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Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer (Review)

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Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer.
Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD006650.
DOI: 10.1002/14651858.CD006650.pub4.

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[Intervention Review]

Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2015.

Citation: Akl EA, Kahale LA, Barba M, Neumann I, Labedi N, Terrenato I, Sperati F, Muti P, Schünemann H. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No.: CD006650. DOI: 10.1002/14651858.CD006650.pub4.

ABSTRACT

Background

Cancer increases the risk of thromboembolic events in patients including those receiving anticoagulation treatments.

Objectives

To compare the efficacy and safety of low molecular weight heparin (LMWH) and oral anticoagulants for the long-term treatment of venous thromboembolism (VTE) in patients with cancer.

Search methods

We conducted a comprehensive search for studies of anticoagulation in cancer patients including 1. a February 2013 electronic search of: the Cochrane Central Register of Controlled Trials (CENTRAL Issue 12, 2012), MEDLINE, and EMBASE; 2. a handsearch of conference proceedings; 3. checking of references of included studies; 4. use of the 'related citation' feature in PubMed; and 5. a search of clinicaltrials.gov for ongoing studies.

Selection criteria

We included randomized controlled trials (RCTs) comparing long-term treatment with LMWH versus oral anticoagulants (vitamin K antagonist (VKA) or ximelagatran) in patients with cancer and symptomatic objectively confirmed VTE.

Data collection and analysis

Using a standardized data form, we extracted data on methodological quality, participants, interventions and outcomes of interest: survival, recurrent VTE, major bleeding, minor bleeding, thrombocytopenia, and postphlebitic syndrome. We assessed the quality of evidence at the outcome level following the GRADE approach.

Main results

Of 9559 identified citations, 10 RCTs (11 reports) were eligible and reported data for 1981 patients with cancer. We excluded 14 studies in which patients with cancer constituted study subgroups, but did not report outcome data for them. Meta-analysis of seven RCTs comparing LMWH with VKA found no statistically significant survival benefit (hazard ratio (HR) 0.96; 95% confidence interval (CI) 0.81 to 1.14) but a statistically significant reduction in VTE (HR 0.47; 95% CI 0.32 to 0.71). The remaining findings did not exclude a beneficial or harmful effect of LMWH compared with VKA for the outcomes of major bleeding (RR 1.07; 95% CI 0.52 to 2.19), minor bleeding (RR 0.89; 95% CI 0.51 to 1.55), or thrombocytopenia (RR 0.98; 95% CI 0.57 to 1.66). We judged the quality of evidence as low for mortality, major bleeding, and minor bleeding, and as moderate for recurrent VTE.

One RCT comparing dabigatran with VKA did not exclude beneficial or harmful effects of one agent over the other. One RCT comparing six months' extension of anticoagulation with 18 months of ximelagatran 24 mg twice daily versus no extended ximelagatran did not exclude beneficial or harmful effects for the outcomes of reduction in VTE, mortality, and minor bleeding. One RCT comparing once-weekly subcutaneous injection of idraparinux for three or six months versus standard treatment (parenteral anticoagulation followed by warfarin or acenocoumarol) suggested a reduction in recurrent VTE (HR 0.39; 95% CI 0.14 to 1.11) at six months, but did not exclude beneficial or harmful effects for the outcomes of mortality (HR 0.99; 95% CI 0.66 to 1.48) and major bleeding (RR 1.04; 95% CI 0.39 to 2.83).

Authors' conclusions

For the long-term treatment of VTE in patients with cancer, LMWH compared with VKA reduces venous thromboembolic events but not mortality. The decision for a patient with cancer and VTE to start long-term LMWH versus oral anticoagulation should balance the benefits and harms and integrate the patient's values and preferences for the important outcomes and alternative management strategies.

PLAIN LANGUAGE SUMMARY

Blood thinners for the long-term treatment of blood clots in patients with cancer

Background

Patients with cancer are at an increased risk of developing blood clots and might respond differently to blood thinners (anticoagulants) compared with patients without cancer.

Study characteristics

We searched scientific databases for clinical trials looking at the effects of long-term treatment with different blood thinners on blood clot recurrence in people with cancer with a confirmed diagnosis of deep venous thrombosis (a blood clot in the legs) or pulmonary thrombosis (a blood clot in the lungs). We included trials of adults and children with either solid tumors or blood cancer irrespective of the type of cancer treatment. The trials looked at survival, recurrent blood clot, bleeding, blood platelet levels (which are involved in blood clotting), and postphlebitic syndrome (a complication of long-term blood clots). The evidence is current to February 2013.

Key results

We found 10 studies with 1981 patients with cancer. The studies found that low molecular weight heparins (injectable blood thinners) were superior to vitamin K antagonists (oral blood thinners) in reducing the recurrence of blood clots. The available data suggested that both drugs have equal effects on death and the side effect of bleeding.

Quality of the evidence

We were unable to include several possibly relevant studies because the required data were not available. We judged the quality of the evidence for recurrence of blood clots as moderate and the quality of the evidence as low for death and bleeding.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Low molecular weight heparin compared with vitamin K antagonist for patients with cancer requiring long-term anticoagulation for venous thromboembolism

Patient or population: patients with cancer requiring long-term anticoagulation for VTE
Settings: outpatient
Intervention: LMWH
Comparison: VKA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	VKA	LMWH				
Mortality Follow-up: 3-6 months (at any point)	399 per 1000	383 per 1000 (323 to 451)	**RR** 0.96 (0.81 to 1.13)	897 (3 studies)	⊕⊕◯◯ **low**[1,2]	-
Recurrent VTE Follow-up: 3-6 months	140 per 1000	71 per 1000 (49 to 106)	**RR** 0.51 (0.35 to 0.76)	964 (4 studies)	⊕⊕⊕◯ **moderate**[2]	-
Major bleeding Follow-up: 3-6 months	60 per 1000	64 per 1000 (31 to 131)	**RR** 1.07 (0.52 to 2.19)	1092 (4 studies)	⊕⊕◯◯ **low**[1,2]	-
Minor bleeding Follow-up: 3-6 months	176 per 1000	156 per 1000 (90 to 272)	**RR** 0.89 (0.51 to 1.55)	1091 (4 studies)	⊕⊕◯◯ **low**[2]	-
Postphlebitic syndrome - not reported	-	-	Not estimable	-	-	Not reported

*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; **LMWH:** low molecular weight heparin; **RR:** risk ratio; **VKA:** vitamin K antagonist; **VTE:** venous thromboembolism.

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] CI includes values suggesting both no effect and values suggesting either benefit or harm.
[2] We could not obtain data for subgroups of patients with cancer in 11 RCTs.

BACKGROUND

Table 1 lists a glossary of terms.

Description of the condition

The presence of cancer increases the risk of venous thromboembolism (VTE) four- to six-fold (Heit 2000). Cancer-related interventions such as chemotherapy, hormonal therapy, and indwelling central venous catheters also increase the risk of VTE (Heit 2000). Similarly, patients undergoing surgery for cancer have a higher risk of VTE than patients undergoing surgery for benign diseases (Gallus 1997; Kakkar 1970). Furthermore, patients with cancer and VTE have a higher risk of death than patients with cancer alone or with VTE alone (Levitan 1999; Sorensen 2000).

Patients with cancer also have different benefits and risks from anticoagulant treatment than patients without cancer. For instance, during oral anticoagulation therapy for VTE, patients with cancer, compared with patients without cancer, have a higher incidence of recurrent VTE (27.1 versus 9.0 events per 100 patient-years, P value = 0.003) and of major bleeding (13.3 versus 2.2 events per 100 patient-years, P value = 0.002) (Hutten 2000).

Description of the intervention

Low molecular weight heparins (LMWHs) do not have intrinsic anticoagulant activity but potentiate the activity of antithrombin III in inhibiting activated coagulation factors. These agents constitute indirect anticoagulants as their activity is mediated by plasma cofactors. LMWHs are not absorbed orally and must be administered parenterally by subcutaneous injections (Hirsh 1993).

Vitamin K antagonists (VKA) have been the mainstay of oral anticoagulant therapy since the 1950s. Well-designed clinical trials have shown the effectiveness of VKAs for the primary and secondary prevention of several venous and arterial thrombotic diseases (Ansell 2008).

How the intervention might work

Several systematic reviews have compared LMWH and VKA in the long-term treatment of VTE, but in populations not restricted to patients with cancer (Conti 2003; Iorio 2003; van der Heijden 2007). The review by van der Heijden et al. did not complete a preplanned subgroup analysis in patients with cancer as the required data were not specifically reported (van der Heijden 2007). The review by Conti et al. did not conduct a meta-analysis in the subgroup of patients with cancer (Conti 2003). In the review by Iorio et al., one meta-analysis in the subgroup of patients with cancer found no statistically significant difference in mortality (OR 1.13; 95% CI 0.54 to 2.38).

Why it is important to do this review

The subgroup analysis in Iorio 2003 did not report on the comparative safety of LMWH and VKA (Iorio 2003). The Cochrane Collaboration has recognized that addressing all important outcomes including harm is of great importance to make evidence-based healthcare decisions. The last update of this Cochrane systematic review concluded that the existing evidence suggested a reduction in venous thromboembolic events in patients with cancer but not mortality (Akl 2011). Since 2011, there have been publications of studies assessing the newer oral anticoagulants, so we aimed to update this systematic review to capture and include any such studies relevant to our question.

OBJECTIVES

To compare the efficacy and safety of LMWH and oral anticoagulants for the long-term treatment of VTE in patients with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Patients with cancer with a confirmed diagnosis of VTE (deep venous thrombosis (DVT) or pulmonary embolism (PE)). Patients could have been of any age group (including children), with either solid or hematologic cancer, at any stage of their cancer, and irrespective of the type of cancer therapy.

DVT should have been diagnosed using one the following objective diagnostic tests: venography, ^{125}I-fibrinogen-uptake test, impedance plethysmography, or Doppler-ultrasound. PE should have been diagnosed using one of the following objective diagnostic tests: pulmonary perfusion/ventilation scans, computed tomography, or pulmonary angiography).

Types of interventions

We included studies comparing long-term treatment with LMWH versus oral anticoagulants (VKA or ximelagatran). There should have been no differences in how the study groups were treated besides the main intervention (e.g. the type of initial anticoagulation), that is, studies should have treated patient groups similarly apart from the intervention of interest.

Types of outcome measures

Primary outcomes

- Survival.

Secondary outcomes

- Symptomatic recurrent DVT.
- Symptomatic recurrent PE.
- Major bleeding.
- Minor bleeding.
- Thrombocytopenia.
- Postphlebitic syndrome.

We accepted the definitions of major bleeding, minor bleeding, thrombocytopenia, and postphlebitic syndrome of the authors of the original studies as long as they were standardized.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in patients with cancer. We conducted the original electronic search in January 2007 and updated it in February 2010 and in February 2013. We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, 2012), MEDLINE (1966 onward; accessed via Ovid), EMBASE (1980 onward; accessed via Ovid), and ISI Web of Science (February 2010). The search strategies combined terms relating to the anticoagulants, cancer, and study design. We list the search strategies in Appendix 1 and Appendix 2.

Searching other resources

In addition to the electronic search, we used a number of supplemental search strategies. We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982 up to June 2013) and of the American Society of Hematology (ASH, starting with its 2003 issue up to June 2013). We reviewed the reference lists of included papers, relevant papers, and related systematic reviews (Conti 2003; van der Heijden 2007). We used the 'related citation' feature in PubMed to identify additional papers. We used ISI Web of Science to identify papers citing the landmark studies. We used no language restrictions. We also searched ClinicalTrials.gov (clinicaltrials.gov/) for ongoing studies.

Data collection and analysis

Selection of studies

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

Data extraction and management

For English articles, two review authors independently extracted the data from each study and resolved their disagreements by discussion or by consulting a third review author. For non-English articles, one review author extracted data. The collected data related to the following.

Participants

- Demographic characteristics (e.g. age, sex).
- Cancer characteristics (e.g. histologic type, site of origin, stage, time since diagnosis, estimated life expectancy, current cancer treatments, performance status).
- Whether participants had DVT, PE, or both.
- Number of patients in each treatment arm.

Interventions

- Type and dosage schedule of LMWH.
- Intensity of VKA.
- Dosage schedule of ximelagatran.
- Type (unfractionated heparin (UFH) versus LMWH versus fondaparinux) and duration of initial anticoagulation.
- Co-interventions including radiation therapy, chemotherapy, and hormonal therapy (type and duration).

Outcomes

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

For binary data, we extracted the reported outcome data necessary to conduct intention-to-treat (ITT) analyses. We collected outcome event rates whenever they were reported in each trial. When the authors did not report and could not provide the number of events at specific time points, two biostatisticians estimated these numbers independently and in duplicate from survival curves, if available.

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

Assessment of risk of bias in included studies

We assessed risk of bias at the study level using The Cochrane Collaboration's 'Risk of bias' tool. Two review authors independently assessed the methodologic quality of each included study and resolved any disagreements by discussion. Methodologic criteria included the following:

- adequate sequence generation;
- allocation concealment;
- patient blinding;
- provider blinding;
- data collector blinding;
- outcome assessor blinding;
- analyst blinding;
- percentage followed up and whether incomplete outcome data were addressed;
- whether the study was free of selective outcome reporting;
- whether the study was stopped early for benefit;
- whether the analysis followed the ITT principle.

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

Measures of treatment effect

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

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Determining participants with missing data

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

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

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

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

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

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

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

Assessing the risk of bias associated with participants with missing data

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

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

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

- for the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 5.

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

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

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

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

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, estimation of the percentage heterogeneity between trials that cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2011), and by a formal statistical test of the significance of the heterogeneity. If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Assessment of reporting biases

We assessed reporting bias by trying to identify whether the study was included in a trial registry, whether a protocol was available, and whether the methods section provided a list of outcomes (to assess selective outcome reporting bias). We compared the list of outcomes from those sources to the outcomes reported in the published paper.

We created inverted funnel plots of individual study results plotted against sample size in order to evaluate possible publication bias.

Data synthesis

We calculated the agreement between the two independent review authors for the assessment of eligibility using the kappa statistic.

We analyzed, when possible, both time-to-event data and binary data.

For time-to-event data, we pooled the log(HR) values using a random-effects model and the generic inverse variance facility of Review Manager 5 (RevMan 2012).

For binary data, for a specific outcome, and for each trial, we used the ITT principle to calculate the RR separately for each study. We then pooled the results of the different studies using a random-effects model.

We assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We evaluated heterogeneity across trials using the I^2 statistic, based on the following classification with the value of I^2: 0 to 30 = low; 30 to 60 = moderate and worthy of investigation; 60 to 90 = severe and worthy of understanding; and 90 to 100 = allowing aggregation only with major caution.

Sensitivity analysis

We conducted sensitivity analysis by excluding the study of lowest methodologic quality (Cesarone 2003), and then a study that used a different initial anticoagulant in the two study arms (post hoc analysis) (Hull 2006).

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

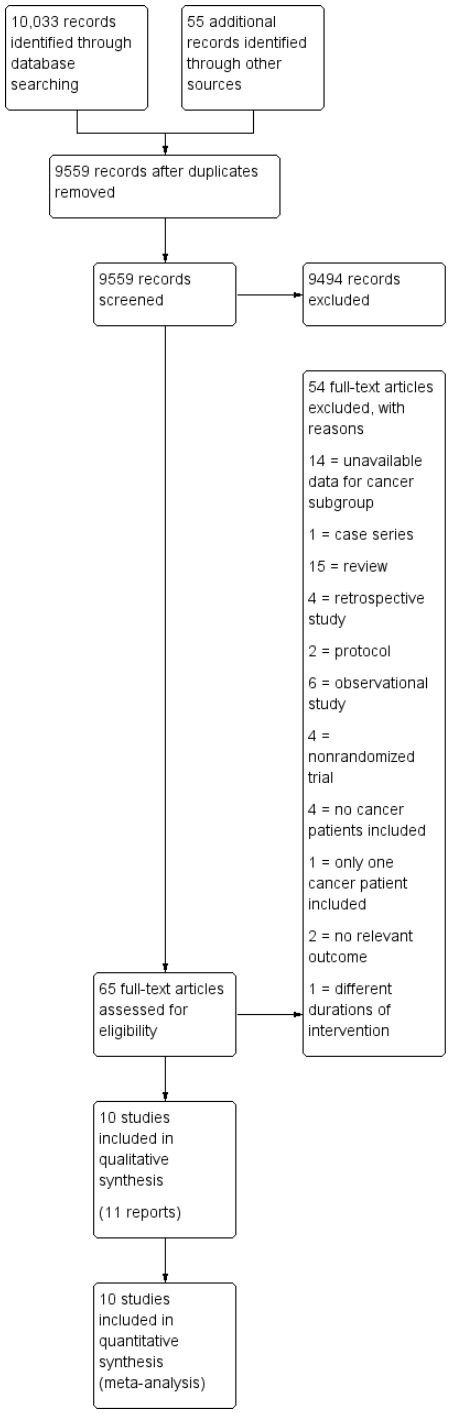
RESULTS

Description of studies

Results of the search

The February 2013 search strategy identified 9559 citations (after removal of duplicates) from which we removed the results of our January 2010 search. The title and abstract screening of the 9559 unique citations identified 65 as potentially eligible for this review. We included 10 studies (11 reports) and excluded the remaining 54 studies. Figure 1 shows the study flow diagram. Agreement between authors for study eligibility was excellent (kappa = 0.94).

Figure 1. Study flow diagram.



Included studies

We included 10 RCTs (11 reports) with 1981 patients with cancer for which outcome data were available (see Characteristics of included studies table). Nine studies were published in full text (Deitcher 2006; Hull 2006; Lee 2003; Lopez-Beret 2001; Meyer 2002; Schulman 2003; Schulman 2009; Romera 2009; van Doormaal 2010), and one was published as an abstract (Cesarone 2003). Seven RCTs compared a LMWH with a VKA for the long-term treatment of VTE (Cesarone 2003; Deitcher 2006; Hull 2006; Lee 2003; Lopez-Beret 2001; Meyer 2002; Romera 2009); only one of these studies used a different initial anticoagulant in the two study arms (LMWH in the LMWH group and UFH in the VKA group) (Hull 2006). One study compared dabigatran with warfarin for six months (Schulman 2009). One study with a subgroup of patients with cancer compared 18 months of extended treatment with ximelagatran versus placebo, after six months of anticoagulant therapy in patients with cancer (Schulman 2003). One RCT compared a once-weekly subcutaneous injection of idraparinux for three or six months versus standard treatment (tinzaparin, enoxaparin, or dose-adjusted intravenous heparin followed by warfarin or acenocoumarol).

Excluded studies

Of the 54 excluded studies, in 14 studies, patients with cancer constituted study subgroups but their outcome data were not available (Beckman 2003; Das 1996; Daskalopoulos 2005; Fiessinger 2005; Gonzalez-Fajardo 1999; Hull 2007; Hull 2009; Kucher 2005; Levine 1995; Lopaciuk 1999; Massicotte 2003; Pérez-de-Llano 2010; Pini 1994; Veiga 2000). We excluded the remaining 40 studies for the following reasons: case series (one study), review (15 studies), retrospective (four studies), protocol (two studies), observational (six studies), trial but not randomized and controlled (four studies), no cancer patients included (four studies), only one patient with cancer was included (one study), no relevant outcome (two studies), and not intervention of interest (study compared different duration of interventional drugs) (one study). See Characteristics of excluded studies table.

Risk of bias in included studies

Figure 2 shows the methodologic quality graph and Figure 3 shows the summary of the quality of the included studies. The methodologic quality varied by outcome. For the comparison of LMWH with VKA, the quality of evidence was low for mortality, major bleeding, and minor bleeding and moderate for recurrent VTE (Summary of findings for the main comparison).

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

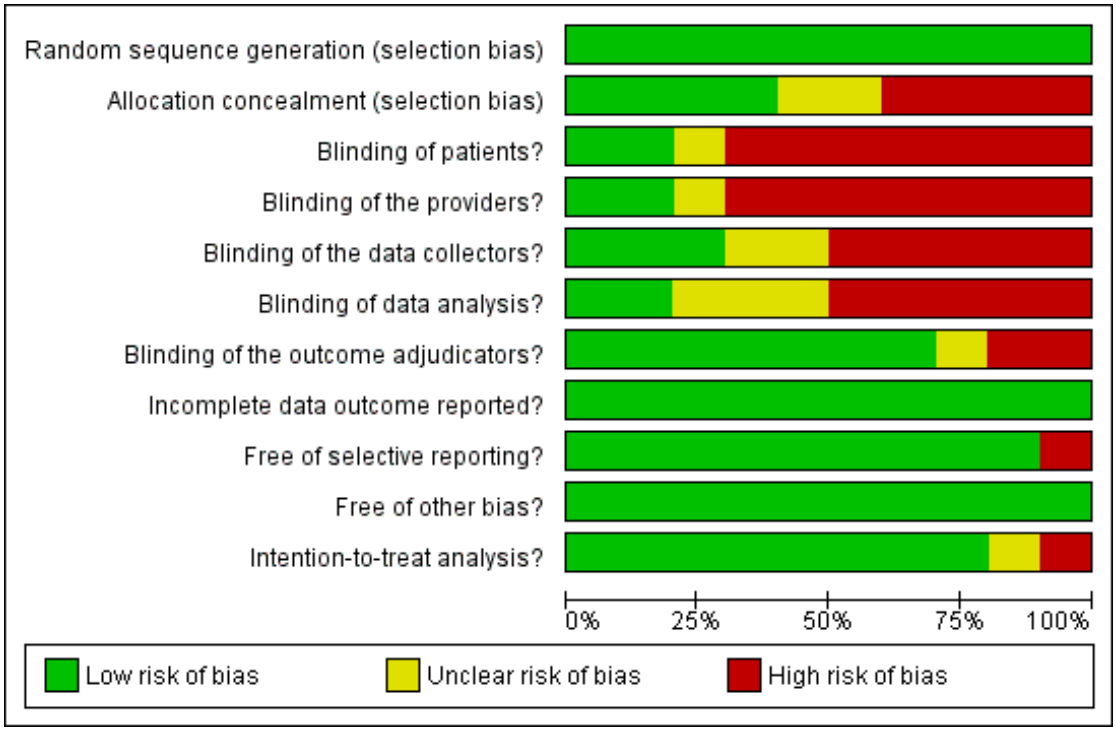
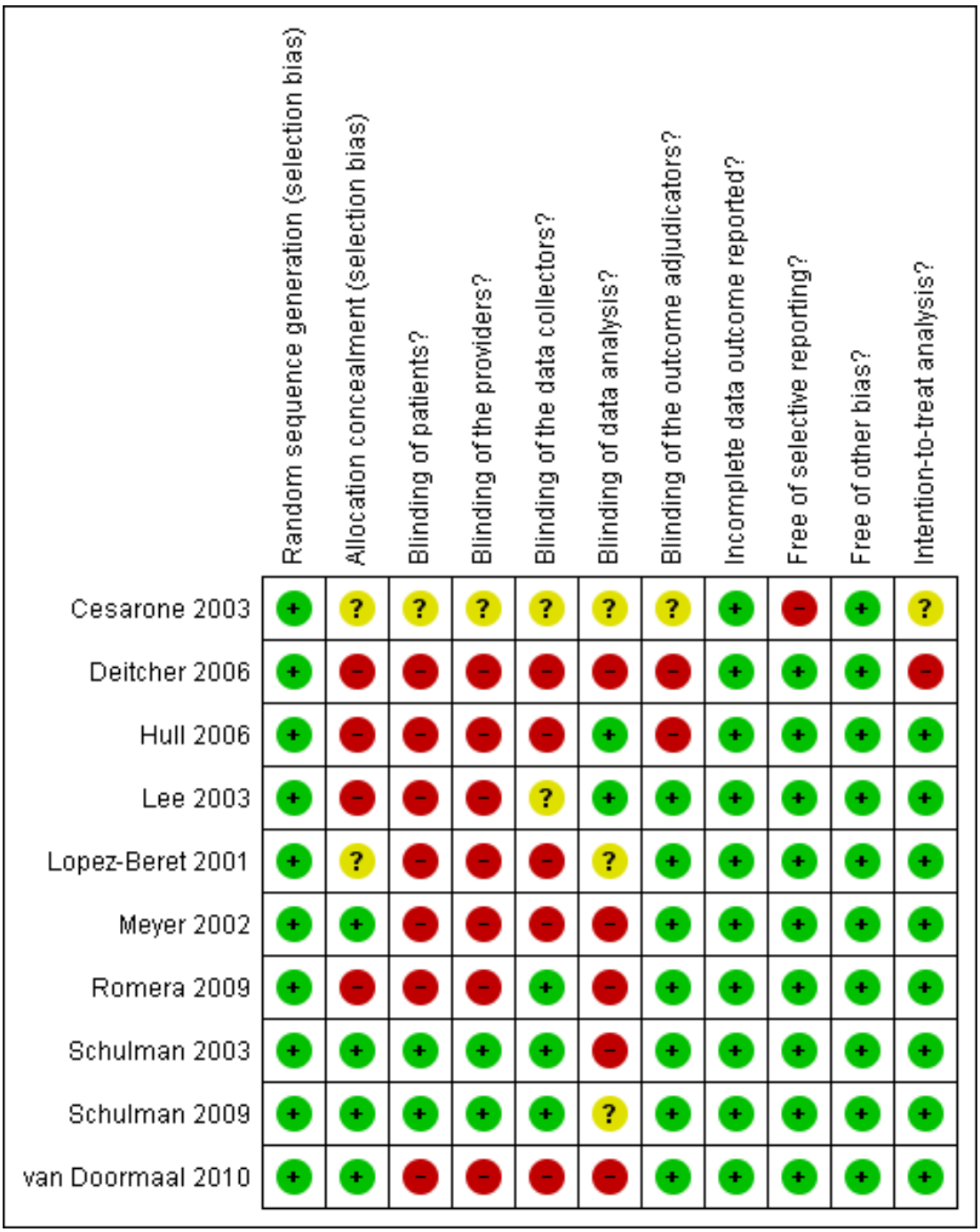


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

The concealment of allocation was adequate in seven trials (Hull 2006; Lee 2003; Meyer 2002; Romera 2009; Schulman 2003; Schulman 2009; van Doormaal 2010), and unclear in the other three (Cesarone 2003; Deitcher 2006; Lopez-Beret 2001).

Blinding

Three studies blinded patients (Romera 2009; Schulman 2003; Schulman 2009), three studies blinded caregivers (Romera 2009; Schulman 2003; Schulman 2009), three studies blinded data collectors (Romera 2009; Schulman 2003; Schulman 2009), eight studies blinded outcome adjudicators (Hull 2006; Lee 2003; Lopez-Beret 2001; Meyer 2002; Schulman 2003; Schulman 2009; Romera 2009; van Doormaal 2010), and five studies blinded data analysts (Hull 2006; Lee 2003; Meyer 2002; Schulman 2003; Schulman 2009).

Incomplete outcome data

The percentage follow-up ranged from 89% to 100%.

Selective reporting

We did not suspect selective reporting of outcomes for any of the studies except for Cesarone 2003 as there was no report on the bleeding events. The cancer subgroup data were missing for a large number of studies.

Other potential sources of bias

Eight studies conducted analysis consistent with the ITT principle (Hull 2006; Lee 2003; Lopez-Beret 2001; Meyer 2002; Schulman 2003; Schulman 2009; Romera 2009; van Doormaal 2010). This was not clear in two studies (Cesarone 2003; Deitcher 2006). One study was stopped early for benefit (Meyer 2002).

Another potential source of bias is the screening for asymptomatic VTE in three of the nine included studies (Lopez-Beret 2001; Meyer 2002; Romera 2009).

Effects of interventions

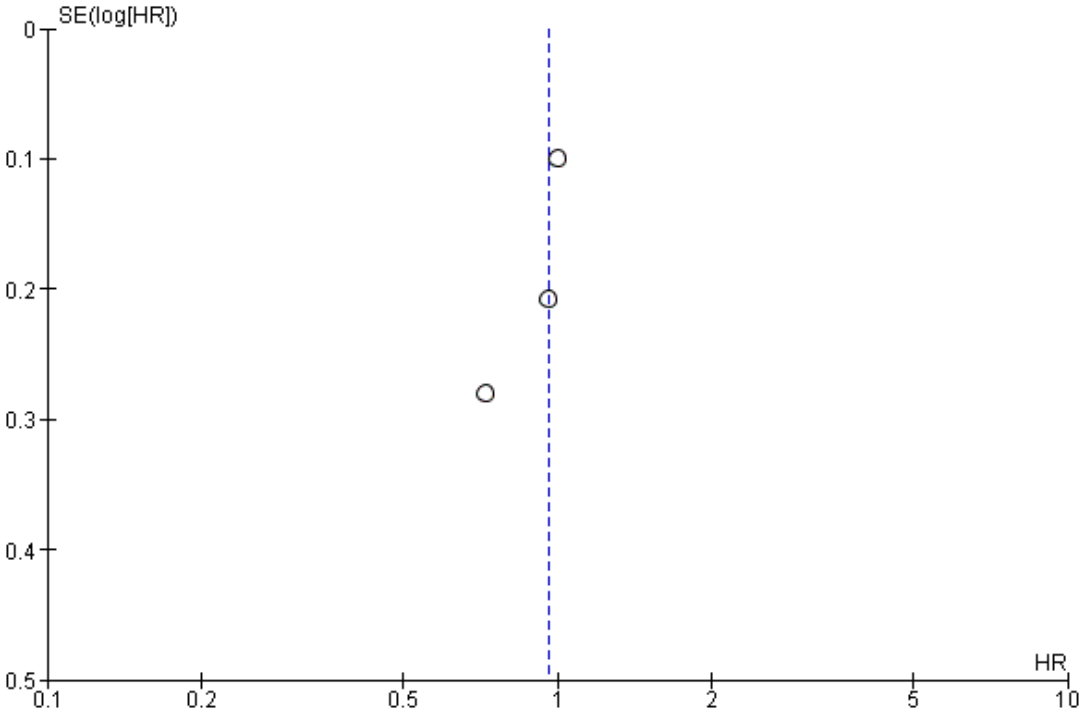
See: **Summary of findings for the main comparison** Low molecular weight heparin compared with vitamin K antagonist for patients with cancer requiring long-term anticoagulation for venous thromboembolism

Low molecular weight heparin versus vitamin K antagonist

Survival

We used time-to-event data reported by two studies (Lee 2003; Meyer 2002), and supplied by the author of a third study (Hull 2006). The pooled analysis showed no statistically significant survival benefit of LMWH over VKA (HR 0.96; 95% CI 0.81 to 1.14; I^2 = 0%) (Analysis 1.1) (Figure 4).

Figure 4. Funnel plot of comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), outcome: 1.1 Survival (time-to-event).



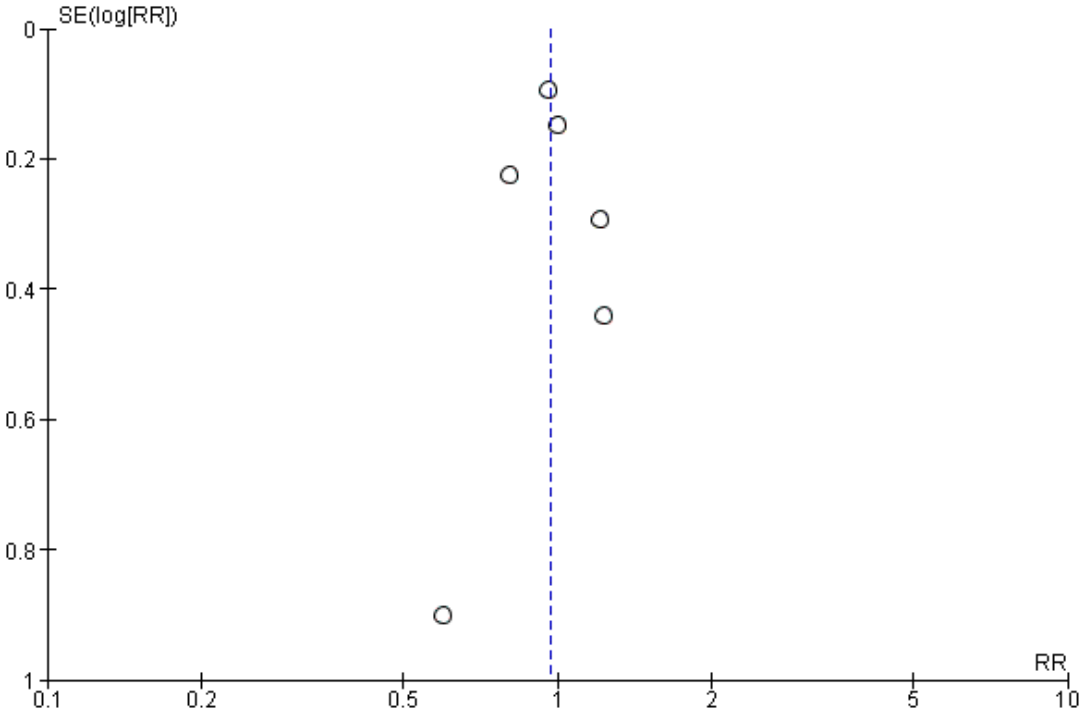
Three studies reported all-cause mortality at three months (Cesarone 2003; Hull 2006; Meyer 2002). The pooled analysis did not exclude clinically significant benefit or harm with LMWH compared with VKA (RR 0.77; 95% CI 0.46 to 1.28; I^2 = 17%) (Analysis 1.2). The results were consistent in a sensitivity analysis excluding the study published as an abstract (Cesarone 2003) (RR 0.76; 95% CI 0.37 to 1.55; I^2 = 56%), and in a sensitivity analysis excluding the study that used a different initial anticoagulant in the two study arms (Hull 2006) (RR 0.51; 95% CI 0.25 to 1.04; I^2 = 0%).

Three studies reported all-cause mortality at six months (Deitcher 2006; Lee 2003; Meyer 2002). The pooled analysis showed no statistically significant difference between LMWH and VKA (RR 0.96; 95% CI 0.81 to 1.13; I^2 = 0%) (Analysis 1.3).

We finally pooled data from all studies irrespective of the timing of outcome assessment and using the six-month data from the study by Meyer et al. The pooled analysis showed no statistically significant difference between LMWH and VKA (RR 0.97; 95% CI 0.84 to 1.11; I^2 = 0%) (Analysis 1.4). The results were consistent in a sensitivity analysis excluding the study published as an abstract (Cesarone 2003) (RR 0.97; 95% CI 0.85 to 1.10; I^2 = 0%), and in a sensitivity analysis excluding the study that used a different initial anticoagulant in the two study arms (Hull 2006) (RR 0.97; 95% CI 0.84 to 1.11; I^2 = 0%).

The inverted funnel plot for the outcome of all-cause mortality did not suggest publication bias (Figure 5).

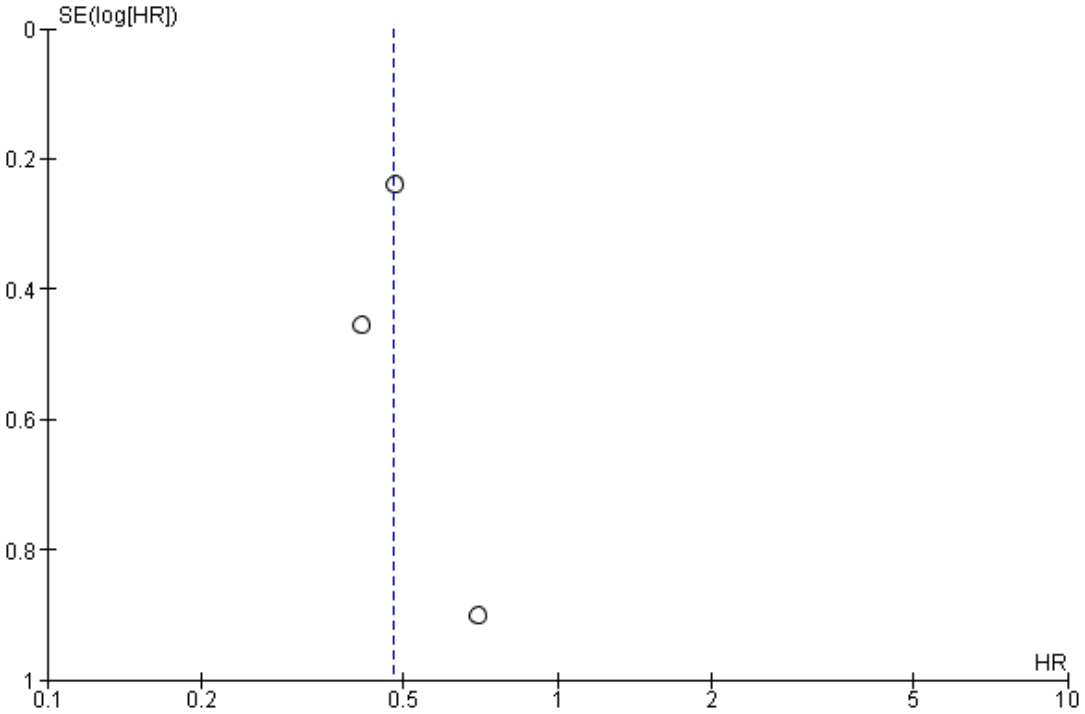
Figure 5. Funnel plot of comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), outcome: 1.4 Mortality (at any time point).



Recurrent venous thromboembolism

We used time-to-event data reported by two studies (Lee 2003; Meyer 2002), and supplied by the author of a third study (Hull 2006). The pooled analysis showed a statistically significant benefit of LMWH over VKA (HR 0.47; 95% CI 0.32 to 0.71; I^2 = 0%) (Analysis 1.5) (Figure 6). The results were consistent in a binary data analysis including five studies (RR 0.50; 95% CI 0.35 to 0.71; I^2 = 0%) (Analysis 1.6) (Deitcher 2006; Hull 2006; Lee 2003; Meyer 2002; Romera 2009), and a sensitivity analysis excluding the study that used a different initial anticoagulant in the two study arms (RR 0.51; 95% CI 0.35 to 0.76; I^2 = 0%) (Hull 2006).

Figure 6. Funnel plot of comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), outcome: 1.5 Recurrent venous thromboembolism (time-to-event).



Since the primary meta-analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses using the a priori plausible assumptions detailed in the methods section. The effect estimate remained statistically significant even when using the most stringent plausible assumption (RR 0.53; 95% CI 0.38 to 0.75).

None of the studies reported DVT and PE as separate outcomes.

Bleeding outcomes

Four studies assessed bleeding outcomes (Deitcher 2006; Hull 2006; Lee 2003; Meyer 2002). The pooled analysis did not exclude a beneficial or harmful effect of LMWH compared with VKA for major bleeding (RR 1.07; 95% CI 0.52 to 2.19; I^2 = 46%) (Analysis 1.7) (Figure 7) or minor bleeding (RR 0.89; 95% CI 0.51 to 1.55; I^2 = 77%) (Analysis 1.8) (Figure 8). The results were consistent in a sensitivity analysis excluding the study that used a different initial anticoagulant in the two study arms for the outcomes of minor bleeding (RR 0.80; 95% CI 0. 37 to 1.73; I^2 = 84%) and major bleeding (RR 1.13; 95% CI 0.39 to 3.31; I^2 = 64%) (Hull 2006).

Figure 7. Forest plot of comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), outcome: 1.7 Major bleeding.

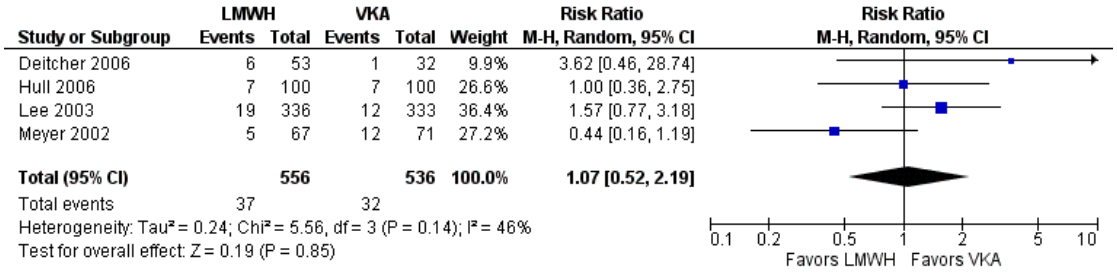
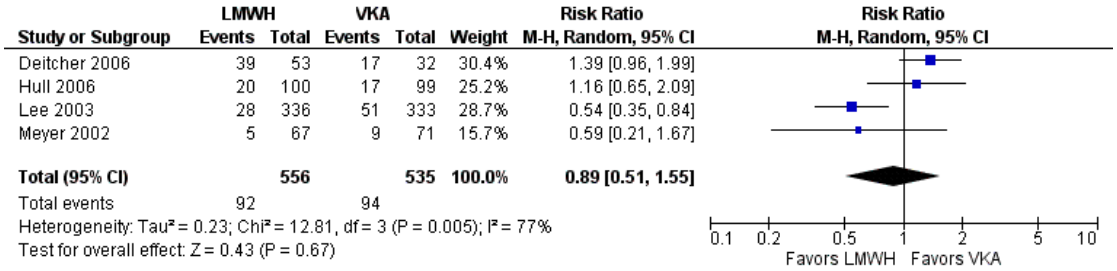


Figure 8. Forest plot of comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), outcome: 1.7 Bleeding.



Thrombocytopenia

Two studies assessed thrombocytopenia as an outcome (Hull 2006; Meyer 2002). The pooled analysis did not exclude a beneficial or harmful effect of LMWH compared with VKA (RR 0.98; 95% CI 0.57 to 1.66; I^2 = 0%) (Analysis 1.9). The results were consistent in a sensitivity analysis excluding the study that used a different initial anticoagulant in the two study arms (RR 0.89; 95% CI 0.49 to 1.60) (Hull 2006).

Postphlebitic syndrome

None of the studies reported postphlebitic syndrome as an outcome.

Dabigatran versus warfarin

We obtained outcome data for the cancer subgroup directly from the authors. The study by Schulman 2009 did not exclude a beneficial or harmful effect with dabigatran compared with warfarin with respect to mortality (RR 0.89; 95% CI 0.30 to 2.61), recurrent VTE (RR 0.59; 95% CI 0.10 to 3.43), major bleeding (RR 1.48; 95% CI 0.37 to 5.94), and thrombocytopenia (RR 6.25; 95% CI 0.33 to 118.38).

Extended ximelagatran versus no extended ximelagatran

We obtained outcome data for the cancer subgroup directly from the authors. Following initial anticoagulant treatment for six months, 18 months' extended treatment with ximelagatran 24 mg twice daily did not exclude a beneficial or harmful effect for the ourcomes of reduction in VTE (RR 0.47; 95% CI 0.04 to 4.94), mortality (RR 1.41; 95% CI 0.25 to 7.91), or minor bleeding (RR 1.08; 95% CI 0.44 to 2.62) (Schulman 2003).

Idraparinux versus standard anticoagulation therapy

The study by van Doormaal 2010 compared once-weekly subcutaneous injection of idraparinux for three or six months versus standard treatment (parenteral anticoagulation followed by warfarin

or acenocoumarol). The reported findings suggested a reduction in recurrent VTE (HR 0.39; 95% CI 0.14 to 1.11) at six months, but did not exclude beneficial or harmful effects for the outcomes of mortality (HR 0.99; 95% CI 0.66 to 1.48) and major bleeding (RR 1.04 95% CI 0.39 to 2.83).

DISCUSSION

Summary of main results

For the long-term treatment of VTE in patients with cancer, LMWH compared with VKA provided no statistically significant survival benefit but a statistically and patient important reduction in VTE. The findings did not exclude a beneficial or harmful effect of LMWH compared with VKA in terms of bleeding outcomes or thrombocytopenia. For dabigatran compared with warfarin, a beneficial or harmful effect on mortality, major bleeding, and thrombocytopenia could also not be excluded. Extended treatment with ximelagatran following six months of anticoagulant therapy could not be exclude a beneficial or harmful effect on reduced VTE, mortality, and minor bleeding d. For once-weekly subcutaneous injection of idraparinux compared with standard treatment, the findings suggested a reduction in recurrent VTE, but did not exclude beneficial or harmful effects for the outcomes of mortality and bleeding.

Overall completeness and applicability of evidence

While the reduction in venous thromboembolic events with LMWH is expected to reduce thrombosis-related mortality, this did not translate into an observed reduction in all-cause mortality. This finding is not apparently explained by an increase in any specific-cause mortality (e.g. fatal bleeding), but might be due to the lack of power to detect a reduction in all-cause mortality. Similarly, the size of the available evidence was not large enough to rule out beneficial or harmful effects for many comparisons (e.g. effects of LMWH versus VKA on bleeding, effects of dabigatran versus VKA on all outcomes).

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

Quality of the evidence

For the comparison of LMWH versus VKA, the pooled results for bleeding outcomes (LMWH versus VKA comparison) showed moderate to severe heterogeneity. Unfortunately, the number of pooled studies was relatively small to allow us to explore the causes of heterogeneity by conducting subgroup analyses. We judged the quality of evidence as low for mortality, major bleeding, and minor bleeding, and moderate for recurrent VTE (Summary of findings for the main comparison).

Potential biases in the review process

Our systematic approach to searching, study selection, and data extraction should have minimized the likelihood of missing relevant studies. This increases the confidence in the internal validity of our findings. A major limitation of this review is that we were unable to include in the meta-analyses 11 eligible RCTs with subgroups of patients with cancer because relevant data were not reported and not obtainable from the authors. However, the inverted funnel plot for the outcome of all-cause mortality did not suggest publication bias. This suggests that the treatment effect from those 11 RCTs should be similar to the one estimated from the included studies. One has to keep in mind that funnel plots have limited power to detect bias if the number of studies is small (Higgins 2006).

Agreements and disagreements with other studies or reviews

Of the three published systematic reviews comparing LMWH and VKA in the long-term treatment of VTE (Conti 2003; Iorio 2003; van der Heijden 2007), only the study by Iorio et al. conducted a meta-analysis in the subgroup of patients with cancer and found no statistically significant difference in mortality (OR 1.13; 95% CI 0.54 to 2.38). This finding is consistent with the results of our meta-analysis.

Two of the three systematic reviews showed no statistically significant reduction of recurrent VTE by LMWH compared with VKA when the meta-analysis was not restricted to patients with cancer (Iorio 2003; van der Heijden 2007). However, our meta-analysis showed a significant reduction in recurrent VTE in patients with cancer. The reason for this possible differential effect in patients with cancer is not clear.

AUTHORS' CONCLUSIONS

Implications for practice

The decision for a patient with cancer and venous thromboembolism (VTE) to start long-term low molecular weight heparin (LMWH) versus oral anticoagulation should balance the benefits and harms and integrate the patient's values and preferences for outcomes and management options (Haynes 2002). While

LMWH decreases the incidence of VTE and possibly of death, it might be more costly and less acceptable because of its subcutaneous route of administration.

Implications for research

Future research should compare LMWH versus other anticoagulants such as ximelagatran and fondaparinux. There is also a need for research assessing patients' values and preferences regarding long-term anticoagulant agents for treating VTE. Researchers should consider making the raw data from randomized controlled trials (RCTs) available for individual patient data meta-analysis. Further RCTs including subgroups of patients with cancer should report separate results for these subgroups.

ACKNOWLEDGEMENTS

We thank Dr. Buller, Dr. Deitcher, Dr. Harenberg, Dr. Huisman, Dr. Hull, Dr. Prandoni, Dr. Reomera, Dr. Schulman, and Dr. Siragusa for their assistance. We thank Ms. Ann Grifasi for her administrative support.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Gynaecological Cancer Group.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Cesarone 2003

Methods	Randomized trial
Participants	199 patients with cancer patients with DVT 17 drop-outs, 182 patients completed the study
Interventions	Intervention: enoxaparin 100 IU/kg twice daily x 3 months Control: coumadin (target INR 3) x 3 months
Outcomes	Duration of follow-up: 3 months • Mortality • Major bleeding • Recurrent DVT or PE but no data available Diagnostic tests of DVT: ultrasound
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised outpatient trial"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of patients?	Unclear risk	Comment: not reported
Blinding of the providers?	Unclear risk	Comment: not reported
Blinding of the data collectors?	Unclear risk	Comment: not reported
Blinding of data analysis?	Unclear risk	Comment: not reported
Blinding of the outcome adjudicators?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	91.5% follow-up
Free of selective reporting?	High risk	Abstract did not report bleeding events
Free of other bias?	Low risk	Study not reported as stopped early for benefit
Intention-to-treat analysis?	Unclear risk	Comment: not reported

Deitcher 2006

Methods	Randomized clinical trial
Participants	102 patients with active cancer with DVT, PE, or both; 85% Caucasian, mean age 64 years, 46% male, previous VTE 8.7%
Interventions	Intervention: enoxaparin 1 mg/kg twice daily x 5 days followed by 1.0-1.5 mg/kg daily x 175 days (group 1a); enoxaparin 1.5 mg/kg daily x 175 days (group 1b) Control: enoxaparin 1 mg/kg twice daily x 5 days followed by warfarin (target INR 2-3) for a total of 180 days Co-intervention: chemotherapy, radiation therapy, or both (not better specified) Discontinued treatment: 52 of 102 patients overall
Outcomes	Duration of follow-up: 1 year • Mortality • Symptomatic recurrent VTE • Major bleeding • Minor bleeding No scheduled radiologic surveillance for VTE was conducted
Notes	Funding: Aventis Pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated"
Allocation concealment (selection bias)	High risk	Quote: "This pilot feasibility study was conducted as a randomised, open label….trial"
Blinding of patients?	High risk	Quote: "open label" Comment: probably not
Blinding of the providers?	High risk	Quote: "open label" Comment: probably not
Blinding of the data collectors?	High risk	Quote: "open label" Comment: probably not
Blinding of data analysis?	High risk	Quote: "open label" Comment: probably not
Blinding of the outcome adjudicators?	High risk	Quote: "open label" Comment: probably not

Deitcher 2006 (*Continued*)

Incomplete data outcome reported?	Low risk	% follow-up: from table 2, there were no participants lost to follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention-to-treat analysis?	High risk	Quote: "safety evaluations were performed on the safety populations defined as all randomised patients who received at least 1 dose of the study medication The intent to treat population included all patient in safety population who had at least 1 follow up measurement" Quote: "of the 101 patients in the safety sample, 91 were included in the intend to treat analysis" Comment: definitely no

Hull 2006

Methods	Randomized clinical trial
Participants	200 patients with cancer (solid or hematologic) with proximal DVT with or without PE Minimum age 18 years; minimum life expectancy 3 months, 50% male, 19% had previous VTE
Interventions	Interventions: tinzaparin 175 antiXa/kg SC daily for 12 weeks Control: UFH either 5000 U or 80 U/kg for 5 days followed by VKA (target INR 2-3) for 12 weeks
Outcomes	Duration of follow-up: 12 months • Recurrent VTE evaluated at 3 and 12 months • Bleeding (major and minor) evaluated at 3 months • Mortality at 3 and 12 months Diagnostic test for recurrent VTE: venography or compression ultrasonography
Notes	Funding: Canadian Institute for Health Research, industry grant, Leo Pharmaceutical, Pharmion Pharmaceutical, and DuPont Pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-derived randomised treatment schedule was used; within the each stratum, the randomised schedule was balanced in blocks of 2 and 4"

Hull 2006 (*Continued*)

Allocation concealment (selection bias)	High risk	Quote: "multicenter, open-label randomised design"
Blinding of patients?	High risk	Quote: "open label clinical trial" Quote: "A double-blind design was not feasible due to geographic location of many of the centres and necessarily large number of primary care physicians providing anticoagulant monitoring" Comment: probably no
Blinding of the providers?	High risk	Quote: "open label clinical trial" Quote: "A double-blind design was not feasible due to geographic location of many of the centres and necessarily large number of primary care physicians providing anticoagulant monitoring" Comment: probably no
Blinding of the data collectors?	High risk	Quote: "open label clinical trial" Quote: "A double-blind design was not feasible due to geographic location of many of the centres and necessarily large number of primary care physicians providing anticoagulant monitoring" Comment: probably no
Blinding of data analysis?	Low risk	Quote: "open label clinical trial" Quote: "A double-blind design was not feasible" Comment: probably no
Blinding of the outcome adjudicators?	High risk	Quote: "Adjudication was made by 2 committee members not involved in the patient's care, and disputes were resolved independently by a third. Members of the committee were unaware of the patients' treatment assignments" Comment: probably yes
Incomplete data outcome reported?	Low risk	99% follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol but a protocol is clearly mentioned in the discussion. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected Comment: probably yes
Intention-to-treat analysis?	Low risk	Only 1% lost to follow-up and all patients randomized included in the analyses of outcomes Comment: probably yes

Lee 2003

Methods	Randomized clinical trial
Participants	676 patients with active cancer and with DVT, PE, or both; ECOG 1 or 2 Mean age 63 years, 49% male,11% history of DVT/PE
Interventions	Intervention: dalteparin 200 IU/kg daily x 1 month followed by 150 IU/kg daily x 5 months Control: dalteparin 200 IU/kg daily x 5-7 days followed by warfarin or acenocoumarol (target INR 2-3) x 6 months; 46% of time on target
Outcomes	Duration of follow-up: 6 months • Symptomatic recurrent DVT and PE • Clinically overt bleeding (both major bleeding and any bleeding) • Mortality Diagnostic tests for DVT: ultrasonography, venography Diagnostic tests for PE: lung scan, angiography, autopsy
Notes	Funding: Pharmacia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomizations was stratified according to the clinical center and centralized at the coordinating and methods center"
Allocation concealment (selection bias)	High risk	Quote: "the open label design could be a potential source of bias"
Blinding of patients?	High risk	Quote: "we performed a multicenter, randomised, open label, clinical trial" Quote: "we believed that a double blind design would not logistically feasible or safe in patient with cancer" Comment: probably no
Blinding of the providers?	High risk	Quote: "we performed a multicenter, randomised, open label, clinical trial" Quote: "we believed that a double blind design would not logistically feasible or safe in patient with cancer" Comment: probably no
Blinding of the data collectors?	Unclear risk	Quote: "we performed a multicenter, randomised, open label, clinical trial" Quote: "we believed that a double blind design would not logistically feasible or safe in patient with cancer" Comment: probably no

Lee 2003 (*Continued*)

Blinding of data analysis?	Low risk	Quote: "a blinded reassessment of the sample size was specified in the protocol" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "all suspected events were reviewed by a central adjudication committee whose members were unaware of the patient's treatment assignments" Comment: probably yes
Incomplete data outcome reported?	Low risk	99% follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit. no other bias suspected Comment: probably yes
Intention-to-treat analysis?	Low risk	Quote: "an analysis of efficacy end points was performed according to intention to treat principle and included all randomised patients who had a confirmed, qualifying thrombotic event and active cancer" Comment: definitely yes

Lopez-Beret 2001

Methods	Randomized clinical trial
Participants	35 patients with known malignancy; treated for symptomatic DVT of the lower limbs Minimum age 18 years, mean age 65.7 years
Interventions	Intervention: nadroparin 1.025 AXa IU/10 kg twice daily for 3 days then randomized to nadroparin 1.025 antiXa IU/10 kg twice daily Control: nadroparin 1.025 AXa IU/10 kg twice daily for 3 days then randomized to acenocoumarol (target INR 2-3) for 3-6 months. After the 3rd month, nadroparin was switched to once daily. 68% of INR values were on target
Outcomes	Mortality DVT, PE, asymptomatic VTE, major bleeding, venous insufficiency Duplex scan exam performed during routine vascular clinic visits at 1, 3, 6, and 12 months
Notes	Funding: not reported

Risk of bias

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

Lopez-Beret 2001 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "patients were allocated at random on third day to receive a LMWH or an OA [oral anticoagulant]"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of patients?	High risk	Quote: "in view of the nature of the treatments, it was not possible to use a double design for the study" Comment: probably no
Blinding of the providers?	High risk	Quote: "in view of the nature of the treatments, it was not possible to use a double design for the study" Comment: probably no
Blinding of the data collectors?	High risk	Quote: "in view of the nature of the treatments, it was not possible to use a double design for the study" Comment: probably no
Blinding of data analysis?	Unclear risk	Quote: "in view of the nature of the treatments, it was not possible to use a double design for the study" Comment: probably no
Blinding of the outcome adjudicators?	Low risk	Quote: "the final allocation of all potential outcome events, including deaths, was made by an independent panel of physicians" Comment: probably yes
Incomplete data outcome reported?	Low risk	100% follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention-to-treat analysis?	Low risk	No loss to follow-up and all patients randomized included in the analyses of outcomes

Meyer 2002

Methods	Randomized clinical trial
Participants	146 patients with cancer (solid or hematologic; active or in remission but on treatment) ; with PE, DVT, or both Minimum age 18 years; minimum life expectancy 3 months, mean age 65.5 years, 45% male

Meyer 2002 (*Continued*)

Interventions	Intervention: enoxaparin 1.5 mg/kg daily x 3 month Control: enoxaparin 1.5 mg/kg daily x 4 days followed by warfarin (target INR 2-3) x 3 months; 41% of time on target The continuation and nature of anticoagulant treatment after 3 months were left to the attending physician Co-intervention: not reported
Outcomes	Duration of follow-up: 3 and 6 months • Asymptomatic VTE • Symptomatic and objectively confirmed recurrent VTE • Major bleeding • Minor bleeding • Thrombocytopenia Screening tests for VTE: radiologic surveillance Diagnostic tests for DVT: venography or compression ultrasonography Diagnostic tests for PE: pulmonary angiography or ventilation perfusion scanning
Notes	Funding: Aventis, Assistance Publique, Hospitaux de Paris

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocation was balanced at each center in blocks of 4"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was performed using pre sealed treatment boxes"
Blinding of patients?	High risk	Quote: "this study was a multicenter, open label, randomised trial" Comment: probably no
Blinding of the providers?	High risk	Quote: "this study was a multicenter, open label, randomised trial" Comment: probably no
Blinding of the data collectors?	High risk	Quote: "this study was a multicenter, open label, randomised trial" Comment: probably no
Blinding of data analysis?	High risk	Quote: "this study was a multicenter, open label, randomised trial" Comment: probably no
Blinding of the outcome adjudicators?	Low risk	Quote: "all potential outcome events were assessed by an independent adjudication committee whose members were unaware of the treatment assignment"

Meyer 2002 (*Continued*)

		Comment: probably yes
Incomplete data outcome reported?	Low risk	99% follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Comment: study not reported as stopped early for benefit
Intention-to-treat analysis?	Low risk	Quote: "analysis was performed on an intention to treat basis"

Romera 2009

Methods	Randomized trial
Participants	69 patients with cancer (study subgroup) and symptomatic proximal DVT Minimum age 18 years, mean age 61 years
Interventions	Intervention: tinzaparin SC in a fixed dose of 175 IU anti-Xa per kg once daily for 6 months Control: acenocoumarol 3 mg orally, which was subsequently adjusted to achieve an INR of 2-3 All patients received tinzaparin SC in a fixed dose of 175 IU anti-Xa per kg once daily
Outcomes	VTE (no data available for other outcomes in patients with cancer) Scheduled radiologic surveillance for VTE was conducted at 1, 6, and 12 months after entry Screening testing for DVT: none Diagnostic testing for DVT: duplex ultrasonography
Notes	Funding: Hospital Universitari de Bellvitge, LEO Pharma

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to either LMWH group SQ [subcutaneous] or LMWH followed by acenocoumarol"
Allocation concealment (selection bias)	High risk	Quote: "A randomised, open-label trial" Comment: not reported
Blinding of patients?	High risk	Quote: "we performed a randomised open label clinical trial" Comment: probably no

Romera 2009 (*Continued*)

Blinding of the providers?	High risk	Quote: "we performed a randomised open label clinical trial" Comment: probably no
Blinding of the data collectors?	Low risk	Quote: "All objective diagnostic tests were interpreted by specialists who were not involved in the study" Quote: "the ultrasonic evaluations were performed blindly" Comment: probably yes
Blinding of data analysis?	High risk	Quote: "we performed a randomised open label clinical trial" Comment: probably no
Blinding of the outcome adjudicators?	Low risk	Quote: "All objective diagnostic tests were interpreted by specialists who were not involved in the study" Quote: "the ultrasonic evaluations were performed blindly" Comment: probably yes
Incomplete data outcome reported?	Low risk	100% follow-up
Free of selective reporting?	Low risk	Study is registered (NCT00689520). All relevant outcomes listed on the registration page as well in the methods section of the published manuscript are reported on Comment: yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected Comment: probably yes
Intention-to-treat analysis?	Low risk	Quote: "Two patients (one from each group) who developed symptoms of pulmonary embolism on the same day of randomisation were also included in the analysis" Comment: probably yes

Schulman 2003

Methods	Double-blind randomized trial
Participants	66 patients with active cancer in the previous 5 years (study subgroup); treated for DVT or PE for 6 months without recurrence Minimum age 18 years, mean age 57 years
Interventions	Intervention: initial anticoagulant treatment for 6 months; extended treatment with ximelagatran 24 mg twice daily x 18 months Control: initial anticoagulant treatment for 6 months; placebo x 18 months
Outcomes	Duration of follow-up: 18 months • Mortality • Asymptomatic recurrent VTE (DVT and PE)

	• Major bleeding • Minor bleeding (no data available for patients with cancer patients subgroup) No scheduled radiologic surveillance for VTE was conducted
Notes	Funding: AstraZeneca

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "use of a computer-generated randomizations list"
Allocation concealment (selection bias)	Low risk	Quote: "the treatment group assignment was concealed from all the investigators and their staff at the coordinating center and the clinical centers and from clinical monitors"
Blinding of patients?	Low risk	Quote: "multicenter, double blind, placebo-controlled parallel group study" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "multicenter, double blind, placebo-controlled parallel group study" Comment: probably yes
Blinding of the data collectors?	Low risk	Quote: "multicenter, double blind, placebo-controlled parallel group study" Comment: probably yes
Blinding of data analysis?	High risk	Quote: "multicenter, double blind, placebo-controlled parallel group study" Comment: probably no
Blinding of the outcome adjudicators?	Low risk	Quote: "all suspected recurrent VTE events, including those ruled out by local investigators, were adjudicated by a central, independent, blinded endpoint committee" Comment: definitely yes
Incomplete data outcome reported?	Low risk	100% follow-up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes

Schulman 2003 (*Continued*)

Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: definitely yes
Intention-to-treat analysis?	Low risk	Quote: "All analyses presented are based on the treatment period for the intention to treat population, which was defined as all patients from whom any data were available after randomizations, and who took at least one dose of the study medication" Quote: "Five patients in each group were excluded from the intention-to-treat population since no data were available for them after randomizations" Comment: probably yes (10 out of 1233 represents less than 1% of the study population)

Schulman 2009

Methods	Randomized double-blind trial
Participants	121 patients with cancer (study subgroup) with DVT, PE, or both Minimum age 18 years; mean age 60.5 years; 94.8% white people, 2.6% black people, 2.6% Asian people
Interventions	Intervention: dabigatran 150 mg twice daily for 6 months Control: warfarin adjusted to achieve an INR of 2-3 for 6 months All patients were initially given parenteral anticoagulant therapy for a median of 9 days
Outcomes	Mortality, symptomatic VTE, major bleeding, and minor bleeding at 6 months No scheduled radiologic surveillance for VTE was conducted (no data available in the paper,)
Notes	Funding: Boehringer Ingelheim Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "we used a computer generated randomisation scheme with variable block size stratified according to the presentation"
Allocation concealment (selection bias)	Low risk	Quote: "the treatment group assignment were concealed"
Blinding of patients?	Low risk	Quote: "double blind, double dummy randomised trial" Comment: probably yes

Schulman 2009 (*Continued*)

Blinding of the providers?	Low risk	Quote: "double blind, double dummy randomised trial" Comment: probably yes
Blinding of the data collectors?	Low risk	Quote: "double blind, double dummy randomised trial" Comment: probably yes
Blinding of data analysis?	Unclear risk	Quote: "double blind, double dummy randomised trial" Comment: probably no
Blinding of the outcome adjudicators?	Low risk	Quote: "all suspected outcome event and deaths were classified by central adjudication committees whose members were unaware of the treatment assignments" Comment: definitely yes
Incomplete data outcome reported?	Low risk	99.7% follow-up
Free of selective reporting?	Low risk	Study is registered (NCT00291330). All relevant outcomes listed on the registration page as well in the methods section of the published manuscript are reported on Comment: definitely yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: definitely yes
Intention-to-treat analysis?	Low risk	Quote: "we analysed efficacy to a modified intention to treat principle, since patients who did not receive any study drug were excluded from all analyses as prespecified in the protocol" Comment: probably yes

van Doormaal 2010

Methods	Post hoc analysis in the subgroup of patients with cancer included in the Van Gogh DVT clinical trial (NCT00067093)
Participants	421 patients with a history or current cancer having acute symptomatic and objectively confirmed DVT involving the popliteal, femoral, iliac veins, or the trifurcation of the calf veins, without symptomatic PE 67% with active disease at entry, 53% male, mean age 67 years Quote: "no detailed information on cancer type and stage or co-medication was collected"
Interventions	Intervention: idraparinux 2.5 mg SC once-weekly x 3 or 6 months according to the decision of the treating physician

	Control: standard treatment: tinzaparin, enoxaparin, or intravenous heparin adjusted for the activated partial thromboplastin time ratio (ratio 1.5-2.5), followed by warfarin or acenocoumarol (INR 2-3), which was started within 24 hours after randomization Co-intervention: not reported Quote: "A total of 8% of all patients were randomised in the 3-month arm, and 92% in the 6-month treatment arm" Quote: "The duration of treatment was similar with a median of 183 days in both groups" 75% of participants completed the study medication Quote: "Of idraparinux recipients 48 patients (22%) stopped the study medication before the end of the study compared to 56 (28%) patients in the standard treatment arm"
Outcomes	Duration of follow-up: 6-month treatment period plus additional 3-month follow-up period (median 183 days in both groups) • Symptomatic objectively confirmed recurrent VTE: DVT (follow-up at 3 and 6 months), non-fatal or fatal PE (follow-up at 6 and 9 months) • Clinically relevant major bleeding (follow-up at 3 and 6 months) • Clinically relevant non-major bleeding (follow-up at 3 and 6 months) • All-cause mortality (follow-up at 6 and 9 months) Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none reported in this manuscript, but available from Buller HR, *New England Journal of Medicine* 2007;357:1094-104. For diagnosis of recurrent PE: spiral computed tomography, pulmonary angiography. For diagnosis of recurrent DVT: ultrasonography, venography
Notes	Quote: "This post-hoc analysis is under-powered to adequately test the hypothesis of equivalence and should be considered as hypothesis generating" Quote: "The data were gathered and maintained by the sponsor" Note: Sanofi-Aventis France is idraparinux manufacturer Quote: "The original trial was sponsored by Sanofi-Aventis. Their biostatisticians extracted the data of the present study" Comment: probably not blinded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After giving written informed consent, patients were randomly assigned to receive either idraparinux or standard therapy with the use of a computerized voice-response system" (from Buller HR, *New England Journal of Medicine* 2007;357:1094-104)
Allocation concealment (selection bias)	Low risk	Quote: "After giving written informed consent, patients were randomly assigned to receive either idraparinux or standard therapy with the use of a computerized voice-re-

van Doormaal 2010 (*Continued*)

		sponse system" (from Buller HR, *New England Journal of Medicine* 2007;357:1094-104)
Blinding of patients?	High risk	Open-label study Comment: probably not blinded
Blinding of the providers?	High risk	Open-label study Comment: probably not blinded
Blinding of the data collectors?	High risk	Open-label study Comment: probably not blinded
Blinding of data analysis?	High risk	Open-label study Comment: probably not blinded
Blinding of the outcome adjudicators?	Low risk	Quote: "All suspected outcomes were classified by an independent blinded adjudication committee"
Incomplete data outcome reported?	Low risk	Not reported Comment: probably no loss to follow-up
Free of selective reporting?	Low risk	Post-hoc analysis. Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on except for non-fatal PE Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit No other bias suspected Comment: definitely yes
Intention-to-treat analysis?	Low risk	Quote: "The analyses were calculated in the intention to treat population"

DVT: deep venous thrombosis; ECOG: Eastern Co-operative Oncology Group; INR: international normalized ratio; IU: international units; PE: pulmonary embolism; SC: subcutaneous; U: unit; UFH: unfractionated heparin; VKA: vitamin K antagonist; VTE: venous thromboembolism.

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

Study	Reason for exclusion
Altschuler 1990	Not an RCT (no control group)
Andrea 2003	Review
Astermark 1998	Observational study
Beckman 2003	Study included patients with cancer as a subgroup for which outcome data were not available
Bona 1997	Not an RCT (no control group)
Browse 1974	Review
Burgos 1999	No relevant outcome
Clarke-Pearson 1983	Retrospective study
Clenney 2003	Review
Das 1996	Study included patients with cancer as a subgroup for which outcome data were not available
Daskalopoulos 2005	Study included patients with cancer as a subgroup for which outcome data were not available
Eriksson 2005	Too few patients with cancer (1 in LMWH group)
Farred 2004	Not an RCT
Ferretti 2005	Review
Ferretti 2006	Review of another study
Fiessinger 2005	Study included patients with cancer as a subgroup for which outcome data were not available
Gonzalez-Fajardo 1999	Study included patients with cancer as a subgroup for which outcome data were not available
Hull 1996	Protocol
Hull 2000	Protocol
Hull 2007	Study included patients with cancer as a subgroup for which outcome data were not available
Hull 2009	Study included patients with cancer as a subgroup for which outcome data were not available
Hyers 2005	Review
Iorio 2003	Review

(*Continued*)

Kakkar 2003	No patients with cancer
King 2005	Retrospective study
Kovacs 2005	Observational study
Kucher 2005	Study included patients with cancer as a subgroup for which outcome data were not available
Lee 2005	Review
Lee 2006	Review
Levine 1995	Study included patients with cancer as a subgroup for which outcome data were not available
Levine 2003	Review
Lopaciuk 1999	Study included patients with cancer as a subgroup for which outcome data were not available
Loprinzi 1999	No relevant outcome
Massicotte 2003	Study included patients with cancer as a subgroup for which outcome data were not available
McCan 2000	Review
Olin 1987	Retrospective study
Palareti 2000	Observational study
Partsch 2001	Observational study
Pinede 2001	No patients with cancer
Pini 1994	Study included patients with cancer as a subgroup for which outcome data were not available
Pérez-de-Llano 2010	Study included patients with cancer as a subgroup for which outcome data were not available
Schulman 2006	No patients with cancer
Schwartz 2005	Case series
Scott 2003	Review
Shattil 1984	Review
Siragusa 2010	Not intervention of interest: different duration of interventional drugs
Solymoss 1999	Review

(*Continued*)

Stine 2004	Retrospective study
Streiff 2006	Review
Suarez Alvarez 2003	Not an RCT (no control group)
Taliani 2003	Observational study
Tedoldi 1993	No patients with cancer in study
Veiga 2000	Study included patients with cancer as a subgroup for which outcome data were not available
Vucic 2002	Observational study

LMWH: low molecular weight heparin; RCT: randomized controlled trial.

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

Kamphuisen 2010(Longheva)

Trial name or title	Longheva
Methods	Multicenter, multinational, randomized, open-label trial
Participants	Participants with malignancy (all types, solid and hematologic) who have received 6-12 months of anticoagulation for VTE and have an indication for continuing anticoagulation
Interventions	Intervention: weight-adjusted scheme of LMWH for 6 additional months, 65-75% of full therapeutic dose Control: vitamin K antagonists for 6 additional months
Outcomes	Symptomatic recurrent VTE (DVT and PE) All clinically relevant bleeding (i.e. major bleeding and other clinically relevant non-major bleeding) All-cause mortality
Starting date	August 2010
Contact information	Prof. Pieter W. Kamphuisen, telephone: 0031503612943, email: p.w.kamphuisen@umcg.n
Notes	Funding: Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)

Lee 2013

Trial name or title	CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. PROTOCOL
Methods	Phase III, multinational, concealed, randomized, active-controlled, open-label trial with blinded adjudication
Participants	Adults diagnosed with active cancer and a histologically or cytologically confirmed solid tumor or hematologic malignancy
Interventions	Intervention: tinzaparin 175 IU/kg once daily for 180 days (almost 6 months) Control: warfarin once daily (target INR 2.0-3.0) overlapping with initial tinzaparin 175 IU/kg once daily (5-10 days)
Outcomes	Duration of follow-up: 1 month after last day of treatment (at 6 months) • Symptomatic DVT • Symptomatic non-fatal PE • Fatal PE • Incidental proximal DVT (popliteal vein or higher) • Incidental proximal PE (segmental arteries or larger) • Major bleeding • Clinically relevant nonmajor bleeding • All-cause mortality • Heparin-induced thrombocytopenia • Risk factors for recurrent VTE • Post-thrombotic syndrome • Health-related quality of life • Healthcare resource utilization
Starting date	August 2010
Contact information	Email: Agnes.Lee@phsa.ca
Notes	NCT01130025 Funding: LEO Pharma

Noble 2013 (ALICAT)

Trial name or title	ALICAT
Methods	Randomized, open-label, multicenter, mixed methods feasibility study
Participants	Intervention: LMWH at treatment dose according to body weight for further 6 months Control: no LMWH
Interventions	Participants aged ≥ 16 years with locally advanced or metastatic cancer receiving LMWH for treatment of catheter-associated thrombosis for 5 months
Outcomes	Quality of life Toxicities, including bleeding events and VTEs

Noble 2013 (ALICAT) (*Continued*)

Starting date	March 2013
Contact information	Dr. Joanna D Smith, telephone: +44 (0)2920 687463, email: sealjd@cf.ac.uk
Notes	Funding: Cardiff University

DVT: deep venous thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; VTE: venous thromboembolism.

DATA AND ANALYSES

Comparison 1. Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival (time-to-event)	3	1009	HR (Random, 95% CI)	0.96 [0.81, 1.14]
2 Mortality (at 3 months)	3	519	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.46, 1.28]
3 Mortality (at 6 months)	3	897	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.13]
4 Mortality (at any time point)	6	1310	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.11]
5 Recurrent venous thromboembolism (time-to-event)	3	1008	HR (Random, 95% CI)	0.47 [0.32, 0.71]
6 Recurrent venous thromboembolism	5	1162	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.35, 0.71]
7 Major bleeding	4	1092	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.52, 2.19]
8 Minor bleeding	4	1091	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.51, 1.55]
9 Thrombocytopenia	2	341	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.57, 1.66]

Comparison 2. Dabigatran versus vitamin K antagonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	121	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.30, 2.61]
2 Recurrent venous thromboembolism	1	121	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.10, 3.43]
3 Major bleeding	1	121	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.37, 5.94]
4 Thrombocytopenia	1	121	Risk Ratio (M-H, Random, 95% CI)	6.25 [0.33, 118.38]

Comparison 3. Ximelagtran versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	66	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.25, 7.91]
2 Minor bleeding	1	66	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.44, 2.62]
3 Recurrent venous thromboembolism	1	66	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 4.94]

Analysis 1.1. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 1 Survival (time-to-event).

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 1 Survival (time-to-event)

Study or subgroup	LMWH N	VKA N	log [HR] (SE)	HR IV,Random,95% CI	Weight	HR IV,Random,95% CI
Hull 2006	100	99	-0.0429 (0.207)		17.1 %	0.96 [0.64, 1.44]
Lee 2003	336	336	-0.004 (0.1)		73.5 %	1.00 [0.82, 1.21]
Meyer 2002	67	71	-0.3285 (0.28)		9.4 %	0.72 [0.42, 1.25]
Total (95% CI)	**503**	**506**			**100.0 %**	**0.96 [0.81, 1.14]**

Heterogeneity: Tau² = 0.0; Chi² = 1.19, df = 2 (P = 0.55); I² =0.0%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 2 Mortality (at 3 months).

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 2 Mortality (at 3 months)

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cesarone 2003	2/96	3/86		8.1 %	0.60 [0.10, 3.49]
Hull 2006	20/100	19/99		56.5 %	1.04 [0.59, 1.83]
Meyer 2002	8/67	17/71		35.4 %	0.50 [0.23, 1.08]
Total (95% CI)	**263**	**256**		**100.0 %**	**0.77 [0.46, 1.28]**

Total events: 30 (LMWH), 39 (VKA)

Heterogeneity: Tau² = 0.04; Chi² = 2.40, df = 2 (P = 0.30); I² =17%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 3 Mortality (at 6 months).

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 3 Mortality (at 6 months)

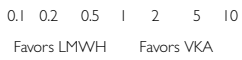
Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Deitcher 2006	22/53	11/32		8.2 %	1.21 [0.68, 2.15]
Lee 2003	130/336	136/338		77.8 %	0.96 [0.80, 1.16]
Meyer 2002	22/67	29/71		13.9 %	0.80 [0.52, 1.25]
Total (95% CI)	**456**	**441**		**100.0 %**	**0.96 [0.81, 1.13]**

Total events: 174 (LMWH), 176 (VKA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.23$, df = 2 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 4 Mortality (at any time point).

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 4 Mortality (at any time point)

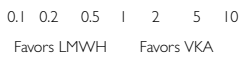
Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cesarone 2003	2/96	3/86		0.6 %	0.60 [0.10, 3.49]
Deitcher 2006	22/53	11/32		6.0 %	1.21 [0.68, 2.15]
Hull 2006	47/99	47/99		23.3 %	1.00 [0.75, 1.34]
Lee 2003	130/336	136/336		57.2 %	0.96 [0.79, 1.15]
Lopez-Beret 2001	7/17	6/18		2.7 %	1.24 [0.52, 2.94]
Meyer 2002	22/67	29/71		10.2 %	0.80 [0.52, 1.25]
Total (95% CI)	**668**	**642**		**100.0 %**	**0.97 [0.84, 1.11]**

Total events: 230 (LMWH), 232 (VKA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 5 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 5 Recurrent venous thromboembolism (time-to-event).

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

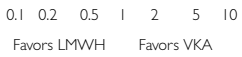
Outcome: 5 Recurrent venous thromboembolism (time-to-event)

Study or subgroup	LMWH N	VKA N	log [HR] (SE)	HR IV,Random,95% CI	Weight	HR IV,Random,95% CI
Hull 2006	99	99	-0.8819 (0.455)		20.6 %	0.41 [0.17, 1.01]
Lee 2003	336	336	-0.734 (0.24)		74.1 %	0.48 [0.30, 0.77]
Meyer 2002	67	71	-0.3567 (0.9)		5.3 %	0.70 [0.12, 4.08]
Total (95% CI)	**502**	**506**			**100.0 %**	**0.47 [0.32, 0.71]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.28$, df = 2 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 3.60 (P = 0.00031)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 6 Recurrent venous thromboembolism.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 6 Recurrent venous thromboembolism

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Deitcher 2006	4/53	3/32		6.2 %	0.81 [0.19, 3.37]
Hull 2006	7/99	16/99		17.9 %	0.44 [0.19, 1.02]
Lee 2003	27/336	53/336		66.2 %	0.51 [0.33, 0.79]
Meyer 2002	2/67	3/71		4.1 %	0.71 [0.12, 4.10]
Romera 2009	2/36	7/33		5.7 %	0.26 [0.06, 1.17]
Total (95% CI)	**591**	**571**		**100.0 %**	**0.50 [0.35, 0.71]**

Total events: 42 (LMWH), 82 (VKA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.39$, df = 4 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 3.84 (P = 0.00013)

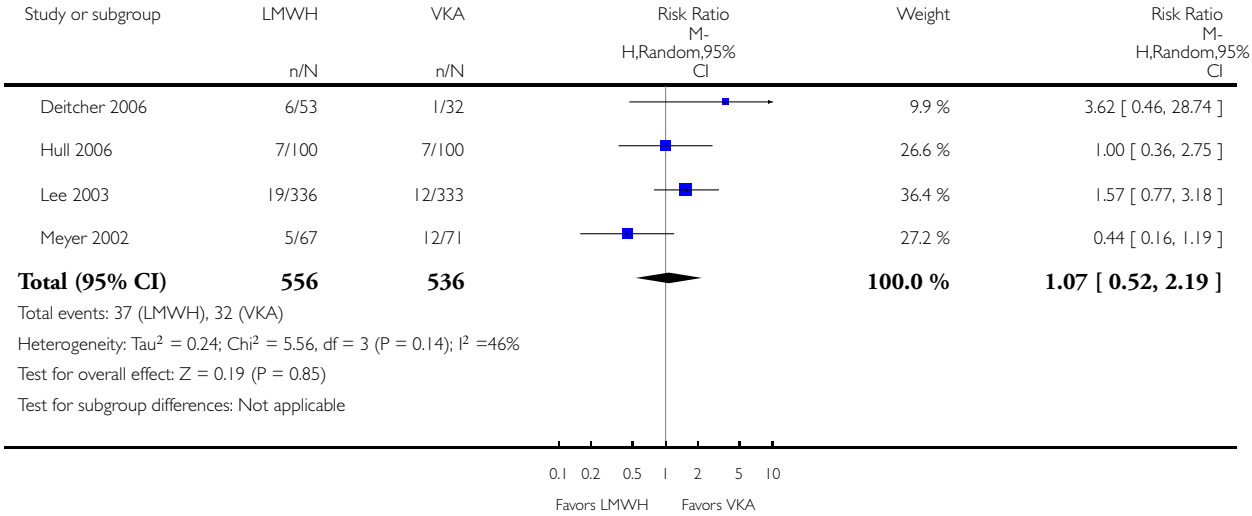
Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 7 Major bleeding.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 7 Major bleeding

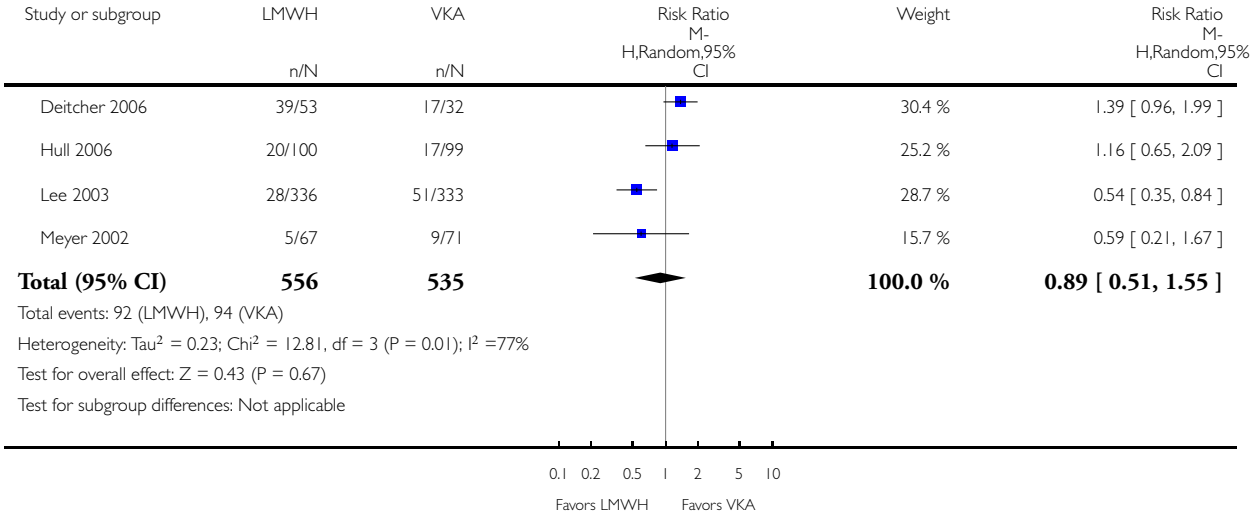


Analysis 1.8. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 8 Minor bleeding.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 8 Minor bleeding



Analysis 1.9. Comparison 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA), Outcome 9 Thrombocytopenia.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 1 Low molecular weight heparin (LMWH) versus vitamin K antagonist (VKA)

Outcome: 9 Thrombocytopenia

Study or subgroup	LMWH n/N	VKA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hull 2006	6/100	4/99		18.5 %	1.49 [0.43, 5.10]
Meyer 2002	16/71	18/71		81.5 %	0.89 [0.49, 1.60]
Total (95% CI)	**171**	**170**		**100.0 %**	**0.98 [0.57, 1.66]**

Total events: 22 (LMWH), 22 (VKA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 0.08 (P = 0.93)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Dabigatran versus vitamin K antagonist, Outcome 1 Mortality.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 2 Dabigatran versus vitamin K antagonist

Outcome: 1 Mortality

Study or subgroup	Dabigatran n/N	Warfarin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Schulman 2009	6/64	6/57		100.0 %	0.89 [0.30, 2.61]
Total (95% CI)	**64**	**57**		**100.0 %**	**0.89 [0.30, 2.61]**

Total events: 6 (Dabigatran), 6 (Warfarin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.83)

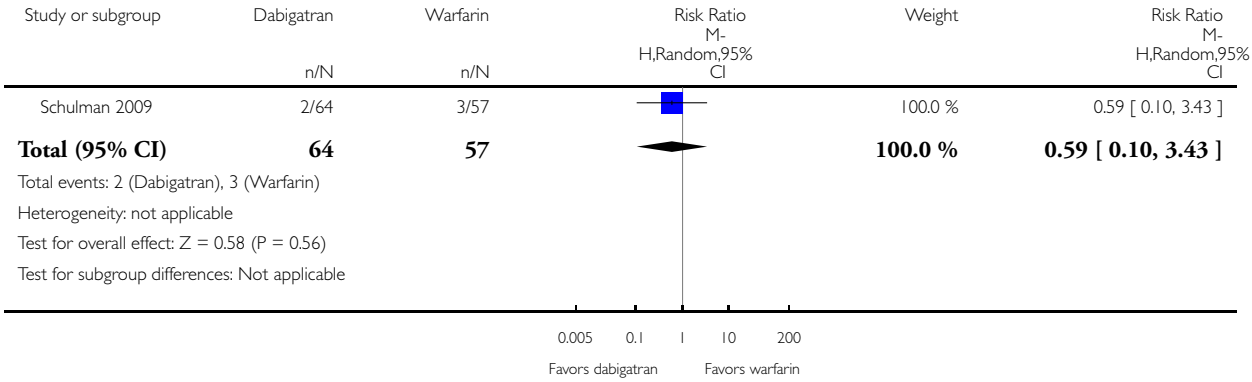
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Dabigatran versus vitamin K antagonist, Outcome 2 Recurrent venous thromboembolism.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 2 Dabigatran versus vitamin K antagonist

Outcome: 2 Recurrent venous thromboembolism

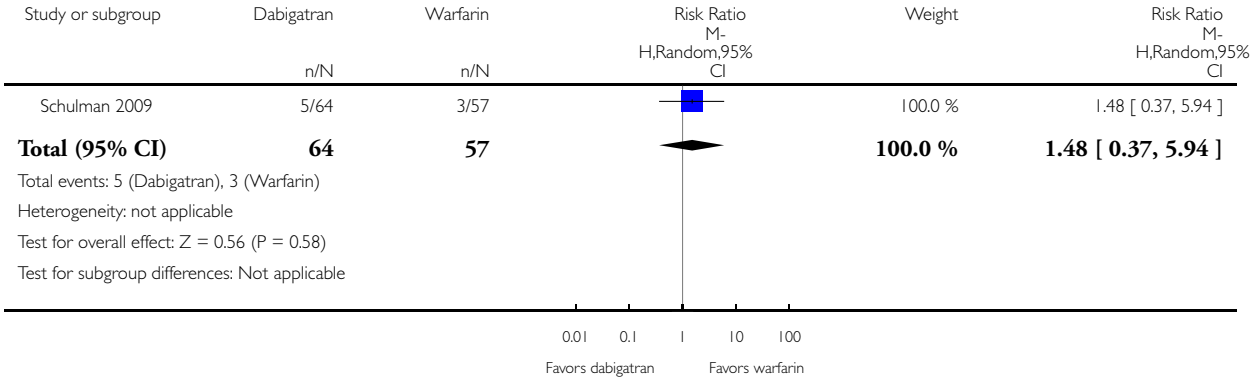


Analysis 2.3. Comparison 2 Dabigatran versus vitamin K antagonist, Outcome 3 Major bleeding.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 2 Dabigatran versus vitamin K antagonist

Outcome: 3 Major bleeding

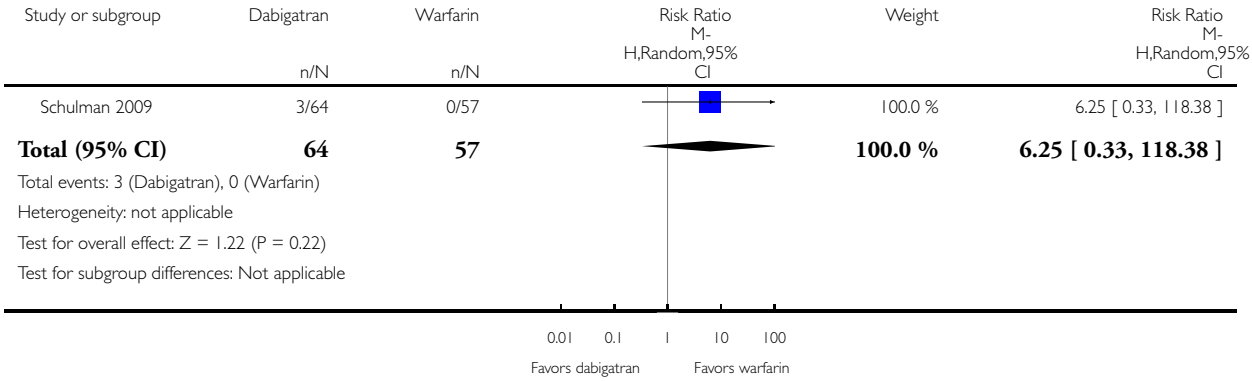


Analysis 2.4. Comparison 2 Dabigatran versus vitamin K antagonist, Outcome 4 Thrombocytopenia.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 2 Dabigatran versus vitamin K antagonist

Outcome: 4 Thrombocytopenia



Analysis 3.1. Comparison 3 Ximelagtran versus placebo, Outcome 1 Mortality.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 3 Ximelagtran versus placebo

Outcome: 1 Mortality

Study or subgroup	Ximelagtran n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Schulman 2003	3/34	2/32		100.0 %	1.41 [0.25, 7.91]
Total (95% CI)	**34**	**32**		**100.0 %**	**1.41 [0.25, 7.91]**
Total events: 3 (Ximelagtran), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.39 (P = 0.69)					
Test for subgroup differences: Not applicable					

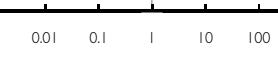
Analysis 3.2. Comparison 3 Ximelagtran versus placebo, Outcome 2 Minor bleeding.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 3 Ximelagtran versus placebo

Outcome: 2 Minor bleeding

Study or subgroup	Ximelagtran n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Schulman 2003	8/34	7/32		100.0 %	1.08 [0.44, 2.62]
Total (95% CI)	**34**	**32**		**100.0 %**	**1.08 [0.44, 2.62]**
Total events: 8 (Ximelagtran), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.87)					
Test for subgroup differences: Not applicable					

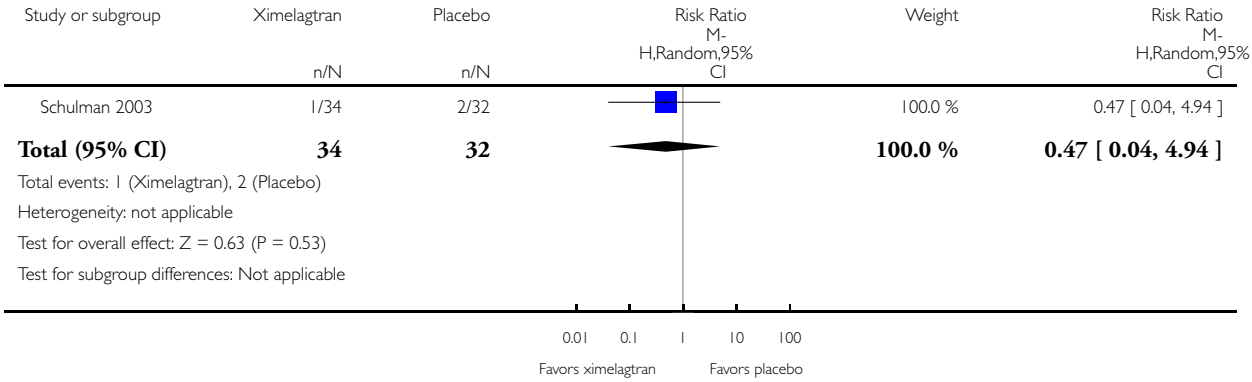


Analysis 3.3. Comparison 3 Ximelagtran versus placebo, Outcome 3 Recurrent venous thromboembolism.

Review: Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer

Comparison: 3 Ximelagtran versus placebo

Outcome: 3 Recurrent venous thromboembolism



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Adjuvant therapy	A therapy given in addition to the primary treatment to decrease the risk of the cancer recurrence or to assist in the cure
Anticoagulation	The process of hindering the clotting of blood especially by treatment with an anticoagulant
Antithrombotic	Used against or tending to prevent thrombosis (clotting)
Coagulation	Clotting
Deep vein thrombosis (DVT)	A condition marked by the formation of a thrombus within a deep vein (as of the leg or pelvis) that may be asymptomatic or be accompanied by symptoms (as swelling and pain) and that is potentially life-threatening if dislodgment of the thrombus results in pulmonary embolism
Fondaparinux	An anticoagulant medication
Hemostatic system	The system that shortens the clotting time of blood and stops bleeding
Heparin	An enzyme occurring especially in the liver and lungs that prolongs the clotting time of blood by preventing the formation of fibrin. 2 forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low molecular weight heparins (LMWH)

Table 1. Glossary (*Continued*)

Impedance plethysmography	A technique that measures the change in blood volume (venous blood volume as well as the pulsation of the arteries) for a specific body segment
Kappa statistic	A measure of degree of nonrandom agreement between observers, measurements of a specific categorical variable, or both
Metastasis	The spread of a cancer cells from the initial or primary site of disease to another part of the body
Parenteral nutrition	The practice of feeding a patient intravenously, circumventing the gastrointestinal tract
Pulmonary embolism (PE)	Embolism of a pulmonary artery or one of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock, and sometimes death
Thrombocytopenia	Persistent decrease in the number of blood platelets that is often associated with hemorrhagic conditions
Thrombosis	The formation or presence of a blood clot within a blood vessel
Vitamin K antagonists	Anticoagulant medications that are used for anticoagulation. Warfarin is a vitamin K antagonist
Warfarin	An anticoagulant medication that is a vitamin K antagonist that is used for anticoagulation
Ximelagatran	An anticoagulant medication

APPENDICES

Appendix 1. Full search strategies for the electronic databases

Database	Strategy
Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue)	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA

(*Continued*)

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

(*Continued*)

	mon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 fondaparinux/ #11 (fondaparinux OR Arixtra).tw #12 ximelagatran/ #13 (ximelagatran OR Exanta).tw #14 (Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban).tw. #15 5 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 #16 Neoplasm/ #17 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #18 16 OR 17 #19 Random:.tw. OR clinical trial:.mp. OR exp health care quality #20 animals/ NOT human/ #21 19 NOT 20 #22 15 AND 18 AND 21
ISI (International Scientific Information) the Web of Science	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor #8 random$ OR placebo$ OR versus OR vs OR double blind OR double-blind OR compar$ OR controlled #9 6 AND 7 AND 8

Appendix 2. Full search strategies for electronic databases - update 2013

Database	Strategy
CENTRAL (issue 12, 2012)	#1 MeSH descriptor: [Heparin] explode all trees #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum) #3 MeSH descriptor: [Coumarins] explode all trees #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA) #5 (fondaparinux or arixtra) #6 (ximelagatran or exanta) #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Neoplasms] explode all trees #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) #11 #9 or #10 #12 #8 and #10
MEDLINE	#1 exp Heparin/ #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw #3 exp Coumarins/ #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw #5 (fondaparinux or arixtra).tw. #6 (ximelagatran or exanta).tw. #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw #8 1 or 2 or 3 or 4 or 5 or 6 or 7 #9 exp Neoplasms/ #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw #11 9 or 10 #12 8 and 11 #13 randomised controlled trial.pt. #14 controlled clinical trial.pt. #15 randomized.ab. #16 placebo.ab. #17 drug therapy.fs. #18 randomly.ab. #19 trial.ab. #20 groups.ab. #21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 #22 12 and 21 #23 exp animals/ not humans.sh. #24 22 not 23

(*Continued*)

EMBASE	#1 heparin/ #2 exp low molecular weight heparin/ #3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw #4 exp coumarin derivative/ #5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw #6 (fondaparinux or arixtra).tw. #7 (ximelagatran or exanta).tw. #8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 #10 exp neoplasm/ #11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw #12 10 or 11 #13 9 and 12 #14 crossover procedure/ #15 double-blind procedure/ #16 randomised controlled trial/ #17 single-blind procedure/ #18 random*.mp. #19 factorial*.mp. #20 (crossover* or cross over* or cross-over*).mp. #21 placebo*.mp. #22 (double* adj blind*).mp. #23 (singl* adj blind*).mp. #24 assign*.mp. #25 allocat*.mp. #26 volunteer*.mp. #27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 #28 13 and 27 #29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/ #30 28 not 29

Appendix 3. Detailed statistical data abstraction

Outcome: Mortality at 3 months		
Study Name	**LMWH**	**UFH**

(*Continued*)

	Events	No Rand	No most likely to have MPD		No less likely to have MPD[1]	No with available outcome data (for CCA) [2]	Events	No Rand	No more likely to have MPD		No less likely to have MPD	No. with available outcome data (for CCA)
			Pre-trt[3]	Post-trt [					Pre-trt	Post-trt		
Cesarone 2003	2	96	0	0	0	96	3	86	0	0	0	86
Hull 2006	20	100	0	0	0	100	19	100	0	1	0	100-1=99
Meyer 2002	8	71	0	4[5]	0	71-4=67	17	75	0	4	0	75-4=71

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.
[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
[5] "8 (4 in each group) were considered not evaluable by the outcome adjudication committee" (Applies to both arms)

Outcome: Mortality at 6 months										
Study Name	**LMWH**					**UFH**				
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA)	Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for

(*Continued*)

						[2]						CCA)
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt		
Deitcher 2006	22	32+36=68	1+5+4=10	3+2=5	10+19=29	68-10-5=53	11	34	0	2	16	34-2=32
Lee A, 2003	130	338	0	2[5]	0	338-2=336	136	338	0	2	0	338-2=336
Meyer 2002	22	71	0	4[6]	0	71-4=67	29	75	0	4	0	75-4=71
Van Doormal 2010	50	220	0	0	48	220	48	201	0	0	56	201

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.
[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
[5]"Two patients in each group were excluded from the efficacy analysis because they did not have a qualifying thrombotic event: one patient had a thrombosis in an arm vein, one had an asymptomatic thrombus in the leg, and the other two did not have a confirmed pulmonary embolism"
[6]"8 (4 in each group) were considered not evaluable by the outcome adjudication committee" (Applies to both arms)

Outcome: Mortality at any point

Study Name	**LMWH**					**UFH**				
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA) [2]	Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)

(*Continued*)

			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt		
Cesarone 2003	2	96	0	0	0	96	3	86	0	0	0	86
Hull 2006	47	100	0	1	0	100-1=99	47	100	0	1	0	100-1=99
Van Doormal 2010	50	220	0	0	48	220	48	201	0	0	56	201
Lee A, 2003	130	338	0	2[5]	0	338-2=336	136	338	0	2	0	338-2=336
Deitcher 2006	22	32+36=68	1+5+4=10	3+2=5	10+19=29	68-10-5=53	11	34	0	2	16	34-2=32
Meyer 2002	22	71	0	4[6]	0	71-4=67	29	75	0	4	0	75-4=71
Lopez-Beret 2001	7[7]	17	0	0	0	17	6	18	0	0	0	18

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.
[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
[5]"Two patients in each group were excluded from the efficacy analysis because they did not have a qualifying thrombotic event: one patient had a thrombosis in an arm vein, one had an asymptomatic thrombus in the leg, and the other two did not have a confirmed pulmonary embolism"
[6] "8 (4 in each group) were considered not evaluable by the outcome adjudication committee" (Applies to both arms)
[7]"Thirteen patients with cancer at an advanced stage died because of the progression of their neoplastic disease: seven (41.2%) of 17 patients with malignancy in the LMWH group and six (33.3%) of 18 with cancer in the OA group."

Outcome: Recurrent VTE

Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD		No less likely to have MPD[1]	No with available outcome data (for CCA) [2]	Events	No Rand	No more likely to have MPD		No less likely to have MPD	No. with available outcome data (for CCA)
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt		
Romera 2009	2	36	0	0	0	36	7	33	0	0	0	33
Deitcher 2006	4	32+36=68	1+5+4=10	3+2=5	10+19=29	68-10-5=53	3	34	0	2	16	34-2=32
Hull 2006	7	100	0	1	0	100-1=99	16	100	0	1	0	100-1=99
Van Doormaal 2010	5	220	0	0	48	220	12	201	0	0	56	201
Lee A, 2003	27	338	0	2[5]	0	338-2=336	53	338	0	2	0	338-2=336
Meyer 2002	2	71	0	4[6]	0	71-4=67	3	75	0	4	0	75-4=71

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5]"Two patients in each group were excluded from the efficacy analysis because they did not have a qualifying thrombotic event: one patient had a thrombosis in an arm vein, one had an asymptomatic thrombus in the leg, and the other two did not have a confirmed pulmonary embolism"

[6] "8 (4 in each group) were considered not evaluable by the outcome adjudication committee" (Applies to both arms)

Outcome: Major Bleeding												
Study Name	**LMWH**						**UFH**					
	Events	No Rand	No most likely to have MPD		No less likely to have MPD[1]	No with available outcome data (for CCA) [2]	Events	No Rand	No more likely to have MPD		No less likely to have MPD	No. with available outcome data (for CCA)
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt		
Van Doormaal 2010	8	220	0	0	48	220	7	201	0	0	56	201
Deitcher 2006	6	32+36=68	1+5+4=10	3+2=5	10+19=29	68-10-5=53	1	34	0	2	16	34-2=32
Hull 2006	7	100	0	0	0	100	7	100	0	1	0	100-1=99
Lee A, 2003	19	338	0	2[5]	0	338-2=336	12	338	3[6]	2	0	338-2-3=333
Meyer 2002	5	71	0	4[7]	0	71-4=67	12	75	0	4	0	75-4=71

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.
[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
[5]"Two patients in each group were excluded from the efficacy analysis because they did not have a qualifying thrombotic event: one patient had a thrombosis in an arm vein, one had an asymptomatic thrombus in the leg, and the other two did not have a confirmed pulmonary embolism"

[6]"Three patients assigned to oral anticoagulant therapy did not receive the study drug and were excluded from the safety analyses. Nineteen of 338 patients in the dalteparin group (6 percent) and 12 of 335 patients who received oral anticoagulant therapy (4 percent) had major bleeding"
[7] "8 (4 in each group) were considered not evaluable by the outcome adjudication committee"(Applies to both arms)

Outcome: Minor Bleeding												
Study Name	**LMWH**						**UFH**					
	Events	No Rand	No most likely to have MPD		No less likely to have MPD[1]	No with available outcome data (for CCA) [2]	Events	No Rand	No more likely to have MPD		No less likely to have MPD	No. with available outcome data (for CCA)
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt		
van Doormaal 2010	18	220	0	0	48	220	20	201	0	0	56	201
Deitcher 2006	39	32+36=68	1+5+4=10	3+2=5	10+19=29	68-10-5=53	17	34	0	2	16	34-2=32
Hull 2006	20	100	0	0	0	100	17	100	0	1	0	100-1=99
Meyer 2002	5	71	0	4[6]	0	71-4=67	9	75	0	4	0	75-4=71
Lee A, 2003	28[7]	338	0	2[8]	0	338-2=336	51	338	3[9]	2	0	338-2-3=333

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.
[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
[5]Refers to both major and minor bleeding events. In this case I suggest not to report this outcome at 3 months.
[6]"8 (4 in each group) were considered not evaluable by the outcome adjudication committee" [6] (Applies to both arms)

[7]"Nineteen of 338 patients in the dalteparin group (6 percent) and 12 of 335 patients who received oral anticoagulant therapy (4 percent) had major bleeding (P=0.27). The respective rates of any bleeding were 14 percent and 19 percent (P=0.09)."
[8]"Two patients in each group were excluded from the efficacy analysis because they did not have a qualifying thrombotic event: one patient had a thrombosis in an arm vein, one had an asymptomatic thrombus in the leg, and the other two did not have a confirmed pulmonary embolism"
[9]"Three patients assigned to oral anticoagulant therapy did not receive the study drug and were excluded from the safety analyses. Nineteen of 338 patients in the dalteparin group (6 percent) and 12 of 335 patients who received oral anticoagulant therapy (4 percent) had major bleeding"

Outcome: Thrombocytopenia

Study Name	**LMWH**						**UFH**						
	Events	No Rand	No most likely to have MPD		No less likely to have MPD[1]	No with available outcome data (for CCA) [2]	Events	No Rand	No more likely to have MPD		No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt			
Hull 2006	6	100	0	0	0	100	4	100	0	1	0	100-1=99	
Meyer 2002	16	71	0	4[5]	0	71-4=67	18	75	0	4	0	75-4=71	

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin.
[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
[5]"8 (4 in each group) were considered not evaluable by the outcome adjudication committee" [5] (Applies to both arms)

WHAT'S NEW

Date	Event	Description
11 February 2015	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2008

Date	Event	Description
25 June 2014	Amended	Table format update
4 June 2014	New citation required but conclusions have not changed	Data abstraction verified and detailed statistical data included as appendix Data reanalyzed by using a complete case analysis approach for the primary meta-analysis
9 February 2013	New search has been performed	Search Updated
28 November 2012	Amended	Author contact details amended
9 May 2011	New search has been performed	Search updated 7 February 2010. One new RCT was identified.
9 May 2011	New citation required but conclusions have not changed	One new randomized controlled trial (RCT) identified and added to review. New authors also added

CONTRIBUTIONS OF AUTHORS

EAA: protocol development, search for trials, screening, data extraction, data analysis, manuscript drafting, review co-ordination.LK: screening, data extraction, data analysis.MB: data extraction, data analysis.IN: screening.NL: data abstraction, manuscript drafting.SR: screening, data extraction.IT: screening, data extraction.FS: screening, data extraction.PM: data analysis, methodologic advice.HJS: protocol development, search for trials, data extraction, data analysis, methodologic advice.

DECLARATIONS OF INTEREST

HJS: no personal payments from for-profit sponsors related to the subject matter since 2010. EAA and HJS are members of the executive committee of the American College of Chest Physicians' Antithrombotic Therapy Guidelines.

SOURCES OF SUPPORT

Internal sources

- State University of New York at Buffalo, Department of Medicine, USA.
- Italian National Cancer Institute Regina Elena Rome, Italy.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anticoagulants [adverse effects; *therapeutic use]; Azetidines [therapeutic use]; Benzimidazoles [therapeutic use]; Benzylamines [therapeutic use]; Dabigatran [therapeutic use]; Hemorrhage [chemically induced]; Heparin, Low-Molecular-Weight [therapeutic use]; Neoplasms [*complications]; Oligosaccharides [therapeutic use]; Randomized Controlled Trials as Topic; Venous Thromboembolism [*drug therapy; etiology; mortality]; Vitamin K [antagonists & inhibitors]; beta-Alanine [analogs & derivatives; therapeutic use]

MeSH check words

Humans