 (picotamide or picotinamide).ti,ab.

88 satigrel.ti,ab.

89 vorapaxar.ti,ab.

90 indobufen.ti,ab.

91 or/12-90

92 11 and 91

93 exp NEOPLASMS/

94 exp Antineoplastic Agents/

95 exp Neoplasm Metastasis/

96 exp Antineoplastic Protocols/

97 (malignan* or neoplas* or cancer*).ti,ab.

98 (carcinoma* or adenocarcinoma*).ti,ab.

99 (tumour* or tumor*).ti,ab.

100 (glio* or leukemia).ti,ab.

(Continued)

	101 myeloma.ti,ab.	
	102 oncolog*.ti,ab.	
	103 metastas*.ti,ab.	
	104 chemotherap*.ti,ab.	
	105 or/93-104	
	106 92 and 105	
	107 randomized controlled trial.pt.	
	108 controlled clinical trial.pt.	
	109 randomized.ab.	
	110 placebo.ab.	
	111 drug therapy.fs.	
	112 randomly.ab.	
	113 trial.ab.	
	114 groups.ab.	
	115 or/107-114	
	116 exp animals/ not humans.sh.	
	117 115 not 116	
	118 106 and 117	
	119 (2017* or 2018* or 2019*).ed.	
	120 118 and 119	
EMBASE 2017, 2018, 2019 AND 2020 only	1 thrombosis/	8 January 2019 – 1280
	2 thromboembolism/	9 July 2019 – 547
	3 exp venous thromboembolism/	14 October 2019 – 219
	4 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboembol* or thrombos* or embol* or microembol*).ti,ab.	3 August 2020 – 717
	5 exp lung embolism/	
	6 (PE or DVT or VTE).ti,ab.	
	7 ((vein* or ven*) adj thromb*).ti,ab.	
	8 (blood adj3 clot*).ti,ab.	
	9 (pulmonary adj3 clot*).ti,ab.	
	10 (lung adj3 clot*).ti,ab.	
	11 or/1-10	
	12 exp anticoagulant agent/	
	13 exp heparin/	

(Continued)

14 exp antithrombin/

15 exp anticoagulant therapy/

16 exp bandage/

17 exp blood clotting factor 10a inhibitor/

18 exp intermittent pneumatic compression device/

19 exp antithrombocytic agent/

20 exp phosphodiesterase inhibitor/

21 exp tetrazole derivative/

22 (anticoagul* or anti-coagu*).ti,ab.

23 heparin*.ti,ab.

24 UFH.ti,ab.

25 LMWH.ti,ab.

26 LMH.ti,ab.

27 (Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren).ti,ab.

28 (Clexane or klexane or lovenox).ti,ab.

29 Fragmin.ti,ab.

30 Innohep.ti,ab.

31 clivarin*.ti,ab.

32 (danaproid or danaparoid).ti,ab.

33 antixarin.ti,ab.

34 (Zibor or cy 222 or embolex or monoembolex).ti,ab.

35 (Kabi-2165 or Kabi 2165).ti,ab.

36 (emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169).ti,ab.

37 (fr-860 or fr860 or cy-216 or cy216).ti,ab.

38 (kb101 or lomoparan or orgaran).ti,ab.

39 (fluxum or lohepa or lowhepa).ti,ab.

40 (ave 5026 or ave5026).ti,ab.

41 (M118 or RO-1).ti,ab.

42 coumar*.ti,ab.

43 ((warfarin or vitamin) adj3 antagonist*).ti,ab.

44 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or al-documar or carfin or jantoven or kumatox or lawarin or marevan or prothro-madin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab.

(Continued)

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

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

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

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

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

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

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

52 (rivaroxaban or Xarelto).ti,ab.

53 (betrixaban or PRT054021).ti,ab.

54 apixaban.ti,ab.

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

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

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

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

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

60 (edoxaban or lixiana).ti,ab.

61 etexilate.ti,ab.

62 agatroban.ti,ab.

63 (stocking* or hosier* or tight* or sock* or bandag*).ti,ab.

64 (jobst or surepress or activa or kendall or elbeo or levante or lloveras or cette or sigvaris or solidea or medilast or VenoTrain* or Ulcertec or ComfortPro or Comfort-Pro or "Ulcer Kit").ti,ab.

65 (compres* or ICD).ti,ab.

66 (foot adj3 impulse).ti,ab.

67 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).ti,ab.

68 ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj2 inhibit*).ti,ab.

69 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) adj2 (antagonist or inhibitor)).ti,ab.

70 thienopyridine.ti,ab.

71 (ticlopidine or Ticlid).ti,ab.

72 (clopidogrel or Plavix).ti,ab.

73 (Prasugrel or Effient or Efient or Prasita).ti,ab.

74 (ticagrelor or AZD6140 or Brilinta).ti,ab.

75 (elinogrel or PRT060128 or PRT-060128).ti,ab.

(Continued)

76 (cangrelor or AR-C6993* or ARC6993*).ti,ab.

77 (SCH530348 or SCH-530348).ti,ab.

78 E5555.ti,ab.

79 (terutroban or Triplion).ti,ab.

80 (aspirin* or nitroaspirin or ASA).ti,ab.

81 acetylsalicylic acid.ti,ab.

82 acetyl salicylic acid*.ti,ab.

83 (triflusal or disgren).ti,ab.

84 (Cilostazol or Pletal or Pletaal).ti,ab.

85 (dipyridamol* or Persantine).ti,ab.

86 (OPC-13013 or OPC13013).ti,ab.

87 (picotamide or picotinamide).ti,ab.

88 satigrel.ti,ab.

89 vorapaxar.ti,ab.

90 indobufen.ti,ab.

91 or/12-90

92 11 and 91

93 exp neoplasm/

94 exp antineoplastic agent/

95 exp metastasis/

96 (malignan* or neoplas* or cancer*).ti,ab.

97 (carcinoma* or adenocarcinoma*).ti,ab.

98 (tumour* or tumor*).ti,ab.

99 (glio* or leukemia).ti,ab.

100 myeloma.ti,ab.

101 oncolog*.ti,ab.

102 metastas*.ti,ab.

103 chemotherap*.ti,ab.

104 or/93-103

105 92 and 104

106 randomized controlled trial/

107 controlled clinical trial/

108 random$.ti,ab.

109 randomization/

(Continued)

	110 intermethod comparison/	
	111 placebo.ti,ab.	
	112 (compare or compared or comparison).ti.	
	113 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	
	114 (open adj label).ti,ab.	
	115 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	
	116 double blind procedure/	
	117 parallel group$1.ti,ab.	
	118 (crossover or cross over).ti,ab.	
	119 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	
	120 (assigned or allocated).ti,ab.	
	121 (controlled adj7 (study or design or trial)).ti,ab.	
	122 (volunteer or volunteers).ti,ab.	
	123 trial.ti.	
	124 or/106-123	
	125 105 and 124	
	126 (2017* or 2018* or 2019*).dc.	
	127 125 and 126	
CINAHL 2017, 2018, 2019 AND 2020 only	S118 S116 AND S117	8 January 2019 – 93
	S117 EM 2017 OR EM 2018 OR EM 2019	9 July 2019 – 22
	S116 S100 AND S115	14 October 2019 – 40
	S115 S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114	3 August 2020 – 100
	S114 MH "Random Assignment"	
	S113 MH "Triple-Blind Studies"	
	S112 MH "Double-Blind Studies"	
	S111 MH "Single-Blind Studies"	
	S110 MH "Crossover Design"	
	S109 MH "Factorial Design"	
	S108 MH "Placebos"	
	S107 MH "Clinical Trials"	
	S106 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study"	

(Continued)

S105 TX crossover OR "cross-over"

S104 AB placebo*

S103 TX random*

S102 TX trial*

S101 TX "latin square"

S100 S87 AND S99

S99 S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98

S98 TX chemotherap*

S97 TX metastas*

S96 TX oncolog*

S95 TX myeloma

S94 TX glio* or leukemia

S93 TX tumour* or tumor*

S92 TX carcinoma* or adenocarcinoma*

S91 TX malignan* or neoplas* or cancer*

S90 (MH "Neoplasm Metastasis+")

S89 (MH "Antineoplastic Agents+")

S88 (MH "Neoplasms+")

S87 S11 AND S86

S86 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 ...

S85 TX indobufen

S84 TX vorapaxar

S83 TX satigrel

S82 TX picotamide or picotinamide

S81 TX OPC-13013 or OPC13013

S80 TX dipyridamol* or Persantine

S79 TX Cilostazol or Pletal or Pletaal

S78 TX triflusal or disgren

S77 TX acetyl salicylic acid*

S76 TX acetylsalicylic acid

(Continued)

S75 TX aspirin* or nitroaspirin or ASA

S74 TX terutroban or Triplion

S73 TX E5555

S72 TX SCH530348 or SCH-530348

S71 TX cangrelor or AR-C6993* or ARC6993*

S70 TX elinogrel or PRT060128 or PRT-060128

S69 TX ticagrelor or AZD6140 or Brilinta

S68 TX Prasugrel or Effient or Efient or Prasita

S67 TX clopidogrel or Plavix

S66 TX ticlopidine or Ticlid

S65 TX thienopyridine

S64 TX (platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) N2 (antagonist or inhibitor)

S63 TX (gp* or glycoprotein* or protease or P2Y12 or TXA2) N2 inhibit*

S62 TX antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*

S61 TX foot N3 impulse

S60 TX compres* or ICD

S59 TX jobst or surepress or activa or kendall or elbeo or levante or lloveras or cette or sigvaris or solidea or medilast or VenoTrain* or Ulcertec or ComfortPro or Comfort-Pro or "Ulcer Kit"

S58 TX stocking* or hosier* or tight* or sock* or bandag*

S57 TX agatroban

S56 TX etexilate

S55 TX edoxaban or lixiana

S54 TX GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893

S53 TX YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*

S52 TX PRT-054021 or PRT054021

S51 TX DU-176b or DU176b

S50 TX BMS-562247 or BMS-562247 or ELIQUIS

S49 TX apixaban

S48 TX betrixaban or PRT054021

S47 TX rivaroxaban or Xarelto

S46 TX FX* N4 (antag* or inhib* or block*)

S45 TX Factor X* N4 (antag* or inhib* or block*)

(Continued)

S44 TX S35972 or S-35972

S43 TX AZD0837 or AZD-0837

S42 TX ximelagatran or Exanta or Exarta or melagatran

S41 TX BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048

S40 TX thrombin N3 inhib*

S39 TX VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or al-documar or carfin or jantoven or kumatox or lawarin or marevan or prothro-madin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin

S38 TX (warfarin or vitamin) N3 antagonist*

S37 TX coumar*

S36 TX M118 or RO-1

S35 TX ave 5026 or ave5026

S34 TX fluxum or lohepa or lowhepa

S33 TX kb101 or lomoparan or orgaran

S32 TX fr-860 or fr860 or cy-216 or cy216

S31 TX emt-966 or emt966 or emt-967 or emt977 or pk-10169 or pk10169

S30 TX Kabi-2165 or Kabi 2165

S29 TX Zibor or cy 222 or embolex or monoembolex

S28 TX antixarin

S27 TX danaproid or danaparoid

S26 TX clivarin*

S25 TX Innohep

S24 TX Fragmin

S23 TX Clexane or klexane or lovenox

S22 TX Ariven or Arteven or Calcilean or Hepalean or Hepathrom or Leparan or Lipo-Hepin or Liquaemin or Liquemin or Pabyrin or Pularin or Thromboliquine or Vetren

S21 TX LMH

S20 TX LMWH

S19 TX UFH

S18 TX heparin*

S17 TX anticoagul* or anti-coagu*

S16 (MH "Phosphodiesterase Inhibitors+")

S15 (MH "Platelet Aggregation Inhibitors+")

S14 (MH "Elastic Bandages")

(Continued)

	S13 (MH "Heparin+") S12 (MH "Anticoagulants+") S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 S10 TX lung N3 clot* S9 TX pulmonary N3 clot* S8 TX blood N3 clot* S7 TX ((vein* or ven*) n thromb*) S6 TX PE or DVT or VTE S5 (MH "Pulmonary Embolism") S4 TX thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol* S3 (MH "Venous Thromboembolism") S2 (MH "Thromboembolism") S1 (MH "Thrombosis")	
AMED 2017, 2018, 2019 AND 2020 only	1 Thrombosis/ 2 Thromboembolism/ 3 (thrombus* or thrombopro* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* or microembol*).ti,ab. 4 exp Pulmonary embolism/ 5 (PE or DVT or VTE).ti,ab. 6 ((vein* or ven*) adj thromb*).ti,ab. 7 (blood adj3 clot*).ti,ab. 8 (pulmonary adj3 clot*).ti,ab. 9 (lung adj3 clot*).ti,ab. 10 or/1-9 11 exp Anticoagulants/ 12 exp Heparin/ 13 exp Bandages/ 14 exp Platelet Aggregation Inhibitors/ 15 (anticoagul* or anti-coagu*).ti,ab. 16 heparin*.ti,ab. 17 UFH.ti,ab. 18 LMWH.ti,ab. 19 LMH.ti,ab. 20 coumar*.ti,ab.	8 January 2019 – 0 9 July 2019 – 0 14 October 2019 – 0 3 August 2020 – 0

(Continued)

21 ((warfarin or vitamin) adj3 antagonist*).ti,ab.

22 (VKA or phenindione or Sinthrome or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin).ti,ab.

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

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

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

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

27 (rivaroxaban or Xarelto).ti,ab.

28 (stocking* or hosier* or tight* or sock* or bandag*).ti,ab.

29 (jobst or surepress or activa or kendall or elbeo or levante or lloveras or cette or sigvaris or solidea or medilast or VenoTrain* or Ulcertec or ComfortPro or Comfort-Pro or "Ulcer Kit").ti,ab.

30 (compres* or ICD).ti,ab.

31 (foot adj3 impulse).ti,ab.

32 (antiplatelet* or anti-platelet* or antiaggreg* or anti-aggreg*).ti,ab.

33 ((gp* or glycoprotein* or protease or P2Y12 or TXA2) adj2 inhibit*).ti,ab.

34 ((platelet or thromboxane or thrombocyte or cyclooxygenase or cyclo-oxygenase or phosphodiesterase or fibrinogen or PAR-1) adj2 (antagonist or inhibitor)).ti,ab.

35 (ticlopidine or Ticlid).ti,ab.

36 (clopidogrel or Plavix).ti,ab.

37 (aspirin* or nitroaspirin or ASA).ti,ab.

38 acetylsalicylic acid.ti,ab.

39 acetyl salicylic acid*.ti,ab.

40 (Cilostazol or Pletal or Pletaal).ti,ab.

41 (dipyridamol* or Persantine).ti,ab.

42 or/11-41

43 10 and 42

44 exp Neoplasms/

45 exp Antineoplastic agents/

46 exp Neoplasm metastasis/

47 (malignan* or neoplas* or cancer*).ti,ab.

48 (carcinoma* or adenocarcinoma*).ti,ab.

49 (tumour* or tumor*).ti,ab.

50 (glio* or leukemia).ti,ab.

(Continued)

51 myeloma.ti,ab.

52 oncolog*.ti,ab.

53 metastas*.ti,ab.

54 chemotherap*.ti,ab.

55 or/44-54

56 43 and 55

57 exp CLINICAL TRIALS/

58 RANDOM ALLOCATION/

59 DOUBLE BLIND METHOD/

60 Clinical trial.pt.

61 (clinic* adj trial*).tw.

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

63 PLACEBOS/

64 placebo*.tw.

65 random*.tw.

66 PROSPECTIVE STUDIES/

67 or/57-66

68 56 and 67

69 ("2017" or "2018" or "2019").yr.

70 68 and 69

Appendix 2. Abbreviations and scientific terms

Abbreviation	Scientific description	Lay description
	Anticoagulation therapy	Blood-thinning therapy
GES	Graduated elastic stockings	Special socks that improve blood flow in the leg veins and prevent blood from pooling in the legs
	Incidence	Number of newly diagnosed diseases, in this review cases of VTE
IPC	Intermittent pneumatic compression	A mechanical intervention using an air pump and inflatable leggings to provide pulsing pressure that pushes blood through the veins
	Primary prophylaxis	Primary protective treatment aiming at the prevention of disease development
	Thromboprophylaxis	Treatment to prevent the development of blood clots

(Continued)

VTE	Venous thromboembolism	Blood clots

WHAT'S NEW

Date	Event	Description
17 December 2020	New search has been performed	Searches rerun. Six new studies included, five new studies excluded, six new ongoing studies identified.
17 December 2020	New citation required and conclusions have changed	New author joined the review team. Searches rerun. Six new studies included, five new studies excluded, six new ongoing studies identified. Text updated to reflect current Cochrane standards. Conclusions changed. The authors' Declarations of interest have been updated to reflect the review's compliance with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy.

HISTORY

Protocol first published: Issue 5, 2010
Review first published: Issue 2, 2012

Date	Event	Description
11 December 2020	Amended	Clarification message added to the Declarations of interest statement about the review's compliance with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy.
9 July 2016	New search has been performed	Searches rerun. Five additional studies were added to the included studies. Two additional studies excluded on full-text basis.
9 July 2016	New citation required and conclusions have changed	Searches rerun. Five additional studies were added to the included studies. Two additional studies excluded on full-text basis. New authors joined the review team. 'Summary of findings' tables added. Conclusions not changed.
24 July 2013	New search has been performed	Searches rerun. Twelve additional studies were added to the included studies and nine additional studies to the excluded studies.
24 July 2013	New citation required but conclusions have not changed	Searches rerun. Twelve additional studies were added to the included studies and nine additional studies to the excluded studies. Risk of bias was reassessed in all included trials. Conclusions not changed. Change in author team.

CONTRIBUTIONS OF AUTHORS

Contribution to previous versions of this review are found in Di Nisio 2010; Di Nisio 2012; Di Nisio 2014; and Di Nisio 2016.

Contributions to the current version.

AWSR: acquisition of data, risk of bias assessments, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, grading of the evidence.

EP: analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

MC: acquisition of data, risk of bias assessments, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

EV: acquisition of data, risk of bias assessments, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, grading of the evidence.

MDN: oversight, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

DECLARATIONS OF INTEREST

AWSR: none.
EP: none.
MC: none.
EV: none.
MDN: has declared that he has received consultancy fees from Bayer, Daiichi Sankyo, LEO Pharma, BMS-Pfizer and Aspen, outside of the submitted work.

When the previous version of this review was published (Di Nisio 2016 *), the authors declared the below conflicts of interest. From 29 October 2020, the above conflicts of interest were declared. These conflicts applied during the period that the review update was in preparation.*

MDN: I have received consultancy fees from Bayer, Grifols, and Daiichi Sankyo not related to the present review.
EP: none known
MC: none known
MDT: none known
IR: none known
AWSR: none known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, we added fatal PE to the secondary outcomes.

The protocol specified that we would evaluate heterogeneity in results between trials with the I^2 statistic (Higgins 2003; Rücker 2008). However, we added the variance estimate Tau^2 to indicate and interpret heterogeneity, as added to forest plots by default.

For the comparison of LMWH versus no thromboprophylaxis, we could not perform stratified analyses of the main outcomes by differences in the use of cointerventions in the trial groups due to poor reporting. Although we were unable to analyse dosage as a continuous variable, we could stratify the analyses according to trials using prophylactic dosage versus those using other (higher than prophylactic) dosages. We could not use the univariable random-effects meta-regression model by dosage of intervention.

Compared to earlier versions of this review, we added a stratified analysis by the risk of selective outcome reporting (low versus high or unclear risk), which is one of the standard risk of bias items in Cochrane Reviews.

We planned to perform meta-regression on both treatment duration and follow-up duration. The treatment duration equalled the follow-up duration in all studies except in Pelzer 2015 and Meyer 2018. Therefore, we only analysed the effect of treatment duration on major bleeding and symptomatic VTE for the comparison LMWH versus no thromboprophylaxis. In all other comparisons, there was no exploration of the effects of participant or trial characteristics on symptomatic VTE or major bleeding due to the low number of studies identified.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ambulatory Care; Anticoagulants [adverse effects] [*therapeutic use]; Antineoplastic Agents [adverse effects]; Antithrombins [therapeutic use]; Bias; Factor Xa Inhibitors [therapeutic use]; Hemorrhage [chemically induced]; Heparin [adverse effects] [therapeutic use]; Heparin, Low-Molecular-Weight [adverse effects] [therapeutic use]; Neoplasms [complications] [*drug therapy]; Primary Prevention [*methods]; Pulmonary Embolism [etiology] [prevention & control]; Randomized Controlled Trials as Topic; Venous Thromboembolism [etiology] [*prevention & control]; Warfarin [adverse effects] [therapeutic use]

MeSH check words

Adult; Child; Humans