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Anticoagulation for perioperative thromboprophylaxis in people with cancer (Review)

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Anticoagulation for perioperative thromboprophylaxis in people with cancer (Review)

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[Intervention Review]

Anticoagulation for perioperative thromboprophylaxis in people with cancer

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ABSTRACT

Background

The choice of the appropriate perioperative thromboprophylaxis for people with cancer depends on the relative benefits and harms of different anticoagulants.

Objectives

To systematically review the evidence for the relative efficacy and safety of anticoagulants for perioperative thromboprophylaxis in people with cancer.

Search methods

This update of the systematic review was based on the findings of a comprehensive literature search conducted on 14 June 2018 that included a major electronic search of Cochrane Central Register of Controlled Trials (CENTRAL, 2018, Issue 6), MEDLINE (Ovid), and Embase (Ovid); handsearching of conference proceedings; checking of references of included studies; searching for ongoing studies; and using the 'related citation' feature in PubMed.

Selection criteria

Randomized controlled trials (RCTs) that enrolled people with cancer undergoing a surgical intervention and assessed the effects of low-molecular weight heparin (LMWH) to unfractionated heparin (UFH) or to fondaparinux on mortality, deep venous thrombosis (DVT), pulmonary embolism (PE), bleeding outcomes, and thrombocytopenia.

Data collection and analysis

Using a standardized form, we extracted data in duplicate on study design, participants, interventions outcomes of interest, and risk of bias. Outcomes of interest included all-cause mortality, PE, symptomatic venous thromboembolism (VTE), asymptomatic DVT, major bleeding, minor bleeding, postphlebotic syndrome, health related quality of life, and thrombocytopenia. We assessed the certainty of evidence for each outcome using the GRADE approach ([GRADE Handbook](#)).

Main results

Of 7670 identified unique citations, we included 20 RCTs with 9771 randomized people with cancer receiving preoperative prophylactic anticoagulation. We identified seven reports for seven new RCTs for this update.

The meta-analyses did not conclusively rule out either a beneficial or harmful effect of LMWH compared with UFH for the following outcomes: mortality (risk ratio (RR) 0.82, 95% confidence interval (CI) 0.63 to 1.07; risk difference (RD) 9 fewer per 1000, 95% CI 19 fewer to 4 more; moderate-certainty evidence), PE (RR 0.49, 95% CI 0.17 to 1.47; RD 3 fewer per 1000, 95% CI 5 fewer to 3 more; moderate-certainty evidence), symptomatic DVT (RR 0.67, 95% CI 0.27 to 1.69; RD 3 fewer per 1000, 95% CI 7 fewer to 7 more; moderate-certainty evidence), asymptomatic DVT (RR 0.86, 95% CI 0.71 to 1.05; RD 11 fewer per 1000, 95% CI 23 fewer to 4 more; low-certainty evidence), major bleeding (RR 1.01, 95% CI 0.69 to 1.48; RD 0 fewer per 1000, 95% CI 10 fewer to 15 more; moderate-certainty evidence), minor bleeding (RR 1.01, 95% CI 0.76 to 1.33; RD 1 more per 1000, 95% CI 34 fewer to 47 more; moderate-certainty evidence), reoperation for bleeding (RR 0.93, 95% CI 0.57 to 1.50; RD 4 fewer per 1000, 95% CI 22 fewer to 26 more; moderate-certainty evidence), intraoperative transfusion (mean difference (MD) -35.36 mL, 95% CI -253.19 to 182.47; low-certainty evidence), postoperative transfusion (MD 190.03 mL, 95% CI -23.65 to 403.72; low-certainty evidence), and thrombocytopenia (RR 3.07, 95% CI 0.32 to 29.33; RD 6 more per 1000, 95% CI 2 fewer to 82 more; moderate-certainty evidence). LMWH was associated with lower incidence of wound hematoma (RR 0.70, 95% CI 0.54 to 0.92; RD 26 fewer per 1000, 95% CI 39 fewer to 7 fewer; moderate-certainty evidence). The meta-analyses found the following additional results: outcomes intraoperative blood loss (MD -6.75 mL, 95% CI -85.49 to 71.99; moderate-certainty evidence); and postoperative drain volume (MD 30.18 mL, 95% CI -36.26 to 96.62; moderate-certainty evidence).

In addition, the meta-analyses did not conclusively rule out either a beneficial or harmful effect of LMWH compared with Fondaparinux for the following outcomes: any VTE (DVT or PE, or both; RR 2.51, 95% CI 0.89 to 7.03; RD 57 more per 1000, 95% CI 4 fewer to 228 more; low-certainty evidence), major bleeding (RR 0.74, 95% CI 0.45 to 1.23; RD 8 fewer per 1000, 95% CI 16 fewer to 7 more; low-certainty evidence), minor bleeding (RR 0.83, 95% CI 0.34 to 2.05; RD 8 fewer per 1000, 95% CI 33 fewer to 52 more; low-certainty evidence), thrombocytopenia (RR 0.35, 95% CI 0.04 to 3.30; RD 14 fewer per 1000, 95% CI 20 fewer to 48 more; low-certainty evidence), any PE (RR 3.13, 95% CI 0.13 to 74.64; RD 2 more per 1000, 95% CI 1 fewer to 78 more; low-certainty evidence) and postoperative drain volume (MD -20.00 mL, 95% CI -114.34 to 74.34; low-certainty evidence).

Authors' conclusions

We found no difference between perioperative thromboprophylaxis with LMWH versus UFH and LMWH compared with fondaparinux in their effects on mortality, thromboembolic outcomes, major bleeding, or minor bleeding in people with cancer. There was a lower incidence of wound hematoma with LMWH compared to UFH.

PLAIN LANGUAGE SUMMARY

Blood thinners for the prevention of blood clots in people with cancer undergoing surgery

Background

People with cancer undergoing surgery are at an increased risk of blood clots. Blood thinners (anticoagulants) administered to prevent these clots include unfractionated heparin (UFH) infused intravenously (into a vein), low-molecular weight heparin (LMWH) injected subcutaneously (under the skin) once or twice per day, and fondaparinux. These blood thinners may have different effectiveness and safety profiles.

Study characteristics

We searched scientific databases for clinical trials looking at the effects of blood thinners on death, pulmonary embolism (blood clot in the lungs), deep vein thrombosis (blood clot in the veins of the legs), bruising, bleeding, and need for blood transfusion in people with cancer having operations. We included trials of adults and children of any age or sex with either solid tumors or blood cancer irrespective of the type of cancer treatment. The evidence is current to 14 June 2018.

Key results

We found 20 studies that included 9771 people with cancer. The evidence did not identify any difference between the effects of LMWH and UFH on death, getting a blood clot, or bleeding. There was less bruising around the wound following the operation with LMWH compared with UFH. Fondaparinux may have reduced the risk of getting a blood clot.

Reliability of evidence

The reliability of evidence varied from low to moderate across the outcomes of interest.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. LMWH prophylaxis compared to UFH prophylaxis in people with cancer without VTE undergoing a surgery

LMWH prophylaxis compared to UFH prophylaxis in people with cancer without VTE undergoing a surgery

Patient or population: People with cancer with perioperative thromboprophylaxis

Settings: Inpatient

Intervention: LMWH

Comparison: UFH

Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with UFH prophylaxis	Risk difference with LMWH pro- phylaxis
Mortality follow up: range 1 weeks to 3 months	4260 (8 RCTs)	⊕⊕⊕⊖ MODERATE ¹	RR 0.82 (0.63 to 1.07)	Study population 51 per 1000	 9 fewer per 1000 (19 fewer to 4 more)
Any PE follow up: range 1 weeks to 3 months	5588 (14 RCTs)	⊕⊕⊕⊖ MODERATE ²	RR 0.49 (0.17 to 1.47)	Study population 6 per 1000	 3 fewer per 1000 (5 fewer to 3 more)
Symptomatic DVT follow up: range 1 weeks to 3 months	2250 (8 RCTs)	⊕⊕⊕⊖ MODERATE ³	RR 0.67 (0.27 to 1.69)	Study population 10 per 1000	 3 fewer per 1000 (7 fewer to 7 more)
Symptomatic DVT measured as asympto- matic DVT follow up: range 1 weeks to 3 months	4938 (12 RCTs)	⊕⊕⊕⊖ LOW ^{4 5}	RR 0.86 (0.71 to 1.05)	Study population 79 per 1000	 11 fewer per 1000 (23 fewer to 4 more)
Major bleeding follow up: range 1 weeks to 3 months	3473 (9 RCTs)	⊕⊕⊕⊖ MODERATE ⁶	RR 1.01 (0.69 to 1.48)	Study population 31 per 1000	 0 fewer per 1000 (10 fewer to 15 more)
Minor bleeding follow up: range 1 weeks to 3 months	1194 (2 RCTs)	⊕⊕⊕⊖ MODERATE ⁷	RR 1.01 (0.76 to 1.33)	Study population	

				142 per 1000	1 more per 1000 (34 fewer to 47 more)
Wound hematoma follow up: range 1 weeks to 3 months	2827 (6 RCTs)	⊕⊕⊕⊖ MODERATE ^{8 9}	RR 0.70 (0.54 to 0.92)	Study population	
				86 per 1000	26 fewer per 1000 (39 fewer to 7 fewer)
Reoperation for bleeding follow up: range 1 weeks to 3 months	1246 (4 RCTs)	⊕⊕⊕⊖ MODERATE ¹⁰	RR 0.93 (0.57 to 1.50)	Study population	
				51 per 1000	4 fewer per 1000 (22 fewer to 26 more)
Intraoperative transfusion follow up: range 1 weeks to 3 months	737 (2 RCTs)	⊕⊕⊕⊖ LOW ^{11 12}	-		MD 35.36 lower (253.19 lower to 182.47 higher)
Postoperative transfusion follow up: range 1 weeks to 3 months	734 (2 RCTs)	⊕⊕⊕⊖ LOW ^{13 14}	-		MD 190.03 higher (23.65 lower to 403.72 higher)
Intraoperative blood loss follow up: range 1 weeks to 3 months	761 (4 RCTs)	⊕⊕⊕⊖ MODERATE ¹⁵	-		MD 6.75 lower (85.49 lower to 71.99 higher)
Postoperative drain volume follow up: range 1 weeks to 3 months	1459 (3 RCTs)	⊕⊕⊕⊖ MODERATE ¹⁶	-		MD 30.18 higher (36.26 lower to 96.62 higher)
Thrombocytopenia follow up: range 1 weeks to 3 months	683 (2 RCTs)	⊕⊕⊕⊖ MODERATE ¹⁷	RR 3.07 (0.32 to 29.33)	Study population	
				3 per 1000	6 more per 1000 (2 fewer to 82 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

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

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

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

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

- 1 Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (19 fewer per 1000 absolute reduction) and possibility of no effect (4 more per 1000 absolute increase), including 197 events in total.
- 2 Downgraded due to serious imprecision. Low event rate, 26 events in total
- 3 Downgraded due to serious imprecision. Low event rate, 18 events in total
- 4 Downgraded by one level due to serious inconsistency, outcome measured as surrogate outcome
- 5 Downgraded due to serious imprecision. 95% CI is consistent with the possibility of important benefit (23 fewer more per 1000 absolute reduction) and possibility of harm (4 more per 1000 increase), including 367 events in total.
- 6 Downgraded due to serious imprecision. 95% CI is consistent with the possibility of important benefit (10 fewer more per 1000 absolute reduction) and possibility of harm (15 more per 1000 increase), including 107 events in total.
- 7 Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (34 fewer per 1000 absolute reduction) and possibility of no effect (47 more per 1000 absolute increase), including 170 events in total.
- 8 Downgraded due to serious risk of bias; allocation concealment was not clear in 5 out of 6 studies.
- 9 Downgraded due to serious imprecision. Low event rate, 206 events in total
- 10 Downgraded due to serious imprecision. 95% CI is consistent with the possibility of benefit (22 fewer per 1000 absolute reduction) and possibility of important harm (26 more per 1000 absolute increase), including 61 events in total.
- 11 Downgraded due to serious inconsistency. I² = 98%; Dahan 1990 included patients undergoing thoracic surgery for cancer whereas Koppenhagen 1992 included patients undergoing major elective abdominal surgery
- 12 Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (253.19 mL less) and possibility of harm (182.47 mL more)
- 13 Downgraded due to serious inconsistency. I² = 83%; Dahan 1990 included patients undergoing thoracic surgery for cancer whereas Koppenhagen 1992 included patients undergoing major elective abdominal surgery
- 14 Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (23.65mL less) and possibility of harm (40.3.72mL more)
- 15 Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (85.49 mL less) and possibility of harm (71.99 mL more)
- 16 Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (36.26 mL less) and possibility of harm (96.62 mL more)
- 17 Downgraded due to serious imprecision. Low event rate, 4 events in total

Summary of findings 2. LMWH prophylaxis compared to fondaparinux prophylaxis in people with cancer without VTE undergoing a surgical procedure

LMWH prophylaxis compared to fondaparinux prophylaxis in people with cancer without VTE undergoing a surgical procedure

Patient or population: People with perioperative thromboprophylaxis in people with cancer

Settings: Inpatient

Intervention: LMWH

Comparison: Fondaparinux

Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Fondaparinux prophylaxis	Risk difference with LMWH prophylaxis
Mortality - not reported	-	-	-	-	-

Any VTE follow up: 3 months	1806 (3 RCTs)	⊕⊕⊕⊕ LOW ^{1 2}	RR 2.51 (0.89 to 7.03)	Study population	
				38 per 1000	57 more per 1000 (4 fewer to 228 more)
Major Bleeding follow up: 3 months	2339 (3 RCTs)	⊕⊕⊕⊕ LOW ^{2 4}	RR 0.74 (0.45 to 1.23)	Study population	
				29 per 1000	8 fewer per 1000 (16 fewer to 7 more)
Minor Bleeding	398 (2 RCTs)	⊕⊕⊕⊕ LOW ^{5 6}	RR 0.83 (0.34 to 2.05)	Study population	
				49 per 1000	8 fewer per 1000 (33 fewer to 52 more)
Thrombocytopenia	282 (1 RCT)	⊕⊕⊕⊕ LOW ^{7 8}	RR 0.35 (0.04 to 3.30)	Study population	
				21 per 1000	14 fewer per 1000 (20 fewer to 48 more)
Any Pulmonary em- bolism	116 (1 RCT)	⊕⊕⊕⊕ LOW ⁹	RR 3.10 (0.13 to 74.64)	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
				Low	
				1 per 1000	2 more per 1000 (1 fewer to 74 more)
Postoperative drain volume	116 (1 RCT)	⊕⊕⊕⊕ LOW ¹⁰	-	The mean postoperative drain volume was 0 ml	MD 20 ml lower (114.34 lower to 74.34 higher)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

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

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

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

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

- ¹ Downgraded by one level for concerns about both imprecision and indirectness. 95% CI is consistent with the possibility for benefit (4 per 1000 absolute reduction) and possibility of important harm (22 per 1000 absolute increase), including 99 events in total. VTE events included both symptomatic and asymptomatic events for patients with cancer which introduces some level of indirectness.
- ² Downgraded by one level due to high risk of bias (lack of allocation concealment and incomplete outcome data in Agnelli 2005; lack of blinding of patients and personnel and incomplete outcome data in Hata 2016 unclear allocation concealment in Song 2018)
- ³ Although the event rate used from the fondaparinux arm includes asymptomatic events, it is very close to rate of symptomatic VTE (3.1%) found in a retrospective cohort Changolkar 2014
- ⁴ Downgraded for serious imprecision. 95% CI is consistent with the possibility for important benefit (16 per 1000 absolute reduction) and possibility of important harm (7 per 1000 absolute increase), including 60 events in total.
- ⁵ Downgraded for high risk of bias (lack of blinding of patients and personnel and incomplete outcome data in Hata 2016 and unclear allocation concealment in Song 2018)
- ⁶ Downgraded for serious imprecision. 95% CI is consistent with the possibility for important benefit (33 per 1000 absolute reduction) and possibility of important harm (52 per 1000 absolute increase), including 18 events in total.
- ⁷ Downgraded for high risk of bias (lack of blinding of patients and personnel and incomplete outcome data in Hata 2016)
- ⁸ Downgraded for serious imprecision. 95% CI is consistent with the possibility for important benefit (20 per 1000 absolute reduction) and possibility of important harm (48 per 1000 absolute increase), including 4 events in total.
- ⁹ Downgraded by two levels for very serious imprecision. 95% CI is consistent with the possibility for important benefit (1 per 1000 absolute reduction) and possibility of important harm (78 per 1000 absolute increase), including 1 event in total.
- ¹⁰ Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (114.34 mL less) and possibility of harm (74.34 mL more)

BACKGROUND

Description of the condition

People with cancer undergoing surgical procedures have a higher risk of venous thromboembolism (VTE) (deep venous thrombosis (DVT) or pulmonary embolism (PE), or both) than people without cancer (Gallus 1997; Kakkar 1970; Rahr 1992). It is estimated that cancer triples the risk of postoperative DVT (Edmonds 2004). Moreover, people with cancer and VTE have an increased risk of dying than people with VTE alone or with cancer alone (Levitan 1999; Sorensen 2000). It has been suggested that thromboprophylaxis might be less effective in people with cancer due to the prothrombotic state associated with malignancy (Flordal 1996; Gallus 1997).

Description of the intervention

Unfractionated heparin (UFH), and low-molecular weight heparins (LMWH) do not have intrinsic anticoagulant activity but potentiate the activity of antithrombin III in inhibiting activated coagulation factors. These agents constitute indirect anticoagulants as their activity is mediated by plasma cofactors. Heparin and its low molecular weight derivatives are not absorbed orally and must be administered parenterally (Hirsh 1993). Both UFH and LMWH, in addition to fondaparinux, have been used for perioperative thromboprophylaxis in people with cancer undergoing surgery.

How the intervention might work

Through their anticoagulant effect, UFH and LMWH reduce the incidence of both DVT and PE and subsequently reduce the incidence of VTE-associated mortality (Barritt 1960). At the same time, they increase the risk of bleeding that might be potentiated by the presence of surgical wounds.

Why it is important to do this review

Two systematic reviews found that heparins were superior to no anticoagulation in the prevention of DVT and PE in people undergoing colorectal (Borly 2005) or general surgery (Mismetti 2001). Mismetti 2001 found that among general surgery people, LMWH and UFH had similar efficacy and safety irrespective of cancer status. However, the authors did not provide the estimates of the relative effects of the two medications in people with cancer. The last update of this Cochrane systematic review (16 trials enrolling 12,890 participants) found no any significant differences in the relative benefits and harms of the two medications (Akl 2014).

OBJECTIVES

To systematically review the evidence for the relative efficacy and safety of anticoagulants for perioperative thromboprophylaxis in people with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People with cancer planned to undergo a surgical intervention. People could have been of any age with either solid or hematologic cancer and at any stage of their cancer irrespective of the type of cancer therapy.

We included studies with subgroups of people with cancer that did not report subgroup specific data when people with cancer constituted 50% or more of the total population. Otherwise, we excluded them from the systematic review.

Types of interventions

Experimental arms: any anticoagulant.

- Low-molecular weight heparin (LMWH)
- Unfractionated heparin (UFH)
- Fondaparinux

We were interested in comparisons of any combination of the three management options listed above. We excluded studies that compared different types of LMWH or any anticoagulant to placebo. The protocol should have planned to provide all other co interventions (e.g. chemotherapy) similarly in the intervention and comparison group.

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Pulmonary embolism (PE). PE events had to be suspected clinically, and diagnosed using an objective diagnostic test such as: pulmonary perfusion/ventilation scans, computed tomography, pulmonary angiography, or autopsy.
- Symptomatic deep venous thrombosis (DVT). DVT events had to be suspected clinically, and diagnosed using an objective diagnostic test such as: venography, ¹²⁵I-fibrinogen-uptake test, impedance plethysmography, or compression ultrasound.
- Asymptomatic DVT. DVT detected by screening and diagnosed using an objective diagnostic test such as: venography, ¹²⁵I-fibrinogen-uptake test, impedance plethysmography, or compression ultrasound.
- Bleeding outcomes:
 - major bleeding: we accepted the authors' definitions of major bleeding
 - minor bleeding: we accepted the authors' definitions of minor bleeding
 - wound hematoma
 - reoperation for bleeding
 - transfusion (intraoperative, postoperative)
 - intraoperative blood loss
 - postoperative drain volume
- Thrombocytopenia.
- Health related quality of life.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in participants with cancer. We conducted comprehensive searches on 14 June 2018, following the original electronic searched in January 2007, February 2010, February 2013, and February 2016. We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6), MEDLINE Ovid (starting 1946), and Embase Ovid (starting 1980). For each database, the search strategies combined terms for anticoagulants, terms for cancer, and a search filter for RCTs. We used no language restrictions. We listed the full search strategies for each of the electronic databases in [Appendix 1](#); [Appendix 2](#); and [Appendix 3](#).

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982 up to June 2018) and of the American Society of Hematology (ASH, starting with its 2003 issue up to June 2018). We also searched [ClinicalTrials.gov](#) and [World Health Organization International Clinical Trials Registry Platform](#) for ongoing studies. We reviewed the reference lists of papers included in this review and of other relevant systematic reviews. We used the 'related citation' feature in PubMed to identify additional articles and 'citation tracking' of included studies in Web of Science Core Collection. In addition, we contacted experts in the field to check for unpublished and ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (CFM and LAK) independently screened the title and abstract of identified citations for potential eligibility. We retrieved the full text of articles judged potentially eligible by at least one review author. Two review authors then independently screened the full-text articles for eligibility using a standardized form with explicit inclusion and exclusion criteria (as detailed in the [Criteria for considering studies for this review](#) section). The two review authors resolved any disagreements about which articles were eligible by discussion or by consulting a third review author (EAA).

Data extraction and management

Two review authors (CFM and IGT) independently extracted data from each included study and resolved their disagreements by discussion. We aimed to collect data related to participants, interventions, outcomes, and others.

Participants

- Number of people in each treatment arm
- Number of people randomized to each treatment arm
- Number of people followed up in each treatment arm
- Number of withdrawals from treatment in each treatment arm
- Demographic characteristics (e.g. age, sex)
- Cancer characteristics (e.g. type, location, site of origin, stage, time since diagnosis, estimated life expectancy, current cancer treatments, performance status)
- Description of the surgical procedure

- History of VTE
- Use of indwelling central venous catheters (CVC)

Interventions

- Type of anticoagulant: LMWH, UFH, or fondaparinux
- Dose: prophylactic versus therapeutic
- Duration of treatment
- Cointerventions including radiation therapy, chemotherapy, and hormonal therapy (type and duration)

Outcomes

We attempted to extract both time-to-event data (for all-cause mortality) and categorical data (for all outcomes). However, none of the studies reported time-to-event data for people with cancer. For dichotomous data, we extracted data necessary to conduct a complete-case analysis as the primary analysis. For continuous data, we extracted mean and standard deviation (SD) separately for each arm.

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

Other

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

- source of funding
- ethical approval
- conflict of interest
- intention-to-treat (ITT) analysis

Assessment of risk of bias in included studies

We assessed risk of bias at the trial level using Cochrane's 'Risk of bias' tool ([Higgins 2011](#)). Two review authors (CFM and LAK) independently assessed the risk of bias for each included trial and resolved any disagreements by discussion. 'Risk of bias' criteria included:

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data (percentage of follow-up and whether this was addressed)
- selective reporting
- other bias (whether the trial was stopped early for benefit)

See [Dealing with missing data](#) section about assessing risk of bias associated with participants with missing data.

Measures of treatment effect

We collected and analyzed risk ratios (RRs) for categorical data, and mean differences (MD) for continuous data, with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Determining participants with missing data

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

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

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

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

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

- denominator: (number of participants randomized) – (number of participants most likely with missing data, both pre- and postintervention initiation);
- numerator: number of participants with observed events (i.e. participants who had at least one event for the outcome of interest during their available follow-up time).

For continuous data, we planned to use the reported mean and SD for each study arm for participants actually followed up by the trial authors.

Assessing the risk of bias associated with participants with missing data

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

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

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

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

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

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

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

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

Assessment of heterogeneity

We assessed heterogeneity among trials by visual inspection of forest plots, estimation of the percentage heterogeneity among trials that could not be ascribed to sampling variation (I^2 test) (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this (see *Subgroup analysis and investigation of heterogeneity* section).

Assessment of reporting biases

We assessed for selective outcome reporting by trying to identify whether the study was included in a trial registry, whether a protocol was available, and whether the methods section provided a list of outcomes. We compared the list of outcomes from those sources to the outcomes reported in the published paper. Also, we created funnel plots to assess publication.

Data synthesis

For dichotomous data, we calculated the RR separately for each study (DerSimonian 1986; RevMan 2014), and for continuous data, we calculated the MD separately for each trial. When analyzing data related to participants who were reported as not compliant, we attempted to adhere to the principles of ITT analysis. We

approached the issue of non-compliance independently from that of missing data ([Alshurafa 2012](#)). We then pooled the results of the different studies using a random-effects model.

'Summary of findings' tables

We created 'Summary of findings' tables and assessed the certainty of evidence for all outcomes using the GRADE approach ([GRADE Handbook](#)).

Subgroup analysis and investigation of heterogeneity

We planned to explore substantial heterogeneity by conducting subgroup analyses based on the characteristics of participants (type, severity, and stage of cancer, and whether people were on cancer treatment or not). We did not conduct any subgroup analyses because of the relatively small number of trials and the inclusion of different types of cancer in the same trial.

Sensitivity analysis

Unlike the 2014 update of this review, we included studies published as abstracts only in the sensitivity analysis. When the primary meta-analysis of a specific outcome found a statistically significant effect, we conducted sensitivity meta-analyses to assess the risk of bias associated with missing participant data.

RESULTS

Description of studies

Results of the search

[Figure 1](#) shows the study flow diagram. As of June 2018, the search strategy identified 7670 unique citations after removal of duplicates. In total, the title and abstract screening identified 167 citations as potentially eligible for this review. The full-text screening of the 167 citations identified 32 full reports for 20 eligible RCTs ([Agnelli 2005](#); [Baykal 2001](#); [Bergqvist 1990](#); [Bergqvist 1997](#) (ENOXACAN); [Boncinelli 2001](#); [Dahan 1990](#); [Encke 1988](#) (EFS); [Fricker 1988](#); [Gallus 1993](#); [Goldhaber 2002](#); [Hata 2016](#); [Kakkar 1997](#); [Kakkar 2005](#); [Kopenhagen 1992](#); [Onarheim 1986](#); [Song 2018](#); [Von Tempelhoff 1997](#); [Von Tempelhoff 2000](#); [Ward 1998](#)), and one RCT published as an abstract ([Godwin 1993](#)). We excluded the remaining 135 full texts. One eligible study did not provide outcome data that could be included in the meta-analysis so we summarized its results narratively ([Kakkar 2005](#)). We identified seven reports for six RCTs not included in previous version of this review. We identified one ongoing study ([Safi 2011](#)).

Figure 1. Study flow diagram. CVC: central venous catheter; LMWH: low-molecular weight heparin; RCT: randomized controlled trial; UFH: unfractionated heparin; VTE: venous thromboembolism.

Figure 1. (Continued)

included in
quantitative
synthesis
(meta-analysis)

Included studies

We included 20 RCTs in this review (Agnelli 2005; Baykal 2001; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Dahan 1990; Encke 1988 (EFS); Fricker 1988; Gallus 1993; Godwin 1993; Goldhaber 2002; Hata 2016; Kakkar 1997; Kakkar 2005; Koppenhagen 1992; Onarheim 1986; Song 2018; Von Tempelhoff 1997; Von Tempelhoff 2000; Ward 1998). One of these trials was published as an abstract (Godwin 1993). See [Characteristics of included studies](#) table.

Participant characteristics

Trials were conducted in people with cancer undergoing the following types of surgery: gynecologic (four trials; Baykal 2001; Von Tempelhoff 1997; Von Tempelhoff 2000; Ward 1998), abdominal or pelvic (eight trials; Agnelli 2005; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Encke 1988 (EFS); Fricker 1988; Godwin 1993; Koppenhagen 1992; Onarheim 1986), thoracic (one trial; Dahan 1990), abdominal or thoracic (two trials; Gallus 1993; Song 2018), prostate (one trial; Boncinelli 2001), neurosurgery (one trial; Goldhaber 2002), urologic (one trial; Hata 2016), and unspecified (two trials; Kakkar 1997; Kakkar 2005). Mean age of participants varied from 46 to 71 years across included trials.

Interventions

Types of LMWH studied were: enoxaparin (four trials; Baykal 2001; Bergqvist 1997 (ENOXACAN); Goldhaber 2002; Hata 2016); dalteparin (five trials; Agnelli 2005; Bergqvist 1990; Fricker 1988; Onarheim 1986; Ward 1998); nadroparin (four trials; Boncinelli 2001; Dahan 1990; Encke 1988 (EFS); Song 2018); orgaran (one trial; Gallus 1993); normiflo (one trial; Godwin 1993); certoparin (two trials; Kakkar 2005; Von Tempelhoff 2000); clivarine (one trial; Kakkar 1997); and not specified (two trials; Koppenhagen 1992; Von Tempelhoff 1997). All trials started thromboprophylaxis preoperatively.

Outcomes

Comparison 1: low-molecular weight heparin versus unfractionated heparin

- Eight trials reported mortality (Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Gallus 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Von Tempelhoff 2000). Kakkar 2005 reported overall mortality in all trial participants but not by group.
- 14 trials reported PE (Baykal 2001; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Dahan 1990; Encke 1988 (EFS); Fricker 1988; Gallus 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Von Tempelhoff 1997; Ward 1998). Kakkar 2005 reported overall incidence of PE in all trial participants but not by group.

- Eight trials reported symptomatic DVT (Baykal 2001; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Fricker 1988; Goldhaber 2002; Koppenhagen 1992; Onarheim 1986; Ward 1998).
- 12 trials reported asymptomatic DVT (Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Dahan 1990; Encke 1988 (EFS); Fricker 1988; Gallus 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Von Tempelhoff 1997).
- Nine trials reported major bleeding (Baykal 2001; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Dahan 1990; Fricker 1988; Gallus 1993; Goldhaber 2002; Kakkar 1997; Onarheim 1986).
- Two trials reported minor bleeding (Bergqvist 1997 (ENOXACAN); Fricker 1988).
- Six trials reported wound hematoma (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Kakkar 1997; Koppenhagen 1992; Onarheim 1986).
- Four trials reported reoperation for bleeding (Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Gallus 1993; Onarheim 1986).
- Two trials reported intraoperative transfusion (Dahan 1990; Koppenhagen 1992).
- Two trials reported postoperative transfusion (Dahan 1990; Koppenhagen 1992).
- Four trials reported intraoperative blood loss (Baykal 2001; Dahan 1990; Gallus 1993; Onarheim 1986).
- Three trials reported postoperative drain volume (Baykal 2001; Encke 1988 (EFS); Koppenhagen 1992).
- Two trials reported thrombocytopenia (Bergqvist 1997 (ENOXACAN); Onarheim 1986).

Comparison 2: low-molecular weight heparin versus fondaparinux

- One trial reported any PE (Song 2018)
- Three trials reported VTE (Agnelli 2005; Hata 2016; Song 2018).
- Three trials reported major bleeding (Agnelli 2005; Hata 2016; Song 2018).
- Two trials reported minor bleeding (Hata 2016; Song 2018).
- One trial reported thrombocytopenia (Hata 2016).
- One trial reported postoperative drain volume (Song 2018).

Excluded studies

We excluded 135 reports of 80 trials from this review for the following reasons: not population of interest, hospitalized people (11 studies); not population of interest, ambulatory people (27 studies); not population of interest, people with CVC (seven studies); not population of interest, people with VTE (19 studies); not comparison of interest, preoperative versus postoperative anticoagulation (two studies); not comparison of interest, mechanical versus pharmacologic (12 studies); not comparison of interest, different dosages of LMWH (one study); not comparison of interest, different dosages of UFH (two studies); not comparison of interest, UFH versus placebo (four studies); not

comparison of interest, LMWH versus placebo (six studies); not comparison of interest, different types of LMWH (two studies); not comparison of interest, defibrotide versus UFH (one study); not comparison of interest, defibrotide versus placebo (one study); not comparison of interest, extended versus limited duration of anticoagulation (25 studies); not design of interest, a systematic review (one study); no outcomes of interest (two studies), and

no outcome data available for cancer people (12 studies). See [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Figure 2 presents the 'Risk of bias' graph while Figure 3 presents the 'Risk of bias' summary associated with the outcomes: mortality, PE, DVT, and major bleeding.

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agnelli 2005	+	?	+	+	-	+	+
Baykal 2001	+	+	+	+	+	+	+
Bergqvist 1990	+	?	+	+	+	+	+
Bergqvist 1997 (ENOXACAN)	+	?	+	+	-	+	+
Boncinelli 2001	+	?	-	+	+	+	+
Dahan 1990	?	?	-	+	+	?	+
Encke 1988 (EFS)	+	?	-	+	?	+	+
Fricker 1988	?	?	-	+	+	+	+
Gallus 1993	+	+	-	+	?	+	+
Godwin 1993	?	?	-	+	+	+	+
Goldhaber 2002	+	?	+	+	-	+	+
Hata 2016	+	+	-	+	-	+	+
Kakkar 1997	?	?	+	+	-	+	+
Kakkar 2005	+	?	+	+	?	+	-
Kopenhagen 1992	+	?	+	+	-	+	+
Onarheim 1986	+	?	+	+	+	+	+
Song 2018	+	?	+	+	+	+	+
Von Tempelhoff 1997	?	?	+	+	+	+	+
Von Tempelhoff 2000	+	+	+	+	+	-	+
Ward 1998	+	+	-	+	-	+	+

Figure 3. (Continued)

Allocation

The method of sequence generation was unclear in five studies (Dahan 1990; Fricker 1988; Godwin 1993; Kakkar 1997; Von Tempelhoff 1997), but adequate in the remaining one.

Allocation was adequately concealed in five trials (Baykal 2001; Gallus 1993; Hata 2016; Von Tempelhoff 2000; Ward 1998). It was unclear whether it was adequately concealed in the remaining 14 trials.

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be definitely blinded in 12 studies (Agnelli 2005; Baykal 2001; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Goldhaber 2002; Kakkar 1997; Kakkar 2005; Koppenhagen 1992; Onarheim 1986; Song 2018; Von Tempelhoff 1997; Von Tempelhoff 2000), and definitely not blinded in the remaining eight studies.

Blinding of outcome assessment (detection bias)

We judged outcome assessors to be definitely blinded in all 20 studies.

Incomplete outcome data

Follow-up was satisfactory in all the trials with the following percentages: 72% in Agnelli 2005; 100% in Baykal 2001; 100% in Bergqvist 1990; 56% in Bergqvist 1997 (ENOXACAN); 100% in Boncinelli 2001; 100% in Dahan 1990; 100% in Encke 1988 (EFS); 100% in Fricker 1988; 95% in Gallus 1993; 100% in Godwin 1993; 96% in Goldhaber 2002; 94% in Hata 2016; 99% in Kakkar 1997; 100% in Kakkar 2005; 97% in Koppenhagen 1992; 100% in Onarheim 1986; 100% in Song 2018; 100% in Von Tempelhoff 1997; 100% in Von Tempelhoff 2000; and 97% in Ward 1998.

We judged incomplete outcome data to be with low risk of bias in 10 studies (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Dahan 1990; Fricker 1988; Godwin 1993; Onarheim 1986; Song 2018; Von Tempelhoff 1997; Von Tempelhoff 2000); high risk in seven studies (Agnelli 2005; Bergqvist 1997 (ENOXACAN); Goldhaber 2002; Hata 2016; Kakkar 1997; Koppenhagen 1992; Ward 1998); and unclear risk of bias in the remaining studies.

Selective reporting

The outcomes listed in the methods section were reported in the results section for all trials. Von Tempelhoff 2000 appeared to have collected data on VTE outcomes but did not report them, so was at high risk of bias. It was unclear whether Dahan 1990 had any reporting bias.

Other potential sources of bias

The only trial that was stopped early was Kakkar 2005. We judged the associated risk of bias to be high because the reason to stop was that the study would not be sufficiently powered to show superiority of certoparin over UFH.

Effects of interventions

See: [Summary of findings for the main comparison LMWH prophylaxis compared to UFH prophylaxis in people with cancer without VTE undergoing a surgery](#); [Summary of findings 2 LMWH prophylaxis compared to fondaparinux prophylaxis in people with cancer without VTE undergoing a surgical procedure](#)

Comparison 1: low-molecular weight heparin versus unfractionated heparin

Fourteen trials reported LMWH versus UFH (Baykal 2001; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Dahan 1990; Encke 1988 (EFS); Fricker 1988; Gallus 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Von Tempelhoff 1997; Ward 1998).

All-cause mortality

Meta-analysis of eight trials reporting data on 4260 participants did not conclusively rule out a mortality reduction with LMWH compared with UFH (RR 0.82, 95% CI 0.63 to 1.07; RD 9 fewer per 1000, 95% CI 19 fewer to 4 more; [Analysis 1.1](#)); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important ($I^2 = 0\%$;) (Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Gallus 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Von Tempelhoff 2000). Kakkar 2005 found no difference in outcomes between the two treatment regimens. The inverted funnel plot for the primary outcome of mortality did not suggest publication bias, but there were relatively few trials to permit an accurate assessment ().

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Pulmonary embolism

Meta-analysis of 14 trials reporting data on 5588 participants did not conclusively rule out a reduction or increase in PE with LMWH compared with UFH (RR 0.49, 95% CI 0.17 to 1.47; RD 3 fewer per 1000, 95% CI 5 fewer to 3 more; $I^2 = 0\%$; [Analysis 1.2](#)) (Baykal 2001; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Boncinelli 2001; Dahan 1990; Encke 1988 (EFS); Fricker 1988; Gallus 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Von Tempelhoff 1997; Ward 1998). These results did not change in a meta-analysis including the study published as an abstract (RR 0.52, 95% CI 0.20 to 1.34;) (Godwin 1993). The inverted funnel plot for PE did not suggest publication bias, but there were relatively few trials to permit an accurate assessment.

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Symptomatic deep venous thrombosis

Meta-analysis of eight trials reporting data on 2250 participants did not conclusively rule out a symptomatic DVT reduction or increase with LMWH compared with UFH (RR 0.67, 95% CI 0.27 to 1.69; RD

3 fewer per 1000, 95% CI 7 fewer to 7 more; $I^2 = 0\%$; [Analysis 1.3](#)) ([Baykal 2001](#); [Bergqvist 1997 \(ENOXACAN\)](#); [Boncinelli 2001](#); [Fricker 1988](#); [Goldhaber 2002](#); [Kopenhagen 1992](#); [Onarheim 1986](#); [Ward 1998](#)).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Asymptomatic deep venous thrombosis

Meta-analysis of 12 trials reporting data on 4938 participants did not conclusively rule out a reduction in asymptomatic DVT with LMWH compared with UFH (RR 0.86, 95% CI 0.71 to 1.05; RD 11 fewer per 1000, 95% CI 23 fewer to 4 more; $I^2 = 0\%$; [Analysis 1.4](#)) ([Bergqvist 1990](#); [Bergqvist 1997 \(ENOXACAN\)](#); [Boncinelli 2001](#); [Dahan 1990](#); [Encke 1988 \(EFS\)](#); [Fricker 1988](#); [Gallus 1993](#); [Goldhaber 2002](#); [Kakkar 1997](#); [Kopenhagen 1992](#); [Onarheim 1986](#); [Von Tempelhoff 1997](#)). These results did not substantively change in a meta-analysis including the study published as an abstract (RR 0.87, 95% CI 0.70 to 1.07) ([Godwin 1993](#)). The inverted funnel plot for asymptomatic DVT did not suggest publication bias, but there were relatively few trials to permit an accurate assessment (Figure 10).

The certainty of evidence was low ([Summary of findings for the main comparison](#)).

Bleeding outcomes

Major bleeding

Meta-analysis of nine trials reporting data on 3473 participants did not conclusively rule out a reduction or increase in major bleeding with LMWH compared with UFH (RR 1.01, 95% CI 0.69 to 1.48; RD 0 fewer per 1000, 95% CI 10 fewer to 15 more; $I^2 = 0\%$; [Analysis 1.5](#)) ([Baykal 2001](#); [Bergqvist 1997 \(ENOXACAN\)](#); [Boncinelli 2001](#); [Dahan 1990](#); [Fricker 1988](#); [Gallus 1993](#); [Goldhaber 2002](#); [Kakkar 1997](#); [Onarheim 1986](#)). The inverted funnel plot for major bleeding did not suggest publication bias, but there were relatively few trials to permit an accurate assessment.

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Minor bleeding

Meta-analysis of two trials reporting data on 1194 participants did not conclusively rule out a reduction or increase in minor bleeding with LMWH compared with UFH (RR 1.01, 95% CI 0.76 to 1.33; RD 1 more per 1000, 95% CI 34 fewer to 47 more; $I^2 = 0\%$; [Analysis 1.6](#)) ([Bergqvist 1997 \(ENOXACAN\)](#); [Fricker 1988](#)).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Wound hematoma

Meta-analysis of six trials assessing 2827 participants found a reduction in wound hematomas with LMWH compared with UFH (RR 0.70, 95% CI 0.54 to 0.92; RD 26 fewer per 1000, 95% CI 39 fewer to 7 fewer; $I^2 = 0\%$; [Analysis 1.7](#)) ([Baykal 2001](#); [Bergqvist 1990](#); [Boncinelli 2001](#); [Kakkar 1997](#); [Kopenhagen 1992](#); [Onarheim 1986](#)).

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

effect estimate remained statistically significant even when using the most stringent plausible assumption (RR 0.73, 95% CI 0.56 to 0.95).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Reoperation for bleeding

Meta-analysis of four trials reporting data on 1246 participants did not conclusively rule out a reduction or increase in re operations for bleeding with LMWH compared with UFH (RR 0.93, 95% CI 0.57 to 1.50; RD 4 fewer per 1000, 95% CI 22 fewer to 26 more; $I^2 = 0\%$; [Analysis 1.8](#)) ([Bergqvist 1997 \(ENOXACAN\)](#); [Boncinelli 2001](#); [Gallus 1993](#); [Onarheim 1986](#)).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Transfusion: intraoperative

Two trials reporting data on 737 participants found no difference in intraoperative transfusion volume with LMWH compared with UFH (MD -35.36 mL, 95% CI -253.19 to 182.47; [Analysis 1.9](#)) ([Dahan 1990](#); [Kopenhagen 1992](#)).

The certainty of evidence was low ([Summary of findings for the main comparison](#)).

Transfusion: postoperative

Two trials assessing 734 participants found no difference in postoperative transfusions with LMWH compared with UFH (MD 190.03 mL, 95% CI -23.65 to 403.72; [Analysis 1.10](#)) ([Dahan 1990](#); [Kopenhagen 1992](#)).

The certainty of evidence was low ([Summary of findings for the main comparison](#)).

Intraoperative blood loss

Meta-analysis of four trials reporting data on 761 participants found no difference in intraoperative blood loss with LMWH compared with UFH (MD -6.75 mL, 95% CI to -85.49 to 71.99; [Analysis 1.11](#)) ([Baykal 2001](#); [Dahan 1990](#); [Gallus 1993](#); [Onarheim 1986](#)).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Postoperative drain volume

Meta-analysis of three trials reporting data on 1459 participants found no difference in postoperative drain volume with LMWH compared with UFH (MD 30.18 mL, 95% CI -36.26 to 96.62; [Analysis 1.12](#)) ([Baykal 2001](#); [Encke 1988 \(EFS\)](#); [Kopenhagen 1992](#)).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Thrombocytopenia

Meta-analysis of two trials reporting data on 683 participants did not conclusively rule out a thrombocytopenia reduction or increase with LMWH compared to UFH (RR 3.07, 95% CI 0.32 to 29.33; RD 6 more per 1000, 95% CI 2 fewer to 82 more; [Analysis 1.13](#)) ([Bergqvist 1997 \(ENOXACAN\)](#); [Onarheim 1986](#)). The RR was reduced substantively in a meta-analysis including the study published as an abstract ([Godwin 1993](#)) (RR 1.20, 95% CI 0.41 to 3.50).

The certainty of evidence was moderate ([Summary of findings for the main comparison](#)).

Heparin-induced thrombocytopenia

We found no trials reporting the relative effects of LMWH and UFH on heparin-induced thrombocytopenia (HIT).

Health related quality of life

We found no trials reporting the relative effects of LMWH and UFH on health related quality of life.

Comparison 2: low-molecular weight heparin versus fondaparinux

Three trials compared LMWH versus fondaparinux ([Agnelli 2005](#); [Hata 2016](#); [Song 2018](#)).

All-cause mortality

Neither trial reported all-cause mortality.

Any pulmonary embolism

The one study reporting data on 116 participants did not rule out an increase or decrease risk of any PE with LMWH compared with fondaparinux (RR 3.13, 95% CI 0.13 to 74.64; RD 2 more per 1000, 95% CI 1 fewer to 78 more; [Analysis 2.1](#)) ([Song 2018](#)).

The certainty of evidence was low ([Summary of findings 2](#)).

Symptomatic and asymptomatic deep venous thrombosis

Venous thromboembolism

Meta-analysis of three trials reporting data on 1806 participants did not rule out an increase or decrease risk in VTE with LMWH compared with fondaparinux (RR 2.51, 95% CI 0.89 to 7.03; RD 57 more per 1000, 95% CI 4 fewer to 228 more; [Analysis 2.2](#)); $I^2 = 31\%$) ([Agnelli 2005](#); [Hata 2016](#); [Song 2018](#)).

The certainty of evidence was low ([Summary of findings 2](#)).

Bleeding outcomes

Major bleeding

Meta-analysis of three trials reporting data on 2339 participants did not rule out an increase or decrease in major bleeding with LMWH compared with fondaparinux (RR 0.74, 95% CI 0.45 to 1.23; RD 8 fewer per 1000, 95% CI 16 fewer to 7 more; $I^2 = 0\%$; [Analysis 2.3](#)) ([Agnelli 2005](#); [Hata 2016](#); [Song 2018](#)).

The certainty of evidence was low ([Summary of findings 2](#)).

Minor bleeding

Meta-analysis of two trials reporting data on 398 participants did not rule out an increase or decrease in minor bleeding with LMWH compared with fondaparinux (RR 0.83, 95% CI 0.34 to 2.05; RD 8 fewer per 1000, 95% CI 33 fewer to 52 more; [Analysis 2.4](#);) ([Hata 2016](#); [Song 2018](#)).

The certainty of evidence was low ([Summary of findings 2](#)).

Wound hematoma

Neither trial reported wound hematoma.

Reoperation for bleeding

Neither trial reported reoperation for bleeding.

Transfusion: intraoperative

Neither trial reported intraoperative transfusion.

Transfusion: postoperative

Neither trial reported postoperative transfusion.

Intraoperative blood loss

Neither trial reported intraoperative blood loss.

Postoperative drain volume

The one study reporting data on 116 participants found no difference in postoperative drain volume with LMWH compared with fondaparinux (MD -20 mL, 95% CI -114.34 to 74.34; [Analysis 2.5](#)) ([Song 2018](#)).

The certainty of evidence was low ([Summary of findings 2](#)).

Thrombocytopenia

The one study reporting data on 282 participants did not rule out an increase or decrease in thrombocytopenia with LMWH compared with fondaparinux (RR 0.35, 95% CI 0.04 to 3.30; RD 14 fewer per 1000, 95% CI 20 fewer to 48 more; [Analysis 2.6](#)) ([Hata 2016](#)).

The certainty of evidence was low ([Summary of findings 2](#)).

Health related quality of life

We found no trials reporting the relative effects of LMWH and fondaparinux on health related quality of life.

DISCUSSION

Summary of main results

We did not conclusively rule out either beneficial or harmful effects of LMWH compared with UFH; and LMWH compared with fondaparinux for the outcomes of mortality, symptomatic DVT, PE, minor bleeding, and major bleeding. There was a lower incidence of wound hematoma with LMWH compared to UFH; None of the trials reported on HIT. The certainty of evidence per outcome ranged from low to moderate.

Overall completeness and applicability of evidence

While the absence of a statistically significant difference might reflect a true absence of effect of LMWH on some VTE outcomes, this could also be related to insufficient power to detect important differences between drugs. Another potential explanation is the relatively low baseline risks for the different outcomes (e.g. the baseline risk for PE was 0.6%).

These trials recruited people with variety of cancer types and stages, which should increase the applicability of the results.

All included trials started anticoagulant treatment preoperatively. Consequently, it is not certain how the results apply to anticoagulant treatment started postoperatively. However, one systematic review found no statistically significant differences in blood loss when the first dose of enoxaparin was administered 12 hours before surgery versus postoperatively ([Einstein 2007](#)).

Quality of the evidence

For the comparison of LMWH versus UFH, we judged the certainty of evidence as moderate for mortality, PE, symptomatic DVT, asymptomatic DVT, minor bleeding, major bleeding, wound hematoma, reoperation for bleeding, intraoperative blood loss, postoperative drain volume, and thrombocytopenia, and as low for intraoperative transfusion and postoperative transfusion. The certainty of evidence per outcome ranged from low to moderate.

For the comparison of LMWH versus fondaparinux, we judged the certainty of evidence as low for all outcomes.

Screening participants for DVT may have biased the results of 13 included trials (Agnelli 2005; Bergqvist 1990; Bergqvist 1997 (ENOXACAN); Dahan 1990; Encke 1988 (EFS); Fricker 1988; Gallus 1993; Godwin 1993; Goldhaber 2002; Kakkar 1997; Koppenhagen 1992; Onarheim 1986; Song 2018). If screening detects thromboses, participants are typically therapeutically anticoagulated. Some of the participants with asymptomatic events may have developed symptomatic VTE, had screening testing not been undertaken and anticoagulant therapy not been administered. As a result, the number of symptomatic VTE events in this review, and the differential effect of LMWH versus UFH on symptomatic events, may have been underestimated.

Potential biases in the review process

Our systematic approach to searching, study selection, and data extraction should have minimized the likelihood of missing relevant trials. We excluded 12 trials that included participants with cancer as subgroups but did not report on their outcome data. The cancer subgroups in these trials included 3185 participants compared with 9771 randomized participants included in the current analysis. This may have introduced bias.

The relatively small number of trials and the inclusion of different types of malignancies, different types of surgical procedures, different dosing of anticoagulant medications, and different follow-up periods in the same trials precluded us from conducting the subgroup analyses to explore effect modifiers.

Agreements and disagreements with other studies or reviews

One systematic review of thromboprophylaxis in colorectal surgery reported no differences between LMWH and UFH in their effects on preventing DVT or PE, or both (odds ratio (OR) 1.01, 95% CI 0.67 to 1.52) (Borly 2005). One systematic review compared the effects of UFH and LMWH thromboprophylaxis on thrombocytopenia and HIT (Martel 2005). Most of the included trials were in orthopedic surgery and only two trials prospectively examined HIT and reported 10 events (all in the UFH group). The meta-analysis found an OR of 0.10 (95% CI 0.01 to 0.82) for HIT and 0.47 (95% CI 0.22 to 1.02) for thrombocytopenia, favoring LMWH. Another meta-analysis comparing therapeutic doses of UFH and LMWH reported no differential effect on HIT (RR 1.33, 95% CI 0.77 to 2.30) (Morris 2007). One other systematic review comparing the effects of UFH and LMWH thromboprophylaxis reported no difference in minor complications, major complications, or the discontinuation of prophylaxis (Leonardi 2007).

AUTHORS' CONCLUSIONS

Implications for practice

Given the lack of clear evidence of superiority of one medicine over the other as a result of this imprecision, clinicians should base their choice on cost and patient preferences using an individualized decision-making process. The American College of Chest Physicians (ACCP) 9th iteration of the antithrombotic guidelines does not recommend using either of the two anticoagulants of interest over the other in people with cancer undergoing surgical interventions (Gould 2012).

Implications for research

Despite the large number of participants enrolled in these trials, there is still some lack of precision for several critical outcomes. This is partly because several trials assessed surrogate outcome (asymptomatic deep venous thrombosis (DVT)) instead of patient-important outcomes such as DVT and pulmonary embolism. Researchers can use these results to plan additional randomized controlled trials to either exclude or confirm a superiority of one of the two drugs over the other on patient-important outcomes.

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For our update of these reviews, we followed Cochrane methods using the same eligibility criteria and outcomes used previously. The ASH guidelines group used slightly different methods that generated slightly different results. For example, the ASH guideline panel agreed to prioritize different outcomes; include unpublished data; include abstracts; use different definitions for

duration of treatment; and rate certainty of evidence slightly differently for some outcomes, for instance because of imprecision or indirectness. These differences are not described in this publication. Instead, they will be described in the ASH guideline publication.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agnelli 2005

Methods	Randomized double-blind double-dummy study
Participants	1941 (67.9%) participants undergoing abdominal surgery for cancer, expected to last > 45 minutes under general anesthesia and aged > 60 years, or aged > 40 years with ≥ 1 additional risk factors for thromboembolic complications in 131 hospitals in 22 countries
Interventions	Intervention: fondaparinux 2.5 mg subcutaneously once daily started 6 h after surgical closure plus placebo Control: dalteparin 2500 U subcutaneously once daily started 2 h before induction of anesthesia and 12 h later than 5000 U once-daily plus placebo
Outcomes	Duration of follow-up: 10 days (for screening) and 30 days (for symptomatic) days postoperation <ul style="list-style-type: none"> • Symptomatic and asymptomatic VTE (PE and DVT) • Major bleeding <p>Screening test for DVT: bilateral ascending contrast venography of the legs</p> <p>Diagnostic test for DVT: ultrasonography of the leg veins followed by bilateral venography</p> <p>Diagnostic test for PE: high-probability lung scan, pulmonary angiography, helical computed tomography, or at autopsy</p>
Notes	Funding: Sanofi-Synthelabo and NV Organon Ethical approval: "the study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and local regulations." Conflict of interest: "none of the authors had financial conflicts of interest in relation to the study." Intention-to-treat analysis: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "double-blind double-dummy randomized study" Comment: probably yes
Allocation concealment (selection bias)	Unclear risk	Not reported

Agnelli 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind double-dummy randomized study. Patients given fondaparinux received a placebo injection 2 h before surgery and again 12 h later to correspond with the dalteparin dosing schedule. Patients given dalteparin received a placebo injection 6 h after surgery." Comment: definitely yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "study outcome measures, including venography results, clinically suspected thromboembolic and bleeding events, and deaths, were adjudicated by a central independent committee that was unaware of the patients' treatment assignment and the local assessment." Comment: definitely yes
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison between MPD rate (VTE: 536/1941 = 27.61%) and event rate (VTE: 88/1408 = 6.25%)
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Baykal 2001

Methods	Randomized double-blind trial
Participants	102 participants aged 40-70 years, non-smokers and no history of peripheral arterial disease or thrombosis, undergoing surgery for gynecologic malignancy. Mean age: 57 years, previous VTE: not reported
Interventions	Intervention: enoxaparin 2500 U subcutaneously 2 h preoperatively then once daily (LMWH) Control: UFH 5000 U subcutaneously every 8 h Discontinued treatment: not clear
Outcomes	Duration of follow-up: not clear <ul style="list-style-type: none"> • Mortality • DVT • PE • Intraoperative bleeding • Wound hematomas • Blood transfusion • Catheter drainage <p>Screening testing for DVT/PE: none</p> <p>Diagnostic testing for DVT: duplex ultrasonography and if required venography</p> <p>Diagnostic test for PE: ventilation-perfusion scan and pulmonary arteriography</p>

Baykal 2001 (Continued)

Notes

Funding: Eczacibasi-Rhône Poulenc, Turkey

Ethical approval: not reported

Conflict of interest: not reported

Intention-to-treat analysis: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to author contact: random number table
Allocation concealment (selection bias)	Low risk	According to author contact: "sequentially numbered sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomised double blind trial" Comment: according to author contact: yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the surgical team and those collecting laboratory and clinical data were not informed about the prophylactic anticoagulation being used." Comment: according to author contact: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Bergqvist 1990

Methods	Randomized double-blind multicenter trial
Participants	637 (64%) participants aged ≥ 40 years, with cancer undergoing major elective general abdominal surgery (study subgroup) from 7 centers Mean age: 71 years, men 52% (329/637), previous VTE 6% (40/637)
Interventions	Intervention: dalteparin 5000 U subcutaneously at 22.00 h on the evening preoperatively then twice daily for 5-8 days (an LMWH) Control: UFH 5000 U/0.2 ml subcutaneously 2 h preoperatively then twice daily from 5 to 8 days Discontinued treatment: not clear
Outcomes	Duration of follow-up: 30 days

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Bergqvist 1990 (Continued)

- DVT
- PE
- Hemorrhage
- Mortality
- Bleeding

Screening testing for DVT: iodine-radiolabeled fibrinogen uptake test for 7 days

Diagnostic test for PE: scintigraphy

Notes	<p>Funding: Swedish Medical Research Council (No. 00759)</p> <p>Ethical approval: study approved by Ethics Committee, University of Lund, and local ethics committees</p> <p>Conflict of interest: not reported</p> <p>Intention-to-treat analysis: not reported</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a total of 1040 patients were randomised"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "randomised double blind multicenter trial"</p> <p>Comment: definitely yes</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>No placebo used</p> <p>Comment: not reported, probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	<p>Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on</p> <p>Comment: probably no</p>
Other bias	Low risk	<p>Study not reported as stopped early for benefit</p> <p>Comment: probably no</p>

Bergqvist 1997 (ENOXACAN)

Methods	Randomized double-blind multicenter trial
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Bergqvist 1997 (ENOXACAN) (Continued)

Participants	<p>1116 participants undergoing planned curative abdominal or pelvic surgery for cancer (study sub-group) were randomized in the study. Venograms were inadequate in 460 (41.3%) leaving "631 evaluable patients."</p> <p>Minimum age: 40 years. Mean age: 68.5 years, 53% men, previous DVT 3% (20/631)</p>
Interventions	<p>Intervention: enoxaparin 40 mg (0.2 ml) subcutaneously started 2 h before surgery (an LMWH) and then once daily in addition to placebo twice daily</p> <p>Control: low-dose UFH 5000 U (0.2 ml) subcutaneously started 2 h before surgery and then 3 times daily</p> <p>Discontinuation treatment: 243/556 participants randomized to LMWH and 241/560 participants randomized to UFH</p>
Outcomes	<p>Duration of follow-up: 3 months</p> <ul style="list-style-type: none"> • DVT • Asymptomatic DVT • PE plus DVT • Minor bleeding • Major bleeding • Thrombocytopenia • Mortality • Hemorrhage <p>Screening testing for DVT/PE: venography "Scheduled bilateral ascending venography was performed 24 hours after the last injection of the trial substance."</p> <p>Diagnostic test for DVT: venography; "If the patient developed clinical symptoms or signs of DVT, unilateral venography was performed within 24h."</p> <p>Diagnostic test for PE: ventilation-perfusion lung scan or pulmonary angiography, or both</p>
Notes	<p>Funding: Swedish Medical Research Council grant No. 00759</p> <p>Ethical approval: "the study was performed according to the Declaration of Helsinki and good clinical practice. Regional ethics committees in the various countries approved the trial."</p> <p>Conflict of interest: not reported</p> <p>Intention-to-treat analysis: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "separate randomisation were made per country and per hospital to one of two groups."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind randomised trial" Comment: definitely yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the venographic results were evaluated and agreed on by an independent panel before the code was broken."

Bergqvist 1997 (ENOXACAN) (Continued)

Comment: definitely yes

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison between MPD rate (symptomatic DVT: 485/1116 = 43.45%; asymptomatic DVT: 485/1116 = 43.45%); and event rate (symptomatic DVT: 10/631 = 1.58%; asymptomatic DVT: 91/631 = 14.42%)
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Boncinelli 2001

Methods	Randomized trial
Participants	50 participants aged 45 to 75 years with localized prostate cancer (stage T1c-T2) undergoing radical retropubic prostatectomy for prostate cancer Mean age: 60 years, previous VTE: not reported
Interventions	Intervention: calcium nadroparin 2850 IU (0.3 mL) given as single daily subcutaneously (an LMWH) started 12 h before surgery Control: UFH 5000 U subcutaneously 3 times daily started 2 h before surgery In both groups, prophylaxis began preoperatively and maintained throughout the hospital stay (mean 15 days) Discontinued treatment: none
Outcomes	Duration of follow-up: 15 days <ul style="list-style-type: none"> DVT PE Major bleeding Hematoma in the postoperative period <p>Screening testing for DVT/PE: none</p> <p>Diagnostic testing for DVT/PE: ultrasound-Doppler</p>
Notes	Funding: not reported Ethical approval: not reported Conflict of interest: not reported Intention-to-treat analysis: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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Boncinelli 2001 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned two groups."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behavior across intervention group (e.g. differential drop-out, differential cross-over to an alternative intervention, or differential administration of co interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Comment: not reported, probably not, however the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Dahan 1990

Methods	Randomized trial
Participants	100 participants undergoing thoracic surgery for cancer; aged > 18 years Mean age: 59 years, 92% men, previous VTE: not reported
Interventions	Intervention: nadroparin 7500 U subcutaneously 12 h preoperatively and 12 h postoperatively until the second postoperative day then 10,000 U once daily on postoperative days 3-7 Control: UFH 5000 U subcutaneously 2 h preoperatively and 12 h postoperatively then 3 times daily until the second postoperative day then a dose adjusted to activated partial thromboplastin time on postoperative days 3-7 twice daily Discontinued treatment: none
Outcomes	Duration of follow-up: not clear <ul style="list-style-type: none"> • DVT • PE • Perioperative bleeding and postoperative bleeding • Major bleeding <p>Screening testing for DVT/PE: participants were screened with ¹²⁵I-fibrinogen uptake test</p>

Dahan 1990 (Continued)

Diagnostic testing for DVT/PE: none

Notes	Funding: not reported
	Ethical approval: not reported
	Conflict of interest: not reported
	Intention-to-treat analysis: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised study"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Quote: "This trial was a prospective multicentre, partially double-blind;" "a first phase conducted double blindly from day - 1 (D - 1) to D + 2"; "a second, open phase from D3 to D7" Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behavior across intervention group (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Quote: "partially double blind;" "first phase conducted double blind"; "a second, open phase from D3 to D7" Comment: probably not blinded; however, the knowledge of the assigned intervention was not likely to impact the analysis of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Unclear risk	Study not registered. No published protocol. No outcomes listed in methods section Comment: unclear
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Encke 1988 (EFS)

Methods	Randomized multicenter trial
Participants	704 participants aged > 40 years with cancer (37% study subgroup) and scheduled for elective abdominal surgery

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Encke 1988 (EFS) (Continued)

Mean age: 61 years, 52% men, previous VTE: not reported

Interventions	<p>Intervention: fraxiparin 7500 anti-Xa U subcutaneously (an LMWH)</p> <p>Control: calcium heparin 5000 U subcutaneously 3 times daily</p> <p>Treatment initiated 2 h before surgery, second injection given 8 h after surgery. Subsequent injections given every 24 h between 07.00 and 10.00 h from the 1st to the 7th postoperative day</p> <p>Discontinuation treatment: not clear</p>
Outcomes	<p>Duration of follow-up: 7 days</p> <ul style="list-style-type: none"> • DVT • Asymptomatic DVT • PE • Hemorrhage • Mortality <p>Screening testing for DVT/PE: radiolabeled iodine fibrinogen leg scanning on the day of the surgery and then daily for 7 consecutive days</p> <p>Diagnostic testing for DVT/: phlebography</p> <p>Diagnostic testing for PE: ventilation-perfusion scanning or angiography</p>
Notes	<p>Funding: Sanofi Labaz, GmbH, Pharmzeutische Preparare</p> <p>Ethical approval: trial protocol approved by Ethical Committee of the University of Frankfurt</p> <p>Conflict of interest: not reported</p> <p>Intention-to-treat analysis: no. Quote: "In all, 1909 patients qualified for the trial and were randomized. However, 13 of these patients received neither Fraxiparin nor Calciparin and therefore were excluded from analysis of efficacy and tolerance." "A total of 35 patients (21 in the Fraxiparin group and 14 in the calcium heparin group) did not receive the full study medication for various reasons; they were, however, included in the final analysis."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patients were assigned to treatment with either Fraxiparin or calcium heparin following randomised schedule."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>No placebo used</p> <p>Quote: "the trial was not performed in double blind manner."</p> <p>Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>No placebo used</p> <p>Quote: "the trial was not performed in double blind manner."</p>

Encke 1988 (EFS) (Continued)

		Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Fricker 1988

Methods	Randomized trial
Participants	80 participants aged ≥ 40 years undergoing surgery for abdominal and pelvic malignancy Mean age: 57.6 years, 93% women, previous VTE 13.7%
Interventions	Intervention: 2500 anti-Xa U subcutaneously 2 h before surgery and 12 h after the first injection and then dalteparin sodium (Fragmin) 5000 anti-Xa U injection every morning for 10 days Control: calcium heparin 5000 IU subcutaneously injection 2 h before the surgery and then at 8-h intervals for the next 10 days Discontinuation of treatment: 0
Outcomes	Follow-up: 10 days <ul style="list-style-type: none"> • DVT • Asymptomatic DVT • PE • Postoperative bleeding • Wound hematoma <p>Screening testing for DVT/PE: radiolabeled fibrinogen tests used for postoperative screening of DVT</p> <p>Diagnostic testing for DVT: venography</p> <p>Diagnostic testing for PE: lung scintigraphy with 99mTc-aggregated albumin perfusion study</p>
Notes	Funding: not reported Ethical approval: approved by local Ethics Committee (Groupe de Recherche sur le Medicament, Université Louis Pasteur, Strasbourg, France) Conflict of interest: not reported Intention-to-treat analysis: not reported

Risk of bias

Fricker 1988 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "eighty patients undergoing pelvic or abdominal surgery for cancer were randomised in two groups."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Quote: "we have undertaken a prospective open randomised trial." Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Quote: "the trial was not performed in double blind manner." Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Gallus 1993

Methods	Randomized double-blind trial
Participants	514 participants aged > 40 years undergoing major abdominal or thoracic surgery for cancer at the Royal Melbourne and Austin Hospitals (Melbourne, Australia), the Middlemore Hospital (Auckland, New Zealand), and the Flinders Medical Centre (Adelaide, Australia) Mean age: 65 years, 62% men, previous VTE 2.5%
Interventions	Intervention: organan 750 U subcutaneously 1-2 h preoperatively then at 12-h intervals × 6 days (an LMWH) Control: UFH 5000 U subcutaneously 1-2 h preoperatively then at 12-h intervals × 6 days Discontinued treatment: 16/241 randomized to LMWH and 7/249 randomized to UFH
Outcomes	Duration of follow-up: 4-6 weeks after discharge from hospital. Follow-up period defined as starting 2 days after end of trial therapy • DVT

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Gallus 1993 (Continued)

- PE
- Bleeding
- Mortality

Screening test for DVT: radiolabeled fibrinogen tests used for screening of postoperative DVT every 2nd day on the week days

Diagnostic test for DVT: ascending contrast medium venography

Diagnostic test for PE: ventilation-perfusion lung scanning

Notes

Funding: Organon International, Oss, The Netherlands

Ethical approval: trial protocol approved by relevant institutional clinical investigations committees

Conflict of interest: not reported

Intention-to-treat analysis: yes, quote: "intent to treat analysis showed statistically non-significant toward trend towards less VT [venous thrombosis] during Organon prophylaxis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using predetermined randomisation sequences for each trial center."
Allocation concealment (selection bias)	Low risk	Quote: "coded ampoules of Organon and Na [sodium] heparin were supplied by Organon International B.V. and dispensed in numbered boxes by hospital pharmacies using predetermined randomisation sequences for each trial center." Comment: yes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Quote: "double blind multicenter trial" Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Comment: probably not; however, knowledge of assigned intervention may not have impacted the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: judgment based on comparison between MPD rate (asymptomatic DVT: 23/513 = 4.48%, PE: 23/513 = 4.48%) and event rate (asymptomatic DVT 47/490 = 9.59%, PE 4/513 = 0.77%)
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Godwin 1993

Methods	Randomized double-blind trial
Participants	904 participants undergoing abdominal or pelvic surgery for cancer Mean age: not reported, % males: not reported, previous VTE % not reported
Interventions	Intervention: RDH (Normiflo) 50 U/kg subcutaneously 2 h preoperatively and then 50 U/kg twice daily or 90 U/Kg once daily (an LMWH) Control: UFH 5000 U subcutaneously 2 h preoperatively and then 5000 U twice daily Discontinued treatment: 0
Outcomes	Duration of follow-up: not clear <ul style="list-style-type: none"> • DVT • PE • Bleeding • Mortality <p>Screening testing for DVT: preoperatively by non-invasive venous tests, either impedance plethysmography or duplex ultrasound scan</p> <p>Diagnostic testing for DVT: venography</p> <p>Diagnostic testing for PE: ventilation-perfusion lung scan or pulmonary angiography</p>
Notes	Funding: KabiVitrum Ethical approval: not reported Conflict of interest: not reported Intention-to-treat analysis: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a total of 904 patients were randomised into three groups."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Quote: "double blind randomised trial" Comment: definitely not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used

Godwin 1993 (Continued)

Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Goldhaber 2002

Methods	Randomized, double-blind clinical trial
Participants	150 participants undergoing craniotomy for primary or metastatic brain tumor
Interventions	Intervention: enoxaparin 40 mg subcutaneously in the morning and a placebo injection in the evening Control: UFH 5000 U subcutaneously twice daily Cointervention: perioperative prophylaxis with graduated compression stockings and sequential intermittent pneumatic compression devices
Outcomes	Duration of follow-up: 30 days <ul style="list-style-type: none"> DVT PE Bleeding complications (wound hematoma, postoperative wound bleeding, gastric bleeding) <p>Screening testing for DVT/PE: duplex venous ultrasonography examination</p> <p>Diagnostic testing for DVT/PE: criterion for diagnosing DVT was loss of venous compressibility</p>
Notes	Funding: clinical research grant from Aventis Ethical approval: not reported Conflict of interest: not reported Intention-to-treat analysis: yes, quote: "Patients were analyzed according to the intention-to-treat principle."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "one hundred fifty patients were randomized from June 1999 through September 2001, 75 patients to each of the two prophylaxis strategies." Comment: probably yes

Goldhaber 2002 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomized, prospective, double-blind clinical trial Quote: "either enoxaparin, 40 mg, in the morning and a placebo injection in the evening vs 5,000 U of subcutaneous unfractionated heparin bid [twice daily]. Drug assignment was double blinded." Comment: definitely yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: varied by outcome; high for mortality with judgment based on comparison between MPD rate (mortality: 5/150 = 3.33%) and event rate (mortality: 0/150); high risk for symptomatic DVT (MPD rate: 10/150 = 6.66% and event rate 0/150)
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Hata 2016

Methods	Prospective, single-blind, non-inferiority randomized trial
Participants	298 participants aged ≥ 40 year undergoing surgery for urologic malignancies Mean age: 64 years, 94% men
Interventions	Intervention: enoxaparin (a LMWH) 2000 U subcutaneously twice daily Control: fondaparinux 2.5 mg subcutaneously once daily Cointervention: mechanical thromboprophylaxis
Outcomes	Duration of follow-up: up to 3 months <ul style="list-style-type: none"> VTE (probably symptomatic and asymptomatic: "Blood DD [D-dimer] and SFMC [soluble fibrin monomer complex] levels were measured by latex immunoagglutination assay (LSI Medience Corporation, Tokyo, Japan) before surgery, on PODs [postoperative days] 1, 3 and 5, and whenever VTE or other complications were suspected") Major bleeding Minor bleeding <p>Screening testing for DVT/PE: none</p> <p>Diagnostic testing for DVT/PE: multi detector-row computed tomography.</p>
Notes	Funding: Glaxo Smith Kline KK and Kaken Pharmaceutical Co. Ltd

Hata 2016 (Continued)

Ethical approval: carried out under the Declaration of Helsinki and applicable clinical practice. Institutional ethics committees approved the study protocol, and informed consent was obtained from all participants.

Conflict of interest: none declared

Intention-to-treat analysis: yes, quote: "All the analyses were carried out in the intention-to-treat."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "prospective, single blind, non-inferiority randomized trial" Personal communication with the author, "It was done by a software as a randomization." Comment: probably yes
Allocation concealment (selection bias)	Low risk	Personal communication with the author: "Allocation was concealed" Comment: definitely yes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was used. Quote: "prospective, single blind, non-inferiority randomized trial...all (surgeons) were blinded to drug allocation until the end of the surgical procedure." Personal communication with the author, "All surgeons and medical staff were blinded to drug allocation until the end of the surgical procedure. All patients were blinded to it before they were given the allocation drug." Comment: probably not, knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Quote: "prospective, single blind, non-inferiority randomized trial...all (surgeons) were blinded to drug allocation until the end of the surgical procedure." Personal communication with the author, "All surgeons and medical staff were blinded to drug allocation until the end of the surgical procedure. All patients were blinded to it before they were given the allocation drug." Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Rate of participants who did not receive allocated treatment 5% in intervention and control arms Comment: judgment based on comparison between MPD rate (VTE: 16/298 = 5.36%) and event rate (VTE: 2/282 = 0.7%)
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no

Hata 2016 (Continued)

Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no
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Kakkar 1997

Methods	Randomized double-blind trial
Participants	706 participants aged ≥ 40 years with an underlying malignancy (of 1351 participants (52%)) undergoing general or gynecologic surgery Mean age: 59.6 years, % men not reported, previous VTE % not reported
Interventions	Intervention: reviparin sodium (a LMWH) 1750 anti-Xa IU subcutaneously once daily with 2nd injection of saline (placebo) 12 h later Control: UFH 5000 IU subcutaneously every 12 h Treatment commenced 2 h prior to surgery followed by 2nd injection 8 h postoperatively and continued for at least 5 days (longer if the participant was still confined to bed) Discontinued treatment: 0
Outcomes	Duration of follow-up: not clear <ul style="list-style-type: none"> • Mortality • DVT • PE • Bleeding complications • Wound hematoma • Wound complications (hematoma, oozing, bruising) • Injection site complications (hemorrhage, hypersensitivity, inflammation, pain) <p>Screening testing for DVT/PE: scheduled radioactive fibrinogen uptake test was done daily for DVT screening</p> <p>Diagnostic testing for DVT: phlebography</p> <p>Diagnostic testing for PE: ventilation-perfusion lung scanning, pulmonary angiography, or both</p>
Notes	Funding: Knoll AG, Germany Ethical approval: "the study was conducted in compliance with the revised Declaration of Helsinki, Good Clinical Practice (GCP), and the regulations of the national health authorities of each country." Conflict of interest: not reported Intention-to-treat analysis: yes, quote: "the study was analysed in accordance with the intention-to-treat principle."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated"

Kakkar 1997 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind multicenter trial;" "patients were randomly allocated to receive either LMWH 1750 anti-Xa IU administered subcutaneously (SC) once daily with a second injection of saline (placebo) 12 hours later, or UFH 5000 IU SC every 12 hours." Comment: probably yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the final diagnosis of DVT or PE was based on the assessment of a blinded expert committee." Comment: probably yes; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: varies: low for asymptomatic DVT with judgment based on comparison between MPD rate (asymptomatic DVT 9/1351 = 0.66%) and event rate (asymptomatic DVT 58/1342 = 4.32%). Might be considered as high risk for mortality with MPD rate 9/1351 = 0.66% and event rate 8/1342 = 0.59%.
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Kakkar 2005

Methods	Randomized double-blind controlled trial
Participants	6124 (27%) participants aged > 40 years undergoing surgery of ≥ 30 minutes' duration at 67 centers in Germany, Austria, and the Czech Republic Minimum age 40 years, mean age 62 years, % men not reported, previous VTE % not reported
Interventions	Intervention: LMWH certoparin 3000 anti-Xa IU subcutaneously once daily Control: UFH 5000 IU, administered subcutaneously 3 times daily Discontinued treatment: not applicable
Outcomes	Duration of follow-up: 14 days <ul style="list-style-type: none"> • Mortality • PE • Blood transfusion • Bleeding complications (wound hematoma, postoperative wound bleeding) • Thrombocytopenia Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none (fatal PE determined by autopsy)

Kakkar 2005 (Continued)

Notes

Funding: Novartis Pharma GmbH, Nürnberg, Germany

Ethical approval: conducted in accordance with the Declaration of Helsinki. The ethics review board at each local center approved the study, under the supervision and guidance of a central ethics committee (The Ethics Committee, Regensburg).

Conflict of interest: not reported

Intention-to-treat analysis: yes, quote: "the analyses included all randomised patients (intention-to-treat)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to one of two treatment groups using a centralised computer generated randomizations list."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind clinical trial;" "placebo injections were given to Certoparin patients to conform to the double blind trial design." Comment: definitely yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The statistical analysis was performed by an independent statistician and under the guidance of the Steering Committee." Comment: unclear; however, the knowledge of the assigned intervention may not have impacted the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up 100% for mortality; 70% for fatal PE
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on Comment: probably no
Other bias	High risk	Quote: "the decision was taken to end the study prematurely as the study would not be sufficiently powered to show superiority of Certoparin over UFH." Comment: probably yes

Kopenhagen 1992

Methods	Prospective, randomized, double-blind multicentric study
Participants	673 participants aged ≥ 40 years undergoing major elective abdominal surgery 54.5% receiving LMWH and 58.5% receiving low-dose heparin had malignant diseases
Interventions	Intervention: 1 injection of LMWH sodium heparin 3,000 anti-Xa U subcutaneously and 2 placebo injections per day started 2 h prior to surgery

Kopenhagen 1992 (Continued)

Control: 3 applications of UFH 5000 U subcutaneously per day started 2 h prior to surgery

Discontinued treatment: 13 participants in LMWH group and 7 in heparin group

Outcomes	<p>Duration of follow-up: not clear</p> <ul style="list-style-type: none"> • Mortality • DVT • PE • Bleeding complications • Wound hematoma • Wound complications <p>Screening test for DVT: radiofibrinogen uptake test</p> <p>Diagnostic test for DVT: phlebography</p>
Notes	<p>Funding: not reported</p> <p>Ethical approval: not reported</p> <p>Conflict of interest: not reported</p> <p>Intention-to-treat analysis: not reported</p> <p>Quote: "39 patients (78.0%) who developed DVT suffered from malignant diseases, compared to 330 (50.5%) without DVT."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "prospective, randomized, double-blind multicentric study"</p> <p>Comment: probably yes</p>
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "prospective, randomized, double-blind multicentric study;" "the patients received either one injection of LMWH and two placebo injections or three applications of 5,000 U of unfractionated heparin per day."</p> <p>Comment: probably yes</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Not reported</p> <p>Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Comment: judgment based on comparison between MPD rate (mortality: 20/673 = 2.9% symptomatic DVT: 20/673 = 2.9%) and event rate (mortality 5/653 = 0.76% symptomatic DVT 7/653 = 1.07%)</p>
Selective reporting (reporting bias)	Low risk	<p>Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on</p> <p>Comment: probably no</p>
Other bias	Low risk	Study not reported as stopped early for benefit

Kopenhagen 1992 (Continued)

Comment: probably no

Onarheim 1986

Methods	Randomized double-blind trial
Participants	52 participants aged ≥ 40 years; undergoing surgery for gastric, colonic, and rectal malignancy Mean age: 70.35 years, % men not reported, previous VTE 5.8%
Interventions	Intervention: dalteparin 5000 IU subcutaneously 2 h preoperatively then once daily for 6 days and placebo injection given each evening Control: heparin Kabi 2165 5000 U subcutaneously 2 h preoperatively then twice daily for 6 days Discontinued treatment: not clear
Outcomes	Duration of follow-up: 30 days <ul style="list-style-type: none"> • Mortality • DVT • PE • Major bleeding • Wound hematoma • Thrombocytopenia <p>Screening testing for DVT/PE: radioactive fibrinogen uptake test used for DVT screening and performed preoperatively and then daily or every 2nd day for at least 7 postoperative days</p> <p>Diagnostic testing for DVT/PE: phlebography</p>
Notes	Funding: Kabivitrum Ethical approval: study approved by hospital's ethical committee. Conflict of interest: not reported Intention-to-treat analysis: yes, quote: "the data collected from 52 patients were therefore uniformly analysed on an "intention to treat" basis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated to receive conventional heparin (heparin group) or LMWH KABI 2165 (LMWH group)."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind trial;" "a placebo injection was given each evening, in order in order to keep the study completely blind." Comment: probably yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported

Onarheim 1986 (Continued)

Quote: "double blind trial;" "a placebo injection was given each evening, in order in order to keep the study completely blind."

Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Song 2018

Methods	Randomized double-blind parallel-group trial
Participants	A total of 129 patients aged between 18 to 75, with esophageal cancer patients and undergoing minimally invasive esophagectomy were enrolled from January 2011 to July 2012.
Interventions	Intervention: fondaparinux sodium 2.5 mg subcutaneously once daily starting 6h after procedures. Control: nadroparin calcium 2850 anti-Xa IU subcutaneously once daily starting 6h after procedures. Discontinued treatment: 3 participant in LMWH group and 1 in fondaparinux group
Outcomes	Duration of follow-up: 7 days <ul style="list-style-type: none"> • DVT • PE • Major bleeding • Minor bleeding <p>Screening testing for DVT/PE: ultrasound machine was used for DVT screening and was performed immediately after admission to SICU and on the postoperative day 7.</p> <p>Diagnostic testing for DVT/PE: computed tomography pulmonary angiography (CTPA).</p>
Notes	Funding: No Ethical approval: The Ethics Committee of Zhongshan Hospital approved the protocol (No. 2010-186) Conflict of interest: No Intention-to-treat analysis: yes, Quote: "All primary analyses were performed on an intention-to-treat basis." Registered in ClinicalTrials.gov (NCT01267305)

Risk of bias

Anticoagulation for perioperative thromboprophylaxis in people with cancer (Review)

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Song 2018 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Immediately after admission in SICU, the participants randomly received either subcutaneous nadroparin calcium 2850 IU (Fraxiparine®, Glaxo Smith Kline, UK, Group H) or fondaparinux sodium 2.5 mg (Arixtra®, Glaxo Smith Kline, UK, Group F) once daily in a 1:1 ratio based on a computer-generated randomization list."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order to achieve a double-blind study, the two kinds of anticoagulants were loaded into the similar syringes before use."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: 100%
Selective reporting (reporting bias)	Low risk	Study registered in ClinicalTrials.gov (NCT01267305). The protocol was published (No. 2010-186), All relevant outcomes listed in the methods section were reported on. Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Von Tempelhoff 1997

Methods	Randomized double-blind trial
Participants	60 participants with ovarian cancer undergoing surgery and chemotherapy Mean age 56.7 years, previous VTE 3.3%
Interventions	Intervention: LMWH, certoparin sodium 3000 anti-Xa U/day subcutaneously plus 2 placebo injections Control: UFH 5000 IU/day subcutaneously 3 times a day Prophylaxis was begun 2 h before operation and continued until the 7th postoperative day Discontinuation treatment: 0
Outcomes	Duration of follow-up: 7 days <ul style="list-style-type: none"> DVT Asymptomatic DVT

Von Tempelhoff 1997 (Continued)

Screening testing for DVT/PE: impedance plethysmography was used for DVT screening on days 1, 3, 5, 7, and 10

Diagnostic testing for DVT/PE: ascending phlebography

Notes	Funding: not reported
	Ethical approval: not reported
	Conflict of interest: not reported
	Intention-to-treat analysis: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "all patients were eligible for surgery and randomised to receive either daily LMWH or UFH."
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all 60 patients were randomised in double blind manner to receive either LMWH or UFH." "The dose of the LMWH was once 3000 anti Xa units/day s.c. [subcutaneously] plus 2 placebo injections and of UFH three times 5000 IU/day s.c." Comment: probably yes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Von Tempelhoff 2000

Methods	Randomized double-blind trial
Participants	350 participants with either histologically confirmed carcinoma of the breast, endometrium, vulva, or vagina, or with suspected ovarian malignancy; minimum age 40 years; mean age 61 years
Interventions	Intervention: certoparin 3000 anti-Xa U subcutaneously once daily plus 2 placebo injections (0.9% saline)

Von Tempelhoff 2000 (Continued)

Control: UFH 5000 IU subcutaneously 3 times daily

Initial injection 2 h before the surgery always contained active drug. In both treatment arms, study medication was given at 8-h intervals until 7th postoperative day

Discontinuation treatment: not clear

Outcomes	<p>Duration of follow-up: median of 1849 days in LMWH group and 1954 days in UFH group</p> <ul style="list-style-type: none"> Mortality (the 1 relevant outcome listed in the methods section was reported on) <p>Screening testing for DVT/PE: none</p> <p>Diagnostic testing for DVT/PE: none</p>
Notes	<p>Funding: Novartis, Germany</p> <p>Ethical approval: study protocol reviewed and approved by an independent Ethics Committee</p> <p>Conflict of interest: not reported</p> <p>Intention-to-treat analysis: no, quote: "patients were not randomised according to intention to treat principle."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "patient who randomly received LMW [low-molecular weight] heparin (certoparin) compared to patients given UF [unfractionated] heparin for thrombosis prophylaxis during primary surgery."</p> <p>Comment: probably yes, particularly given the method of allocation concealment used</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "the boxes and ampoules of both heparins were labelled with a trial code number but were identical in appearance so neither the patient nor the staff were aware of the kind of heparin administered."</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "randomised double blind trial" "LMW [low-molecular heparin] heparin was given at a dose of 3,000 anti-Xa units subcutaneously once daily in combination with 2 placebo injections (0.9% NaCl) [sodium chloride]." "The boxes and ampoules of both heparins were labeled with a trial code number but were identical in appearance so neither the patient nor the staff were aware of the kind of heparin administered." "The list with the trial code numbers remained at the manufacturer and the double-blind conditions (medical staff, patients, and investigators) were maintained until the database was closed, and protocols were inspected by a study monitor."</p> <p>Comment: definitely yes</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Not reported</p> <p>Comment: probably not, however the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up 100%

Von Tempelhoff 2000 (Continued)

Selective reporting (reporting bias)	High risk	Study appeared to have collected data on VTE outcomes but did not report them Comment: probably yes
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

Ward 1998

Methods	Randomized controlled trial
Participants	566 consecutive women attending the Gynaecological Oncology Unit at the Royal Women's Hospital, Brisbane, for planned surgery Mean age; 55 years, 461 (81%) participants had malignant disease
Interventions	Intervention: dalteparin sodium (Fragmin; an LMWH) 5000 U subcutaneously once daily Control: sodium heparin 5000 U subcutaneously twice daily Both interventions were given as subcutaneous injection at a site distant from the surgical site, most commonly into the thigh 12 h prior to surgery and continued for 5 days or until full activity was resumed, whichever was the longer. Cointervention: compression stockings and intermittent calf-compression devices were also used by a small number of women with a previous history of DVT or PE.
Outcomes	Duration of follow-up: 6 weeks postoperative <ul style="list-style-type: none"> DVT PE Blood transfusion <p>Screening testing for DVT/PE: none</p> <p>Diagnostic testing for DVT/PE: ventilation-perfusion lung scans, Doppler ultrasound, or venography, depending on the clinical situation</p>
Notes	Funding: not reported Ethical approval: "approval had previously been granted to the study by the ethics committee of the hospital" Conflict of interest: not reported Intention-to-treat analysis: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was by computer-generated random numbers and was concealed from the treating surgeon until after the operation."
Allocation concealment (selection bias)	Low risk	Quote: "randomization was by computer-generated random numbers and was concealed from the treating surgeon until after the operation."

Ward 1998 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used Comment: probably not, knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported Comment: probably not; however, the knowledge of the assigned intervention may not have impacted the assessment of the physiologic outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: judgment based on comparison between MPD rate (symptomatic DVT: 14/566 = 2.47%; PE: 14/566 = 2.47%) and event rate (symptomatic DVT: 1/552 = 0.18%; PE 6/552: = 1.08%)
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on Comment: probably no
Other bias	Low risk	Study not reported as stopped early for benefit Comment: probably no

DVT: deep venous thrombosis; h: hour; IU: international units; LMWH: low-molecular weight heparin; MPD: missing participant data ; PE: pulmonary embolism; U: unit; UFH: unfractionated heparin; V/Q: ventilation-perfusion; VTE: venous thromboembolism.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agnelli 1998	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic and mechanical thromboprophylaxis vs mechanical thromboprophylaxis only)
Agnelli 2015 (AMPLIFY)	Not population of interest (people with cancer with VTE); included 2 reports
Alikhan 2003 (MEDENOX)	Not population of interest (hospitalized people with cancer) OR not comparison of interest (anticoagulation vs no anticoagulation); included 2 reports
Arbeit 1981	Comparison not of interest: UFH vs no anticoagulant
Attaran 2010	Comparison not of interest: different doses of LMWH
Auer 2011a	Comparison not of interest: extended vs standard perioperative thromboprophylaxis
Auer 2011b	Not population of interest (people with cancer without VTE who had a surgical procedure) OR not comparison of interest (continue or discontinue thromboprophylaxis)
Bergqvist 1986	Study included people with cancer as a subgroup for which outcome data were not available.
Bergqvist 1988	Study included people with cancer as a subgroup for which outcome data were not available.
Bergqvist 2006	Comparison not of interest: extended vs standard duration of thromboprophylaxis

Study	Reason for exclusion
Bigg 1992	Not population of interest (surgical setting)
Boneu 1993	Study included people with cancer as a subgroup for which outcome data were not available.
Borstad 1988	Study included people with cancer as a subgroup for which outcome data were not available.
Borstad 1992	Study included people with cancer as a subgroup for which outcome data were not available.
Bricchi 1991	Comparison not of interest: UFH vs no anticoagulant
Cade 1983	Comparison not of interest: study compared efficacy of a higher dose of heparin (7500 U twice daily) with the commonly used dose of 5000 U
Cahan 2000	Outcome not of interest: study reported tPA and PAI-1 activity
Caprini 2003	Outcome not of interest: study compared the relative risk of bleeding when starting enoxaparin 2 h vs 12 h before surgery for colorectal cancer.
Chodri 2002	Comparison not of interest: extended vs standard duration of thromboprophylaxis
Ciftci 2012	Not population of interest (ambulatory people with cancer without VTE) OR not intervention of interest (oral anticoagulant)
Clark-Pearson 1990a	Comparison not of interest: UFH vs no anticoagulant
Clark-Pearson 1990b	Comparison not of interest: comparison between 2 doses of UFH
Clarke-Pearson 1983	Comparison not of interest: UFH vs no anticoagulant
Clarke-Pearson 1984	Comparison not of interest: LMWH vs no anticoagulant
Clarke-Pearson 1993	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic thromboprophylaxis vs mechanical thromboprophylaxis)
Cohen 2006	Not population of interest (hospitalized)
Cohen 2007 (PREVENT)	Not population of interest (hospitalized people with cancer) OR not comparison of interest (anticoagulation vs no anticoagulation); included 3 reports
Couban 2005	Not population of interest (people with cancer with CVC without VTE); included 3 reports
Di Somma 1992	Comparison not of interest: defibrotide vs heparin
Dickinson 1998	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic thromboprophylaxis vs mechanical thromboprophylaxis vs both)
Dindelli 1990	Comparison not of interest: defibrotide
Gondret 1995	Comparison not of interest: LMWH vs no anticoagulant
Haas 2011	Not population of interest (hospitalized people with cancer) OR not comparison of interest (LMWH vs UFH); included 3 reports

Study	Reason for exclusion
Harenberg 1996	Not population of interest (hospitalized people with cancer) OR not comparison of interest (LMWH vs UFH); included 2 reports
Ho 1999	Comparison not of interest: LMWH vs no anticoagulant
Jorgensen 2002	Meta-analysis
Kakkar 1989	Study included people with cancer as a subgroup for which outcome data were not available.
Kakkar 1985	Study included people with cancer as a subgroup for which outcome data were not available.
Kakkar 2009	Comparison not of interest: Extended vs time-limited thromboprophylaxis
Kakkar 2010 (CANBESURE)	Not population of interest (people with cancer who had a surgical procedure) OR not comparison of interest (continue vs discontinue thromboprophylaxis); included 2 reports
Kakkar 2010a	Comparison not of interest: Extended vs time-limited thromboprophylaxis
Kakkar 2010b	Comparison not of interest: different types of LMWH
Kakkar 2014 (SAVE-ABDO)	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (initiate prophylaxis before vs after surgery); included 2 reports
Khorana 2017 (PHACS)	Not population of interest (ambulatory people with cancer without VTE) OR not comparison of interest (parenteral anticoagulant); included 2 reports
Larocca 2012	Not comparison of interest (LMWH vs aspirin)
Lausen 1998	Comparison was not of interest: extended vs time-limited thromboprophylaxis
Lee 2015 (CATCH)	Not population of interest (people with cancer with VTE); included 9 reports
Liezorovicz 1991	Study included people with cancer as a subgroup for which outcome data were not available.
Limmer 1994	Study included people with cancer as a subgroup for which outcome data were not available.
Macbeth 2016 (FRAGMATIC)	Not population of interest (ambulatory people with cancer without VTE) OR not comparison of interest (parenteral anticoagulant); included 4 reports
Macdonald 2003	Study included people with cancer as a subgroup for which outcome data were not available.
Marassi 1993	Comparison not of interest: LMWH vs no anticoagulant
Maxwell 2001	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic thromboprophylaxis vs mechanical thromboprophylaxis)
Mazilu 2014 (OVIDIUS)	Not population of interest (people with cancer with VTE)
Murakami 2002	Not population of interest (surgical setting)
Nagata 2015	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic thromboprophylaxis vs mechanical thromboprophylaxis)

Study	Reason for exclusion
Nurmohamed 1995	Data for outcome of interest not available from report or author
Nurmohamed 1996	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic and mechanical thromboprophylaxis vs mechanical thromboprophylaxis only)
Palumbo 2011	Not population of interest (ambulatory people with low-risk multiple myeloma without VTE) OR not comparison of interest (aspirin vs warfarin); included 6 reports
Pelzer 2015 (CONKO-004)	Not population of interest (ambulatory people with cancer without VTE) OR not comparison of interest (parenteral anticoagulant); included 10 reports
Prins 2014 (EINSTEIN)	Not population of interest (people with cancer with VTE); included 2 reports
Raskob 2016 (HOKUSAI)	Not population of interest (people with cancer with VTE); included 3 reports
Raskob 2018 (HOKUSAI)	Not population of interest (people with cancer with VTE); included 1 report
Rasmussen 2006	Comparison not of interest: LMWH (4 weeks) vs LMWH (1 week)
Sakon 2010	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic thromboprophylaxis vs mechanical thromboprophylaxis)
Samama 1988	Study included people with cancer as a subgroup for which outcome data were not available.
Schulman 2003	Not population of interest (people with VTE)
Schulman 2013 (RE-MEDY)	Not population of interest (people with cancer with VTE)
Schulman 2015 (RECOVER)	Not population of interest (people with cancer with VTE)
Shukla 2008	Comparison not of interest: LMWH vs no anticoagulant
Simonneau 2006	Comparison not of interest: different types of LMWH
Song 2014	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic and mechanical thromboprophylaxis vs mechanical thromboprophylaxis only)
Tang 2012	Comparison not of interest: LMWH vs no anticoagulant
Vadhan-Raj 2013	Not population of interest (ambulatory people with cancer without VTE) OR not comparison of interest (parenteral anticoagulant)
Vedovati 2014a	Comparison was not of interest: extended vs standard duration of thromboprophylaxis
Vedovati 2014b	Not population of interest (people with cancer who had a surgical procedure) OR not comparison of interest (continue vs discontinue thromboprophylaxis); included 5 reports
Verso 2008	Not population of interest (people with cancer with CVC without VTE); included 4 reports
Young 2017 (SELECT-D)	Not population of interest (people with cancer with VTE); included 1 report

Study	Reason for exclusion
Zheng 2014	Not population of interest (people with cancer without VTE undergoing a surgical procedure) OR not comparison of interest (pharmacologic and mechanical thromboprophylaxis vs mechanical thromboprophylaxis only)
Zwicker 2013 (MICRO TEC)	Not population of interest (ambulatory people with cancer without VTE) OR not comparison of interest (parenteral anticoagulant); included 2 reports

CVC: central venous catheter; h: hour; LMWH: low-molecular weight heparin; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator; UFH: unfractionated heparin; VTE: venous thromboembolism.

Characteristics of ongoing studies [ordered by study ID]

Safi 2011

Trial name or title	A Randomized, Controlled, Open Label Study of the Efficacy and Safety of the Low Molecular Weight Heparin (LMWH), Lovenox™ (Enoxaparin) versus Heparin™ (Unfractionated Heparin) for Prevention of Venous Thromboembolism (VTE) in Gynecologic Oncology Patients
Methods	Phase IIIB, randomized, open-label, non-comparative controlled trial
Participants	150 gynecologic oncology participants with diagnosis of malignancy or suspension of malignancy in the Kingdom of Saudi Arabia who required major surgery or admission for the prevention of VTE, aged > 18 years
Interventions	Intervention: enoxaparin (LMWH) subcutaneously Control: UFH subcutaneously
Outcomes	<ul style="list-style-type: none"> Any thromboembolic events Mortality Major bleeding Time to thromboembolic event Adverse events <p>Diagnostic test for thromboembolic events: spiral computed tomography or ventilation-perfusion scan, Doppler ultrasound, and coagulation profile parameter</p>
Starting date	October 2009
Contact information	Faisal Safi, MD Gynecology
Notes	<p>NCT01356329</p> <p>Status as of June 2018: suspended (difficulty enrolling participants)</p> <p>Sponsor: National Guard Health Affairs</p>

LMWH: low-molecular weight heparin; UFH: unfractionated heparin; VTE: venous thromboembolism.

DATA AND ANALYSES

Comparison 1. Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	8	4260	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.63, 1.07]
2 Pulmonary embolism (PE)	14	5588	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.17, 1.47]
3 Symptomatic deep venous thrombosis (DVT)	8	2250	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.27, 1.69]
4 Asymptomatic DVT	12	4938	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.05]
5 Major bleeding	9	3473	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.69, 1.48]
6 Minor bleeding	2	1194	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.33]
7 Wound hematoma	6	2827	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.54, 0.92]
8 Reoperation for bleeding	4	1246	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.57, 1.50]
9 Intraoperative transfusion	2	737	Mean Difference (IV, Random, 95% CI)	-35.36 [-253.19, 182.47]
10 Postoperative transfusion	2	734	Mean Difference (IV, Random, 95% CI)	190.03 [-23.65, 403.72]
11 Intraoperative blood loss	4	761	Mean Difference (IV, Random, 95% CI)	-6.75 [-85.49, 71.99]
12 Postoperative drain volume	3	1459	Mean Difference (IV, Random, 95% CI)	30.18 [-36.26, 96.62]
13 Thrombocytopenia	2	683	Risk Ratio (M-H, Random, 95% CI)	3.07 [0.32, 29.33]

Analysis 1.1. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 1 All-cause mortality.

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=1.45(P=0.15)$					
Favors LMWH 0.01 0.1 1 10 100 Favors UFH					

Analysis 1.2. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 2 Pulmonary embolism (PE).

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baykal 2001	0/42	0/51			Not estimable
Bergqvist 1990	0/311	2/326		10.69%	0.21[0.01,4.35]
Bergqvist 1997 (ENOXACAN)	0/312	2/319		10.69%	0.2[0.01,4.24]
Boncinelli 2001	0/25	0/25			Not estimable
Dahan 1990	0/50	0/50			Not estimable
Encke 1988 (EFS)	0/355	0/349			Not estimable
Fricker 1988	0/39	5/40		11.74%	0.09[0.01,1.63]
Gallus 1993	2/241	2/249		20.67%	1.03[0.15,7.28]
Goldhaber 2002	0/72	0/73			Not estimable
Kakkar 1997	1/665	3/677		16.86%	0.34[0.04,3.25]
Kopenhagen 1992	0/323	3/330		11.12%	0.15[0.01,2.81]
Onarheim 1986	0/25	0/27			Not estimable
Von Tempelhoff 1997	0/28	0/32			Not estimable
Ward 1998	5/271	1/281		18.23%	5.18[0.61,44.09]
Total (95% CI)	2759	2829		100%	0.49[0.17,1.47]
Total events: 8 (LMWH), 18 (UFH)					
Heterogeneity: $\tau^2=0.51$; $\chi^2=7.85$, $df=6(P=0.25)$; $I^2=23.59\%$					
Test for overall effect: $Z=1.27(P=0.21)$					
Favors LMWH 0.01 0.1 1 10 100 Favors UFH					

Analysis 1.3. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 3 Symptomatic deep venous thrombosis (DVT).

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baykal 2001	0/42	0/51			Not estimable
Bergqvist 1997 (ENOXACAN)	4/312	6/319		53.61%	0.68[0.19,2.39]
Boncinelli 2001	0/25	0/25			Not estimable
Fricker 1988	0/39	0/40			Not estimable
Goldhaber 2002	0/69	0/71			Not estimable
Kopenhagen 1992	3/323	4/330		38.11%	0.77[0.17,3.4]
Onarheim 1986	0/25	0/27			Not estimable
Ward 1998	0/271	1/281		8.27%	0.35[0.01,8.45]
Total (95% CI)	1106	1144		100%	0.67[0.27,1.69]
Total events: 7 (LMWH), 11 (UFH)					
Heterogeneity: $\tau^2=0$; $\chi^2=0.2$, $df=2(P=0.91)$; $I^2=0\%$					
Test for overall effect: $Z=0.84(P=0.4)$					
Favors LMWH 0.01 0.1 1 10 100 Favors UFH					

Analysis 1.4. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 4 Asymptomatic DVT.

Analysis 1.5. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 5 Major bleeding.

Analysis 1.6. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 6 Minor bleeding.

Analysis 1.7. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 7 Wound hematoma.

Analysis 1.8. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 8 Reoperation for bleeding.

Analysis 1.9. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 9 Intraoperative transfusion.

Analysis 1.10. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 10 Postoperative transfusion.

Analysis 1.11. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 11 Intraoperative blood loss.

Analysis 1.12. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 12 Postoperative drain volume.

Analysis 1.13. Comparison 1 Low-molecular weight heparin (LMWH) versus unfractionated heparin (UFH), Outcome 13 Thrombocytopenia.

Comparison 2. Low molecular weight heparin (LMWH) versus Fondaparinux

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any pulmonary embolism	1	116	Risk Ratio (M-H, Random, 95% CI)	3.10 [0.13, 74.64]
2 Any venous thromboembolism (VTE)	3	1806	Risk Ratio (M-H, Random, 95% CI)	2.51 [0.89, 7.03]
3 Major Bleeding	3	2339	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.45, 1.23]
4 Minor Bleeding	2	398	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.34, 2.05]
5 Postoperative drain volume	1	116	Mean Difference (IV, Random, 95% CI)	-20.0 [-114.34, 74.34]
6 Thrombocytopenia	1	282	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.30]

Analysis 2.1. Comparison 2 Low molecular weight heparin (LMWH) versus Fondaparinux, Outcome 1 Any pulmonary embolism.

Analysis 2.2. Comparison 2 Low molecular weight heparin (LMWH) versus Fondaparinux, Outcome 2 Any venous thromboembolism (VTE).

Analysis 2.3. Comparison 2 Low molecular weight heparin (LMWH) versus Fondaparinux, Outcome 3 Major Bleeding.

Analysis 2.4. Comparison 2 Low molecular weight heparin (LMWH) versus Fondaparinux, Outcome 4 Minor Bleeding.

Analysis 2.5. Comparison 2 Low molecular weight heparin (LMWH) versus Fondaparinux, Outcome 5 Postoperative drain volume.

Analysis 2.6. Comparison 2 Low molecular weight heparin (LMWH) versus Fondaparinux, Outcome 6 Thrombocytopenia.

APPENDICES

Appendix 1. Full search strategies for the electronic databases: update 2010

Database	Strategy
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(Continued)

CENTRAL (the Cochrane Library, latest issue)	<p>#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran</p> <p>#2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA</p> <p>#3 fondaparinux OR Arixtra</p> <p>#4 ximelagatran OR Exanta</p> <p>#5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban</p> <p>#6 1 OR 2 OR 3 OR 4 OR 5</p> <p>#7 malignan\$ OR neoplasm\$ OR cancer OR carcinoma\$ OR adenocarcinoma OR tumour OR tumor</p> <p>#8 6 AND 7</p>
MEDLINE	<p>#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 (fondaparinux OR Arixtra).tw #11 (ximelagatran OR Exanta).tw</p> <p>#12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw.</p> <p>#13 5 OR 9 OR 10 OR 11 OR 12</p> <p>#14 Neoplasms/ #15 (malignan\$ OR neoplasm\$ OR cancer OR carcinoma\$ OR adenocarcinoma OR tumour OR tumor).tw #16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19</p>
Embase	<p>#1 Heparin/ #2 heparin.tw #3 Low Molecular Weight Heparin/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarin derivative/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 fondaparinux/ #11 (fondaparinux OR Arixtra).tw #12 ximelagatran/ #13 (ximelagatran OR Exanta).tw</p> <p>#14 (Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban).tw.</p> <p>#15 5 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14</p> <p>#16 Neoplasm/</p>

(Continued)

	#17 (malignan\$ OR neoplasm\$ OR cancer OR carcinoma\$ OR adenocarcinoma OR tumour OR tumor).tw #18 16 OR 17 #19 Random:.tw. OR clinical trial:.mp. OR exp health care quality #20 animals/ NOT human/ #21 19 NOT 20 #22 15 AND 18 AND 21
ISI (International Scientific Information) the Web of Science	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan\$ OR neoplasm\$ OR cancer OR carcinoma\$ OR adenocarcinoma OR tumour OR tumor #8 random\$ OR placebo\$ OR versus OR vs OR double blind OR double-blind OR compar\$ OR controlled #9 6 AND 7 AND 8

Appendix 2. Full search strategies for the electronic databases: update 2013

Database	Strategy
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Heparin] explode all trees #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum) #3 MeSH descriptor: [Coumarins] explode all trees #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anti-coagulant or vitamin K antagonist or VKA) #5 (fondaparinux or arixtra) #6 (ximelagatran or exanta) #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Neoplasms] explode all trees #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) #11 #9 or #10 #12 #8 and #10
MEDLINE	#1 exp Heparin/

(Continued)

#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or organan or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.

#3 exp Coumarins/

#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anti-coagulant or vitamin K antagonist or VKA).tw.

#5 (fondaparinux or arixtra).tw.

#6 (ximelagatran or exanta).tw.

#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.

#8 1 or 2 or 3 or 4 or 5 or 6 or 7

#9 exp Neoplasms/

#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.

#11 9 or 10

#12 8 and 11

#13 randomized controlled trial.pt.

#14 controlled clinical trial.pt.

#15 randomized.ab.

#16 placebo.ab.

#17 drug therapy.fs.

#18 randomly.ab.

#19 trial.ab.

#20 groups.ab.

#21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

#22 12 and 21

#23 exp animals/ not humans.sh.

#24 22 not 23

Embase

#1 heparin/

#2 exp low molecular weight heparin/

#3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or organan or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.

#4 exp coumarin derivative/

#5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anti-coagulant or vitamin K antagonist or VKA).tw.

(Continued)

- #6 (fondaparinux or arixtra).tw.
- #7 (ximelagatran or exanta).tw.
- #8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
- #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- #10 exp neoplasm/
- #11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
- #12 10 or 11
- #13 9 and 12
- #14 crossover procedure/
- #15 double-blind procedure/
- #16 randomized controlled trial/
- #17 single-blind procedure/
- #18 random*.mp.
- #19 factorial*.mp.
- #20 (crossover* or cross over* or cross-over*).mp.
- #21 placebo*.mp.
- #22 (double* adj blind*).mp.
- #23 (singl* adj blind*).mp.
- #24 assign*.mp.
- #25 allocat*.mp.
- #26 volunteer*.mp.
- #27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
- #28 13 and 27
- #29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
- #30 28 not 29

Appendix 3. Full search strategies for the electronic databases: update 2018

Database	Strategy
CENTRAL (the Cochrane Library, 2018, Issue 1)	<p>#1 MeSH descriptor: [Anticoagulants] explode all trees</p> <p>#2 (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedel-</p>

(Continued)

parin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock)

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

#4 MeSH descriptor: [Coumarins] explode all trees

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

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

#7 thrombin near inhibitor*

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

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

#10 TSOAC* or NOAC* or DOAC*

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

#12 MeSH descriptor: [Neoplasms] explode all trees

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

#14 #13 or #14

#15 #11 and #14

MEDLINE

RCT search strategy:

1. exp Anticoagulants/

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

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

4. exp Coumarins/

(Continued)

5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumac-etate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetra-lyl).mp.
6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan sulfate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
7. (thrombin adj inhibitor*).mp.
8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razax-aban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Neoplasms/
13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adeno-ma*).tw.
14. 12 or 13
15. 11 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. clinical trials as topic.sh.
21. randomly.ab.
22. trial.ti.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. (animals not (humans and animals)).sh.
25. 23 not 24
26. 15 and 25

Systematic Review search strategy:

1. exp Anticoagulants/
2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or cer-toparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or He-palean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Epa-

(Continued)

- rina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.
3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
4. exp Coumarins/
5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.
6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan sulfate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
7. (thrombin adj inhibitor*).mp.
8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Neoplasms/
13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adeno-ma*).tw.
14. 12 or 13
15. 11 and 14
16. (review or review, tutorial or review, academic).pt.
17. (medline or medlars or embase or pubmed or cochrane).tw,sh.
18. (scisearch or psychinfo or psycinfo).tw,sh.
19. (psychlit or psyclit).tw,sh.
20. cinahl.tw,sh.
21. ((hand adj2 search*) or (manual* adj2 search*)).tw,sh.
22. (electronic database* or bibliographic database* or computeri?ed database* or online database*).tw,sh.
23. (pooling or pooled or mantel haenszel).tw,sh.
24. (peto or dersimonian or der simonian or fixed effect).tw,sh.
25. (retraction of publication or retracted publication).pt.
26. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 16 and 26

(Continued)

28. meta-analysis.pt.
29. meta-analysis.sh.
30. (meta-analys* or meta analys* or metaanalys*).tw,sh.
31. (systematic* adj5 review*).tw,sh.
32. (systematic* adj5 overview*).tw,sh.
33. (quantitativ* adj5 review*).tw,sh.
34. (quantitativ* adj5 overview*).tw,sh.
35. (methodologic* adj5 review*).tw,sh.
36. (methodologic* adj5 overview*).tw,sh.
37. (integrative research review* or research integration).tw.
38. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 27 or 38
41. 15 and 39

Embase

RCT search strategy:

1. exp anticoagulant agent/
2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or cer-toparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or He-palean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Epa-rina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or He-parin Lock).mp.
3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
4. exp coumarin derivative/
5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumac-etate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetra-lyl).mp.
6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan sulfate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
7. (thrombin adj inhibitor*).mp.
8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razax-aban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.

(Continued)

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp neoplasm/
13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.
14. 12 or 13
15. 11 and 14
16. crossover procedure/
17. double-blind procedure/
18. randomized controlled trial/
19. single-blind procedure/
20. random*.mp.
21. factorial*.mp.
22. (crossover* or cross over* or cross-over*).mp.
23. placebo*.mp.
24. (double* adj blind*).mp.
25. (singl* adj blind*).mp.
26. assign*.mp.
27. allocat*.mp.
28. volunteer*.mp.
29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 15 and 29

Systematic Review search strategy:

1. exp anticoagulant agent/
2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or cer-toparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or organan or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or organan or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.
3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
4. exp coumarin derivative/
5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumac-etate or phenindione or Diphenadione or Tiocloamarol or Racumi or Marcoumar or Marcumar or

(Continued)

- Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.
6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan sulfate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
7. (thrombin adj inhibitor*).mp.
8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
10. (TSOAC* or NOAC* or DOAC*).ti,ab,kw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp neoplasm/
13. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.
14. 12 or 13
15. 11 and 14
16. exp review/
17. (literature adj3 review*).ti,ab.
18. exp meta analysis/
19. exp "Systematic Review"/
20. 16 or 17 or 18 or 19
21. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
22. RETRACTED ARTICLE/
23. 21 or 22
24. 20 and 23
25. (systematic* adj2 (review* or overview)).ti,ab.
26. (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*).ti,ab.
27. 24 or 25 or 26
28. 15 and 27

Appendix 4. Grade evidence profile: low-molecular weight heparin versus unfractionated heparin

Question: LMWH prophylaxis compared to UFH prophylaxis in patients with cancer without VTE undergoing a surgery (Q10a)

Setting: Inpatient surgical

Certainty assessment							Nº of patients		Effect		Certain-ty	Importance
Nº of studies	Study de-sign	Risk of bias	Incon-sistency	Indirect-ness	Impreci-sion	Other consid-erations	LMWH prophy-laxis	UFH prophy-laxis	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 1 weeks to 3 months)												
8	Ran-domised trials	Not seri-ous	Not seri-ous	Not seri-ous	Serious ^a	None	88/2105 (4.2%)	109/2155 (5.1%)	RR 0.82 (0.63 to 1.07)	9 fewer per 1000 (from 4 more to 19 fewer)	⊕⊕⊕⊕ MODER-ATE	CRITICAL
Any PE (follow up: range 1 weeks to 3 months)												
14	Ran-domised trials	Not seri-ous	Not seri-ous	Not seri-ous	Serious ^b	None	8/2759 (0.3%)	18/2829 (0.6%)	RR 0.49 (0.17 to 1.47)	3 fewer per 1000 (from 3 more to 5 fewer)	⊕⊕⊕⊕ MODER-ATE	CRITICAL
Symptomatic DVT (follow up: range 1 weeks to 3 months)												
8	Ran-domised trials	Not seri-ous	Not seri-ous	Not seri-ous	Serious ^c	None	7/1106 (0.6%)	11/1144 (1.0%)	RR 0.67 (0.27 to 1.69)	3 fewer per 1000 (from 7 fewer to 7 more)	⊕⊕⊕⊕ MODER-ATE	CRITICAL
Symptomatic DVT measured as asymptomatic DVT (follow up: range 1 weeks to 3 months)												
12	Ran-domised trials	Not seri-ous	Not seri-ous	Serious ^d	Serious ^e	None	169/2443 (6.9%)	198/2495 (7.9%)	RR 0.86 (0.71 to 1.05)	11 fewer per 1000 (from 4 more to 23 fewer)	⊕⊕⊕⊕ LOW	CRITICAL
Major bleeding (follow up: range 1 weeks to 3 months)												
9	Ran-domised trials	Not seri-ous	Not seri-ous	Not seri-ous	Serious ^f	None	53/1714 (3.1%)	54/1759 (3.1%)	RR 1.01 (0.69 to 1.48)	0 fewer per 1000 (from 10 fewer to 15 more)	⊕⊕⊕⊕ MODER-ATE	CRITICAL
Minor bleeding (follow up: range 1 weeks to 3 months)												
2	Ran-domised trials	Not seri-ous	Not seri-ous	Not seri-ous	Serious ^g	None	85/594 (14.3%)	85/600 (14.2%)	RR 1.01 (0.76 to 1.33)	1 more per 1000 (from 34 fewer to 47 more)	⊕⊕⊕⊕ MODER-ATE	CRITICAL
Wound hematoma (follow up: range 1 weeks to 3 months)												

(Continued)

6	Ran- domised trials	Not seri- ous ^h	Not seri- ous	Not seri- ous	Serious ⁱ	None	83/1391 (6.0%)	123/1436 (8.6%)	RR 0.70 (0.54 to 0.92)	26 fewer per 1000 (from 7 fewer to 39 fewer)	⊕⊕⊕○ MODER- ATE	CRITICAL
Reoperation for bleeding (follow up: range 1 weeks to 3 months)												
4	Ran- domised trials	Not seri- ous	Not seri- ous	Not seri- ous	Serious ^j	None	29/619 (4.7%)	32/627 (5.1%)	RR 0.93 (0.57 to 1.50)	4 fewer per 1000 (from 22 fewer to 26 more)	⊕⊕⊕○ MODER- ATE	CRITICAL
Intraoperative transfusion (follow up: range 1 weeks to 3 months)												
2	Ran- domised trials	Not seri- ous	Serious ^k	Not seri- ous	Serious ^l	None	364	373	-	MD 35.36 lower (253.19 lower to 182.47 higher)	⊕⊕○○ LOW	CRITICAL
Postoperative transfusion (follow up: range 1 weeks to 3 months)												
2	Ran- domised trials	Not seri- ous	Serious ^m	Not seri- ous	Serious ⁿ	None	363	371	-	MD 190.03 higher (23.65 lower to 403.72 higher)	⊕⊕○○ LOW	CRITICAL
Intraoperative blood loss (follow up: range 1 weeks to 3 months)												
4	Ran- domised trials	Not seri- ous	Not seri- ous	Not seri- ous	Serious ^o	None	377	384	-	MD 6.75 lower (85.49 lower to 71.99 higher)	⊕⊕⊕○ MODER- ATE	CRITICAL
Postoperative drain volume (follow up: range 1 weeks to 3 months)												
3	Ran- domised trials	Not seri- ous	Not seri- ous	Not seri- ous	Serious ^p	None	725	734	-	MD 30.18 higher (36.26 lower to 96.62 higher)	⊕⊕⊕○ MODER- ATE	CRITICAL
Thrombocytopenia (follow up: range 1 weeks to 3 months)												
2	Ran- domised trials	Not seri- ous	Not seri- ous	Not seri- ous	Serious ^q	None	3/337 (0.9%)	1/346 (0.3%)	RR 3.07 (0.32 to 29.33)	6 more per 1000 (from 2 fewer to 82 more)	⊕⊕⊕○ MODER- ATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

- a. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (19 fewer per 1000 absolute reduction) and possibility of no effect (4 more per 1000 absolute increase), including 197 events in total.
- b. Downgraded due to serious imprecision. Low event rate, 26 events in total
- c. Downgraded due to serious imprecision. Low event rate, 18 events in total
- d. Downgraded by one level due to serious inconsistency, outcome measured as surrogate outcome
- e. Downgraded due to serious imprecision. 95% CI is consistent with the possibility of important benefit (23 fewer more per 1000 absolute reduction) and possibility of harm (4 more per 1000 increase), including 367 events in total.
- f. Downgraded due to serious imprecision. 95% CI is consistent with the possibility of important benefit (10 fewer more per 1000 absolute reduction) and possibility of harm (15 more per 1000 increase), including 107 events in total.
- g. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (34 fewer per 1000 absolute reduction) and possibility of no effect (47 more per 1000 absolute increase), including 170 events in total.
- h. Downgraded due to serious risk of bias; allocation concealment was not clear in 5 out of 6 studies.
- i. Downgraded due to serious imprecision. Low event rate, 206 events in total
- j. Downgraded due to serious imprecision. 95% CI is consistent with the possibility of benefit (22 fewer per 1000 absolute reduction) and possibility of important harm (26 more per 1000 absolute increase), including 61 events in total.
- k. Downgraded due to serious inconsistency. $I^2 = 98\%$; [Dahan 1990](#) included patients undergoing thoracic surgery for cancer whereas [Kopenhagen 1992](#) included patients undergoing major elective abdominal surgery
- l. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (253.19 mL less) and possibility of harm (182.47 mL more)
- m. Downgraded due to serious inconsistency. $I^2 = 83\%$; [Dahan 1990](#) included patients undergoing thoracic surgery for cancer whereas [Kopenhagen 1992](#) included patients undergoing major elective abdominal surgery
- n. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (23.65mL less) and possibility of harm (40.3.72mL more)
- o. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (85.49 mL less) and possibility of harm (71.99 mL more)
- p. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (36.26 mL less) and possibility of harm (96.62 mL more)
- q. Downgraded due to serious imprecision. Low event rate, 4 events in total

Appendix 5. Grade evidence profile: low-molecular weight heparin versus fondaparinux

Question: LMWH prophylaxis compared to Fondaparinux prophylaxis in patients with cancer without VTE undergoing a surgical procedure (Q10b)

Setting: Inpatient surgical

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH prophylaxis	Fondaparinux prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Any VTE (follow up: 3 months)												
3	Randomised trials	Serious ^a	Not serious	Not serious	Serious ^b	None	65/907 (7.2%)	34/899 (3.8%)	RR 2.51 (0.89 to 7.03)	57 more per 1000 (from 4 fewer to 228 more) ^c	⊕⊕○○ LOW	CRITICAL
Major Bleeding (follow up: 3 months)												
3	Randomised trials	Serious ^a	Not serious	Not serious	Serious ^d	None	26/1182 (2.2%)	34/1157 (2.9%)	RR 0.74 (0.45 to 1.23)	8 fewer per 1000 (from 7 more to 16 fewer)	⊕⊕○○ LOW	CRITICAL
Minor Bleeding												
2	Randomised trials	Serious ^e	Not serious	Not serious	Serious ^f	None	8/195 (4.1%)	10/203 (4.9%)	RR 0.83 (0.34 to 2.05)	8 fewer per 1000 (from 33 fewer to 52 more)	⊕⊕○○ LOW	CRITICAL
Thrombocytopenia												
1	Randomised trials	Serious ^g	Not serious	Not serious	Serious ^h	None	1/138 (0.7%)	3/144 (2.1%)	RR 0.35 (0.04 to 3.30)	14 fewer per 1000 (from 20 fewer to 48 more)	⊕⊕○○ LOW	CRITICAL
Any Pulmonary embolism												
1	Randomised trials	Not serious	Not serious	Not serious	Very serious ⁱ	None	1/57 (1.8%)	0/59 (0.0%)	RR 3.10 (0.13 to 74.64)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
								0.1%		2 more per 1000		

(from 1 fewer to 74 more)

(Continued)

Postoperative drain volume

1	Ran- domised trials	Not seri- ous	Not seri- ous	Not seri- ous	Very se- rious j	None	57	59	-	MD 20 ml lower (114.34 lower to 74.34 higher)	⊕⊕⊕⊕ LOW
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CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

- a. Downgraded by one level due to high risk of bias (lack of allocation concealment and incomplete outcome data in Agnelli 2005; lack of blinding of patients and personnel and incomplete outcome data in Hata 2016 unclear allocation concealment in Song 2018)
- b. Downgraded by one level for concerns about both imprecision and indirectness. 95% CI is consistent with the possibility for benefit (4 per 1000 absolute reduction) and possibility of important harm (22 per 1000 absolute increase), including 99 events in total. VTE events included both symptomatic and asymptomatic events for patients with cancer which introduces some level of indirectness.
- c. Although the event rate used from the fondaparinux arm includes asymptomatic events, it is very close to rate of symptomatic VTE (3.1%) found in a retrospective cohort Changolkar 2014
- d. Downgraded for serious imprecision. 95% CI is consistent with the possibility for important benefit (16 per 1000 absolute reduction) and possibility of important harm (7 per 1000 absolute increase), including 60 events in total.
- e. Downgraded for high risk of bias (lack of blinding of patients and personnel and incomplete outcome data in Hata 2016 and unclear allocation concealment in Song 2018)
- f. Downgraded for serious imprecision. 95% CI is consistent with the possibility for important benefit (33 per 1000 absolute reduction) and possibility of important harm (52 per 1000 absolute increase), including 18 events in total.
- g. Downgraded for high risk of bias (lack of blinding of patients and personnel and incomplete outcome data in Hata 2016)
- h. Downgraded for serious imprecision. 95% CI is consistent with the possibility for important benefit (20 per 1000 absolute reduction) and possibility of important harm (48 per 1000 absolute increase), including 4 events in total.
- i. Downgraded by two levels for very serious imprecision. 95% CI is consistent with the possibility for important benefit (1 per 1000 absolute reduction) and possibility of important harm (78 per 1000 absolute increase), including 1 event in total.
- j. Downgraded due to serious imprecision. 95% CI is consistent with the possibility for important benefit (114.34 mL less) and possibility of harm (74.34 mL more)

WHAT'S NEW

Date	Event	Description
25 February 2019	Amended	Additional text added to Acknowledgements.

HISTORY

Review first published: Issue 11, 2011

Date	Event	Description
14 June 2018	New citation required but conclusions have not changed	Review title changed to <i>Anticoagulation for perioperative thromboprophylaxis in people with cancer</i> . Added new comparison (low-molecular weight heparin versus fondaparinux).
14 June 2018	New search has been performed	Search updated to 14 June 2018. Seven new studies identified
25 March 2015	Amended	Standard deviations of intra-operative blood loss outcome for trial Dahan 1990 are corrected.
3 March 2014	Amended	Data reanalyzed by using a complete case analysis approach for the primary meta-analysis

Date	Event	Description
3 March 2014	New citation required but conclusions have not changed	Data abstraction verified and detailed statistical data included as appendix

CONTRIBUTIONS OF AUTHORS

CFM: screening, full-text retrieval, data extraction, manuscript drafting, review co-ordination

LAK: searching for trials, screening, data extraction, data analysis, manuscript drafting, review co-ordination

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

IGT: screening, full-text retrieval, data extraction, manuscript drafting

IEI: data extraction

VY: screening, full-text retrieval

IT: screening, data extraction

FS: screening, data extraction

MB: screening, full-text retrieval, data extraction,

HS: protocol development, data interpretation, methodologic expertise

EAA: protocol development, data analysis, manuscript drafting, methodologic expertise, review co-ordination

DECLARATIONS OF INTEREST

CFM: declares no conflicts of interests

LAK: declares no conflicts of interests

MBH: declares no conflicts of interests.

IGT: declares no conflicts of interests.

IEI: declares no conflicts of interests

VY: declares no conflicts of interests.

IT: declares no conflicts of interests

FS: declares conflicts of interests

MB: declares conflicts of interests

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

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

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- No sources of support supplied

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- American Society of Hematology, USA.

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INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*administration & dosage] [adverse effects]; Blood Loss, Surgical [statistics & numerical data]; Blood Transfusion [statistics & numerical data]; Hemorrhage [chemically induced]; Heparin [*administration & dosage] [adverse effects]; Heparin, Low-Molecular-Weight [*administration & dosage] [adverse effects]; Neoplasms [mortality] [*surgery]; Postoperative Complications [mortality] [*prevention & control]; Pulmonary Embolism [prevention & control]; Randomized Controlled Trials as Topic; Thrombocytopenia [prevention & control]; Thrombosis [mortality] [*prevention & control]; Venous Thrombosis [prevention & control]

MeSH check words

Humans