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

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[Intervention Review]

Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

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ABSTRACT

Background

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

Objectives

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

Search methods

For this update, the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched May 2013), CENTRAL (2013, Issue 5), and clinical trials registries (up to June 2013).

Selection criteria

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

Data collection and analysis

Data were extracted on methodological quality, patients, interventions, and outcomes including symptomatic VTE and major bleeding as the primary effectiveness and safety outcomes, respectively.

Main results

We identified 12 additional RCTs (6323 patients) in the updated search so that this update considered 21 trials with a total of 9861 patients, all evaluating pharmacological interventions and performed mainly in patients with advanced cancer. Overall, the risk of bias varied from low to high. One large trial of 3212 patients found a 64% (risk ratio (RR) 0.36, 95% confidence interval (CI) 0.22 to 0.60) reduction of symptomatic VTE with the ultra-low molecular weight heparin (uLMWH) semuloparin relative to placebo, with no apparent difference in major bleeding (RR 1.05, 95% CI 0.55 to 2.00). LMWH, when compared with inactive control, significantly reduced the incidence of symptomatic VTE (RR 0.53, 95% CI 0.38 to 0.75; no heterogeneity, Tau^2 = 0%) with similar rates of major bleeding events (RR 1.30, 95% CI 0.75 to 2.23). In patients with multiple myeloma, LMWH was associated with a significant reduction in symptomatic VTE when compared with the vitamin K antagonist warfarin (RR 0.33, 95% CI 0.14 to 0.83), while the difference between LMWH and aspirin was not statistically significant (RR 0.51, 95% CI 0.22 to 1.17). No major bleeding was observed in the patients treated with LMWH or warfarin and in less than 1% of those treated with aspirin. Only one study evaluated unfractionated heparin against inactive control and found an incidence of major bleeding of 1% in both study groups while not reporting on VTE. When compared with placebo, warfarin was associated with a statistically insignificant reduction of symptomatic VTE (RR 0.15, 95% CI 0.02 to 1.20). Antithrombin, evaluated in one study involving paediatric patients, had no significant effect on VTE nor major bleeding when compared with inactive control. The new oral factor Xa inhibitor apixaban was evaluated in a phase-II dose finding study that suggested a promising low rate of major bleeding (2.1% versus 3.3%) and symptomatic VTE (1.1% versus 10%) in comparison with placebo.

Authors' conclusions

In this update, we confirmed that primary thromboprophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in ambulatory cancer patients treated with chemotherapy. In addition, the uLMWH semuloparin significantly reduced the incidence of symptomatic VTE. However, the broad confidence intervals around the estimates for major bleeding suggest caution in the use of anticoagulation and mandate additional studies to determine the risk to benefit ratio of anticoagulants in this setting. Despite the encouraging results of this review, routine prophylaxis in ambulatory cancer patients cannot be recommended before safety issues are adequately addressed.

PLAIN LANGUAGE SUMMARY

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

Cancer patients are more likely than patients without cancer to develop blood clots in their veins (venous thromboembolism or VTE). Chemotherapy further increases this risk. Yet bleeding at the site of the cancer and a relative decrease in the number of platelets in the blood (thrombocytopenia) that is caused by chemotherapy may make cancer patients more likely to have bleeding complications with medicines used to prevent and treat blood clots (anticoagulants). This systematic review looked at the effectiveness and safety of anticoagulants when used to prevent blood clots in cancer patients receiving chemotherapy. Twenty-one randomised controlled studies (9861 patients) were included. Low molecular weight heparin and the ultra-low molecular weight semuloparin were associated with a significant reduction in symptomatic blood clots without increasing the risk of major bleeding overall. There was no clear survival benefit for semuloparin or low molecular weight heparin. In patients with multiple myeloma, low molecular weight heparin significantly reduced the incidence of blood clots when compared with the vitamin K antagonist warfarin, while the difference with aspirin was not significant. There were no major bleeds with low molecular weight heparin or warfarin, and in patients treated with aspirin the rate was below 1%. Unfractionated heparin was evaluated in one study, which reported a similar low percentage (1%) of bleeding with both heparin and an inactive control. There was no mention of blood clots in the two study groups. Data for warfarin in comparison with placebo were too limited to support the use of warfarin in the prevention of blood clots in cancer patients. Antithrombin was evaluated in one study in children and had no significant effect on blood clots or major bleeding when compared with an inactive control. A small pilot study evaluated the new oral anticoagulant apixaban and found a low rate of bleeding and blood clots in comparison with placebo.

The quality of the studies that were reviewed ranged from low to high, such that future studies may change our confidence in the estimates and the size of the estimates.The small number of studies and patients and the low number of clinical events prevented the review authors from determining the potential influence of age and type or stage of cancer on treatment effects and providing more definitive conclusions about the risk of bleeding in association with anticoagulants. None of the studies tested intermittent pneumatic compression or graduated elastic stockings for the prevention of VTE.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Low molecular weight heparin (LMWH) compared with placebo or no LMWH for primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy

Patient or population: ambulatory cancer patients receiving chemotherapy
Settings: outpatient clinics
Intervention: LMWH
Comparison: placebo or no LMWH

Outcomes	Illustrative comparative risk (95% CI)*		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Placebo or no anticoagulant	LMWH				
Symptomatic VTE	52 per 1000	28 per 1000 (20 to 39)	RR 0.53 [0.38, 0.75]	3246 (8)	⊕⊕⊕ moderate[2]	
Major bleeding	14 per 1000	18 per 1000 (11 to 31)	RR 1.30 [0.75, 2.23]	3984 (9)	⊕⊕ low[3]	
Symptomatic PE	12 per 1000	7 per 1000 (3 to 16)	RR 0.59 [0.26, 1.36]	2712 (5)	⊕⊕ low[4]	
1-year mortality	586 per 1000	557 per 1000 (492 to 639)	RR 0.95 [0.84, 1.09]	2268 (7)	⊕⊕⊕⊕ high	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio.
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The assumed risk is calculated from the median control group risk across the studies.
[2] Downgraded (1 level) because 4 out of 8 trials were not double-blinded trials and for indirectness, as 2 out of 8 trials used dosages exceeding typical prophylactic dosages.
[3] Downgraded (2 levels) because the 95% CI includes both negligible effect and appreciable benefit or appreciable harm; 3 out of 9 trials were not double-blinded, and 2 out of 9 trials did not use standard definitions to ascertain major bleeding.
[4] Downgraded (2 levels) because the 95% CI includes both negligible effect and appreciable benefit or appreciable harm; risk of selective outcome reporting, with only 5 out of 10 trials reporting symptomatic PE.

BACKGROUND

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

Description of the condition

The incidence of VTE is higher in patients with cancer compared with those without cancer. Compared with an incidence of about 0.1% in the general population, the rate of VTE in patients with cancer has been reported to vary between 0.6% and about 8% (Khorana 2009). Chemotherapy has been recognised as an independent predictor for symptomatic VTE with reported rates of from 11% (Otten 2004) up to 75% (Khorana 2009) depending on the type of chemotherapeutic agent used. The risk of thrombosis in cancer patients receiving chemotherapy seems to vary based on the stage of the disease, ranging from 3% to 5% in patients with early-stage cancer to 30% in those with metastatic or advanced malignancy (Khorana 2009). The benefit-risk ratio of primary prophylaxis in ambulatory patients with cancer who are receiving chemotherapy is not well established and current guidelines do not recommend routine thromboprophylaxis in such patients (Lyman 2013).

Description of the intervention

Currently available drugs for the prevention of VTE are vitamin K antagonists (VKAs), unfractionated heparin (UFH), low molecular weight heparins (LMWH) and fondaparinux. In fact, each one of these agents presents disadvantages for long-term prophylaxis in the ambulatory patient with cancer. Heparins and fondaparinux, as well as the new ultra-LMWH (uLMWH) semuloparin, require daily subcutaneous injections, which represent a considerable burden for the patient. Of note is that marketing applications for the uLMWH semuloparin have been withdrawn worldwide and it is therefore unlikely to ever be commercially available (EMEA 2012). VKAs require frequent monitoring for dose adjustments and can be difficult to administer because of nausea and vomiting, poor nutrition and interaction with other medications. New oral anticoagulants such as direct thrombin and factor Xa inhibitors offer the potential advantages of an oral route of administration, absence of laboratory monitoring requirements and fewer pharmacological interactions. In general, the use of anticoagulants in cancer patients is more challenging than in patients without cancer, aggravated by a higher rate of recurrent thrombotic events and bleeding complications (Hutten 2000; Prandoni 2002). In the study by Prandoni and colleagues the 12-month cumulative incidence of recurrent VTE and major bleeding was 20.7% and 12.4%, respectively, in patients with cancer compared with 6.8% and 4.9%, respectively, in patients without cancer (Prandoni 2002). Interestingly, recurrent VTE and bleeding events were related to cancer severity and apparently were not explained by under- or over-anticoagulation. Possible mechanisms underlying these associations include the procoagulant state induced by cancer itself, treatments for cancer (for example chemotherapy), as well as the decline in the patient's general condition leading to immobilisation. Bleeding at the site of the cancer and the relative decrease in the number of platelets in the blood (thrombocytopenia) secondary to chemotherapy may at least partly explain the increase in bleeding events. Currently available mechanical interventions for the prevention of VTE include intermittent pneumatic compression and graduated elastic stockings. These non-pharmacological interventions may be a valid option in cancer patients who are at risk of bleeding, however evidence supporting their benefit and to assure no harm is limited.

Why it is important to do this review

The overall burden of VTE in patients with cancer is steadily increasing as a result of an aging population, greater awareness, frequent staging assessments using sensitive imaging techniques, prothrombotic anticancer treatments, as well as the growing cancer population that is due to the aforementioned aging. Provision of widespread primary thromboprophylaxis for ambulatory cancer patients who receive chemotherapy may help in preventing this complication. However, the efficacy of thromboprophylaxis needs to be balanced against the risks, such as (major) bleeding events. We are not aware of any systematic review summarising the evidence on the benefits and risks of primary prophylaxis in this setting.

OBJECTIVES

Our main objective was to assess the efficacy and safety of primary thromboprophylaxis for VTE in ambulatory patients with cancer receiving chemotherapy compared with placebo or no thromboprophylaxis. The secondary objective was to compare the efficacy and safety of different types of primary thromboprophylaxis by stratifying the main results per type of drug or mechanical intervention, and by aggregating results from head-to-head comparisons.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised trials were eligible.

Types of participants

Ambulatory outpatients of any age (including paediatric patients) with either a solid or haematological cancer, at any stage, and receiving chemotherapy were eligible. Studies of patients receiving anticoagulation for a previous VTE or an indication other than VTE were excluded if data could not be extracted separately for patients not on anticoagulants. Studies evaluating prophylaxis for catheter-related thrombosis were excluded since this is already the subject of another Cochrane review (Akl 2011).

Types of interventions

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

Types of outcome measures

Primary outcomes

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

Secondary outcomes

Secondary outcomes included symptomatic PE; symptomatic DVT; asymptomatic VTE; overall VTE; minor bleeding; one-year overall mortality; arterial thromboembolic events; superficial venous thrombosis; quality of life; number of patients experiencing any adverse event and patients experiencing any serious adverse event. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding. Serious adverse events were defined as events resulting in patient hospitalisation, prolongation of hospitalisation, persistent or significant disability, congenital abnormality or birth defect of offspring, life-threatening events or death. For trials using LMWH as the intervention or control, heparin-induced thrombocytopenia (HIT) and the incidence of osteoporosis, as defined by the trial authors, were recorded. We considered all outcomes as binary outcomes except for quality of life, which was considered as a continuous outcome.

Search methods for identification of studies

Electronic searches

For this update, the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched May 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 5), part of *The Cochrane Library* (www.thecochranelibrary.com). See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used, are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

The TSC searched the following clinical trials registries (last searched June 2013) by combining the search terms cancer and thrombo*:

- World Health Organization (WHO) International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/);
- Current Controlled Trials (www.controlled-trials.com).

Searching other resources

The review authors searched the reference lists of identified studies and contacted content experts and trialists for relevant references. One review author screened the conference proceedings of the American Society of Clinical Oncology (from 2009 to 2011) and the International Society of Thrombosis and Haemostasis (from 2003 to March 2012), combining the search terms of venous thrombosis, vein thrombosis, or pulmonary embolism with cancer or tumour. Studies were included if adequate information could be obtained either from the abstract or from personal communication.

Data collection and analysis

Selection of studies

Two review authors independently reviewed the titles and abstracts identified from the database searches to determine whether the inclusion criteria were satisfied. Any disagreement was resolved through discussion between the review authors. The review authors were not blinded to the journal, institution or results of the study. No language restrictions were applied. Studies with insufficient information were reassessed if additional information became available from the trial authors. Reasons for excluding studies were documented. In the event of multiple reports relating to the same trial, we considered them all.

Data extraction and management

Two review authors independently extracted the data from the included studies on standardised forms, and any disagreements were resolved by consensus. Collected information included methodological quality, characteristics of the patients participating in the studies, characteristics of the intervention and control groups, and outcome characteristics of every group of patients. Whenever possible, we extracted the results from an intention-to-treat analysis. If effect sizes could not be calculated, we contacted the trial authors for additional data.

Assessment of risk of bias in included studies

Two review authors independently assessed randomisation, blinding and adequacy of analyses (Juni 2001; Rutjes 2009). Disagreements were resolved by consensus.

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

Concealment of allocation was considered adequate if patients and the investigators responsible for patient selection were unable to predict before allocation which treatment was next. Methods considered adequate included central randomisation; pharmacy-controlled randomisation using identical pre-numbered containers; and sequentially numbered, sealed, opaque envelopes. Blinding of patients and therapists was considered adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used. Assessors were considered blinded if this was explicitly mentioned by the investigators.

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

Measures of treatment effect

Results are shown as summary risk ratios (RRs) for dichotomous variables; a 95% confidence interval (CI) was determined for each estimate. We used inverse-variance random-effects model meta-analysis to combine the trials (DerSimonian 1986). In the case of statistically significant overall estimates, we also calculated clinical effect summary statistics such as the number needed to treat to benefit one patient (NNT) or the number needed to treat to harm one patient (NNH) to express the final results of the review.

Assessment of heterogeneity

Heterogeneity of the treatment effect between trials was measured using the variance estimate Tau^2 as currently recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A Tau^2 of 0.04 is typically interpreted to indicate low heterogeneity, 0.09 to indicate moderate, and 0.16 to indicate high heterogeneity across trials (Rutjes 2012; Spiegelhalter 2004).

Assessment of reporting biases

We evaluated publication bias and other biases related to small study size using funnel plots, plotting the RRs on the vertical

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

Data synthesis

In the main analyses, data were analysed and presented by stratifying for the type of thromboprophylaxis used. We planned to explore the between trial heterogeneity by stratifying the main outcomes for the following trial characteristics: age (below or equal to 65 years versus above 65 years); type of cancer, stage of cancer (metastatic versus non-metastatic); type of major bleeding (according to definition versus unclear or different definition); concealment of allocation (adequate versus inadequate or unclear); blinding (adequate versus inadequate or unclear); analysis in accordance with the intention-to-treat principle (yes versus no or unclear); trial size; and differences in the use of co-interventions in the trial groups. We planned to use univariate random-effects model meta-regression (Thompson 1999) to determine whether treatment effects were affected by these factors and by three continuous variables at trial level: dosage of intervention, treatment duration, and length of follow up. The data analysis was performed in RevMan 5 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Stratified analyses and funnel plot exploration were done in STATA release 12.1 (StataCorp, College Station, Texas).

RESULTS

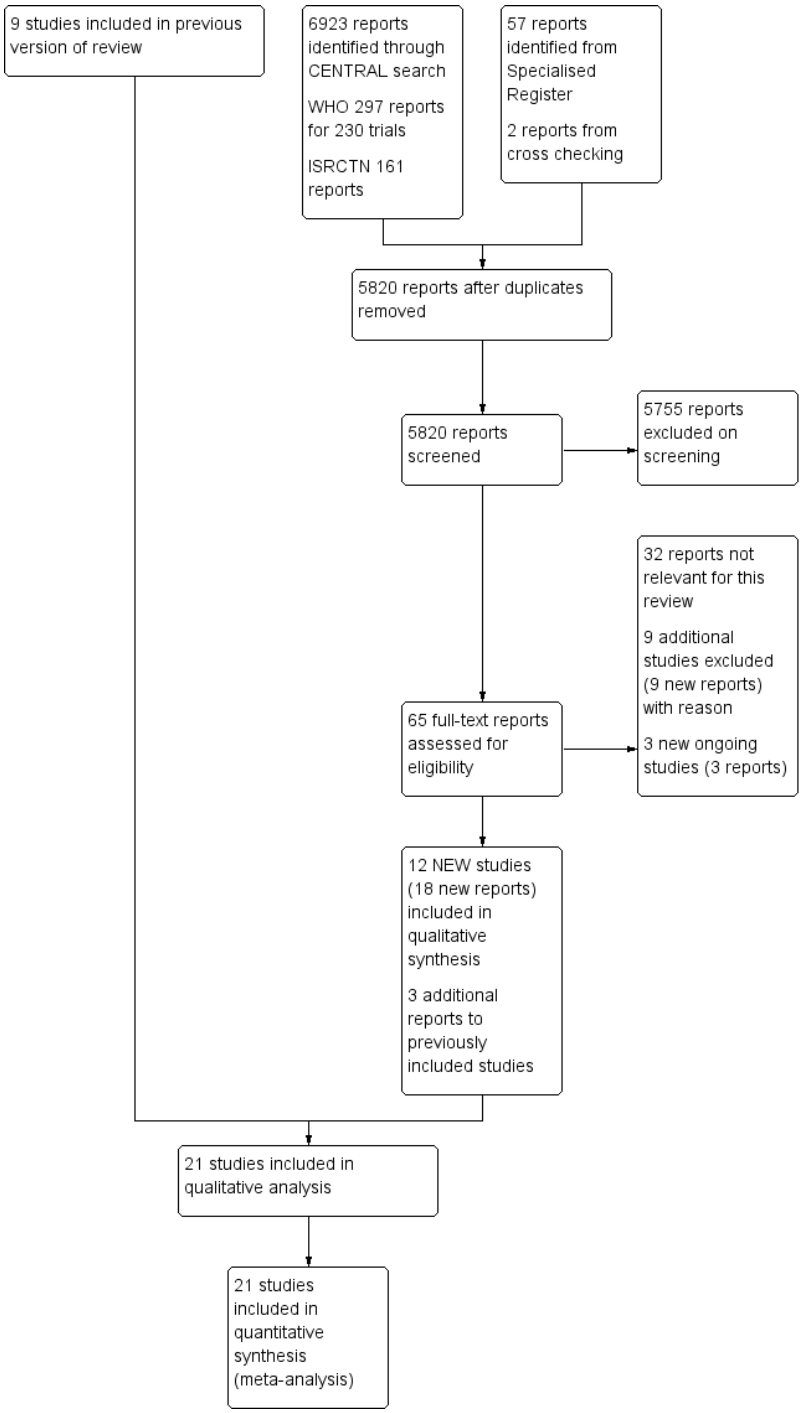
Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Following title and abstract screening, 65 reports were considered to be potentially eligible for the update.

Included studies

Following full text analysis we identified an additional 12 studies (Agnelli 2012; Chahinian 1989; Klerk 2005; Larocca 2012; Lebeau 1994; Levine 2012; Maraveyas 2012; Maurer 1997; Pelzer 2009; van Doormaal 2011; Zacharski 1981; Zwicker 2013) which met our selection criteria. One of these had been excluded (Klerk 2005) and four had been ongoing (Agnelli 2012; Levine 2012; Maraveyas 2012; Pelzer 2009) in the previous version of the review. This made a total of 21 included studies in the review.

The 21 completed randomised controlled trials (RCTs) randomised a total of 9861 patients. The treatment that was evaluated consisted of: uLMWH semuloparin (Agnelli 2012), LMWH (Agnelli 2009; Altinbas 2004; Haas 2012; Kakkar 2004; Klerk 2005; Larocca 2012; Maraveyas 2012; Palumbo 2011; Pelzer 2009; Perry 2010; Sideras 2006; van Doormaal 2011; Zwicker 2013), UFH (Lebeau 1994), the VKA warfarin (Chahinian 1989; Levine 1994; Maurer 1997; Palumbo 2011; Zacharski 1981), antithrombin (Mitchell 2003), and the new oral direct factor Xa inhibitor apixaban (Levine 2012). None of the included RCTs used non-pharmacological prophylaxis as the intervention. In 14 (7969 patients, 81%) of the 21 studies inclusion was restricted to patients with locally advanced or metastatic cancer, in one study limited cancer was included, in two studies both early and advanced disease, while in the remaining four studies the stage was not clear (see Characteristics of included studies).

One study assessed the uLMWH semuloparin versus placebo.

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

Thirteen studies assessed LMWH and 11 of them used an inactive control or placebo for comparison. These 11 trials varied in the duration and type of LMWH, including eight weeks to 48 months of subcutaneous (sc) dalteparin, enoxaparin, certoparin or nadroparin. The dose of LMWH was prophylactic in the majority of the studies and intermediate (Pelzer 2009) or therapeutic (Maraveyas 2012) in one study each. In two studies initial therapeutic LMWH was followed by intermediate doses (Klerk 2005; van Doormaal 2011). Ten of these 11 studies reported a mean age at study entry of 65 years or lower, whereas Pelzer 2009 did not describe the group ages.

- Agnelli 2009 recruited patients (n = 1150) with metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian or head and neck cancer and randomised them to nadroparin (3800 IU anti-Xa sc, od) versus placebo. Study treatment started on the same day as chemotherapy and was given for the duration of the chemotherapy or up to a maximum of 120 days (± 10 days).

- Altinbas 2004 recruited patients (n = 84) with histologically confirmed small cell lung carcinoma and randomised them to standard anticancer treatment with or without dalteparin (5000 IU sc, od). Dalteparin was stopped with disease progression or at the end of the 18 weeks of chemotherapy.

- Haas 2012 recruited patients with metastatic breast cancer (n = 353) or non-small cell lung carcinoma (n = 547) and receiving first- or second-line chemotherapy. They were randomised to six months of certoparin (3000 IU sc, od) versus placebo.

- Kakkar 2004 recruited patients (n = 385) with histologically confirmed locally advanced or metastatic malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary or uterus and randomised them to dalteparin (5000 IU sc, od) versus placebo. Study treatment was given for one year or until the patient died, whichever occurred sooner.

- Klerk 2005 recruited patients (n = 302) with metastasised or locally advanced solid tumours and randomised them to nadroparin versus placebo. Study treatment was given using prefilled syringes containing a fixed volume of nadroparin (antifactor Xa 9500 U/mL) or placebo according to the patient's weight: 0.4 mL for those weighing less than 50 kg, 0.6 mL for those weighing between 50 and 70 kg, and 0.8 mL for those weighing more than 70 kg. Study treatment was to be administered sc twice daily (bid) during the initial 14 days of treatment and od thereafter for another four weeks.

- Maraveyas 2012 recruited patients (n = 123) with advanced pancreatic cancer and randomised them to dalteparin (200 IU/kg sc, od for four weeks followed by 150 IU/kg for a further eight weeks) in combination with gemcitabine versus gemcitabine alone. After 12 weeks, continuing dalteparin prophylaxis was not recommended, but was left to the discretion of the investigator.

- Pelzer 2009 recruited patients (n = 312) with histologically or cytologically confirmed advanced pancreatic cancer. Patients were randomised to standard anticancer treatment with or without enoxaparin (1 mg/kg od) for three months, started simultaneously with palliative systemic chemotherapy; after 12 weeks of initial chemotherapy all patients who had not progressed received the standard therapy with or without enoxaparin (40 mg od) for an additional three months.

- Perry 2010 recruited patients (n = 186) with newly diagnosed, pathologically confirmed WHO grade 3 or grade 4 glioma and randomised them to six months of dalteparin (5000 IU sc, od) versus placebo starting within the first month after surgery. Patients were allowed to continue the study medication for 12 months.

- Sideras 2006 recruited patients (n = 138) with advanced breast cancer who did not respond to first-line chemotherapy, advanced prostate cancer resistant to primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer. In the first part of the study patients were randomised to dalteparin (5000 IU sc, od) versus placebo while in the second part patients were randomised to dalteparin (5000 IU sc, od) plus standard clinical care versus standard clinical care alone. Dalteparin (or placebo) was given for 18 weeks or until disease progression.

- van Doormaal 2011 recruited patients (n = 503) with non-small cell lung cancer (stage IIIB), hormone-refractory prostate cancer, or locally advanced pancreatic cancer and randomised them to standard anticancer treatment with or without nadroparin. Subcutaneous nadroparin was administered for six weeks (two weeks at therapeutic dose and four weeks at half therapeutic dose). The patients were eligible to receive additional cycles of nadroparin (two weeks at therapeutic dose and four weeks washout period) for a maximum of six cycles.

- Zwicker 2013 recruited patients (n = 34) with histologically confirmed advanced stage malignancy which included adenocarcinoma of the pancreas (locally advanced or metastatic), colorectal (stage IV), non-small cell lung cancer (stage III or IV), relapsed or stage IV ovarian, or surgically unresectable or metastatic gastric adenocarcinoma. Patients were randomised to enoxaparin (40 mg sc, od) for two months or observation.

In the other two studies LMWH was compared against an active control.

- Larocca 2012 recruited patients (n = 342) with newly diagnosed multiple myeloma treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone-lenalidomide consolidation. Patients were randomised to aspirin (100 mg/d) or LMWH (enoxaparin 40 mg/d). Prophylaxis was provided during the four (28-day) cycles of induction and the six (28-day) cycles of consolidation therapy.

- Palumbo 2011 recruited patients (n = 667) with previously untreated myeloma who received thalidomide-containing regimens and randomised them to aspirin (100 mg/d), low-dose warfarin (1.25 mg/d) or LMWH (enoxaparin 40 mg/d). The prophylaxis was administered during the three cycles of induction therapy in patients ≤ 65 years and during the first six cycles of induction therapy in patients > 65 years.

VKA warfarin was compared against an inactive control in four studies.

- Chahinian 1989 recruited patients (n = 328) with extensive carcinoma of the lung and randomised them to warfarin (dose to maintain a prothrombin 1.5 to twice the control values) versus no warfarin. Warfarin was continued throughout the course of chemotherapy.

- Levine 1994 recruited patients (n = 311) with metastatic stage IV breast carcinoma who had been receiving first-line or second-line chemotherapy for four weeks or less and randomised them to warfarin (target of International Normalised Ratio (INR) 1.3 to 1.9) versus placebo. Study treatment began either at the start of chemotherapy or within the next four weeks and continued until one week after termination of chemotherapy.

- Maurer 1997 recruited patients (n = 347) with limited-stage small cell lung cancer who were to receive chemotherapy and radiotherapy and randomised them to warfarin or no warfarin. Warfarin (dose of 10 mg/day for the first three days and then at a dose to maintain the prothrombin time between 1.4 and 1.6 times the local institutional control standards) was continued through the complete course of chemotherapy and radiation therapy and was stopped three weeks after the last cycle of chemotherapy.

- Zacharski 1981 recruited patients (n = 50) with small cell lung cancer and randomised them to warfarin (dose to prolong the prothrombin time to approximately two times the control value) versus no warfarin.

UFH, antithrombin and the factor Xa inhibitor apixaban were evaluated against inactive control or placebo in one study each.

- Lebeau 1994 recruited patients (n = 277) with limited and extensive small cell lung cancer who had not been previously treated with chemotherapy or radiotherapy. The dose of UFH was initially adapted to weight (500 IU/kg/d) then adjusted by clotting times (to between two and three times the control value). UFH was administered in two or three daily injections for five weeks and stopped one week after the second course of chemotherapy.

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

- Mitchell 2003 recruited paediatric patients (n = 85) newly diagnosed with acute lymphoblastic leukaemia and randomised them to receive, or not, weekly infusions of antithrombin.

Excluded studies

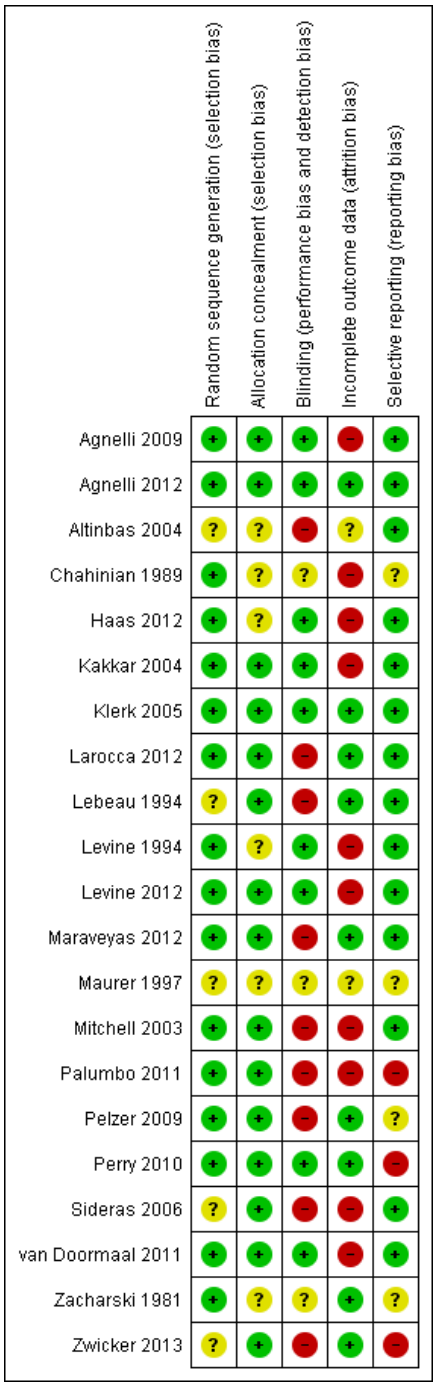
Nine additional studies were excluded in this update (ABEL study 2005; Baz 2005; Haas 2011; Kessler 2011; Levin 2008; Niesvizky 2007; Pandya 2002; Weber 2008; Zangari 2003) making a total of 23 excluded studies. The reasons for exclusion were: other design than a RCT (Baz 2005; Kessler 2011; Meister 2008; Minnema 2004; Paydas 2008; Zangari 2003); studies on perioperative thromboprophylaxis (Bergqvist 1983; Heilmann 1995; Hills 1972; Macintyre 1974; Maxwell 2000; Sideras 2007; Welti 1981); inclusion of hospitalised cancer patients (Eichinger 2008; Haas 2011; Poniewierski 1987; Weber 2008); no relevant outcomes reported (Rajan 1995); no eligible intervention (Niesvizky 2007); prophylaxis was for catheter-related thrombosis (Kwaan 2007). Three studies were terminated early: ABEL study 2005 because of difficulties with recruitment; Levin 2008 because of a drug supply issue; and Pandya 2002, with no reason for study termination reported.

There were three studies added to ongoing studies (NCT00239980; NCT00662688; NCT00718354) making a total of seven (NCT00239980; NCT00320255; NCT00519805; NCT00662688; NCT00718354; NCT00876915; NCT00966277).

Risk of bias in included studies

The risks of bias in the included studies are shown in Figure 2.

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



Allocation

The random sequence was adequately generated in 16 studies (Agnelli 2009; Agnelli 2012; Chahinian 1989; Haas 2012; Kakkar 2004; Klerk 2005; Larocca 2012; Levine 1994; Levine 2012; Maraveyas 2012; Mitchell 2003; Palumbo 2011; Pelzer 2009; Perry 2010; van Doormaal 2011; Zacharski 1981) but was unclear in the remainder due to poor reporting.

Allocation was adequately concealed in 15 studies included in the meta-analysis (Agnelli 2009; Agnelli 2012; Kakkar 2004; Klerk 2005; Larocca 2012; Lebeau 1994; Levine 2012; Maraveyas 2012; Mitchell 2003; Palumbo 2011; Pelzer 2009; Perry 2010; Sideras 2006; van Doormaal 2011; Zwicker 2013) and was unclear in the remainder due to poor reporting.

Blinding

Nine studies had a double-blinded design (Agnelli 2009; Agnelli 2012; Haas 2012; Kakkar 2004; Klerk 2005; Levine 1994; Levine 2012; Perry 2010; van Doormaal 2011) and eight were open studies (Altinbas 2004; Larocca 2012; Lebeau 1994; Maraveyas 2012; Maurer 1997; Mitchell 2003; Palumbo 2011; Pelzer 2009; Sideras 2006; Zwicker 2013). In three studies (Chahinian 1989; Maurer 1997; Zacharski 1981) blinding was unclear due to poor reporting.

Incomplete outcome data

Nine studies performed the analysis according to the intention-to-treat principle (Agnelli 2012; Klerk 2005; Larocca 2012; Lebeau 1994; Maraveyas 2012; Pelzer 2009; Perry 2010; Zacharski 1981; Zwicker 2013) while in 10 studies the percentages of patients randomised and subsequently excluded from the analyses ranged from 1.3% to 10% (Agnelli 2009; Chahinian 1989; Haas 2012; Kakkar 2004; Levine 1994; Levine 2012; Mitchell 2003; Palumbo 2011; Sideras 2006; van Doormaal 2011); these were considered to be at high risk of bias. The study involving paediatric patients used a per protocol analysis and excluded 22% of the patients that were initially enrolled (Mitchell 2003); it was considered to be at high risk of bias. Attrition bias was unclear in Altinbas 2004 and Maurer 1997.

Selective reporting

Fourteen studies were judged to be free of selective reporting (Agnelli 2009; Agnelli 2012; Altinbas 2004; Haas 2012; Kakkar 2004; Klerk 2005; Larocca 2012; Lebeau 1994; Levine 1994; Levine 2012; Maraveyas 2012; Mitchell 2003; Sideras 2006; van Doormaal 2011). For three studies (Chahinian 1989; Maurer 1997; Zacharski 1981) one or more outcomes were reported in the results but were not anticipated in the methods sections of the publications. In four studies (Palumbo 2011; Pelzer 2009; Perry 2010; Zwicker 2013) not all outcomes were reported in the results.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table

See Summary of findings for the main comparison.

Anticoagulants versus control

uLMWH versus placebo

Primary outcomes

In one large trial of 3212 patients (Agnelli 2012), semuloparin was associated with a significant reduction in symptomatic VTE (RR 0.36, 95% CI 0.22 to 0.60), corresponding to a NNT of 46 (95% CI 31 to 87). There were 19/1589 major bleeding events in the semuloparin group versus 18/1583 in the placebo group (RR 1.05, 95% CI 0.55 to 2.00).

In patients with lung and pancreatic cancers, semuloparin reduced symptomatic VTE by 64% (9/591 versus 25/589, RR 0.36, 95% CI 0.17 to 0.76) and by 78% (3/126 versus 14/128, RR 0.22, 95% CI 0.06 to 0.74), respectively. Rates of major bleeding were not reported separately for these types of cancer.

Secondary outcomes

The risk of symptomatic PE was reduced by 52% (RR 0.48, 95% CI 0.22 to 1.01), and symptomatic DVT (RR 0.32, 95% CI 0.13 to 0.63) and overall VTE (RR 0.36, 95% CI 0.22 to 0.60) were reduced by about two thirds with semuloparin. Semuloparin did not influence one-year survival (RR 1.02, 95% CI 0.96 to 1.08). The incidence of serious adverse events or thrombocytopenia was similar in the semuloparin and placebo groups (26% versus 25%, 7.1% versus 7.6%, respectively), with no cases of HIT.

LMWH versus inactive control

Primary outcomes

The clinical trials evaluating LMWH against an inactive control varied in the duration and type of LMWH, including eight weeks

to 48 months of subcutaneous dalteparin, enoxaparin, certoparin or nadroparin. The dose of LMWH was prophylactic in the majority of the studies, and intermediate (Pelzer 2009) or therapeutic (Maraveyas 2012) in one study each. In two studies initial therapeutic LMWH was followed by intermediate doses (Klerk 2005; van Doormaal 2011). Based on pooled estimates from eight RCTs LMWH, when compared with inactive control, was associated with a significant reduction in symptomatic VTE (RR 0.53, 95% CI 0.38 to 0.75) (Figure 3) in the absence of heterogeneity (Tau^2 = 0). This corresponded to a NNT of 41 (95% CI 31 to 77) assuming a background risk of 52 symptomatic VTE events per 1000 patients (Summary of findings for the main comparison). Funnel plot exploration did not show any evidence of biases associated with small studies (Figure 4). Stratified analyses did not show any effect of the type of LMWH, type of cancer, dosage, or design characteristics on the relative risk of symptomatic VTE (Table 1). Similarly, we found no evidence for a linear association between treatment duration and the risk of symptomatic VTE using meta-regression analysis (P = 0.530).

Figure 3. Forest plot of comparison: 1 Anticoagulants versus control: symptomatic VTE, outcome: 1.2 Symptomatic VTE: LMWH versus inactive control.

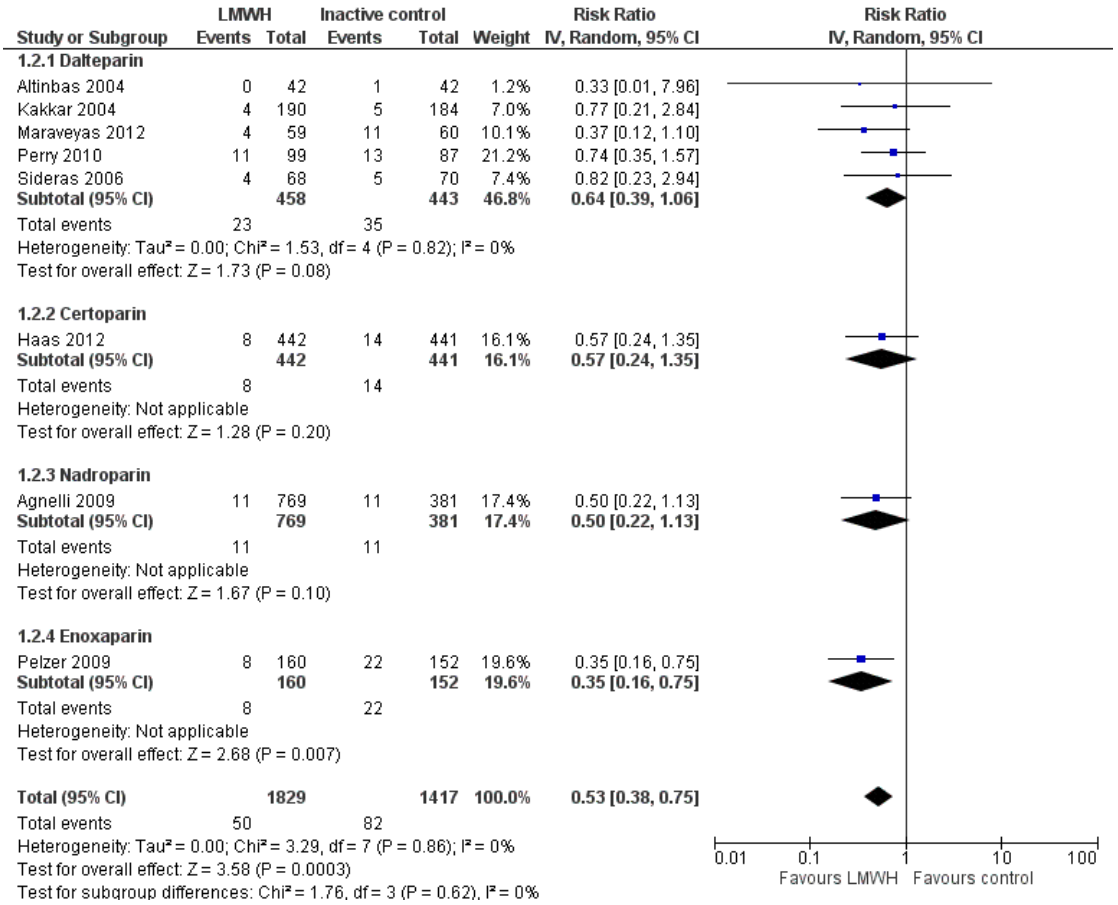
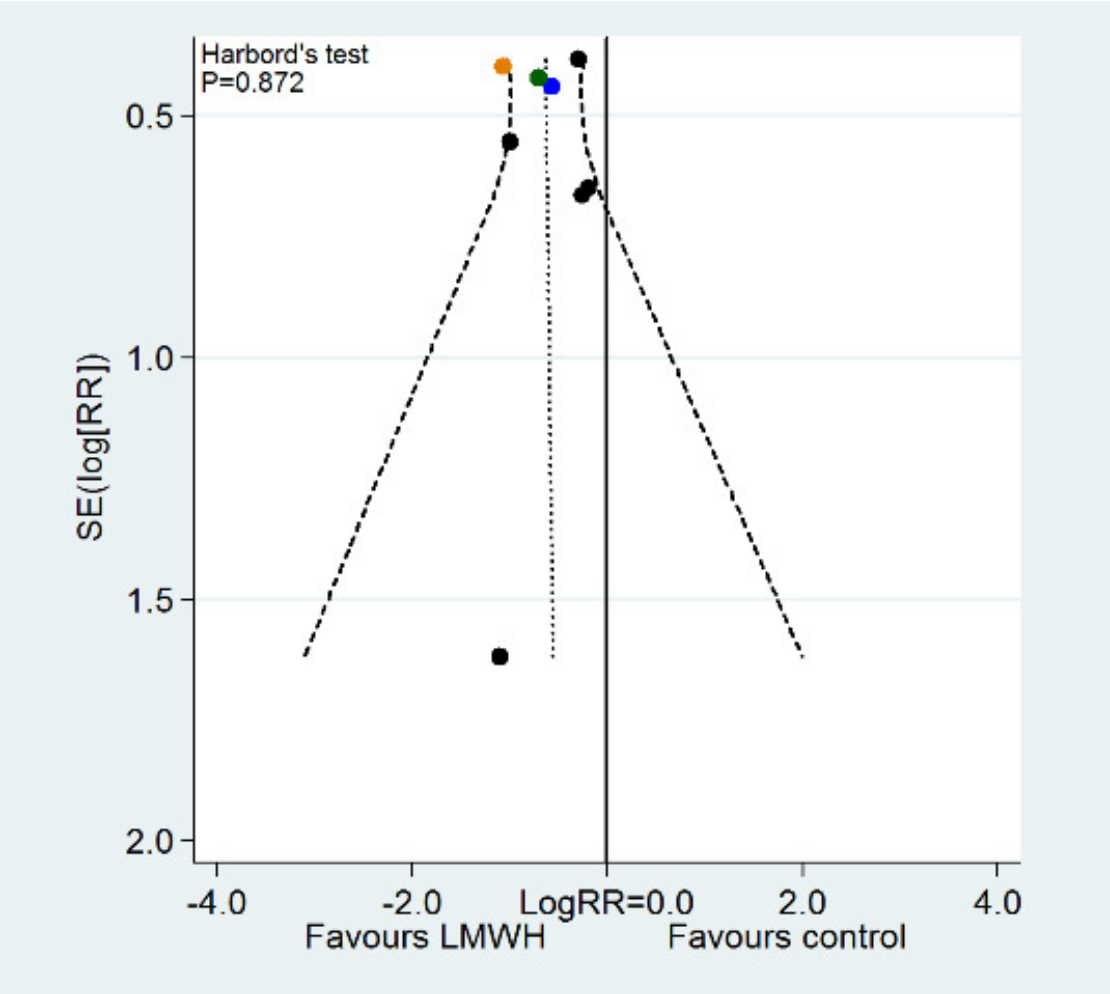


Figure 4. Funnel plot of comparison: 1 Anticoagulants versus control: symptomatic VTE, outcome: 1.2 Symptomatic VTE: LMWH versus inactive control.



The difference in major bleeding was not statistically significant (RR 1.30, 95% CI 0.75 to 2.23) (Figure 5), with large CIs around the estimate and evidence of a moderate to high degree of heterogeneity (Tau^2 = 0.15). Although a slight funnel plot asymmetry was seen visually (Figure 6), asymmetry was not confirmed by the Harbord-Egger's test (P = 0.165). Table 2 presents the results of the stratified analyses. Studies reporting major bleeding according to standard definitions found higher risks (RR 1.87, 95% CI 1.08 to 3.25) than those applying deviant definitions (RR 0.58, 95% CI 0.29 to 1.17; P = 0.036). Similarly, studies using double-blinding reported higher risk estimates than those without (P = 0.036). We found little evidence for an association of the RR with type of cancer, dosage, concealment of allocation, or analysis according to intention to treat. Again, we found little evidence for a linear association between treatment duration and the risk of major bleeding using meta-regression analysis (P = 0.897).

Figure 5. Forest plot of comparison: 2 Anticoagulants versus control: major bleeding, outcome: 2.2 Major bleeding: LMWH versus inactive control.

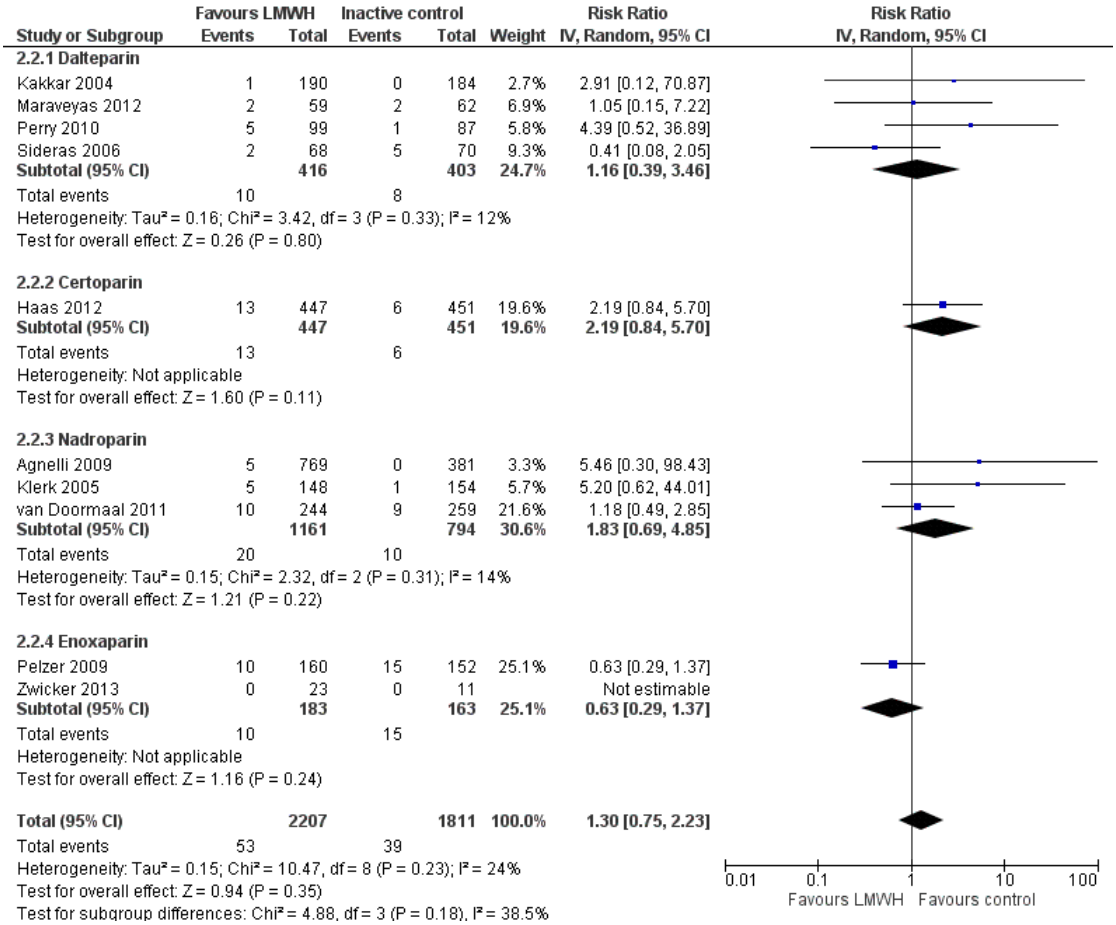
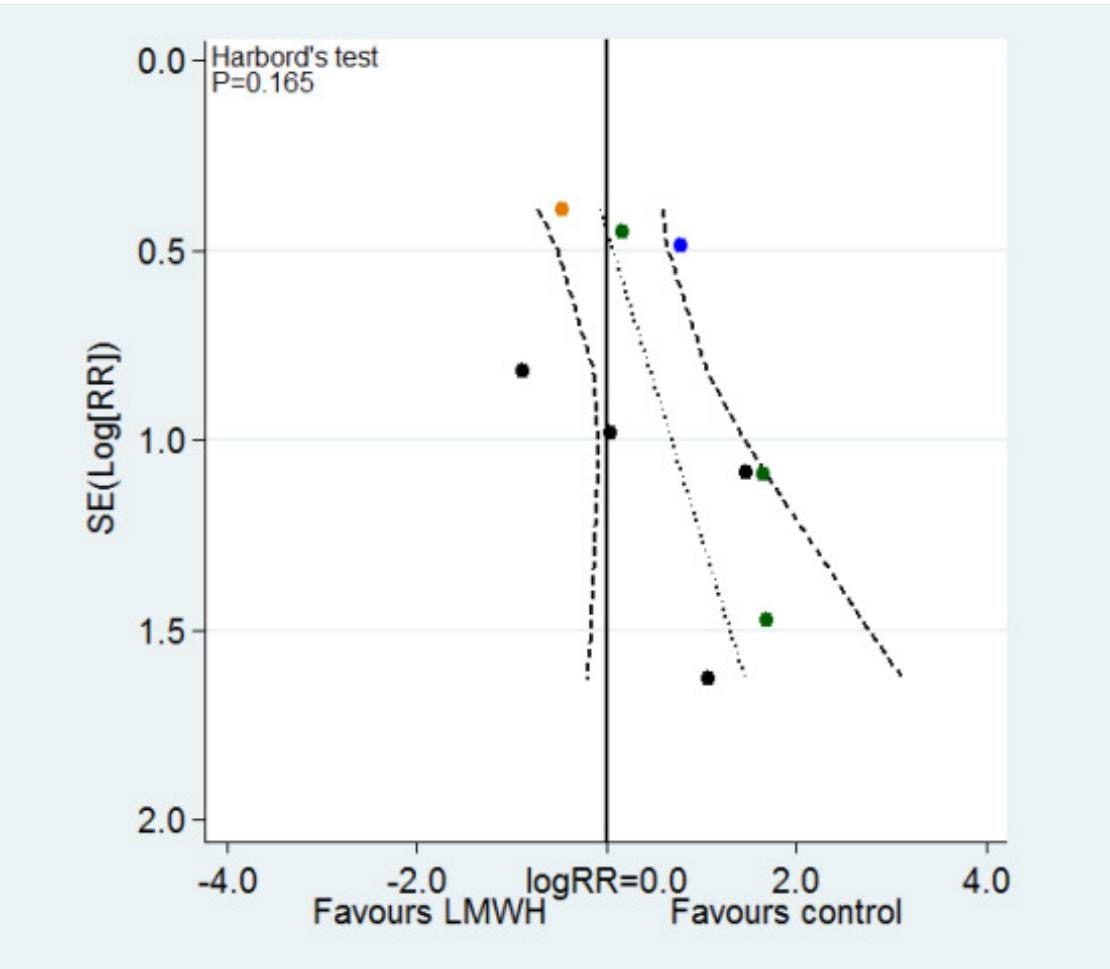


Figure 6. Funnel plot of comparison: 2 Anticoagulants versus control: major bleeding, outcome: 2.2 Major bleeding: LMWH versus inactive control.



Secondary outcomes

There was no significant effect on symptomatic PE (RR 0.59, 95% CI 0.26 to 1.36; Tau^2 = 0). The risk of symptomatic DVT was reduced by 48% (RR 0.52, 95% CI 0.33 to 0.82; Tau^2 = 0) and of overall VTE by 36% (RR 0.64, 95% CI 0.45 to 0.91; Tau^2 = 0.02); whereas there was no statistically significant benefit or harm for asymptomatic VTE, minor bleeding, one-year mortality, superficial venous thrombosis or serious adverse events (Data and analyses). LMWH was associated with a 60% lower incidence of symptomatic arterial thromboembolism (RR 0.40, 95% CI 0.16 to 0.99) in the absence of heterogeneity (Tau^2 = 0). Quality of life was evaluated through questionnaires in only one study and was found to be similar in patients randomised to LMWH and the inactive treatment controls, both at baseline and during the study period (Sideras 2006). Fifty-four per cent and 51% of the patients, respectively, reported decreases in quality of life during the treatment period by a clinically meaningful amount of 10 points on the 100-point scale. Two studies reported no cases of HIT with LMWH use (Haas 2012; Klerk 2005) and Haas 2012 reported objectively verified skeletal events (including all fractures, spinal cord compressions, and requirements for surgery to treat fractures or for bone irradiation) in 16/442 and 19/441 of patients in the LMWH and placebo groups, respectively.

Three studies reported on symptomatic VTE and major bleeding in patients with non-small cell (Haas 2012) or small cell lung cancer (Altinbas 2004), or both (Agnelli 2009). Pooled analysis of these trials showed a significant 56% reduction in symptomatic VTE (RR 0.44, 95% CI 0.21 to 0.89) whereas there was no sta-

tistically significant higher risk of major bleeding with LMWH as compared with the control treatment (RR 1.70, 95% CI 0.66 to 4.38) and no evidence of statistical heterogeneity (Tau^2 = 0) (Table 1; Table 2).

Two studies reported on symptomatic VTE and major bleeding in patients with advanced pancreatic cancer (Maraveyas 2012; Pelzer 2009). Pooled analysis of these trials showed a significant 65% reduction in symptomatic VTE (RR 0.35, 95% CI 0.19 to 0.67) and no increase in major bleeding (RR 0.68, 95% CI 0.33 to 1.39) with LMWH and no evidence of statistical heterogeneity (Tau^2 = 0) (Table 1; Table 2).

LMWH versus active control

In two studies of multiple myeloma patients receiving thalidomide and lenalidomide-based regimens, LMWH was compared against an active control, represented in both studies by aspirin (Larocca 2012; Palumbo 2011) and VKA (warfarin) in one of them (Palumbo 2011). When compared with aspirin, pooled analysis showed a 49% reduction in symptomatic VTE (RR 0.51, 95% CI 0.22 to 1.17) but this finding was not statistically significant. There were 0/385 versus 3/396 major bleeds with LMWH and aspirin. The incidence of symptomatic PE was reduced by 87% (RR 0.13, 95% CI 0.02 to 1.03) but the CIs were wide and the estimate was not significant. Likewise, there were no significant differences between LMWH and aspirin regarding the incidence of symptomatic DVT, minor bleeding and symptomatic arterial thromboembolism. In the study of Palumbo 2011, LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR 0.33, 95% CI 0.14 to 0.83) with no major bleeding events reported in either group. There were no differences between LMWH and warfarin regarding the incidence of symptomatic PE or DVT, minor bleeding and symptomatic arterial thromboembolism.

UFH versus inactive control

UFH was evaluated against inactive control in one study (Lebeau 1994) that did not report on symptomatic or asymptomatic VTE. Major bleeding occurred in 1/138 versus 1/139 of patients, respectively (RR 1.01, 95% CI 0.06 to 15.94; P = 1.00). Additionally, one minor bleed was observed in the UFH group (RR 3.02, 95% CI 0.12 to 73.54). There were no cases of HIT.

VKA versus inactive control

Levine 1994 reported an 85% reduction of symptomatic VTE (RR 0.15, 95% CI 0.02 to 1.20) with warfarin relative to placebo, albeit this finding was not statistically significant. There was no significant effect on major bleeding (RR 0.52, 95% CI 0.05 to 5.71), symptomatic PE (RR 1.05, 95% CI 0.07 to 16.58), symptomatic DVT (RR 0.08, 95% CI 0.00 to 1.42) or minor bleeding (RR 2.44, 95% CI 0.64 to 9.27). No symptomatic arterial thromboembolic events were observed in either group.

Three studies reported major bleeding events within the warfarin and no-warfarin control groups (Chahinian 1989; Maurer 1997; Zacharski 1981) but provided no data on the occurrence of symptomatic or asymptomatic VTE. Pooled analysis of all studies evaluating VKA versus inactive control showed a non-statistically significant four-fold increase in major bleeding (RR 3.82; 95% CI 0.97 to 15.04) with evidence of a high degree of heterogeneity (Tau^2 = 0.71).

VKA versus active control

Palumbo 2011 reported a non-statistically significant difference between VKA (warfarin) and aspirin with regard to symptomatic VTE (RR 1.50, 95% CI 0.74 to 3.04). There were 3/220 major bleeds in the aspirin group and 0/220 in patients treated with warfarin (RR 0.14, 95% CI 0.01 to 2.75; P = 0.20). None of the RRs for the secondary outcomes symptomatic PE or DVT, minor bleeding, and symptomatic arterial thromboembolism reached statistical significance (Palumbo 2011).

We refer to the previous section for the description of the comparison of VKA with LMWH.

Antithrombin versus inactive control

Antithrombin was assessed in one study that recruited paediatric patients (Mitchell 2003). The effects of antithrombin on major bleeding (RR 0.78, 95% CI 0.03 to 18.57) and overall VTE (RR 0.84, 95% CI 0.41 to 1.73) were not statistically significant.

Factor Xa inhibitors versus placebo

In a phase-II dose-finding study, Levine 2012 observed 0/32, 0/30, 2/33, and 1/30 major bleeding events in the groups receiving apixaban 5 mg, 10 mg, 20 mg, and placebo, respectively, for an overall rate of major bleeding in the 93 apixaban patients of 2.1% versus 3.3% in the placebo group. There were three (10%) symptomatic DVTs or PEs in the placebo group while one patient (1.1%) in the 20 mg apixaban group experienced a DVT in the arm. Two patients in the 5 mg and one in the 20 mg apixaban groups (3.2%) experienced an adverse event, graded as 3 or higher, which was possibly or probably related to treatment, compared with none in the placebo group.

DISCUSSION

Summary of main results

The uLMWH semuloparin and LMWH, when used as primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy, are associated with a 64% and 47% reduction in symptomatic VTE, respectively. Data on the incidence of major bleeding for semuloparin and LMWH were inconclusive relative to inactive treatment; the confidence intervals were wide so that a clinically relevant increased risk could not be excluded. The available data did not show statistically significant effects of LMWH on symptomatic PE and of semuloparin or LMWH on one-year mortality. One study in myeloma patients receiving thalidomide or lenalidomide-based regimens showed that LMWH was associated with a 67% lower risk of symptomatic VTE compared with warfarin, but this study was underpowered to show differences on major bleeding. The lack of a placebo or non-active control group does not allow firm judgements about the efficacy and safety of LMWH or warfarin in myeloma patients who are receiving thalidomide or lenalidomide-based regimens. The reduction of symptomatic VTE with warfarin in non-myeloma patients was not statistically significant and was potentially associated with an increase in major bleeding. Apixaban was evaluated only in a dose-finding study and antithrombin in a relatively small trial involving paediatric patients. No RCT evaluated mechanical interventions.

Quality of the evidence

The methodological quality of the included studies varied from low to high (Figure 2). We found no evidence of bias related to small study size, such as publication biases. An inspection of the funnel plot and formal analysis of asymmetry did not indicate asymmetry for the primary efficacy outcome (Figure 4) and although visual inspection showed a slight asymmetry for the main safety outcome the Harbord-Egger test was not significant (Figure 6). The overall quality of the evidence was considered moderate for the outcome symptomatic VTE due to the risk of bias related to concealment of allocation and blinding. For major bleeding, the evidence was considered to be of low quality because the confidence intervals included both appreciable benefit and appreciable harm, and three out of nine trials were not conducted in a double-blind manner (Summary of findings for the main comparison).

Potential biases in the review process

Our systematic approach to searching, study selection and data extraction followed that of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). It is unlikely that we have missed relevant trials, but frequent updates of this review are warranted given that several new trials were identified since the previous version of this review that covered published trials up to May 2011 (Di Nisio 2012). Data extraction errors were minimised by the use of two independent assessors (MDN, EP). Judgements on the grade of evidence were discussed with a third assessor (AR). We acknowledge that quality assessment leaves room for different interpretations, especially where the quality of reporting is poor. Following Cochrane guidance, we inserted quotes and the arguments on which we based our judgements, allowing the reader to reach different conclusions. Our systematic approach and the consistency of the results (lack of significant heterogeneity) increase confidence in the internal validity of our findings.

One limitation in the interpretation of this review is the 'no difference' findings. The lack of difference may be related to the small number of RCTs and small number of studied patients or events, or both, as well as the absence of a true effect. In this regard, the overall low number of events may have limited the possibility of demonstrating a significant effect of, for example, LMWH on symptomatic PE. Similarly, the non-significant association between semuloparin and LMWH and major bleeding events could indeed be the result of the relatively low number of events observed. For example, in the trial by Agnelli 2012, which evaluated semuloparin, there were only a total of 37 major bleeds. Thus while the point estimate is 1.05 (seemingly reassuring) the upper value of the 95% confidence interval is 2.00, which means that there could have been at most a doubling of the major bleeding risk.

Another limitation related to the small number of RCTs or poor reporting, or both, was our inability to conduct subgroup analyses for the primary efficacy outcome. We had planned to explore the impact of the stage of cancer (metastatic versus non-metastatic); trial size; and differences in the use of co-interventions in the trial groups on the treatment effect. Subgroup analysis by type of cancer was performed for the lung and pancreatic cancers, albeit the data for the pooled analysis were derived from only three and two studies, respectively. The lack of reporting as well as the heterogeneity of the cancers treated did not allow us to assess the importance of background chemotherapy on the response to thromboprophylaxis. Finally, the lack of evidence precluded any inference on the use of mechanical prophylaxis.

Agreements and disagreements with other studies or reviews

The evidence on the use of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy was summarised by Rana 2009 and more recently by Lyman 2013. The current systematic review adds substantial evidence to the narrative description provided by Rana 2009 as our systematic search identified 14 additional studies (Agnelli 2012; Altinbas 2004; Kakkar 2004; Klerk 2005; Larocca 2012; Lebeau 1994; Levine 2012; Maraveyas 2012; Mitchell 2003; Palumbo 2011; Pelzer 2009; Sideras 2006; van Doormaal 2011; Zwicker 2013). While most of the studies evaluated LMWH, additional data were available for other anticoagulants such as the new uLMWH semuloparin, the new orally administered factor Xa inhibitor apixaban, unfractionated heparin (UFH) and antithrombin. Five of these studies evaluated

the effects of prophylactic doses of LMWH on survival as the primary outcome while reporting VTE events as secondary outcomes (Altinbas 2004; Kakkar 2004; Klerk 2005; Sideras 2006; van Doormaal 2011). Although the focus was not on VTE and some cases may have been underdiagnosed, the overall incidence of symptomatic VTE was comparable with the other studies included in the review. In the recent update of Lyman 2013, nine RCTs and three systematic reviews including the previous version of the current Cochrane review were considered (Di Nisio 2012). In addition to a more comprehensive search of the literature, another advantage of this review over the other reviews is that we provided pooled estimates with 95% confidence intervals for both efficacy and safety outcomes, allowing a better estimation of the risks and benefits of thromboprophylaxis in this setting. Lastly, the use of a larger dataset allowed us to stratify multiple outcomes by the type of treatment. Despite these differences, our conclusions are in line with those of Rana 2009 and Lyman 2013 and do not support the widespread use of primary thromboprophylaxis in ambulatory cancer patients. Although both LMWH and semuloparin appear to reduce the incidence of symptomatic VTE, we can not exclude a significant increase in major bleeding. In a previous meta-analysis of six studies comparing LMWH versus inactive control, Kuderer 2009 obtained similar estimates of effects for symptomatic VTE and major bleeding. This work was published only as an abstract with limited data on the methods and type of analysis performed, which hampers any comparison with the current meta-analysis. Other narrative reviews recently summarised the evidence on the use of thromboprophylaxis for VTE in ambulatory cancer patients (Aikens 2013; Maxwell 2012). These reviews lacked a systematic search of the literature and, as for Rana 2009 and Lyman 2013, no meta-analysis or evaluation of study quality items and assessment of risk of bias were performed.

The conclusions of our review differ to some extent from the most recent guidelines of the American College of Chest Physicians (Kahn 2012) that suggest primary thromboprophylaxis with LMWH or UFH in ambulatory patients with solid tumours who have additional risk factors (that is previous venous thrombosis, immobilisation, angiogenesis inhibitors, thalidomide and lenalidomide) for VTE and a low risk of bleeding. Specific risk factors and the combination of risk factors in risk scores may help to identify subgroups with a higher risk of VTE that may benefit substantially from prophylaxis (Ay 2010; Khorana 2008; Khorana 2009; Khorana 2009a). In a post hoc analysis of the SAVE-ONCO study, rates of VTE within the placebo arm were 5.4% in the high-risk population and down to 1.3% in the lower-risk population (George 2011). The greatest reduction in VTE with thromboprophylaxis was observed among moderate to high-risk patients with no apparent increased incidence of clinically relevant bleeding across the various levels of VTE risk. Similarly in the post hoc analysis of the PROTECHT study, rates of VTE were 11% in the high-risk group down to 3% in the lower-risk group and the stratification of cancer patients reduced the NNT from 50 in the full study population to 15 in the higher-risk group (Verso 2012). While these subgroup analyses suggest that prediction scores have the potential to identify patients with a more favourable benefit-risk profile, the results of ongoing RCTs are eagerly awaited to confirm such an association (NCT00876915). The preliminary findings from the pilot study of Zwicker 2013 suggest that microparticles may be a useful marker to stratify the risk and tailor the use of thromboprophylaxis.

AUTHORS' CONCLUSIONS

Implications for practice

When deciding whether to use primary antithrombotic prophylaxis in ambulatory cancer patients receiving chemotherapy, a clinician needs to determine the patient's baseline risk of VTE and weigh the magnitude of benefit with antithrombotic prophylaxis, especially on major clinical endpoints, against the risk of bleeding. Semuloparin and LMWH were associated with a 64% and 47% lower incidence of symptomatic VTE, respectively, although the absolute differences were relatively small. Neither semuloparin nor LMWH increased major bleeding when compared with inactive control but the confidence intervals were wide; they crossed the line of no difference and the upper limit did not exclude a twice as high risk of bleeding with heparin treatment. This finding could still be the result of the relatively low number of events. Co-morbidities predisposing to bleeding, which often represent an exclusion criterion in RCTs on anticoagulants, might result in a greater number of major bleeding complications and limit the use of thromboprophylaxis in 'real life'. An additional concern may be the use of thromboprophylaxis in some types of cancers, such as those in the brain, which are considered to be at risk for major bleeding; although preliminary data in brain cancer seem reassuring and suggest a similar risk for LMWH and placebo (Perry 2010). Thus, despite the encouraging results of this review, routine prophylaxis in ambulatory cancer patients cannot be recommended before safety issues are adequately addressed. Since this review mainly included patients with locally advanced or metastatic cancer, the results may not be generalizable to patients with earlier stages of cancer. Of note is that marketing applications for the uLMWH semuloparin have been withdrawn worldwide and it is therefore unlikely to ever be commercially available (EMEA 2012).

Data on the use of thromboprophylaxis with anticoagulants other than uLMWH or LMWH appear to be preliminary. Four studies compared the VKA warfarin with placebo or no warfarin but only one reported on VTE. An almost four-fold increase in major bleeding was observed with warfarin, which was close to, but did not reach, statistical significance. While additional studies are needed to clarify the efficacy and safety of warfarin, the bleeding

concerns and the complexity of VKA management discourage the use of warfarin for primary prophylaxis in cancer patients. The lack of an adequate control group in the studies of myeloma patients hampers definite recommendations for one specific thromboprophylaxis over another. In addition, the trials including myeloma patients focused on specific regimens (thalidomide and lenalidomide-based combinations). These findings and conclusions may not apply to all myeloma patients but only to those who are receiving such therapies. Currently, patient subgroups that might benefit from prophylaxis cannot be specified however ongoing studies may provide valuable information in this regard (NCT00876915).

Implications for research

Additional randomised studies are needed to clearly establish the risk to benefit ratio of anticoagulants in ambulatory cancer patients receiving chemotherapy and to identify subgroups that may benefit most from thromboprophylaxis. The evaluation of the benefit of prophylaxis warrants the use of 'hard' outcomes, such as symptomatic PE, and the use of clinically important safety outcomes including major bleeding. Evidence-based thrombotic and bleeding risk assessment scores may help in selecting subgroups that are at lower risk of bleeding complications. Several additional aspects related to thromboprophylaxis deserve further study, such as patient preferences and the effects on the incidence of symptomatic arterial thromboembolism and quality of life. Finally, cost analysis data on the use of anticoagulation in patients with cancer undergoing chemotherapy would be extremely valuable and supportive of a broader application of chemoprophylaxis in the future. Although data from the eight ongoing trials on LMWH and aspirin (Characteristics of ongoing studies) will be invaluable in addressing some of these issues, we still need more RCTs evaluating the effects of newer anticoagulants such as direct Xa inhibitors and direct thrombin inhibitors, which have shown promise in other settings compared with heparin or vitamin K antagonists (Weitz 2012).

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Agnelli 2009 *{published data only}*

* Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, et al.Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncology* 2009;**10**(10):943–9.

Barni S, Labianca R, Agnelli G, Bonizzoni E, Verso M, Mandala M, et al.Chemotherapy-associated thromboembolic risk in cancer outpatients and effect of nadroparin thromboprophylaxis: results of a retrospective analysis of the PROTECHT study. *Journal of Translational Medicine* 2011;**9**:179.

Agnelli 2012 *{published data only}*

Agnelli G, George D, Fisher WD, Kakkar AK, Lassen MR, Mismetti P, et al.Ultra-low-molecular-weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) in cancer patients receiving chemotherapy: consistent beneficial effect across cancer stage and location subgroups. *European Journal of Cancer* 2011;**47**:S222.

* Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, Mismetti P, et al.for the SAVE-ONCO Investigators. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *The New England Journal of Medicine* 2012;**366**(7):601–9.

NCT00694382. A multinational, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of AVE5026 in the prevention of venous thromboembolism (VTE) in cancer patients at high risk for VTE and who are undergoing chemotherapy. Clinicaltrials.gov (accessed 29 July 2014).

Altinbas 2004 *{published data only}*

Altinbas M, Coskun HS, Er O, Ozkan M, Eser B, Unal A, et al.A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. *Journal of Thrombosis and Haemostasis* 2004;**2**(8):1266–71.

Chahinian 1989 *{published data only}*

Chahinian AP, Propert KJ, Ware JH, Zimmer B, Perry MC, Hirsh V, et al.A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the Cancer and Leukemia Group B. *Journal of Clinical Oncology* 1989;**7**(8):993–1002.

Haas 2012 *{published data only}*

Freund M, Kakkar AK, Haas S, Heilmann L, von-Tempelhoff GF, Brom J, et al.A randomized trial of the low molecular weight of heparin certoparin against placebo in the long-term prevention of venous thromboembolism in

patients with metastatic breast cancer. *Blood* 2003;**102**(11 (Pt1)):210a.
* Haas SK, Freund M, Heigener D, Heilmann L, Kemkes-Matthes B, von Tempelhoff GF, TOPIC Investigators. Low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer. *Clinical and Applied Thrombosis Hemostasis* 2012;**18**(2):159–65.
Haas SK, Kakkar AK, Kemkes-Matthes B, Freund M, Gatzemeier U, Heilmann L, et al.Prevention of venous thromboembolism with low-molecular-weight heparin in patients with metastatic breast or lung cancer - Results of the TOPIC studies. Journal of Thrombosis and Haemostasis 2005; Vol. 3, issue 1:Abstract OR059.
Verso M, Gussoni G, Agnelli G. Prevention of venous thromboembolism in patients with advanced lung cancer receiving chemotherapy: a combined analysis of the PROTECHT and TOPIC-2 studies. *Journal of Thrombosis and Haemostasis* 2010;**8**(7):1649–51.

Kakkar 2004 ***{published data only}***
Kakkar AK, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, et al.Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *Journal of Clinical Oncology* 2004;**22**(10):1944–8.

Klerk 2005 ***{published data only}***
Klerk CP, Smorenburg SM, Otten HM, Lensing AW, Prins MH, Piovella F, et al.The effect of low molecular weight heparin on survival in patients with advanced malignancy. *Journal of Clinical Oncology* 2005;**23**(10):2130–5.

Larocca 2012 ***{published data only}***
Cavallo F, Raimondo FD, Harda I, Lupo B, Romano A, Catalano L, et al.A phase III study of enoxaparin vs aspirin as thromboprophylaxis for newly diagnosed myeloma patients treated with lenalidomide-based regimen. Blood 2010; Vol. 116:Abstract 1092.
* Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, et al.Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. *Blood* 2012; **119**(4):933-9, quiz 1093.

Lebeau 1994 ***{published data only}***
Lebeau B, Chastang C, Brechot J-M, Capron F, Dautzenberg B, Delaisements C, et al.Subcutaneous heparin treatment increases survival in small cell lung cancer. "Petites Cellules" Group. *Cancer* 1994;**74**(1):38–45.

Levine 1994 ***{published data only}***
Dickson L, Levine M, Gent M. Efficacy of double-blinding in a randomized controlled trial (RCT) of low dose warfarin to prevent thromboembolic disease in patients with metastatic breast cancer. Fourteenth annual meeting of the Society for Clinical Trials. Hilton Hotel, Orlando, Florida. 1993; Vol. 14:462.
* Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al.Double-blind randomised trial of very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet* 1994;**343**(8902):886–9.

Levine 2012 ***{published data only}***
* Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D, et al.A randomized phase II trial of Apixaban for the prevention of thromboembolism in patients with metastatic cancer. *Journal of Thrombosis and Haemostasis* 2012;**10**(5):807–14.
Liebman H, Levine MN, Deitchman D, Julian J, Escalante CP, O'Brien MC, et al.Apixaban in patients with metastatic cancer: a randomized phase II feasibility study. *Journal of Thrombosis and Haemostasis* 2009;**7 Suppl 2**:Abstract PP-WE-489.
NCT00320255. A randomized, double-blind, placebo-controlled study of apixaban for the prevention of thromboembolic events in patients undergoing treatment for advanced cancer: A phase 2 pilot study. Clinicaltrials.gov (accessed 29 July 2014).

Maraveyas 2012 ***{published data only}***
Maraveyas A, Ettelaie C, Echrish H, Li C, Gardiner E, Greenman J, et al.Weight-adjusted dalteparin for prevention of vascular thromboembolism in advanced pancreatic cancer patients decreases serum tissue factor and serum-mediated induction of cancer cell invasion. *Blood Coagulation and Fibrinolysis* 2010;**21**(5):452–8.
* Maraveyas A, Waters J, Roy R, Fyfe D, Propper D, Lofts F, et al.Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *European Journal of Cancer* 2012;**48**(9):1283–92.
NCT00462852. A phase II randomised study of chemo-anticoagulation (gemcitabine-dalteparin) vs chemotherapy alone (Gemcitabine) for locally advanced and metastatic pancreatic adenocarcinoma. Clinicaltrials.gov (accessed 29 July 2014).

Maurer 1997 ***{published data only}***
Maurer LH, Herndon JE II, Hollis DR, Aisner J, Carey RW, Skarin AT, et al.Randomized trial of chemotherapy and radiation therapy with or without warfarin for limited-stage small-cell lung cancer: a Cancer and Leukemia Group B study. *Journal of Clinical Oncology* 1997;**15**(11):3378–87.

Mitchell 2003 ***{published data only}***
Mitchell L, Andrew M, Hanna K, Abshire T, Halton J, Wu J, et al.Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia. Results of the PAARKA study. *Thrombosis and Haemostasis* 2003;**90**(2):235–44.

Palumbo 2011 ***{published data only}***
Cavo M, Palumbo A, Bringhen S, Di RF, Patriarca F, Rossi D, et al.Phase III study of enoxaparin versus aspirin versus lowdose warfarin as thromboprophylaxis for patients with newly diagnosed multiple myeloma treated upfront with thalidomide-containing regimens. *Haematologica* 2010;**95 Suppl 2**:391, Abstract 0941.
Palumbo A, Cavo M, Bringhen S, Patriarca F, Rossi D, Petrucci MT, et al.A phase III study of enoxaparin versus

aspirin versus low-dose warfarin as thromboprophylaxis for patients with newly diagnosed multiple myeloma treated up-front with thalidomide based-regimens. Haematologica 2009; Vol. 94 Suppl 2:213.
* Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F, et al.Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *Journal of Clinical Oncology* 2011;**29**: 986–93.
Palumbo A, Rus C, Cavallo F, Bertola A, Petrucci MT, Liberati AM, et al.Enoxaparin or aspirin for the prevention of recurrent thromboembolism in newly diagnosed myeloma patients treated with melphalan and prednisone plus thalidomide or lenalidomide. Haematologica 2006; Vol. 91 Suppl 1.

Pelzer 2009 ***{published data only}***
ISRCTN02140505. A prospective, randomised trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy. ISRCTN register 2008 (accessed 29 July 2014).
* Pelzer U, Deutschinoff G, Opitz B, Stauch M, Reitzig P, Hahnfeld S, et al.A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy. First results of the CONKO-004 trial. Onkologie-DGHO meeting Oct 2009 2009:Abstract 580.
Pelzer U, Deutschinoff G, Opitz B, Stauch M, Reitzig P, Hahnfeld S, et al.The impact of low molecular weight heparin in first-line pancreatic cancer treatment - Final results of the CONKO-004 trial. *Onkologie* 2010;**33**(6): 200.
Pelzer U, Hilbig A, Stieler J, Roll L, Riess H, Dörken B, et al.A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy (PROSPECT - CONKO 004). Onkologie 2005; Vol. 28 Suppl 3:Abstract 151.
Pelzer U, Oettle H, Stauch M, Opitz B, Stieler J, Scholten T, et al.Prospective, randomized open trial of enoxaparin in patients with advanced pancreatic cancer undergoing first-line chemotherapy. XXIst Congress of the International Society on Thrombosis and Haemostasis; 2007 Jul 6-12; Geneva. 2007:Abstract P-T-488.
Riess H, Pelzer U, Hilbig A, Stieler J, Opitz B, Scholten T, et al.Rationale and design of PROSPECT-CONKO 004: a prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy). *BMC Cancer* 2008;**8**:361.

Perry 2010 ***{published data only}***
* Perry JR, Julian JA, Laperriere NJ, Geerts W, Agnelli G, Rogers LR, et al.PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *Journal of Thrombosis and Haemostasis* 2010;**8**(9):1959–65.
Perry JR, Rogers L, Laperriere N, Julian J, Geerts W, Agnelli G, et al.PRODIGE: A phase III randomized placebo-controlled trial of thromboprophylaxis using dalteparin low molecular weight heparin (LMWH) in patients with newly diagnosed malignant glioma. *Journal of Clinical Oncology* 2007;**25**(18 Suppl):2011.

Sideras 2006 ***{published data only}***
Sideras K, Schaefer PL, Okuno SH, Sloan JA, Kutteh L, Fitch TR, et al.Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial. *Mayo Clinic Proceedings* 2006;**81**(6):758–67.

van Doormaal 2011 ***{published data only}***
van Doormaal FF, Di Nisio M, Otten H-M, Richel DJ, Prins M, Buller HR. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. *Journal of Clinical Oncology* 2011;**29** (15):2071–6.

Zacharski 1981 ***{published data only}***
Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ Jr, Forcier RJ, et al.Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. Final report of VA Cooperative Study #75. *Cancer* 1984;**53**(10):2046–52.
* Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ Jr, Forcier RJ, et al.Effect of warfarin on survival in small cell carcinoma of the lung. Veterans Administration Study No. 75. *JAMA* 1981;**245**(8):831–5.

Zwicker 2013 ***{published data only}***
Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R, et al.Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). *British Journal of Haematology* 2013;**160**(4):530-7.

References to studies excluded from this review

ABEL study 2005 ***{unpublished data only}***
NCT00324558. Multicenter, randomized, open and sequential study to evaluate the efficacy and safety of bemiparin administration on the response to treatment in patients diagnosed with limited small cell lung cancer. ClinicalTrials.gov 2006 (accessed 29 July 2014).

Baz 2005 ***{published data only}***
Baz R, Li L, Kottke-Marchant K, Srkalovic G, McGowan B, Yiannaki E, et al.The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clinic Proceedings* 2005;**80**(12):1568–74.

Bergqvist 1983 ***{published data only}***
Bergqvist D, Lindblad B. Is it possible to potentiate the thromboprophylactic effect of dextran with elastic compression stockings?. Thrombosis and Haemostasis 1983; Vol. 50, issue 1:247 Abstract 0777.

Eichinger 2008 ***{published data only}***
Eichinger S, Traby L, Kaider A, Quehenberger P, Kyrle PA. Prevention of venous thrombosis in cancer patients: A randomized, double-blind study comparing two different dosages of low-molecular weight heparin. *Blood* 2008;**112** (11):690 Abstract 1977.

Haas 2011 *{published data only}*
Haas S, Schellong SM, Tebbe U, Gerlach H-E, Bauersachs R, Melzer N, et al.Heparin based prophylaxis to prevent venous thromboembolic events and death in patients with cancer - a subgroup analysis of CERTIFY. *BMC Cancer* 2011;**11**:316.

Heilmann 1995 *{published data only}*
Heilmann L, Schneider D, Herrle B, von Tempelhoff G-F, Manstein J, Wolf H. A prospective randomized trial of low molecular weight heparin (LMWH) versus unfractionated heparin (UFH) in patients with gynecologic cancer. Thrombosis and Haemostasis 1995; Vol. 73, issue 6:974 Abstract No 286.

Hills 1972 *{published data only}*
Hills NH, Pflug JJ, Jeyasingh K, Boardman L, Calnan JS. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. *British Medical Journal* 1972;**1**(5793):131–5.

Kessler 2011 *{published data only}*
Kessler P. Prophylaxis and treatment of venous thromboembolism in patients with multiple myeloma. *Onkologie* 2011;**5**(3):160–2.
Kessler P, Pour L, Gregora E, Zemanova M, Penka M, Brejcha M, et al.Czech Myeloma Group. Low molecular weight heparins for thromboprophylaxis during induction chemotherapy in patients with multiple myeloma. *Klinicka Onkologie* 2011;**24**(4):281–6.

Kwaan 2007 *{unpublished data only}*
NCT00004875. Heparin or enoxaparin in patients with cancer. Clinicaltrials.gov 2007 (accessed 29 July 2014).

Levin 2008 *{unpublished data only}*
NCT00790452. A randomized phase II trial of aspirin for primary prophylaxis of venous thromboembolism in glioblastoma. Clinicaltrials.gov 2008 (accessed 29 July 2014).

Macintyre 1974 *{published data only}*
Anonymous. Heparin versus dextran in the prevention of deep-vein thrombosis. A multi-unit controlled trial. *Lancet* 1974;**2**(7873):118–20.

Maxwell 2000 *{published data only}*
Maxwell GL. A prospective randomized trial comparing external pneumatic compression stockings (EPC) to the low molecular weight heparin (LMWH) dalteparin in the prevention of thromboembolic events (TE) among gynecologic oncology patients. Proceedings of the American Society of Clinical Oncology 2000; Vol. 19:388a, Abstract 1535.

Meister 2008 *{published data only}*
Meister B, Kropshofer G, Klein Franke A, Strasak AM, Hager J, Streif W. Comparison of low-molecular-weight heparin and antithrombin versus antithrombin alone for the prevention of symptomatic venous thromboembolism in children with acute lymphoblastic leukemia. *Pediatric Blood and Cancer* 2008;**50**(2):298–303.

Minnema 2004 *{published data only}*
Minnema MC, Breitkreutz I, Auwerda JJ, van-der Holt B, Cremer FW, van-Marion AM, et al.Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. *Leukemia* 2004;**18**(12):2044–6.

Niesvizky 2007 *{published data only}*
Niesvizky R, Martinez-Banos D, Jalbrzikowski J, Christos P, Furst J, De Sancho M, et al.Prophylactic low-dose aspirin is effective antithrombotic therapy for combination treatments of thalidomide or lenalidomide in myeloma. *Leukemia and Lymphoma* 2007;**48**(12):2330-7.

Pandya 2002 *{unpublished data only}*
NCT00031837. A prospective randomized controlled multicenter study of the effect of dalteparin on quality of life in unresectable pancreatic cancer. Clinicaltrials.gov 2002 (accessed 29 July 2014).

Paydas 2008 *{published data only}*
Paydas S. Tailored thromboprophylaxis for patients with multiple myeloma treated by IMIDs. *Leukemia and Lymphoma* 2008;**49**(8):1644–5.

Poniewierski 1987 *{published data only}*
Poniewierski M, Barthels M, Kuhn M, Poliwoda H. Efficacy of low molecular weight heparin (Fragmin) for thromboprophylaxis in medical patients: A randomized double blind trial. *Medizinische Klinik* 1988;**83**(7):241–5.
Poniewierski M, Barthels M, Poliwoda H. The safety and efficacy of a low molecular weight heparin (fragmin) in the prevention of deep vein thrombosis in medical patients: a randomized double-blind trial. Thrombosis and Haemostasis 1987; Vol. 58, issue 1:119 Abstract 425.

Rajan 1995 *{published data only}*
Rajan R, Gafni A, Levine M, Hirsh J, Gent M. Very low-dose warfarin prophylaxis to prevent thromboembolism in women with metastatic breast cancer receiving chemotherapy: an economic evaluation. *Journal of Clinical Oncology* 1995;**13**(1):42–6.

Sideras 2007 *{published data only}*
Sideras K, Schaefer PL, Okuno SH. Low-molecular-weight heparin in patients with advanced cancer: A phase 3 clinical trial. Journal of Vascular Surgery 2007; Vol. 45, issue 4: 861.

Weber 2008 *{published data only}*
Weber C, Merminod T, Herrmann FR, Zulian GB. Prophylactic anti-coagulation in cancer palliative care:a prospective randomised study. *Support Care in Cancer* 2008; **16**(7):847–52.

Welti 1981 *{published data only}*
Welti H. Thrombo-embolytic prophylaxis using physiotherapy with and without low doses of heparin in gynecology and obstetrics. Results of a controlled and randomized multi-cancer study. *Revue Medicale de la Suisse Romande* 1981;**101**(11):925–34.

Zangari 2003 *{published data only}*
Zangari M, Barlogie B, Saghafifar F, Eddlemon P, Jacobson J, Lee CK, et al.Effect of anticoagulation on development

and recurrence of deep vein thrombosis (DVT) in multiple myeloma patients treated with chemotherapy and thalidomide (total therapy II). *Hematology Journal* 2003;**4 Suppl 1**:S248.

References to studies awaiting assessment

Salat 1990 ***{published data only}***
Salat C, Breitruck H, Reinhardt B, Hiller E. Thromboprophylaxis with low molecular weight heparin (LMWH) and conventional low dose heparin in patients with malignant diseases. *Blut* 1990;**61**(2-3):142.

References to ongoing studies

NCT00239980 ***{unpublished data only}***
NCT00239980. A phase II randomized study of Fragmin in ovarian cancer: utility on survival (FOCUS). Clinicaltrials.gov (accessed 29 July 2014). [URL: http://clinicaltrials.gov/ct2/show/NCT00239980?term=NCT00239980&rank=1]

NCT00320255 ***{unpublished data only}***
NCT00320255. A randomized, double-blind, placebo-controlled study of apixaban for the prevention of thromboembolic events in patients undergoing treatment for advanced cancer: a phase II pilot study. Clinicaltrials.gov (accessed 29 July 2014). [URL: http://clinicaltrials.gov/ct2/show/NCT00320255?term=NCT00320255&rank=1]

NCT00519805 ***{published data only}***
Griffiths GO, Burns S, Noble SI, Macbeth FR, Cohen D, Maughan TS. FRAGMATIC: a randomised phase III clinical trial investigating the effect of fragmin added to standard therapy in patients with lung cancer. *BMC Cancer* 2009;**9**:355.

NCT00662688 ***{unpublished data only}***
NCT00662688. Chemotherapy with or without preventive anticoagulation for metastatic cancer of the pancreas. Clinicaltrials.gov (accessed 29 July 2014). [URL: http://clinicaltrials.gov/ct2/show/NCT00662688?term=NCT00662688&rank=1]

NCT00718354 ***{unpublished data only}***
NCT00718354. Randomized, phase III-b, multi-centre, open-label, parallel study of Enoxaparin (low molecular weight heparin) given concomitantly with chemotherapy vs chemotherapy alone in patients with inoperable gastric and gastro-oesophageal cancer. Clinicaltrials.gov (accessed 29 July 2014). [URL: http://clinicaltrials.gov/ct2/show/NCT00718354?term=NCT00718354&rank=1]

NCT00876915 ***{unpublished data only}***
NCT00876915. A prospective randomized multicenter study of dalteparin prophylaxis in high-risk ambulatory cancer patients. Clinicaltrials.gov (accessed 29 July 2014). [URL: http://clinicaltrials.gov/ct2/show/NCT00876915?term=NCT00876915&rank=1]

NCT00966277 ***{unpublished data only}***
NCT00966277. Randomized clinical trial of dalteparin for primary venous thromboembolism (VTE) prophylaxis in pancreatic cancer patients undergoing chemotherapy treatment. Clinicaltrials.gov (accessed 29 July 2014). [URL: http://clinicaltrials.gov/ct2/show/NCT00966277?term=NCT00966277&rank=1]

Additional references

Aikens 2013
Aikens GB, Rivey MP, Hansen CJ. Primary venous thromboembolism prophylaxis in ambulatory cancer patients. *The Annals of Pharmacotherapy* 2013;**47**(2): 198–209.

Akl 2011
Akl EA, Vasireddi SR, Gunukula S, Yosuico VED, Barba M, Sperati F, et al.Anticoagulation for patients with cancer and central venous catheters. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD006468.pub4]

Ay 2010
Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al.Prediction of venous thromboembolism in cancer patients. *Blood* 2010;**116**(24):5377–82.

DerSimonian 1986
DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177–88.

EMEA 2012
European Medicines Agency (EMEA). Withdrawal of the marketing authorisation application for Mulsevo (semuloparin sodium). http://www.emea.europa.eu/docs/en˙GB/document˙library/Medicine˙QA/2012/07/WC500130168.pdf 2012 (Accessed 11 December 2012).

George 2011
George D, Agnelli G, Fisher W, Kakkar A, Lassen MR, Mismetti P, et al.Venous thromboembolism (VTE) prevention with semuloparin in cancer patients Initiating chemotherapy: benefit-risk assessment by VTE risk in SAVE-ONCO. *Blood* 2011;**118: Abstract 206**.

Guyatt 2008
Guyatt G, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7656): 924–6.

Harbord 2006
Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20): 3443–57.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Available from www.cochrane-handbook.org. Chichester, UK: John Wiley & Sons.

Hutten 2000
Hutten B, Prins M, Gent M, Ginsberg J, Tijsen JG, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *Journal of Clinical Oncology* 2000;**18**(17):3078–83.

Juni 2001
Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303):42–6.

Kahn 2012
Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al.Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**(2 Suppl): e195S–226S.

Khorana 2008
Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;**111**(10):4902–7.

Khorana 2009
Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *Journal of Clinical Oncology* 2009;**27**(29):4839–47.

Khorana 2009a
Khorana AA, Streiff MB, Farge D, Mandala M, Debourdeau P, Cajfinger F, et al.Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. *Journal of Clinical Oncology* 2009;**27**(29):4919–26.

Kuderer 2009
Kuderer NM, Khorana AA, Francis CW, Lyman GH, Falanga A, Ortel TL. Low-molecular-weight heparin for venous thromboprophylaxis in ambulatory cancer patients: A meta-analysis. *Journal of Clinical Oncology. ASCO Annual Meeting Proceedings (Post-Meeting Edition)* 2009;**27**(15S): 9537.

Lyman 2013
Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al.Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology* 2013;**31**(24):2189–204.

Maxwell 2012
Maxwell WD, Bennett CL. Thromboprophylaxis guidelines in cancer with a primary focus on ambulatory patients receiving chemotherapy: a review from the southern network on adverse reactions (SONAR). *Seminars in Thrombosis and Hemostasis* 2012;**38**(8):759-67.

Otten 2004
Otten H-M, Mathijssen J, ten Cate H, Soesan M, Inghels M, Richel DJ, et al.Symptomatic venous thromboembolism in cancer patients treated with chemotherapy. An underestimated phenomenon. *Archives of Internal Medicine* 2004;**164**(2):190–4.

Prandoni 2002
Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al.Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; **100**(10):3484–8.

Rana 2009
Rana P, Levine MN. Prevention of thrombosis in ambulatory patients with cancer. *Journal of Clinical Oncology* 2009;**27** (29):4885–8.

Rutjes 2009
Rutjes AW, Nüesch E, Sterchi R, Kalichman L, Hendriks E, Osiri M, et al.Transcutaneous electrostimulation for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/ 14651858.CD002823.pub2]

Rutjes 2012
Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Annals of Internal Medicine* 2012;**157**(3):180–91.

Rücker 2008
Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I^2 in assessing heterogeneity may mislead. *BMC Medical Research Methodology* 2008;**8**(1):79.

Sorensen 2000
Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *The New England Journal of Medicine* 2000;**343**(25):1846–50.

Spiegelhalter 2004
Spiegelhalter DJ, Abrams KR, Myles JP. *Bayesian approaches to clinical trials and health-care evaluation*. Chichester, UK: John Wiley & Sons, 2004.

Sterne 2001
Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *Journal of Clinical Epidemiology* 2001;**54**(10):1046–55.

Thompson 1999
Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Statistics in Medicine* 1999;**18**(20):2693–708.

Verso 2012
Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. *Internal and Emergency Medicine* 2012;**7**(3):291-2.

Weitz 2012

Weitz JI, Eikelboom JW, Samama MM, American College of Chest Physicians. New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**(2 Suppl): e120S–51S.

References to other published versions of this review

Di Nisio 2012

Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, Rutjes AWS. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008500.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Agnelli 2009

Methods	PROTECHT: Multicentre RCT; modified intention-to-treat analysis, including patients who received at least one dose of study treatment
Participants	Ambulatory patients older than 18 years of age who were receiving chemotherapy for metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer. Age: 62.1 years in the nadroparin group; 63.7 years in the placebo group. Previous VTE: 18/1150 (1.6%). Median duration of follow up: 16 weeks
Interventions	LMWH, nadroparin (3800 IU sc, od) Control: placebo Study treatment started on the same day as chemotherapy (the first cycle or a new course) , and given for the duration of chemotherapy or up to a maximum of 120 days (± 10 days)
Outcomes	Primary outcomes: composite of symptomatic venous or arterial thromboembolic events occurring during the study treatment plus 10 days; major bleeding that occurred between randomisation and 48 hours after the last injection of the study drug Secondary efficacy outcomes: asymptomatic thromboembolic events incidentally diagnosed, survival at the end of study treatment and at 12 months, superficial venous thrombosis of the lower limbs, response to chemotherapy, central venous catheter-related complications of possible thrombotic origin Secondary safety outcome: minor bleeding
Notes	Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or low molecular weight heparin other than nadroparin not allowed during the study period Funding: Italfarmaco SpA, Milan, Italy Disclosure of potential conflicts of interest: the scientific director of Italfarmaco was involved as an author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated: use of a computer-generated list, using block randomisation (block size of six) and a 2:1 ratio to allocate to LMWH versus placebo
Allocation concealment (selection bias)	Low risk	Random sequence generation by means of a web-based system: "The randomisation list was generated by an independent statistician" and "The allocation sequence was available online to the investigators using the Hypernet web-based system."

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded RCT. The authors reported the use of pre-filled syringes which were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 769 out of 779 (98.7%) patients randomised were analysed in the LMWH group, 381 out of 387 (98.4%) randomised were analysed in the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

Agnelli 2012

Methods	SAVE-ONCO: Multicentre double-blinded RCT, intention-to-treat for effectiveness and modified intention-to-treat analysis for safety outcomes, including patients who received at least one study dose
Participants	Patients with metastatic or locally advanced solid cancer of the lung, pancreas, stomach, colon or rectum, bladder, or ovary who were beginning to receive a course of chemotherapy. Mean age: 59.8 years in the semuloparin group and 59.4 years in the placebo group. Previous VTE: 2% in the semuloparin and 2.3% in the placebo. Mean duration of follow up: not reported
Interventions	Ultra-LMWH semuloparin (20 mg sc, od) Control: placebo The first dose of the study drug was administered on the first day of a course of chemotherapy (first regimen or a new regimen) continuing for the duration of chemotherapy (intended to be a minimum of 3 months). Median treatment duration was 3.5 months
Outcomes	Primary efficacy outcome: composite of any symptomatic DVT, any non-fatal PE, and death related to VTE Primary safety outcome: clinically relevant bleeding (major and non-major) Secondary efficacy outcome: 1-year overall survival or at the study end date
Notes	Data were analysed by the sponsor (Sanofi) Disclosure of potential conflicts of interest: at the section "The Work Under Consideration for Publication", some of the authors declared they were employed by Sanofi or to have received consulting fee or honorarium and support for travel to meetings by Sanofi-Aventis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	A minimization algorithm was used
Allocation concealment (selection bias)	Low risk	"Randomisation performed centrally by means of an interactive voice-response system"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded RCT. Efficacy and safety outcomes assessed by a central independent adjudication committee, whose members were unaware of the study treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Effectiveness: analyses according to the intention-to-treat analysis Safety: 1589 out of 1608 (98.8%) patient randomised are analysed in the uLMWH group, 1583 out of 1604 (98.7%) patients randomised are analysed in the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the protocol and in the methods section of the full report were addressed in the results or discussion section, except for one outcome mentioned in the protocol only: "Secondary efficacy variables include the initiation of curative treatment by the investigator after VTE". We did not consider the latter to be an outcome in our assessment

Altinbas 2004

Methods	RCT; intention-to-treat analysis for survival outcomes
Participants	Patients between ages 18 and 75 years with histologically confirmed small cell lung carcinoma with an Eastern Cooperative Oncology Group performance status of less than 3 and normal haematological, renal and hepatic function tests. Median age: 58 years (range 34 - 75). Previous VTE: 0/84. Median duration of follow up: 10 months (range 2 - 33 months)
Interventions	LMWH, dalteparin (5000 IU sc, od) Control: no dalteparin Dalteparin was stopped with disease progression or at the end of the 18 weeks of chemotherapy Median duration of treatment was 18 weeks
Outcomes	Primary outcome: overall survival Secondary outcomes: progression-free survival, side effects

Notes	Funding: not reported Disclosure of potential conflicts of interest: not disclosed, no COI forms available	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open study: the trial is reported as a "Chemotherapy-only" versus Chemotherapy + LMWH" trial, without mentioning the use of placebo LMWH, or any attempt to blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Effectiveness: not reported Safety: survival analysed according to the intention-to-treat principle
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

Chahinian 1989

Methods	Multicentre, 3-arm RCT, type of analyses not reported
Participants	Patients with extensive carcinoma of the lung. Patients aged 60 years or older: 55% warfarin and 60% control group; males: 68% and 67%, respectively
Interventions	Intervention: Warfarin to maintain a prothrombin 1.5 to twice the control values Control: no warfarin Warfarin was continued throughout the course of chemotherapy, and it was withheld in patients with brain metastases during cranial irradiation and whenever platelet counts fell below 75,000/μL
Outcomes	Main outcomes: overall survival, failure free survival and cancer response (complete response, partial response and objective response rate) to therapy Secondary outcomes: toxicity
Notes	Funding: grants from the National Cancer Institute, Department of Health and Human Services, and a grant from the T.J. Martell Foundation for Leukemia and Cancer Research Disclosure of potential conflicts of interest: not disclosed, no COI forms available Two out of three available trials arms were considered in this review, as the chemother-

	apy provided was the same in both arms. The excluded trial arm provided a different chemotherapy regimen

Risk of bias

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

Haas 2012

Methods	TOPIC-1 and TOPIC-2: Multicentre RCT, intention-to-treat for effectiveness and modified intention-to-treat analysis for safety outcomes
Participants	Patients with metastatic breast cancer (n = 353) or non-small cell lung carcinoma (n = 547) receiving first- or second-line chemotherapy. In the TOPIC-1 (breast cancer patients) the mean age (SD) was 54.6 (10.3) years and 56.6 (11.0) years in the certoparin and placebo. In the TOPIC-2 (lung cancer patients) the mean age (SD) was 60.8 (9.5) years and 60.3 (10.0) years, respectively. Previous VTE: 0/900
Interventions	LMWH, certoparin (3000 IU sc, od) Control: placebo Study treatment was given for 6 months
Outcomes	Primary outcomes: symptomatic or asymptomatic VTE, major bleeding Secondary outcomes: symptomatic VTE, overall thrombosis rate (to include arterial

	thrombotic events, superficial venous thrombosis, and central-line thrombosis), minor bleeding, thrombocytopenia, heparin-induced thrombocytopenia, osteoporotic fractures, survival Post hoc: mortality, symptomatic or asymptomatic VTE according to tumour stage
Notes	Funding: grant from Novartis Pharma, Nuremberg, Germany Disclosure of potential conflicts of interest: reported to be none The study on breast cancer was prematurely halted after an interim analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using a "computer-generated randomisation list" and "Randomization was block-stratified according to treatment with hormone-based chemotherapy"
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation was poorly reported. Although authors report that "Randomization numbers were allocated sequentially as patients were enrolled at each center." they omit to report if sealed, opaque and consecutively numbered envelopes, coded syringes or other methods were used. In addition, it remains unclear what is meant by randomisation number in "Patients were allocated to the lowest available randomisation number available for each study center."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded placebo controlled RCT. with blinding of patients, physicians and outcome assessors. Quotes: "Efficacy outcomes were validated by a blinded, independent Central Thrombosis Evaluation Team; safety end points were validated by a Data Safety Monitoring Committee consisting of 2 clinicians (blinded to treatment) and an independent statistician with access to the treatment assignments." and "Only the external statistician from the Safety Committee had access to the randomization codes."
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness: 442 out of 447 (98.9%) in the LMWH group and 441 out of 453 (97.4%) in the placebo group analysed Safety: 447 out of 447 (100%) in the

		LMWH and 451 out of 453 (99.6%) in the placebo group analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section. The outcome osteoporotic fracture was incompletely reported though, it remained unclear in which of the TOPIC-2 trial arms the single event occurred. Post hoc analyses were reported transparently

Kakkar 2004

Methods	FAMOUS: Multicentre RCT; modified intention-to-treat analysis for both effectiveness and safety analyses, including patients with at least 1 study dose and 1 follow-up visit
Participants	Patients of 18 and 80 years with histologically confirmed advanced stage III or IV (locally advanced or metastatic) malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus. Age: 62 years in the dalteparin group and 60.9 years in the placebo group. Previous VTE: 0/385. Median duration of follow up: 10 months in the dalteparin group and 9 months in the placebo group
Interventions	LMWH, dalteparin (5000 IU sc, od) Control: placebo (0.9% normal saline) Study treatment given for 1 year or until the patient died, whichever occurred sooner
Outcomes	Primary outcomes: mortality after 1 year of therapy Secondary outcomes: symptomatic, objectively confirmed VTE disease and bleeding complications
Notes	Funding: Pharmacia Corp., New York, NY. Disclosure of potential conflicts of interest: the lead author declared to have acted as a consultant for Pfizer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated: "Randomization was performed centrally by computer-generated code"
Allocation concealment (selection bias)	Low risk	Performed centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial reported as double-blind, with active substance or placebo provided in prefilled syringes. It is not reported whether syringes

		were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 190 out of 196 (96.9%) analysed in the LMWH group, 184 out of 189 (97.4%) analysed in the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

Klerk 2005

Methods	MALT: Multicentre, double-blinded, randomised, placebo-controlled study with intention-to-treat analyses for both effectiveness and safety, including patients who received at least one study dose
Participants	Patients with metastasised or locally advanced solid tumours. Median age (range): 63 years (36 - 86) in the nadroparin group and 64 years (28 - 83) in the placebo group. Previous VTE: 0/302. Mean duration of follow up: 12 months
Interventions	LMWH, nadroparin Control: placebo Pre-fi lled syringes containing a fi xed volume of nadroparin (9500 antifactor Xa U/mL) or placebo were provided according to patient's weight: 0.4 mL for those weighing less than 50 kg, 0.6 mL for those weighing between 50 and 70 kg, and 0.8 mL for those weighing more than 70 kg. Study treatment was to be administered sc bid during the initial 14 days of treatment and od thereafter for another 4 weeks
Outcomes	Primary efficacy outcome: death from any cause Primary safety outcome: major bleeding Secondary safety outcomes: clinically relevant non-major bleeding
Notes	Funding: the study treatment was provided by Sanofi -Synthelabo (Paris, France). The authors state that "protocol design, data collection, and analysis were solely the responsibility of the authors" Disclosure of potential conflicts of interest: the senior author and statistician declared consultancy activities for various pharmaceutical companies, including Sanofi-Synthelabo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated: "Sequentially numbered boxes of syringes with nadroparin or placebo were prepared using a central computer-generated randomization sched-

		ule, stratified for body weight with blocks of four"
Allocation concealment (selection bias)	Low risk	Performed centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial reported as double-blind, with active substance or placebo provided in pre-filled syringes. It is not reported whether syringes were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients enrolled analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section. The authors reported reasons for the discontinuation of the study drug in the results section only, but this was for descriptive purposes, hence unlikely introducing bias

Larocca 2012

Methods	Multicentre, open label, randomised substudy of a phase-III trial with modified intention-to-treat analyses of both effectiveness and safety outcomes, including patients who received at least one study dose
Participants	Patients with newly diagnosed multiple myeloma treated with lenalidomide and low-dose dexamethasone induction and melphalan-prednisone-lenalidomide consolidation. Median age: 57 years in the aspirin group, 58 years in the enoxaparin group. Previous VTE: 0/342
Interventions	Aspirin: 100 mg/day LMWH, enoxaparin (40 mg/day sc) Prophylaxis was provided during the 4 (28-day) cycles of lenalidomide and low-dose dexamethasone and the 6 (28-day) cycles of melphalan-prednisone-lenalidomide consolidation Median treatment duration was 3.6 months for aspirin and 3.5 months for LMWH
Outcomes	Primary endpoint: composite of symptomatic DVT, PE, arterial thrombosis, any acute cardiovascular event or sudden otherwise unexplained death in the first 6 months after randomisation Secondary outcomes: major and minor bleeding, any complications related to thromboprophylaxis
Notes	The main study (RV-MM-PI209) was supported by Fondazione Neoplasie Sangue Onlus, and Celgene supplied free lenalidomide. The authors declared that Celgene had no role in the study design, data analysis, data interpretation, or writing of the report Disclosure of potential conflicts of interest: several authors declared to have received

	honoraria or consultancy fees from various pharmaceutical companies, including Celgene	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based: "simple randomization sequence run by a central computer, which generated an automated assignment procedure that was concealed from the investigators in each study center"
Allocation concealment (selection bias)	Low risk	Performed centrally
Blinding (performance bias and detection bias) All outcomes	High risk	"Open-label" study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

Lebeau 1994

Methods	Multicentre, open label, randomised substudy, with intention-to-treat analyses	
Participants	Patients with limited and extensive small cell lung cancer who had not been previously treated with chemotherapy or radiotherapy	
Interventions	Intervention: chemotherapy with sc UFH. The dose of UFH initially adapted to weight (500 IU/kg/day) then adjusted by clotting times. UFH was administered in two or three daily injections for 5 weeks and stopped 1 week after the second course of chemotherapy Control: chemotherapy without UFH	
Outcomes	Primary outcome: overall survival, response to chemotherapy Secondary outcomes: bleeding, UFH-related thrombocytopenia	
Notes	Funding: none reported. Disclosure of potential conflicts of interest: not disclosed, no COI forms available	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Lebeau 1994 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Unclear: "randomized through a centralized blind telephone assignment procedure"
Allocation concealment (selection bias)	Low risk	Performed centrally: "randomized through a centralized blind telephone assignment procedure"
Blinding (performance bias and detection bias) All outcomes	High risk	Open study: "No bIinding procedure for patients and physicians was used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients enrolled in the randomised substudy were analysed. "No patient was lost to follow up"
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results section

Levine 1994

Methods	Multicentre RCT; intention-to-treat analysis
Participants	Patients with metastatic stage IV breast carcinoma who had been receiving first-line or second-line chemotherapy for 4 weeks or less. Mean age: 57 years in the warfarin group and 56 years in the placebo group. Previous VTE: 2/311 (0.6%). Mean duration of follow up: 199 days (SD 126) for warfarin and 188 days (SD 137) for placebo
Interventions	Warfarin (1 mg daily for 6 weeks and then adjusted to maintain the INR between 1.3 to 1.9) Control: placebo Study treatment began either at the start of chemotherapy or within the next 4 weeks and continued until 1 week after termination of chemotherapy Median treatment duration: 181 days (SD 123) for warfarin and 166 (SD 139) for placebo
Outcomes	Primary outcomes: VTE and arterial thrombosis; major and minor bleeding Secondary outcomes: survival
Notes	Funding: study supported by a grant-in-aid from the National Cancer Institute of Canada Disclosure of potential conflicts of interest: none disclosed, no COI forms available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Levine 1994 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-based: "according to a computer-generated random arrangement."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding "neither patients nor doctors were aware of treatment allocation" and "All outcome events were reviewed by a central adjudicating committee, unaware of treatment allocation" and "placebo patients took an identical inert tablet"
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 152 out of 154 (98.7%) in the warfarin and 159 out of 161 (98.8%) in the placebo group were analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

Levine 2012

Methods	Randomised, double-blind, phase-II trial, intention-to-treat analyses not reported
Participants	Patients receiving either first or second-line chemotherapy for advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian or prostate cancers; cancer of unknown origin; myeloma; or selected lymphomas. Median age (years, range): 57 (41 - 67) in apixaban 5 mg, 60 (39 - 76) in 10 mg, 64 (25 - 86) in 20 mg, and 59 (20 -82) in the placebo group. Previous VTE: 0/125
Interventions	Intervention: factor Xa inhibitor, apixaban (5 mg, 10 mg or 20 mg od oral) Control: placebo Study treatment was given for 12 weeks beginning within 4 weeks of starting chemotherapy Median treatment duration for 5 mg, 10 mg and 20 mg apixaban and placebo: 79.2 (29 - 90) days, 76.0 (16 - 90) days, 73.6 (14 - 92) days and 69.6 (7 - 91) days respectively
Outcomes	Primary outcome: major bleeding or clinically relevant non-major bleeding Secondary outcomes: VTE, grade III or higher adverse events related to study drug
Notes	Trials closed prematurely due to the slow rate of accrual Funding: Bristol-Myers Squibb Disclosure of potential conflicts of interest: no other COI reported, no COI forms available
Risk of bias	

Levine 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based: "Randomisation was performed centrally by contacting a computerised telephone voice response system provided by Bristol Myers Squibb
Allocation concealment (selection bias)	Low risk	Performed centrally: "Randomisation was performed centrally by contacting a computerised telephone voice response system provided by Bristol Myers Squibb" and "BMS generated and kept the randomization schedules."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind" study and "All bleeding and VTE events were adjudicated by a committee unaware of treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 32 out of 32 (100%) analysed in the 5 mg group; 29 out of 30 (96.7%) analysed in the 10 mg, 32 out of 33 (97%) analysed in the 20 mg group and 29 out of 30 (96.7%) in the placebo group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results section

Maraveyas 2012

Methods	RCT, phase-IIb study, intention-to-treat analyses not reported
Participants	Patients with non-resectable, recurrent or metastatic pancreatic adenocarcinoma. Median age: 63 years (40 - 82); males: 59%; patients with metastatic disease: 54%. Previous VTE: 0/123. Median follow-up time: 19.3 months
Interventions	LMWH, dalteparin (200 IU/kg od, sc for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks) and gemcitabine; Control: gemcitabine Continuing dalteparin prophylaxis beyond 12 weeks was not recommended but was also left to the discretion of the investigator
Outcomes	Primary outcome: reduction of all-type vascular thromboembolism during the study period. All-type vascular thromboembolism included DVT, PE, all arterial events (e.g. cerebrovascular accident/myocardial infarction, and all visceral thromboembolic events diagnosed on the basis of clinical symptomatology, post-mortem or incidentally Outcome data kindly provided by the authors: VTE

Notes	Central venous access devices and inferior vena cava filters were not allowed Funding: the Hull and East Yorkshire Hospitals National Health Service Trust; Pfizer provided a grant covering the cost of dalteparin; Lilly provided a grant covering the cost of biostatistics Disclosure of potential conflicts of interest: the lead author has received honoraria and participated in advisory boards for Pfizer. Another author has received travel expenses from Pfizer. None of the other authors has any conflicting interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based: "Patients were randomised in the facilities of the Postgraduate Medical Institute in Hull with software developed by York University" Allocation and stratification was done through remote telephone 'block' randomisation (personal communication)
Allocation concealment (selection bias)	Low risk	Performed centrally at the medical Institute in Hull, for all of the 7 recruiting sites. Allocation and stratification was done through remote telephone 'block' randomisation (personal communication)
Blinding (performance bias and detection bias) All outcomes	High risk	Open study (personal communication)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Effectiveness and safety: 59 out of 60 (98.3%) analysed in the LMWH group and 62 out of 63 (98.4%) analysed in the control group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results section

Maurer 1997

Methods	Multicentre, RCT, intention-to-treat analyses not reported
Participants	Patients with limited-stage small cell lung cancer receiving chemotherapy and radiotherapy. Patients of 60 years or older: 57.6%; males: 64.8%
Interventions	Intervention: Warfarin 10 mg/day for the first three days and then at a dose to maintain the prothrombin time between 1.4 and 1.6 times the local institutional control standards Control: no warfarin

	Warfarin was continued trough the complete course of chemotherapy and radiation therapy and stopped three weeks after the last cycle of chemotherapy Warfarin was administered for a median of 112.5 days
Outcomes	Primary: overall survival and cancer response to therapy Secondary: failure free survival, disease free survival, patterns of relapse, toxicity
Notes	Funding: grants from the National Cancer Institute, Bethesda, MD Disclosure of potential conflicts of interest: not reported, no COI forms available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported and no mentioning of placebo treatment "Patients were randomized to receive warfarin or no warfarin"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	From table 6 in the study paper it is clear that not all randomised patients were analysed, but the exact numbers were not reported
Selective reporting (reporting bias)	Unclear risk	Only the outcomes overall survival and complete tumour response were specified in the methods section. All other outcomes were addressed in the results section only, including the survival analyses at 8 months, 2, 3 and 4 years. Only the 8 months analyses were reported to be exploratory

Mitchell 2003

Methods	PARKAA: Multicentre, open RCT; per protocol analysis
Participants	Paediatric patients newly diagnosed with acute lymphoblastic leukaemia treated with L-asparaginase and a functioning central venous line placed within 2 weeks of initiating induction chemotherapy
Interventions	Thrombate III (infusions once weekly for 4 weeks to increase plasma concentrations of antithrombin to approximately 3.0 U/mL but no more than 4.0 units/mL) Control: standard care

Outcomes	Primary outcomes: clinically symptomatic or asymptomatic thrombotic event in any location; major and minor bleeding Secondary outcomes: surrogate outcome for thrombotic events by measuring markers of thrombin generation
Notes	Patients did receive small amounts of UFH for prophylaxis of central venous line-blockage either by continuous infusion (1 - 3 U/mL) or intermittent flushes (50 - 100 U/mL up to 4 times per day) according to local standard of care Funding: the study was supported by a grant from the Canadian Institutes of Health Research and Bayer Inc Disclosure of potential conflicts of interest: not reported, no COI forms available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated: "Randomisation was performed by the pharmacist-on-call using a computer generated random number list. "
Allocation concealment (selection bias)	Low risk	Performed by the pharmacist-on-call. "Investigators at participating centres were blinded to the randomisation code and unaware of patient treatment allocation until after patients had been randomised."
Blinding (performance bias and detection bias) All outcomes	High risk	Open study, see above and "The PARKAA study was an open, randomised, multi-centre extended phase II clinical study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 25 out of 37 (67.6%) analysed in the antithrombin group; 60 out of 72 (83.3%) analysed in the control group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results section

Palumbo 2011

Methods	Randomised, open label, multicentre study, modified intention-to-treat analysis, including patient receiving at least one study dose
Participants	Patients with previously untreated myeloma who received thalidomide-containing regimens and had no clinical indication or contraindication for a specific antiplatelet or anticoagulant therapy. Median age: aspirin 61 years (55 - 66), warfarin 60 years (54 - 66), heparin 62 years (55 - 66). Median follow-up time: 24.9 months

Interventions	Aspirin (100 mg/d), low-dose warfarin (1.25 mg/d), or LMWH (enoxaparin 40 mg/d). The prophylaxis was administered during the three cycles of induction therapy in patients ≤ 65 years and during the first six cycles of induction therapy in patients > 65 years Median treatment duration: 2.6 months for aspirin, 2.4 months for low-dose warfarin, and 2.6 months for LMWH
Outcomes	Primary outcome: a composite measure of a first episode of objectively confirmed symptomatic DVT, PE, arterial thrombosis, acute myocardial infarction or stroke, or sudden, otherwise unexplained death during the first 6 months from random assignment Secondary outcomes: each component of the composite primary endpoint; long-term cumulative incidence of the primary endpoint; major and minor bleeding events; any toxicity that required interruption of study prophylaxis
Notes	The trial sampled patients from two distinct RCTs, of which patients who received thalidomide-based regimens were eligible to the substudy randomising antithrombotic prophylaxis treatments Karnofsky performance status < 70%: aspirin 25%, warfarin 29%, heparin 30% Funding: none reported Disclosure of potential conflicts of interest: several authors reported paid consultant or advisory roles, honoraria and research funds that were relevant to the subject matter under consideration in their trial report

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based: "A simple random assignment sequence was generated by a centralized computer"
Allocation concealment (selection bias)	Low risk	Performed centrally: "After registration in a centralized database through the Internet and validation of eligibility, patients were randomly allocated to treatments using an automated assignment procedure concealed to the investigators"
Blinding (performance bias and detection bias) All outcomes	High risk	Open study "open-label"
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 220 out of 224 (98.2%) in the aspirin, 220 out of 222 (99.1%) in the warfarin and 219 out of 221 (99.1%) in the LMWH group were analysed. In addition, one patient was not randomised by "clinician mistake"

Selective reporting (reporting bias)	High risk	The outcome 'any toxicity that required interruption of study prophylaxis' was not reported in the final report

Pelzer 2009

Methods	CONKO 004 trial: open, multicentre RCT, intention-to-treat and per protocol analyses
Participants	Chemotherapy-naive patients with histologically or cytologically confirmed advanced pancreatic cancer. Age not reported. Median follow up: 30.4 weeks
Interventions	LMWH, enoxaparin (1 mg/kg od) for 3 months started simultaneous to palliative systemic chemotherapy Control: no enoxaparin
Outcomes	Primary outcome: symptomatic VTE (symptomatic DVT of the leg and/or pelvic and/or PE) within the first 12 weeks Secondary outcomes: symptomatic VTE after 6, 9 and 12 months; asymptomatic DVT during months 6, 9, and 12; major bleeding, overall survival, toxicity of the therapeutic regimen, time to cancer progression, remission at 3, 6, 9 and 12 months, quality of life
Notes	After 12 weeks of initial chemotherapy all patients who had not progressed received the standard therapy with or without enoxaparin (40 mg daily sc) for an additional three months Funding: partially funded by Sanofi-Aventis Disclosure of potential conflicts of interest: on the abstracts, the authors declared to have no conflict of interest. but in the published protocol, one of the authors declared to be employed by Sanofi-Aventis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based: computer-generated, dynamic, central randomisation (personal communication with author)
Allocation concealment (selection bias)	Low risk	Performed centrally: computer-generated, dynamic, central randomisation (personal communication with author)
Blinding (performance bias and detection bias) All outcomes	High risk	Reported as "open" study, with blind assessment of the primary outcome by an "independent blinded review board"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Effectiveness: 160 out of 160 are analysed in the LMWH and 152 out of 152 are anal-

		ysed in the control group Safety: the authors state that an intention-to-treat analysis was performed, but from the conference abstracts, we can not verify if true intention-to-treat analyses were performed
Selective reporting (reporting bias)	Unclear risk	Trial results described in 3 conference abstracts, where not all secondary outcomes were addressed. Final judgment awaits the publication as full report

Perry 2010

Methods	PRODIGE: Multicentre RCT; intention-to-treat analysis
Participants	Patients over 18 years of age with newly diagnosed, pathologically confirmed WHO Grade 3 or Grade 4 glioma. Mean age: 57 years (30 - 81) in the dalteparin group and 55 years (26 - 77) in the placebo group. Previous VTE: 0/186
Interventions	LMWH, dalteparin (5000 IU sc, od) Control: placebo Study treatment was given for 6 months starting within the first month after surgery. Patients were allowed to continue study medication for 12 months Median treatment duration: 183 days for LMWH and 157 days for placebo
Outcomes	Primary outcomes: objectively documented symptomatic DVT or PE occurring during the six months post-randomisation Secondary outcomes: major and all bleeding, quality of life, cognition assessments, and death
Notes	Funding: Pfi zer Inc, Ontario Clinical Oncology Group, Crolla Chair in Brain Tumour Research Disclosure of potential conflicts of interest: the lead author disclosed research support (and funding) by Pfizer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated: "using a computer-generated randomization list"
Allocation concealment (selection bias)	Low risk	Performed centrally: "Consenting patients were randomized by contacting the Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre at the Henderson Research Centre"

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo controlled RCT. "In our study, investigators, patients and outcome assessors were blinded to treatment allocation. In addition, VTE and bleeding outcomes were adjudicated by a central committee unaware of treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient randomised were analysed.
Selective reporting (reporting bias)	High risk	The outcomes quality of life and cognition assessment were mentioned in the methods but not addressed in the results section

Sideras 2006

Methods	Multicentre RCT, type of analyses not reported
Participants	Patients with advanced breast cancer who failed first-line chemotherapy, advanced prostate cancer who failed primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer. Median age for blinded LMWH: 64.5 years; placebo: 63.5 years; unblinded LMWH: 68.5 years; standard care: 70.5 years
Interventions	*First part of the study, double-blinded (52 patients):* LMWH, dalteparin (5000 IU sc, od) plus standard clinical care Control: placebo (saline injections) plus standard clinical care *Second part of the study, open (86 patients):* LMWH, dalteparin (5000 IU sc, od) plus standard clinical care Control: standard clinical care alone. Duration: 18 weeks or until disease progression
Outcomes	Primary outcome: overall survival Secondary outcomes: toxic effects, incidence of thromboembolic events, changes in quality of life
Notes	Funding: Public Health Services grants from the National Cancer Institute, Department of Health and Human Services Disclosure of potential conflicts of interest: not reported and no COI forms available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported

Allocation concealment (selection bias)	Low risk	Performed centrally: "The randomization processes applied were handled through the North Central Cancer Treatment Group (NCCTG) Randomization Office."
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blinded in the first part of the trial, open in the second part
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: 68 out of 69 (98. 6%) were analysed in the LMWH, and 70 out of 72 (97.2%) were analysed in the control group
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

van Doormaal 2011

Methods	INPACT: Multicentre, open label RCT, intention-to-treat analyses for mortality
Participants	Patients with non-small cell lung cancer (stage IIIB), hormone-refractory prostate cancer, or locally advanced pancreatic cancer. Mean age (SD): 65 years (10) in the nadroparin group and 65 years (9.8) in the no nadroparin group. Previous VTE: 0/503. Median duration of follow up: 10.4 months
Interventions	LMWH, nadroparin in addition to standard anticancer treatment Control: standard anticancer treatment Subcutaneous nadroparin was administered for 6 weeks (2 weeks at therapeutic dose, and 4 weeks at half therapeutic dose). The patients were eligible to receive additional cycles of nadroparin (2 weeks at therapeutic dose, and 4 weeks of washout period) for a maximum of 6 cycles Mean duration of treatment: 12.6 weeks
Outcomes	Primary efficacy outcome: all-cause mortality Primary safety outcome: major bleeding Secondary efficacy outcomes: time to disease progression, clinically relevant non-major bleeding, VTE, arterial thromboembolic events
Notes	Funding: the study was supported by a grant from GlaxoSmithKline (Paris, France) Disclosure of potential conflicts of interest: two authors reported consultant or advisory roles honoraria and research funds that were relevant to the subject matter under consideration in their trial report

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Computer-generated: "Allocation of treatment proceeded centrally by using an interactive-voice response system"
Allocation concealment (selection bias)	Low risk	Performed centrally: Allocation of treatment proceeded centrally by using an interactive-voice response system
Blinding (performance bias and detection bias) All outcomes	Low risk	Open study, however "all study outcomes were adjudicated by an independent, blinded committee"
Incomplete outcome data (attrition bias) All outcomes	High risk	Effectiveness and safety: Percentage of patients enrolled and subsequently excluded from the analysis: 2.2% (11/503)
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods section were addressed in the results or discussion section

Zacharski 1981

Methods	Multicentre RCT, type of analyses not reported
Participants	Patients with small-cell lung carcinoma treated with chemotherapy and radiation therapy. Males: 100%. Extensive cancer: 52% warfarin and 48% control group respectively
Interventions	Intervention: warfarin at doses to prolong the prothrombin time to approximately two times the control value Control: no warfarin The median duration of warfarin administration was 27 weeks
Outcomes	Primary efficacy outcomes: survival and cancer response to treatment
Notes	Funding: VA Cooperative Studies Program Disclosure of potential conflicts of interest: not reported, no COI forms available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomisation by hospital and performance status
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported

Zacharski 1981 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients enrolled considered for the analysis. "No patient has been lost to follow-up."
Selective reporting (reporting bias)	Unclear risk	Bleeding was addressed in the results section, but not mentioned in the methods section

Zwicker 2013

Methods	MICROTEC: randomised, multicentre phase II study, use of intention-to-treat analyses reported
Participants	Participants with histologically confirmed advanced stage malignancy for which standard curative therapies did not exist. Eligible malignancies included: adenocarcinoma of the pancreas (locally advanced or metastatic), colorectal (stage IV), non-small cell lung cancer (stage III or IV), relapsed or stage IV ovarian, or surgically unresectable or metastatic gastric adenocarcinoma. Median age was 68.1 yrs (46.6-80.1) in the LMWH and 67.5 yrs (28.8-78.7) in the observation group. Male sex: 61% and 46%, respectively. Overall, 78.8% of the patients had metastatic disease
Interventions	Intervention: LMWH, enoxaparin (40 mg sc, od) Control: observation Treatment was given for 2 months
Outcomes	Primary efficacy outcome: cumulative incidence of VTE (i.e. any symptomatic proximal or distal lower extremity DVT, asymptomatic proximal DVT, symptomatic PE or fatal PE) at 2 months Primary safety outcome: major bleeding Secondary: toxicity and survival
Notes	Funding: the study was supported by grants from the National Institutes of Health, K23 HL84052 (JIZ) and R01 HL095084 (BF), as well as a research grant from Sano fi Disclosure of potential conflicts of interest: one author has served on steering committees for Sanofi; another has received research funds and served on advisory boards for Sanofi and Esai

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported

Allocation concealment (selection bias)	Low risk	Performed centrally: "Study coordination, randomization, and monitoring were performed by the Quality Assurance Office for Clinical Trials (QACT) at Dana Farber/ Harvard Cancer Center."
Blinding (performance bias and detection bias) All outcomes	High risk	Both the treating physicians and patients were blinded to microparticle status in the observation arms. However, patients in the control group were only observed, the use of placebo, blinding method or an independent and blinded adjudication committee was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were analysed. Four of the 70 patients initially enrolled were excluded prior to randomisation
Selective reporting (reporting bias)	High risk	The outcome toxicity was incompletely addressed in the results section

COI: conflict of interest
od: once daily
sc: subcutaneous

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

Study	Reason for exclusion
ABEL study 2005	The study has been terminated early due to difficulties to recruit 130 patients required by protocol. No study results were posted on ClinicalTrials.gov for this study (accessed at http://clinicaltrials.gov/ct2/show/NCT00324558 on 11 December 2012)
Baz 2005	Not an RCT
Bergqvist 1983	Perioperative thromboprophylaxis
Eichinger 2008	Inadequate population: hospitalised cancer patients
Haas 2011	Inadequate population: hospitalised cancer patients
Heilmann 1995	Perioperative thromboprophylaxis
Hills 1972	Perioperative thromboprophylaxis

(*Continued*)

Kessler 2011	Not an RCT
Kwaan 2007	Prophylaxis for catheter-related thrombosis
Levin 2008	This study has been terminated early because of a drug supply issue. Results of a single patient are posted (accessed at http://clinicaltrials.gov/ct2/show/results/NCT00790452 on 11 December 2012)
Macintyre 1974	Perioperative thromboprophylaxis
Maxwell 2000	Perioperative thromboprophylaxis
Meister 2008	Not an RCT
Minnema 2004	Not an RCT
Niesvizky 2007	Inadequate type of intervention: antiplatelet agent versus placebo
Pandya 2002	The study has been terminated early and no study results were posted on ClinicalTrials.gov for this study (accessed at http://clinicaltrials.gov/ct2/show/NCT00031837 on 13 June 2013)
Paydas 2008	Not an RCT
Poniewierski 1987	Inadequate population: hospitalised cancer patients
Rajan 1995	Inadequate outcomes
Sideras 2007	Perioperative thromboprophylaxis
Weber 2008	Inadequate population: hospitalised cancer patients
Welti 1981	Perioperative thromboprophylaxis
Zangari 2003	Not an RCT

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

Salat 1990

Methods	Prospective RCT
Participants	Patients (n = 80) with malignant diseases
Interventions	Unfractionated heparin (2 x 7500 IU/mL) Control: LMWH, dalteparin (5000 IU sc, od)
Outcomes	Thrombosis and haemorrhagic complications

Notes	

od: once daily
sc: subcutaneous

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

NCT00239980

Trial name or title	A phase II randomised study of Fragmin in ovarian cancer: utility on survival (FOCUS)
Methods	Randomised, open label study, Unclear methods of randomisation and allocation concealment
Participants	Women with newly diagnosed, histologically proven epithelial ovarian carcinoma
Interventions	Active Comparator A: LMWH, dalteparin 50 IU/kg sc od for 3 cycles of chemotherapy Active Comparator B: LMWH, dalteparin 100 IU/kg sc od for 3 cycles of chemotherapy Active Comparator C: LMWH, dalteparin 150 IU/kg sc od for 3 cycles of chemotherapy
Outcomes	Primary outcome measures: disease response Secondary outcome measures: symptomatic VTE, bleeding, compliance, death
Starting date	October 2005
Contact information	Elit L, Lee A
Notes	NCT00239980

NCT00320255

Trial name or title	A randomized, double-blind, placebo-controlled study of apixaban for the prevention of thromboembolic events in patients undergoing treatment for advanced cancer: a phase II pilot study
Methods	Randomised, double-blind (subject, investigator), placebo-controlled
Participants	Patients (18 years to 90 years) with advanced or metastatic cancer receiving chemotherapy for at least 90 days and entering the study within 6 weeks of start of chemotherapy
Interventions	Intervention: apixaban (5 mg once daily) Control: placebo Study treatment will be given for 12 weeks
Outcomes	Primary outcomes: major bleeding (fatal or non-fatal) or clinically relevant non-major bleeding Secondary outcomes: symptoms compatible with VTE

NCT00320255 (*Continued*)

Starting date	June 2006
Contact information	
Notes	NCT00320255

NCT00519805

Trial name or title	FRAGMATIC: A randomised phase III clinical trial investigating the effect of fragmin added to standard therapy in patients with lung cancer
Methods	Central randomisation using the method of minimisation and stratifying patients for a number of factors; open label, planned intention-to-treat analysis
Participants	Patients with histopathological or cytological diagnosis of primary bronchial carcinoma (small cell or non-small cell) within the last 6 weeks, age 18 or over, ECOG Performance status 0 to 3
Interventions	LMWH, dalteparin (5000 IU sc, od) plus standard anticancer treatment; dalteparin is given for 24 weeks and started as soon as possible and before first definitive anticancer treatment Control: standard anticancer treatment
Outcomes	Primary outcome: overall survival Secondary outcomes: venous thrombotic event-free survival, serious adverse events, metastasis-free survival, toxicity, quality of life, breathlessness, anxiety and depression, cost effectiveness, cost utility
Starting date	
Contact information	Griffiths GO: griffithsg@cardiff.ac.uk
Notes	

NCT00662688

Trial name or title	Chemotherapy with or without preventive anticoagulation for metastatic cancer of the pancreas
Methods	Randomised, multicentre study. Unclear methods of randomisation and allocation concealment
Participants	Patients with histologically confirmed adenocarcinoma of the pancreas (metastatic disease, not amenable to treatment, no localised or locally advanced disease) receiving treatment with different combinations of gemcitabine and capecitabine
Interventions	Arm 1A: gemcitabine hydrochloride IV over 150 minutes on days 1 and 15 Arm 1B: gemcitabine hydrochloride as in arm 1A and LMWH, dalteparin sc on day 1 Arm 2A: gemcitabine hydrochloride IV over 30 minutes on days 1, 8, and 15 and oral capecitabine every 12 hours on days 1-21 Arm 2B: gemcitabine hydrochloride and capecitabine as in arm 2A and LMWH, dalteparin sc as in arm 1B Treatment is repeated every 28 days in the absence of disease progression or unacceptable toxicity

NCT00662688 (*Continued*)

Outcomes	Primary outcome measures: thromboembolic events Secondary outcome measures: thromboembolic-related survival, progression-free survival, overall survival, time to response of tumour, tolerance of regimens
Starting date	October 2007
Contact information	Chibauldel B
Notes	NCT00662688

NCT00718354

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

NCT00876915

Trial name or title	A prospective randomised multicentre study of dalteparin prophylaxis in high-risk ambulatory cancer patients
Methods	Unclear methods of randomisation, allocation concealment and analysis; open label
Participants	Patients with a histologic diagnosis of malignancy, planned initiation of a new systemic chemotherapy regimen, and a risk score for VTE ≥ 3
Interventions	LMWH, dalteparin (5000 IU sc, od) Control: no dalteparin

NCT00876915 (*Continued*)

Outcomes	Primary outcome: safety and efficacy of prophylaxis with dalteparin compared with no treatment in reducing VTE Secondary outcome: value of tissue factor as a predictive marker for VTE
Starting date	July 2009
Contact information	Francis C
Notes	NCT00876915

NCT00966277

Trial name or title	Randomised clinical trial of dalteparin for primary VTE prophylaxis in pancreatic cancer patients undergoing chemotherapy treatment
Methods	Unclear methods of randomisation, allocation concealment and analysis; open label
Participants	Patients 18 years or older with a diagnosis of advanced stage (unresectable or metastatic) adenocarcinoma of the pancreas planning to initiate systemic chemotherapy within two weeks, ECOG performance status 0 - 2, adequate renal function (creatinine clearance of > 50 mL/min)
Interventions	LMWH, dalteparin (5000 IU sc, od) for 16 weeks Control: no dalteparin
Outcomes	Primary outcome: venous thromboembolic events during 16 weeks of treatment
Starting date	April 2010
Contact information	Vadhan-Raj S
Notes	NCT00966277

od: once daily

sc: subcutaneous

DATA AND ANALYSES

Comparison 1. Anticoagulants versus control: symptomatic VTE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic VTE: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Symptomatic VTE: LMWH vs inactive control	8	3246	Risk Ratio (IV, Random, 95% CI)	0.53 [0.38, 0.75]
2.1 Dalteparin	5	901	Risk Ratio (IV, Random, 95% CI)	0.64 [0.39, 1.06]
2.2 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.57 [0.24, 1.35]
2.3 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.50 [0.22, 1.13]
2.4 Enoxaparin	1	312	Risk Ratio (IV, Random, 95% CI)	0.35 [0.16, 0.75]
3 Symptomatic VTE: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.51 [0.22, 1.17]
4 Symptomatic VTE: LMWH vs warfarin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5 Symptomatic VTE: vitamin K antagonists vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
6 Symptomatic VTE: warfarin vs aspirin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
7 Symptomatic VTE: apixaban vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Anticoagulants versus control: major bleeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major bleeding: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Major bleeding: LMWH vs inactive control	10	4018	Risk Ratio (IV, Random, 95% CI)	1.30 [0.75, 2.23]
2.1 Dalteparin	4	819	Risk Ratio (IV, Random, 95% CI)	1.16 [0.39, 3.46]
2.2 Certoparin	1	898	Risk Ratio (IV, Random, 95% CI)	2.19 [0.84, 5.70]
2.3 Nadroparin	3	1955	Risk Ratio (IV, Random, 95% CI)	1.83 [0.69, 4.85]
2.4 Enoxaparin	2	346	Risk Ratio (IV, Random, 95% CI)	0.63 [0.29, 1.37]
3 Major bleeding: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.76]
4 Major bleeding: LMWH vs warfarin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5 Major bleeding: UFH vs inactive control	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
6 Major bleeding: vitamin K antagonists vs inactive control	4	994	Risk Ratio (IV, Random, 95% CI)	3.82 [0.97, 15.04]

7 Major bleeding: warfarin vs aspirin	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
8 Major bleeding: antithrombin vs placebo	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
9 Major bleeding: apixaban vs placebo	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Anticoagulants versus control: symptomatic PE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic PE: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Symptomatic PE: LMWH vs inactive control	5	2712	Risk Ratio (IV, Random, 95% CI)	0.59 [0.26, 1.36]
2.1 Dalteparin	3	679	Risk Ratio (IV, Random, 95% CI)	0.67 [0.17, 2.64]
2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.50 [0.10, 2.44]
2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.60 [0.14, 2.49]
3 Symptomatic PE: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.13 [0.02, 1.03]
4 Symptomatic PE: LMWH vs warfarin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5 Symptomatic PE: vitamin K antagonists vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
6 Symptomatic PE: warfarin vs aspirin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 4. Anticoagulants versus control: symptomatic DVT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic DVT: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Symptomatic DVT: LMWH vs inactive control	6	2796	Risk Ratio (IV, Random, 95% CI)	0.52 [0.33, 0.82]
2.1 Dalteparin	4	763	Risk Ratio (IV, Random, 95% CI)	0.55 [0.30, 1.02]
2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.50 [0.19, 1.31]
2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.46 [0.18, 1.20]
3 Symptomatic DVT: LMWH vs aspirin	2	782	Risk Ratio (IV, Random, 95% CI)	0.81 [0.32, 2.03]
4 Symptomatic DVT: LMWH vs warfarin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5 Symptomatic DVT: vitamin K antagonists vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

6 Symptomatic DVT: warfarin vs aspirin	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 5. Anticoagulants versus control: asymptomatic VTE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asymptomatic VTE: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Asymptomatic VTE: LMWH vs inactive control	3	2152	Risk Ratio (IV, Random, 95% CI)	0.69 [0.34, 1.43]
2.1 Dalteparin	1	119	Risk Ratio (IV, Random, 95% CI)	0.51 [0.10, 2.67]
2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.74 [0.21, 2.62]
2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.75 [0.26, 2.14]

Comparison 6. Anticoagulants versus control: overall VTE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall VTE: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Overall VTE: LMWH vs inactive control	6	2991	Risk Ratio (IV, Random, 95% CI)	0.64 [0.45, 0.91]
2.1 Dalteparin	1	119	Risk Ratio (IV, Random, 95% CI)	0.41 [0.17, 0.98]
2.2 Nadroparin	3	1955	Risk Ratio (IV, Random, 95% CI)	0.78 [0.48, 1.27]
2.3 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.65 [0.37, 1.15]
2.4 Enoxaparin	1	34	Risk Ratio (IV, Random, 95% CI)	0.16 [0.02, 1.36]
3 Overall VTE: antithrombin vs placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. Anticoagulants versus control: minor bleeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Minor bleeding: LMWH vs inactive control	6	2765	Risk Ratio (IV, Random, 95% CI)	1.26 [0.93, 1.72]
1.1 Dalteparin	4	717	Risk Ratio (IV, Random, 95% CI)	1.25 [0.72, 2.17]
1.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	1.00 [0.69, 1.45]
1.3 Certoparin	1	898	Risk Ratio (IV, Random, 95% CI)	1.96 [1.11, 3.46]
2 Minor bleeding: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	0.70 [0.17, 2.84]

3 Minor bleeding: LMWH vs warfarin	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4 Minor bleeding: UFH vs inactive control	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5 Minor bleeding: vitamin K antagonists vs placebo	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
6 Minor bleeding: warfarin vs aspirin	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
7 Minor bleeding: antithrombin vs placebo	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 8. Anticoagulants versus control: one-year mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 One-year mortality: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 One-year mortality: LMWH vs inactive control	7	2268	Risk Ratio (IV, Random, 95% CI)	0.95 [0.84, 1.09]
2.1 Dalteparin	4	782	Risk Ratio (IV, Random, 95% CI)	0.97 [0.77, 1.21]
2.2 Nadroparin	2	1452	Risk Ratio (IV, Random, 95% CI)	0.95 [0.77, 1.18]
2.3 Enoxaparin	1	34	Risk Ratio (IV, Random, 95% CI)	0.72 [0.34, 1.51]
3 One-year mortality: UFH vs inactive control	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 9. Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic arterial thromboembolism: LMWH vs inactive control	3	1772	Risk Ratio (IV, Random, 95% CI)	0.40 [0.16, 0.99]
1.1 Dalteparin	1	119	Risk Ratio (IV, Random, 95% CI)	0.51 [0.05, 5.46]
1.2 Nadroparin	2	1653	Risk Ratio (IV, Random, 95% CI)	0.38 [0.14, 1.03]
2 Symptomatic arterial thromboembolism: LMWH vs aspirin	2	781	Risk Ratio (IV, Random, 95% CI)	2.01 [0.37, 10.86]
3 Symptomatic arterial thromboembolism: LMWH vs warfarin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo	1	311	Risk Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

5 Symptomatic arterial thromboembolism: warfarin vs aspirin	1	Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 10. Anticoagulants versus control: superficial venous thrombosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Superficial venous thrombosis: LMWH vs inactive control	2	2033	Risk Ratio (IV, Random, 95% CI)	0.83 [0.30, 2.26]
1.1 Certoparin	1	883	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.83 [0.30, 2.26]
2 Superficial venous thrombosis: LMWH vs aspirin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Comparison 11. Anticoagulants versus control: serious adverse events

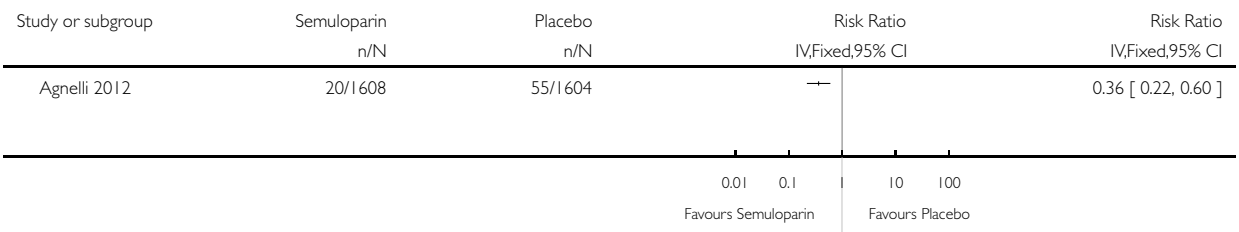
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events: semuloparin vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2 Serious adverse events: LMWH vs inactive control	4	1493	Risk Ratio (IV, Random, 95% CI)	0.89 [0.66, 1.21]
2.1 Dalteparin	3	343	Risk Ratio (IV, Random, 95% CI)	1.22 [0.45, 3.34]
2.2 Nadroparin	1	1150	Risk Ratio (IV, Random, 95% CI)	0.89 [0.68, 1.17]
3 Serious adverse events: apixaban vs placebo	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

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

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 1 Symptomatic VTE: semuloparin vs placebo



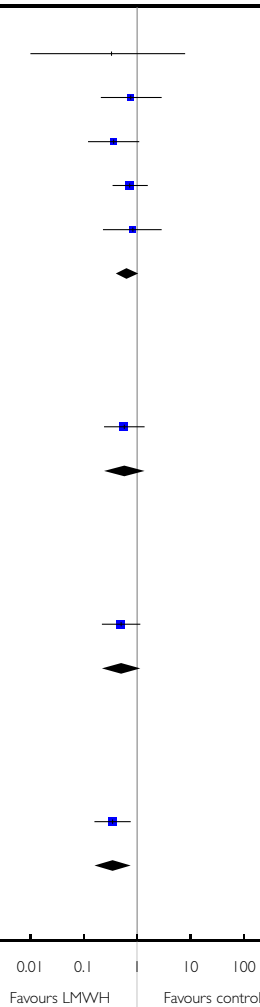
Analysis 1.2. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 2 Symptomatic VTE: LMWH vs inactive control.

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 2 Symptomatic VTE: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Altinbas 2004	0/42	1/42		1.2 %	0.33 [0.01, 7.96]
Kakkar 2004	4/190	5/184		7.0 %	0.77 [0.21, 2.84]
Maraveyas 2012	4/59	11/60		10.1 %	0.37 [0.12, 1.10]
Perry 2010	11/99	13/87		21.2 %	0.74 [0.35, 1.57]
Sideras 2006	4/68	5/70		7.4 %	0.82 [0.23, 2.94]
Subtotal (95% CI)	**458**	**443**		**46.8 %**	**0.64 [0.39, 1.06]**
Total events: 23 (LMWH), 35 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.53, df = 4 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.73 (P = 0.084)					
2 Certoparin					
Haas 2012	8/442	14/441		16.1 %	0.57 [0.24, 1.35]
Subtotal (95% CI)	**442**	**441**		**16.1 %**	**0.57 [0.24, 1.35]**
Total events: 8 (LMWH), 14 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
3 Nadroparin					
Agnelli 2009	11/769	11/381		17.4 %	0.50 [0.22, 1.13]
Subtotal (95% CI)	**769**	**381**		**17.4 %**	**0.50 [0.22, 1.13]**
Total events: 11 (LMWH), 11 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.096)					
4 Enoxaparin					
Pelzer 2009	8/160	22/152		19.6 %	0.35 [0.16, 0.75]
Subtotal (95% CI)	**160**	**152**		**19.6 %**	**0.35 [0.16, 0.75]**
Total events: 8 (LMWH), 22 (Inactive control)					



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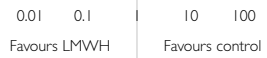
Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 2.68 (P = 0.0074)					
Total (95% CI)	**1829**	**1417**		**100.0 %**	**0.53 [0.38, 0.75]**
Total events: 50 (LMWH), 82 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.29, df = 7 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 3.58 (P = 0.00034)					
Test for subgroup differences: Chi^2 = 1.76, df = 3 (P = 0.62), I^2 =0.0%					



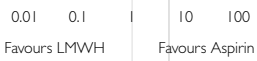
Analysis 1.3. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 3 Symptomatic VTE: LMWH vs aspirin.

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 3 Symptomatic VTE: LMWH vs aspirin

Study or subgroup	LMWH n/N	Aspirin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Larocca 2012	2/166	4/176		24.6 %	0.53 [0.10, 2.86]
Palumbo 2011	6/219	12/220		75.4 %	0.50 [0.19, 1.31]
Total (95% CI)	**385**	**396**		**100.0 %**	**0.51 [0.22, 1.17]**
Total events: 8 (LMWH), 16 (Aspirin)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.58 (P = 0.11)					
Test for subgroup differences: Not applicable					



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

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 4 Symptomatic VTE: LMWH vs warfarin

Study or subgroup	LMWH n/N	Warfarin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	6/219	18/220		0.33 [0.14, 0.83]

Analysis 1.5. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 5 Symptomatic VTE: vitamin K antagonists vs placebo.

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 5 Symptomatic VTE: vitamin K antagonists vs placebo

Study or subgroup	VKA n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 1994	1/152	7/159		0.15 [0.02, 1.20]

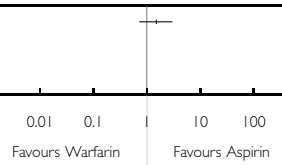
Analysis 1.6. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 6 Symptomatic VTE: warfarin vs aspirin.

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 6 Symptomatic VTE: warfarin vs aspirin

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	18/220	12/220		1.50 [0.74, 3.04]



Analysis 1.7. Comparison 1 Anticoagulants versus control: symptomatic VTE, Outcome 7 Symptomatic VTE: apixaban vs placebo.

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

Comparison: 1 Anticoagulants versus control: symptomatic VTE

Outcome: 7 Symptomatic VTE: apixaban vs placebo

Study or subgroup	Apixaban n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 2012	1/95	3/30		0.11 [0.01, 0.97]

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

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 1 Major bleeding: semuloparin vs placebo

Study or subgroup	Favours Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	19/1589	18/1583		1.05 [0.55, 2.00]

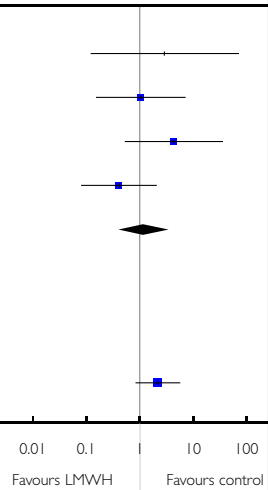
Analysis 2.2. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 2 Major bleeding: LMWH vs inactive control.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 2 Major bleeding: LMWH vs inactive control

Study or subgroup	Favours LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Kakkar 2004	1/190	0/184		2.7 %	2.91 [0.12, 70.87]
Maraveyas 2012	2/59	2/62		6.9 %	1.05 [0.15, 7.22]
Perry 2010	5/99	1/87		5.8 %	4.39 [0.52, 36.89]
Sideras 2006	2/68	5/70		9.3 %	0.41 [0.08, 2.05]
Subtotal (95% CI)	**416**	**403**		**24.7 %**	**1.16 [0.39, 3.46]**
Total events: 10 (Favours LMWH), 8 (Inactive control)					
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 3.42$, df = 3 (P = 0.33); $I^2 = 12\%$					
Test for overall effect: Z = 0.26 (P = 0.80)					
2 Certoparin					
Haas 2012	13/447	6/451		19.6 %	2.19 [0.84, 5.70]



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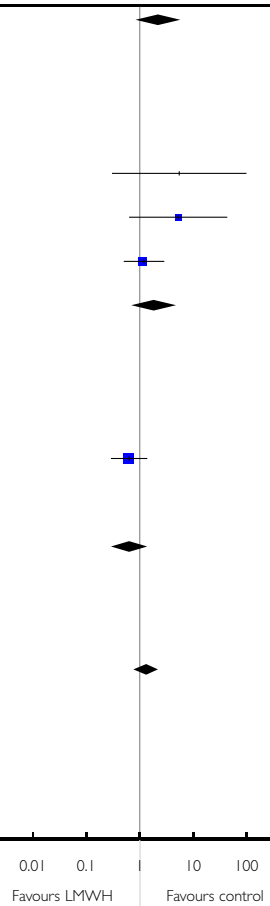
Study or subgroup	Favours LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Subtotal (95% CI)	**447**	**451**		**19.6 %**	**2.19 [0.84, 5.70]**
Total events: 13 (Favours LMWH), 6 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.60 (P = 0.11)					
3 Nadroparin					
Agnelli 2009	5/769	0/381		3.3 %	5.46 [0.30, 98.43]
Klerk 2005	5/148	1/154		5.7 %	5.20 [0.62, 44.01]
van Doormaal 2011	10/244	9/259		21.6 %	1.18 [0.49, 2.85]
Subtotal (95% CI)	**1161**	**794**		**30.6 %**	**1.83 [0.69, 4.85]**
Total events: 20 (Favours LMWH), 10 (Inactive control)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 2.32, df = 2 (P = 0.31); I^2 =14%					
Test for overall effect: Z = 1.21 (P = 0.22)					
4 Enoxaparin					
Pelzer 2009	10/160	15/152		25.1 %	0.63 [0.29, 1.37]
Zwicker 2013	0/23	0/11			Not estimable
Subtotal (95% CI)	**183**	**163**		**25.1 %**	**0.63 [0.29, 1.37]**
Total events: 10 (Favours LMWH), 15 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.24)					
Total (95% CI)	**2207**	**1811**		**100.0 %**	**1.30 [0.75, 2.23]**
Total events: 53 (Favours LMWH), 39 (Inactive control)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 10.47, df = 8 (P = 0.23); I^2 =24%					
Test for overall effect: Z = 0.94 (P = 0.35)					
Test for subgroup differences: Chi^2 = 4.88, df = 3 (P = 0.18), I^2 =39%					



Analysis 2.3. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 3 Major bleeding: LMWH vs aspirin.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 3 Major bleeding: LMWH vs aspirin

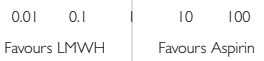
Study or subgroup	Favours LMWH n/N	Favours Aspirin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Larocca 2012	0/166	0/176			Not estimable
Palumbo 2011	0/219	3/220		100.0 %	0.14 [0.01, 2.76]
Total (95% CI)	**385**	**396**		**100.0 %**	**0.14 [0.01, 2.76]**

Total events: 0 (Favours LMWH), 3 (Favours Aspirin)

Heterogeneity: not applicable

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable



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

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 4 Major bleeding: LMWH vs warfarin

Study or subgroup	LMWH n/N	Warfarin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	0/220	0/220		Not estimable

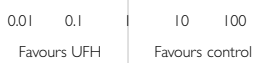
Analysis 2.5. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 5 Major bleeding: UFH vs inactive control.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 5 Major bleeding: UFH vs inactive control

Study or subgroup	UFH n/N	Inactive control n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Lebeau 1994	1/138	1/139		1.01 [0.06, 15.94]



Analysis 2.6. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 6 Major bleeding: vitamin K antagonists vs inactive control.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 6 Major bleeding: vitamin K antagonists vs inactive control

Study or subgroup	VKA n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Chahinian 1989	7/100	0/186		17.3 %	27.77 [1.60, 481.30]
Levine 1994	1/152	2/159		22.2 %	0.52 [0.05, 5.71]
Maurer 1997	12/178	3/169		43.7 %	3.80 [1.09, 13.22]
Zacharski 1981	3/25	0/25		16.7 %	7.00 [0.38, 128.87]
Total (95% CI)	**455**	**539**		**100.0 %**	**3.82 [0.97, 15.04]**

Total events: 23 (VKA), 5 (Inactive control)

Heterogeneity: $Tau^2 = 0.71$; $Chi^2 = 4.68$, df = 3 (P = 0.20); $I^2 = 36\%$

Test for overall effect: Z = 1.92 (P = 0.055)

Test for subgroup differences: Not applicable

Analysis 2.7. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 7 Major bleeding: warfarin vs aspirin.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 7 Major bleeding: warfarin vs aspirin

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	0/220	3/220		0.14 [0.01, 2.75]

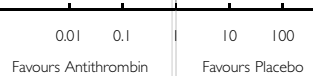
Analysis 2.8. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 8 Major bleeding: antithrombin vs placebo.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 8 Major bleeding: antithrombin vs placebo

Study or subgroup	Antithrombin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Mitchell 2003	0/25	1/60		0.78 [0.03, 18.57]



Analysis 2.9. Comparison 2 Anticoagulants versus control: major bleeding, Outcome 9 Major bleeding: apixaban vs placebo.

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

Comparison: 2 Anticoagulants versus control: major bleeding

Outcome: 9 Major bleeding: apixaban vs placebo

Study or subgroup	Apixaban n/N	Control n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 2012	2/95	1/30		0.63 [0.06, 6.72]

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

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

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 1 Symptomatic PE: semuloparin vs placebo

Study or subgroup	Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	10/1608	21/1604		0.48 [0.22, 1.01]

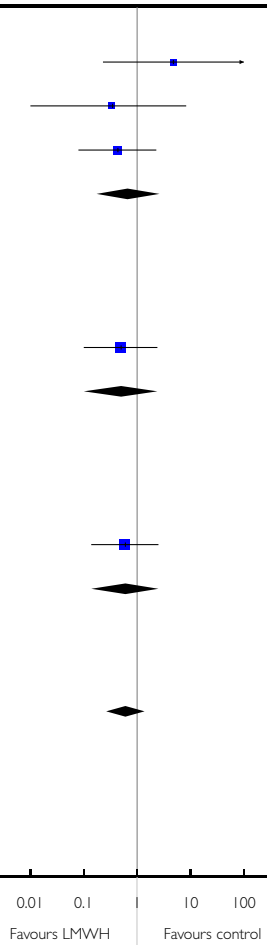
Analysis 3.2. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 2 Symptomatic PE: LMWH vs inactive control.

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

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 2 Symptomatic PE: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Kakkar 2004	2/190	0/184		7.5 %	4.84 [0.23, 100.20]
Maraveyas 2012	0/59	1/60		6.8 %	0.34 [0.01, 8.15]
Perry 2010	2/99	4/87		24.6 %	0.44 [0.08, 2.34]
Subtotal (95% CI)	**348**	**331**		**39.0 %**	**0.67 [0.17, 2.64]**
Total events: 4 (LMWH), 5 (Inactive control)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.06, df = 2 (P = 0.36); I^2 =3%					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Nadroparin					
Agnelli 2009	3/769	3/381		27.1 %	0.50 [0.10, 2.44]
Subtotal (95% CI)	**769**	**381**		**27.1 %**	**0.50 [0.10, 2.44]**
Total events: 3 (LMWH), 3 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
3 Certoparin					
Haas 2012	3/442	5/441		33.9 %	0.60 [0.14, 2.49]
Subtotal (95% CI)	**442**	**441**		**33.9 %**	**0.60 [0.14, 2.49]**
Total events: 3 (LMWH), 5 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
Total (95% CI)	**1559**	**1153**		**100.0 %**	**0.59 [0.26, 1.36]**
Total events: 10 (LMWH), 13 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.14, df = 4 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 1.23 (P = 0.22)					
Test for subgroup differences: Chi^2 = 0.08, df = 2 (P = 0.96), I^2 =0.0%					



Analysis 3.3. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 3 Symptomatic PE: LMWH vs aspirin.

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

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 3 Symptomatic PE: LMWH vs aspirin

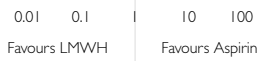
Study or subgroup	LMWH n/N	Aspirin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Larocca 2012	0/166	3/176		49.3 %	0.15 [0.01, 2.91]
Palumbo 2011	0/219	4/220		50.7 %	0.11 [0.01, 2.06]
Total (95% CI)	**385**	**396**		**100.0 %**	**0.13 [0.02, 1.03]**

Total events: 0 (LMWH), 7 (Aspirin)

Heterogeneity: Tau² = 0.0; Chi² = 0.02, df = 1 (P = 0.89); I² =0.0%

Test for overall effect: Z = 1.93 (P = 0.054)

Test for subgroup differences: Not applicable



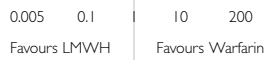
Analysis 3.4. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 4 Symptomatic PE: LMWH vs warfarin.

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

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 4 Symptomatic PE: LMWH vs warfarin

Study or subgroup	LMWH n/N	Warfarin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	0/219	4/220		0.11 [0.01, 2.06]



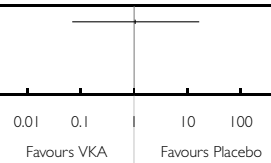
Analysis 3.5. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 5 Symptomatic PE: vitamin K antagonists vs placebo.

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

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 5 Symptomatic PE: vitamin K antagonists vs placebo

Study or subgroup	VKA n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 1994	1/152	1/159		1.05 [0.07, 16.58]



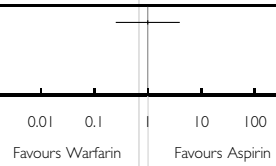
Analysis 3.6. Comparison 3 Anticoagulants versus control: symptomatic PE, Outcome 6 Symptomatic PE: warfarin vs aspirin.

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

Comparison: 3 Anticoagulants versus control: symptomatic PE

Outcome: 6 Symptomatic PE: warfarin vs aspirin

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	4/220	4/220		1.00 [0.25, 3.95]



Analysis 4.1. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 1 Symptomatic DVT: semuloparin vs placebo.

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

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 1 Symptomatic DVT: semuloparin vs placebo

Study or subgroup	Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	11/1608	34/1604		0.32 [0.16, 0.63]

Analysis 4.2. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 2 Symptomatic DVT: LMWH vs inactive control.

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

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 2 Symptomatic DVT: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Altinbas 2004	0/42	1/42		2.1 %	0.33 [0.01, 7.96]
Kakkar 2004	1/190	4/184		4.3 %	0.24 [0.03, 2.15]
Maraveyas 2012	4/59	11/60		17.5 %	0.37 [0.12, 1.10]
Perry 2010	10/99	11/87		31.8 %	0.80 [0.36, 1.79]
Subtotal (95% CI)	**390**	**373**		**55.7 %**	**0.55 [0.30, 1.02]**
Total events: 15 (LMWH), 27 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.97, df = 3 (P = 0.58); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.057)					
2 Nadroparin					
Agnelli 2009	8/769	8/381		21.9 %	0.50 [0.19, 1.31]

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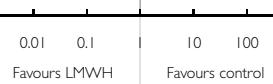
Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Subtotal (95% CI)	**769**	**381**		**21.9 %**	**0.50 [0.19, 1.31]**
Total events: 8 (LMWH), 8 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
3 Certoparin					
Haas 2012	6/442	13/441		22.5 %	0.46 [0.18, 1.20]
Subtotal (95% CI)	**442**	**441**		**22.5 %**	**0.46 [0.18, 1.20]**
Total events: 6 (LMWH), 13 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
Total (95% CI)	**1601**	**1195**		**100.0 %**	**0.52 [0.33, 0.82]**
Total events: 29 (LMWH), 48 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.09, df = 5 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.83 (P = 0.0046)					
Test for subgroup differences: Chi^2 = 0.11, df = 2 (P = 0.95), I^2 =0.0%					



Analysis 4.3. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 3 Symptomatic DVT: LMWH vs aspirin.

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

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 3 Symptomatic DVT: LMWH vs aspirin

Study or subgroup	LMWH n/N	Aspirin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Larocca 2012	2/166	2/176		22.2 %	1.06 [0.15, 7.44]
Palumbo 2011	6/220	8/220		77.8 %	0.75 [0.26, 2.13]
Total (95% CI)	**386**	**396**		**100.0 %**	**0.81 [0.32, 2.03]**
Total events: 8 (LMWH), 10 (Aspirin)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 0.45 (P = 0.65)					
Test for subgroup differences: Not applicable					

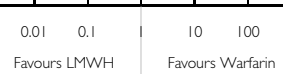
Analysis 4.4. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 4 Symptomatic DVT: LMWH vs warfarin.

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

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 4 Symptomatic DVT: LMWH vs warfarin

Study or subgroup	LMWH n/N	Warfarin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	6/219	14/220		0.43 [0.17, 1.10]



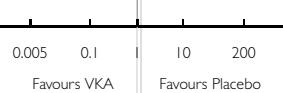
Analysis 4.5. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 5 Symptomatic DVT: vitamin K antagonists vs placebo.

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

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 5 Symptomatic DVT: vitamin K antagonists vs placebo

Study or subgroup	VKA n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 1994	0/152	6/159		0.08 [0.00, 1.42]



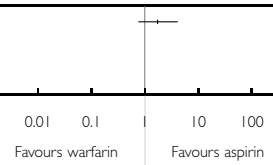
Analysis 4.6. Comparison 4 Anticoagulants versus control: symptomatic DVT, Outcome 6 Symptomatic DVT: warfarin vs aspirin.

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

Comparison: 4 Anticoagulants versus control: symptomatic DVT

Outcome: 6 Symptomatic DVT: warfarin vs aspirin

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	14/220	8/220		1.75 [0.75, 4.09]



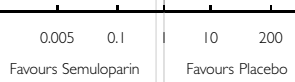
Analysis 5.1. Comparison 5 Anticoagulants versus control: asymptomatic VTE, Outcome 1 Asymptomatic VTE: semuloparin vs placebo.

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

Comparison: 5 Anticoagulants versus control: asymptomatic VTE

Outcome: 1 Asymptomatic VTE: semuloparin vs placebo

Study or subgroup	Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	0/1608	3/1604		0.14 [0.01, 2.76]



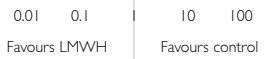
Analysis 5.2. Comparison 5 Anticoagulants versus control: asymptomatic VTE, Outcome 2 Asymptomatic VTE: LMWH vs inactive control.

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

Comparison: 5 Anticoagulants versus control: asymptomatic VTE

Outcome: 2 Asymptomatic VTE: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Maraveyas 2012	2/59	4/60		19.1 %	0.51 [0.10, 2.67]
Subtotal (95% CI)	**59**	**60**		**19.1 %**	**0.51 [0.10, 2.67]**
Total events: 2 (LMWH), 4 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 Nadroparin					
Agnelli 2009	6/769	4/381		33.2 %	0.74 [0.21, 2.62]
Subtotal (95% CI)	**769**	**381**		**33.2 %**	**0.74 [0.21, 2.62]**
Total events: 6 (LMWH), 4 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.64)					
3 Certoparin					
Haas 2012	6/442	8/441		47.7 %	0.75 [0.26, 2.14]
Subtotal (95% CI)	**442**	**441**		**47.7 %**	**0.75 [0.26, 2.14]**
Total events: 6 (LMWH), 8 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
Total (95% CI)	**1270**	**882**		**100.0 %**	**0.69 [0.34, 1.43]**
Total events: 14 (LMWH), 16 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.17, df = 2 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Chi^2 = 0.17, df = 2 (P = 0.92), I^2 =0.0%					



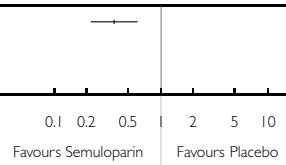
Analysis 6.1. Comparison 6 Anticoagulants versus control: overall VTE, Outcome 1 Overall VTE: semuloparin vs placebo.

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

Comparison: 6 Anticoagulants versus control: overall VTE

Outcome: 1 Overall VTE: semuloparin vs placebo

Study or subgroup	Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	20/1608	55/1604		0.36 [0.22, 0.60]



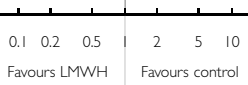
Analysis 6.2. Comparison 6 Anticoagulants versus control: overall VTE, Outcome 2 Overall VTE: LMWH vs inactive control.

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

Comparison: 6 Anticoagulants versus control: overall VTE

Outcome: 2 Overall VTE: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Maraveyas 2012	6/59	15/60		14.7 %	0.41 [0.17, 0.98]
Subtotal (95% CI)	**59**	**60**		**14.7 %**	**0.41 [0.17, 0.98]**
Total events: 6 (LMWH), 15 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.044)					
2 Nadroparin					
Agnelli 2009	18/769	16/381		24.2 %	0.56 [0.29, 1.08]
Klerk 2005	2/148	3/154		3.8 %	0.69 [0.12, 4.09]
van Doormaal 2011	16/244	15/259		23.0 %	1.13 [0.57, 2.24]
Subtotal (95% CI)	**1161**	**794**		**50.9 %**	**0.78 [0.48, 1.27]**
Total events: 36 (LMWH), 34 (Inactive control)					



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Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Heterogeneity: Tau² = 0.01; Chi² = 2.15, df = 2 (P = 0.34); I² =7%					
Test for overall effect: Z = 1.00 (P = 0.32)					
3 Certoparin					
Haas 2012	19/442	29/441		31.7 %	0.65 [0.37, 1.15]
Subtotal (95% CI)	**442**	**441**		**31.7 %**	**0.65 [0.37, 1.15]**
Total events: 19 (LMWH), 29 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					
4 Enoxaparin					
Zwicker 2013	1/23	3/11		2.6 %	0.16 [0.02, 1.36]
Subtotal (95% CI)	**23**	**11**		**2.6 %**	**0.16 [0.02, 1.36]**
Total events: 1 (LMWH), 3 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.094)					
Total (95% CI)	**1685**	**1306**		**100.0 %**	**0.64 [0.45, 0.91]**
Total events: 62 (LMWH), 81 (Inactive control)					
Heterogeneity: Tau² = 0.02; Chi² = 5.50, df = 5 (P = 0.36); I² =9%					
Test for overall effect: Z = 2.47 (P = 0.013)					
Test for subgroup differences: Chi² = 3.28, df = 3 (P = 0.35), I² =9%					

Analysis 6.3. Comparison 6 Anticoagulants versus control: overall VTE, Outcome 3 Overall VTE: antithrombin vs placebo.

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

Comparison: 6 Anticoagulants versus control: overall VTE

Outcome: 3 Overall VTE: antithrombin vs placebo

Study or subgroup	Antithrombin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mitchell 2003	7/25	20/60		0.84 [0.41, 1.73]

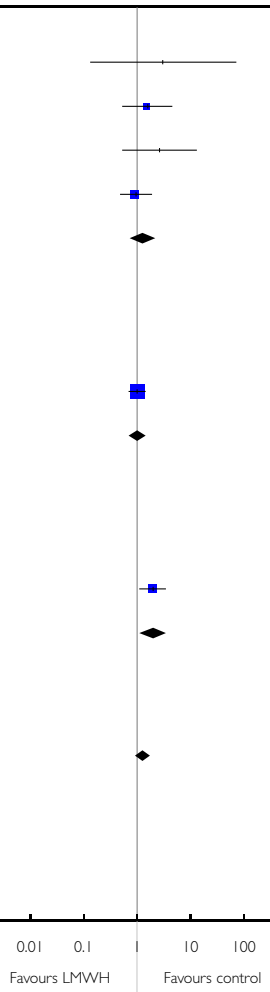
Analysis 7.1. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 1 Minor bleeding: LMWH vs inactive control.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 1 Minor bleeding: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Altinbas 2004	1/42	0/42		0.9 %	3.00 [0.13, 71.61]
Kakkar 2004	8/190	5/184		7.4 %	1.55 [0.52, 4.65]
Maraveyas 2012	5/59	2/62		3.6 %	2.63 [0.53, 13.02]
Sideras 2006	12/68	13/70		16.6 %	0.95 [0.47, 1.93]
Subtotal (95% CI)	**359**	**358**		**28.6 %**	**1.25 [0.72, 2.17]**
Total events: 26 (LMWH), 20 (Inactive control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.84, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
2 Nadroparin					
Agnelli 2009	77/769	38/381		47.2 %	1.00 [0.69, 1.45]
Subtotal (95% CI)	**769**	**381**		**47.2 %**	**1.00 [0.69, 1.45]**
Total events: 77 (LMWH), 38 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.98)					
3 Certoparin					
Haas 2012	33/447	17/451		24.3 %	1.96 [1.11, 3.46]
Subtotal (95% CI)	**447**	**451**		**24.3 %**	**1.96 [1.11, 3.46]**
Total events: 33 (LMWH), 17 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.31 (P = 0.021)					
Total (95% CI)	**1575**	**1190**		**100.0 %**	**1.26 [0.93, 1.72]**
Total events: 136 (LMWH), 75 (Inactive control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.57, df = 5 (P = 0.35); I^2 =10%					
Test for overall effect: Z = 1.49 (P = 0.14)					
Test for subgroup differences: Chi^2 = 3.73, df = 2 (P = 0.16), I^2 =46%					



Analysis 7.2. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 2 Minor bleeding: LMWH vs aspirin.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 2 Minor bleeding: LMWH vs aspirin

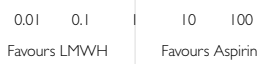
Study or subgroup	LMWH n/N	Aspirin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Larocca 2012	1/166	0/176		18.2 %	3.18 [0.13, 77.51]
Palumbo 2011	3/219	6/220		81.8 %	0.50 [0.13, 1.98]
Total (95% CI)	**385**	**396**		**100.0 %**	**0.70 [0.17, 2.84]**

Total events: 4 (LMWH), 6 (Aspirin)

Heterogeneity: Tau^2 = 0.13; Chi^2 = 1.08, df = 1 (P = 0.30); I^2 =8%

Test for overall effect: Z = 0.49 (P = 0.62)

Test for subgroup differences: Not applicable



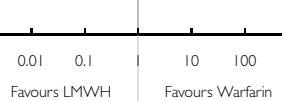
Analysis 7.3. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 3 Minor bleeding: LMWH vs warfarin.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 3 Minor bleeding: LMWH vs warfarin

Study or subgroup	LMWH n/N	Warfarin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	3/219	1/220		3.01 [0.32, 28.75]



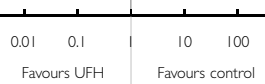
Analysis 7.4. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 4 Minor bleeding: UFH vs inactive control.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 4 Minor bleeding: UFH vs inactive control

Study or subgroup	UFH n/N	Inactive control n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Lebeau 1994	1/138	0/139		3.02 [0.12, 73.54]



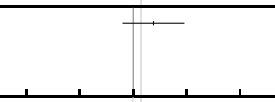
Analysis 7.5. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 5 Minor bleeding: vitamin K antagonists vs placebo.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 5 Minor bleeding: vitamin K antagonists vs placebo

Study or subgroup	VKA n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 1994	7/152	3/159		2.44 [0.64, 9.27]



Analysis 7.6. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 6 Minor bleeding: warfarin vs aspirin.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 6 Minor bleeding: warfarin vs aspirin

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	1/220	6/220		0.17 [0.02, 1.37]

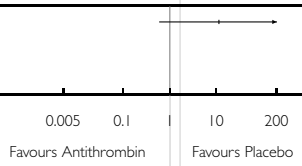
Analysis 7.7. Comparison 7 Anticoagulants versus control: minor bleeding, Outcome 7 Minor bleeding: antithrombin vs placebo.

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

Comparison: 7 Anticoagulants versus control: minor bleeding

Outcome: 7 Minor bleeding: antithrombin vs placebo

Study or subgroup	Antithrombin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Mitchell 2003	2/25	0/60		11.73 [0.58, 235.96]



Analysis 8.1. Comparison 8 Anticoagulants versus control: one-year mortality, Outcome 1 One-year mortality: semuloparin vs placebo.

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

Comparison: 8 Anticoagulants versus control: one-year mortality

Outcome: 1 One-year mortality: semuloparin vs placebo

Study or subgroup	Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	910/1608	890/1604		1.02 [0.96, 1.08]

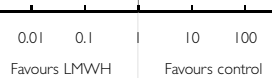
Analysis 8.2. Comparison 8 Anticoagulants versus control: one-year mortality, Outcome 2 One-year mortality: LMWH vs inactive control.

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

Comparison: 8 Anticoagulants versus control: one-year mortality

Outcome: 2 One-year mortality: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Altinbas 2004	18/42	28/42		7.7 %	0.64 [0.43, 0.97]
Kakkar 2004	105/190	112/184		20.4 %	0.91 [0.76, 1.08]
Perry 2010	45/99	32/87		9.7 %	1.24 [0.87, 1.75]
Sideras 2006	45/68	41/70		14.0 %	1.13 [0.87, 1.47]
Subtotal (95% CI)	**399**	**383**		**51.8 %**	**0.97 [0.77, 1.21]**
Total events: 213 (LMWH), 213 (Inactive control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 7.59, df = 3 (P = 0.06); I^2 =60%					
Test for overall effect: Z = 0.29 (P = 0.77)					
2 Nadroparin					
Agnelli 2009	333/769	155/381		22.7 %	1.06 [0.92, 1.23]



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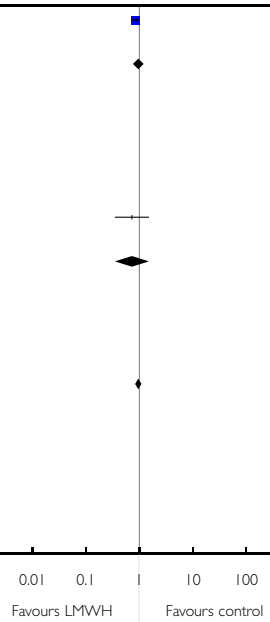
Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Klerk 2005	97/148	118/154		22.7 %	0.86 [0.74, 0.99]
Subtotal (95% CI)	**917**	**535**		**45.4 %**	**0.95 [0.77, 1.18]**
Total events: 430 (LMWH), 273 (Inactive control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 4.32, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 0.43 (P = 0.67)					
3 Enoxaparin					
Zwicker 2013	9/23	6/11		2.8 %	0.72 [0.34, 1.51]
Subtotal (95% CI)	**23**	**11**		**2.8 %**	**0.72 [0.34, 1.51]**
Total events: 9 (LMWH), 6 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.88 (P = 0.38)					
Total (95% CI)	**1339**	**929**		**100.0 %**	**0.95 [0.84, 1.09]**
Total events: 652 (LMWH), 492 (Inactive control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 12.50, df = 6 (P = 0.05); I^2 =52%					
Test for overall effect: Z = 0.70 (P = 0.48)					
Test for subgroup differences: Chi^2 = 0.58, df = 2 (P = 0.75), I^2 =0.0%					



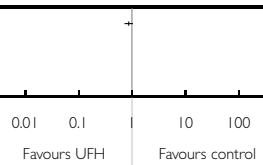
Analysis 8.3. Comparison 8 Anticoagulants versus control: one-year mortality, Outcome 3 One-year mortality: UFH vs inactive control.

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

Comparison: 8 Anticoagulants versus control: one-year mortality

Outcome: 3 One-year mortality: UFH vs inactive control

Study or subgroup	UFH n/N	Inactive control n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Lebeau 1994	83/138	97/139		0.86 [0.72, 1.03]



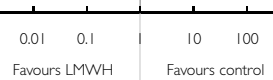
Analysis 9.1. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 1 Symptomatic arterial thromboembolism: LMWH vs inactive control.

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

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 1 Symptomatic arterial thromboembolism: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Maraveyas 2012	1/59	2/60		15.0 %	0.51 [0.05, 5.46]
Subtotal (95% CI)	**59**	**60**		**15.0 %**	**0.51 [0.05, 5.46]**
Total events: 1 (LMWH), 2 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.56 (P = 0.58)					
2 Nadroparin					
Agnelli 2009	3/769	3/381		33.2 %	0.50 [0.10, 2.44]
van Doormaal 2011	3/244	10/259		51.8 %	0.32 [0.09, 1.14]
Subtotal (95% CI)	**1013**	**640**		**85.0 %**	**0.38 [0.14, 1.03]**
Total events: 6 (LMWH), 13 (Inactive control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.91 (P = 0.056)					
Total (95% CI)	**1072**	**700**		**100.0 %**	**0.40 [0.16, 0.99]**
Total events: 7 (LMWH), 15 (Inactive control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 2 (P = 0.89); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.98 (P = 0.048)					
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.82), $I^2 = 0.0\%$					



Analysis 9.2. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 2 Symptomatic arterial thromboembolism: LMWH vs aspirin.

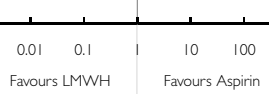
Review: Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 2 Symptomatic arterial thromboembolism: LMWH vs aspirin

Study or subgroup	LMWH n/N	Aspirin n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Larocca 2012	0/166	0/176			Not estimable
Palumbo 2011	4/219	2/220		100.0 %	2.01 [0.37, 10.86]
Total (95% CI)	**385**	**396**		**100.0 %**	**2.01 [0.37, 10.86]**

Total events: 4 (LMWH), 2 (Aspirin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 3 Symptomatic arterial thromboembolism: LMWH vs warfarin.

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

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 3 Symptomatic arterial thromboembolism: LMWH vs warfarin

Study or subgroup	LMWH n/N	Warfarin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	4/219	0/220		9.04 [0.49, 166.92]

Analysis 9.4. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 4 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo.

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

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 4 Symptomatic arterial thromboembolism: vitamin K antagonists vs placebo

Study or subgroup	VKA n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Levine 1994	0/152	0/159			Not estimable
Total (95% CI)	**152**	**159**			**Not estimable**
Total events: 0 (VKA), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

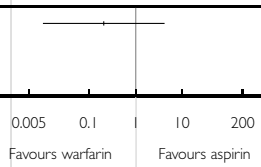
Analysis 9.5. Comparison 9 Anticoagulants versus control: symptomatic arterial thromboembolism, Outcome 5 Symptomatic arterial thromboembolism: warfarin vs aspirin.

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

Comparison: 9 Anticoagulants versus control: symptomatic arterial thromboembolism

Outcome: 5 Symptomatic arterial thromboembolism: warfarin vs aspirin

Study or subgroup	Warfarin n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Palumbo 2011	0/220	2/220		0.20 [0.01, 4.14]



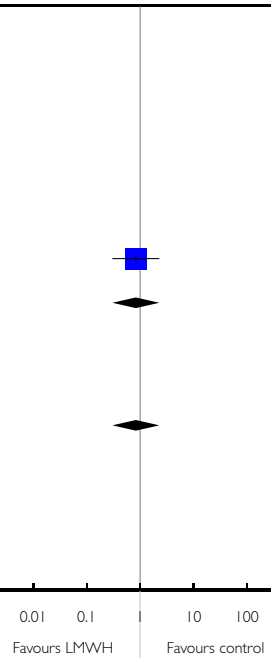
Analysis 10.1. Comparison 10 Anticoagulants versus control: superficial venous thrombosis, Outcome 1 Superficial venous thrombosis: LMWH vs inactive control.

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

Comparison: 10 Anticoagulants versus control: superficial venous thrombosis

Outcome: 1 Superficial venous thrombosis: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Certoparin					
Haas 2012	0/442	0/441			Not estimable
Subtotal (95% CI)	**442**	**441**			**Not estimable**
Total events: 0 (LMWH), 0 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Nadroparin					
Agnelli 2009	10/769	6/381		100.0 %	0.83 [0.30, 2.26]
Subtotal (95% CI)	**769**	**381**		**100.0 %**	**0.83 [0.30, 2.26]**
Total events: 10 (LMWH), 6 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
Total (95% CI)	**1211**	**822**		**100.0 %**	**0.83 [0.30, 2.26]**
Total events: 10 (LMWH), 6 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
Test for subgroup differences: Not applicable					



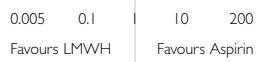
Analysis 10.2. Comparison 10 Anticoagulants versus control: superficial venous thrombosis, Outcome 2 Superficial venous thrombosis: LMWH vs aspirin.

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

Comparison: 10 Anticoagulants versus control: superficial venous thrombosis

Outcome: 2 Superficial venous thrombosis: LMWH vs aspirin

Study or subgroup	LMWH n/N	Aspirin n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Larocca 2012	0/166	4/176		0.12 [0.01, 2.17]



Analysis 11.1. Comparison 11 Anticoagulants versus control: serious adverse events, Outcome 1 Serious adverse events: semuloparin vs placebo.

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

Comparison: 11 Anticoagulants versus control: serious adverse events

Outcome: 1 Serious adverse events: semuloparin vs placebo

Study or subgroup	Semuloparin n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Agnelli 2012	418/1589	403/1583		1.03 [0.92, 1.16]

Analysis 11.2. Comparison 11 Anticoagulants versus control: serious adverse events, Outcome 2 Serious adverse events: LMWH vs inactive control.

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

Comparison: 11 Anticoagulants versus control: serious adverse events

Outcome: 2 Serious adverse events: LMWH vs inactive control

Study or subgroup	LMWH n/N	Inactive control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Dalteparin					
Altinbas 2004	5/42	1/42		2.0 %	5.00 [0.61, 40.99]
Maraveyas 2012	17/59	24/62		28.4 %	0.74 [0.45, 1.24]
Sideras 2006	3/68	2/70		2.9 %	1.54 [0.27, 8.96]
Subtotal (95% CI)	**169**	**174**		**33.4 %**	**1.22 [0.45, 3.34]**
Total events: 25 (LMWH), 27 (Inactive control)					
Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 3.42$, df = 2 (P = 0.18); $I^2 = 42\%$					
Test for overall effect: Z = 0.39 (P = 0.70)					
2 Nadroparin					
Agnelli 2009	121/769	67/381		66.6 %	0.89 [0.68, 1.17]
Subtotal (95% CI)	**769**	**381**		**66.6 %**	**0.89 [0.68, 1.17]**
Total events: 121 (LMWH), 67 (Inactive control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Total (95% CI)	**938**	**555**		**100.0 %**	**0.89 [0.66, 1.21]**
Total events: 146 (LMWH), 94 (Inactive control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.44$, df = 3 (P = 0.33); $I^2 = 13\%$					
Test for overall effect: Z = 0.73 (P = 0.47)					
Test for subgroup differences: $Chi^2 = 0.34$, df = 1 (P = 0.56), $I^2 = 0.0\%$					

Analysis 11.3. Comparison 11 Anticoagulants versus control: serious adverse events, Outcome 3 Serious adverse events: apixaban vs placebo.

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

Comparison: 11 Anticoagulants versus control: serious adverse events

Outcome: 3 Serious adverse events: apixaban vs placebo

Study or subgroup	Apixaban n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Levine 2012	3/95	0/30		2.26 [0.12, 42.56]

ADDITIONAL TABLES

Table 1. Results of stratified analyses on symptomatic venous thromboembolism

Variable	N of trials	N of patients (LMWH)	N of patients (control)	RR (95% CI)	Heterogeneity I^2 / Tau^2	P for interaction
All trials	8	1829	1417	0.53 (0.38 to 0.75)	0.00	
Type of LMWH						0.655
Dalteparin	5	458	443	0.64 (0.39 to 1.06)	0.0% / 0.00	
Certoparin	1	442	441	0.57 (0.24 to 1.35)	NA / NA	
Nadroparin	1	769	381	0.50 (0.22 to 1.13)	NA / NA	
Enoxaparin	1	160	152	0.35 (0.16 to 0.75)	NA / NA	
Type of dosage						0.181
Prophylactic	6	1610	1205	0.63 (0.42 to 0.96)	0.0% / 0.00	

Table 1. Results of stratified analyses on symptomatic venous thromboembolism (*Continued*)

Higher than prophylactic	2	219	212	0.35 (0.19 to 0.67)	0.0% / 0.00	
Type of cancer						0.549
Mixed	3	828	555	0.70 (0.33 to 1.51)	0.0% / 0.00	
Lung	3	509	386	0.44 (0.21 to 0.89)	0.0% / 0.00	
Pancreatic	2	219	212	0.35 (0.19 to 0.67)	0.0% / 0.00	
Glioma	1	99	87	0.74 (0.35 to 1.57)	NA / NA	
Breast cancer	1	174	177	0.76 (0.17 to 3.36)	NA / NA	
Allocation concealment						0.939
Adequate	6	1345	934	0.53 (0.36 to 0.77)	0.0% / 0.00	
Inadequate or unclear	2	484	483	0.55 (0.24 to 1.26)	0.0% / 0.00	
Blinding of patients						0.308
Double-blind	4	1500	1093	0.62 (0.40 to 0.96)	0.0% / 0.00	
Inadequate or unclear blinding	4	329	324	0.41 (0.24 to 0.72)	0.0% / 0.00	
Intention-to-treat analysis						0.582
Yes	3	318	299	0.48 (0.29 to 0.80)	9.8% / 0.02	
No or unclear	5	1511	1118	0.59 (0.36 to 0.97)	0.0% / 0.00	

Table 1. Results of stratified analyses on symptomatic venous thromboembolism (*Continued*)

Selective outcome reporting						0.873
Adequate	6	1570	1178	0.55 (0.35 to 0.85)	0.0% / 0.00	
Incomplete or unclear	2	259	239	0.51 (0.24 to 1.08)	48.3% / 0.14	

P for interaction derived in STATA using the command metareg.

Table 2. Results of stratified analyses on major bleeding

Variable	N of trials	N of patients (LMWH)	N of patients (control)	RR (95% CI)	Heterogeneity I^2 / Tau^2	P for interaction
All trials	9	2184	1800	1.30 (0.75 to 2.23)	23.6% / 0.15	
Type of LMWH						0.592
Dalteparin	4	416	403	1.16 (0.39 to 3.46)	12.4% / 0.16	
Certoparin	1	447	451	2.19 (0.84 to 5.70)	NA / NA	
Nadroparin	3	1161	794	1.83 (0.69 to 4.85)	13.8% / 0.15	
Enoxaparin	1	160	152	0.63 (0.29 to 1.37)	NA / NA	
Type of dosage						0.326
Prophylactic	5	1573	1173	1.81 (0.77 to 4.26)	15.1% / 0.16	
Higher than prophylactic	4	611	627	1.00 (0.53 to 1.92)	19.9% / 0.09	
Type of cancer						0.325
Mixed	5	1220	968	1.29 (0.60 to 2.78)	8.1% / 0.07	

Table 2. Results of stratified analyses on major bleeding (*Continued*)

Lung	2	472	353	1.70 (0.66 to 4.38)	0.0% / 0.00	
Pancreatic	2	219	214	0.68 (0.33 to 1.39)	0.0% / 0.00	
Glioma	1	99	87	4.39 (0.52 to 36.89)	NA / NA	
Breast cancer	1	174	178	7.16 (0.37 to 137.61)	NA / NA	
Definition of major bleeding						0.036
Standard	7	1956	1578	1.87 (1.08 to 3.25)	0.0% / 0.00	
Alternative or unclear	2	228	222	0.58 (0.29 to 1.17)	0.0% / 0.00	
Allocation concealment						0.366
Adequate	8	1737	1349	1.13 (0.62 to 2.03)	18.2% / 0.13	
Inadequate or unclear	1	447	451	2.19 (0.84 to 5.7)	NA / NA	
Blinding of patients						0.036
Double-blind	6	1897	1516	1.97 (1.11 to 3.51)	0.0% / 0.00	
Inadequate or unclear blinding	3	287	284	0.62 (0.33 to 1.20)	0.0% / 0.00	
Intention-to-treat analysis						0.900
Yes	4	466	455	1.45 (0.48 to 4.37)	45.5% / 0.57	
No or unclear	5	1718	1345	1.41 (0.76 to 2.61)	6.0% / 0.03	

Table 2. Results of stratified analyses on major bleeding (*Continued*)

Selective outcome reporting						0.392
Adequate	7	1925	1561	1.50 (0.88 to 2.56)	0.0% / 0.00	
Incomplete or unclear	2	282	250	1.28 (0.21 to 7.95)	64.5% / 1.21	

P for interaction derived in STATA using the command metareg. Studies without events were not included in the meta-regression.

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Thrombosis] this term only	1177
#2	MeSH descriptor: [Thromboembolism] this term only	992
#3	MeSH descriptor: [Venous Thromboembolism] this term only	275
#4	MeSH descriptor: [Venous Thrombosis] explode all trees	2164
#5	(thrombo* or thrombus* or embol*):ti,ab,kw	20638
#6	MeSH descriptor: [Pulmonary Embolism] explode all trees	858
#7	PE or DVT or VTE:ti,ab,kw	2160
#8	((vein* or ven*) near thromb*):ti,ab,kw	4969
#9	blood flow stasis or “vein stasis*” or “venous stasis” or “blood clot”	463
#10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	22030
#11	MeSH descriptor: [Anticoagulants] explode all trees	3463
#12	anticoagul* or anti-coagu*	6197

(*Continued*)

#13	*warfarin or (vitamin near/3 antagonist*) or VKA or Nicoumalone or phenindione or acenocoumarol* or Sinthrome or dicoumarol* or nicoumalone or phenprocoumon or Marcoumar or Marcumar or Falithrom or AVK or bishydroxycoumarin* or couma* or phenprocoumon* or aldocumar or carfin or jantoven or kumatox or lawarin or marevan or prothromadin or sofarin or tedicumar or tintorane or waran or warfant or warfilone or warnerin	2905
#14	LMWH or UFH or heparin or nadroparin* or fraxiparin* or enoxaparin or ULMWH	7990
#15	Clexane or klexane or lovenox or dalteparin or Fragmin or ardeparin or dalteparin	636
#16	normiflo or tinzaparin or logiparin or Innohep or certoparin or sandoparin or reviparin or clivarin*	377
#17	danaproid or danaparoid or antixarin or ardeparin* or bemiparin*	109
#18	Zibor or cy 222 or embolex or monoembolex or parnaparin*	98
#19	rd 11885 or tedelparin or Kabi-2165 or Kabi 2165	69
#20	emt-966 or emt-967 or "pk-10 169" or pk-10169 or pk10169 or cy-216 or cy216	81
#21	seleparin* or tedegliparin or seleparin* or tedegliparin*	13
#22	wy90493 or "wy 90493" or "kb 101" or kb101	24
#23	lomoparan or orgaran or parnaparin or fluxum or lohepa or lowhepa or "op 2123" or parvoparin or AVE5026	91
#24	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or # 19 or #20 or #21 or #22 or #23	12663
#25	MeSH descriptor: [Bandages] explode all trees	2017
#26	stocking* or hosier* or tight* or sock* or bandag*	4536
#27	jobst or surepress or activa or kendall or elbeo or levante or lloveras or cette or sigvaris or solidea or medilast or VenoTrain* or Ulcertec or ComfortPro or Comfort-Pro or "Ulcer Kit"	728
#28	MeSH descriptor: [Intermittent Pneumatic Compression Devices] this term only	80

(*Continued)*

#29	compres* or ICD	6181
#30	foot near/3 impulse	12
#31	#25 or #26 or #27 or #28 or #29 or #30	10536
#32	MeSH descriptor: [Factor Xa] explode all trees and with qualifiers: [Antagonists & inhibitors - AI]	182
#33	Factor X* near/4 (antag* or inhib* or block*):ti,ab,kw (Word variations have been searched)	18483
#34	FX* near/4 (antag* or inhib* or block*):ti,ab,kw (Word variations have been searched)	30
#35	10* near/4 (antag* or inhib* or block*)	2690
#36	fondapar* or Arixtra:ti,ab,kw (Word variations have been searched)	176
#37	idraparinux or "SANORG 34006" or Sanorg-34006 or Sanorg34006 or SSR-126517 or SSR126517:ti,ab,kw (Word variations have been searched)	24
#38	Idrabiotaparinux or SSR-126517-E:ti,ab,kw (Word variations have been searched)	9
#39	*arinux:ti,ab,kw (Word variations have been searched)	204
#40	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39	20917
#41	rivaroxaban or Xarelto:ti,ab,kw (Word variations have been searched)	110
#42	Bay-597939 or Bay597939:ti,ab,kw (Word variations have been searched)	0
#43	betrixaban or PRT054021:ti,ab,kw (Word variations have been searched)	5
#44	apixaban:ti,ab,kw (Word variations have been searched)	50
#45	BMS-562247 or BMS-562247 or ELIQUIS:ti,ab,kw (Word variations have been searched)	0
#46	*aban:ti,ab,kw (Word variations have been searched)	354

(*Continued)*

#47	DU-176b or DU176b:ti,ab,kw (Word variations have been searched)	8
#48	PRT-054021 or PRT-054021:ti,ab,kw (Word variations have been searched)	0
#49	YM150 or YM-150 or LY517717 or LY-517717 or DU-176b or DU176*:ti,ab,kw (Word variations have been searched)	22
#50	GW813893 or "Tak 442" or TAK442 or PD0348292 or GSK-813893 or GSK813893:ti,ab,kw (Word variations have been searched)	1
#51	#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or # 49 or #50	374
#52	MeSH descriptor: [Antithrombins] explode all trees	194
#53	MeSH descriptor: [Hirudin Therapy] explode all trees	79
#54	(thrombin near/3 inhib*) or antithrombin:ti,ab,kw (Word variations have been searched)	1595
#55	hirudin*:ti,ab,kw (Word variations have been searched)	326
#56	*hirudin*:ti,ab,kw (Word variations have been searched)	328
#57	desirudin or bivalirudin or Angiomax or Angiox or hirulog: ti,ab,kw (Word variations have been searched)	189
#58	dabigatran or Pradaxa or Rendix:ti,ab,kw (Word variations have been searched)	102
#59	BIBR-953* or BIBR953* or BIBR-1048 or BIBR1048:ti,ab, kw (Word variations have been searched)	3
#60	ximelagatran or Exanta or Exarta or melagatran:ti,ab,kw (Word variations have been searched)	155
#61	ximelagatran or Exanta or Exarta or melagatran:ti,ab,kw (Word variations have been searched)	155
#62	argatroban or napsagatran or argatra or novastan:ti,ab,kw (Word variations have been searched)	70
#63	lepirudin or Refludan:ti,ab,kw (Word variations have been searched)	18

(*Continued)*

#64	MD805 or MD-805:ti,ab,kw (Word variations have been searched)	7
#65	*gatran:ti,ab,kw (Word variations have been searched)	276
#66	AZD0837 or AZD-0837:ti,ab,kw (Word variations have been searched)	6
#67	#52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or # 60 or #61 or #62 or #63 or #64 or #65 or #66	2018
#68	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees	2722
#69	MeSH descriptor: [Phosphodiesterase Inhibitors] explode all trees	882
#70	phosphodiesterase near/3 inhibitor:ti,ab,kw (Word variations have been searched)	1125
#71	platelet near/3 inhibitor:ti,ab,kw (Word variations have been searched)	2915
#72	antiplatelet or anti-platelet or antiaggreg or anti-aggreg	2021
#73	MeSH descriptor: [Tetrazoles] explode all trees	2281
#74	cilosta*:ti,ab,kw (Word variations have been searched)	264
#75	pletal or pletaal:ti,ab,kw (Word variations have been searched)	4
#76	73963-72-1	3
#77	OPC-13013 or OPC13013:ti,ab,kw (Word variations have been searched)	5
#78	((cyclooxygenase or ADP) near/3 inhib*)	1844
#79	aspirin	8013
#80	(acetyl near/3 salicylic) or ASA or acetylsalicyclic	6895
#81	clopidogrel* or Plavix	1414
#82	prasugrel or Effient or Efient or Prasita or Ticagrelor or Cangrelor or Portola or PRT060 or Brilinta	171
#83	ticlopidine or Ticlid or trapidil or thienopyridine	1588

(*Continued)*

#84	dipyridamo* or Persantin*	1190
#85	glycoprotein near/3 (antagonist or inhibitor)	498
#86	GR144053 or GR-144053 or abciximab or tirofiban or eftifibatid or eptifibatide	931
#87	ReoPro or Integrilin or Aggrastat	174
#88	terutroban	16
#89	picotamide	63
#90	satigrel	16
#91	#68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90	22363
#92	#24 or #31 or #40 or #51 or #67 or #91	59374
#93	MeSH descriptor: [Neoplasms] explode all trees	46049
#94	malignan* or *neoplas* or cancer*:ti,ab,kw (Word variations have been searched)	68775
#95	carcinoma* or adenocarcinoma*:ti,ab,kw (Word variations have been searched)	17753
#96	tumour* or tumor*:ti,ab,kw (Word variations have been searched)	18551
#97	glio* or leukemia:ti,ab,kw (Word variations have been searched)	6586
#98	chemotherapy:ti,ab,kw (Word variations have been searched)	26867
#99	chemoanticoagul*:ti,ab,kw (Word variations have been searched)	0
#100	myeloma:ti,ab,kw (Word variations have been searched)	1795
#101	oncolog*:ti,ab,kw (Word variations have been searched)	8915
#102	metastas*:ti,ab,kw (Word variations have been searched)	7310
#103	MeSH descriptor: [Antineoplastic Agents] explode all trees	9067

(*Continued*)

#104	MeSH descriptor: [Neoplasm Metastasis] explode all trees	3458
#105	#93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104	88206
#106	#92 and #105 in Trials	4351
#107	#10 and #105 in Trials	3231
#108	#106 or #107 in Trials	6923

Appendix 2. Abbreviations and scientific terms

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

WHAT'S NEW

Last assessed as up-to-date: 31 May 2013.

Date	Event	Description
24 July 2013	New citation required but conclusions have not changed	Searches rerun. Twelve additional studies were added to the included studies and nine additional studies to the excluded studies. Risk of bias was reassessed in all included

(*Continued*)

		trials. Conclusions not changed. Change in author team
24 July 2013	New search has been performed	Searches rerun. Twelve additional studies were added to the included studies and nine additional studies to the excluded studies

CONTRIBUTIONS OF AUTHORS

Study conception: Di Nisio

Acquisition of data: Di Nisio, Rutjes

Analysis and interpretation of data: Di Nisio, Porreca, Otten, Rutjes

Drafting of the manuscript: Di Nisio, Rutjes

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Statistical analysis: Di Nisio, Rutjes

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None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we aimed to combine continuous data from quality of life instruments applying, where appropriate, standard inverse-variance random-effects model meta-analysis (DerSimonian 1986). As only one included study reported quality of life data, this was omitted.

The protocol described that we would evaluate heterogeneity in results between trials with the I^2 statistic (Higgins 2003; Rücker 2008). We, however, used the variance estimate Tau^2 to indicate and interpret heterogeneity, as currently advised by the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011). For LMWH compared with inactive control, we could not perform stratified analyses of the main outcomes, by trial size, age, stage of cancer (metastatic versus non metastatic) and differences in the use of co-interventions in the trial groups, due to poor reporting or lack of contrast (trial size and age). Neither could we use the uni-variable random-effects meta-regression model by dosage of intervention. Based on a sample size calculation, to detect a symptomatic VTE rate of 2.7% in the LMWH group and 5.8% in the non-active control group, as observed in our analyses, with a power of 80% and a two-sided alpha of 0.05 about 1450 patients should have been included. Applying this threshold to define large trials, none of the LMWH trials were considered large. The mean age in all studies was 65 years or less, whereas one study omitted to report age (Pelzer 2009). Although we were unable to analyse dosage as a continuous variable, we could stratify the analyses according to trials using prophylactic dosage versus those using other (higher than prophylactic) dosages. The reporting was insufficient to analyse the association between the other criteria and our primary outcomes. We planned to perform meta-regression on both treatment duration and follow-up duration. The treatment duration equalled the follow-up duration in all studies except the one by Pelzer and colleagues (Pelzer 2009), which added one month of follow up after the end of treatment. We therefore only analysed the effect of treatment duration on major bleeding and symptomatic VTE. In all other comparisons, no exploration of the effects of participant or trial characteristics on symptomatic VTE or major bleeding could be done due to the low number of studies identified.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans