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[Intervention Review]

Parenteral anticoagulation in ambulatory patients with cancer

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ABSTRACT

Background

Anticoagulation may improve survival in patients with cancer through a speculated anti-tumour effect, in addition to the antithrombotic effect, although may increase the risk of bleeding.

Objectives

To evaluate the efficacy and safety of parenteral anticoagulants in ambulatory patients with cancer who, typically, are undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.

Search methods

A comprehensive search included (1) a major electronic search (February 2016) of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 1), MEDLINE (1946 to February 2016; accessed via OVID) and Embase (1980 to February 2016; accessed via OVID); (2) handsearching of conference proceedings; (3) checking of references of included studies; (4) use of the 'related citation' feature in PubMed and (5) a search for ongoing studies in trial registries. As part of the living systematic review approach, we are running searches continually and we will incorporate new evidence rapidly after it is identified. This update of the systematic review is based on the findings of a literature search conducted on 14 August 2017.

Selection criteria

Randomized controlled trials (RCTs) assessing the benefits and harms of parenteral anticoagulation in ambulatory patients with cancer. Typically, these patients are undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.

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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 interested included all-cause mortality, symptomatic venous thromboembolism (VTE), symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), major bleeding, minor bleeding, and quality of life. We assessed the certainty of evidence for each outcome using the GRADE approach (GRADE handbook).

Main results

Of 6947 identified citations, 19 RCTs fulfilled the eligibility criteria. These trials enrolled 9650 participants. Trial registries' searches identified nine registered but unpublished trials, two of which were labeled as 'ongoing trials'. In all included RCTs, the intervention consisted of heparin (either unfractionated heparin or low molecular weight heparin). Overall, heparin appears to have no effect on mortality at 12 months (risk ratio (RR) 0.98; 95% confidence interval (CI) 0.93 to 1.03; risk difference (RD) 10 fewer per 1000; 95% CI 35 fewer to 15 more; moderate certainty of evidence) and mortality at 24 months (RR 0.99; 95% CI 0.96 to 1.01; RD 8 fewer per 1000; 95% CI 31 fewer to 8 more; moderate certainty of evidence). Heparin therapy reduces the risk of symptomatic VTE (RR 0.56; 95% CI 0.47 to 0.68; RD 30 fewer per 1000; 95% CI 36 fewer to 22 fewer; high certainty of evidence), while it increases in the risks of major bleeding (RR 1.30; 95% 0.94 to 1.79; RD 4 more per 1000; 95% CI 1 fewer to 11 more; moderate certainty of evidence) and minor bleeding (RR 1.70; 95% 1.13 to 2.55; RD 17 more per 1000; 95% CI 3 more to 37 more; high certainty of evidence). Results failed to confirm or to exclude a beneficial or detrimental effect of heparin on thrombocytopenia (RR 0.69; 95% CI 0.37 to 1.27; RD 33 fewer per 1000; 95% CI 66 fewer to 28 more; moderate certainty of evidence); quality of life (moderate certainty of evidence).

Authors' conclusions

Heparin appears to have no effect on mortality at 12 months and 24 months. It reduces symptomatic VTE and likely increases major and minor bleeding. Future research should further investigate the survival benefit of different types of anticoagulants in patients with different types and stages of cancer. The decision for a patient with cancer to start heparin therapy should balance the benefits and downsides, and should integrate the patient's values and preferences.

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

PLAIN LANGUAGE SUMMARY

Injectable blood thinners (anticoagulants) in patients with cancer

Background
Research evidence suggests that blood thinners may improve the survival of patients with cancer, by preventing life-threatening blood clots and might also have a direct anticancer effect. However, blood thinners can also increase the risk of bleeding, which can be serious and reduce survival. It is therefore important to understand the pros and cons of treatment to allow patients and their doctors to be aware of the balance of risks and benefits.

Study characteristics
We searched the scientific literature for studies of anticoagulants in people with cancer. The evidence is current to 14 August 2017. We included 19 eligible trials.

Key results
We selected 19 trials including 9650 participants with cancer. Most trials included participants with various types of cancer, especially small cell lung cancer, non-small cell lung cancer, and pancreatic cancer. All studies were conducted in the outpatient setting. The results suggest that the effect of injectable blood thinners on survival is uncertain, but if anything of small size. Also the results suggest that injectable blood thinners reduce the risk of blood clots by about half and possibly increase the risk of major bleeding and minor bleeding by 4 more per 1000 and 17 more per 1000, respectively. The effect on quality of life is uncertain.

Certainty of evidence
We judged the certainty of evidence to be high for symptomatic VTE and minor bleeding, and moderate for mortality, major bleeding and quality of life.

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

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SUMMARY OF FINDINGS

Summary of findings 1. Heparin prophylaxis compared with no prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy

Heparin prophylaxis compared with no prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy

P: Ambulatory patients with cancer without VTE receiving systemic therapy

I: Heparin prophylaxis

C: No prophylaxis

S: Outpatient

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with No prophylaxis	Risk difference with Heparin prophylaxis
Mortality follow-up: 12 months	9575 (18 RCTs)	⊕⊕⊕⊖ MODERATE [1]	RR 0.98 (0.93 to 1.03)	Study population	
				504 per 1000	10 fewer per 1000 (35 fewer to 15 more)
Mortality follow-up: 24 months	5229 (14 RCTs)	⊕⊕⊕⊖ MODERATE [1]	RR 0.99 (0.96 to 1.01)	Study population	
				778 per 1000	8 fewer per 1000 (31 fewer to 8 more)
Symptomatic VTE follow-up: 12 months	9036 (16 RCTs)	⊕⊕⊕⊕ HIGH	RR 0.56 (0.47 to 0.68)	Study population	
				68 per 1000	30 fewer per 1000 (36 fewer to 22 fewer)
Major bleeding follow-up: 12 months	9592 (18 RCTs)	⊕⊕⊕⊖ MODERATE [2]	RR 1.30 (0.94 to 1.79)	Study population	
				14 per 1000	4 more per 1000 (1 fewer to 11 more)
Minor bleeding follow-up: 12 months	9245 (16 RCTs)	⊕⊕⊕⊕ HIGH	RR 1.70 (1.13 to 2.55)	Study population	
				24 per 1000	17 more per 1000 (3 more to 37 more)

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Thrombocytopenia	5832 (12 RCTs)	⊕⊕⊕⊖ MODERATE [3]	RR 0.69 (0.37 to 1.27)	Study population	
				105 per 1000	33 fewer per 1000 (66 fewer to 28 more)
Quality of life impairment	2241 (2 RCTs)	⊕⊕⊕⊖ MODERATE [4]	-	Macbeth 2016 (FRAGMATIC): " There was no difference between the two groups with respect to quality-adjusted life years gained in the first year... No difference in overall quality of life at 6 months (P = .94) or at 12 months (P = .89)... Overall quality of life did not change significantly over the study period".Sideras 2006: "The QOL and SDS scores were similar, both at baseline and during the protocol period, in patients randomized to receive LMWH vs those not randomized to receive LMWH."	

*__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 quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision: Confidence interval includes values suggesting clinically significant benefit and values suggesting no effect.
[2] Downgraded one level due to serious imprecision: Confidence interval includes values suggesting clinically significant harm and values suggesting no effect.
[3] Downgraded one level due to serious imprecision: Confidence interval includes values suggesting clinically significant benefit and values suggesting harm.
[4] Downgraded one level due to serious risk of bias: Both studies were open-label studies (lack of blinding may impact the patient-reported subjective outcomes)

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BACKGROUND

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

Description of the condition

Since the 1930s, scientists have been exploring the effects of anticoagulation on cancer (Smorenburg 2001). Studies have implicated the tumor-mediated activation of the hemostatic system in both the formation of tumor stroma and in tumor metastasis (Dvorak 1986; Francis 1998; Levine 2003). There is also evidence that heparin inhibits expression of oncogenes and formation of thrombin and fibrin induced by cancer cells (Smorenburg 2001). In addition, heparin potentially inhibits intravascular arrest of cancer cells and thus metastasis (Smorenburg 2001).

Description of the intervention

Heparin and low molecular weight heparins (LMWHs), fondaparinux and danaparoid 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. Recombinant hirudin, bivalirudin and argatroban directly inhibit thrombin and are classified as direct anticoagulants (Hirsh 2008). Heparin and its low molecular weight derivatives are not absorbed orally and must be administered parenterally by intravenous infusion or subcutaneous injections (Hirsh 1993).

How the intervention might work

Researchers have hypothesized that heparin may improve outcomes in patients with cancer through an anti-tumor effect in addition to its antithrombotic effect (Thodiyil 2002). In a 1992 clinical trial comparing nadroparin, a LMWH, with unfractionated heparin in patients with proven deep vein thrombosis (DVT), nadroparin unexpectedly reduced mortality in the subgroup of patients with cancer (Prandoni 1992). At the same time, anticoagulants increase the risk for bleeding. In fact, in patients with venous thrombosis on anticoagulation, the risk of bleeding was higher if patients had cancer and correlated with the extent of cancer (Prandoni 2002). Heparins are also known to cause thrombocytopenia (reduced numbers of platelets) and heparin-induced thrombocytopenia (HIT) syndrome (Girolami 2006).

Why it is important to do this review

We initially conducted this and other reviews on this topic and their updates to directly and better inform clinical practice guidelines. The last update of this systematic review, published in 2014 (Akl 2014 (parenteral)), identified 15 trials enrolling 7662 participants (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Altinbas 2004; Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS); Klerk 2005 (MALT); Lebeau 1994; Lecumberri 2013 (ABEL); Maraveyas 2012 (FRAGEM); Pelzer 2009 (CONKO-2004); Perry 2010 (PRODIGE); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008). The included trials provided high-certainty evidence for a reduction of venous thromboembolism (VTE) with heparin thromboprophylaxis compared to no heparin thromboprophylaxis. Since then, we have identified three eligible trials addressing this question (Khorana 2017 (PHACS); Macbeth 2016 (FRAGMATIC); Zwicker 2013 (MICRO TEC)) and the full-text publication of a previously included abstract (Pelzer 2015 (CONKO-004).

Living systematic review approach: Following the publication of this current 2017 update of the review, we will maintain it as a living systematic review. This means we will be continually running the searches and rapidly incorporating any newly identified evidence (for more information about the living systematic review approach being piloted by Cochrane, see Appendix 1. We believe a living systematic review approach is appropriate for this review for four reasons. First, the review addresses an important topic for clinical practice; patients with cancer have a relatively high rate of VTE, up to 17.7% (Ay 2010). In addition, the occurrence of VTE is associated with a 2.3 increased risk of death in patients with breast and non-small cell lung cancer (NSCLC), 2.5 times lengthening of hospital stay among patients with lung cancer, and 50% higher total cost for patients with lung cancer (Chew 2008, Chew 2007; Connolly 2012). Second, there remains uncertainty in the existing evidence base; the 2014 update of this systematic review found a potential subgroup effect on all-cause mortality at one year, with a possible higher reduction in mortality among patients with small cell lung cancer (SCLC) compared to other types of cancer. Third, we are aware of several recently published and ongoing trials in this area that will be important to incorporate in a timely manner. Fourth, we are planning to use this living systematic review as the basis of a living recommendation in a clinical practice guideline with the American Society of Hematology (Akl 2017). For more information about the living systematic review approach being piloted by Cochane, see Appendix 2.

OBJECTIVES

To evaluate the effectiveness and safety of parenteral anticoagulants in ambulatory patients with cancer. Typically, these patients are undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Participants with cancer with no standard indication for prophylactic anticoagulation (e.g. for acute illness, for central venous line placement, perioperatively) or for therapeutic anticoagulation (e.g. for the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE)). Patients could have been of any age group (including children). Typically, these participants are undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy.

Types of interventions

Intervention arm: parenteral anticoagulants, such as unfractionated heparin or low molecular weight heparin (LMWH).

Comparator intervention: placebo or no intervention.

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The trial protocol should have planned to provide all other co-interventions (e.g. chemotherapy) similarly.

Types of outcome measures

Primary outcomes

- All-cause mortality; pre-specified at 12 months, 24 months and over the duration of the trial.

Secondary outcomes

- Symptomatic 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.
- 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.
- Major bleeding: we accepted the authors' definitions of major bleeding.
- Minor bleeding: we accepted the authors' definitions of minor bleeding.
- Health-related quality of life: had to be measured using a validated tool.
- Thrombocytopenia.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in patients with cancer. We did not use language restrictions. We conducted comprehensive searches on 14 August 2017, following the original electronic searches in January 2007, February 2010, February 2013, and February 2016 (last major search). We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (starting 1946), and Embase (starting 1980; accessed via OVID) . The search strategies combined terms for anticoagulants, terms for cancer and a search filter for RCTs. We list the full search strategies for each of the electronic databases in Appendix 3, Appendix 4, and Appendix 5, respectively.

Living systematic review approach: Since the last major search in February 2016, we have been running searches monthly, using auto-alerts to deliver the monthly yield by email. We will incorporate new evidence rapidly after it is identified. This update of the systematic review is based on the findings of a literature search conducted on 14 August 2017. We will review search methods and strategies approximately yearly, to ensure they reflect any terminology changes in the topic area, or in the databases.

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982 up to August 2017) and of the American Society of Hematology (ASH, starting with its 2003 issue up to August 2017).We also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies. We reviewed the reference lists of papers included in this review and of other relevant systematic reviews. We used the 'related citation' feature in PubMed to identify additional articles and 'citation tracking' of included studies in Web of Science Core Collection.In addition, experts in the field were contacted for information about unpublished and ongoing trials.

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

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts of identified articles for eligibility. We retrieved the full text of articles judged as 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. The two review authors resolved their disagreements by discussion or by consulting a third review author.

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

Data extraction and management

Two review authors independently extracted data from each included study and resolved their disagreements by discussion. We aimed to collect data related to the following.

Participants

- Number of participants randomized to each treatment arm.
- Number of participants followed up in each treatment arm.
- Number of withdrawals from treatment in each treatment arm.
- Population characteristics (age, gender, co-morbidity).
- History of VTE.
- Type of cancer (site and histology).
- Stage of cancer.
- Time since cancer diagnosis.

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Interventions

- Type of anticoagulant: unfractionated heparin, LMWH or fondaparinux.
- Dose: prophylactic versus therapeutic (Table 2).
- Duration of treatment.
- Control: placebo or no intervention.
- Co-interventions including chemotherapy and hormonal therapy, immunotherapy and radiotherapy (type and duration).

Outcomes

We extracted both time-to-event data (for the survival outcome) and dichotomous data (for all outcomes). For mortality, we collected data for the pre-specified time point of 12 months, but also for 24 months and for over the duration of follow-up.

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

For dichotomous data, we extracted data necessary to conduct complete case analysis as the primary analysis. We collected all-cause mortality at one year (time point defined a priori in the protocol) and at two years (time point defined post hoc based upon results reported in the individual RCTs). When we could not obtain the number of events at the time points of interest from the paper or from the authors, two review authors calculated these numbers independently and in duplicate from survival curves, if available (Altinbas 2004; Kakkar 2004 (FAMOUS)). We used the mean of the two estimates when they differed. We assessed agreement between the two authors for each estimated value by calculating the percentage difference, which is the difference between the two estimates divided by the denominator (number of people at risk for the event) and multiplied by 100. For some studies, where VTE is not reported as a separate outcome, we added the number of events of DVT and PE.

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

Other

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

- source of funding;
- ethical approval;
- conflict of interest.

Assessment of risk of bias in included studies

We assessed risk of bias at the study level using the Cochrane 'Risk of bias' tool (Cochrane Handbook). Two review authors independently assessed the risk of bias of each included study and resolved their disagreements by discussion. 'Risk of bias' criteria included:

- adequate sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- percentage of follow-up and whether incomplete outcome data were addressed;
- whether the study was free of selective reporting; and
- whether the study was stopped early for benefit.

See section on Dealing with missing data about assessing risk of bias associated with participants with missing data.

Measures of treatment effect

We collected and analyzed hazard ratios (HRs) for time-to-event data and risk ratios (RRs) for dichotomous data. None of the outcomes of interest was meta-analyzed as a continuous variable.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Determining participants with missing data

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

- "ineligible participants" and "did not receive the first dose" participant categories, which are defined prior to the initiation of the study intervention, most likely have missing participant data;
- "withdrew consent", "lost to follow-up" and "outcome not assessable" participant categories and other category explicitly reported as not being followed-up, which are defined after the initiation of the study intervention, most likely have missing participant data;
- "dead", "experienced adverse events", "non-compliant", "discontinued prematurely" and similarly described participant categories are less likely to have 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, i.e. 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 post-intervention initiation).
- Numerator: number of participants with observed events (i.e. participants who suffered at least one event for the outcome of interest during their available follow-up time).

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For continuous data, we planned to use for each study arm the reported mean and standard deviation 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 progressively challenge the statistical significance of the results of the primary analysis (Akl 2013; Ebrahim 2013).

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

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

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

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

- Denominator: (number of participants randomized) - (number of participants most likely with missing data, pre-intervention initiation).
- Numerator: (number of participants with observed events) + (number of participants most likely with missing data post-intervention initiation, with assumed events).

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

For continuous data, we planned to use the four strategies suggested by Ebrahim and colleagues. 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 standard deviation (SD), we used the median SD from the control arms of all included trials (Ebrahim 2013).

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we attempted to investigate the possible reasons for this (see section on Subgroup analysis and investigation of heterogeneity).

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. We also assessed for possible publication bias by creating an inverted funnel plot for the primary outcome of survival.

Data synthesis

For time-to-event data, we pooled the log(HRs) using a random-effects model (DerSimonian 1986), and the generic inverse variance facility of RevMan 2014. For dichotomous data, we calculated the RR separately for each study. When analyzing data related to participants who were reported as not compliant, we attempted to adhere to the principles of intention-to-treat (ITT) analysis. We approached the issue of non-compliance independently from that of missing data (Alshurafa 2012). We then pooled the results of the different studies using a random-effects model. We assessed the certainty of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE handbook).

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

Subgroup analysis and investigation of heterogeneity

We planned to explore heterogeneity by conducting subgroup analyses based on the characteristics of participants (type and stage of cancer, and whether participants were on cancer treatment or not). In particular, we conducted subgroup analyses for patients with (1) lung cancer (either SCLC or NSCLC) versus those with non-lung cancer; (2) patients with advanced cancer versus those with non-advanced cancer. We included in the lung versus non lung subgroup analysis data from:

- studies that recruited only patients with lung cancer (either SCLC or NSCLC) and studies that recruited only patients with non-lung cancer;
- studies that recruited both lung and non-lung cancer if they provided data for subgroups of patients with lung cancer AND data for subgroups of patients with non-lung cancer;
- studies that recruited both lung and non-lung cancer but did not provide subgroup data, if more than 75% of participants had lung cancer or more than 75% of participants had non-lung cancer.

Similarly for the subgroup analysis for non-advanced cancer. We planned to assess the credibility of subgroup effect, when statistically significant, using the criteria suggested by Sun 2010.

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Sensitivity analysis

We planned for sensitivity analyses excluding trials at high risk of bias. As described above, we also planned for sensitivity meta-analyses to assess the risk of bias associated with missing participant data when the primary meta-analysis of a specific outcome found a statistically significant effect.

RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow diagram. As of August 2017, the search strategy identified a total of 6947 unique citations. The title and abstract screening identified 192 potentially eligible citations. The full-text screening of the full texts of these 192 citations identified 18 eligible RCTs published as full reports (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Altinbas 2004; Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS); Khorana 2017 (PHACS); Klerk 2005 (MALT); Lebeau 1994; Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC); Maraveyas 2012 (FRAGEM); Pelzer 2015 (CONKO-004); Perry 2010 (PRODIGE); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008; Zwicker 2013 (MICRO TEC)), and one RCT published as abstract (Vadhan-Raj 2013) We had also identified two eligible studies published as abstracts but for which we were not able to obtain the necessary data from the authors: Salat 1990, Chazouilleres 1994,. We identified nine registered but unpublished trials: four completed (Borad 2011 (PGPC1); Germonpre 2008 (SYRINGES); Kakkar 2010 (GASTRANOX); Okuno 1999); two terminated (Chibauldel 2008 (PAM07); Pandya 2002); two ongoing (Lars 2008 (RASTEN); Meyer 2017 (PROVE)); and one withdrawn prior to enrolment (Rosovsky 2009).

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Figure 1. Study flow diagram.

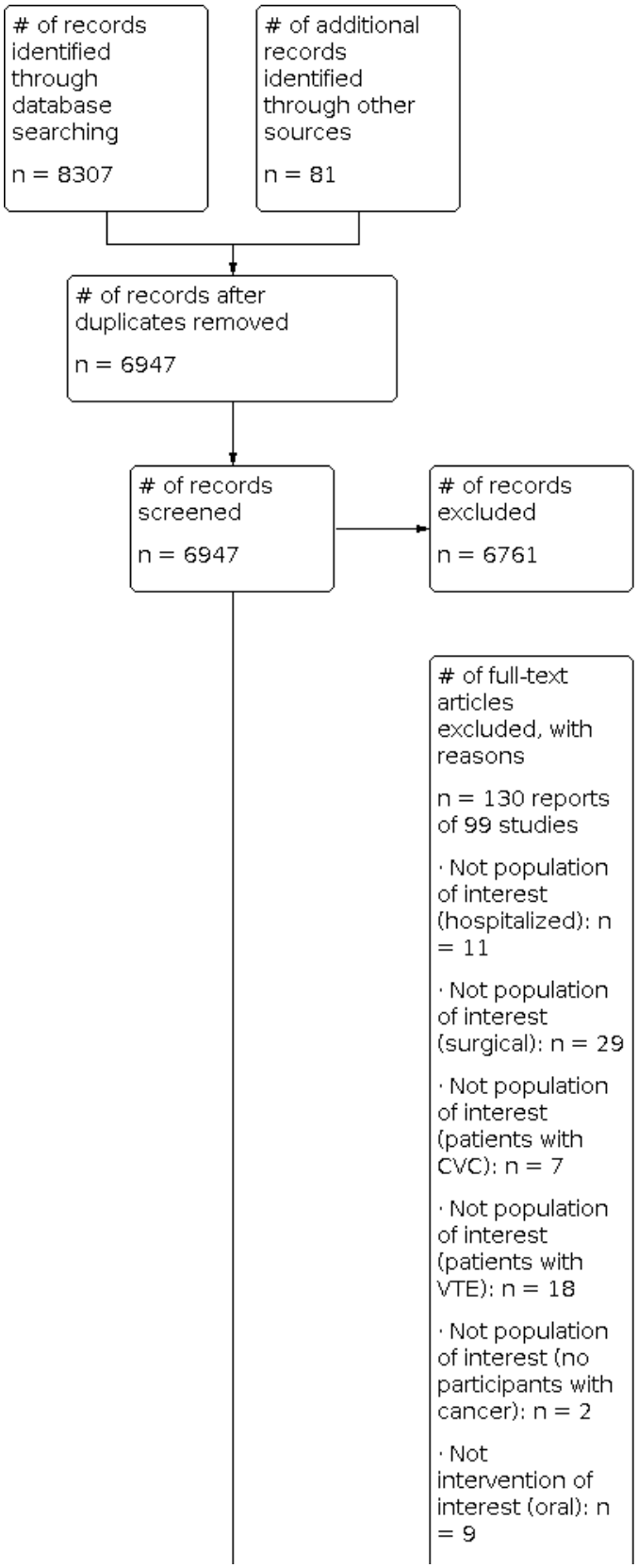

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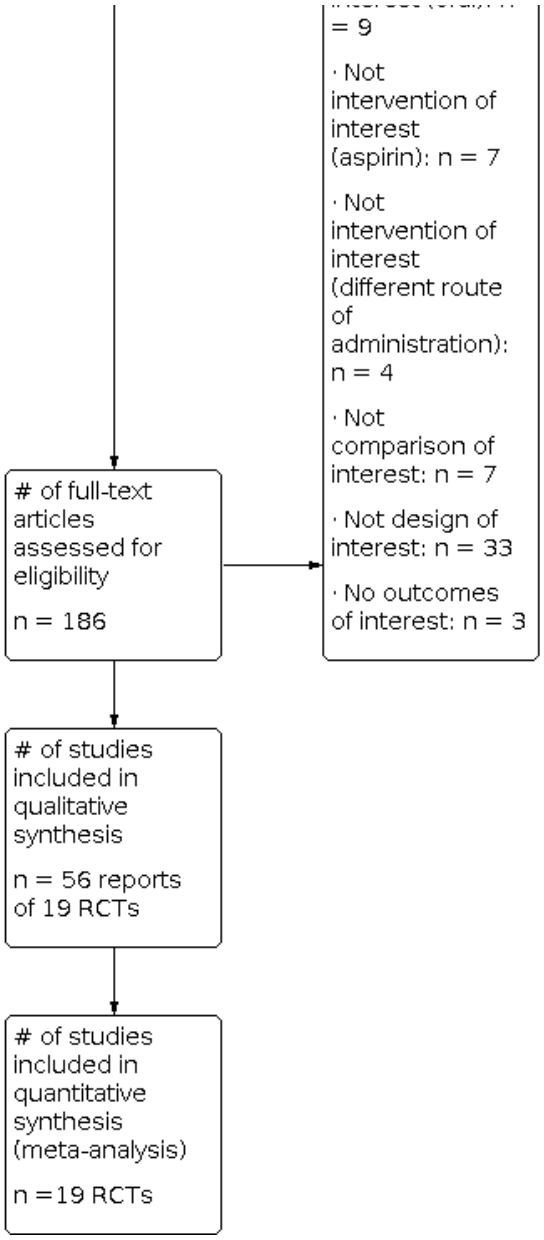
Figure 1. (Continued)



Included studies

The 19 included studies had 9650 participants. One study used unfractionated heparin as the intervention (Lebeau 1994), another used ultra-LMWH (Agnelli 2012 (SAVE-ONCO)), while the other 17 used LMWH as the intervention (Agnelli 2009 (PROTECHT); Altinbas 2004; Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS); Khorana 2017 (PHACS); Klerk 2005 (MALT); Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC); Maraveyas 2012 (FRAGEM); Pelzer 2015 (CONKO-004); Perry 2010 (PRODIGE); Sideras 2006; Vadhan-Raj 2013; van Doormaal 2011 (INPACT); Weber 2008; Zwicker 2013 (MICRO TEC)). We did not identify any study using fondaparinux as the intervention.

Agnelli and colleagues (PROTECHT trial) recruited 1150 ambulatory participants with metastatic or locally advanced cancer (Agnelli 2009 (PROTECHT)). Participants were randomized to receive a prophylactic dose of nadroparin or placebo, each with concomitant chemotherapy. The primary efficacy outcomes were symptomatic DVT, and PE. The secondary efficacy outcomes were asymptomatic thromboembolic events incidentally diagnosed, and survival at the end of study treatment and at 12 months. Study outcomes included survival, asymptomatic VTE, and minor and major bleeding. Follow-up was about 90% in each group.

Agnelli and colleagues (SAVE-ONCO trial) recruited 3212 participants with advanced metastatic or locally advanced cancer. Of the participants, 91% had an ECOG performance status of zero or one and 42% had at least one risk factor for VTE (Agnelli 2012 (SAVE-ONCO)). Participants were randomized to receive either subcutaneous injection of semuloparin or placebo for a minimum of three months. The study outcomes included mortality, PE, symptomatic DVT, major bleeding and minor bleeding. Follow-up

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data were available for 99% of participants for mortality and VTE outcomes. The minimum duration of follow-up was up to three days after last injection, with a median of 3.5 months. The maximum duration of follow-up was 12 months.

Altinbas and colleagues recruited 84 participants with both limited and extensive SCLC and an Eastern Cooperative Oncology Group (ECOG) status < 3 (Altinbas 2004). The ECOG performance Status scale ranges from zero (fully active) to five (dead) (Oken 1982). Participants were randomized to receive either a prophylactic dose of a LMWH (dalteparin) or placebo for 18 weeks or less, in combination with chemotherapy in case of disease progression. Study outcomes included mortality (at 12 and 24 months), symptomatic DVT and bleeding. Follow-up was complete (100%). The minimum and maximum duration of follow-up were two and 33 months, respectively. Hazard ratios (HRs) were estimated from published survival curves.

Haas and colleagues conducted two multi-centre double-blind studies and recruited 900 ambulatory participants receiving chemotherapy for disseminated metastatic breast carcinoma (Haas 2012 (TOPIC 1); n = 353) or stage III/IV NSCLC carcinoma (Haas 2012 (TOPIC 2); n = 547). Participants were randomized to receive either subcutaneous certoparin or placebo for six months. The study outcomes included mortality, confirmed VTE, PE, DVT, thrombocytopenia, major bleeding and minor bleeding. A number of participants were not included in the intention-to-treat (ITT) analysis but it is not reported whether they were followed up. The minimum duration of follow-up was six months.

Kakkar and colleagues recruited 385 participants with advanced stage III or IV malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary or uterus, and a minimum life expectancy of three months (Kakkar 2004 (FAMOUS)). Participants were randomized to receive either a prophylactic dose of a LMWH (dalteparin) or placebo for 12 months, with no restriction on concomitant chemotherapy or radiotherapy. The study outcomes included mortality (at 12, 24 and 36 months), symptomatic VTE (PE, DVT), major bleeding and minor bleeding. Follow-up data were available for 374 participants (97%). The minimum duration of follow-up was not reported. The maximum duration of follow-up was 81 months. HRs were estimated from published survival curves, assuming all participants were followed up for 77 months.

Khorana and colleagues conducted a multi-center study and recruited 98 participants with cancer and a Khorana risk score of ≥ 3 (Khorana 2017 (PHACS)). Participants were randomized to subcutaneous dalteparin or observation for a period of 12 weeks. The study outcomes included symptomatic DVT and PE, and clinically significant major and non-major bleeding. Follow-up was complete (100%). The study was terminated early due to low accrual.

Klerk and colleagues (MALT trial) recruited 302 participants with different types of advanced solid malignant tumors and a minimum life expectancy of one month (Klerk 2005 (MALT)). Participants were randomized to receive either a LMWH or a placebo for six weeks, each with concomitant chemotherapy or radiotherapy. Study outcomes included mortality (at six, 12 and 24 months), major bleeding, non-major bleeding and combined major and non-major bleeding. Follow-up was complete (100%). The minimum duration of follow-up was not reported, whereas the maximum duration was 84 months. The HR and its standard error were reported.

Lebeau and colleagues recruited 277 participants with both limited and extensive small cell lung cancer (SCLC), 78% of which had a Karnofsky Performance Scale Index > 80 (Lebeau 1994). The Karnofsky Performance Scale Index ranges from zero (dead) to 100 (normal) (Karnofsky 1948). Participants were randomized to receive either a prophylactic dose of UFH for five weeks or no intervention, in combination with chemotherapy. The study outcomes were mortality (at 12, 24 and 36 months) and bleeding. Follow-up was complete (100%). The minimum duration of follow-up was not reported. The maximum duration of follow-up was 59 months. HRs were estimated from published survival curves, assuming all participants were followed up for 59 months.

Lecumberri and colleagues recruited 38 participants diagnosed with limited SCLC in a multicenter, open-label study (Lecumberri 2013 (ABEL)). Participants were randomized to receive standard chemoradiotherapy or the same therapy plus bemiparin for a maximum of 26 weeks. The study outcomes included all-cause mortality, incidence of VTE, major and minor bleeding, and thrombocytopenia. All outcomes were assessed at 18 months. Follow-up was complete (100%).

Macbeth and colleagues recruited 2202 participants diagnosed with lung cancer (Macbeth 2016 (FRAGMATIC)). Participants were on standard anticancer treatment and randomized to subcutaneous dalteparin or no anticoagulation. The study outcomes included overall survival and bleeding. The median duration of follow-up was 23.1 months.

Maraveyas and colleagues recruited 123 participants with non-resectable, recurrent or metastatic pancreatic adenocarcinoma, Karnofsky performance status (KPS) of 60 to 100, and estimated life expectancy of more than 12 weeks (Maraveyas 2012 (FRAGEM)). Participants were randomized to receive either subcutaneous dalteparin or placebo. The study outcomes included mortality, all-type VTE, DVT, and PE. Data from a range of 55 to 62 participants were used for different outcome assessments. All outcomes were assessed at 12 weeks and one year follow-up.

Pelzer and colleagues recruited 312 chemotherapy-naive participants with advanced pancreatic cancer (Pelzer 2015 (CONKO-004)). Participants were randomized to receive or not to receive additional LMWH (enoxaparin) starting simultaneously with palliative systemic chemotherapy. Study outcomes included overall survival, symptomatic VTE, asymptomatic subclinical DVT and major bleeding. Follow-up for overall survival was about 95.7% in the intervention group and 93.4% in the control group. The median duration of follow-up was 30.4 weeks.

Perry and colleagues recruited 186 participants with newly diagnosed malignant glioma (Perry 2010 (PRODIGE)). Participants were randomized to receive a prophylactic dose of LMWH (dalteparin) or placebo. Study outcomes included objectively documented symptomatic DVT or PE (primary outcome), bleeding (major and all bleeding), quality of life and death. The duration of follow-up was 12 months.

Sideras and colleagues recruited 141 participants with different types of advanced cancer and a minimum life expectancy of 12 weeks and ECOG state zero to two (Sideras 2006). Participants were

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randomized either to a prophylactic dose of a LMWH (dalteparin) or to placebo or no intervention. Study outcomes included overall survival (at 12, 24 and 36 months), VTE and major bleeding. Follow-up data were available for 138 participants (98%). The minimum duration of follow-up was not reported, whereas the maximum duration of follow-up was 24 months. The authors supplied us with unpublished data, giving the HR and its standard error.

Vadhan-Raj and colleagues recruited 75 participants with metastatic or locally advanced pancreatic cancer (Vadhan-Raj 2013). Participants were randomized to receive dalteparin 5000 U SQ daily for 16 weeks during chemotherapy or chemotherapy alone. Assessed outcomes were VTE, DVT and PE. Participants were followed-up for 16 weeks. The study reported complete follow up.

van Doormaal and colleagues recruited 503 participants with prostate carcinoma, NSCLC, or with a locally advanced pancreatic cancer (van Doormaal 2011 (INPACT)). Participants were randomized to receive either subcutaneous nadroparin or no nadroparin. The median duration of follow-up was 10.5 months in the nadroparin group and 10.4 months in the control group. The study outcomes included mortality (at one, two and three years versus at five, 10, 15, 20, 25, 30, 35, 40 months), PE, DVT, major bleeding and minor bleeding. The percentage of participants lost to follow-up was 0.8% and 3.5% from the nadroparin group and the control group respectively.

Weber and colleagues recruited 20 participants with advanced cancer and an estimated life expectancy of less than six months (Weber 2008). Participants were randomized to receive either a prophylactic dose of LMWH (nadroparin) or no treatment, each with concomitant anticancer treatment. Study outcomes included mortality, VTE (including PE and DVT), minor and major bleeding, and thrombocytopenia. Follow-up was complete (100%). The minimum duration of follow-up was reported as three months for mortality, whereas the maximum was 18 months for all outcomes.

Zwicker and colleagues recruited 34 participants with advanced cancer and high tissue factor-bearing microparticles (Zwicker 2013 (MICRO TEC)). Participants were randomized to subcutaneous enoxaparin or observation. The study outcomes included incidence of symptomatic VTE for a follow-up duration of two months. The trial was originally designed as a phase III, then re-adapted to a phase II randomized clinical trial.

Excluded studies

We excluded 99 studies (130 reports) from this review for the following reasons: not population of interest (hospitalized): n = 11; not population of interest (surgical): n = 29; not population of interest (patients with central venous catheter (CVC)): n = 7; not population of interest (patients with VTE): n = 18; not population of interest (no participants with cancer): n = 2; not intervention of interest (oral): n = 9; not intervention of interest (aspirin): n = 7; not intervention of interest (different route of administration): n=4; not comparison of interest: n = 7; not design of interest: n = 33; not outcomes of interest: n = 3.

Risk of bias in included studies

The judgments for the risk of bias are summarized in Figure 2 and Figure 3, respectively.

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

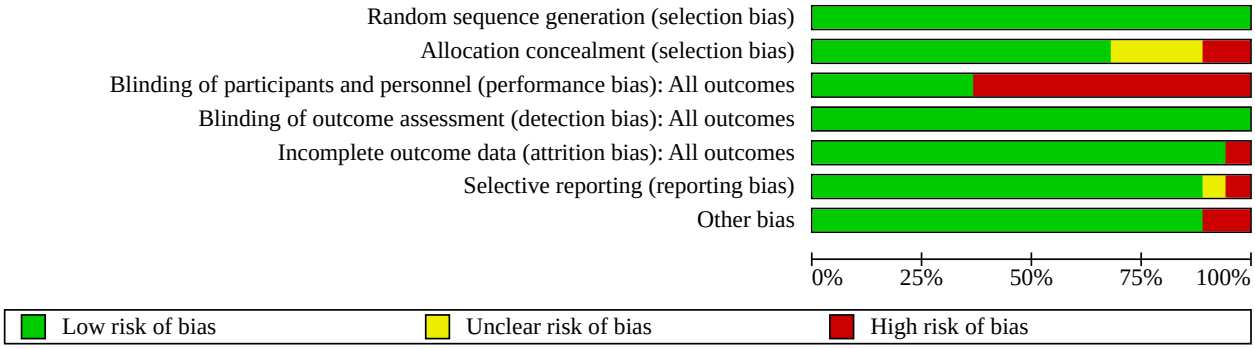

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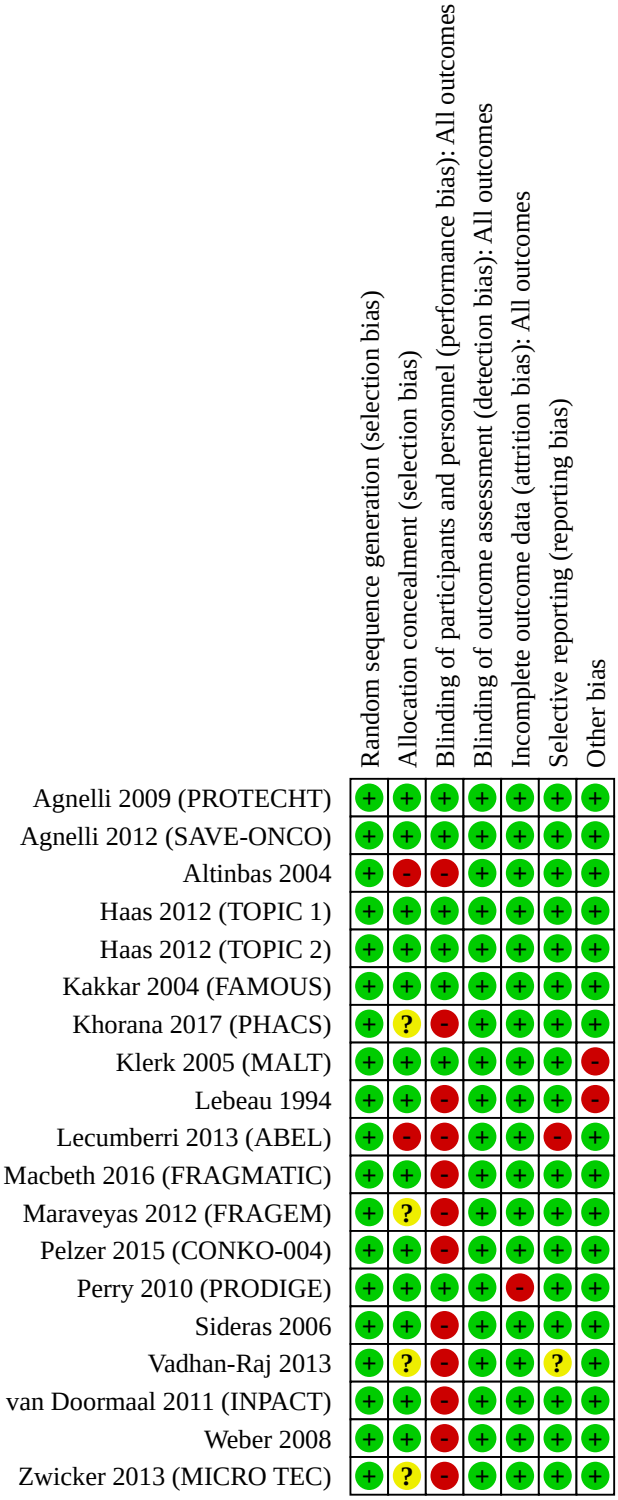
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

We judged allocation to be adequately concealed in 13 of the 19 studies (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS); Klerk 2005 (MALT); Lebeau 1994; Macbeth 2016 (FRAGMATIC); Pelzer 2015 (CONKO-004); Perry 2010 (PRODIGE); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008), and not concealed in two studies (Altinbas 2004; Lecumberri 2013 (ABEL)). Four studies did not report on allocation concealment (Khorana 2017 (PHACS); Maraveyas 2012 (FRAGEM); Vadhan-Raj 2013 Zwicker 2013 (MICRO TEC)).

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be definitely blinded in three studies (Agnelli 2009 (PROTECHT); Klerk 2005 (MALT); Perry 2010 (PRODIGE) and probably blinded in four studies (Agnelli 2012 (SAVE-ONCO); Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS). We judged nine studies as definitely not blinded (Altinbas 2004; Khorana 2017 (PHACS); Lebeau 1994; Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC); Pelzer 2015 (CONKO-004); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008) and three as probably not blinded (Maraveyas 2012 (FRAGEM); Vadhan-Raj 2013 Zwicker 2013 (MICRO TEC).

Blinding of outcome assessment (detection bias)

We judged outcome assessors to be definitely blinded in two studies (Klerk 2005 (MALT); Perry 2010 (PRODIGE) and probably blinded in nine studies (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS); Khorana 2017 (PHACS); Lecumberri 2013 (ABEL); Pelzer 2015 (CONKO-004); van Doormaal 2011 (INPACT). We judged four studies as definitely not blinded due to their open-label design (Altinbas 2004; Macbeth 2016 (FRAGMATIC); Sideras 2006; Weber 2008) and four as probably not blinded. (Lebeau 1994; Maraveyas 2012 (FRAGEM); Vadhan-Raj 2013 Zwicker 2013 (MICRO TEC). However, we judged risk of bias in relation to detection bias as low when reporting on objective outcomes (for all 19 studies) and high when reporting on patient-reported subjective outcomes (for two studies Macbeth 2016 (FRAGMATIC); Sideras 2006).

Incomplete outcome data

Eight studies reported a complete follow-up rate (Altinbas 2004; Khorana 2017 (PHACS); Klerk 2005 (MALT); Lebeau 1994; Lecumberri 2013 (ABEL); Weber 2008;Vadhan-Raj 2013; Zwicker 2013 (MICRO TEC).

Agnelli and colleagues reported an approximate 90% follow-up rate in the PROTECHT trial (Agnelli 2009 (PROTECHT)). In the SAVE-ONCO trial, follow-up data were reported per outcome as follows: for mortality and VTE outcomes, approximately 99% in both the intervention and control groups; for bleeding outcome, 88% in the intervention group and 95% in the control group (Agnelli 2012 (SAVE-ONCO)).

Kakkar and colleagues reported an approximate 97% follow-up rate in both the intervention and contro groups (Kakkar 2004 (FAMOUS)). Pelzer and colleagues reported a 95% follow-up rate in the intervention group and 93% in the control group for the outcome overall survival (Pelzer 2015 (CONKO-004)). Sideras and colleagues reported a 98% follow-up rate (Sideras 2006). van Doormaal and colleagues reported a 97.85% follow-up rate (van Doormaal 2011 (INPACT)). Macbeth and colleagues reported a 94% follow-up rate in the intervention group and 97% in the control group (Macbeth 2016 (FRAGMATIC)).

Only one study reported follow-up data per outcome and not per participant (Maraveyas 2012 (FRAGEM)). The follow-up rates for the outcomes overall survival, VTE incidence, and toxicity ranged between 93% and 98%.

In both studies by Haas and colleagues, it is not reported whether participants not included in the intention-to-treat (ITT) analyses were followed up (Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2)). All participants in the intervention group and 99% of participants in the control group were included in the analysis for TOPIC 1, whereas 98% in the intervention group and 97% in the control group were included for TOPIC 2.

In the study by Perry and colleagues, it is not reported whether participants were followed up among those that did not receive first dose, withdrew consent, or discontinued treatment (Perry 2010 (PRODIGE)). We judged the risk of attrition bias as high since those participants represent 37% of the intervention group and 53% of the control group.

Selective reporting

The outcomes listed in the methods section were reported in the results section for 13 studies (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Kakkar 2004 (FAMOUS); Khorana 2017 (PHACS); Klerk 2005 (MALT); Lebeau 1994; Maraveyas 2012 (FRAGEM); Pelzer 2015 (CONKO-004); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008). Seven studies are registered in ClinicalTrials.gov (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Khorana 2017 (PHACS); Lecumberri 2013 (ABEL); Maraveyas 2012 (FRAGEM); Perry 2010 (PRODIGE); van Doormaal 2011 (INPACT)). One study is registered in the ISRCTN registry (Pelzer 2015 (CONKO-004)).

One study reported on all outcomes except for two listed in the methods section (quality of life and cognition assessment) (Perry 2010 (PRODIGE)). The outcomes of interest were all reported but were not listed in the methods section for one study (Altinbas 2004).

One study had a published protocol and reported on all outcomes listed in the protocol (Pelzer 2015 (CONKO-004)). One study that also had a published protocol reported on all outcomes listed in the protocol except for four that will be reported elsewhere (health economics, health-related quality of life, dyspnea and biomarker studies) (Macbeth 2016 (FRAGMATIC)).

Selective reporting bias was unclear in the study published as an abstract (Vadhan-Raj 2013).

Other potential sources of bias

We questioned whether in the study by Agnelli and colleagues the follow-up time "occurring between randomization and 3 days after the last injection of the study drug" could have potentially led to differential follow-up time between the two groups (Agnelli 2012 (SAVE-ONCO)). However, the authors report that "the duration of treatment was similar in the two study groups, with a median of approximately 3.5 months".

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Klerk and colleagues reported that "chemotherapy was more frequently administered during the period of study treatment in participants receiving placebo, whereas radiotherapy was more frequently given to participants receiving nadroparin"; thus 25% of the nadroparin group and 34% of the placebo group received chemotherapy; 32% of the nadroparin group and 18% of the placebo group received radiotherapy. Having different co-interventions between the two groups might lead to performance bias (Klerk 2005 (MALT)).

Three studies were stopped early due to insufficient accrual (Khorana 2017 (PHACS); Perry 2010 (PRODIGE); Sideras 2006).

We judged that in the study by Lebeau and colleagues participants received similar co-interventions although brain and thoracic irradiation depended on response to treatment. In that study, 11% and 7%, respectively of participants randomized to heparin and control groups received radiotherapy (Lebeau 1994).

In the study by Pelzer and colleagues, the related abstracts published in 2005 and 2007 reported a target recruitment of 540 patients whereas 312 patients were recruited into the trial (Pelzer 2015 (CONKO-004)).

The study by Zwicker and colleagues was originally designed as a phase III randomized clinical trial then re-adapted to a phase II trial. Also, the trial is described as underpowered (Zwicker 2013 (MICRO TEC)).

Effects of interventions

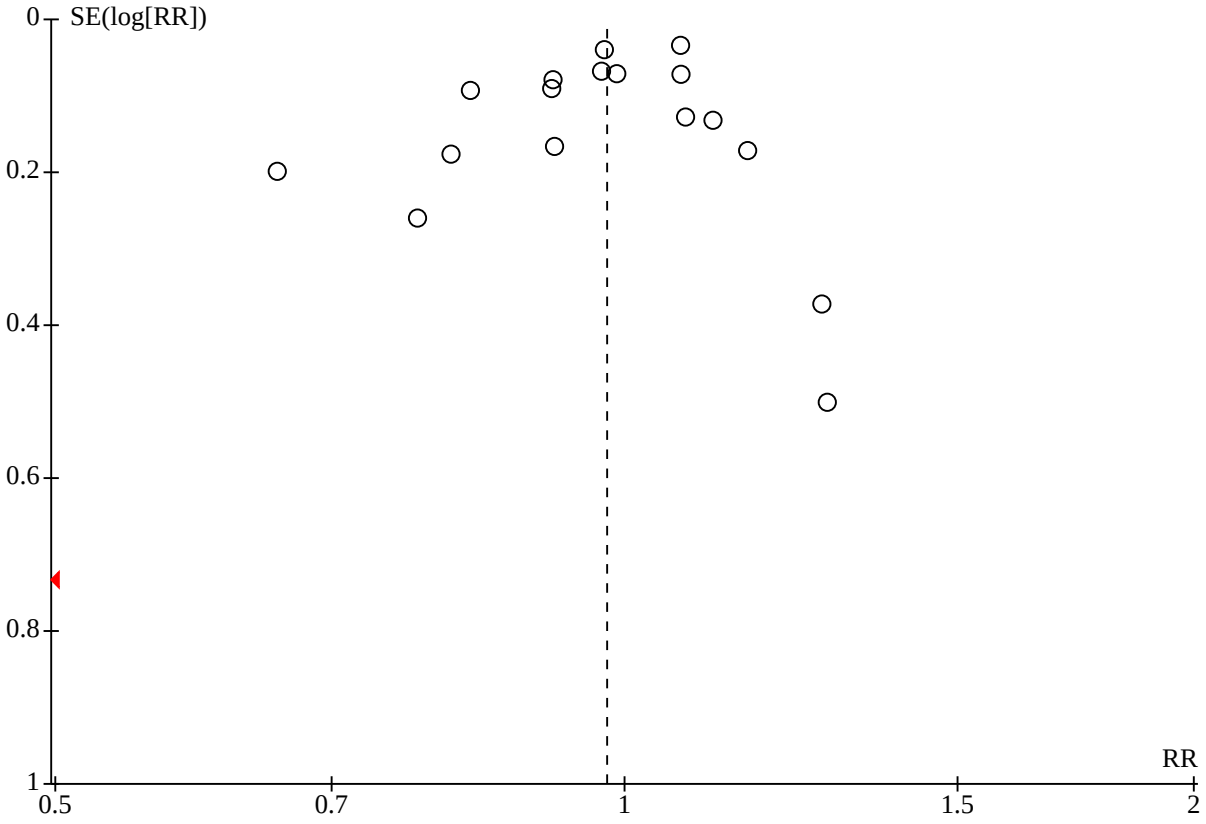
See: **Summary of findings 1** Heparin prophylaxis compared with no prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy

All-cause mortality

All-cause mortality at 12 months

Meta-analysis of the 18 randomized controlled trials (RCTs), including 9575 participants, found that the use of heparin compared to no heparin has no effect on mortality rates at 12 months: risk ratio (RR) 0.98; 95% confidence interval (CI) 0.93 to 1.03; risk difference (RD) 10 fewer per 1000; 95% CI 35 fewer to 15 more (see Analysis 1.1). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) is moderate (I^2 = 31%). The inverted funnel plot for the primary outcome of mortality at one year did not suggest publication bias, but there were relatively few trials to permit an accurate assessment (Figure 4). The certainty of evidence was moderate due to imprecision (Summary of findings 1). Appendix 6 includes the GRADE Evidence Profile (a more detailed version of the Summary of findings 1).

Figure 4. Funnel plot of comparison: 1 Heparin versus placebo, outcome: 1.1 Mortality at 12 months- Main analysis.



In a subgroup analysis of participants with lung cancer (either SCLC or NSCLC) (Altinbas 2004; Haas 2012 (TOPIC 2); Lebeau 1994; Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC); van Doormaal 2011 (INPACT)), versus other types of cancer (that is

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neither SCLC or NSCLC) (Haas 2012 (TOPIC 1); Klerk 2005 (MALT); Maraveyas 2012 (FRAGEM); Pelzer 2015 (CONKO-004); van Doormaal 2011 (INPACT); Weber 2008), the test for subgroup difference was not statistically significant (P value = 0.47).

In a subgroup analysis of participants with advanced cancer (including participants with extensive SCLC) (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Altinbas 2004; Kakkar 2004 (FAMOUS); Klerk 2005 (MALT); Lebeau 1994; Maraveyas 2012 (FRAGEM); Pelzer 2015 (CONKO-004); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008; Zwicker 2013 (MICRO TEC)), versus participants with non-advanced cancer (including participants with limited SCLC) (Altinbas 2004; Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Khorana 2017 (PHACS); Lebeau 1994; Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC); Perry 2010 (PRODIGE)), the test for subgroup effect was not statistically significant (P value = 0.56).

All-cause mortality at 24 months

In a meta-analysis of 14 RCTs, including 5229 participants, we found that heparin compared to no heparin has no effect on mortality rates at 24 months: RR 0.99; 95% CI 0.96 to 1.01; RD 8 fewer per 1000; 95% CI 31 fewer to 8 more (see Analysis 1.4). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) is moderate (I^2 = 27%). The certainty of evidence was moderate due to imprecision (Summary of findings 1).

In a subgroup analysis of participants with advanced cancer (including participants with extensive SCLC) (Kakkar 2004 (FAMOUS); Klerk 2005 (MALT); Pelzer 2015 (CONKO-004); Sideras 2006; van Doormaal 2011 (INPACT); Weber 2008), versus participants with non-advanced cancer (including participants with limited SCLC) (Altinbas 2004; Haas 2012 (TOPIC 1); Haas 2012 (TOPIC 2); Lebeau 1994; Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC); Maraveyas 2012 (FRAGEM); Perry 2010 (PRODIGE)), the test for subgroup effect was not statistically significant (P value = 0.97)

All-cause mortality - time-to-event analysis

Fifteen studies, including 8388 participants, reported data allowing their inclusion in the time-to-event meta-analysis. Meta-analysis indicated that heparin compared to no heparin has no effect on reduction in the risk of death (hazard ratio (HR) 0.93; 95% CI 0.84 to 1.03) (see Analysis 1.6). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent moderate heterogeneity (I^2 = 64%).

Symptomatic venous thromboembolism (VTE)

Meta-analysis of 16 RCTs, including 9036 participants, found that heparin reduces the risk of symptomatic VTE compared to no heparin: RR 0.56; 95% CI 0.47 to 0.68; RD 30 fewer per 1000; 36 fewer to 22 fewer (see Analysis 1.7). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) is not important (I^2 = 0%). Results did not change in a sensitivity analysis including the study published as abstract (Vadhan-Raj 2013): RR 0.56, 95% CI 0.46 to 0.67. Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the Methods section. The effect estimate remained significant across all four stringent assumptions (Appendix 7). Analysis 1.9 and Analysis 1.10 respectively show the separate analyses for PE and symptomatic DVT. The inverted funnel plot for symptomatic VTE did not suggest publication bias, but there were relatively few trials to permit an accurate assessment (Figure 5). The certainty of evidence was high (Summary of findings 1).

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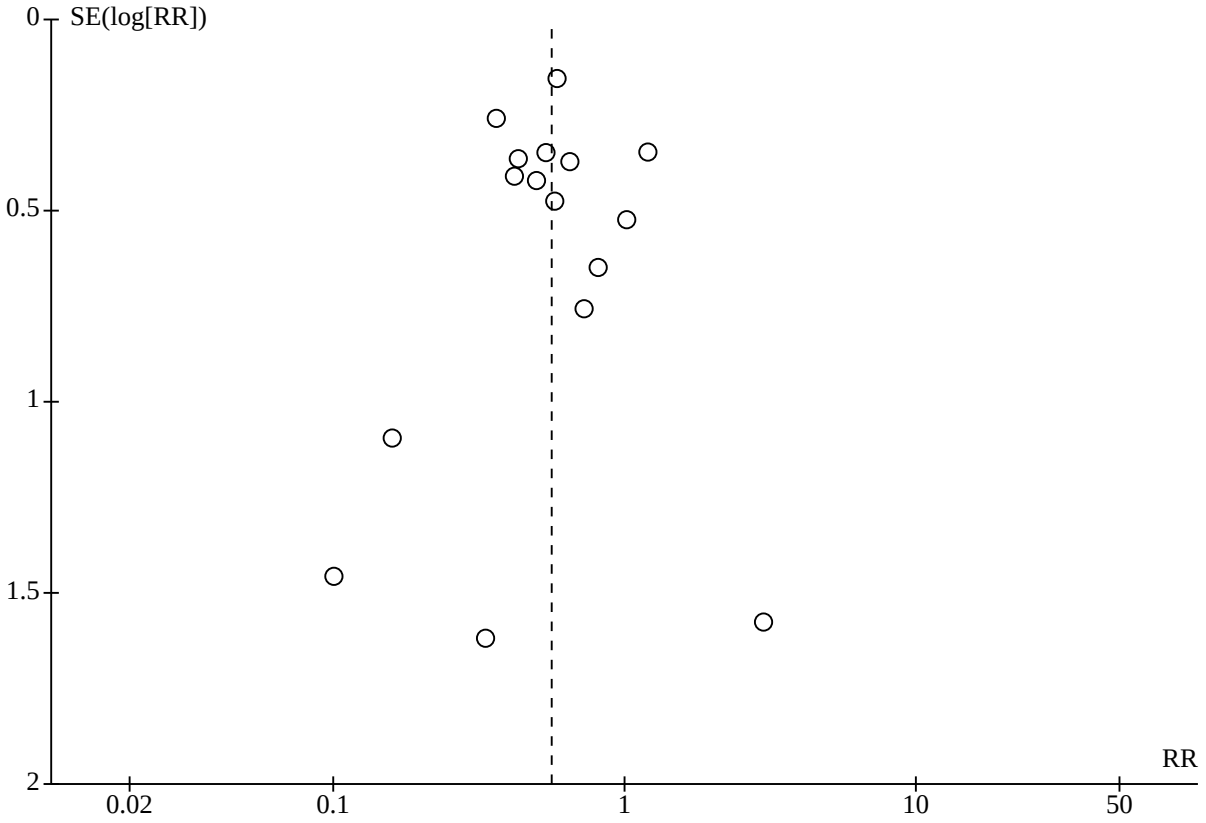
Figure 5. Funnel plot of comparison: 1 Heparin versus placebo, outcome: 1.7 Symptomatic VTE- Main analysis.



In a subgroup analysis of participants with lung cancer (either SCLC or NSCLC), (Agnelli 2009 (PROTECHT); Agnelli 2012 (SAVE-ONCO); Altinbas 2004; Haas 2012 (TOPIC 2) Lecumberri 2013 (ABEL); Macbeth 2016 (FRAGMATIC)) versus participants with any type of cancer (that is neither SCLC or NSCLC), (Kakkar 2004 (FAMOUS); Khorana 2017 (PHACS); Sideras 2006; van Doormaal 2011 (INPACT); Zwicker 2013 (MICRO TEC)) the test for subgroup effect was not statistically significant (P value 0.21).

Major bleeding

Meta-analysis of 18 RCTs, including 9592 participants, showed that heparin likely increases the risk of major bleeding compared to no heparin: RR 1.30; 95% CI 0.94 to 1.79; RD 4 more per 1000; 95% CI 1 fewer to 11 more) (see Analysis 1.11). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent no heterogeneity (I^2 = 0%). The certainty of evidence was moderate due to imprecision (Summary of findings 1).

In a subgroup analysis of participants with lung cancer (either SCLC or NSCL) (Altinbas 2004; Haas 2012 (TOPIC 2); Lebeau 1994; Lecumberri 2013 (ABEL); ; Macbeth 2016 (FRAGMATIC)), versus participants with any type of cancer (that is neither SCLC or NSCLC) (Haas 2012 (TOPIC 1); Klerk 2005 (MALT); Pelzer 2015 (CONKO-004); Perry 2010 (PRODIGE); Weber 2008), the test for subgroup effect was not statistically significant (P value = 0.61).

Minor bleeding

Meta-analysis of 16 RCTs, including 9245 participants, found that heparin causes an increase in the risk of minor bleeding compared to no heparin: RR 1.70; 95% CI 1.13 to 2.55; RD 17 more per 1000; 3 more to 37 more) (see Analysis 1.13). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent moderate heterogeneity (I^2 = 53%). Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the Methods section. The effect estimate did not lose significance across all four stringent assumptions (Appendix 7). The certainty of evidence was high (Summary of findings 1).

Thrombocytopenia

Meta-analysis of 12 RCTs, including 5832 participants, failed to show or to exclude a beneficial or detrimental effect of heparin on the risk of thrombocytopenia compared to no heparin (RR 0.69; 95% CI 0.37 to 1.27; RD 33 fewer per 1000; 95% CI 66 fewer to 28 more) (see Analysis 1.14). The I^2 value indicates that the percentage of the variability in effect estimates that is due to heterogeneity rather than chance may represent high heterogeneity (I^2 = 83%). The certainty of evidence was moderate due to imprecision (Summary of findings 1).

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Health-related quality of life

Two studies assessed quality of life, one using the Uniscale and the Symptom Distress Scale (SDS) (Sideras 2006), the other using the Hospital Anxiety and Depression Score and EQ-5D (Macbeth 2016 (FRAGMATIC)). Both studies concluded that the scores for the two scales were similar for the two study groups, both at baseline and at follow-up. The certainty of evidence was moderate due to risk of bias (Summary of findings 1).

Sensitivity analyses

The sensitivity analysis excluding the one study at high risk of bias, Altinbas 2004, from the analyses did not change the results significantly. We have presented above the sensitivity meta-analyses to assess the risk of bias associated with missing participant data.

DISCUSSION

Summary of main results

Parenteral anticoagulation (with either unfractionated heparin or low molecular weight heparin (LMWH)) appears to have no effect on mortality in patients with cancer, who have no therapeutic or prophylactic indication for anticoagulation. While parenteral anticoagulation reduces venous thromboembolism (VTE), it likely increases major bleeding and minor bleeding. We did not identify any study using fondaparinux as an anticoagulant.

Overall completeness and applicability of evidence

The included studies recruited patients with a variety of cancer types and stages, which should increase the applicability of the results. The results apply best to LMWH, given that only one study evaluated unfractionated heparin. Unfortunately, not enough data were available to evaluate the impact of the intervention on bleeding outcomes or on quality of life. The latter outcome is important given the potential burden of daily subcutaneous injections.

As mentioned above, we identified three eligible studies for which we were not able to obtain the necessary data from the authors. Chazouilleres 1994 recruited 51 participants with unresectable hepatocellular carcinoma and reported a lower short-term mortality rate with LMWH. Salat 1990 did not report on mortality outcome. Vadhan-Raj 2013a randomized 75 participants with metastatic or locally advanced pancreatic cancer and reported a trend towards a reduction in VTE.

Quality of the evidence

Our systematic approach to searching, study selection and data extraction should have minimized the likelihood of missing relevant studies. The certainty of evidence was high for symptomatic VTE and minor bleeding, moderate for mortality, major bleeding and quality of life.

Potential biases in the review process

The inclusion of different types of cancer in the same study precluded us from conducting the subgroup analyses to explore effect modifiers such as type and stage of cancer. The interpretation of findings is also limited by not including data from the trials published as abstracts only. Also, for two studies we had to calculate the number of mortality events at 12 and 24 months from the survival curves (Altinbas 2004; Kakkar 2004 (FAMOUS)). Also, there might be potential bias associated with multiple testing in the planned meta-analyses and currently there are no plans to adjust meta-analyses for multiple testing.

Agreements and disagreements with other studies or reviews

A recent review by Che and colleagues assessed the effect of LMWH compared with no heparin in patients with cancer with no history of VTE (Che 2013). Similar to our findings, the review found that LMWH significantly reduced the risk of VTE and increased the risk of bleeding. Moreover, this study did not focus on the type of intervention or type of participants, for example the pooled participants included patients being started on thromboprophylaxis due the placement of a central venous catheter (CVC), or in the perioperative setting. Our review eligibility criteria focused on parenteral anticoagulation in ambulatory patients with cancer, i.e. reducing clinical heterogeneity.

Another Cochrane systematic review conducted by Di Nisio and colleagues assessed the efficacy and safety of primary thromboprophylaxis in ambulatory patients with cancer receiving chemotherapy (Di Nisio 2016). The review found that LMWH, when compared with inactive control, significantly reduced the incidence of symptomatic VTE, whereas there was no statistically significant effects on major bleeding, asymptomatic VTE, minor bleeding, one-year mortality, symptomatic arterial thromboembolism, superficial thrombophlebitis or serious adverse events. The authors included various interventions for both prophylactic and therapeutic purposes in different populations. The interventions included parenteral anticoagulants (LMWH, unfractionated heparin), oral agents (Vitamin K antagonists (VKA), direct oral anticoagulants (DOAC), aspirin, antithrombin), and placebo. The populations included patients without VTE, with VTE, with multiple myeloma, and pediatrics. We tackled most of these comparisons in separate Cochrane reviews (Akl 2014 (initial); Akl 2014 (long-term); Akl 2014 (oral))

Another recent publication by Phan and colleagues, studying the efficacy of heparin-based medications for prevention of VTE, found a significant reduction in VTE with an odds ratio (OR) of 0.56 (95% confidence interval (CI) 0.45 to 0.71) (Phan 2014). However, that review had limitations in comparison to ours. That review did not include four studies we deemed to be eligible (Altinbas 2004; Pelzer 2015 (CONKO-004); Sideras 2006; Weber 2008). The reported reason for not including two of these studies was that VTE was not assessed (Altinbas 2004; Sideras 2006). There was no reference to the two other studies (Sideras 2006; Weber 2008). Secondly, Phan 2014 included in the review the Young 2009 trial, assessing anticoagulation in patients with a CVC. This introduced increased clinical heterogeneity. We have included that trial in a separate Cochrane review evaluating prophylaxis for catheter-related thrombosis (Akl 2014 (CVC)). Unlike the review conducted by Phan 2014, we did not include in the VTE meta-analysis the trial conducted by Klerk and colleagues (Klerk 2005 (MALT)) because the number of VTE events reported pertains to participants who discontinued the study drug prematurely because they developed VTE; the paper does not report the total number of VTE observed in the trial. Moreover, Phan 2014 focused solely on VTE and did not assess other patient-important outcomes, such as mortality.

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Similary, another systematic review conducted by Ben Aharon and colleagues assessing the efficacy and safety of primary thromboprophylaxis with LMWH in ambulatory participants with solid malignancies (Ben-Aharon 2014) found that primary prophylaxis with LMWH reduced symptomatic VTE (RR and the rate of PE especially in the subgroup of participants with lung and pancreatic cancers. They found no significant effect for anticoagulation on one-year mortality or major bleeding.

Another systematic review conducted by Zhang and colleagues assessed whether anticoagulation improves survival and VTE outcomes in participants with lung cancer exclusively with no indication for anticoagulation (Zhang 2013). Anticoagulation showed a survival benefit, prolonged life expectancy, and reduced the risk of VTE in participants with lung cancer with no indication for anticoagulants, especially for those with SCLC, whereas our review included a wider range of patients with various types of cancer.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review found no survival benefit from heparin therapy in patients with cancer patients. Heparin did decrease the number of thrombotic events with likely increases in major bleeding and minor bleeding.

The decision for a patient with cancer to start heparin therapy in the absence of a standard therapeutic or prophylactic indication should balance the benefits and downsides, and should integrate the patient's values and preferences (Haynes 2002). Patients with a high preference for a reduction in VTE and limited aversion to potential bleeding, and who do not consider heparin (both unfractionated heparin or low molecular weight heparin (LMWH)) therapy a burden, may opt to use heparin, while those with aversion to bleeding may not. Decisions at a health system level would have to consider the cost-effectiveness of such as practice.

Implications for research

There is a need to understand the effects of heparin (including unfractionated heparin and LMWH) and other anticoagulants in patients with different types and subtypes (small cell lung cancer versus others) and stages (advanced versus not advanced) of cancers, as well as with existing comorbidites. Similarly, there is a need to understand the differential effects of different types, dosing, schedules and duration of therapy (Alifano 2004). Some of the ongoing, or as yet unpublished studies may provide such information (Kakkar 2010 (GASTRANOX); Meyer 2017 (PROVE). Also, our forthcoming individual patient data (IPD) meta-analysis will be useful in clarifying how the type and stage of cancer modify the effect of parenteral anticoagulation.

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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 2009 (PROTECHT)

Study characteristics	
Methods	Randomized clinical trial
Participants	1166 participants with metastatic or locally advanced lung, breast, gastrointestinal (stomach, colon-rectum, pancreas), ovarian or head and neck cancer undergoing chemotherapy

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Agnelli 2009 (PROTECHT) *(Continued)*

	Mean age 63, males 48%, previous VTE 1.6%
Interventions	Intervention: subcutaneous LMWH nadroparin calcium 3800 IU anti-Xa once daily for up to a maximum of 4 months Control: placebo Co-intervention: both groups received chemotherapy Discontinued treatment: 273 of 779 participants randomized to the intervention group and 111 of 387 participants randomized to the control group
Outcomes	Follow-up duration for the following outcomes: median of 111 and 113 days in the nadroparin and placebo groups, respectively • Survival (4 months and 12 months follow-up • Asymptomatic thromboembolic events diagnosed during tests performed for other purposes (4 months follow-up) • Major bleeding (4 months follow-up) • Minor bleeding (4 months follow-up **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: reported "Italfarmaco" • Ethical approval: reported "The study was done in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board at each study centre, and written informed consent was obtained from all patients before randomisation" • Conflict of interest: "CB is the scientific director of Italfarmaco. All other authors declared that they had no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list was generated by an independent statistician who used a standard permuted block of six without stratification. The list was generated with SAS version 8.2."
Allocation concealment (selection bias)	Low risk	Quote: "The system assigned the next free number in accordance with the randomisation sequence. Participants and investigators did not know whether study drug or placebo was being given, since pre-filled syringes were used which were identical in appearance."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment assignments were masked from all study personnel and participants for the duration of the study." Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All the study outcomes were assessed by an independent adjudication committee, whose members were unaware of the participants' study group allocation." Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data trial report figure 1: • We calculated a 89.9% follow-up rate in the intervention group and 90.2% follow-up rate in the control group (using data from the "not treated", "consent withdrawal" and "lost to follow-up" categories)

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Agnelli 2009 (PROTECHT) *(Continued)*

Selective reporting (reporting bias)	Low risk	As compared to information on ClinicalTrials.gov. All outcomes listed in the methods section were reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Agnelli 2012 (SAVE-ONCO)

Study characteristics	
Methods	Randomized. multicenter clinical trial
Participants	3212 participants with advanced metastatic or locally advanced cancer of the lung, pancreas, stomach, colon, rectum, bladder, or ovary solid tumors, planned to receive chemotherapy Mean age 60, males 60%, white 77%, 91% ECOG performance status 0 or 1, 42% with at least 1 risk factor for VTE
Interventions	Intervention: subcutaneous injection of semuloparin 20 mg once daily for a minimum of 3 months Control: placebo Co-intervention: both groups started chemotherapy Discontinued treatment: 560 of 1608 participants randomized to the intervention group and 595 of 1604 participants randomized to the control group
Outcomes	Follow-up duration for the following outcomes: up to 3 days after last injection, which had a median of 3.5 months • Symptomatic DVT • PE • Clinically relevant bleeding (major and non-major) • Overall survival (at 1 year after randomization or at the study end date - planned 7 months after randomization of the last participant to be enrolled) **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: reported "Sanofi" • Ethical approval: reported "The study was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board or ethics committee at each study center. Written informed consent was obtained from all patients before randomization. The data and safety monitoring board was responsible for monitoring the safety of the patients included in the trial" • Conflict of interest: reported " GA received consulting fee (Sanofi-Aventis), support for travel (Sanofi-Aventis), had consultancy relationship (Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo), and received payment for lectures (Bayer Healthcare, Bristol Myers Squibb, Sanofi-Aventis).· UC had employment relationship (Sanofi-Aventis) and received stock (Sanofi-Aventis).· WF received support for travel (Sanofi-Aventis), grants (Bayer Healthcare, Bristol Myers Squibb, Sanofi-Aventis), payment for lectures (Bayer Healthcare), Travel/accommodations/· meeting expenses (Bayer Healthcare, Pfizer), and had consultancy relationship (Bayer Healthcare, Pfizer).· DG received consulting fee (Sanofi-Aventis) and payment for lectures (Sanofi-Aventis).· AK received consulting fee (Sanofi-Aventis), support for travel (Sanofi-Aventis), had consultancy relationship (Sanofi-Aventis, Pfizer Inc, Eisai Inc, Glaxo SmithKline, Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb), grants (Sanofi-Aventis, Pfizer Inc, Eisai Inc, Bayer Healthcare, Boehringer Ingelheim), and payment for lectures (Bayer Healthcare, Bristol Myers Squibb, Sanofi-Aventis, Pfizer Inc, Eisai Inc, Glaxo SmithKline,

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Agnelli 2012 (SAVE-ONCO) *(Continued)*

Boehringer Ingelheim).· MRL received consulting fee (Sanofi-Aventis), support for travel (Sanofi-Aventis), payment for lectures (Bayer Healthcare, Bristol Myers Squibb), had consultancy relationship (Astra Tech, Bristol Myers Squibb, Pfizer Inc, Astellas, Bayer Healthcare).· FL had employment relationship (Sanofi-Aventis) and received stock (Sanofi-Aventis).· PM received consulting fee (Sanofi-Aventis) and support for travel (Sanofi-Aventis).· PPM declares no conflict of interest.· AGGT received consulting fee (Steering Committee), support for travel (Bayer Healthcare, Astellas, Takeda), payment for lectures (Glaxo SmithKline, Boehringer Ingelheim), and had consultancy relationship (Bayer Healthcare, Astellas, Takeda)."

- ITT Quote: "All patients who underwent randomizations were included in the primary efficacy population (intention-to-treat population)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally by means of an interactive voice-response system. ... To balance the study groups, a minimization algorithm was used that took into account the following three factors: site of primary cancer, cancer stage (metastatic or locally advanced), and geographic region."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally by means of an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "SAVE-ONCO was a randomised, double-blind, multicenter trial." Comment: probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Efficacy and bleeding outcomes were assessed by a central independent adjudication committee, whose members were unaware of the study treatment." Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from trial report appendix: • For mortality and VTE outcomes, we calculated a 99.6% follow-up rate in the intervention group and 99.9% follow-up rate in the control group (using data from the "lost to follow-up" category) • For bleeding outcome, we calculated a 88.37% follow-up rate in the intervention group and 95% follow-up rate in the control group (using data from the "not treated" and "lost to follow-up" categories)
Selective reporting (reporting bias)	Low risk	As compared to information on ClinicalTrials.gov. All outcomes listed in the methods section were reported on in the results section
Other bias	Low risk	• The follow-up time "occurring between randomization and 3 days after the last injection of the study drug" could have potentially led to differential follow-up time between the two groups. However, the authors report that "the duration of treatment was similar in the two study groups, with a median of approximately 3.5 months." • Study not reported as stopped early for benefit

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Altinbas 2004

Study characteristics	
Methods	Randomized clinical trial
Participants	84 participants with histologically confirmed SCLC (both limited and extensive) undergoing combination chemotherapy Median age 58; 81% males; ECOG performance status < 3; country: Turkey
Interventions	Intervention: subcutaneous LMWH dalteparin 5000 IU once daily for up to a maximum of 18 weeks (less than 18 if disease progressed) Control: no LMWH Co-intervention: both groups received chemotherapy Discontinued treatment: 0 participants
Outcomes	Follow-up duration for the following outcomes: median of 10 months; range 2 to 33 months • All-cause mortality (at 12 and 24 months) • Symptomatic DVT (no PE events; personal communication with author) • Bleeding **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: not reported • Ethical approval: not reported • Conflict of interest: not reported • HR not adjusted (analyses were univariate) • ITT Quote: "Survival was analysed on an intent-to-treat basis

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Open list generated by computer program" (personal communication with author)
Allocation concealment (selection bias)	High risk	Quote: "Open list generated by computer program" (personal communication with author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Personal communication with author Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only for staging and evaluation of response to the treatment but not for the outcomes of interest (personal communication with author) Comment: definitely not blinded; however, probably low risk given that the lack of blinding may not impact the physiologic objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up (personal communication with author)

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Altinbas 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified. No outcomes listed in the methods section. However, all outcomes of interest were reported
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Haas 2012 (TOPIC 1)

Study characteristics	
Methods	Randomized, multicenter trial
Participants	353 ambulatory participants receiving first- or second-line chemotherapy for objectively proven, disseminated metastatic breast carcinoma Mean age 55 years, postmenopausal 66% Participants were enrolled from 39 centers in Germany, Czech Republic, Ukraine, Romania and Belarus.
Interventions	Intervention: subcutaneous certoparin 3000 IU once daily for up to 6 months Control: placebo Co-intervention: both groups received chemotherapy
Outcomes	Follow-up duration for the following outcomes: outcomes were assessed at 6 months follow-up • Overall mortality • Confirmed VTE • Confirmed symptomatic or asymptomatic DVT (proximal or distal) • Confirmed symptomatic PE • Major bleeding • Minor bleeding • Thrombocytopenia **Screening test for DVT**: compression ultrasound at weeks 2, 4, 8, 12, 16, 20 and 24
Notes	• Funding: reported (Novartis Pharma GmbH, Germany) • Ethical approval: reported "Study protocols were approved by local ethics committees and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Efficacy outcomes were validated by a blinded, independent Central Thrombosis Evaluation Team; safety end points were validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments" • Conflict of interest: reported " The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article." • ITT Quote: "Efficacy analyses were performed on the intention-to-treat population."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to placebo or certoparin sodium using a computer-generated randomizations list. ... Randomization was block-stratified according to treatment with hormone-based chemotherapy."

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Haas 2012 (TOPIC 1) *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Only the external statistician from the Safety Committee had access to the randomizations codes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind... placebo-controlled trial" Comment: probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Efficacy outcomes were validated by a blinded, independent Central Thrombosis Evaluation Team; safety end points were validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments." Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	A number of participants were not included in the ITT analysis but it is not reported whether they were followed up for outcome assessments: • 2 out of 179 participants from the control group (one did not receive treatment and one was excluded "because a post-baseline thrombosis screening was not conducted or because the patient was diagnosed with thrombosis on baseline screening"
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified. All outcomes listed in the methods section were reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Haas 2012 (TOPIC 2)

Study characteristics	
Methods	Randomized, multicenter trial
Participants	547 ambulatory participants receiving first- or second-line chemotherapy for stage III/IV non–small cell lung carcinoma Mean age 60.5, males 83% Participants were enrolled from 39 centers in Germany, Czech Republic, Ukraine, Romania and Belarus
Interventions	Intervention: subcutaneous certoparin 3000 IU once daily for up to 6 months Control: placebo Co-intervention: both groups received chemotherapy Discontinued treatment: 5 of 273 participants randomized to the intervention group and 9 of 274 participants randomized to the control group
Outcomes	Follow-up duration for the following outcomes: outcomes were assessed at 6 months follow-up • Overall mortality • Confirmed VTE • Confirmed symptomatic or asymptomatic DVT (proximal or distal) • Confirmed symptomatic PE

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Haas 2012 (TOPIC 2) *(Continued)*

- Major bleeding
- Minor bleeding
- Thrombocytopenia

Screening test for DVT: compression ultrasound at weeks 2, 4, 8, 12, 16, 20 and 24

Notes	• Funding: reported (Novartis Pharma GmbH, Germany) • Ethical approval: reported "Study protocols were approved by local ethics committees and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Efficacy outcomes were validated by a blinded, independent Central Thrombosis Evaluation Team; safety end points were validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments" • Conflict of interest: reported " The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to placebo or certoparin sodium using a computer-generated randomizations list. ... Randomization was block-stratified according to treatment with hormone-based chemotherapy."
Allocation concealment (selection bias)	Low risk	Quote: "Only the external statistician from the Safety Committee had access to the randomizations codes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind... placebo-controlled trial" Comment: probably blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Efficacy outcomes were validated by a blinded, independent Central Thrombosis Evaluation Team; safety end points were validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments." Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	A number of participants were not included in the ITT analysis but it is not reported whether they were followed up for outcome assessments: • 5 out of 273 participants from the intervention group and 9 out of 273 participants from the control group ("because a post-baseline thrombosis screening was not conducted or because the patient was diagnosed with thrombosis on baseline screening")
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified. All outcomes listed in the methods section were reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

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Kakkar 2004 (FAMOUS)

Study characteristics	
Methods	Randomized, multicenter clinical trial
Participants	385 participants with histologically confirmed advanced stage III or IV (locally advanced or metastatic) malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary or uterus; minimum life expectancy 3 months; median age 61 IQR (53 to 68), 43% males; 10 centers (7 in the UK, 2 in Canada and 1 in Italy)
Interventions	Intervention: subcutaneous LMWH (dalteparin) 5000 IU self-injected once daily for 12 months Control: placebo Co-intervention: "Thirty-four percent of the dalteparin group and 31% of the placebo group received chemotherapy while participating in the study, with 8% receiving radiotherapy in both groups … no restriction on concomitant chemotherapy or radiotherapy" Discontinued treatment: 0 of 196 participants randomized to the intervention group and 0 of 189 participants randomized to the control arm
Outcomes	Follow-up duration for the following outcomes: maximum of 77 months • Mortality (at 12, 24 and 36 months) • Symptomatic VTE (PE, DVT) • Major bleeding • Minor bleeding **Screening test for DVT/PE**: not reported **Diagnostic testing for DVT/PE**: "diagnosis determined according to local practices"; "not reviewed centrally"
Notes	• Funding: reported" Pharmacia Corp, New York" • Ethical approval: reported "All patients gave written informed consent after institutional ethical committee review and approval of the trial protocol. The study was conducted according to the ethical standards stated in the Helsinki Declaration." • Conflict of interest: "The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Ajay K. Kakkar, Pfizer. Received-more than $2,000 a year from a company for either of the last 2 years: Ajay K. Kakkar, Pfizer." • ITT quote: "All patients who gave informed consent and who had at least one injection of study drug or placebo constituted the intent-to-treat population for efficacy and safety analyses" • Comment: investigators excluded participants who did not have at least one injection of study drug or placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally by computer-generated code"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally by computer-generated code"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled study" Comment: probably blinded

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Kakkar 2004 (FAMOUS) *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled study" Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Withdrawal of consent before commencing the study medication resulted in 11 patients (six patients in the dalteparin group and five in the placebo group) not being included in the analyses. The remaining 374 patients were analysed for both efficacy and safety" Comment:we calculated a 97% follow-up rate in the intervention group and 97.4% follow-up rate in the control group
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified. All outcomes listed in the methods section are reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Khorana 2017 (PHACS)

Study characteristics	
Methods	Randomized clinical trial
Participants	98 participants from 6 sites (University of Rochester Medical Center, Duke University, Rochester General Hospital, Highland Hospital and Interlakes Oncology, Roswell Park Cancer Institute, Ottawa General Hospital, and University of California, Davis Medical Center) Males 58%, age mean 59, pancreatic cancer 37% Planned initiation of a new systemic chemotherapy regimen, Khorana risk score of ≥3
Interventions	Intervention: either dalteparin 5000 units subcutaneously daily Control: observation for a period of 12 weeks
Outcomes	Follow-up duration for the following outcomes: 13 weeks (12 weeks of treatment and 1 week of observation) • Symptomatic lower extremity DVT • Symptomatic PE • Symptomatic upper extremity thrombosis • Unsuspected DVT • Unsuspected PE • Clinically significant major bleeding • Clinically significant non-major bleeding **Screening test for DVT in lower extremities**: Compression ultrasonography of lower extremities at 4, 8 and 12 weeks (at time of regularly scheduled chemotherapy cycle visits) **Screening test for PE:** CT chest at end of study
Notes	• Funding: reported "National Heart, Lung, and Blood Institute, National Cancer Institute, the Sondra and Stephen Hardis Chair in Oncology Research and the Scott Hamilton CARES Initiative" • Ethical approval: reported "The study was approved by the Institutional Review Board (IRB) of the University of Rochester and subsequently by IRBs at each individual site. Study oversight was provided

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Khorana 2017 (PHACS) *(Continued)*

by a Data Safety and Monitoring Committee which included two hematologist/oncologists and one biostatistician at the University of Rochester. This Committeemet quarterly, and reviewed data related to adverse events"

- Conflict of interest: not reported
- ITT quote: "All analyses were based on intention-to-treat principle"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Enrolled subjects were center-stratified and block-randomized in balanced blocks of 4 consecutively enrolled participants within each center, using a web-based software program."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "We chose not to use placebo injections because of ethical considerations and concerns about patient acceptance of placebo injections" Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Thrombotic events were adjudicated by a thrombosis adjudication committee, comprising 2 radiologists who reviewed de-identified imaging studies and were blinded to treatment assignment" Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	Low risk	As compared to information on ClinicalTrials.gov. All outcomes listed in the methods section were reported on in the results section
Other bias	Low risk	Quote: "The study was terminated early due to low accrual" No other bias suspected

Klerk 2005 (MALT)

Study characteristics

Methods	Randomized clinical trial
Participants	302 participants with different types of solid malignant tumors, "that could not be treated curatively" including: colorectal, breast, lung gastric, esophageal, liver, gallbladder, Klatskin, prostate, pancreatic, cervical, urothelial, renal, ovarian, melanoma, endometrial and other cancers; minimum life expectancy 1 month, stratified according to life expectancy (< or > 6 months); median age 64; 52% males
Interventions	Intervention: subcutaneous LMWH (nadroparin) 9500 antifactor Xa U/mL for 6 weeks; 2 weeks therapeutic dose (twice daily) then 4 weeks prophylactic dose (once daily) Control: placebo Co-intervention: both arms started concomitant antineoplastic therapy (chemotherapy, radiotherapy, hormonal therapy, other antineoplastic treatment)

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Klerk 2005 (MALT) *(Continued)*

Outcomes	Follow-up duration for the following outcomes: mean of 12 months • Mortality from any cause (at 6, 12 and 24 months) • Major bleeding • Clinically relevant non-major bleeding • All clinically relevant bleeding (major and non-major combined) **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: reported "Sanofi provided study medication" • Ethical approval: reported "The study was approved by the respective institutional review boards of each participating center." • Conflict of interest: reported " The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/advisory role: Martin H. Prins, Aventis, Sanofi-Synthelabo, Organon,Yamanouchi, Mitsubishi, Corvas; Harry R. Buller, Aventis, Sanofi-Synthelabo, Organon, Yamanouchi, Mitsubishi, Corvas. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration form and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue." • HR adjusted for: life expectancy (< 6 versus >= 6 months), WHO performance status (1 or less, 2, 3 or more) concomitant treatment (chemotherapy, radiotherapy, hormonal therapy, other antineoplastic treatment), type of cancer (breast, colorectal, cervical or other) and histology (adeno, squamous, other)" • Quote: "All primary analyses were performed on an intention-to-treat principle"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Sequentially numbered boxes of syringes with nadroparin or placebo were prepared using a central computer-generated randomizations schedule"
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered boxes of syringes with nadroparin or placebo were prepared using a central computer-generated randomizations schedule"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled study". Personal communication with authors: "Patients, healthcare providers, data collectors and outcome adjudicators were blinded." Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double-blind, placebo controlled study". Personal communication with authors: "Patients, healthcare providers, data collectors and outcome adjudicators were blinded." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were observed until death or until the end of the study". "No patients were lost to follow-up" Comment: complete follow-up
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified. All outcomes listed in methods section are reported on in the results section. However study does not report number of thrombotic events. Personal communication with authors: "VTE was not an endpoint of the study and it was not standardly registered per protocol"

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Klerk 2005 (MALT) *(Continued)*

Other bias	High risk	• Study not reported as stopped early for benefit • "Chemotherapy was more frequently administered during the period of study treatment in patients receiving placebo, whereas radiotherapy was more frequently given to patients receiving nadroparin." (25% of the nadroparin group and 34% of the placebo group received chemotherapy, 32% of the nadroparin group and 18% of the placebo group received radiotherapy)

Lebeau 1994

Study characteristics	
Methods	Randomized clinical trial
Participants	277 participants with histologically diagnosed SCLC both limited and extensive; 78% had Karnofsky Performance Scale index > 80; 85% older than 50; 91% males
Interventions	Intervention: 2 or 3 daily subcutaneous injections of heparin adjusted initially by weight (500 IU/kg/day) then adjusted by clotting times for 5 weeks Control: no heparin Co-intervention: participants initially were randomized between two chemotherapy regimens (sequential or alternating). "Those who did not respond received only two courses of chemotherapy. Complete responders received eight courses of chemotherapy and then were randomized either to receive or not receive thoracic radiotherapy. Partial responders either pursued chemotherapy until a relapse occurred or received thoracic irradiation if their disease remained apparently limited."
Outcomes	Follow-up duration for the following outcomes: maximum of 84 months • Overall survival (at 12, 24 and 36 months) • Bleeding **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: not reported • Ethical approval: reported "The entire protocol of this therapeutic trial was presented to the Ethical Committee of School of Medicine Broussais-Hotel Dieu. Patients gave informed consent before to be included." • Conflict of interest: not reported • ITT Quote: "Analysis was made on an intention-to-treat basis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomized through a centralized blind telephone assignment procedure"
Allocation concealment (selection bias)	Low risk	Quote: "Randomized through a centralized blind telephone assignment procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No blinding procedure for patients and physicians was used because overall survival was chosen as the major endpoint" Comment: definitely not blinded

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Lebeau 1994 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "No blinding procedure for patients and physicians was used because overall survival was chosen as the major endpoint" Comment: probably not blinded; however, probably low risk given that the lack of blinding may not impact the physiologic objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient was lost to follow-up" Comment: complete follow-up
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified. The outcomes listed in the methods section are reported on in the results section
Other bias	High risk	Study not reported as stopped early for benefit Comment: randomization may have been affected due to differential co-intervention (radiotherapy)

Lecumberri 2013 (ABEL)

Study characteristics	
Methods	Multicenter, randomized, open-label study (ABEL study)
Participants	38 participants diagnosed with limited SCLC
Interventions	Intervention: bemiparin (3500 IU/day) for 26 weeks, starting on the first day of chemotherapy Control: no bemiparin Co-intervention: homogeneous standard treatment with platinum-based chemotherapy + radiotherapy for 6 cycles
Outcomes	Follow-up duration for the following outcomes: 18 months • All-cause mortality • Incidence of VTE • Major bleeding • Minor bleeding • Thrombocytopenia **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: reported "Instituto Cientifico y Tecnologico de Navarra, Universidad de Navarra" • Ethical approval: reported "The study protocol was written by members of the steering committee of the trial and was approved by the Spanish Medicine Agency and the University of Navarra ethics committee as well as by the ethics committees at each participating hospital. Written informed consent was obtained from all patients before randomization." • Conflict of interest: reported " Drs. Lecumberri and Rocha report receiving investigational grant support and consulting and lecture fees from Rovi. No other potential conflict of interest relevant to this article was reported." • ITT Quote: "Efficacy was measured either in the intention to treat population (ITT), including all randomised patients that received at least one dose of the allocated treatment, and in the per protocol population (PP), that comprised all patients that completed treatment as planned."
Risk of bias	

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Lecumberri 2013 (ABEL) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed through an automatic central randomizations system, with stratification according to center, sex, age and Eastern Cooperative Oncology Group (ECOG) performance status"
Allocation concealment (selection bias)	High risk	Quote: "Designed as an open-label study, the control group did not receive a matched placebo and both, investigators and patients, were aware of the result of the randomization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Designed as an open-label study, the control group did not receive a matched placebo and both, investigators and patients, were aware of the result of the randomization" Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "There was no central adjudication committee. In any case, radiologists at all sites were not aware of the treatment arms and clinical records were carefully monitored by an independent CRO. ... Complementary tests for the evaluation of the response were performed by radiologists unaware of the treatment arm in which patients had been allocated" Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient who had been enrolled was subsequently found to be ineligible after review of the records" Comment: complete follow-up
Selective reporting (reporting bias)	High risk	As compared to information on ClinicalTrials.gov. Different statistical data reported in the abstract from the 5th International Conference on Thrombosis and Hemostasis Issues in Cancer: Oral Communications/Thrombosis Research 125 (2010) S161–5
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Macbeth 2016 (FRAGMATIC)

Study characteristics	
Methods	Randomized phase III trial
Participants	2202 participants with newly diagnosed newly diagnosed lung cancer of any stage and histology
Interventions	Intervention: LMWH (Dalteparin) given daily at 5,000 IU, 0.2 mL, subcutaneously for 24 weeks Control: No anticoagulation Co-intervention: standard anticancer treatment
Outcomes	Follow-up duration for the following outcomes at 3- to 4-week intervals up to week 24, then at 9 months and 1 year, and then every 6 months until death: • Overall survival • Bleeding

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Macbeth 2016 (FRAGMATIC) *(Continued)*

Screening and diagnostic testing for DVT/PE: not reported

Notes	• Funding: reported "Cancer Research UK Grant No. CR UK/06/007, an educational grant from Pfizer, and the National Institute for Health Research Cancer Network; sponsored by Velindre National Health Service Trust, Cardiff; and coordinated by the Cancer Research UK core-funded Wales Cancer Trials Unit at Cardiff University." • Ethical approval: reported "All patients gave written informed consent before study entry and the trial protocol was approved by the UK Medicines and Healthcare Products Regulatory Agency and a multicenter research ethics committee" • Conflict of interest: reported "FM: No relationship to disclose; SN: Consulting or Advisory Role (Bristol-Myers Squibb, Leo Pharma); Speakers' Bureau (Leo Pharma, Pfizer); Research Funding (Leo Pharma); Travel, Accommodations, Expenses (Leo Pharma, Pfizer); JE: No relationship to disclose; SA: Stock or Other Ownership (AstraZeneca, Glaxo SmithKline) DC: No relationship to disclose; KH: Research Funding (CSL Behring (Inst), Novartis (Inst)); DK: No relationship to disclose; SL: Employment (Blackrock Clinic); Stock or Other ownership (Allergy4All); Speakers' Bureau (Glaxo SmithKline, Menorini); ML: No relationship to disclose; BM: No relationship to disclose; PJW: No relationship to disclose; WA: Honoraria (Amgen); Consulting or Advisory Role (Eli Lilly, Boehringer Ingelheim); Speakers' Bureau (Amgen); Research Funding (Bristol-Myers Squibb, Abbvie, Amgen); JD: Travel, Accommodations, Expenses (Boehringer Ingelheim); DF: Employment (Eli Lilly); Leadership (Eli Lilly); Stock or Other Ownership (Eli Lilly); Expert Testimony (Eli Lilly); CB: Honoraria (Merck Serono, Roche); Travel, Accommodations, Expenses (Merck Serono); GG: Consulting or Advisory Role (Glaxo SmithKline, SIRTEX)" • ITT Quote: "All analyses were performed using intention to treat." • This study is conducted in the adjuvant setting

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomly assigned to receive either LMWH or no LMWH, by use of a computer algorithm using the method of minimization and a random element."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation concealment was by research nurses (who recruited patients) telephoning the Wales Cancer Trials Unit, where randomization and treatment allocation was done by a trial/data manager using a computerized system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study had an open-label design" Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study had an open-label design" Comment: definitely not blinded; probably low risk for physiologic objective outcomes given that the lack of blinding may not impact the latter and probably high risk for patient-reported subjective outcomes given that the lack of blinding may impact the latter
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram: • Among 1,101 participants in the LMWH group, 250 withdrew from treatment and 64 withdrew completely • Among 1,101 participants in the comparison group, 40 withdrew from treatment and 34 withdrew completely

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Macbeth 2016 (FRAGMATIC) *(Continued)*

		Comment: we calculated a 94% follow-up rate in the intervention group and 97% follow-up rate in the control group (participants that withdrew completely were lost to follow-up, based on personal communication with the author)
Selective reporting (reporting bias)	Low risk	Quote: "The trial protocol was approved by the UK Medicines and Healthcare Products Regulatory Agency and a multicenter research ethics committee. The full trial protocol is accessible online." Comment: outcomes listed in the protocol and methods section in the manuscript are reported on in the results section except for: "Detailed results from health economics, health-related quality of life, dyspnea, and biomarker studies will be reported elsewhere."
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Maraveyas 2012 (FRAGEM)

Study characteristics	
Methods	Randomized controlled phase IIb trial
Participants	123 participants with histopathological or cytological diagnosis of non-resectable, recurrent or metastatic pancreatic adenocarcinoma Mean age 63 years, males 59%, locally advanced disease 46%, metastatic disease 54%, KPS > 80 75%, any prior treatment 59%, estimated life expectancy > 12 weeks
Interventions	Intervention: LMWH (weight-adjusted dalteparin) given subcutaneously at 200 IU/kg once daily for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks. Control: No anticoagulation Co-intervention: both arms received chemotherapy
Outcomes	Follow-up duration for the following outcomes: all outcomes were assessed at 12 weeks and 1-year follow-up • Overall survival • All-type VTE • "Classical" deep vein thrombosis • PE **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: reported "Hull and East Yorkshire Hospitals Trust. Pharmacia-Pfizer provided a grant covering cost of dalteparin for this study. Eli-Lily provided a grant covering the cost of the scientific substudy and the fees of the biostatistician." • Ethical approval: reported "All patients were required to give written, informed consent before being randomised. The trial was run in accordance with the Declaration of Helsinki." • Conflict of interest: reported " A.M. has received honoraria and participated in advisory boards for Pfizer. G.B. has received travel expenses fromPfizer. None of the other authors has any conflicting interests"
Risk of bias	

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Maraveyas 2012 (FRAGEM) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised in the facilities of the Postgraduate Medical Institute in Hull with software developed by York University. The block randomisation method was followed and patients were stratified for stage (locally advanced versus metastatic) and performance status (KPS 90–100 versus 60–80)."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported Comment: probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "There was no VTE adjudication committee" Comment: probably not blinded; however, probably low risk given that the lack of blinding may not impact the physiologic objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Six patients did not complete the 12-week WAD; three due to death (cholangitis, pneumonia and progressive disease), two due to hemorrhage (ISTH 'severe') and one due to patient preference." "Two patients, one from each arm withdrew consent soon after randomisation and were excluded from all analyses." Data from trial report figure 1: • In the intervention group, the follow-up rates for OS, VTE incidence, and toxicity were 98.4%, 95.2%, and 93.6% respectively • In the control group, the follow up-rates for OS, VTE incidence, and toxicity were 98.3%, 98.3%, and 95% respectively
Selective reporting (reporting bias)	Low risk	As compared to information on ClinicalTrials.gov. The outcomes listed in the protocol and methods section in the manuscript are reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Pelzer 2015 (CONKO-004)

Study characteristics	
Methods	Prospective, open-label, randomized, multicenter and group-sequential trial
Participants	312 participants with advanced pancreatic cancer who were treated with first-line chemotherapy in an outpatient setting with or without enoxaparin
Interventions	Intervention: subcutaneous LMWH (enoxaparin) intermediate dose - 1 mg/kg daily for the first 3 months followed by 40 mg daily until disease progression Control: no LMWH

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Pelzer 2015 (CONKO-004) *(Continued)*

	Co-intervention: ambulant first-line chemotherapy (randomized to either intensified GFFC therapy (gemcitabine, 5-FU, folinic acid, cisplatin) or to GEM therapy (gemcitabine only))
Outcomes	Follow-up duration for the following outcomes up to 3 months • Overall survival • Symptomatic VTE • Asymptomatic subclinical DVT • Major bleeding **Screening and diagnostic testing for DVT/PE**: not reported
Notes	• Funding: reported "Charité–Forschungsförderung, Arbeitsgemeinschaft Internistische Onkologie, Deutsche Krebsgesellschaft, Amgen, Eli Lilly, and sanofi-aventis, which provided enoxaparin free of charge" • Ethical approval: reported "The trial was approved by the scientific and research ethics committees of the participating institutions. International announcement was made at the International Standard Randomised Controlled Trial Number register and at the controlled-trials register. The protocol and study were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Furthermore, we adhered to the national principles for the proper execution of the clinical examination of drugs (Bundesanzeiger No. 243 of 30.12.1987), the national regulations of theGerman-drug law, and the German drug test guidelines" • Conflict of interest: reported " *Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.* Employment or Leadership Position: None Consultant or Advisory Role: Helmut Oettle, Celgene (C), Eli Lilly (C), Fresenius (C); Hanno Riess, sanofi-aventis (C) Stock Ownership: None Honoraria: Helmut Oettle, Celgene; Hanno Riess, sanofi-aventis, Roche, Amgen, Bayer, Novartis, Eli Lilly Research Funding: Helmut Oettle, Celgene, Eli Lilly Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: Uwe Pelzer, sanofi-aventis, Roche, Eli Lilly, Amgen; Jens M. Stieler, sanofi-aventis, Roche, Eli Lilly, Amgen" • ITT Quote: "All analyses were performed in the intent-to-treat setting."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated random numbers generated at the study coordination center at the Charité–Universitätsmedizin Berlin"
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated random numbers generated at the study coordination center at the Charité–Universitätsmedizin Berlin"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Prospective, open-label, randomized, multicenter and group-sequential trial" Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All symptomatic VTEs and major hemorrhages were documented using the serious adverse event form, centrally reviewed and evaluated by an independent, blinded event review board (ERB)." Comment: probably blinded
Incomplete outcome data (attrition bias)	Low risk	We calculated a 95.7% follow-up rate in the intervention group and 93.4% follow-up rate in the control group, for the outcome OS.

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Pelzer 2015 (CONKO-004) *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Study registered in the ISRCTN registry and published protocol identified. The outcomes listed in the protocol and methods section in the manuscript are reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit. However, 312 participants were recruited into the trial whereas the earlier published abstracts (Pelzer 2005; Pelzer 2007) reported a target recruitment of 540 participants

Perry 2010 (PRODIGE)

Study characteristics	
Methods	Randomized, placebo-controlled trial
Participants	186 adults with newly diagnosed malignant glioma Mean age 56 years, males 60%, perioperative DVT prophylaxis 55%, KPS 90 40%, mean time (days) from surgery to randomization 22
Interventions	Intervention: subcutaneous LMWH (dalteparin sodium) 5000 IU once daily for 6 months; treatment beyond 6 months was optional Control: placebo Co-intervention: the use of concurrent therapy with ASA, NSAID and dextran was permitted but discouraged
Outcomes	Follow-up duration for the following outcomes: all participants were followed in clinic monthly for the first 6 months post-randomization and then at 9 and 12 months • Documented symptomatic DVT or PE • Major bleeding (48 hours after the last injection of study medication) • Minor bleeding (48 hours after the last injection of study medication) • Mortality (over the 12 months from the time of randomization) **Screening test for DVT/PE**: not reported **Diagnostic testing for DVT/PE**: for DVT with venography or compression ultrasound; for PE with autopsy, a high probability ventilation-perfusion lung scan, conventional pulmonary angiogram, CT pulmonary angiogram, or objectively demonstrated DVT in participants with a clinical suspicion of PE and a non-high probability lung scan
Notes	• Funding: reported "Pfizer Inc, Ontario Clinical Oncology Group, Crolla Chair in Brain Tumour Research (JP) • Ethical approval: reported "Written informed consent was obtained from all eligible patients. The study protocol was approved by the Institutional Review Board of each participating center." • Conflict of interest: reported "Funding and research support by Pfizer Inc, Ontario Clinical Oncology Group, Crolla Chair in Brain Tumour Research (J.P.)" • HR adjusted for the following strata: center, tumor grade (3 versus 4), KPS (< 60 versus 70 or more), and time from surgery to randomization (< 2 weeks versus 2 to 4 weeks)" • We noted the following discrepancy: in the abstract, the 12-month mortality rates were reported as 47.8% for LMWH and 45.4% for placebo (which correspond to 47 and 40 events); in the text the number of events are reported as being 45 and 32 • ITT Quote: "The intention-to-treat principle was used in all analyses."

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Perry 2010 (PRODIGE) *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocations were pre-determined using a computer-generated randomizations list with random size permuted blocks"
Allocation concealment (selection bias)	Low risk	Quote: "Consenting patients were randomised by contacting the Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre at the Henderson Research Centre, Hamilton, Ontario."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, patients and outcome assessors were blinded to treatment allocation." Comment: definitely blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators, patients and outcome assessors were blinded to treatment allocation." Comment: definitely blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	It is not reported whether the following participants were followed up for outcome assessments: • Among 99 participants in the intervention group, 2 did not receive first dose, 6 withdrew consent, and 29 discontinued treatment • Among 87 participants in the control group, 1 did not receive first dose, 10 withdrew consent, and 35 discontinued treatment
Selective reporting (reporting bias)	Low risk	As compared to information on ClinicalTrials.gov and the methods section in the manuscript: VTE, bleeding, and mortality outcomes were reported whereas quality of life and cognition assessments outcomes were not reported in the results section
Other bias	Low risk	Stopped early but for slow accrual No other bias suspected

Sideras 2006

Study characteristics	
Methods	Blinded, placebo-controlled, randomized clinical trial changed to open-labeled clinical trial
Participants	141 participants with advanced breast, prostate, lung or colorectal cancer Mean age 68 years, males 60%, minimum life expectancy 12 weeks; ECOG performance status 0 to 2
Interventions	Subcutaneous LMWH (dalteparin) 5000 U once daily versus placebo for unclear duration; then changed to LMWH (dalteparin) 5000 U once daily versus no intervention; duration not specified; with concomitant chemotherapy and/or radiotherapy
Outcomes	Follow-up duration for the following outcomes: • Overall survival (at 12, 24 and 36 months) • VTE • Major bleeding

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Sideras 2006 *(Continued)*

- Quality of life (measured by Uniscale, and the Symptom Distress Scale (SDS))

Screening test for DVT/PE: not reported
Diagnostic testing for DVT/PE: decided by the primary clinician

Notes	• Funding: reported "governmentally funded, pharmaceutical company supplied drug and placebo" • Ethical approval: not reported • Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization handled through the North Central Cancer Treatment Group (NCGTG) Randomization Office using a dynamic allocation method"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization handled through the North Central Cancer Treatment Group (NCGTG) Randomization Office using a dynamic allocation method"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: • Initially, the study was double-blinded and placebo-controlled. However, because of low accrual, the study became open-labeled • Probably blinded initially; then definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: • Initially, the study was double-blinded and placebo-controlled. However, because of low accrual, the study became open-labeled • Probably blinded initially; then definitely not blinded; probably low risk for the physiologic objective outcomes given that the lack of blinding may not impact them; and probably high risk for the patient-reported subjective outcomes given that the lack of blinding may impact the latter
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 98% follow-up Quote: "Three patients, 1 randomised to blinded LMWH and 2 to unblinded LMWH, dropped out before receiving any protocol therapy."
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified
Other bias	Low risk	Quote: "The protocol accrual was stopped before reaching the prestudy planned accrual goal by the NCCTG Data Monitoring Committee because of a slower than predicted protocol accrual rate, with the knowledge (provided by an interim analysis report) that the patient survival rates were numerically worse on one arm of the blinded study." Comment: study was stopped early for insufficient accrual but not for benefit

Vadhan-Raj 2013

Study characteristics

Methods	Randomized-controlled trial

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Vadhan-Raj 2013 *(Continued)*

Participants	87 patients with metastatic or locally advanced pancreatic cancer planned to start chemotherapy
Interventions	Intervention: LMWH (Dalteparin) given at 5000 units subcutaneously, daily for 16 weeks Control: no dalteparin, only chemotherapy
Outcomes	Follow-up duration for the following outcomes: 16 weeks (study duration) • Venous thromboembolic events (VTE) rate • PE • DVT **Screening testing for DVT/PE**: not reported **Diagnostic testing for DVT/PE**: not reported
Notes	• Funding: not reported in the abstract • Ethical approval: not reported • conflict of interest: not reported • Intention to treat analysis: "All 75 patients were evaluable for response in an intent-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients with metastatic or locally advanced pancreatic cancer planned to start chemotherapy were randomized 1:1 to dalteparin and control arms, stratified for the presence of metastasis and central venous catheter (CVC)."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably an open-label trial Comment: Probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Probably an open-label trial Comment: probably not blinded; however, probably low risk given that the lack of blinding may not impact the physiologic objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quoting "All 75 patients were evaluable for response in an intent-to-treat analysis." Comment: Complete follow up
Selective reporting (reporting bias)	Unclear risk	No pertinent details available from the abstract
Other bias	Low risk	Probably, not stopped early for benefit. No further details available from the abstract

van Doormaal 2011 (INPACT)

Study characteristics

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van Doormaal 2011 (INPACT) *(Continued)*

Methods	Randomized, multicenter study
Participants	503 participants with histologically or cytologically documented prostate carcinoma within 6 months after diagnosis of hormone-refractory state, NSCLC without clinically significant pleural effusion within 3 months after diagnosis of stage IIIB, or with a locally advanced pancreatic cancer within 3 months after diagnosis with a minimum life expectancy of less than 3 months at entry; and a KPS of fewer than 60 points Mean age 65 years, males 80%, prostate cancer 40%, NSCLC 33%, pancreatic cancer 27%, 80% KPS < or equal 80
Interventions	Intervention: LMWH (nadroparin) given subcutaneously at body weight-adjusted therapeutic doses for 2 weeks followed by half-therapeutic doses for an additional 4 weeks. After these initial 6 weeks, participants were eligible to receive additional cycles of nadroparin (2 weeks at therapeutic dose, and 4 weeks of washout period). The total duration of study drug administration was 46 weeks, including the washout periods, which was also the minimum duration of follow-up Control: no anticoagulation Co-intervention: standard anticancer treatment
Outcomes	Follow-up duration for the following outcomes: median of 10.5 months in the nadroparin group and 10.4 months in the control group (a minimum of 46 weeks) • All-cause mortality (at 5, 10, 15, 20, 25, 30, 35, 40 months) • Venous thromboembolic events (DVT/PE at weeks 6 and 10, then at 6-week intervals) • Major bleeding (at weeks 6 and 10, then at 6-week intervals) • Non-major bleeding (at weeks 6 and 10, then at 6-week intervals) **Screening test for DVT/PE**: not reported **Diagnostic testing for DVT/PE**: echo-doppler for DVT and spiral CT scan for PE
Notes	• Funding: reported "GlaxoSmithKline (Paris, France)" • Ethical approval: reported "The study was approved by the respective institutional review boards. All included patients signed an informed consent." • Conflict of interest: reported " *Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.* Employment or Leadership Position: None Consultant or Advisory Role: Martin Prins, GlaxoSmithKline (C); Harry R. Buller, GlaxoSmithKline (C) Stock Ownership: None Honoraria: Martin Prins, GlaxoSmithKline Research Funding: Harry R. Buller, GlaxoSmithKline Expert Testimony: None Other Remuneration: None" • ITT Quote: "All of these analyses were based on the intention-to-treat principle."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation of treatment proceeded centrally by using an interactive-voice response system"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation of treatment proceeded centrally by using an interactive-voice response system"

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van Doormaal 2011 (INPACT) *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label study" Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All potential outcome events were reviewed by an independent adjudication committee blinded to treatment assignment." Comment: probably blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	A number of participants were described as having discontinued treatment but it is not reported whether they were followed up for outcome assessments: • 173 out of 239 participants from the intervention group (among which 27 reported as lost to follow-up or withdrew consent) and 184 out of 258 participants from the control group (among which 1 reported as lost to follow-up or withdrew consent) • Quote: "0.8% and 3.5% of patients were lost to follow-up from the nadroparin and the control group respectively." • Comment: 97.85% of participants were followed up
Selective reporting (reporting bias)	Low risk	As compared to information on ClinicalTrials.gov. The outcomes listed in the protocol and methods section in the manuscript are reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Weber 2008

Study characteristics	
Methods	Prospective, open, randomized study
Participants	20 participants with advanced cancer with a minimum life expectancy of 6 months Mean age 70 years, males 45% FIM score 123, WHO performance status 2.5
Interventions	Intervention: subcutaneous LMWH (nadroparin) 2850/3800 U (< 70/> 70 kg) once daily for unclear duration Control: no LMWH Co-intervention: both arms received concomitant anticancer treatment
Outcomes	Follow-up duration for the following outcomes: 18 months • Mortality (at 3, 6, 12 and 15 months) • Symptomatic VTE • PE • DVT • Major bleeding • Minor bleeding • Thrombocytopenia

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Weber 2008 *(Continued)*

	Screening test for DVT/PE: not reported **Diagnostic testing for DVT/PE**: echo-doppler for DVT and spiral CT scan for PE
Notes	• Funding: not reported • Ethical approval: reported "The study was approved by the Ethic and Research Committee of University Hospitals of Geneva" • Conflict of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The sequence of treatments was randomly assigned in blocks of constant size (n = 20)."
Allocation concealment (selection bias)	Low risk	Quote: "Sets of 20 sealed envelopes (10 Yes and 10 No) were numbered consecutively. The sequence of treatments was randomly assigned in blocks of constant size."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Prospective open randomised study" Comment: definitely not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Prospective open randomised study" Comment: definitely not blinded; however, probably low risk given that the lack of blinding may not impact the physiologic objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient was lost to follow-up" Comment: complete follow-up
Selective reporting (reporting bias)	Low risk	Study not registered and no published protocol identified.. The outcomes listed in the methods section are reported on in the results section
Other bias	Low risk	Study not reported as stopped early for benefit No other bias suspected

Zwicker 2013 (MICRO TEC)

Study characteristics

Methods	Randomized phase II trial
Participants	34 participants with locally advanced or metastatic cancer and highTFMP. The number of participants randomized was 23 to the intervention group and 11 to the observation group. Moreover, 32 participants with low TFMP were placed into the observation group
Interventions	Intervention: subcutaneous LMWH (Enoxaparin) given at 40 mg once daily Control: observation
Outcomes	Follow-up duration for the following outcomes: 2 months • VTE (symptomatic or proximal)

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Zwicker 2013 (MICRO TEC) *(Continued)*

Screening test for DVT/PE: baseline lower extremity ultrasound evaluations for DVT; not reported for PE

Diagnostic testing for DVT/PE: compression ultrasound for DVT; pulmonary angiography, ventilation/perfusion lung scan, spiral CT for PE

Notes

- Funding: reported "Grants from the National Institutes of Health, K23 HL84052 (JIZ) and R01 HL095084(BF), as well as a research grant from Sanofi (JIZ)."
- Ethical approval: reported "All patients voluntarily gave written informed consent prior to initiation of study procedures. The protocol was approved by the institutional review boards of the 10 participating medical centres and centrally by the Dana Farber/Harvard Cancer Center"Conflict of interest: reported " HAL has served on steering committees for Sanofi; CMK has received research funds and served on advisory boards for Sanofi and Esai. No other authors report relevant conflicts of-interest."
- Quote: "The study was originally initiated as a phase III trial but due to external constraints was reconfigured as a randomized phase II trial with the primary objective of prospectively determining the cumulative incidence of VTE in the three arms."
- Comment: data on cumulative incidence of VTE at 2 months were reported on in randomized participants with cancer and high TFMP
- ITT Quote: "Patients were analysed on an intention-to-treat basis following randomization."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomized phase II trial"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported Comment: probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported Comment: probably low risk given that the lack of blinding may not impact the physiologic objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apparently there are complete follow-up data for all the participants randomized
Selective reporting (reporting bias)	Low risk	Study not registered in ClinicalTrials.gov and no published protocol identified. The outcomes listed in the methods section are reported on in the results section
Other bias	Low risk	Quote: "Although the study was not formally powered to compare the cumulative incidence of patients with higher levels of tissue factor-bearing microparticles randomized to enoxaparin or observation, the use of enoxaparin resulted in an 80% risk reduction compared to observation." Comment: This trial was originally designed as a phase III, then re-adapted to a phase II randomized clinical trial. The trial is described as underpowered

5-FU: fluorouracil; **ASA:** acetylsalicylic acid; **CRO:** contract research organization; **CT:** computed tomography; **DVT:** deep vein thrombosis; **ECOG:** Eastern Co-operative Oncology Group; **FDA:** (US) Food and Drug Administration;**FIM:** functional impedance score; **HR:** hazard ratio; **ISRCTN:** International Standard Randomised Controlled Trial Number; **ITT:** intention-to-treat;**IV:** intravenous; **IQR:** interquartile

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range; **ISTH:** International Society on Thrombosis and Haemostasis; **IU:** international units; **kg:** kilogram; **KPS:** Karnofsky Performance Status; **LMWH:** low molecular weight heparin; **mg:** milligram; mg/m2: milligram/square meter; **mL:** milliliter; **NEJM:** New England Journal of Medicine; **NSAID:** non-steroidal anti-inflammatory drugs; **NSCLC:** non-small cell lung cancer; **OS:** overall survival; **PE:** pulmonary embolism; **TFMP:** tissue factor bearing microparticles; **SCLC:** small cell lung cancer;**U:** units; **UK:** United Kingdom; **VTE:** venous thromboembolism; **WAD:** weight-adjusted dalteparin; **WHO:** World Health Organization;

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

Study	Reason for exclusion
Agnelli 1998	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Agnelli 2005	Not population of interest (surgical setting)
Agnelli 2015 (AMPLIFY)	Not the population of interest (patients with cancer with VTE); includes 2 reports
Alifano 2005	Not a study of interest (letter to the editor)
Alikhan 2003 (MEDENOX)	Not the population of interest (hospitalized patients with cancer); includes 2 reports
Arbit 2005	Not a study of interest (letter to the editor)
Auer 2011	Not the population of interest (patients with cancer without VTE who had a surgical procedure)
Barberi-Heyob 1995	Not a study of interest (letter to the editor)
Barkagan 1997	Not the comparison of interest (LMWH versus vitamin K antagonists versus UFH)
Bigg 1992	Not population of interest (surgical setting)
Bitsch 1990	Not the intervention of interest (topical heparin)
Blaszczyk 1970	Not a study of interest (not randomized)
Buckman 2005	Not the comparison of interest (no control group)
Cahan 2000	Not intervention of interest (oral AC)
Cavallo 2010	Not the comparison of interest (LMWH versus aspirin)
Chojnowski 2002	Not the outcome of interest (no survival outcome)
Cicco 2009	Not the intervention of interest
Clarke-Pearson 1993	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Cohen 1997	Not population of interest (surgical setting)
Cohen 2003	Not population of interest (hospitalitzed)
Cohen 2006	Not population of interest (hospitalitzed)
Cohen 2007 (PREVENT)	Not the population of interest (hospitalized patients with cancer); includes 3 reports
Couban 2005	Not the population of interest (patients with cancer with CVC without VTE); includes 3 reports
Craven 2001	Not a study of interest (letter to the editor)

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Study	Reason for exclusion
Crossno 2009	Not a study of interest (letter to the editor)
Demir 2006	Not the intervention of interest (oral anticoagulant)
Demir 2007	Not the intervention of interest (oral anticoagulant)
Dickinson 1998	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Di Nisio 2005	Not a study of interest (review)
Edlis 1976	Not the comparison of interest (no control group)
Eichinger 2008	Not the comparison of interest (different doses of LMWH)
Elias 1972	Not a study of interest (case series)
Elias 1973a	Not a study of interest (not randomized)
Elias 1973b	Not a study of interest (case series)
Elias 1973c	Not a study of interest (not randomized)
Elias 1974	Not a study of interest (case series)
Elias 1975	Not a study of interest (not randomized)
Elit 2012	Not the comparison of interest (comparing 3 different doses of LMWH)
Fielding 1992	Not the intervention of interest (intraportal infusion with heparin)
Goldhaber 2002	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Graf 1994	Not the comparison of interest (LMWH versus vitamin K antagonists)
Graf 1996	Not the comparison of interest (LMWH versus vitamin K antagonists)
Green 1992	Not a study of interest (letter to the editor)
Guimbretiere 1982	Not a study of interest (not randomized)
Haas 2011	Not the population of interest (hospitalized patients with cancer); includes 3 reports
Harenberg 1996	Not the population of interest (hospitalized patients with cancer); includes 2 reports
Hata 2016	Not population of interest (surgical setting)
Hoppensteadt 2011	Not the intervention of interest (oral anticoagulant)
Kakkar 2010 (CANBESURE)	Not the population of interest (patients with cancer who had a surgical procedure); includes 2 reports
Kakkar 2014 (SAVE-ABDO)	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure); includes 2 reports
Kohanna 1983	Not a study of interest (retrospective study)

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Study	Reason for exclusion
Koppenhagen 1992	Not population of interest (surgical setting)
Larocca 2012	Not the comparison of interest (LMWH versus aspirin)
Lecumberri 2005	Not a study of interest (review)
Lee 2015 (CATCH)	Not the population of interest (patients with cancer with VTE); includes 9 reports
Lemoine 2005	Not a study of interest (editorial)
Levine 1994	Not the intervention of interest (oral anticoagulant)
Levine 2005	Not a study of interest (letter to the editor)
Levine 2012	Not the intervention of interest (oral anticoagulant)
Liebman 2009	Not the intervention of interest (oral anticoagulant)
Loprinzi 1999	Not the intervention of interest (oral anticoagulant)
Loynes 2002	Not the intervention of interest (case report)
Lykke 2003	Not a study of interest (review)
Mammen 2004	Not a study of interest (preface)
Maraveyas 2010	Not the outcome of interest (no survival outcome)
Maxwell 2001	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Mazilu 2014 (OVIDIUS)	Not the population of interest (patients with cancer with VTE)
Meyer 2007	Not a study of interest (letter to the editor)
Mousa 2001	Not the population of interest (patients without cancer)
Munstedt 1996	Not the intervention of interest (consisted of only 2 doses of LMWH)
Murakami 2002	Not population of interest (surgical setting)
Nagata 2015	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Nash 2000	Not a study of interest (letter to the editor)
Nishioka 2007	Not a study of interest (review)
Nitti 1997	Not the intervention of interest (intraportal infusion with heparin)
Nurmohamed 1996	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Palumbo 2011	Not the comparison of interest (aspirin versus warfarin); includes 6 reports
Prins 2014 (EINSTEIN)	Not the population of interest (patients with cancer with VTE)
Raskob 2016 (HOKUSAI)	Not the population of interest (patients with cancer with VTE)

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Study	Reason for exclusion
Retik 1962	Not the population of interest (patients without cancer)
Rohwedder 1977	Not the comparison of interest (no control group)
Sakon 2010	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Schulman 2003	Not population of interest (patients with VTE)
Schulman 2013 (RE-MEDY)	Not the population of interest (patients with cancer with VTE)
Schulman 2015 (RECOVER)	Not the population of interest (patients with cancer with VTE)
Siragusa 1999	Not a study of interest (letter to the editor)
Song 2014	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)
Spigel 2005	Not a study of interest (review)
Stanford 1979	Not the intervention of interest (oral anticoagulant)
Tethi 2011	Not the intervention of interest (oral anticoagulant)
Traby 2010	Not the comparison of interest (different dosages of enoxaparin)
Vedovati 2014	Not the population of interest (patients with cancer who had a surgical procedure); includes 5 reports
Verso 2008	Not the population of interest (patients with cancer with CVC without VTE); includes 4 reports
Von Hugo 1981	Not the outcome of interest (no survival outcome)
Ward 1998	Not population of interest (surgical setting)
Wester 1996	Not the population of interest (patients with cancer with VTE); includes 2 reports
Wojtukiewicz 2003	Not the comparison of interest (no control group)
Zacharski 2003	Not a study of interest (editorial)
Zheng 2014	Not the population of interest (patients with cancer without VTE undergoing a surgical procedure)

AC: anticoagulant; CVC: central venous catheter; LMWH: low molecular weight heparin; UFH: unfractionated heparin; VTE: venous thromboembolism

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

Borad 2011 (PGPC1)

Study name	A randomized phase II open-label study to assess the efficacy & safety of gemcitabine + Abraxane® with or without ODSH (2-0, 3-0 desulfated heparin) as first line treatment of metastatic pancreatic cancer
Methods	Type: interventional Allocation: randomized

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Borad 2011 (PGPC1) *(Continued)*

	Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	60 participants with histologically confirmed metastatic adenocarcinoma of the pancreas for which potential curative measures, such as resection of an isolated metastasis, are not available and no prior radiotherapy or chemotherapy. Male or non-pregnant and non-lactating female and ≥ 18 to ≤ 75 years of age with acceptable coagulation studies and ECOG performance status ≤ 1
Interventions	Intervention: ODSH (IV bolus at 4 mg/kg will be administered in 5 minutes immediately after completion of gemcitabine administration. ODSH 48-hour IV continuous infusion at 0.375 mg/kg/hour should be started immediately after the ODSH IV bolus has been administered) Control: no ODSH Co-intervention: gemcitabine + nab-paclitaxel
Outcomes	Progression-free survival Incidence of adverse events & toxicity Overall survival Objective tumor response
Starting date	November 2011
Contact information	Jocelyn Harmon, BS, CCRC (602) 358 8385 jharmon@tgen.org Amy Stoll, MS, CCRP (602) 358-8319 astoll@tgen.org
Notes	Status as of August 2017: Completed (not published yet)

Chibauldel 2008 (PAM07)

Study name	Chemotherapy with or without preventive anticoagulation for metastatic cancer of the pancreas
Methods	Study type: interventional Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: supportive care
Participants	Patients with a histologically confirmed metastatic adenocarcinoma of the pancreas
Interventions	Intervention: dalteparin: 5000 IU subcutaneous injection, from day 1 to day 28 Control: no dalteparin Co-intervention: chemotherapy at investigator's discretion

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Chibauldel 2008 (PAM07) *(Continued)*

Outcomes	Thromboembolic events Progression-free survival Overall survival Tolerance of regimens
Starting date	October 2007
Contact information	Benoist Chibauldel, MD Hopital Saint Antoine
Notes	Sponsor: Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) Status as of August 2017: Terminated (not published yet)

Germonpre 2008 (SYRINGES)

Study name	Low molecular weight heparin in advanced non small cell lung cancer (NSCLC): a randomized open label phase III study evaluating the effect of enoxaparin (Clexane) on survival and symptom control in patients with stage IIIB and IV NSCLC undergoing a cisplatin based first line chemotherapy: the SYRINGES Trial
Methods	Study type: interventional Allocation: randomized Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	Locally advanced or metastatic NSCLC (stage IIIB or IV)
Interventions	Intervention: enoxaparin daily 1 mg/kg/day sc Control: no enoxaparin Co-intervention: cisplatin 75 mg/m^2 d1 and docetaxel 75 mg/m^2 d1 (every 3 weeks for 4 cycles)
Outcomes	Progression-free survival Incidence of total documented thromboembolic and hemorrhagic events
Starting date	June 2008
Contact information	Paul R Germonpre, MD PhD Universiteit Antwerpen
Notes	Sponsor: University Hospital, Antwerp Universiteit Antwerpen Status as of August 2017: Completed (not published yet)

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Kakkar 2010 (GASTRANOX)

Study name	Overall survival of inoperable gastric/gastrooesophageal cancer subjects on treating with LMWH + chemotherapy(CT) vs standard CT (GASTRANOX)
Methods	Study type: interventional Allocation: randomized Control: active control Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label
Participants	Patients with inoperable gastric and gastro-esophageal cancer
Interventions	Enoxaparin (once daily dose of 1 mg/kg of body weight for 6 months) given concomitantly with chemotherapy versus chemotherapy alone
Outcomes	Primary outcome measures: event-free survival (EFS) - composite endpoint of overall survival plus free of symptomatic VTE (time frame: up to 1 year from start of treatment) Secondary outcome measures: incidence of symptomatic VTE, overall survival, major and minor hemorrhages during chemotherapy and/or up to 30 days after last dose is provided. Serious adverse events, all reported adverse events, heparin induced thrombocytopenia (time frame: up to 1 year from the start of treatment)
Starting date	July 2008
Contact information	Janice M Maganji, MBBS. +00 44 7824836535; mailto:mmaganji%40tri-london.ac.uk?subject=NCT00718354, TRI0702, Overall Survival of Inoperable Gastric/GastroOesophageal Cancer Subjects on Treating With LMWH + Chemotherapy(CT) vs Standard CT
Notes	Principal Investigator: Ajay K Kakkar, PhD Thrombosis Research Institute Sponsors and Collaborators Thrombosis Research Institute http://clinicaltrials.gov/ct2/show/NCT00718354 Status as of August 2017: Completed (not published yet)

Lars 2008 (RASTEN)

Study name	A randomized phase III study of standard treatment +/- enoxaparin in small cell lung cancer
Methods	Study type: interventional Allocation: randomized Endpoint classification: safety/efficacy study Intervention model: single-group assignment Masking: open-label Primary purpose: treatment
Participants	Histologically or cytologically verified SCLC, all stages

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Lars 2008 (RASTEN) *(Continued)*

Interventions	Intervention: enoxaparin Control: no enoxaparin Co-intervention: cisplatinum or carboplatin
Outcomes	Overall survival Toxicity
Starting date	June 2008
Contact information	Lars EK, MD +46 46 17 73 40 lars.ek@skane.se Jan Sundberg, RN
Notes	Sponsor: Lund University Hospital Status as of August 2017: Ongoing but not recruiting participants

Meyer 2017 (PROVE)

Study name	Long-term Prophylaxis of Venous Thromboembolism with low-molecular-weight heparin in patients with metastatic lung cancer
Methods	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Outcomes Assessor Primary Purpose: Prevention
Participants	Adult patients aged ≥ 18 years with stage IV lung cancer and elevated D-dimer
Interventions	Intervention: Tinzaparin sodium subcutaneous tinzaparin 4,500 IU once daily for six months. Control: No intervention- usual care
Outcomes	All VTE events (symptomatic and asymptomatic PE and DVT) Major bleeding Death
Starting date	April 2017
Contact information	Guy Meyer, MD +31 156 093461 guy.meyer@aphp.fr
Notes	Status as of August 2017: This study is not yet open for participant recruitment.

Okuno 1999

Study name	Phase III double-blind trial comparing low-molecular weight heparin (LMWH) versus placebo in patients with advanced cancer

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Okuno 1999 *(Continued)*

Methods	Study type: interventional Allocation: randomized Primary purpose: treatment
Participants	Patients with a histologically or cytologically proven breast, lung, colorectal or prostate cancer that has failed prior chemotherapy or hormone therapy. No active CNS metastases. Hormone receptor status: not specified
Interventions	Intervention: low molecular weight heparin (dalteparin) Control: no dalteparin Co-intervention: standard therapy
Outcomes	Quality of life
Starting date	December 1998
Contact information	Scott Okuno, MD Mayo Clinic
Notes	Sponsor: North Central Cancer Treatment Group National Cancer Institute (NCI) Status as of August 2017: Completed (not published yet)

Pandya 2002

Study name	A prospective randomized controlled multicenter study of the effect of dalteparin on quality of life in unresectable pancreatic cancer
Methods	Study type: interventional Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open-label Primary purpose: treatment
Participants	Patients with histologically or cytologically confirmed pancreatic adenocarcinoma or poorly differentiated carcinoma of the pancreas that is considered ineligible for curative resection
Interventions	Intervention: 5000 anti-Xa units of dalteparin subcutaneously once daily for 6 months Control: no dalteparin Co-intervention: gemcitabine IV over 30 minutes once weekly on weeks 1 to 7 for the first course only
Outcomes	Quality of life Survival Frequency of symptomatic venous thromboembolic complications

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Pandya 2002 *(Continued)*

	Safety as measured by the occurrence of bleeding complications
Starting date	October 2002
Contact information	Gary Morrow National Cancer Institute (NCI)
Notes	Kishan J. Pandya, MD University of Rochester Status as of August 2017: Terminated (not published yet)

Rosovsky 2009

Study name	A randomized phase II study to evaluate the effect of two different doses of enoxaparin sodium in combination with standard chemotherapy (cisplatin plus etoposide) with respect to time to tumor progression (TTP) in patients with newly diagnosed extensive stage small cell lung cancer (SCLC) without underlying venous thromboembolism
Methods	Study type: interventional Allocation: randomized Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open-label
Participants	Patients with newly diagnosed extensive stage SCLC without underlying venous thromboembolism
Interventions	Group A: active comparator; cisplatin and etoposide Group B: experimental; cisplatin and etoposide, plus low-dose enoxaparin sodium Group C: experimental; cisplatin and etoposide, plus high-dose enoxaparin sodium
Outcomes	Primary outcome measures: to evaluate the prophylactic and treatment doses of enoxaparin sodium given in combination with standard chemotherapy compared to standard chemotherapy alone with respect to time to tumor progression in this patient population (time frame: 2 years) Secondary outcome measures: to determine the effect of 2 different doses of enoxaparin sodium in combination with chemotherapy and chemotherapy alone on biomarkers of angiogenesis and to identify if these markers correlate with overall survival and progression-free survival (time frame: 2 years) (designated as safety issue: no) To evaluate toxicity and determine the rates of bleeding complications in this patient population (time frame: 2 years)
Starting date	July 2008
Contact information	Rachel Rosovsky, MD, MPH
Notes	Principal Investigator: Rachel Rosovsky, MD, MPH; Massachusetts General Hospital Sponsors and Collaborators: Massachusetts General Hospital; Dana-Farber Cancer Institute; Beth Israel Deaconess Medical Center; North Shore Medical Center; Sanofi-Aventis http://clinicaltrials.gov/ct2/show/NCT00916669 Status as of August 2017: This study has been withdrawn prior to enrolment.

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CNS: central nervous system; CT: computerized tomography; DVT: deep vein thrombosis; ECOG: Eastern Co-operative Oncology Group; EFS: event-free survival; IU: international unit; IV: intravenous; LMWH: low molecular weight heparin; OD: once daily; PE: pulmonary embolism; SC: subcutaneous; SCLC: small cell lung cancer; VTE: venous thromboembolism

DATA AND ANALYSES

Comparison 1. Heparin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality at 12 months- Main analysis	18	9575	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
1.2 Mortality at 12 months- Subgroups Lung vs non-Lung Cancer	12	4768	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.86, 1.03]
1.2.1 Lung Cancer (SCLC or NSCLC)	6	3204	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
1.2.2 non-Lung Cancer	7	1564	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.03]
1.3 Mortality at 12 months- Subgroups Advanced vs non-Advanced	18	9575	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.94, 1.03]
1.3.1 Advanced cancer	12	6115	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.02]
1.3.2 Non-advanced cancer	8	3460	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.75, 1.12]
1.4 Mortality at 24 months- Main Analysis	14	5229	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.01]
1.5 Mortality at 24 months- Subgroups Advanced vs non-Advanced	14	5229	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.01]
1.5.1 Advanced cancer	6	1554	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
1.5.2 Non-advanced cancer	8	3675	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
1.6 Mortality over duration of study	15		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.84, 1.03]
1.7 Symptomatic VTE- Main analysis	16	9036	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.47, 0.68]
1.8 Symptomatic VTE- Subgroups Lung vs non-Lung Cancer	11	8090	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.43, 0.63]
1.8.1 Lung Cancer (SCLC or NSCLC)	6	4217	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.41, 0.68]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.8.2 Non-lung cancer	7	3873	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.37, 0.70]
1.9 PE	14	8867	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.47, 0.80]
1.10 Symptomatic DVT	14	8867	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.33, 0.63]
1.11 Major bleeding- Main analysis	18	9592	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.94, 1.79]
1.12 Major bleeding- Subgroups Lung vs non-Lung Cancer	10	4163	Risk Ratio (M-H, Random, 95% CI)	1.62 [1.02, 2.56]
1.12.1 Lung Cancer (SCLC or NS-CLC)	5	3035	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.77, 2.73]
1.12.2 Non-lung cancer	5	1128	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.94, 3.58]
1.13 Minor bleeding	16	9245	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.13, 2.55]
1.14 Thrombocytopenia	12	5832	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.37, 1.27]

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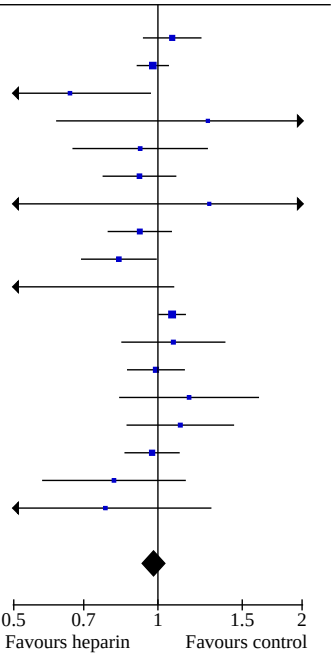
Analysis 1.1. Comparison 1: Heparin versus placebo, Outcome 1: Mortality at 12 months- Main analysis

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2009 (PROTECHT)	333	700	155	349	9.0%	1.07 [0.93 , 1.23]
Agnelli 2012 (SAVE-ONCO)	698	1584	714	1581	15.6%	0.98 [0.90 , 1.05]
Altinbas 2004	19	42	29	42	1.8%	0.66 [0.44 , 0.97]
Haas 2012 (TOPIC 1)	15	174	12	177	0.5%	1.27 [0.61 , 2.64]
Haas 2012 (TOPIC 2)	55	268	59	264	2.5%	0.92 [0.66 , 1.27]
Kakkar 2004 (FAMOUS)	103	190	109	184	6.7%	0.92 [0.77 , 1.09]
Khorana 2017 (PHACS)	8	50	6	48	0.3%	1.28 [0.48 , 3.42]
Klerk 2005 (MALT)	88	131	107	146	8.0%	0.92 [0.79 , 1.07]
Lebeau 1994	79	138	96	139	6.4%	0.83 [0.69 , 0.99]
Lecumberri 2013 (ABEL)	2	20	7	18	0.1%	0.26 [0.06 , 1.08]
Macbeth 2016 (FRAGMATIC)	668	1037	642	1067	17.0%	1.07 [1.00 , 1.14]
Maraveyas 2012 (FRAGEM)	41	59	40	62	3.9%	1.08 [0.84 , 1.38]
Pelzer 2015 (CONKO-004)	111	153	104	142	9.1%	0.99 [0.86 , 1.14]
Perry 2010 (PRODIGE)	45	92	32	76	2.3%	1.16 [0.83 , 1.63]
Sideras 2006	45	68	41	69	3.7%	1.11 [0.86 , 1.44]
van Doormaal 2011 (INPACT)	138	212	160	239	9.7%	0.97 [0.85 , 1.11]
Weber 2008	8	10	10	10	2.2%	0.81 [0.57 , 1.14]
Zwicker 2013 (MICRO TEC)	13	23	8	11	1.1%	0.78 [0.47 , 1.29]
Total (95% CI)		**4951**		**4624**	**100.0%**	**0.98 [0.93 , 1.03]**
Total events:	2469		2331			

Heterogeneity: Tau² = 0.00; Chi² = 24.80, df = 17 (P = 0.10); I² = 31%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



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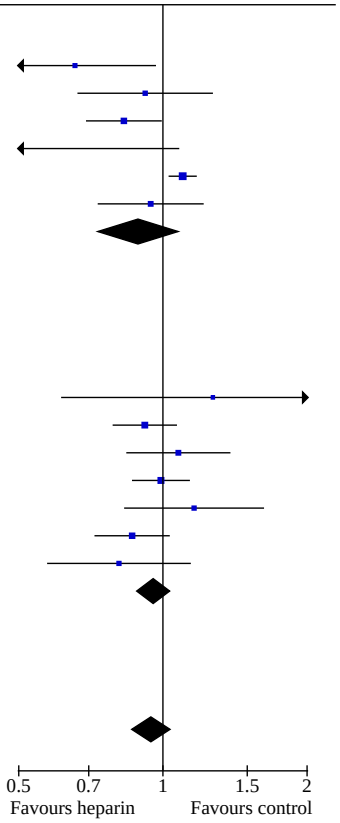
Analysis 1.2. Comparison 1: Heparin versus placebo, Outcome 2: Mortality at 12 months- Subgroups Lung vs non-Lung Cancer

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Lung Cancer (SCLC or NSCLC)						
Altinbas 2004	19	42	29	42	4.3%	0.66 [0.44 , 0.97]
Haas 2012 (TOPIC 2)	55	268	59	264	5.6%	0.92 [0.66 , 1.27]
Lebeau 1994	79	138	96	139	10.6%	0.83 [0.69 , 0.99]
Lecumberri 2013 (ABEL)	2	20	7	18	0.4%	0.26 [0.06 , 1.08]
Macbeth 2016 (FRAGMATIC)	668	1037	625	1067	16.5%	1.10 [1.03 , 1.18]
van Doormaal 2011 (INPACT)	46	81	53	88	7.6%	0.94 [0.73 , 1.22]
Subtotal (95% CI)		**1586**		**1618**	**44.9%**	**0.89 [0.73 , 1.08]**
Total events:	869		869			
Heterogeneity: Tau² = 0.03; Chi² = 18.84, df = 5 (P = 0.002); I² = 73%						
Test for overall effect: Z = 1.22 (P = 0.22)						
1.2.2 non-Lung Cancer						
Haas 2012 (TOPIC 1)	15	174	12	177	1.5%	1.27 [0.61 , 2.64]
Klerk 2005 (MALT)	88	131	107	146	12.0%	0.92 [0.79 , 1.07]
Maraveyas 2012 (FRAGEM)	41	59	40	62	7.8%	1.08 [0.84 , 1.38]
Pelzer 2015 (CONKO-004)	111	153	104	142	12.8%	0.99 [0.86 , 1.14]
Perry 2010 (PRODIGE)	45	92	32	76	5.3%	1.16 [0.83 , 1.63]
van Doormaal 2011 (INPACT)	89	163	107	169	10.7%	0.86 [0.72 , 1.03]
Weber 2008	8	10	10	10	5.1%	0.81 [0.57 , 1.14]
Subtotal (95% CI)		**782**		**782**	**55.1%**	**0.95 [0.88 , 1.03]**
Total events:	397		412			
Heterogeneity: Tau² = 0.00; Chi² = 5.51, df = 6 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Total (95% CI)		**2368**		**2400**	**100.0%**	**0.94 [0.86 , 1.03]**
Total events:	1266		1281			
Heterogeneity: Tau² = 0.01; Chi² = 26.77, df = 12 (P = 0.008); I² = 55%						
Test for overall effect: Z = 1.23 (P = 0.22)						
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%						



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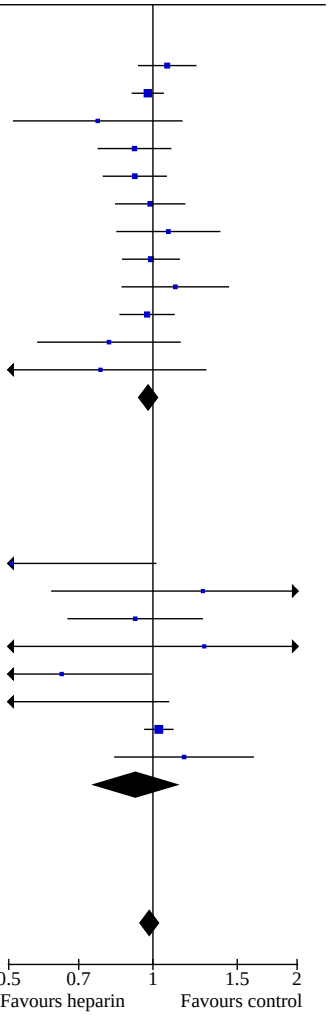
Analysis 1.3. Comparison 1: Heparin versus placebo, Outcome 3: Mortality at 12 months- Subgroups Advanced vs non-Advanced

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Advanced cancer						
Agnelli 2009 (PROTECHT)	333	700	155	349	8.3%	1.07 [0.93 , 1.23]
Agnelli 2012 (SAVE-ONCO)	698	1584	714	1581	19.2%	0.98 [0.90 , 1.05]
Altinbas 2004	12	19	14	17	1.2%	0.77 [0.51 , 1.15]
Kakkar 2004 (FAMOUS)	103	190	109	184	5.6%	0.92 [0.77 , 1.09]
Klerk 2005 (MALT)	88	131	107	146	7.1%	0.92 [0.79 , 1.07]
Lebeau 1994	57	74	64	82	6.1%	0.99 [0.83 , 1.17]
Maraveyas 2012 (FRAGEM)	41	59	40	62	3.0%	1.08 [0.84 , 1.38]
Pelzer 2015 (CONKO-004)	111	153	104	142	8.4%	0.99 [0.86 , 1.14]
Sideras 2006	45	68	41	69	2.8%	1.11 [0.86 , 1.44]
van Doormaal 2011 (INPACT)	138	212	160	239	9.1%	0.97 [0.85 , 1.11]
Weber 2008	8	10	10	10	1.6%	0.81 [0.57 , 1.14]
Zwicker 2013 (MICRO TEC)	13	23	8	11	0.8%	0.78 [0.47 , 1.29]
Subtotal (95% CI)		**3223**		**2892**	**73.0%**	**0.98 [0.93 , 1.02]**
Total events:	1647		1526			
Heterogeneity: Tau² = 0.00; Chi² = 7.78, df = 11 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
1.3.2 Non-advanced cancer						
Altinbas 2004	7	23	15	25	0.4%	0.51 [0.25 , 1.02]
Haas 2012 (TOPIC 1)	15	174	12	177	0.4%	1.27 [0.61 , 2.64]
Haas 2012 (TOPIC 2)	55	268	59	264	1.8%	0.92 [0.66 , 1.27]
Khorana 2017 (PHACS)	8	50	6	48	0.2%	1.28 [0.48 , 3.42]
Lebeau 1994	21	64	29	57	1.0%	0.64 [0.42 , 0.99]
Lecumberri 2013 (ABEL)	2	20	7	18	0.1%	0.26 [0.06 , 1.08]
Macbeth 2016 (FRAGMATIC)	625	1037	625	1067	21.3%	1.03 [0.96 , 1.10]
Perry 2010 (PRODIGE)	45	92	32	76	1.7%	1.16 [0.83 , 1.63]
Subtotal (95% CI)		**1728**		**1732**	**27.0%**	**0.92 [0.75 , 1.12]**
Total events:	778		785			
Heterogeneity: Tau² = 0.03; Chi² = 13.33, df = 7 (P = 0.06); I² = 47%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**4951**		**4624**	**100.0%**	**0.98 [0.94 , 1.03]**
Total events:	2425		2311			
Heterogeneity: Tau² = 0.00; Chi² = 21.63, df = 19 (P = 0.30); I² = 12%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%						



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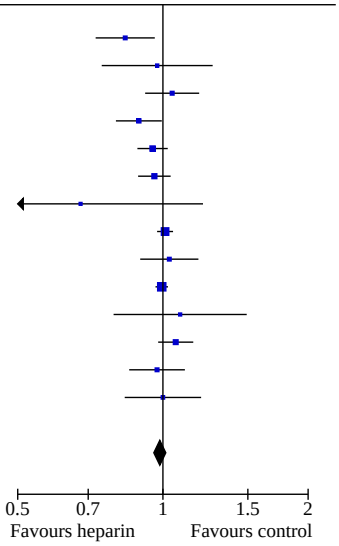
Analysis 1.4. Comparison 1: Heparin versus placebo, Outcome 4: Mortality at 24 months- Main Analysis

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Altinbas 2004	35	42	42	42	3.6%	0.84 [0.73 , 0.96]
Haas 2012 (TOPIC 1)	66	174	69	177	1.1%	0.97 [0.75 , 1.27]
Haas 2012 (TOPIC 2)	174	268	164	264	4.3%	1.05 [0.92 , 1.19]
Kakkar 2004 (FAMOUS)	139	190	151	184	5.7%	0.89 [0.80 , 0.99]
Klerk 2005 (MALT)	117	131	137	146	10.6%	0.95 [0.89 , 1.02]
Lebeau 1994	122	138	128	139	9.6%	0.96 [0.89 , 1.04]
Lecumberri 2013 (ABEL)	9	20	12	18	0.2%	0.68 [0.38 , 1.21]
Macbeth 2016 (FRAGMATIC)	870	1037	886	1067	20.9%	1.01 [0.97 , 1.05]
Maraveyas 2012 (FRAGEM)	52	59	53	62	3.8%	1.03 [0.90 , 1.18]
Pelzer 2015 (CONKO-004)	150	153	140	142	24.4%	0.99 [0.97 , 1.02]
Perry 2010 (PRODIGE)	46	92	35	76	0.8%	1.09 [0.79 , 1.49]
Sideras 2006	66	68	63	69	8.6%	1.06 [0.98 , 1.16]
van Doormaal 2011 (INPACT)	138	212	160	239	4.1%	0.97 [0.85 , 1.11]
Weber 2008	10	10	10	10	2.3%	1.00 [0.83 , 1.20]
Total (95% CI)		**2594**		**2635**	**100.0%**	**0.99 [0.96 , 1.01]**
Total events:	1994		2050			

Heterogeneity: Tau² = 0.00; Chi² = 17.87, df = 13 (P = 0.16); I² = 27%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



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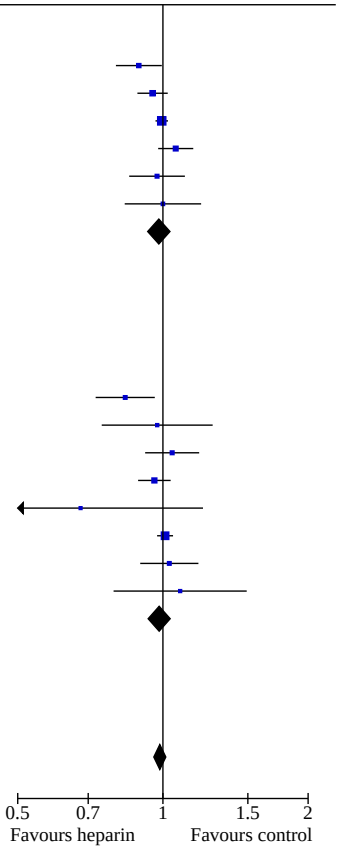
Analysis 1.5. Comparison 1: Heparin versus placebo, Outcome 5: Mortality at 24 months- Subgroups Advanced vs non-Advanced

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Advanced cancer						
Kakkar 2004 (FAMOUS)	139	190	151	184	5.7%	0.89 [0.80 , 0.99]
Klerk 2005 (MALT)	117	131	137	146	10.6%	0.95 [0.89 , 1.02]
Pelzer 2015 (CONKO-004)	150	153	140	142	24.4%	0.99 [0.97 , 1.02]
Sideras 2006	66	68	63	69	8.6%	1.06 [0.98 , 1.16]
van Doormaal 2011 (INPACT)	138	212	160	239	4.1%	0.97 [0.85 , 1.11]
Weber 2008	10	10	10	10	2.3%	1.00 [0.83 , 1.20]
Subtotal (95% CI)		**764**		**790**	**55.6%**	**0.98 [0.93 , 1.03]**
Total events:	620		661			
Heterogeneity: Tau² = 0.00; Chi² = 11.90, df = 5 (P = 0.04); I² = 58%						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.5.2 Non-advanced cancer						
Altinbas 2004	35	42	42	42	3.6%	0.84 [0.73 , 0.96]
Haas 2012 (TOPIC 1)	66	174	69	177	1.1%	0.97 [0.75 , 1.27]
Haas 2012 (TOPIC 2)	174	268	164	264	4.3%	1.05 [0.92 , 1.19]
Lebeau 1994	122	138	128	139	9.6%	0.96 [0.89 , 1.04]
Lecumberri 2013 (ABEL)	9	20	12	18	0.2%	0.68 [0.38 , 1.21]
Macbeth 2016 (FRAGMATIC)	870	1037	886	1067	20.9%	1.01 [0.97 , 1.05]
Maraveyas 2012 (FRAGEM)	52	59	53	62	3.8%	1.03 [0.90 , 1.18]
Perry 2010 (PRODIGE)	46	92	35	76	0.8%	1.09 [0.79 , 1.49]
Subtotal (95% CI)		**1830**		**1845**	**44.4%**	**0.98 [0.93 , 1.04]**
Total events:	1374		1389			
Heterogeneity: Tau² = 0.00; Chi² = 10.38, df = 7 (P = 0.17); I² = 33%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**2594**		**2635**	**100.0%**	**0.99 [0.96 , 1.01]**
Total events:	1994		2050			
Heterogeneity: Tau² = 0.00; Chi² = 17.87, df = 13 (P = 0.16); I² = 27%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						



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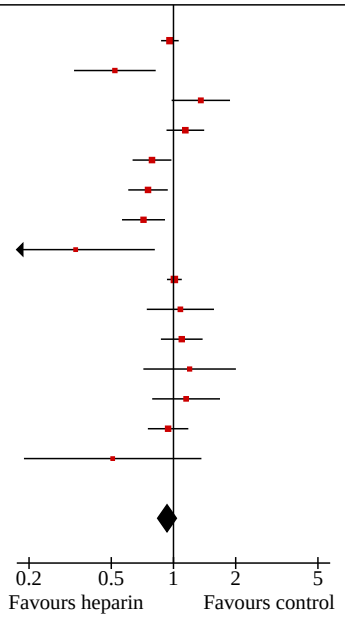
Analysis 1.6. Comparison 1: Heparin versus placebo, Outcome 6: Mortality over duration of study

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Agnelli 2012 (SAVE-ONCO)	-0.04	0.05	12.2%	0.96 [0.87 , 1.06]
Altinbas 2004	-0.6531	0.2321	3.8%	0.52 [0.33 , 0.82]
Haas 2012 (TOPIC 1)	0.3047	0.1659	5.9%	1.36 [0.98 , 1.88]
Haas 2012 (TOPIC 2)	0.1322	0.1071	8.8%	1.14 [0.93 , 1.41]
Kakkar 2004 (FAMOUS)	-0.2395	0.1103	8.6%	0.79 [0.63 , 0.98]
Klerk 2005 (MALT)	-0.2838	0.1123	8.5%	0.75 [0.60 , 0.94]
Lebeau 1994	-0.334	0.1222	7.9%	0.72 [0.56 , 0.91]
Lecumberri 2013 (ABEL)	-1.09	0.45	1.3%	0.34 [0.14 , 0.81]
Macbeth 2016 (FRAGMATIC)	0.01	0.0421	12.6%	1.01 [0.93 , 1.10]
Maraveyas 2012 (FRAGEM)	0.0769	0.191	4.9%	1.08 [0.74 , 1.57]
Pelzer 2015 (CONKO-004)	0.0922	0.1185	8.1%	1.10 [0.87 , 1.38]
Perry 2010 (PRODIGE)	0.18	0.263	3.1%	1.20 [0.72 , 2.00]
Sideras 2006	0.1406	0.1927	4.9%	1.15 [0.79 , 1.68]
van Doormaal 2011 (INPACT)	-0.06	0.115	8.3%	0.94 [0.75 , 1.18]
Weber 2008	-0.6774	0.5044	1.0%	0.51 [0.19 , 1.37]
Total (95% CI)			**100.0%**	**0.93 [0.84 , 1.03]**

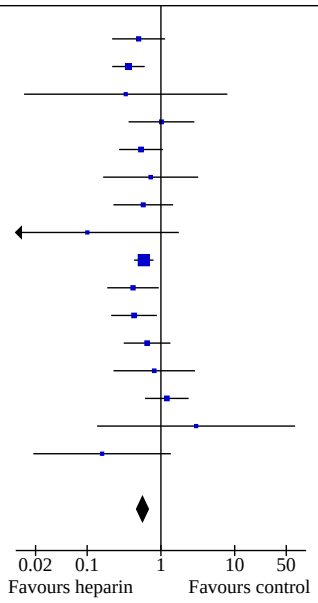
Heterogeneity: Tau² = 0.02; Chi² = 39.33, df = 14 (P = 0.0003); I² = 64%
Test for overall effect: Z = 1.36 (P = 0.18)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Heparin versus placebo, Outcome 7: Symptomatic VTE- Main analysis

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2009 (PROTECHT)	11	700	11	349	4.9%	0.50 [0.22 , 1.14]
Agnelli 2012 (SAVE-ONCO)	20	1584	55	1581	13.1%	0.36 [0.22 , 0.60]
Altinbas 2004	0	42	1	42	0.3%	0.33 [0.01 , 7.96]
Haas 2012 (TOPIC 1)	7	174	7	177	3.2%	1.02 [0.36 , 2.84]
Haas 2012 (TOPIC 2)	12	268	22	264	7.2%	0.54 [0.27 , 1.06]
Kakkar 2004 (FAMOUS)	3	190	4	184	1.5%	0.73 [0.16 , 3.20]
Khorana 2017 (PHACS)	6	50	10	48	3.9%	0.58 [0.23 , 1.46]
Lecumberri 2013 (ABEL)	0	20	4	18	0.4%	0.10 [0.01 , 1.75]
Macbeth 2016 (FRAGMATIC)	61	1037	107	1067	36.8%	0.59 [0.43 , 0.79]
Maraveyas 2012 (FRAGEM)	7	59	17	60	5.2%	0.42 [0.19 , 0.94]
Pelzer 2015 (CONKO-004)	10	160	22	152	6.6%	0.43 [0.21 , 0.88]
Perry 2010 (PRODIGE)	11	92	14	76	6.3%	0.65 [0.31 , 1.35]
Sideras 2006	4	68	5	69	2.1%	0.81 [0.23 , 2.89]
van Doormaal 2011 (INPACT)	16	212	15	239	7.3%	1.20 [0.61 , 2.37]
Weber 2008	1	10	0	10	0.4%	3.00 [0.14 , 65.90]
Zwicker 2013 (MICRO TEC)	1	23	3	11	0.7%	0.16 [0.02 , 1.36]
Total (95% CI)		**4689**		**4347**	**100.0%**	**0.56 [0.47 , 0.68]**
Total events:	170		297			

Heterogeneity: Tau² = 0.00; Chi² = 14.73, df = 15 (P = 0.47); I² = 0%
Test for overall effect: Z = 6.15 (P < 0.00001)
Test for subgroup differences: Not applicable



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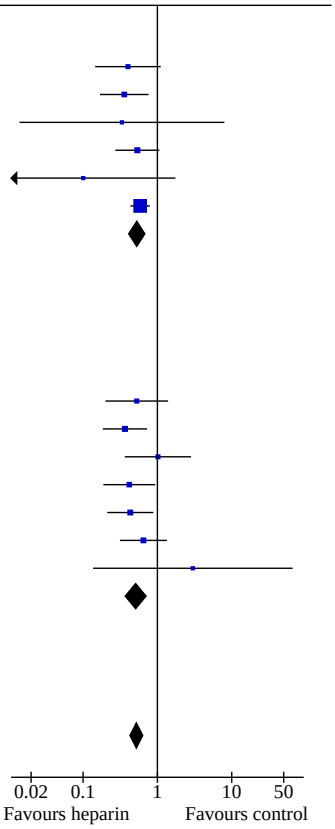
Analysis 1.8. Comparison 1: Heparin versus placebo, Outcome 8: Symptomatic VTE- Subgroups Lung vs non-Lung Cancer

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Lung Cancer (SCLC or NSCLC)						
Agnelli 2009 (PROTECHT)	7	199	7	80	3.8%	0.40 [0.15 , 1.11]
Agnelli 2012 (SAVE-ONCO)	9	591	25	589	6.9%	0.36 [0.17 , 0.76]
Altinbas 2004	0	42	1	42	0.4%	0.33 [0.01 , 7.96]
Haas 2012 (TOPIC 2)	12	268	22	264	8.4%	0.54 [0.27 , 1.06]
Lecumberri 2013 (ABEL)	0	20	4	18	0.5%	0.10 [0.01 , 1.75]
Macbeth 2016 (FRAGMATIC)	61	1037	107	1067	42.6%	0.59 [0.43 , 0.79]
Subtotal (95% CI)		**2157**		**2060**	**62.4%**	**0.53 [0.41 , 0.68]**
Total events:	89		166			
Heterogeneity: Tau² = 0.00; Chi² = 3.15, df = 5 (P = 0.68); I² = 0%						
Test for overall effect: Z = 5.01 (P < 0.00001)						
1.8.2 Non-lung cancer						
Agnelli 2009 (PROTECHT)	8	570	8	301	4.1%	0.53 [0.20 , 1.39]
Agnelli 2012 (SAVE-ONCO)	11	1017	30	1015	8.3%	0.37 [0.18 , 0.73]
Haas 2012 (TOPIC 1)	7	174	7	177	3.7%	1.02 [0.36 , 2.84]
Maraveyas 2012 (FRAGEM)	7	59	17	60	6.0%	0.42 [0.19 , 0.94]
Pelzer 2015 (CONKO-004)	10	160	22	152	7.6%	0.43 [0.21 , 0.88]
Perry 2010 (PRODIGE)	11	92	14	76	7.3%	0.65 [0.31 , 1.35]
Weber 2008	1	10	0	10	0.4%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**2082**		**1791**	**37.6%**	**0.51 [0.37 , 0.70]**
Total events:	55		98			
Heterogeneity: Tau² = 0.00; Chi² = 4.77, df = 6 (P = 0.57); I² = 0%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
Total (95% CI)		**4239**		**3851**	**100.0%**	**0.52 [0.43 , 0.63]**
Total events:	144		264			
Heterogeneity: Tau² = 0.00; Chi² = 7.95, df = 12 (P = 0.79); I² = 0%						
Test for overall effect: Z = 6.48 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



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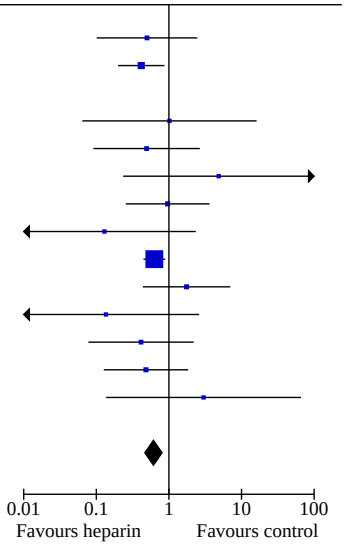
Analysis 1.9. Comparison 1: Heparin versus placebo, Outcome 9: PE

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2009 (PROTECHT)	3	700	3	349	2.9%	0.50 [0.10 , 2.46]
Agnelli 2012 (SAVE-ONCO)	10	1584	24	1581	13.7%	0.42 [0.20 , 0.87]
Altinbas 2004	0	42	0	42		Not estimable
Haas 2012 (TOPIC 1)	1	174	1	177	1.0%	1.02 [0.06 , 16.14]
Haas 2012 (TOPIC 2)	2	268	4	264	2.6%	0.49 [0.09 , 2.67]
Kakkar 2004 (FAMOUS)	2	190	0	184	0.8%	4.84 [0.23 , 100.20]
Khorana 2017 (PHACS)	4	50	4	48	4.2%	0.96 [0.25 , 3.62]
Lecumberri 2013 (ABEL)	0	20	3	18	0.9%	0.13 [0.01 , 2.34]
Macbeth 2016 (FRAGMATIC)	49	1037	80	1067	61.8%	0.63 [0.45 , 0.89]
Maraveyas 2012 (FRAGEM)	5	59	3	62	3.8%	1.75 [0.44 , 7.01]
Pelzer 2015 (CONKO-004)	0	160	3	152	0.8%	0.14 [0.01 , 2.61]
Perry 2010 (PRODIGE)	2	92	4	76	2.6%	0.41 [0.08 , 2.19]
van Doormaal 2011 (INPACT)	3	212	7	239	4.1%	0.48 [0.13 , 1.84]
Weber 2008	1	10	0	10	0.8%	3.00 [0.14 , 65.90]
Total (95% CI)		**4598**		**4269**	**100.0%**	**0.61 [0.47 , 0.80]**
Total events:	82		136			

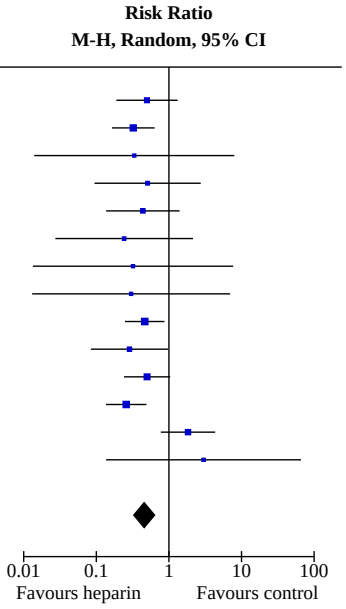
Heterogeneity: Tau² = 0.00; Chi² = 9.25, df = 12 (P = 0.68); I² = 0%
Test for overall effect: Z = 3.54 (P = 0.0004)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Heparin versus placebo, Outcome 10: Symptomatic DVT

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2009 (PROTECHT)	8	700	8	349	8.7%	0.50 [0.19 , 1.32]
Agnelli 2012 (SAVE-ONCO)	11	1584	34	1581	14.4%	0.32 [0.16 , 0.64]
Altinbas 2004	0	42	1	42	1.0%	0.33 [0.01 , 7.96]
Haas 2012 (TOPIC 1)	2	174	4	177	3.5%	0.51 [0.09 , 2.74]
Haas 2012 (TOPIC 2)	4	268	9	264	6.6%	0.44 [0.14 , 1.40]
Kakkar 2004 (FAMOUS)	1	190	4	184	2.1%	0.24 [0.03 , 2.15]
Khorana 2017 (PHACS)	0	50	1	48	1.0%	0.32 [0.01 , 7.67]
Lecumberri 2013 (ABEL)	0	20	1	18	1.1%	0.30 [0.01 , 6.97]
Macbeth 2016 (FRAGMATIC)	14	1037	31	1067	15.7%	0.46 [0.25 , 0.87]
Maraveyas 2012 (FRAGEM)	3	59	11	62	6.0%	0.29 [0.08 , 0.98]
Pelzer 2015 (CONKO-004)	10	160	19	152	13.0%	0.50 [0.24 , 1.04]
Perry 2010 (PRODIGE)	10	92	32	76	15.3%	0.26 [0.14 , 0.49]
van Doormaal 2011 (INPACT)	13	212	8	239	10.4%	1.83 [0.77 , 4.33]
Weber 2008	1	10	0	10	1.1%	3.00 [0.14 , 65.90]
Total (95% CI)		**4598**		**4269**	**100.0%**	**0.46 [0.33 , 0.63]**
Total events:	77		163			

Heterogeneity: Tau² = 0.08; Chi² = 16.59, df = 13 (P = 0.22); I² = 22%
Test for overall effect: Z = 4.67 (P < 0.00001)
Test for subgroup differences: Not applicable



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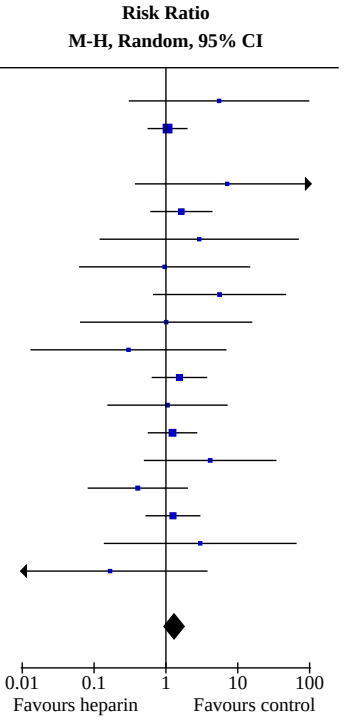
Analysis 1.11. Comparison 1: Heparin versus placebo, Outcome 11: Major bleeding- Main analysis

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2009 (PROTECHT)	5	700	0	349	1.2%	5.49 [0.30 , 99.04]
Agnelli 2012 (SAVE-ONCO)	19	1584	18	1581	25.4%	1.05 [0.56 , 2.00]
Altinbas 2004	0	42	0	42		Not estimable
Haas 2012 (TOPIC 1)	3	174	0	177	1.2%	7.12 [0.37 , 136.83]
Haas 2012 (TOPIC 2)	10	268	6	264	10.5%	1.64 [0.61 , 4.45]
Kakkar 2004 (FAMOUS)	1	190	0	184	1.0%	2.91 [0.12 , 70.87]
Khorana 2017 (PHACS)	1	50	1	48	1.4%	0.96 [0.06 , 14.92]
Klerk 2005 (MALT)	5	131	1	146	2.3%	5.57 [0.66 , 47.08]
Lebeau 1994	1	138	1	139	1.4%	1.01 [0.06 , 15.94]
Lecumberri 2013 (ABEL)	0	20	1	18	1.1%	0.30 [0.01 , 6.97]
Macbeth 2016 (FRAGMATIC)	12	1037	8	1067	13.2%	1.54 [0.63 , 3.76]
Maraveyas 2012 (FRAGEM)	2	59	2	62	2.8%	1.05 [0.15 , 7.22]
Pelzer 2015 (CONKO-004)	13	160	10	152	16.6%	1.24 [0.56 , 2.73]
Perry 2010 (PRODIGE)	5	92	1	76	2.3%	4.13 [0.49 , 34.60]
Sideras 2006	2	68	5	69	4.1%	0.41 [0.08 , 2.02]
van Doormaal 2011 (INPACT)	10	212	9	239	13.4%	1.25 [0.52 , 3.02]
Weber 2008	1	10	0	10	1.1%	3.00 [0.14 , 65.90]
Zwicker 2013 (MICRO TEC)	0	23	1	11	1.1%	0.17 [0.01 , 3.79]
Total (95% CI)		**4958**		**4634**	**100.0%**	**1.30 [0.94 , 1.79]**
Total events:	90		64			

Heterogeneity: Tau² = 0.00; Chi² = 11.17, df = 16 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable



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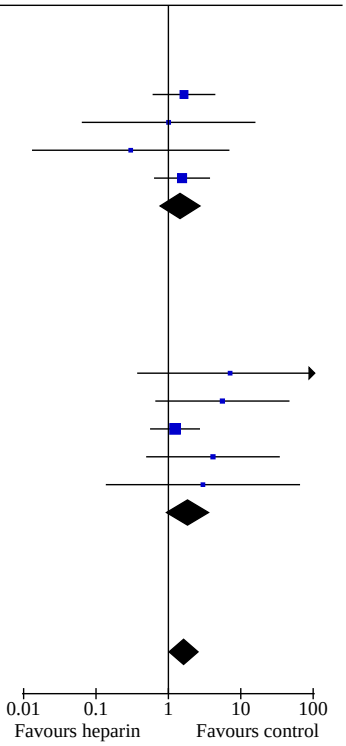
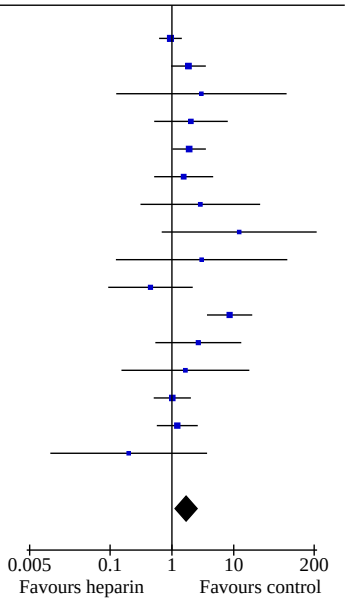
Analysis 1.12. Comparison 1: Heparin versus placebo, Outcome 12: Major bleeding- Subgroups Lung vs non-Lung Cancer

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Lung Cancer (SCLC or NSCLC)						
Altinbas 2004	0	42	0	42		Not estimable
Haas 2012 (TOPIC 2)	10	268	6	264	21.2%	1.64 [0.61 , 4.45]
Lebeau 1994	1	138	1	139	2.8%	1.01 [0.06 , 15.94]
Lecumberri 2013 (ABEL)	0	20	1	18	2.1%	0.30 [0.01 , 6.97]
Macbeth 2016 (FRAGMATIC)	12	1037	8	1067	26.6%	1.54 [0.63 , 3.76]
Subtotal (95% CI)		**1505**		**1530**	**52.7%**	**1.45 [0.77 , 2.73]**
Total events:	23		16			
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.12.2 Non-lung cancer						
Haas 2012 (TOPIC 1)	3	174	0	177	2.4%	7.12 [0.37 , 136.83]
Klerk 2005 (MALT)	5	131	1	146	4.6%	5.57 [0.66 , 47.08]
Pelzer 2015 (CONKO-004)	13	160	10	152	33.4%	1.24 [0.56 , 2.73]
Perry 2010 (PRODIGE)	5	92	1	76	4.7%	4.13 [0.49 , 34.60]
Weber 2008	1	10	0	10	2.2%	3.00 [0.14 , 65.90]
Subtotal (95% CI)		**567**		**561**	**47.3%**	**1.84 [0.94 , 3.58]**
Total events:	27		12			
Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 4 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						
Total (95% CI)		**2072**		**2091**	**100.0%**	**1.62 [1.02 , 2.56]**
Total events:	50		28			
Heterogeneity: Tau² = 0.00; Chi² = 4.88, df = 8 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						



Analysis 1.13. Comparison 1: Heparin versus placebo, Outcome 13: Minor bleeding

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2009 (PROTECHT)	57	700	30	349	13.3%	0.95 [0.62 , 1.45]
Agnelli 2012 (SAVE-ONCO)	26	1584	14	1581	11.2%	1.85 [0.97 , 3.54]
Altinbas 2004	1	42	0	42	1.5%	3.00 [0.13 , 71.61]
Haas 2012 (TOPIC 1)	6	174	3	177	5.7%	2.03 [0.52 , 8.01]
Haas 2012 (TOPIC 2)	27	268	14	264	11.4%	1.90 [1.02 , 3.54]
Kakkar 2004 (FAMOUS)	8	190	5	184	7.3%	1.55 [0.52 , 4.65]
Khorana 2017 (PHACS)	3	50	1	48	2.8%	2.88 [0.31 , 26.74]
Klerk 2005 (MALT)	5	131	0	146	1.8%	12.25 [0.68 , 219.43]
Lebeau 1994	1	138	0	139	1.5%	3.02 [0.12 , 73.54]
Lecumberri 2013 (ABEL)	2	20	4	18	4.7%	0.45 [0.09 , 2.17]
Macbeth 2016 (FRAGMATIC)	50	1037	6	1067	9.3%	8.57 [3.69 , 19.91]
Maraveyas 2012 (FRAGEM)	5	58	2	62	4.6%	2.67 [0.54 , 13.24]
Perry 2010 (PRODIGE)	2	92	1	76	2.5%	1.65 [0.15 , 17.87]
Sideras 2006	13	68	13	69	10.7%	1.01 [0.51 , 2.03]
van Doormaal 2011 (INPACT)	13	212	12	239	10.1%	1.22 [0.57 , 2.62]
Weber 2008	0	10	2	10	1.7%	0.20 [0.01 , 3.70]
Total (95% CI)		**4774**		**4471**	**100.0%**	**1.70 [1.13 , 2.55]**
Total events:	219		107			
Heterogeneity: Tau² = 0.28; Chi² = 32.19, df = 15 (P = 0.006); I² = 53%						
Test for overall effect: Z = 2.53 (P = 0.01)						
Test for subgroup differences: Not applicable						



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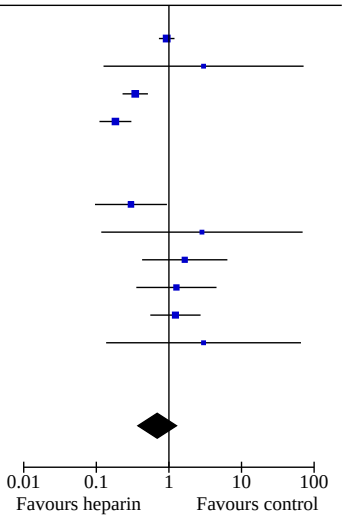
Analysis 1.14. Comparison 1: Heparin versus placebo, Outcome 14: Thrombocytopenia

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Agnelli 2012 (SAVE-ONCO)	113	1584	121	1581	16.6%	0.93 [0.73 , 1.19]
Altinbas 2004	1	42	0	42	3.0%	3.00 [0.13 , 71.61]
Haas 2012 (TOPIC 1)	25	174	74	177	15.9%	0.34 [0.23 , 0.51]
Haas 2012 (TOPIC 2)	16	268	86	264	15.3%	0.18 [0.11 , 0.30]
Klerk 2005 (MALT)	0	131	0	146		Not estimable
Lebeau 1994	0	138	0	139		Not estimable
Lecumberri 2013 (ABEL)	3	20	9	18	10.7%	0.30 [0.10 , 0.94]
Pelzer 2015 (CONKO-004)	1	160	0	152	3.0%	2.85 [0.12 , 69.45]
Perry 2010 (PRODIGE)	6	92	3	76	9.3%	1.65 [0.43 , 6.39]
Sideras 2006	5	68	4	69	9.8%	1.27 [0.36 , 4.52]
van Doormaal 2011 (INPACT)	12	212	11	239	13.2%	1.23 [0.55 , 2.73]
Weber 2008	1	10	0	10	3.2%	3.00 [0.14 , 65.90]
Weber 2008	0	10	0	10		Not estimable
Total (95% CI)		**2909**		**2923**	**100.0%**	**0.69 [0.37 , 1.27]**
Total events:	183		308			

Heterogeneity: Tau² = 0.57; Chi² = 51.78, df = 9 (P < 0.00001); I² = 83%
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Adjuvant therapy	Assisting in the amelioration or cure of disease
Anticoagulation	The process of hindering the clotting of blood especially by treatment with an anticoagulant
Antithrombotic	Used against or tending to prevent thrombosis (clotting)
Bacteremia	The presence of bacteria in the blood
Central venous line	Synthetic tube that is inserted into a central (large) vein of a patient to provide temporary intravenous access for the administration of fluid, medication or nutrients
Coagulation	Clotting
Deep vein thrombosis (DVT)	A condition marked by the formation of a thrombus within a deep vein (as of the leg or pelvis) that may be asymptomatic or be accompanied by symptoms (such as swelling and pain) and that is potentially life-threatening if dislodgment of the thrombus results in pulmonary embolism
Fibrin	A white insoluble fibrous protein formed from fibrinogen by the action of thrombin, especially in the clotting of blood
Fondaparinux	An anticoagulant medication
Hemostatic system	The system that shortens the clotting time of blood and stops bleeding

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Table 1. Glossary *(Continued)*

Heparin	An enzyme occurring especially in the liver and lungs that prolongs the clotting time of blood by preventing the formation of fibrin. Two forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low molecular weight heparins (LMWH)
Impedance plethysmography	A technique that measures the change in blood volume (venous blood volume as well as the pulsation of the arteries) for a specific body segment
Kappa statistics	A measure of degree of non-random agreement between observers and/or measurements of a specific categorical variable
Metastasis	The spread of cancer cells from the initial or primary site of disease to another part of the body
Oncogene	A gene having the potential to cause a normal cell to become cancerous
Osteoporosis	A condition that especially affects older women and is characterized by a decrease in bone mass with decreased density and enlargement of bone spaces producing porosity and brittleness
Parenteral nutrition	The practice of feeding a patient intravenously, circumventing the gut
Pulmonary embolism (PE)	Embolism of a pulmonary artery or one of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock and sometimes death
Stroma	The supporting framework of an organ typically consisting of connective tissue
Thrombin	A proteolytic enzyme formed from prothrombin that facilitates the clotting of blood by catalyzing conversion of fibrinogen to fibrin
Thrombocytopenia	Persistent decrease in the number of blood platelets that is often associated with hemorrhagic conditions
Thrombosis	The formation or presence of a blood clot within a blood vessel
Vitamin K antagonists	Anticoagulant medications that are used for anticoagulation. Warfarin is a vitamin K antagonist
Warfarin	An anticoagulant medication that is a vitamin K antagonist, which is used for anticoagulation
Ximelagatran	An anticoagulant medication

Table 2. LMWH: definitions of prophylactic and therapeutic dosages

LMWH	Generic name	Prophylactic dose	Therapeutic dose
Lovenox	Enoxaparin	40 mg once daily	1 mg/kg twice daily
Fragmin	Dalteparin	2500 to 5000 units once daily	200 U/kg once daily or 100 U/kg twice daily
Innohep, Logiparin	Tinzaparin	4500 units once daily	90 U/kg twice daily
Fraxiparine	Nadroparin	35 to 75 anti-Xa international units/kg once daily	175 anti-Xa int. units/kg once daily
Certoparin	Sandoparin	3000 anti-Xa international units once daily	—

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APPENDICES

Appendix 1. Living systematic review protocol

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

Search methods for identification of studies

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

As additional steps to inform the living systematic review, we will contact corresponding authors of ongoing studies as they are identified and ask them to advise when results are available, and to share early or unpublished data. We will contact the corresponding authors of any newly included studies for advice as to other relevant studies. We will conduct citation tracking of included studies in Web of Science Core Collection on an ongoing basis. For that purpose, we have set up citation alerts in Web of Science Core Collection. We will manually screen the reference list of any newly included studies, and identified relevant guidelines and systematic reviews. Also, we will use the 'related citation' feature in PubMed to identify additional articles.

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

Selection of studies

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

Data synthesis

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

Other

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

Appendix 2. Cochrane's living systematic review pilots

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

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

Appendix 3. Full search strategies for the electronic databases - Update 2010

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Database	Strategy
MEDLINE	#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR 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 #12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw. #13 5 OR 9 OR 10 OR 11 OR 12 #14 Neoplasms/ #15 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19
Embase	#1 Heparin/ #2 heparin.tw #3 Low Molecular Weight Heparin/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarin derivative/ #7 Warfarin/ #8 (warfarin OR coumadin OR 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 #14 (Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban).tw. #15 5 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 #16 Neoplasm/ #17 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #18 16 OR 17 #19 Random:.tw. OR clinical trial:.mp. OR exp health care quality #20 animals/ NOT human/ #21 19 NOT 20 #22 15 AND 18 AND 21
ISI (International Scientific Information) the Web of Science	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran

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	#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
CENTRAL (the Cochrane Library, latest issue)	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR 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 6 AND 7

Appendix 4. Full search strategies for the electronic databases - Update 2013

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

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	#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 orgaran 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 anticoagulant or vitamin K antagonist or VKA).tw. #6 (fondaparinux or arixtra).tw. #7 (ximelagatran or exanta).tw. #8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw. #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 #10 exp neoplasm/ #11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw. #12 10 or 11 #13 9 and 12 #14 crossover procedure/ #15 double-blind procedure/ #16 randomized controlled trial/ #17 single-blind procedure/ #18 random*.mp. #19 factorial*.mp.

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	#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
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 anticoagulant or vitamin K antagonist or VKA) #5 (fondaparinux or arixtra) #6 (ximelagatran or exanta) #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Neoplasms] explode all trees #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) #11 #9 or #10 #12 #8 and #10

Appendix 5. Full search strategies for the electronic databases - Update 2018

Database	Strategy
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 cer-

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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 Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

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

4. exp Coumarins/

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

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

7. (thrombin adj inhibitor*).mp.

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

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

10. RIVAROXABAN/

11. DABIGATRAN/

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

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

14. exp Neoplasms/

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

16. 14 or 15

17. 13 and 16

18. randomized controlled trial.pt.

19. controlled clinical trial.pt.

20. randomized.ab.

21. placebo.ab.

22. clinical trials as topic.sh.

23. randomly.ab.

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(Continued)

24. trial.ti.

25. 18 or 19 or 20 or 21 or 22 or 23 or 24

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

27. 25 not 26

28. 17 and 27

Systematic Review search strategy:

1. exp Anticoagulants/

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

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

4. exp Coumarins/

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

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

7. (thrombin adj inhibitor*).mp.

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

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

10. RIVAROXABAN/

11. DABIGATRAN/

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

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

14. exp Neoplasms/

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

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	16. 14 or 15 17. 13 and 16 18. (review or review,tutorial or review, academic).pt. 19. (medline or medlars or embase or pubmed or cochrane).tw,sh. 20. (scisearch or psychinfo or psycinfo).tw,sh. 21. (psychlit or psyclit).tw,sh. 22. cinahl.tw,sh. 23. ((hand adj2 search*) or (manual* adj2 search*)).tw,sh. 24. (electronic database* or bibliographic database* or computeri?ed database* or online database*).tw,sh. 25. (pooling or pooled or mantel haenszel).tw,sh. 26. (peto or dersimonian or der simonian or fixed effect).tw,sh. 27. (retraction of publication or retracted publication).pt. 28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 29. 18 and 28 30. meta-analysis.pt. 31. meta-analysis.sh. 32. (meta-analys* or meta analys* or metaanalys*).tw,sh. 33. (systematic* adj5 review*).tw,sh. 34. (systematic* adj5 overview*).tw,sh. 35. (quantitativ* adj5 review*).tw,sh. 36. (quantitativ* adj5 overview*).tw,sh. 37. (methodologic* adj5 review*).tw,sh. 38. (methodologic* adj5 overview*).tw,sh. 39. (integrative research review* or research integration).tw. 40. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 41. 29 or 40
Embase	**RCT search strategy:** 1. exp anticoagulant agent/ 2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

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(Continued)

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

4. exp coumarin derivative/

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

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

7. (thrombin adj inhibitor*).mp.

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

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

10. rivaroxaban/

11. dabigatran/

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

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

14. exp neoplasm/

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

16. 14 or 15

17. 13 and 16

18. crossover procedure/

19. double-blind procedure/

20. randomized controlled trial/

21. single-blind procedure/

22. random*.mp.

23. factorial*.mp.

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

25. placebo*.mp.

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

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

28. assign*.mp.

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(Continued)

29. allocat*.mp.

30. volunteer*.mp.

31. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32. 17 and 31

Systematic Review search strategy:

1. exp anticoagulant agent/

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

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

4. exp coumarin derivative/

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

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

7. (thrombin adj inhibitor*).mp.

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

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

10. rivaroxaban/

11. dabigatran/

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

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

14. exp neoplasm/

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

16. 14 or 15

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(Continued)

	17. 13 and 16 18. exp review/ 19. (literature adj3 review*).ti,ab. 20. exp meta analysis/ 21. exp "Systematic Review"/ 22. 18 or 19 or 20 or 21 23. (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. 24. RETRACTED ARTICLE/ 25. 23 or 24 26. 22 and 25 27. (systematic* adj2 (review* or overview)).ti,ab. 28. (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*).ti,ab. 29. 26 or 27 or 28 30. 17 and 29
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Anticoagulants] explode all trees #2 (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin* or danaproid or danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock) #3 FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216 #4 MeSH descriptor: [Coumarins] explode all trees #5 (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-bis-coumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl) #6 (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix) #7 thrombin near inhibitor* #8 factor Xa inhibitor* or antithrombin* or anticoagul* #9 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

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(Continued)

	#10 MeSH descriptor: [Rivaroxaban] this term only
	#11 MeSH descriptor: [Dabigatran] this term only
	#12 target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*
	#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
	#14 MeSH descriptor: [Neoplasms] explode all trees
	#15 malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*
	#16 #14 or #15
	#17 #13 and #16

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Appendix 6. GRADE Evidence Profile

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Heparin prophylaxis**	**No prophylaxis**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow-up: 12 months)												
18	randomised trials	not serious	not serious	not serious	serious [a]	none	2469/4951 (49.9%)	2331/4624 (50.4%)	**RR 0.98** (0.93 to 1.03)	**10 fewer per 1000** (from 15 more to 35 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality (follow-up: 24 months)												
14	randomised trials	not serious	not serious	not serious	serious [a]	none	1994/2594 (76.9%)	2050/2635 (77.8%)	**RR 0.99** (0.96 to 1.01)	**8 fewer per 1000** (from 31 fewer to 8 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Symptomatic VTE (follow-up: 12 months)												
16	randomised trials	not serious	not serious	not serious	not serious	none	170/4689 (3.6%)	297/4347 (6.8%)	**RR 0.56** (0.47 to 0.68)	**30 fewer per 1000** (from 36 fewer to 22 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
PE (follow-up: 12 months)												
14	randomised trials	not serious	not serious	not serious	not serious	none	82/4598 (1.8%)	136/4269 (3.2%)	**RR 0.61** (0.47 to 0.80)	**12 fewer per 1000** (from 6 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Symptomatic DVT (follow-up: 12 months)												
14	randomised trials	not serious	not serious	not serious	not serious	none	77/4598 (1.7%)	163/4269 (3.8%)	**RR 0.46** (0.33 to 0.63)	**21 fewer per 1000** (from 26 fewer to 14 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Major bleeding (follow up: 12 months)												

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(Continued)

18	randomised trials	not serious	not serious	not serious	serious [b]	none	90/4958 (1.8%)	64/4634 (1.4%)	**RR 1.30** (0.94 to 1.79)	**4 more per 1000** (from 1 fewer to 11 more)	⊕⊕⊕○ MODERATE	CRITICAL
Minor bleeding (follow-up: 12 months)												
16	randomised trials	not serious	not serious	not serious	not serious	none	219/4774 (4.6%)	107/4471 (2.4%)	**RR 1.70** (1.13 to 2.55)	**17 more per 1000** (from 3 more to 37 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Thrombocytopenia												
12	randomised trials	not serious	not serious	not serious	serious [c]	none	183/2909 (6.3%)	308/2923 (10.5%)	**RR 0.69** (0.37 to 1.27)	**33 fewer per 1000** (from 66 fewer to 28 more)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life impairment												
2	randomised trials	serious [d]	not serious	not serious	not serious	none	Macbeth 2016 (FRAGMATIC): " There was no difference between the two groups with respect to quality-adjusted life years gained in the first year... No difference in overall quality of life at 6 months (P = .94) or at 12 months (P = .89)... Overall quality of life did not change significantly over the study period". Sideras 2006: "The QOL and SDS scores were similar, both at baseline and during the protocol period, in patients randomized to receive LMWH vs those not randomized to receive LMWH."				⊕⊕⊕○ MODERATE	CRITICAL

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

Explanations

a. Confidence interval includes values suggesting clinically significant benefit and values suggesting no effect.

b. Confidence interval includes values suggesting clinically significant harm and values suggesting no effect.

c. Confidence interval includes values suggesting clinically significant benefit and values suggesting harm.

d. Both studies were open-label studies (lack of blinding may impact the patient-reported subjective outcomes)

Appendix 7. Detailed results of sensitivity analyses

Outcome	Symptomatic VTE
CCA effect estimate	RR 0.56 (95% CI 0.47 to 0.68)
Sensitivity analysis	
RI $1.5_{intervention}$ $1_{control}$	0.57 (95% CI 0.47 to 0.69)
RI $2_{intervention}$ $1_{control}$	0.58 (95% CI 0.47 to 0.71)
RI $3_{intervention}$ $1_{control}$	0.60 (95% CI 0.48 to 0.75)
RI $5_{intervention}$ $1_{control}$	0.63 (95% CI 0.49 to 0.80)

Outcome	**Minor bleeding**
CCA effect estimate	RR 1.70 (95% CI 1.13 to 2.55)
Sensitivity analysis	
RI $1_{intervention}$ $1.5_{control}$	1.66 (1.11 to 2.49)
RI $1_{intervention}$ $2_{control}$	1.65 (1.09 to 2.46)
RI $1_{intervention}$ $3_{control}$	1.59 (1.05 to 2.41)
RI $1_{intervention}$ $5_{control}$	1.52 (1.00 to 2.31)

Appendix 8. Full search Strategies for the electronic databases - Update 2020

Medline RCT

1. exp Anticoagulants/
2. (anticoagulant* or anti-coagulant*).tw.
3. (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or

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"UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or 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.
5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
6. exp Coumarins/
7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.
8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldocumar).mp.
9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
10. (thrombin adj inhibitor*).mp.
11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
13. RIVAROXABAN/
14. DABIGATRAN/
15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp Neoplasms/
19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.
20. 18 or 19
21. 17 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. drug therapy.fs.
27. randomly.ab.
28. trial.ti.
29. groups.ab.
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. (animals not (humans and animals)).sh.
32. 30 not 31
33. 21 and 32

Embase RCT

1. exp anticoagulant agent/
2. (anticoagulant* or anti-coagulant*).tw.
3. (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or

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"UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or 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.
5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
6. exp coumarin derivative/
7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.
8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldocumar).mp.
9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
10. (thrombin adj inhibitor*).mp.
11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
13. rivaroxaban/
14. dabigatran/
15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp.
16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp neoplasm/
19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.
20. 18 or 19
21. 17 and 20
22. crossover procedure/
23. double-blind procedure/
24. randomized controlled trial/
25. single-blind procedure/
26. random*.mp.
27. factorial*.mp.
28. (crossover* or cross over* or cross-over*).mp.
29. placebo*.mp.
30. (double* adj blind*).mp.
31. (singl* adj blind*).mp.
32. assign*.mp.
33. allocat*.mp.
34. volunteer*.mp.
35. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 21 and 35

Central

#1 MeSH descriptor: [Anticoagulants] explode all trees
#2 anticoagulant* or anti-coagulant*

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#3 (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
#4 (LMWH* or Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin)
#5 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
#6 MeSH descriptor: [Coumarins] explode all trees
#7 coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones
#8 (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldocumar)
#9 Dermatan Sulfate or (Chondroitin Sulfate near B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix)
#10 thrombin near inhibitor*
#11 factor Xa inhibitor* or antithrombin* or anti-thrombin* or anti-coagul* or anticoagul*
#12 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or “YM 150” or Iprivask or argatrovan or pradax* or Xarelto or “BIBR-953” or “BIBR-953ZW” or “BAY 59-7939” or “BMS-562247” or “DU-176” or “DU-176b”)
#13 target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*
#14 MeSH descriptor: [Rivaroxaban] this term only
#15 MeSH descriptor: [Dabigatran] this term only
#16 "BIBR 953" or "BIBR 953 ZW" or Dabigatran or "HSDB 8062" or Pradaxa or "UNII-I0VM4M70GC"
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH descriptor: [Neoplasms] explode all trees
#19 malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*
#20 #18 or #19
#21 #17 and #20

Medline SR

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

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lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or 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.
5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
6. exp Coumarins/
7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.
8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldocumar).mp.
9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
10. (thrombin adj inhibitor*).mp.
11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
13. RIVAROXABAN/
14. DABIGATRAN/
15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp Neoplasms/
19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.
20. 18 or 19
21. 17 and 20
22. Meta-Analysis as Topic/
23. meta analy$.tw.
24. metaanaly$.tw.
25. Meta-Analysis/
26. (systematic adj (review$1 or overview$1)).tw.
27. exp Review Literature as Topic/
28. 22 or 23 or 24 or 25 or 26 or 27
29. cochrane.ab.
30. embase.ab.
31. (psychlit or psyclit).ab.
32. (psychinfo or psycinfo).ab.
33. (cinahl or cinhal).ab.
34. science citation index.ab.
35. bids.ab.
36. cancerlit.ab.
37. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. reference list$.ab.
39. bibliograph$.ab.
40. hand-search$.ab.
41. relevant journals.ab.
42. manual search$.ab.
43. 38 or 39 or 40 or 41 or 42
44. selection criteria.ab.
45. data extraction.ab.
46. 44 or 45

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47. Review/
48. 46 and 47
49. Comment/
50. Letter/
51. Editorial/
52. animal/
53. human/
54. 52 not (52 and 53)
55. 49 or 50 or 51 or 54
56. 28 or 37 or 43 or 48
57. 56 not 55
58. 21 and 57

Embase SR

1. exp anticoagulant agent/
2. (anticoagulant* or anti-coagulant*).tw.
3. (Heparin or Adomiparin or alpha-Heparin or Arteven or "AVE-5026" or CY 222 or "Depo-Heparin" or "EINECS 232-681-7" or Fluxum or "Hed-heparin" or Hepathrom or HSDB 3094 or KB 101 or "Lipo-hepin" or M 118 or "M 118REH" or M118 or Octaparin or OP 386 or OP 622 or Pabyrin or Pularin or Subeparin or Sublingula or Thromboliquine or Triofiban or "UNII-1K5KDI46KZ" or "UNII-4QW4AN84NQ" or "UNII-5R0L1D739E" or "UNII-7UQ7X4Y489" or "UNII-9816XA9004" or "UNII-E47C0NF7LV" or "UNII-M316WT19D8" or "UNII-P776JQ4R2F" or "UNII-S79O08V79F" or "UNII-T2410KM04A" or "UNII-V72OT3K19I" or "UNII-VL0L558GCB" or Vetren or Vitrum AB or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or "Hep-lock" or enoxaparin* or klexane or lovenox or fragmin* or normiflo or logiparin or innohep or danaproid or danaparoid or orgaran or antixarin or hibor or zibor or ivor or badyket or lohepa or lowhepa or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or fondaparinux or Arixtra or UFH or Hepalean or Panheprin).mp.
4. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane or lovenox or dalteparin or fragmin or ardeparin* or normiflo or tinzaparin or logiparin or innohep or 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.
5. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.
6. exp coumarin derivative/
7. (coumarin* or chromonar or coumestrol or esculin or isocoumarin* or psoralens or pyranocoumarins or umbelliferones).tw.
8. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl or coumadin* or warfant or marevan or aldocumar).mp.
9. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.
10. (thrombin adj inhibitor*).mp.
11. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.
12. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.
13. rivaroxaban/
14. dabigatran/
15. (BIBR 953 or BIBR 953 ZW or Dabigatran or HSDB 8062 or Pradaxa or UNII-I0VM4M70GC).mp.
16. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp neoplasm/
19. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.
20. 18 or 19
21. 17 and 20
22. exp Meta Analysis/

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

Appendix 9. Study eligibility for subgroup analysis

I. Mortality at 12 months

a. Lung vs non-Lung

Name of study	Lung CA			non-Lung CA		
	Included patients only with Lung Cancer	Included patients with Lung and non-Lung CA AND provided subgroup data for patients with Lung CA	Included patients with Lung and non-Lung CA AND >75% of patients had Lung CA	Included patients only with non-Lung Cancer	Included patients with Lung and non-Lung CA AND provided subgroup data for patients with non-Lung CA	Included patients with Lung and non-Lung CA AND >75% of patients had non-Lung CA
Altinbas 2004	x					
Haas 2012 (TOPIC 1)				x		
Haas 2012 (TOPIC 2)	x					
Klerk 2005 (MALT)						x
Lebeau 1994		x				

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(Continued)

Lecumberri 2013 (ABEL)	x					
Macbeth 2016 (FRAGMATIC)	x					
Maraveyas 2012 (FRAGEM)				x		
Pelzer 2015 (CONKO-004)						x
Perry 2010 (PRODIGE)	x					
van Doormaal 2011 (INPACT)		x			x	

b. Advanced vs non-Advanced

Name of study	**Advanced CA**			**non-Advanced CA**		
	Included patients only with Advanced Cancer	Included patients with Advanced and non-Advanced CA AND provided subgroup data for patients with Advanced CA	Included patients with Advanced and non-Advanced CA AND >75% of patients had Advanced CA	Included patients only with non-Advanced Cancer	Included patients with Advanced and non-Advanced CA AND provided subgroup data for patients with non-Advanced CA	Included patients with Advanced and non-Advanced CA AND >75% of patients had non-Advanced CA
Agnelli 2009 (PROTECHT)	x					
Agnelli 2012 (SAVE-ONCO)	x					
Altinbas 2004		x			x	
Haas 2012 (TOPIC 1)				x		
Haas 2012 (TOPIC 2)				x		
Kakkar 2004 (FAMOUS)	x					
Khorana 2017 (PHACS)				x		
Klerk 2005 (MALT)	x					
Lebeau 1994		x			x	
Lecumberri 2013 (ABEL)				x		
Macbeth 2016 (FRAGMATIC)				x		
Maraveyas 2012 (FRAGEM)	x					
Pelzer 2015 (CONKO-004)	x					

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(Continued)

Perry 2010 (PRODIGE)		x
Sideras 2006	x	
van Doormaal 2011 (INPACT)	x	
Weber 2008	x	
Zwicker 2013 (MICRO TEC)	x	

II. Mortality at 24 months

a. Advanced vs non-Advanced

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Name of study	Advanced CA			non-Advanced CA		
	Included patients only with Advanced Cancer	Included patients with Advanced and non-Advanced CA AND provided subgroup data for patients with Advanced CA	Included patients with Advanced and non-Advanced CA AND >75% of patients had Advanced CA	Included patients only with non-Advanced Cancer	Included patients with Advanced and non-Advanced CA AND provided subgroup data for patients with non-Advanced CA	Included patients with Advanced and non-Advanced CA AND >75% of patients had non-Advanced CA
Altinbas 2004		x			x	
Haas 2012 (TOPIC 1)				x		
Haas 2012 (TOPIC 2)				x		
Kakkar 2004 (FAMOUS)	x					
Klerk 2005 (MALT)	x					
Lebeau 1994		x			x	
Lecumberri 2013 (ABEL)				x		
Macbeth 2016 (FRAGMATIC)				x		
Maraveyas 2012 (FRAGEM)	x					
Pelzer 2015 (CONKO-004)	x					
Perry 2010 (PRODIGE)				x		
Sideras 2006	x					
van Doormaal 2011 (INPACT)	x					
Weber 2008	x					

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III. Symptomatic VTE

a. Lung vs non-Lung

Name of study	Lung CA			non-Lung CA		
	Included patients only with Lung Cancer	Included patients with Lung and non-Lung CA AND provided subgroup data for patients with Lung CA	Included patients with Lung and non-Lung CA AND >75% of patients had Lung CA	Included patients only with non-Lung Cancer	Included patients with Lung and non-Lung CA AND provided subgroup data for patients with non-Lung CA	Included patients with Lung and non-Lung CA AND >75% of patients had non-Lung CA
Agnelli 2009 (PROTECHT)		x			x	
Agnelli 2012 (SAVE-ONCO)		x			x	
Altinbas 2004	x					
Haas 2012 (TOPIC 1)				x		
Haas 2012 (TOPIC 2)	x					
Lecumberri 2013 (ABEL)	x					
Macbeth 2016 (FRAGMATIC)	x					
Maraveyas 2012 (FRAGEM)				x		
Pelzer 2015 (CONKO-004)						x
Perry 2010 (PRODIGE)				x		
Weber 2008						x

IV. Major Bleeding

a. Lung vs non-Lung

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Name of study	Lung CA			non-Lung CA		
	Included patients only with Lung Cancer	Included patients with Lung and non-Lung CA AND provided subgroup data for patients with Lung CA	Included patients with Lung and non-Lung CA AND >75% of patients had Lung CA	Included patients only with non-Lung Cancer	Included patients with Lung and non-Lung CA AND provided subgroup data for patients with non-Lung CA	Included patients with Lung and non-Lung CA AND >75% of patients had non-Lung CA
Altinbas 2004	x					
Haas 2012 (TOPIC 1)				x		
Haas 2012 (TOPIC 2)	x					
Klerk 2005 (MALT)						x
Lebeau 1994	x					
Lecumberri 2013 (ABEL)	x					
Macbeth 2016 (FRAGMATIC)	x					
Pelzer 2015 (CONKO-004)						x
Perry 2010 (PRODIGE)	x					
Weber 2008						x

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WHAT'S NEW

Date	Event	Description
10 September 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 August 2021 (new information identified but unlikely to change results/conclusions). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.

HISTORY

Review first published: Issue 3, 2007

Date	Event	Description
17 February 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2021 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
29 October 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 October 2020 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
17 June 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2020 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 March 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2020 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
2 January 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 November 2019 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
7 October 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 August 2019 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have

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Date	Event	Description
		been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
9 July 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 June 2019 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
7 May 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 24 April 2019 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
25 February 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2019 (new information identified but unlikely to change results/conclusions) As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
29 November 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 November 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
2 October 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 September 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
9 August 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 July 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
28 June 2018	Amended	Search date updated.
28 June 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
28 June 2018	Amended	Declaration of interest updated.
23 April 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 March 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.

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Date	Event	Description
25 March 2015	Amended	Observed events of major bleeding and VTE outcomes for trial Pelzer 2015 (CONKO-004) have been corrected.
5 March 2014	New citation required but conclusions have not changed	Data abstraction verified and detailed statistical data included as an appendix. Data reanalyzed by using a complete case analysis approach for the primary meta-analysis. Sensitivity analysis conducted for outcomes with significant results in the primary meta-analysis.
9 February 2013	New search has been performed	Updated search identified five new eligible studies.
28 November 2012	Amended	Author contact details amended.
6 December 2010	New search has been performed	Text revised.
7 February 2010	New citation required but conclusions have not changed	Updated search, February 2010.
15 May 2007	New citation required and conclusions have changed	Substantive amendment. We updated the classification of heterogeneity. We considered the following classification of heterogeneity based on the value of I^2: 0% to 30% = low; 30% to 60% = moderate and worthy of investigation; 60% to 90% = severe and worthy of understanding; 90% to 100% = allowing aggregation only with major caution (Julian Higgins, personal communication). We rephrased the abstract conclusion as follows: "This review suggests a survival benefit of heparin in cancer patients in general, and in patients with small cell lung cancer in particular." We also added the following to the 4th paragraph of the Discussion ("Interpretation of the findings of this review is limited by the moderate heterogeneity…"): "The interpretation of findings is also limited by not including data from the seven trials published as abstracts only."

CONTRIBUTIONS OF AUTHORS

EAA: protocol development, data analysis, manuscript drafting, methodological expertise, review co-ordination. LAK: searching for trials, screening, data extraction, data analysis, manuscript drafting, review co-ordination. MH: screening, full-text retrieval, data extraction, manuscript drafting. CM: screening, full-text retrieval, data extraction. MB: screening, full-text retrieval, data extraction. FS: screening, full-text retrieval, data extraction. IT: screening, full-text retrieval, data extraction.VY: screening, full-text retrieval, data extraction. AS: methodological expertise related to the living systematic review approach. HJS: protocol development, data interpretation, methodological expertise.

DECLARATIONS OF INTEREST

HJS: panel member of the ASH VTE in cancer patients, Vice-Chair of the ASH VTE guidelines and played various leadership roles from 1999 until 2014 with ACCP VTE guidelines. EAA served on the executive committee the ACCP Antithrombotic Therapy Guidelines published in 2016. All other co-authors declare no conflicts of interests.

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- No sources of support provided

External sources

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- American Society of Hematology, USA

  This project was supported by the American Society of Hematology

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update includes new section relevant to living systematic reviews, which are included in the Methods and also described in Appendix 1.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*administration & dosage] [adverse effects]; Cause of Death; Hemorrhage [chemically induced] [epidemiology]; Heparin [*administration & dosage] [adverse effects]; Heparin, Low-Molecular-Weight [administration & dosage]; Neoplasms [*mortality]; Quality of Life; Randomized Controlled Trials as Topic; Survival Analysis; Time Factors; Venous Thromboembolism [epidemiology] [*prevention & control]; Warfarin [administration & dosage]

MeSH check words

Humans

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