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Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer (Review)

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[Intervention Review]

Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

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ABSTRACT

Background

Compared to patients without cancer, patients with cancer who receive anticoagulant treatment for venous thromboembolism are more likely to develop recurrent venous thromboembolism (VTE).

Objectives

To compare the efficacy and safety of three types of parenteral anticoagulants for the initial treatment of VTE in patients with cancer.

Search methods

A comprehensive search for studies of anticoagulation in cancer patients including a February 2010 electronic search of: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and ISI Web of Science.

Selection criteria

Randomized clinical trials (RCTs) comparing low molecular weight heparin (LMWH), unfractionated heparin (UFH), and fondaparinux in patients with cancer and objectively confirmed VTE.

Data collection and analysis

Using a standardized data form, data was extracted in duplicate on methodological quality, participants, interventions, and outcomes of interest that included mortality, recurrent VTE, major bleeding, minor bleeding, postphlebitic syndrome, quality of life, and thrombocytopenia.

Main results

Of 3986 identified citations, 16 RCTs were eligible: 13 compared LMWH to UFH, two compared fondaparinux to heparin, and one compared dalteparin to tinzaparin. Meta-analysis of 11 studies showed a statistically significant reduction in mortality at three months of follow up with LMWH compared with UFH (relative risk (RR) 0.71; 95% confidence interval (CI) 0.52 to 0.98). There was little

change in the effect estimate after excluding studies of lower methodological quality (RR 0.72; 95% CI 0.52 to 1.00). A meta-analysis of three studies comparing LMWH with UFH showed no statistically significant reduction in VTE recurrence (RR 0.78; 95% CI 0.29 to 2.08). The overall quality of evidence was low for LMWH versus UFH due to imprecision and likely publication bias. There were no statistically significant differences between heparin and fondaparinux for the outcomes of death (RR 1.27; 95% CI 0.88 to 1.84), recurrent VTE (RR 0.95; 95% CI 0.57 to 1.60), major bleeding (RR 0.79; 95% CI 0.39 to1.63) or minor bleeding (RR 1.50; 95% CI 0.87 to 2.59). The one study comparing dalteparin to tinzaparin did not find a statistically significant difference in mortality (RR 0.86; 95% CI 0.43 to 1.73).

Authors' conclusions

LMWH is possibly superior to UFH in the initial treatment of VTE in patients with cancer. Additional trials focusing on patient important outcomes will further inform the questions addressed in this review.

PLAIN LANGUAGE SUMMARY

Blood thinners for the initial treatment of blood clots in patients with cancer

Patients with cancer are at an increased risk of blood clots. The blood thinner administered in the first few days can consist of unfractionated heparin (infused intravenously) or low molecular weight heparin (injected subcutaneously once or twice per day). These two blood thinners may have different efficacies and safety profiles. In this systematic review, data from 13 studies suggest that low molecular weight heparin is superior to unfractionated heparin in reducing mortality. However, there is not enough evidence to prove superiority in reducing recurrence of blood clots. We did not find data to compare the safety profile of these two medications.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

LMWH compared to UFH for the initial treatment of venous thromboembolism in patients with cancer

Patient or population: patients with the initial treatment of venous thromboembolism in patients with cancer
Settings: Inpatient or outpatient
Intervention: LMWH
Comparison: UFH

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	UFH	LMWH				
Death at 3 months Follow-up: median 3 months	**189 per 1000**	**134 per 1000** (98 to 185)	**RR 0.71** (0.52 to 0.98)	801 (11 studies)	⊕⊕◯◯ **low**[1,2,3]	
Recurrent VTE Follow-up: median 3 months	**96 per 1000**	**75 per 1000** (28 to 200)	**RR 0.78** (0.29 to 2.08)	371 (3 studies)	⊕⊕◯◯ **low**[3,4,5]	
Major bleeding - not reported	See comment	See comment	Not estimable	-	See comment	There is indirect evidence that both LMWH and UFH increase the risk of major bleeding compared with no anticoagulation
Post phlebitic syndrome - not reported	See comment	See comment	Not estimable	-	See comment	
Quality of life - not reported	See comment	See comment	Not estimable	-	See comment	

Thrombocytopenia - not reported	See comment	See comment	Not estimable	-	See comment

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Of the 11 studies, 10 clearly concealed allocation, one blinded patients, providers or data collectors, 11 blinded outcome adjudicators, and 10 used ITT.
[2] A relatively small number of events
[3] We excluded 11 studies from the systematic review because the data for the cancer subgroup analysis was not reported. Of the 13 included studies, only three reproted on the recurrence VTE outcome. An analysis of the same question not restricted to patients with cancer, demonstrated a likely publication bias in favor of LMWH.
[4] Of the 3 studies, 2 clearly concealed allocation, none blinded patients, providers or data collectors, 3 blinded outcome adjudicators, and 2 used ITT.
[5] CI includes values suggesting benefit and values suggesting harm

BACKGROUND

Glossary of terms found in Table 1

Description of the condition

Cancer status by itself increases the risk of venous thromboembolism (VTE) by four to six fold (Heit 2000). In addition, therapeutic interventions such as chemotherapy, hormonal therapy, and indwelling central venous catheters increase the risk of VTE in these patients (Heit 2000). Similarly, patients undergoing surgery for cancer have a higher risk of VTE than those undergoing surgery for benign diseases (Gallus 1997; Kakkar 1970). Patients with cancer and VTE have a higher risk of death than patients with cancer alone or VTE alone (Levitan 1999; Sorensen 2002).

This heightened hypercoagulable state might alter the response to anticoagulant treatment and the risk of bleeding. Compared to patients without cancer, patients with cancer who receive anticoagulant treatment for VTE are more likely to develop recurrent VTE with an annual risk of 21% to 27%, a two to threefold risk increase (Hutten 2000; Prandoni 2002). These patients are also more likely to develop major bleeding with an annual risk of 12% to 13%, a two to six fold risk increase (Hutten 2000; Prandoni 2002).

Description of the intervention

Heparin, low molecular weight heparins (LMWHs), fondaparinux, and danaparoid do not have intrinsic anticoagulant activity but potentiate the activity of antithrombin III in inhibiting activated coagulation factors. These agents constitute indirect anticoagulants as their activity is mediated by plasma cofactors. Recombinant hirudin, bivalirudin, and argatroban directly inhibit thrombin and are classified as direct anticoagulants (Hirsh 2008). Heparin and its low molecular weight derivatives are not absorbed orally and must be administered parenterally by intravenous infusion or subcutaneous injection (Hirsh 1993).

How the intervention might work

In the initial treatment of VTE, low molecular weight heparins (LMWH) and unfractionated heparin (UFH) might have a different comparative efficacy in patients with cancer than in patients without cancer. Subgroup analyses of a Cochrane systematic review showed that in patients without cancer there was no statistically significant difference between the effects of LMWH and UFH on overall mortality (odds ratio (OR) 0.97; 95% CI 0.61 to 1.56) (van Dongen 2007). However, in patients with cancer, LMWH resulted in a lower overall mortality compared to UFH (OR 0.53; 95% CI 0.33 to 0.85).

Why it is important to do this review

No systematic review has focused on the initial treatment of VTE in patients with cancer. While the above mentioned Cochrane review subgroup analysis compared the efficacy of these two drug classes it did not report on the safety of LMWH and UFH in this patient group. Furthermore, The Cochrane Collaboration has recognized that addressing all important outcomes including harm is of great importance to make evidence-based health care decisions. In addition, an analysis that includes an evaluation of direct comparative trials and subgroup analysis could prevent the potential pitfalls of subgroup analysis (Oxman 2002). A subgroup refers to a segment of the studied population with a specific characteristic that is relevant to the question under consideration (for example a subgroup of cancer patients with advanced disease).

OBJECTIVES

To compare the efficacy and safety of three types of parenteral anticoagulants (that is fixed dose low molecular weight heparin, adjusted dose unfractionated heparin, and fondaparinux) for the initial 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 and a confirmed diagnosis of VTE (acute deep venous thrombosis or pulmonary embolism). Patients could have been of any age group (including pediatric patients) with either solid or hematological cancer and at any stage of their cancer irrespective of the type of cancer therapy.

To include patients, deep venous thrombosis should have been diagnosed using one the following objective diagnostic tests: venography, ^{125}I-fibrinogen uptake test, impedance plethysmography, or Doppler ultrasound. Pulmonary embolism should have been diagnosed using one the following objective diagnostic tests: pulmonary perfusion or ventilation scans, computed tomography, pulmonary angiography).

Types of interventions

We considered comparisons of the following agents used in initial parenteral anticoagulation (typically the first five to 10 days): LMWH, UFH, or fondaparinux. We excluded studies in which thrombolytic therapy (for example streptokinase) was part of the intervention. The protocol should have planned to provide all other co-interventions (for example chemotherapy) similarly.

Types of outcome measures

Primary outcomes

- All cause mortality

Secondary outcomes

- Symptomatic recurrent deep venous thrombosis; events had to be diagnosed using one of the following objective diagnostic tests: venography, ^{125}I-fibrinogen uptake test, impedance plethysmography, or Doppler ultrasound
- Symptomatic recurrent pulmonary embolism; events had to be diagnosed using one of the following objective diagnostic tests: pulmonary perfusion or ventilation scans, computed tomography, pulmonary angiography or autopsy
- Major bleeding
- Minor bleeding
- Postphlebitic syndrome
- Quality of life
- Thrombocytopenia

We accepted the authors' definitions of major bleeding, minor bleeding, thrombocytopenia, and postphlebitic syndrome 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 electronically searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1), MEDLINE (1966 onwards; accessed via Ovid), EMBASE (1980 onwards; 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.

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO) (starting with its first volume, 1982) and American Society of Hematology (ASH) (starting with its 2003 issue). We reviewed the reference lists of papers included this review and of other relevant systematic reviews (Dolovich 2000; Gould 1999; Hettiarachchi 1999; Quinlan 2004; Siragusa 1996; van Dongen 2007). We used the related article feature in PubMed to identify additional articles. We did not use language restrictions.

Data collection and analysis

Selection of studies

Two 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 author. Two 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). The two authors resolved any disagreements about which articles were eligible by discussion or by consulting a third author.

Data extraction and management

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

Participants

- Demographic characteristics (e.g., age, sex)
- Cancer characteristics (e.g., type, location, stage, time since diagnosis, estimated life expectancy, current cancer treatments, performance status)
- Whether participants had deep venous thrombosis, pulmonary embolism, or both
- Number of patients in each treatment arm

Interventions

- Type, dosage, and administration schedule of LMWH
- Dosage and administrative schedule of UFH
- Dosage schedule of fondaparinux
- Duration of initial parenteral therapy
- Type (oral anticoagulant versus LMWH) and duration of long-term anticoagulation

Outcomes

We attempted to extract both time to event data (for the survival outcome) and categorical data (for all outcomes). However, none of the studies reported time to event data for patients with cancer. For categorical data, we extracted the reported outcome data necessary to conduct intention-to-treat analyses. Outcome event rates were collected whenever they were reported in a 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

First, we assessed risk of bias at the study level using the Cochrane risk of bias tool. Two review authors independently assessed the methodological quality of each included study and resolved their disagreements by discussion. Methodological 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 intention-to-treat (ITT) principle.

Second, we assessed the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Cochrane Handbook).

Measures of treatment effect

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

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

All but two included studies reported 100% follow up. We analyzed the available data assuming that any data that could be missing were missing at random.

Assessment of heterogeneity

Heterogeneity between trials was assessed by visual inspection of forest plots, estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity. If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

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 assessed publication bias by creating an inverted funnel plot for the primary outcome of survival. We used the trim and fill technique to statistically evaluate the existence of publication bias (Duval 2000). We did not create funnel plots for the other outcomes due to the low number of included trials for each outcome.

Data synthesis

We calculated the agreement between the two independent review authors for the assessment of eligibility using the kappa statistic. For dichotomous data, we calculated the RR separately for each study. We then pooled the results of the different studies using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses based on characteristics of participants but did not conduct them as the needed data were not available.

Sensitivity analysis

We conducted sensitivity analysis by excluding studies with small and unbalanced arms.

RESULTS

Description of studies

Results of the search

The February 2010 search strategy identified a total of 8187 citations from which we removed the results of our January 2007 search. The title and abstract screening of the 8187 unique citations identified 59 as potentially eligible for this review. We included 16 studies and excluded the remaining 43. Agreement between authors for study eligibility was excellent (kappa = 0.94).

Included studies

In all of the 16 included studies cancer patients constituted subgroups. Of these 16 studies, four studies reported data for the cancer subgroups (Prandoni 1992; Simmoneau 1993; Van Doormaal 2009 a; Van Doormaal 2009 b) and three studies (Breddin 2001; Hull 1992; Merli 2001) had follow-up publications reporting the cancer subgroup data (Green 1992; Kakkar 2000; Pineo 1997; Rodgers 1999). For two studies, we obtained the cancer subgroup data from the authors (Galilei 2004; Wells 2005). Seven studies did not report cancer subgroup data (Columbus 1997; Duroux 1991; Koopman 1996; Levine 1996; Lindmaker 1994; Lopaciuk 1992; Simmoneau 1997) so we used the data as reported in two published systematic reviews (Hettiarachchi 1999; van Dongen 2007).

Of the 16 studies, 13 compared a LMWH to UFH (total of 1016 participants), one compared dalteparin to tinzaparin (Wells 2005), one compared fondaparinux to enoxaparin (Van Doormaal 2009 a), and one compared fondaparinux to UFH (Van Doormaal 2009 b). None of the studies specified the types of cancer of the participants. In 15 of the 16 studies the initial parenteral anticoagulation was followed by oral anticoagulation for at least three months. In Duroux 1991, the long-term anticoagulation was either UFH subcutaneously or oral anticoagulation depending on the usual regimen of the participating center (Duroux 1991).

Excluded studies

Of the 43 excluded studies, in 11 studies patients with cancer constituted study subgroups but their outcome data were not available (Albada 1989; Belcaro 1999; Bratt 1990; Buller 2004; Fiessinger 1996; Harenberg 1990; Harenberg 2000; Holm 1986; Hull 2000; Luomanmaki 1996; Riess 2003). We excluded the remaining 32 studies for the following reasons: review (11), case report or series (4), letter to the editor or editorial (4), cohort study (3), no patients with cancer included (3), retrospective study (2), no relevant outcome (2), different long-term management (1), not randomized (1), survey (1).

Risk of bias in included studies

Allocation

Allocation was adequately concealed in 14 studies; it was not clear whether it was adequately concealed in two studies (Breddin 2001; Duroux 1991).

Blinding

All studies blinded outcome assessors. Only two studies blinded data analysts (Galilei 2004; Wells 2005) and only three studies blinded patients and caregivers (Hull 1992; Van Doormaal 2009 a; Wells 2005).

Incomplete outcome data

Follow up was 89% for Breddin 2001, 92% for Duroux 1991, and 100% for the remaining studies.

Selective reporting

We did not suspect selective reporting of outcomes for any of the studies. The cancer subgroup data were missing for a large number of studies.

Other potential sources of bias

Thirteen studies clearly used intention-to-treat analysis (Duroux 1991; Galilei 2004; Hull 1992; Koopman 1996; Levine 1996; Lindmaker 1994; Lopaciuk 1992; Merli 2001; Prandoni 1992; Simmoneau 1997; Van Doormaal 2009 a; Van Doormaal 2009 b; Wells 2005). None of the studies were stopped early for benefit.

Effects of interventions

See: **Summary of findings for the main comparison** LMWH compared to UFH for the initial treatment of venous thromboembolism in patients with cancer; **Summary of findings 2** Fondaparinux compared to heparin for the initial treatment of venous thromboembolism in patients with cancer

Low molecular weight heparin versus unfractionated heparin

Mortality

The number of fatal events was available for 11 studies (801 patients) at three months follow up (Columbus 1997; Duroux 1991; Galilei 2004; Hull 1992; Koopman 1996; Levine 1996; Lindmaker 1994; Lopaciuk 1992; Prandoni 1992; Simmoneau 1993; Simmoneau 1997). The pooled analysis showed a statistically significant mortality reduction in patients treated with LMWH compared with those treated with UFH (RR 0.71; 95% CI 0.52 to 0.98) (Figure 1). No heterogeneity was present (I^2 = 0%). After excluding the three studies with small and imbalanced

arms (Duroux 1991; Lopaciuk 1992; Simmoneau 1993) the benefit remained borderline statistically significant (RR 0.72; 95% CI 0.52 to 1.00). The figure shows the inverted funnel plot for the outcome of death (Figure 2). The trim and fill technique did not suggest publication bias but we still suspected it because 11 studies did not report cancer subgroup data. Figure 3 summarizes the risk of bias for studies assessing this outcome. The quality of the body of evidence for mortality was low due to imprecision and likely publication bias (Summary of findings for the main comparison).

Figure 1. Forest plot of comparison: 1 LMWH vs. UFH, outcome: 1.1 Death at 3 months.

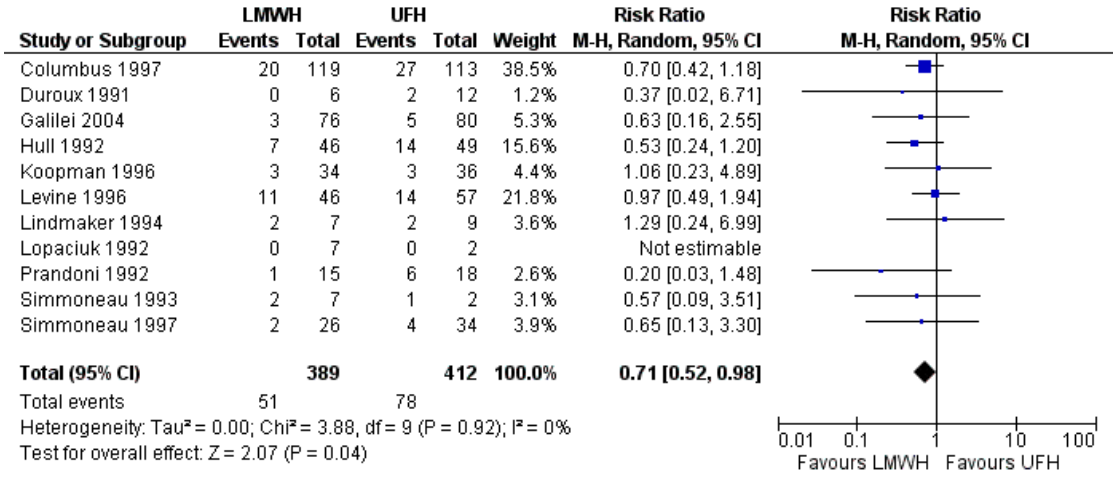


Figure 2. Inverted funnel plot for studies comparing the effect on mortality of LMWH and UFH as the initial anticoagulation in cancer patients with venous thromboembolism

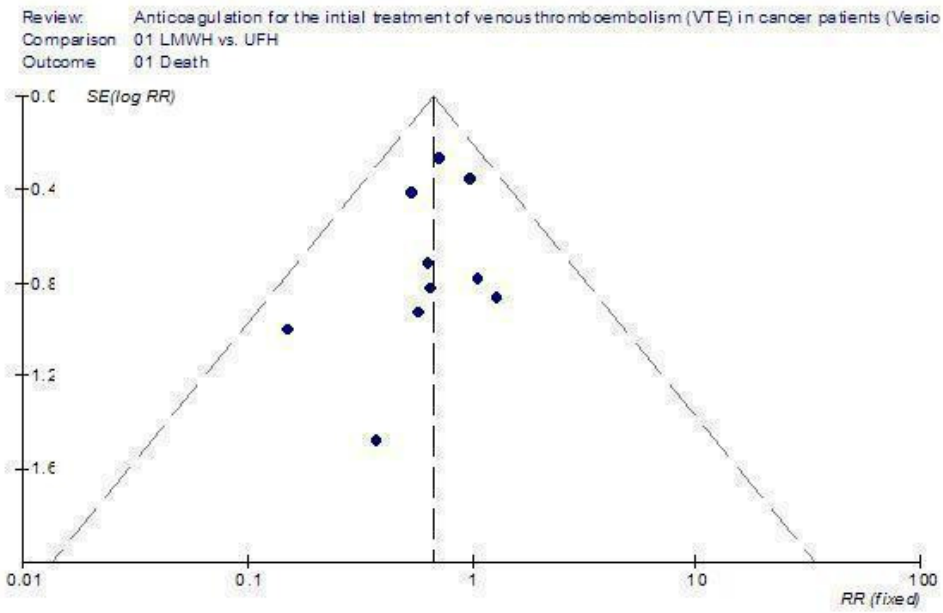
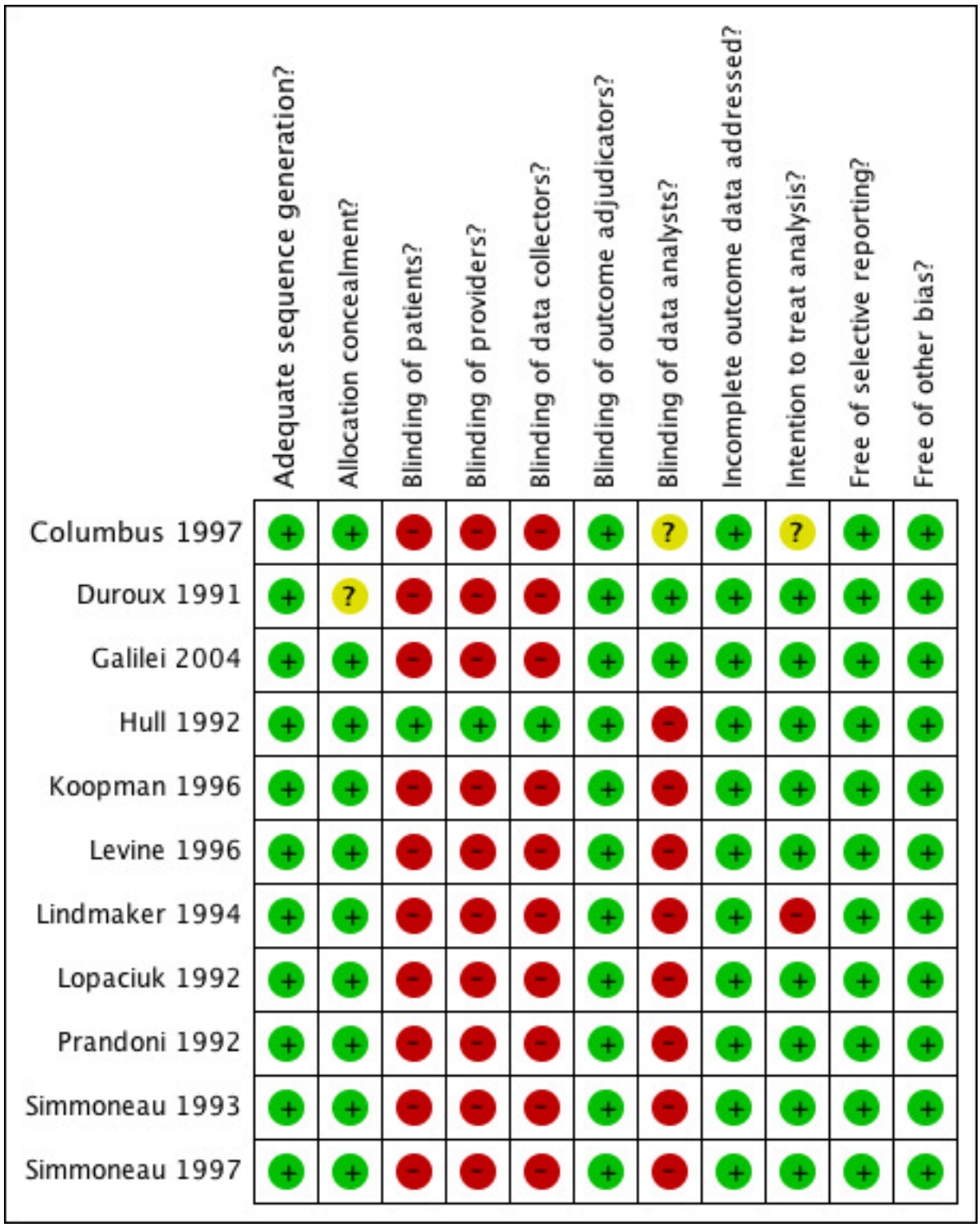


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for included studies assessing mortality (LMWH vs. UFH).



Recurrent venous thromboembolism (VTE)

No data were available for deep venous thrombosis or pulmonary embolism events separately. The data for recurrent VTE events were available for three studies (Breddin 2001; Galilei 2004; Merli 2001). The pooled analysis showed a non-statistically significant advantage of LMWH over UFH (RR 0.78; 95% CI 0.29 to 2.08) with low heterogeneity (I^2 = 32.4%) (Figure 4). Figure 5 summarizes the risk of bias for studies assessing this outcome. The quality of the body of evidence for recurrent VTE was low due to imprecision and likely publication bias (Summary of findings for the main comparison).

Figure 4. Forest plot of comparison: 1 LMWH vs. UFH, outcome: 1.2 Recurrent VTE.

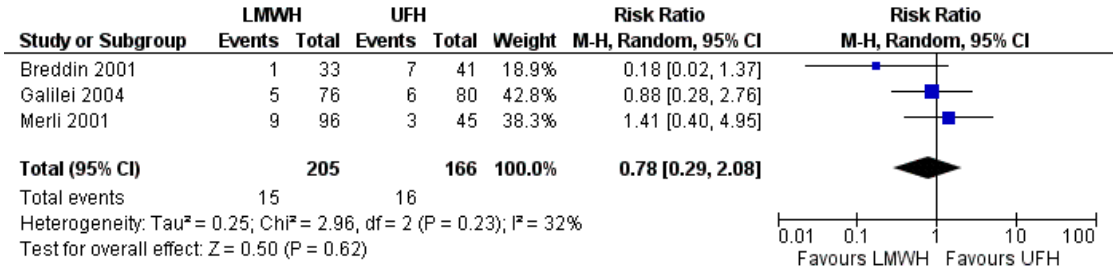
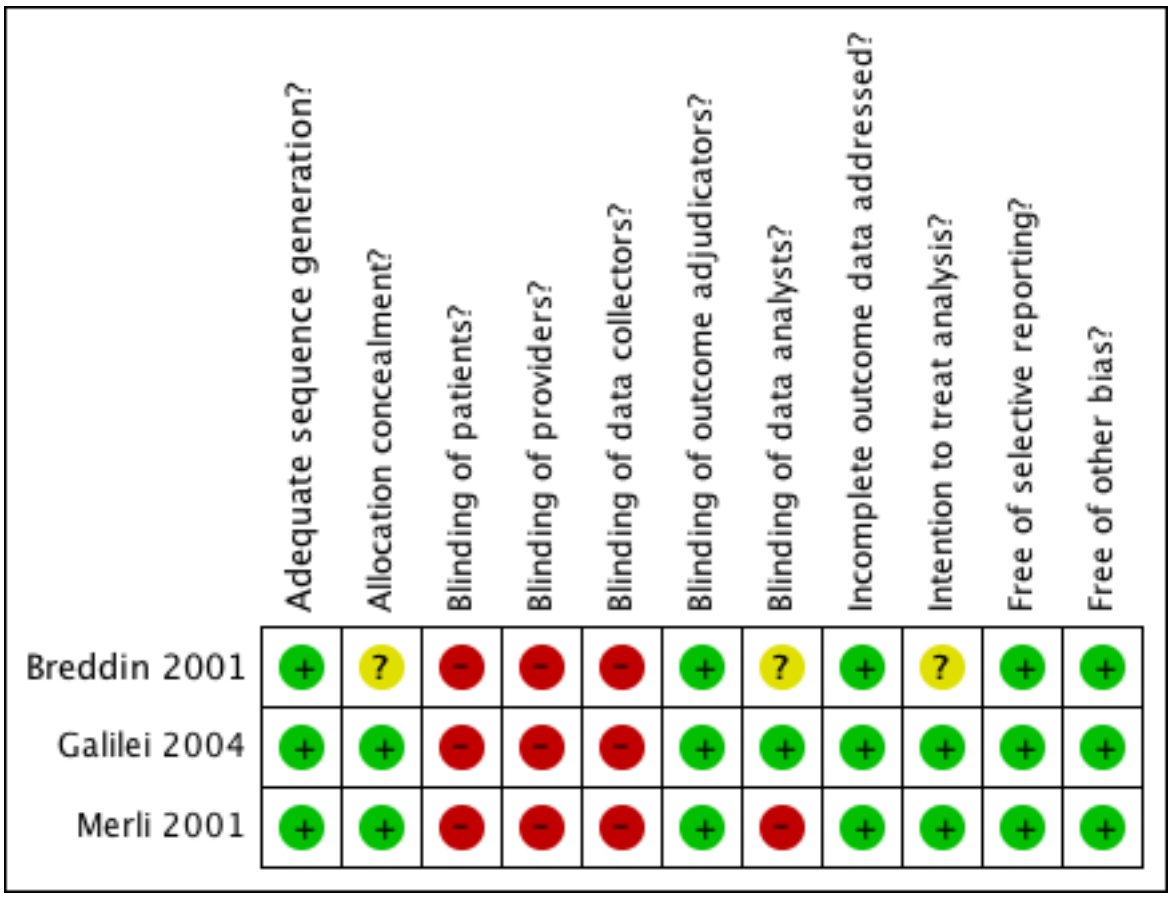


Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for included studies assessing recurrent VTE (LMWH vs. UFH).

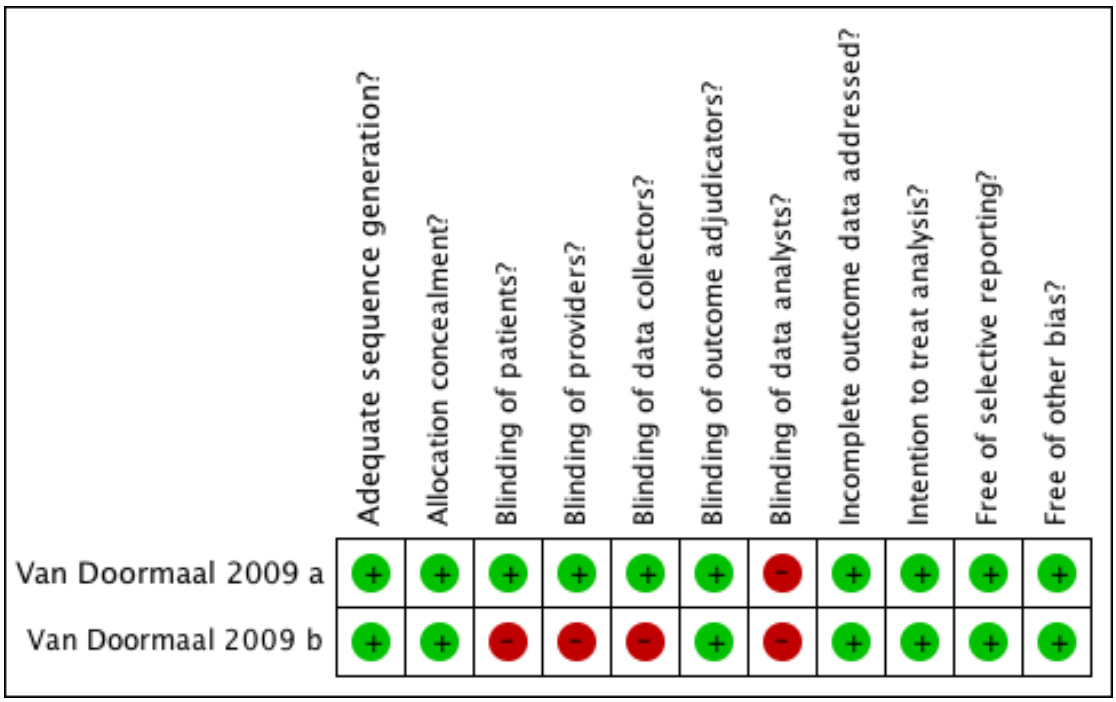


No data were available for bleeding outcomes, thrombocytopenia, postphlebitic syndrome, or quality of life.

Fondaparinux versus unfractionated heparin (UFH)

The pooled results of the two studies comparing fondaparinux to heparin (Van Doormaal 2009 a; Van Doormaal 2009 b) showed no statistically significant difference between the two agents for the outcomes of death (RR 1.27; 95% CI 0.88 to 1.84), recurrent VTE (RR 0.95; 95% CI 0.57 to 1.60), major bleeding (RR 0.79; 95% CI 0.39 to1.63), or minor bleeding (RR 1.50; 95% CI 0.87 to 2.59). Figure 6 summarizes the risk of bias for these two studies. The quality of the body of evidence was moderate for mortality, major bleeding, and minor bleeding due to imprecision; and low for recurrent VTE due to inconsistency and imprecision (Summary of findings 2).

Figure 6. Risk of bias summary: review authors' judgements about each risk of bias item for included studies (fondaparinux vs. heparin).

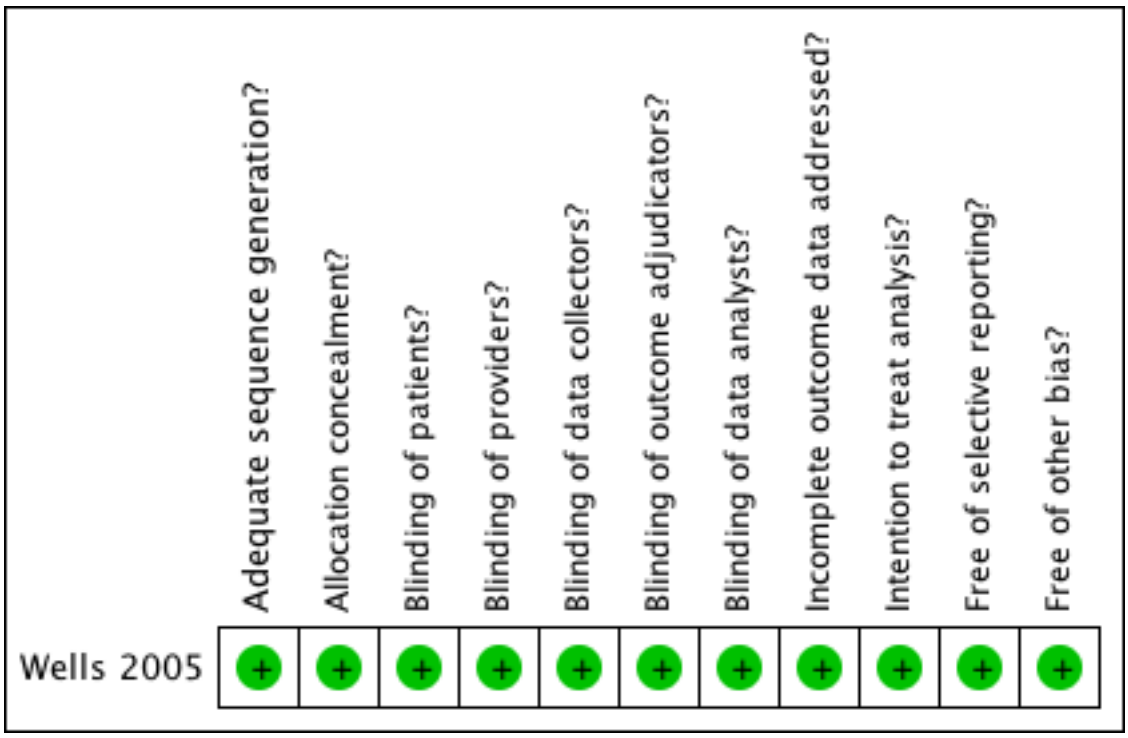


No data were available for thrombocytopenia, postphlebitic syndrome, or quality of life.

Dalteparin versus tinzaparin

The study comparing dalteparin to tinzaparin (Wells 2005) found no statistically significant difference for the outcomes of death (RR 0.86; 95% CI 0.43 to 1.73), VTE recurrence (RR 0.44; 95% CI 0.09 to 2.16), major bleed (RR 2.19; 95% CI 0.20 to 23.42), or minor bleed (RR 0.82; 95% CI 0.30 to 2.21). Figure 7 summarizes the risk of bias for this study. The overall quality of evidence was moderate, due to imprecision.

Figure 7. Risk of bias summary: review authors' judgements about each risk of bias item for the included study (dalteparin to tinzaparin).



ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Fondaparinux compared to heparin for the initial treatment of venous thromboembolism in patients with cancer

Patient or population: patients with the initial treatment of venous thromboembolism in patients with cancer
Settings: Inpatient or outpatient
Intervention: Fondaparinux
Comparison: heparin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	heparin	Fondaparinux				
Death Follow-up: median 3 months	**Study population**		**RR 1.27** (0.88 to 1.84)	477 (2 studies)	⊕⊕⊕◯ **moderate**[1,2]	
	172 per 1000	**218 per 1000** (151 to 316)				
	Medium risk population					
	170 per 1000	**216 per 1000** (150 to 313)				
Recurrent VTE Follow-up: median 3 months	**Study population**		**RR 0.95** (0.57 to 1.6)	477 (2 studies)	⊕⊕◯◯ **low**[1,2,3]	
	117 per 1000	**111 per 1000** (67 to 187)				
	Medium risk population					
	113 per 1000	**107 per 1000** (64 to 181)				

Major bleeding Follow-up: median 3 months	**Study population**		**RR 0.79** (0.39 to 1.63)	477 (2 studies)	⊕⊕⊕◯ **moderate**[1,3]	There is indirect evidence that both fondaparinux and heparin increase the risk of bleeding compared with no anticoagulation
	67 per 1000	**53 per 1000** (26 to 109)				
	Medium risk population					
	67 per 1000	**53 per 1000** (26 to 109)				
Minor bleeding Follow-up: median 3 months	**Study population**		**RR 1.5** (0.87 to 2.59)	477 (2 studies)	⊕⊕⊕◯ **moderate**[2,4]	There is indirect evidence that both fondaparinux and heparin increase the risk of bleeding compared with no anticoagulation
	79 per 1000	**119 per 1000** (69 to 205)				
	Medium risk population					
	81 per 1000	**122 per 1000** (70 to 210)				
Post phlebitic syndrome - not reported	See comment	See comment	Not estimable	-	See comment	
Quality of life - not reported	See comment	See comment	Not estimable	-	See comment	
Thrombocytopenia - not reported	See comment	See comment	Not estimable	-	See comment	

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Of the 2 studies, both concealed allocation, one blinded patients, providers, data collectors and outcome adjudicators, both used ITT and none was stopped early for benefit

[2] CI includes values suggesting benefit and values suggesting harm

[3] I2=85%

[4] I2=38%

DISCUSSION

Summary of main results

This systematic review found a patient important and statistically significant mortality reduction with the use of LMWH compared to UFH in the initial treatment of VTE in patients with cancer. The comparative effect on the incidence of VTE was not statistically significant. There were no statistically significant differences between fondaparinux and heparin nor between dalteparin and tinzaparin in the effects on the outcomes of interest.

Overall completeness and applicability of evidence

The completeness of the data is a major concern in this systematic review. First, of a total of 24 potentially eligible studies we did not include 11 because the authors did not report the needed subgroup data for patients with cancer. These 11 studies would have contributed 340 additional participants to the meta-analysis (801 are currently included). If the treatment effect from those studies was different from the reported effect, their exclusion from the meta-analysis could have biased our results. Moreover, only three of the included studies reported cancer subgroup data for VTE recurrence and none reported cancer subgroup data for the bleeding outcomes.

Second, there is evidence of publication bias in favor of LMWH even when considering all studies comparing subcutaneous UFH to LMWH in the initial management of VTE for any patient (with or without cancer) (see Figure 8, Figure 9, Figure 10 from an unpublished analysis). This affects our confidence in the results of the current analysis suggesting superiority of LMWH over UFH.

Figure 8. Funnel plot for mortality outcome for LMWH vs. SC UFH in all patients (unpublished)

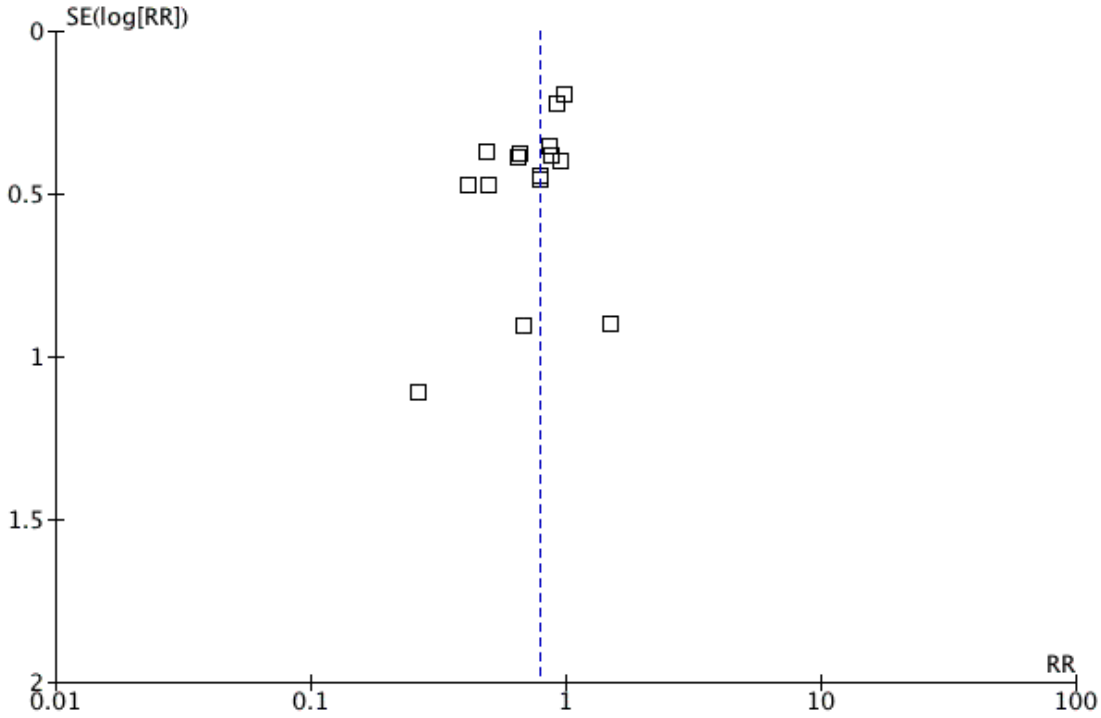


Figure 9. Funnel plot for recurrent VTE outcome for LMWH vs. SC UFH in all patients (unpublished)

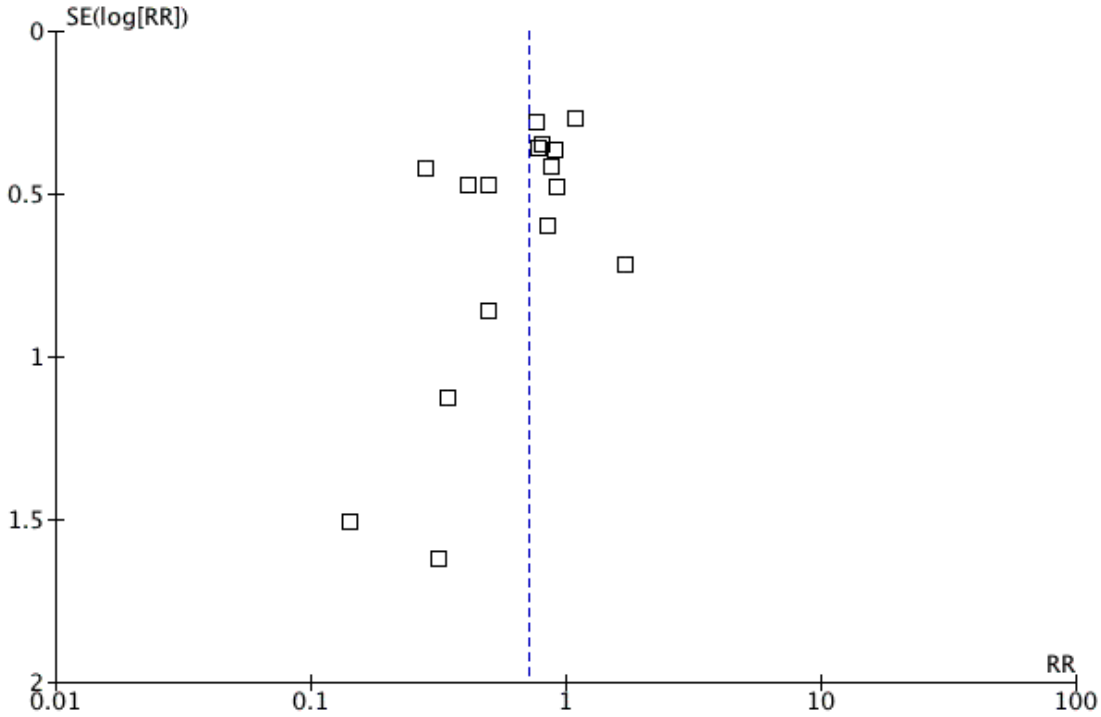
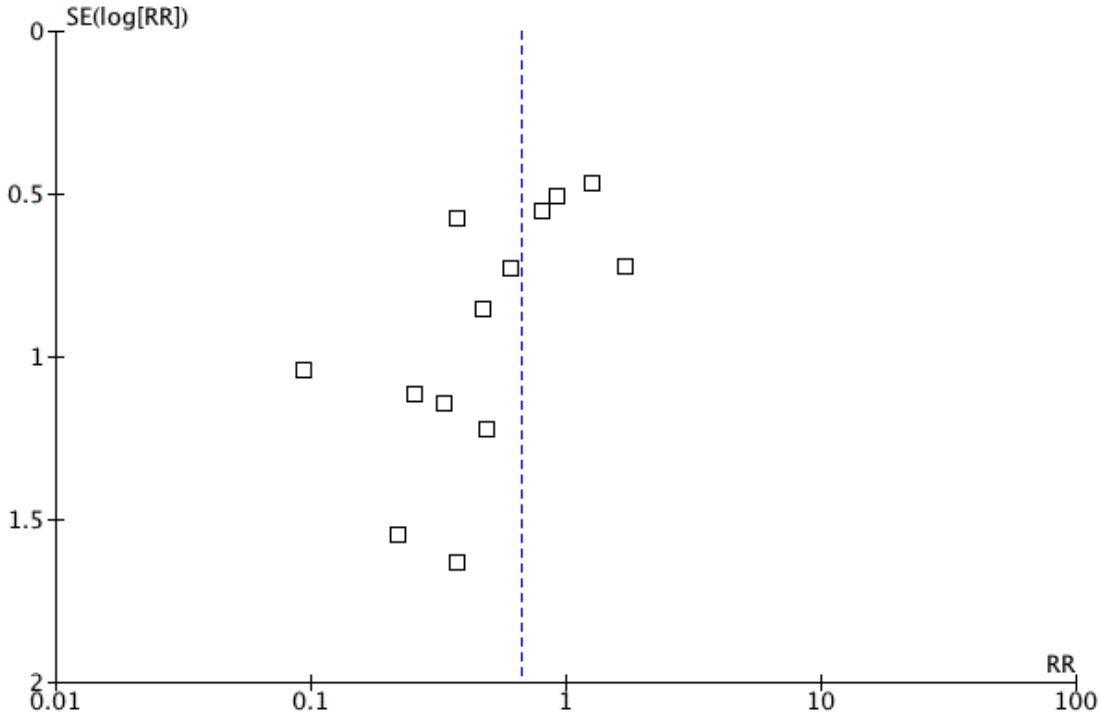


Figure 10. Funnel plot for major bleeding outcome for LMWH vs. SC UFH in all patients (unpublished)



Quality of the evidence

For the LMWH versus UFH comparison, the methodological quality for death and recurrent VTE outcomes was low due to imprecision and likely publication bias. For the fonaparinux versus heparin comparison, the quality of evidence was low for recurrent VTE (due to imprecision and inconsistency) and moderate for mortality and bleeding outcomes (due to imprecision). For the dalteparin versus tinzaparin comparison, the quality of evidence was also moderate for the outcomes of interest due to imprecision.

Potential biases in the review process

A potential limitation of our review is the limitation of the electronic search strategy to patients with cancer, while the data needed for this review came from studies not restricted to this subgroup. However, we think that the supplemental search strategies we used (in addition to the electronic search) were effective. In fact, our search strategy did not miss any of the studies reported in earlier systematic reviews on the topic.

Agreements and disagreements with other studies or reviews

Three previous systematic reviews compared the effects of LMWH and UFH on mortality in patients with cancer and with VTE. A 1999 review by Hettiarachchi et al included nine studies and 629 patients and resulted in an OR of 0.61 (95% CI 0.40 to 0.93) (Hettiarachchi 1999). A review by Gould et al included 279 patients and resulted in an OR of 0.57 (95% CI 0.31 to 1.03) (Gould 1999). Van Dongen et al conducted, in a Cochrane review, a subgroup analysis for patients with cancer and included six studies and 446 patients; it showed an OR of 0.53 (95% CI 0.33 to 0.85) (van Dongen 2007). While the current review includes more studies and patients (11 studies and 801 patients) than the three previous reviews, the resulting effect is consistent.

The two reviews by Hettiarachchi et al and van Dongen et al assessed the comparative efficacy of LMWH and UFH separately in patients with and without cancer (Hettiarachchi 1999; van Dongen 2007). While LMWH was superior to UFH in patients with cancer, as noted above, they were statistically equivalent in patients without cancer, with respective ORs of 0.94 (95% CI 0.60 to 1.47) and 0.97 (95% CI 0.61 to 1.56). However, the authors did not report testing statistically for subgroup effect.

AUTHORS' CONCLUSIONS

Implications for practice

LMWH is possibly superior to UFH in reducing mortality in the initial treatment of VTE in patients with cancer. The confidence in this effect is reduced by both the risk of bias in included studies and the likelihood of publication bias. However, there are additional advantages of LMWH related to subcutaneous administration and outpatient management (O'Brien 1999; Othieno 2007). One factor a patient might need to take into account when making this choice is the potential increase in out of pocket expenses with LMWH.

Implications for research

There is a need to conduct trials comparing anticoagulants in the initial treatment of VTE that are restricted to patients with cancer. Researchers should consider making the raw data of RCTs available for individual patient data meta-analysis. Also, as recognized by the Cochrane Collaboration, addressing all important outcomes including harm is of great importance in making evidence-based healthcare decisions.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Breddin 2001

Methods	Randomized controlled open label trial
Participants	74 cancer patients with DVT but not PE (study subgroup); minimum age of 18 years
Interventions	Intervention: reviparin weight based subcutaneous twice daily Control: UFH IV (continuous infusion of 1250 IU/hour) x 5-7 days Vitamin K antagonist (target INR >2) started on day 1 x 90 days A third group received reviparin subcutaneous once day x 28 days and vitamin K antagonist on days 21-90
Outcomes	Mortality, symptomatic DVT (not clear whether asymptomatic events included), PE, major bleeding
Notes	Funding: Knoll, Germany Follow up: 90 days Radiological surveillance: venography surveillance for DVT conducted at day 21 Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to one of three groups, stratified according to site." Comment: definitely yes
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of patients?	High risk	Quote: "open-label trial" Comment: probably no
Blinding of providers?	High risk	Quote: "open-label trial" Comment: probably no
Blinding of data collectors?	High risk	Quote: "open-label trial" Comment: probably no
Blinding of outcome adjudicators?	Low risk	Quote: "The venogram were assessed by two members of an independent committee who were unaware of the patients' treatment assignments and of whether the venograms were obtained before or after treatment." Comment: definitely yes

Breddin 2001 (*Continued*)

Blinding of data analysts?	Unclear risk	Not reported Comment: probably no
Incomplete outcome data addressed?	Low risk	89% follow-up rate for VTE recurrence
Intention to treat analysis?	Unclear risk	Not reported
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Columbus 1997

Methods	Randomized controlled trial
Participants	232 cancer patients with proximal or distal DVT, PE or both; minimum age of 18 years
Interventions	Intervention: reviparin weight based subcutaneous twice daily at home Control: UFH IV (target aPTT 1.5-2.5) in the hospital x 5 days. Coumarin derivative (target INR >2) started on 1st or 2nd day x 12 weeks
Outcomes	Mortality, recurrent symptomatic venous thromboembolism, bleeding
Notes	Funding: Knoll AG Follow up: 12 weeks Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: patients could be treated at home, but he decision to do so was left to the treating physician

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with a computer algorithm." Comment: definitely yes
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with a computer algorithm and the use of a central 24-hour telephone service that recorded information on the patient before the treatment assignment was disclosed." Comment: central randomization
Blinding of patients?	High risk	Quote: "open international, randomized clinical trial" Comment: probably not

Columbus 1997 (*Continued*)

Blinding of providers?	High risk	Quote: "open international, randomized clinical trial" Comment: probably not
Blinding of data collectors?	High risk	Quote: "open international, randomized clinical trial" Comment: probably not
Blinding of outcome adjudicators?	Low risk	Quote: "Information on all suspected outcome events and deaths was reviewed and classified by a central adjudication committee whose members were unaware of the treatment assignments." Comment: definitely yes
Blinding of data analysts?	Unclear risk	unclear
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Unclear risk	Not reported
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Duroux 1991

Methods	Randomized controlled trial
Participants	18 cancer patients with proximal DVT but no PE; minimum age 18 years
Interventions	Intervention: CY216 (fraxiparin) 255 antiXa U/Kg twice daily x 10 days Control: UFH IV (target aPTT 1.5-2) x10 days After day 10 each center continued its usual anticoagulant regimen either by subcutaneous UFH at adjusted doses or by oral anticoagulants x 12 weeks
Outcomes	Death, venous thromboembolism (venogram detected DVT), bleeding
Notes	Funding: Sanofi-Choay Follow up: 12 weeks Radiological surveillance:venography surveillance for DVT conducted at day 10 Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Study was a randomized parallel group trial" Comment: probably yes

Duroux 1991 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of patients?	High risk	Quote: "Treatment could not be given double-blinded because of the different methods of administration and primarily the need for dose adjustment in the UFH group." Comment: probably not
Blinding of providers?	High risk	Quote: "Treatment could not be given double-blinded because of the different methods of administration and primarily the need for dose adjustment in the UFH group." Comment: probably not
Blinding of data collectors?	High risk	Quote: "Treatment could not be given double-blinded because of the different methods of administration and primarily the need for dose adjustment in the UFH group." Comment: probably not
Blinding of outcome adjudicators?	Low risk	Quote: "Principal judgement criterion was evaluated blinded by two independent radiologists(coded films)." Comment: definitely yes
Blinding of data analysts?	High risk	Quote: "Treatment could not be given double-blinded because of the different methods of administration and primarily the need for dose adjustment in the UFH group." Comment: probably not
Incomplete outcome data addressed?	Low risk	92% follow-up rate.
Intention to treat analysis?	Low risk	Quote: "An intention-to-treat analysis including patients with premature cessation of treatment but in whom there was a D10 venogram was also undertaken." Comment: probably yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Galilei 2004

Methods	Randomized controlled study
Participants	156 cancer patients (study subgroup) with DVT of lower extremities and/or PE; minimum age of 18 years; minimum life expectancy of 3 months
Interventions	Intervention: nadroparin 80U/kg twice daily Control: UFH 1st dose weight adjusted IV, subsequent doses SC twice daily (target aPTT 50-90s) x 5 days warfarin (target INR 2-3) started the first two days x 12 weeks
Outcomes	Death; symptomatic recurrent VTE ; major bleeding, heparin induced thrombocytopenia
Notes	Funding: Gentium SpA, Como, Italy Follow up: 3months Radigological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed with a computer algorithm." Comment: definitely yes
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed with a computer algorithm and the use of a 24 hour telephone service that recorded patient information before disclosure of the treatment assigned." Comment: definitely yes
Blinding of patients?	High risk	Quote: "open multicenter clinical trial" Comment: probably not
Blinding of providers?	High risk	Quote: "open multicenter clinical trial" Comment: probably not
Blinding of data collectors?	High risk	Quote: "open multicenter clinical trial" Comment: probably not
Blinding of outcome adjudicators?	Low risk	Quote: "Information on all suspected outcome events and deaths was reviewed and classified by a central adjudication committee blinded to treatment assignment" Comment: definitely yes
Blinding of data analysts?	Low risk	Quote: "open multicenter clinical trial" Comment: probably not

Galilei 2004 (*Continued*)

Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	Quote: "Both analyses were performed on an intention-to-treat basis and included all patients who were randomly assigned to either strategy" Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Hull 1992

Methods	Randomized controlled trial
Participants	95 cancer patients with proximal DVT (study subgroup); minimum age of 18 years
Interventions	Intervention: tinzaparin 175 antiXa U/kg subcutaneous once daily Control: UFH IV (target aPTT 1.5-2.5) x 6 days Warfarin (target INR 2-3) started on day 2 for 3 months
Outcomes	Mortality, symptomatic venous thromboembolism, bleeding
Notes	Funding: Heart and Stroke Foundation of Alberta and Novo Nordisk Follow up: 3 months Radiologica surveillance: no scheduled radiological surveillance for VTE was conducted Setting: inpatient

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A randomized, computer-derived treatment schedule was used to assign the patients to receive intravenous heparin or subcutaneous low molecular-weight heparin."
Allocation concealment (selection bias)	Low risk	Quote: "Before randomization, patients were stratified into groups according to a randomized, computer-derived treatment schedule was used to assign the patients to receive intravenous heparin or subcutaneous low molecular-weight heparin." Comment: probably yes

Hull 1992 (*Continued*)

Blinding of patients?	Low risk	Quote: "double blinded clinical trial." Comment: probably yes
Blinding of providers?	Low risk	Quote: "double blinded clinical trial." Comment: probably yes
Blinding of data collectors?	Low risk	Quote: "double blinded clinical trial." Comment: probably yes
Blinding of outcome adjudicators?	Low risk	Quote: "Central adjudication committee was made by two committee members not involved in the patient's care, and disputes were resolved independently by a third. " Comment: definitely yes
Blinding of data analysts?	High risk	Quote: "double blinded clinical trial." Comment: probably not
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	No loss to follow up and all patients randomized included in the analyses of outcomes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Koopman 1996

Methods	Randomized controlled study
Participants	70 cancer patients with proximal DVT without PE (study subgroup); minimum age of 18 years; minimum life expectancy of 6 months
Interventions	Intervention: nadroparin weight based subcutaneous twice daily at home Control: UFH IV (target aPTT 1.5-2) x 5 days Oral anticoagulation (target INR 2-3) started x 3 months
Outcomes	Death, recurrent symptomatic venous thromboembolism, major bleeding
Notes	Funding: Sanofi Winthrop Follow up: 6 months No scheduled radiological surveillance for VTE was conducted Setting: standard heparin was administered at the hospital and LMWH patient were allowed to be treated at home

Koopman 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "After the patients gave informed consent, randomization (stratified according to center) was achieved by means of a central 24 hour telephone service."
Allocation concealment (selection bias)	Low risk	Quote: "After the patients gave informed consent, randomization (stratified according to center) was achieved by means of a central 24 hour telephone service."
Blinding of patients?	High risk	Quote: "This was an unblinded study"
Blinding of providers?	High risk	Quote: "This was an unblinded study"
Blinding of data collectors?	High risk	Quote: "This was an unblinded study"
Blinding of outcome adjudicators?	Low risk	Quote: "Documentation of all potential outcome events, including deaths, was submitted to an independent adjudication committee whose members were unaware of the treatment assignments."
Blinding of data analysts?	High risk	Quote: "This was an unblinded study"
Incomplete outcome data addressed?	Low risk	99% follow-up rate
Intention to treat analysis?	Low risk	Quote: "The analyses were performed on an intention to treat basis"
Free of selective reporting?	Low risk	Study not registered. No published protocol. All the outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Levine 1996

Methods	Randomized controlled study
Participants	103 cancer patients with proximal or distal DVT without PE (study subgroup)
Interventions	Intervention: enoxaparin 1 mg/kg subcutaneous twice daily at home Control: UFH IV (target aPTT 60-85s) x 5 days Warfarin (target INR 2-3) started on evening of 2nd day for at least 3 months
Outcomes	Death, recurrent symptomatic venous thromboembolism, bleeding

Notes	Funding: not reported Follow up: 90 days Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: LMWH given as outpatient (mean hospital stay=1.1±2.9 days); UFH given as inpatient (mean hospital stay=2.2±3.8 days)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to treatment through randomization over the telephone from a central line" Comment: definitely yes
Allocation concealment (selection bias)	Low risk	Quote: "Patients were assigned to treatment through randomization over the telephone from a central line" Comment: definitely yes
Blinding of patients?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of providers?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of data collectors?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of outcome adjudicators?	Low risk	Quote: "All reported outcome events were reviewed by a central adjudication committee whose members were unaware of the treatment assignments" Comment: definitely yes
Blinding of data analysts?	High risk	Comment: probably not as no mention of blinding
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	No clear mention of ITT analysis. However, probably yes as no patients were lost to follow up and there was no mention of cross over
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Lindmaker 1994

Methods	Randomized controlled study
Participants	16 cancer patients with DVT (below the inguinal ligament) but no PE (study subgroup) ; minimum age of 18 years
Interventions	Intervention: Fragmin 200 IU/Kg subcutaneous once daily Control: UFH IV (target aPTT 1.5-3) x 5 days Warfarin (target INR 2-3) x 3 months
Outcomes	Death, symptomatic pulmonary embolism, bleeding
Notes	Funding: Pharmacia AB Follow up: 6 months Radiological surveillance:no scheduled radiological surveillance for VTE was conducted Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was organized centrally using sealed envelopes stratified for each center in a block size of 20"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was organized centrally using sealed envelopes stratified for each center in a block size of 20"
Blinding of patients?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of providers?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of data collectors?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of outcome adjudicators?	Low risk	Quote: "All venograms were interpreted by a radiologist who did not know which of the treatments the patient had received or in which order the venogram has been performed."
Blinding of data analysts?	High risk	Comment: probably not as no mention of blinding
Incomplete outcome data addressed?	Low risk	100% follow-up rate

Lindmaker 1994 (*Continued*)

Intention to treat analysis?	High risk	"Of the 204 patients, 14 treated with UFH and 10 with Fragmin were excluded from the efficacy analysis"
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Lopaciuk 1992

Methods	Randomized controlled trial
Participants	9 cancer patients with proximal or calf DVT without PE (study subgroup)
Interventions	Intervention: nadroparin 92 antiXa U/kg twice daily Control: UFH 1st dose IV, subsequent dose subcutaneous twice daily (target aPTT 1. 5-2.5) x 10 days Acenocoumarol (target INR 2-3) started the 7th day x at least 3 months
Outcomes	Death, symptomatic pulmonary embolism, recurrent DVT, bleeding
Notes	Funding: Sanofi Follow up: 3 months Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Study was a prospective, open, stratified, and randomized multicenter trial with a blind evaluation of phlebographic results"
Allocation concealment (selection bias)	Low risk	Quote: "they were randomly allocated by using a sealed envelope to either Fraxiparine or UFH group" Comment: no mention of sequential numbering and opacity
Blinding of patients?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of providers?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of data collectors?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes

Lopaciuk 1992 (*Continued*)

Blinding of outcome adjudicators?	Low risk	Quote: "blind evaluation of phlebographic results" Comment: yes for evaluation of DVT events
Blinding of data analysts?	High risk	Comment: probably not as no mention of blinding
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	No clear mention of ITT analysis. However, probably yes as no patients were lost to follow up and there was no mention of cross over
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	study not stopped early for benefit

Merli 2001

Methods	Randomized controlled trial
Participants	141 cancer patients with DVT or PE (study subgroup); minimum age of 18 years
Interventions	Intervention: enoxaparin 1 mg/kg subcutaneous twice daily or 1.5 mg/kg subcutaneous once daily Control: UFH IV (target aPTT 55-80s) x 5 days Warfarin (target INR 2-3) started within 72h x 3 months
Outcomes	Mortality, symptomatic recurrent VTE, bleeding, drug induced thrombocytopenia
Notes	Funding: Aventis Follow up: 3 months Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization numbers were affixed to sealed treatment kits that contained study medication and were provided by the study sponsor"
Blinding of patients?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes

Merli 2001 (*Continued*)

Blinding of providers?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of data collectors?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of outcome adjudicators?	Low risk	Quote: "Outcome adjudication committee, which provided blinded outcome assignments for incidence outcomes"
Blinding of data analysts?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	Quote: "The efficacy analysis was performed on two study samples: all treated patients, who received at least one dose of study medication, and evaluable patients, which excluded all patients who met at least one of the criteria for non evaluability" Comment: the first analysis is ITT
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Prandoni 1992

Methods	Randomized controlled trial
Participants	33 cancer patients with proximal DVT (study subgroup), minimum age of 18 years
Interventions	Intervention: enoxaparin weight based subcutaneous twice daily Control: UFH IV (target aPTT 1.5-2.0) x 10 days Coumarin (target INR 2-3) started on day 7 for at least 3 months
Outcomes	Death, symptomatic recurrent DVT, symptomatic pulmonary embolism
Notes	Funding: not reported Follow up: 1, 3, 6 months Radiological surveillance:no scheduled radiological surveillance for VTE was conducted Setting: not reported

Risk of bias

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

Prandoni 1992 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated treatment by a prescribed randomisation schedule." Comment: definitely yes
Allocation concealment (selection bias)	Low risk	Quote: "Treatment was allocated by the sealed envelop method" Comment: definitely yes
Blinding of patients?	High risk	Quote: "Because the two regimens were given by different routes and because dose adjustments were necessary in the standard heparin group, we could not use a double blind design" Comment: probably not
Blinding of providers?	High risk	Quote: "Because the two regimens were given by different routes and because dose adjustments were necessary in the standard heparin group, we could not use a double blind design" Comment: probably not
Blinding of data collectors?	High risk	Quote: "Because the two regimens were given by different routes and because dose adjustments were necessary in the standard heparin group, we could not use a double blind design" Comment: probably not
Blinding of outcome adjudicators?	Low risk	Quote: "All clinical endpoints were reviewed by an adjudication committee from the coordinating center, unaware of treatment allocation or other details of patients. " Comment: definitely yes
Blinding of data analysts?	High risk	Quote: "Because the two regimens were given by different routes and because dose adjustments were necessary in the standard heparin group, we could not use a double blind design" Comment: probably not
Incomplete outcome data addressed?	Low risk	100% follow-up rate.
Intention to treat analysis?	Low risk	Quote: "intention to treat analysis was used"
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Simmoneau 1993

Methods	Randomized controlled study
Participants	9 cancer patients with proximal DVT (study subgroup); minimum age of 18 years
Interventions	Intervention: enoxaparin 1 mg/kg subcutaneous twice daily Control: UFH IV (target aPTT 1.5-2.5) x 10 days Oral anticoagulation (target INR 2-3) started on day 10 for at least 3 months
Outcomes	Death, recurrent symptomatic venous thromboembolism, bleeding
Notes	Funding: not reported Followup: 3 months Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization code was drafted by means of a standard random number table randomizing in blocks of four"
Allocation concealment (selection bias)	Low risk	Quote: "The patients' treatment assignments were taken from sealed envelopes."
Blinding of patients?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of providers?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of data collectors?	High risk	Comment: probably not as no mention of blinding and the compared drugs administered using 2 different routes
Blinding of outcome adjudicators?	Low risk	Quote: "Venograms, perfusion lung scans, and pulmonary angiograms were subsequently reviewed by a central independent panel of two consultant specialists unaware of the treatment allocation" Comment: definitely yes
Blinding of data analysts?	High risk	Comment: probably not as no mention of blinding
Incomplete outcome data addressed?	Low risk	100% follow-up rate

Simmoneau 1993 (*Continued*)

Intention to treat analysis?	Low risk	No clear mention of ITT analysis. However, probably yes as no patients were lost to follow up and there was no mention of cross over
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Simmoneau 1997

Methods	Randomized controlled trial
Participants	60 cancer patients with PE (study subgroup); minimum age of 18 years; minimum life expectancy of 3 months
Interventions	Intervention: tinzaparin 175 antiXa U/kg subcutaneous once daily Controll: UFH IV (target aPTT 2-3) x 5 days Oral anticoagulation (target INR 2-3) started on 1st to 3rd day x at least 3 months
Outcomes	Death, symptomatic recurrent venous thrombus, major bleeding
Notes	Funding: Leo Pharmaceuticals Follow up: 90 days Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: the mean duration of anticoagulant treatment at a therapeutic dose before randomization was 18+/-6 hours in the patients assigned to unfractionated heparin and 18+/- 7hours in the patients assigned to low molecular weight heparin

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "central randomization was performed"
Allocation concealment (selection bias)	Low risk	Quote: "central randomization was performed with the use of a 24 hour computer service"
Blinding of patients?	High risk	Quote: "unblinded trial" Comment: probably not
Blinding of providers?	High risk	Quote: "unblinded trial" Comment: probably not
Blinding of data collectors?	High risk	Quote: "unblinded trial" Comment: probably not

Simmoneau 1997 (*Continued*)

Blinding of outcome adjudicators?	Low risk	Quote: "All the scans were reviewed independently and scored accordingly to this method by two readers, each unaware of the patient's treatment assignment" Comment: definitely yes
Blinding of data analysts?	High risk	Quote: "unblinded trial" Comment: probably not
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	Quote: "The primary analysis was performed on an intention to treat basis" Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

Van Doormaal 2009 a

Methods	Randomized controlled study
Participants	237 cancer patients with DVT, minimum age 18 years
Interventions	Intervention: fondaparinx was given subcutaneously once daily in fixed dose (5 mg if patients weighted less than 50 kg, or 7.5 mg if they weighted between 50 and 100 kg, or 10 mg if they weighted more than 100kg) and also received twice daily subcutaneous injections of placebo that appeared identical to enoxaparin Control: enoxaparin was given subcutaneously twice daily in a dose of 1mg/kg of body weight and a once daily subcutaneous injections of placebo that appeared identical to fondaparinux In all patients, VKA therapy was begun as soon as possible but not later than 72 hours after commencing initial therapy
Outcomes	Death, symptomatic recurrent VTE, bleeding
Notes	Funding: Sanofi/ Organon Follow up: 90 days Radiological surveillance: no scheduled radiological surveillance for VTE was conducted Setting: drug has administered by a home care service for home treatment

Risk of bias

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

Van Doormaal 2009 a (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned by a computerized interactive voice response system"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned by a computerized interactive voice response system"
Blinding of patients?	Low risk	Quote: "double-blinded, placebo controlled study" Comment: probably yes
Blinding of providers?	Low risk	Quote: "double-blinded, placebo controlled study" Comment: probably yes
Blinding of data collectors?	Low risk	Quote: "double-blinded, placebo controlled study" Comment: probably yes
Blinding of outcome adjudicators?	Low risk	Quote: "The study used central adjudication for all clinical outcome events" Comment: definitely yes
Blinding of data analysts?	High risk	Quote: "double-blinded, placebo controlled study" Comment: probably not
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	Quote: "The analyses were calculated in the intention to treat populations" Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in methods section are reported on in the results section. All outcomes of interest, except for quality of life, reported
Free of other bias?	Low risk	Study not reported as stopped early for benefit

Van Doormaal 2009 b

Methods	Randomized controlled study
Participants	240 cancer patients with acute symptomatic PE, with or with out associated DVT, minimum age 18 years
Interventions	Intervention: fondaparinx was given subcutaneously once daily in fixed dose(5 mg if patients weighted less than 50 kg, or 7.5 mg if they weighted between 50 and 100 kg, or 10 mg if they weighted more than 100kg) for 5-10 days Control: UFH received an initial intravenous bolus of at least 5000 international units, followed by at least 2500 international units per hour, administered as a continuous

	intravenous infusion. The infusion was adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.5 times control value In all patients, VKA therapy was begun as soon as possible but not later than 72 hours after commencing initial therapy and continued for at least 3 months
Outcomes	Death, symptomatic recurrent VTE, bleeding
Notes	Funding: Sanofi/ Organon Follow up: 90 days Radiologic surveillance: no scheduled radiological surveillance for VTE was conducted Setting: 14.5 % of fondaparinux group received outpatient basis treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed at a central location with the use of a computerized, interactive voice response system that recorded information about the patient before his or her treatment assignment" Comment: definitely yes
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed at a central location with the use of a computerized, interactive voice response system that recorded information about the patient before his or her treatment assignment" Comment: definitely yes
Blinding of patients?	High risk	Quote: "was conducted on an open-label basis" Comment: not blinded
Blinding of providers?	High risk	Quote: "was conducted on an open-label basis" Comment: not blinded
Blinding of data collectors?	High risk	Quote: "was conducted on an open-label basis" Comment: not blinded
Blinding of outcome adjudicators?	Low risk	Quote: "All suspected outcome events were reviewed and classified by a central adjudication committee whose members were unaware of the treatment assignment" Comment: definitely yes
Blinding of data analysts?	High risk	Quote: "was conducted on an open-label basis" Comment: not blinded
Incomplete outcome data addressed?	Low risk	100% follow-up rate

Van Doormaal 2009 b (*Continued*)

Intention to treat analysis?	Low risk	Quote: "Efficacy analyses were based on data from all the patients who had been randomly assigned to a study group, whereas safety analyses were based on data from all the patients who actually received treatment." Comment: yes for efficacy outcomes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in methods section are reported on in the results section. All outcomes of interest, except for quality of life, reported
Free of other bias?	Low risk	Study not reported as stopped early for benefit

Wells 2005

Methods	Randomized controlled trial
Participants	113 cancer patients with upper or lower extremity, minimum age of 18 years
Interventions	Intervention: tinzaparin 175 IU/kg subcutaneous once daily Control: dalteparin SC 200 IU/kg once daily. Patients had to receive therapy on an outpatient basis
Outcomes	Deaths; symptomatic recurrent VTE; major bleeding; minor bleeding
Notes	Funding: none Follow up: 3 months Radiological surveillance:no scheduled radiological surveillance for VTE was conducted Setting: patients had receive therapy on outpatient basis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed in a computer generated blocks, with the block size unknown to the investigators" Comment: definitely yes
Allocation concealment (selection bias)	Low risk	Quote: "Randomization assignments were concealed in opaque envelopes. Envelopes were opened sequentially and only after patient consent form was signed" Comment: definitely yes
Blinding of patients?	Low risk	Based on personal communication with author

Wells 2005 (*Continued*)

Blinding of providers?	Low risk	Quote: "All physicians and nurses who were involved in the patient's care were blinded except for the nurse who provided the initial care to the patient" Comment: definitely yes
Blinding of data collectors?	Low risk	Quote: "All physicians and nurses who were involved in the patient's care were blinded except for the nurse who provided the initial care to the patient" Comment: probably yes
Blinding of outcome adjudicators?	Low risk	Quote: "All physicians and nurses who were involved in the patient's care were blinded except for the nurse who provided the initial care to the patient" Comment: definitely yes
Blinding of data analysts?	Low risk	Based on personal communication with author
Incomplete outcome data addressed?	Low risk	100% follow-up rate
Intention to treat analysis?	Low risk	Quote: "The primary analysis was intention to treat" Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on
Free of other bias?	Low risk	Study not stopped early for benefit

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

Study	Reason for exclusion
Albada 1989	Data for cancer subgroup not available
Altundag 2005	Letter to editor
Anton 2001	Review
Bauer 2000	Editorial
Belcaro 1999	Data for cancer subgroup not available
Bick 2003	Review
Booth 1981	Case report

(*Continued*)

Bratt 1985	No relevant clinical outcomes
Bratt 1990	Data for cancer subgroup not available
Brooks 1969	Case report
Buller 2004	Data for cancer subgroup not available
Dolovich 2004	Review
Douketis 2000	Cohort study
Eikelboom1998	Case series
Elly 1969	Case report
Fiessinger 1996	Data for cancer subgroup not available
Gould 1999	Review
Green 1992	Letter to editor
Haage 2002	Review
Handeland 1990	No cancer patients in the study
Harenberg 2000	Data for cancer subgroup not available
Harenberg 1990	Data for cancer subgroup not available
Hettiarachchi 1998	Review
Holm 1986	Data for cancer subgroup not available
Holmstrom 1999	Review
Hull 2000	Data for cancer subgroup not available
Hull 2006	Different long-term management: LMWH in intervention arm and vitamin K antagonists in control arm
Jahanzeb 2005	Review
Leizorovicz 1994	Review
Levine 2001	Review
Luomanmaki 1996	Data for cancer subgroup not available

(*Continued*)

Martin-Carbonero2002	Cohort study
Menzoian 1983	Retrospective study
Naschitz 1994	Review
Prandoni 1988	No control group
Prandoni 1990	No cancer patients in the study
Prandoni 2005	Review
Riess 2003	Data for cancer subgroup not available
Sakuragi 2003	Retrospective study
Siragusa 2005	Not randomized
Turchetti 2003	Cohort study
Warkentin 1995	No relevant outcome
Wong 2003	Survey

DATA AND ANALYSES

Comparison 1. LMWH versus UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 3 months	11	801	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.98]
2 Recurrent VTE	3	371	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.29, 2.08]

Comparison 2. Fondaparinux versus heparin

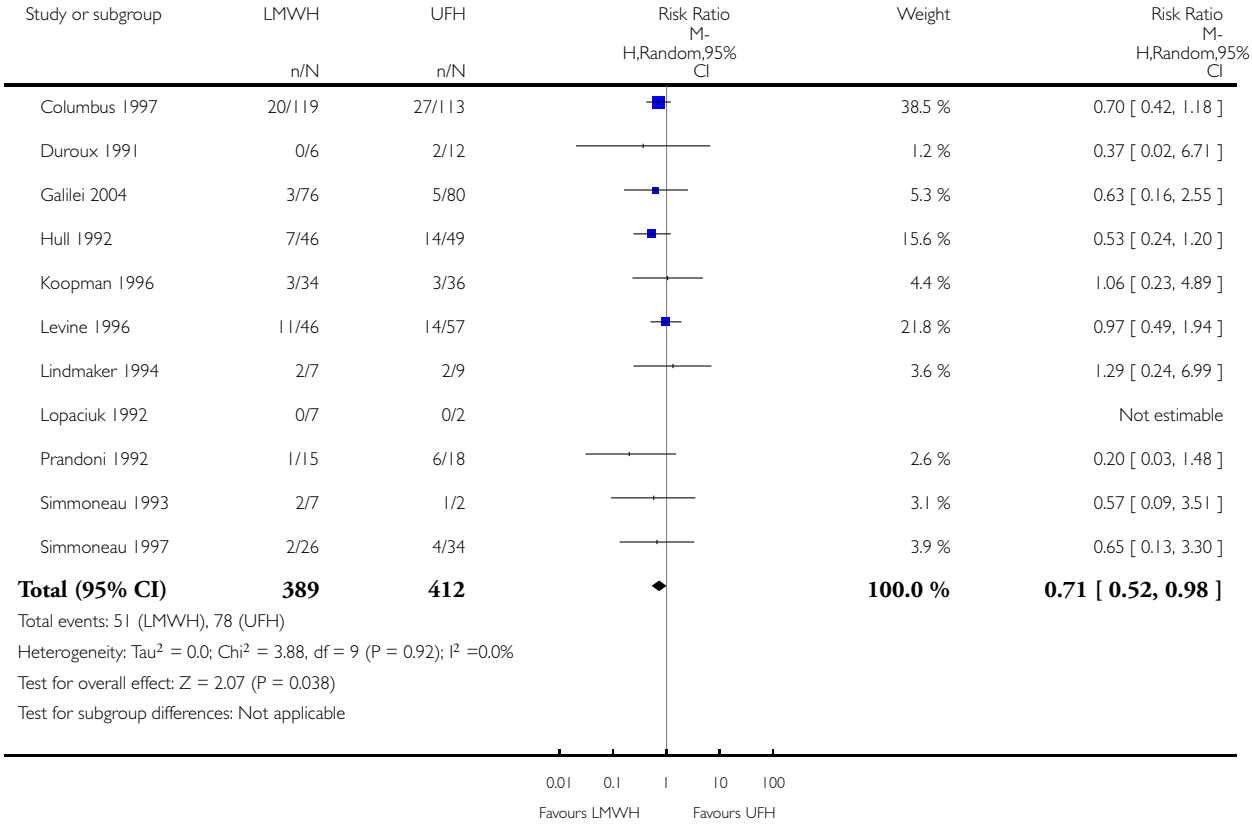
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	477	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.88, 1.84]
2 Recurrent VTE	2	477	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.57, 1.60]
3 Major bleeding	2	477	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.39, 1.63]
4 Minor bleeding	2	477	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.87, 2.59]

Analysis 1.1. Comparison 1 LMWH versus UFH, Outcome 1 Death at 3 months.

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

Comparison: 1 LMWH versus UFH

Outcome: 1 Death at 3 months

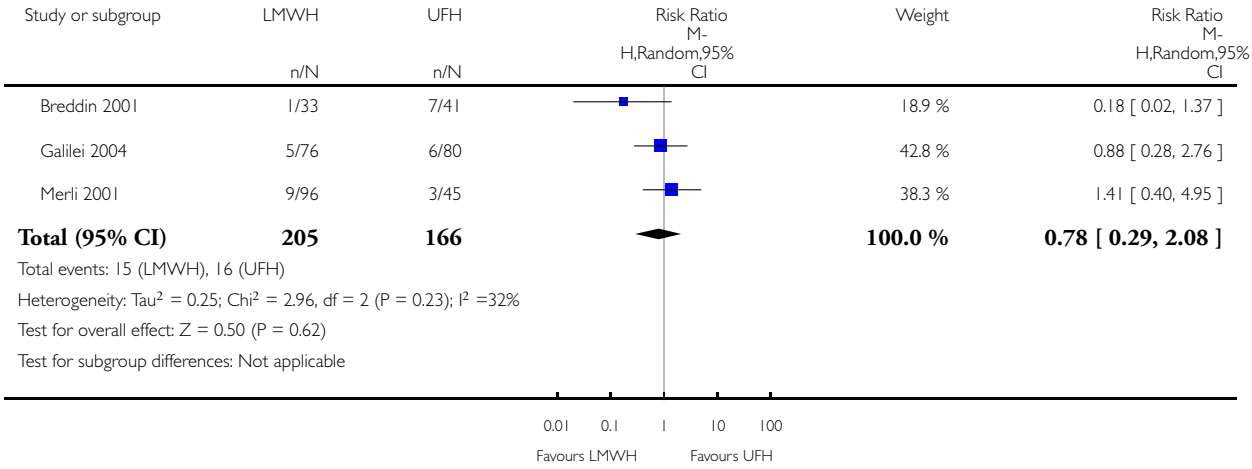


Analysis 1.2. Comparison 1 LMWH versus UFH, Outcome 2 Recurrent VTE.

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

Comparison: 1 LMWH versus UFH

Outcome: 2 Recurrent VTE

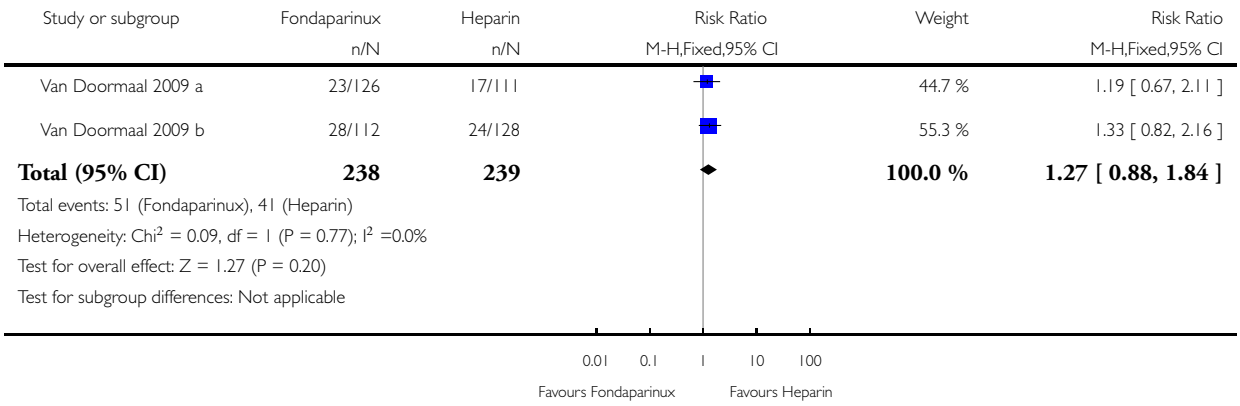


Analysis 2.1. Comparison 2 Fondaparinux versus heparin, Outcome 1 Death.

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

Comparison: 2 Fondaparinux versus heparin

Outcome: 1 Death

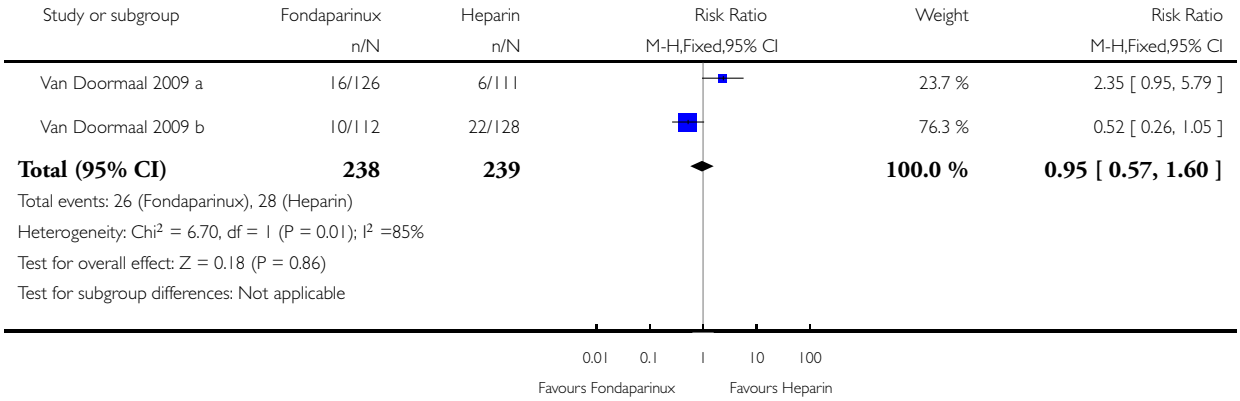


Analysis 2.2. Comparison 2 Fondaparinux versus heparin, Outcome 2 Recurrent VTE.

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

Comparison: 2 Fondaparinux versus heparin

Outcome: 2 Recurrent VTE

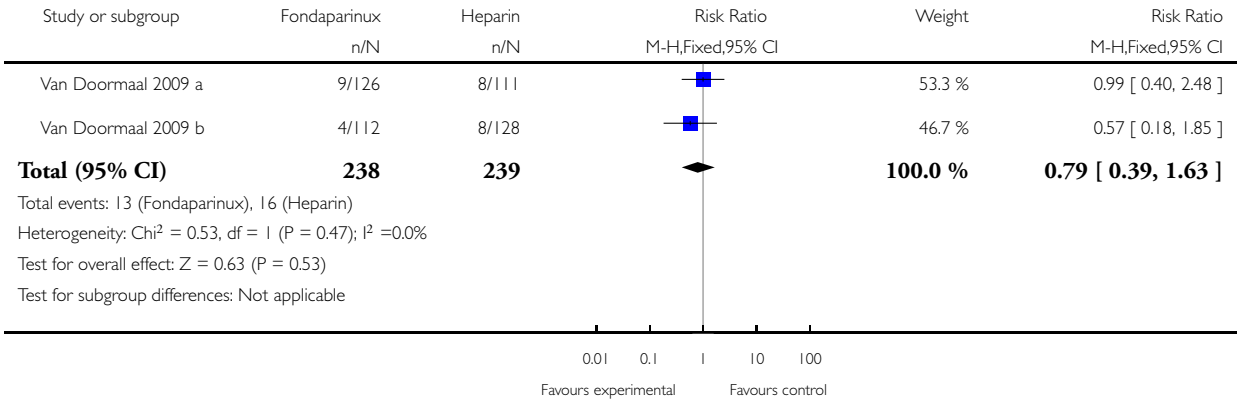


Analysis 2.3. Comparison 2 Fondaparinux versus heparin, Outcome 3 Major bleeding.

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

Comparison: 2 Fondaparinux versus heparin

Outcome: 3 Major bleeding

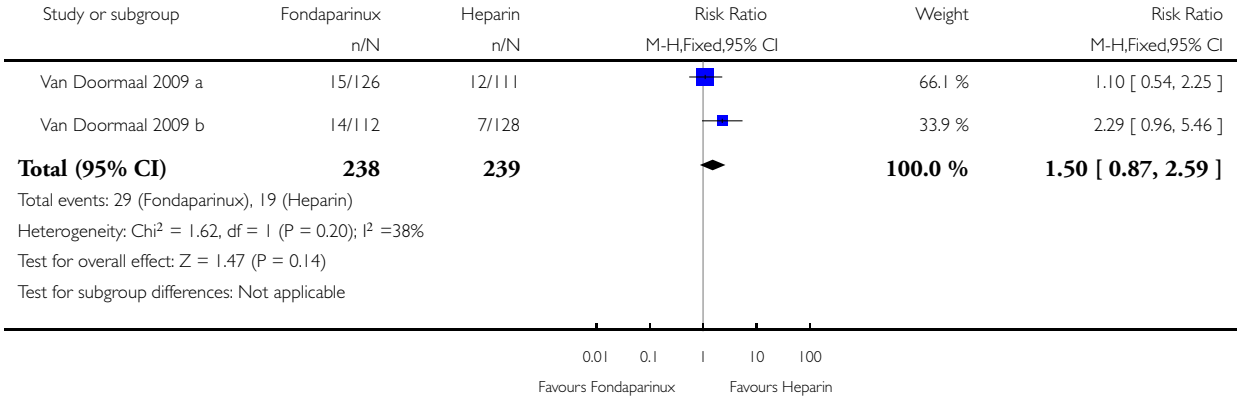


Analysis 2.4. Comparison 2 Fondaparinux versus heparin, Outcome 4 Minor bleeding.

Review: Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer

Comparison: 2 Fondaparinux versus heparin

Outcome: 4 Minor bleeding



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
A priori	made before or without examination; not supported by factual study
Adjuvant therapy	assisting in the amelioration, or cure of disease
Anticoagulation	the process of hindering the clotting of blood especially by treatment with an anticoagulant
Antithrombotic	used against or tending to prevent thrombosis (clotting)
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
Haemostatic 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. Two forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low molecular weight heparins (LMWH)
Heterogeneity	the quality or state of being heterogeneous, i.e. incongruous. This is a statistical technique to check whether study results are consistent
Hypercoagulable state	a state of excessive affinity to clotting
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 and/or measurements of a specific categorical variable
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 gut
Pulmonary embolism (PE)	embolism of a pulmonary artery or one of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock, and sometimes death
Thrombocytopenia	persistent decrease in the number of blood platelets that is often associated with hemorrhagic conditions

Table 1. Glossary (*Continued*)

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. Search strategies for the electronic databases

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

(*Continued*)

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

(*Continued*)

	#8 random$ OR placebo$ OR versus OR vs OR double blind OR double-blind OR compar$ OR controlled #9 6 AND 7 AND 8
CENTRAL (*The Cochrane Library*, latest issue)	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor #8 6 AND 7

FEEDBACK

Cochrane Editorial Unit's report on feedback on anticoagulants reviews, 15 February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at http://www.editorial-unit.cochrane.org/anticoagulants-feedback.

Reply

N/A

Contributors

N/A

WHAT'S NEW

Date	Event	Description
28 November 2012	Amended	Author contact details updated

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 1, 2008

Date	Event	Description
13 January 2011	New citation required but conclusions have not changed	Updated search (February 2010)
13 January 2011	New search has been performed	Text revisions incorporated. New author added.
5 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

EAA: protocol development, search for trials, screening, data extraction, data analysis, manuscript drafting, review coordination. SR: screening, data extraction. MB: screening, data extraction.

FS: screening, data extraction.

IT: screening, data extraction.

PM: data analysis, methodological advice.

HJS: protocol development, search for trials, data extraction, data analysis, methodological advice.

DECLARATIONS OF INTEREST

None

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

- Research Grants, Not specified.

H Schünemann: no personal payments from for-profit sponsors. Research grants and honoraria were received by research accounts or received by a research group that he belongs to from AstraZeneca, Amgen, Chiesi Foundation, Lily, and Pfizer, Roche and UnitedBioSource for development or consulting regarding quality of life instruments for chronic respiratory diseases and as lecture fees related to the methodology of evidence based practice guideline development and research methodology. Institutions or organizations that he is affiliated with likely receive funding from for-profit sponsors that are supporting infrastructure and research that may serve his work.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*therapeutic use]; Dalteparin [therapeutic use]; Fibrinolytic Agents [therapeutic use]; Hemorrhage [chemically induced]; Heparin [therapeutic use]; Heparin, Low-Molecular-Weight [therapeutic use]; Neoplasms [*complications]; Polysaccharides [therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Secondary Prevention; Venous Thromboembolism [*drug therapy; mortality]

MeSH check words

Humans