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Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer (Review)

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[Intervention Review]

Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

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ABSTRACT

Background

The choice of the appropriate perioperative thromboprophylaxis in patients with cancer depends on the relative benefits and harms of low molecular weight heparin (LMWH) and unfractionated heparin (UFH).

Objectives

To update a systematic review of the evidence for the relative efficacy and safety of LMWH and UFH for perioperative thromboprophylaxis in patients with cancer.

Search methods

We performed a comprehensive search for trials of anticoagulation in patients with cancer including a February 2013 electronic search of: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. We also handsearched conference proceedings, reviewed reference list of included studies, used the 'related citations' feature in PubMed, and searched clinicaltrials.gov for ongoing studies.

Selection criteria

Randomized controlled trials (RCTs) that enrolled patients with cancer undergoing a surgical intervention and compared the effects of LMWH to UFH on mortality, deep venous thrombosis (DVT), pulmonary embolism (PE), bleeding outcomes, or thrombocytopenia.

Data collection and analysis

Two review authors independently used a standardized form to extract in duplicate data on participants, interventions, outcomes of interest, and risk of bias. Where possible, we conducted meta-analyses using the random-effects model.

Main results

Of 9559 identified unique citations, we included 16 RCTs with 12,890 patients with cancer, all using preoperative prophylactic anticoagulation. We identified no new study with this update. The overall quality of evidence was moderate. The meta-analyses did not conclusively rule out either a beneficial or harmful effect of LMWH compared with UFH for the following outcomes: mortality (risk ratio (RR) 0.89; 95% confidence interval (CI) 0.74 to 1.08), PE (RR 0.73; 95% CI 0.34 to 1.54), symptomatic DVT (RR 0.50; 95% CI 0.20 to 1.28), asymptomatic DVT (RR 0.81; 95% CI 0.66 to 1.01),major bleeding (RR 0.85; 95% CI 0.52 to 1.37), and minor bleeding (RR 0.92; 95% CI 0.47 to 1.79). LMWH was associated with lower incidence of wound hematoma (RR 0.68; 95% CI 0.52 to 0.88) but higher volume of intraoperative transfusion (mean difference (MD) 74 mL; 95% CI 47 to 102). The meta-analyses found no statistically significant differences for any of the following outcomes: reoperation for bleeding (RR 0.72; 95% CI 0.06 to 8.48) , intraoperative blood loss (MD= -6mL; 95% CI -85 to 72), postoperative transfusion (MD= 79mL; 95% CI -54 to 211), postoperative drain volume (MD= 27mL; 95% CI -44 to 98), and thrombocytopenia (RR 1.33; 95% CI 0.59 to 3.00).

Authors' conclusions

We found no difference between perioperative thromboprophylaxis with LMWH versus UFH in their effects on mortality, thromboembolic outcomes, major bleeding, or minor bleeding in patients with cancer. Further trials are needed to evaluate the benefits and harms of different heparin thromboprophylaxis strategies in this population more thoroughly.

PLAIN LANGUAGE SUMMARY

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

Background

Patients with cancer undergoing surgical procedures are at an increased risk of blood clots. The blood thinner administered to prevent these clots can be either an unfractionated heparin (UFH) or low molecular weight heparin (LMWH). These two blood thinners may have different effectiveness and safety profiles.

Study characteristics

We searched scientific databases for clinical trials looking at the effects of UFH and LMWH on death, pulmonary embolism (blood clot in the lungs), deep vein thrombosis (blood clot in the veins of the legs), bruising, bleeding, and need for blood transfusion in patients having operations. We included people of any age or sex. The evidence is current to February 2013.

Key results

We found 16 studies of 12,890 patients with cancer. There was no evidence to show that LMWH was better than UFH for death, asymptomatic deep vein thrombosis, pulmonary embolism, or bleeding. There was less bruising around the wound and more blood transfusion during the operation with LMWH compared with UFH. Further trials are needed to clarify the effectiveness of LMWH and UFH.

Quality of evidence

The overall quality of evidence of these studies was moderate.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

LMWH compared with UFH for perioperative thromboprophylaxis in patients with cancer

Patient or population: patients with perioperative thromboprophylaxis in patients with cancer
Settings: inpatient
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				
Mortality Follow-up: median 2 weeks	**42 per 1000**	**37 per 1000** (31 to 45)	**RR 0.89** (0.74 to 1.08)	9938 (9 studies)	⊕⊕⊕◯ **moderate**[1]	
PE Follow-up: median 2 weeks	**6 per 1000**	**5 per 1000** (2 to 10)	**RR 0.73** (0.34 to 1.54)	5825 (13 studies)	⊕⊕⊕◯ **moderate**[1]	
DVT (symptomatic) Follow-up: median 2 weeks	**9 per 1000**	**4 per 1000** (2 to 11)	**RR 0.5** (0.2 to 1.28)	3233 (8 studies)	⊕⊕⊕◯ **moderate**[1]	
Major bleeding Follow-up: median 2 weeks	**47 per 1000**	**40 per 1000** (25 to 65)	**RR 0.85** (0.52 to 1.37)	3533 (8 studies)	⊕⊕⊕◯ **moderate**[1]	
Wound hematoma Follow-up: median 2 weeks	**105 per 1000**	**72 per 1000** (55 to 93)	**RR 0.68** (0.52 to 0.88)	2442 (6 studies)	⊕⊕⊕◯ **moderate**[2]	

Thrombocytopenia Follow-up: median 2 weeks	**11 per 1000**	**15 per 1000** (6 to 33)	**RR 1.33** (0.59 to 3)	1911 (4 studies)	⊕⊕◯◯ **low**[1,2]

*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; **DVT:** deep venous thrombosis; **LMWH:** low molecular weight heparin; **PE:** pulmonary embolism; **RR:** risk ratio; **UFH:** unfractionated heparin.

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

[1] The 95% CI includes both negligible effect and important benefit or important harm.
[2] Possible selective outcome reporting as few of the 16 included studies report on this outcome.

BACKGROUND

Description of the condition

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

Description of the intervention

Unfractionated heparin (UFH), and low molecular weight heparins (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. Heparin and its low molecular weight derivatives are not absorbed orally and must be administered parenterally (Hirsh 1993).

How the intervention might work

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

Why it is important to do this review

Two systematic reviews had found that in patients undergoing colorectal (Borly 2005) or general surgery (Mismetti 2001), heparins are superior to no anticoagulation in the prevention of DVT and PE. Mismetti et al. found that among general surgery patients, LMWH and UFH had similar efficacy and safety irrespective of cancer status (Mismetti 2001). However, the authors did not provide the estimates of the relative effects of the two medications in patients with cancer. Our latent version of this Cochrane review did not find any statistically significant differences in the relative benefits and harms of the two medications (Akl 2011).

OBJECTIVES

To update a systematic review of the evidence for the relative efficacy and safety of LMWH and UFH for perioperative thromboprophylaxis 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 planned to undergo a surgical intervention. We included studies with subgroup of patients with cancer that did not report subgroup specific data, when cancer patients constituted 50% or more of the total population.Otherwise, we excluded them from the systematic review.

Types of interventions

Intervention: LMWH.
Comparator: UFH.
The protocol should have planned to provide all other co-interventions similarly in the intervention and comparison group.

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Symptomatic PE.
- Symptomatic DVT.
- Asymptomatic DVT.
- Bleeding outcomes:
  - major bleeding;
  - minor bleeding;
  - wound hematoma;
  - reoperation for bleeding;
  - transfusion (intraoperative, postoperative);
  - intraoperative blood loss;
  - postoperative drain volume.
- Thrombocytopenia.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for trials of anticoagulation in patients with cancer. We applied no language restrictions. We conducted the original electronic search in January 2007 and updated it in February 2010 and in February 2013. We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, 2012), MEDLINE (1966 to February 2013; accessed via Ovid), EMBASE (1980 to February 2013; 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 2010 and 2013 search strategies in Appendix 1 and Appendix 2.

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO) (starting with its first volume, 1982 up to June 2013) and American Society of Hematology (ASH) (starting with its 2003 issue up to June 2013). We reviewed the reference lists of reports included this review and of other relevant systematic reviews. We used the 'related citations' feature in PubMed to identify additional articles. We searched ClinicalTrials.gov for ongoing studies (clinicaltrials.gov/).

Data collection and analysis

Selection of studies

Two review authors independently screened the title and abstract of identified citations for potential eligibility. We retrieved the full text of articles judged potentially eligible by at least one review author. Two review authors then independently screened the full-text 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 review authors resolved any disagreements about which articles were eligible by discussion or by consulting a third review author.

Data extraction and management

We developed and used a standardized data extraction form. Two review authors independently extracted data from each included study and resolved their disagreements by discussion. We aimed to collect the following data.

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).
- Description of the surgical procedure.
- History of VTE.
- Use of indwelling central venous catheters.

Interventions

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

Outcomes

We attempted to extract both time to event data (for all-cause mortality) and categorical data (for all outcomes). However, none of the studies reported time to event data for patients with cancer. For categorical data, we extracted the reported outcome data necessary to conduct intention-to-treat (ITT) analyses. For continuous data, we extracted mean and standard deviation (SD) separately for each arm.

We attempted to contact study authors for incompletely reported data. We determined a priori to consider abstracts only if study 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 trial level using The Cochrane Collaboration's 'Risk of bias' tool. Two review authors independently assessed the risk of bias for each included trial and resolved any disagreements by discussion. Risk of bias criteria included:

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

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

Measures of treatment effect

We analyzed hazard ratios (HRs) for time to event data, risk ratios (RRs) for categorical data, and mean differences (MD)for continuous data, with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Determining participants with missing data

It was not clear whether certain participant categories (e.g. those described as "withdrew consent" or "experienced adverse events") were actually followed up by the 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" (LTFU) participant categories, which were defined after the initiation of the study intervention, most likely had missing participant data;
- "dead", "experienced adverse events", "noncompliant", "discontinued prematurely" (and similarly described) participant categories, less likely have had missing participant data.

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

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

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 had at least one event for the outcome of interest during their available FU time).

For continuous data, we used the reported mean and SD for each study arm 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 (LTFU) compared with those with available data (FU) in the same arm ($RI_{LTFU/FU}$) = 1; for the intervention arm, $RI_{LTFU/FU}$ = 1.5;
- for the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 2;
- for the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 3;
- for the control arm, $RI_{LTFU/FU}$ = 1; for the intervention arm, $RI_{LTFU/FU}$ = 5.

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

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

Assumed events were 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

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

Assessment of reporting biases

We assessed the potential for publication bias by examining funnel plots corresponding to the primary meta-analysis of the primary outcome.

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

Data synthesis

For categorical data, we calculated the RR separately for each trial for the incidence of outcomes by treatment arm. We then pooled the results of the different trials using a random-effects model.

For continuous data, we calculated the SMD separately for each trial. We then pooled the results of the different trials using a random-effects model.

We planned to pool clinically similar trials.

We assessed the quality of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Higgins 2009).

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

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

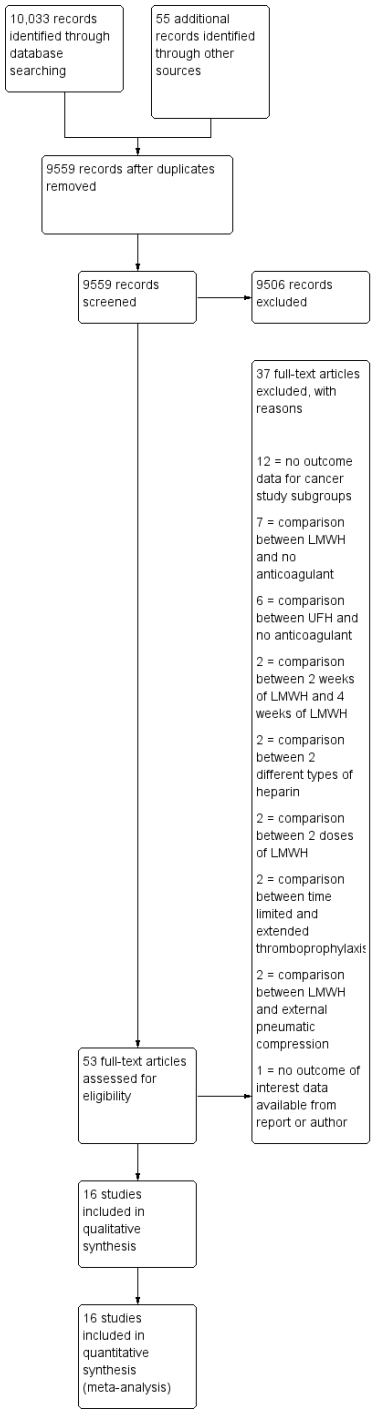
RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow diagram. The February 2013 search strategy identified 9559 citations from which we removed the results of our February 2010 search. In total, the title and abstract screening of the 9559 unique citations identified 53 potentially eligible citations. The full-text screening of the 53 citations identified 16 eligible trials and excluded the remaining 37. We identified no new study with this update. One ongoing study Safi 2011 was identified. Agreement between review authors for study eligibility was excellent (kappa = 0.94).

Figure 1. Study flow diagram.



Included studies

We included 16 trials in this review (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; Haas 2005; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986; von Tempelhoff 1997; von Tempelhoff 2000). One of these trials was published as an abstract (Godwin 1993). See Characteristics of included studies table.

Design of studies

All included studies were RCTs.

Patient characteristics

Trials were conducted in patients with cancer undergoing the following types of surgery: gynecologic (four trials; Baykal 2001; Heilmann 1998; von Tempelhoff 1997; von Tempelhoff 2000), abdominal or pelvic (seven trials; Bergqvist 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Godwin 1993; McLeod 2001; Onarheim 1986), thoracic (one trial; Dahan 1990), abdominal or thoracic (one trial; Gallus 1993), prostate (one trial; Boncinelli 2001), and unspecified (two trials; Haas 2005; Kakkar 1997). Mean age of participants varied from 51 to 71 years across included trials.

Interventions

Types of LMWH studied were: enoxaparin (three trials; Baykal 2001; Enoxacan 1997; McLeod 2001); dalteparin (three trials; Bergqvist 1990; Fricker 1988; Onarheim 1986); nadroparin (three trials; Boncinelli 2001; Dahan 1990; EFS 1988); orgaran (one trial; Gallus 1993); normiflo (one trial; Godwin 1993); certoparin (three trials; Haas 2005; Heilmann 1998; von Tempelhoff 2000); clivarine (one trial; Kakkar 1997); and not specified (one trial; von Tempelhoff 1997;). All trials started thromboprophylaxis preoperatively.

Outcomes

- Nine trials reported on mortality (Baykal 2001; Bergqvist 1990; Enoxacan 1997; Gallus 1993; Haas 2005; Heilmann 1998; Kakkar 1997; Onarheim 1986; von Tempelhoff 2000).
- Thirteen trials reported on PE (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986).
- Eight trials reported on symptomatic DVT (Baykal 2001; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Fricker 1988; Godwin 1993; Kakkar 1997; Onarheim 1986).
- Eleven trials reported on asymptomatic DVT (Bergqvist 1990; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; Kakkar 1997; McLeod 2001; Onarheim 1986; von Tempelhoff 1997).
- Eight trials reported on major bleeding (Baykal 2001; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986).
- Three trials reported on minor bleeding (Enoxacan 1997; Heilmann 1998; McLeod 2001).
- Six trials reported on wound hematoma (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Heilmann 1998; Kakkar 1997; Onarheim 1986).
- Two trials reported on reoperation for bleeding (Heilmann 1998; Onarheim 1986).
- One trial reported on intraoperative transfusion (Dahan 1990).
- One trial reported on postoperative transfusion (Dahan 1990).
- Four trials reported on intraoperative blood loss (Baykal 2001; Dahan 1990; Gallus 1993; Onarheim 1986).
- Two trials reported on postoperative drain volume (Baykal 2001; EFS 1988).
- Four trials reported on thrombocytopenia (Enoxacan 1997; Godwin 1993; Heilmann 1998; Onarheim 1986).
- None of the trials reported on heparin-induced thrombocytopenia (HIT).

Excluded studies

We excluded 37 trials from this review. Of these 37 trials, 12 included patients with cancer as study subgroups but did not report outcomes on these subgroups. The reason for excluding the remaining 16 trials were: comparison was between LMWH and no anticoagulation (seven trials); comparison was between UFH and no anticoagulation (six trials); comparison was between two weeks of treatment with LMWH and four weeks of treatment with LMWH (two trials); comparison of two different doses of heparin (three trials); comparison of two different types of LMWH (two trials); comparison between time limited and extended thromboprophylaxis (two trials); comparison between LMWH and external pneumatic compression (two trials); and data for the outcome of interest not available from report or author (one trial). See Characteristics of excluded studies table.

Risk of bias in included studies

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

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

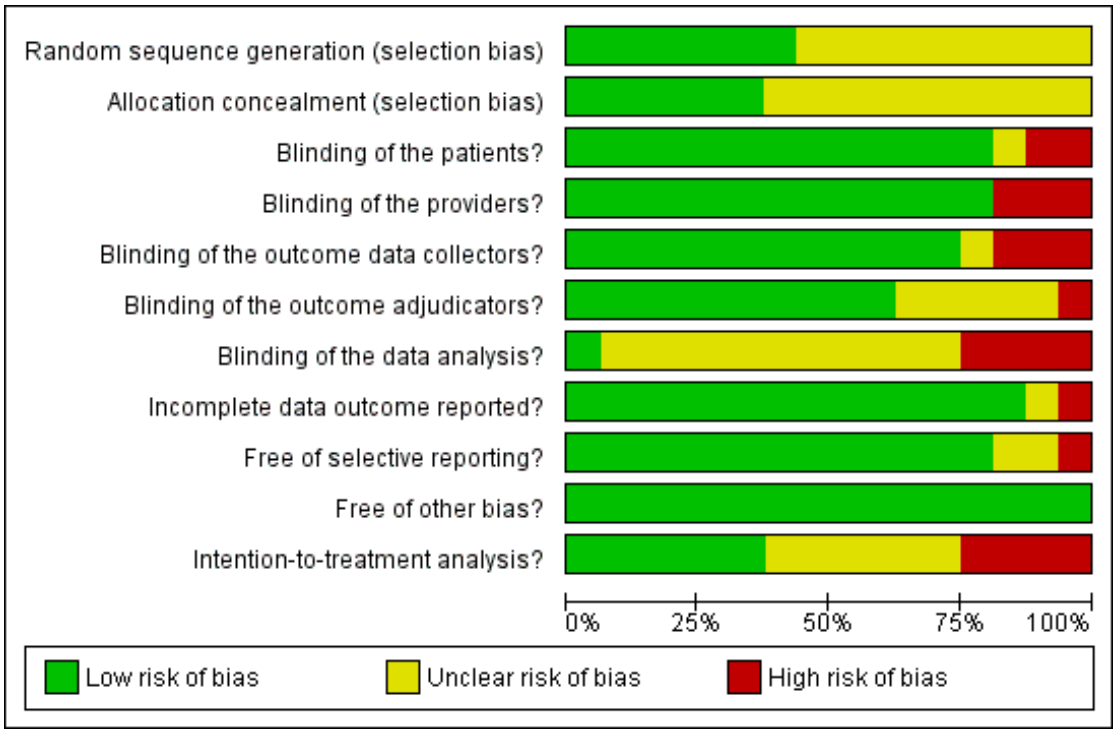
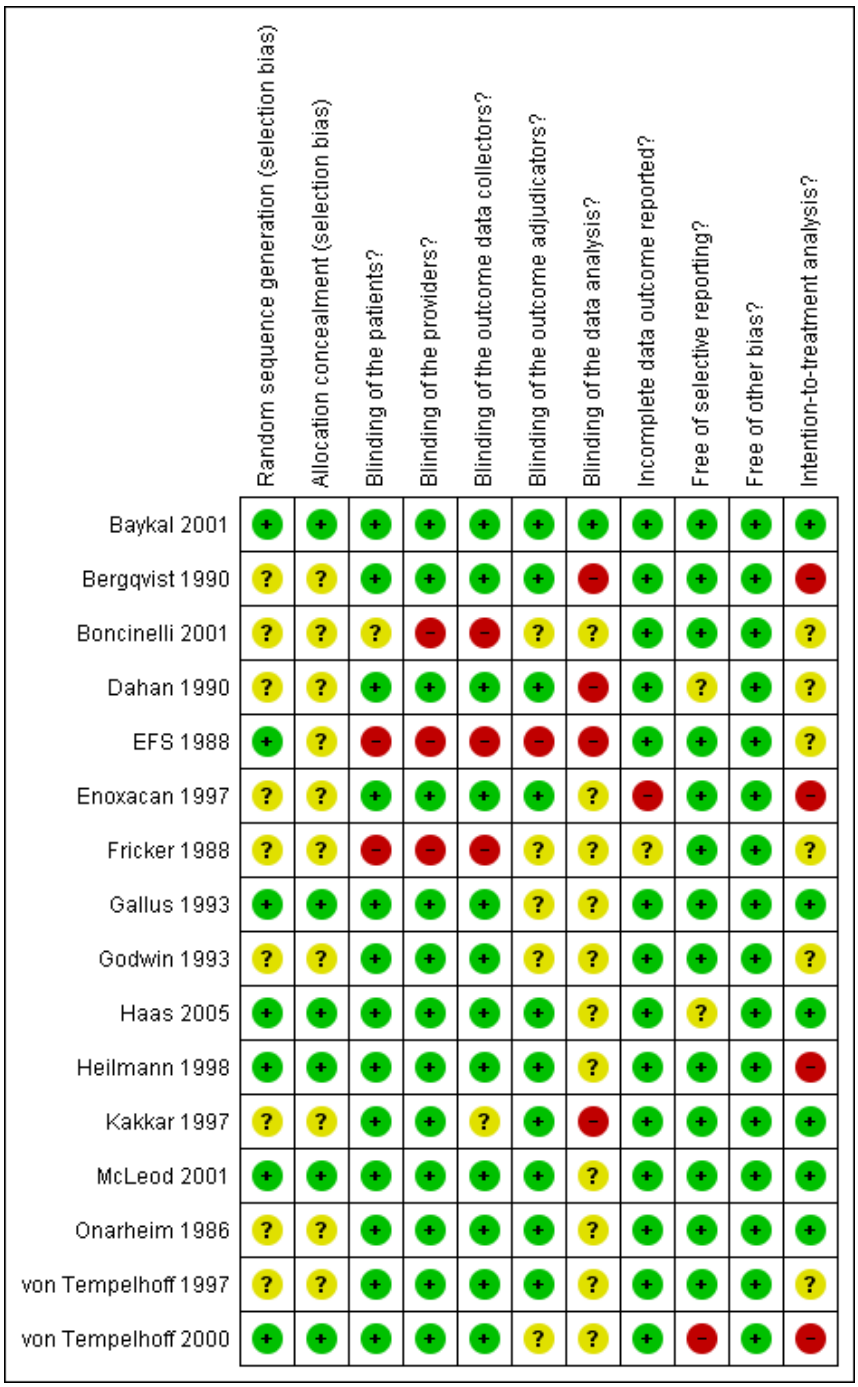


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

Sequence generation was unclear in nine studies (Bergqvist 1990; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Fricker 1988; Godwin 1993; Kakkar 1997; Onarheim 1986; von Tempelhoff 1997), but adequate in the remaining one. Allocation was adequately concealed in six trials (Baykal 2001; Gallus 1993; Haas 2005; Heilmann 1998; McLeod 2001; von Tempelhoff 2000). Allocation was not reported in 10 trials (Bergqvist 1990; Boncinelli 2001; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Godwin 1993; Kakkar 1997; Onarheim 1986; von Tempelhoff 1997).

Blinding

All but three trials clearly blinded patients and providers: blinding status was unclear in one trial (Boncinelli 2001), and was clearly not done in two trials (EFS 1988; Fricker 1988). All but four trials clearly blinded data collectors: blinding status was unclear in two trials (Boncinelli 2001; McLeod 2001), and was clearly not done in two trials (EFS 1988; Fricker 1988). All but seven trials clearly blinded outcome adjudicators: blinding status was unclear in six trials (Boncinelli 2001; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; von Tempelhoff 2000), and clearly not done in one trial (EFS 1988). Blinding of the data analyst was clearly performed in one trial (Baykal 2001), and clearly not done in four trials (Bergqvist 1990; Dahan 1990; EFS 1988; Kakkar 1997); it was unclear in the remainder of the trials.

Incomplete outcome data

FU was satisfactory in all the trials with the following percentages: 96% in Bergqvist 1990; 99% in EFS 1988; 95% in Gallus 1993; 89% in Godwin 1993; 91% in Heilmann 1998; 97% in Kakkar 1997; 94% in McLeod 2001; and 100% in the remaining trials.

Selective reporting

The outcomes listed in the methods section were reported in the results section for all trials. von Tempelhoff 2000 appears to have collected data on VTE outcomes but did not report them. It was unclear whether Dahan 1990 had any reporting bias.

Other potential sources of bias

The only trial that was stopped early was Haas 2005. We judged the associated risk of bias to be low because stoppage was related to insufficient recruitment and not to benefit.

Six trials reported adhering to the ITT principle (Baykal 2001; Gallus 1993; Haas 2005; Kakkar 1997; McLeod 2001; Onarheim 1986); three trials reported not adhering to the ITT principle (Bergqvist 1990; Enoxacan 1997; Heilmann 1998); seven trials did not report on the adherence to the ITT principle (Boncinelli 2001; Dahan 1990; EFS 1988; Fricker 1988; Godwin 1993; von Tempelhoff 1997; von Tempelhoff 2000).

Effects of interventions

See: **Summary of findings for the main comparison** LMWH compared with UFH for perioperative thromboprophylaxis in patients with cancer

Appendix 3 shows the detailed statistical data abstraction.

Mortality

Meta-analysis of nine trials reporting data on 9938 patients did not conclusively rule out a mortality reduction with LMWH compared with UFH (RR 0.89; 95% CI 0.74 to 1.08): the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important (I^2 = 0%) (Baykal 2001; Bergqvist 1990; Enoxacan 1997; Gallus 1993; Haas 2005; Heilmann 1998; Kakkar 1997; Onarheim 1986; von Tempelhoff 2000) (Figure 4). The inverted funnel plot suggested no publication bias (Figure 5). The quality of evidence was moderate (Summary of findings for the main comparison).

Figure 4. Forest plot of comparison: 1 LMWH versus UFH, outcome: 1.1 Mortality.

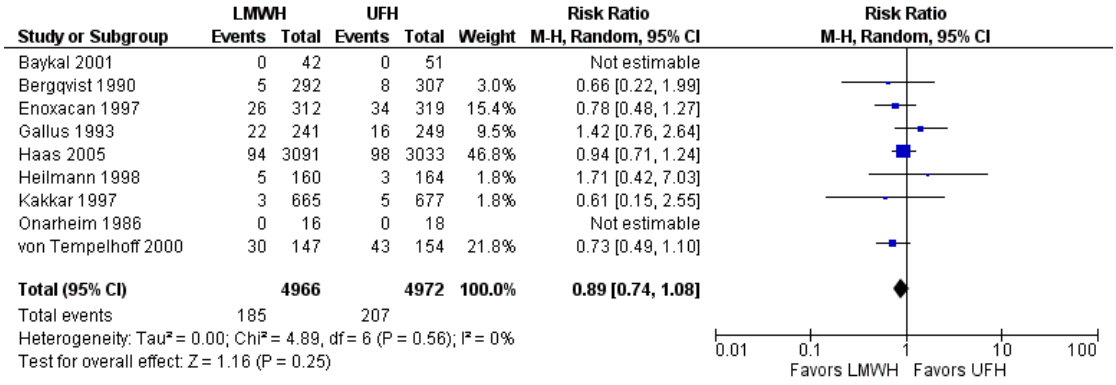
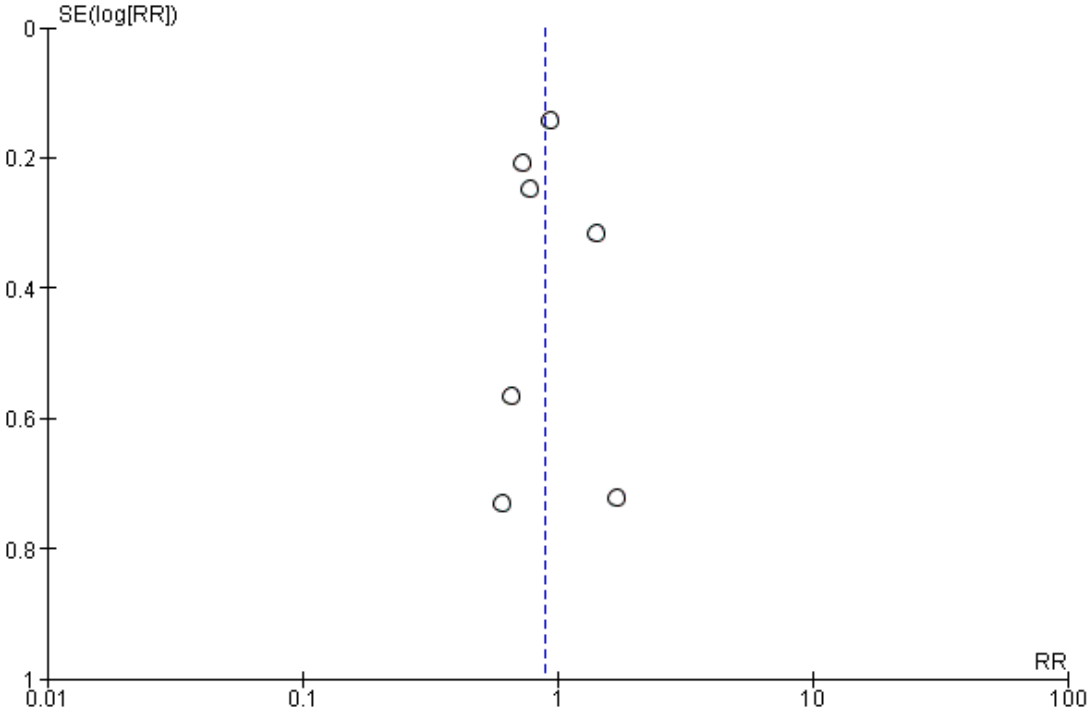


Figure 5. Funnel plot of comparison: 1 LMWH versus UFH, outcome: 1.1 Mortality.



Pulmonary embolism

Meta-analysis of 13 trials reporting data on 5825 patients did not conclusively rule out a decrease or increase in PE with LMWH compared with UFH (RR 0.73; 95% CI 0.34 to 1.54); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not im-

portant (I^2 = 0%) (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986).

Symptomatic deep venous thrombosis

Meta-analysis of eight trials reporting data on 3233 patients did not conclusively rule out a symptomatic DVT reduction or increase with LMWH compared with UFH (RR 0.50; 95% 0.20 to 1.28); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important (I^2 = 0%) (Baykal 2001; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Fricker 1988; Godwin 1993; Kakkar 1997; Onarheim 1986). The quality of evidence was moderate (Summary of findings for the main comparison).

Asymptomatic deep venous thrombosis

Meta-analysis of 11 trials reporting data on 5418 patients did not conclusively rule out a reduction in asymptomatic DVT with LMWH compared with UFH (RR 0.81; 95% CI 0.66 to 1.01); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important (I^2 = 4%) (Bergqvist 1990; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; Kakkar 1997; McLeod 2001; Onarheim 1986; von Tempelhoff 1997).

Major bleeding

Meta-analysis of eight trials reporting data on 3533 patients did not conclusively rule out a reduction or increase with LMWH compared with UFH (RR 0.85; 95% CI 0.52 to 1.37); the percentage of the variability in effect estimates that was due to heterogeneity among studies rather than sampling error (chance) represented some heterogeneity (I^2 = 34%) (Baykal 2001; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986). The quality of evidence was moderate (Summary of findings for the main comparison).

Minor bleeding

Meta-analysis of three trials reporting data on 1914 patients did not conclusively rule out a reduction or increase with LMWH compared with UFH (RR 0.92; 95% CI 0.47 to 1.79); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) represented considerable heterogeneity (I^2 = 76%) (Enoxacan 1997; Heilmann 1998; McLeod 2001).

Wound hematoma

Meta-analysis of six trials assessing 2442 patients showed a reduction with LMWH compared with UFH (RR 0.68; 95% CI 0.52 to 0.88); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important (I^2 = 0%) (Baykal 2001; Bergqvist 1990; Boncinelli 2001; Heilmann 1998; Kakkar 1997; Onarheim 1986).

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 used the priori plausible assumptions detailed in the Methods section. The effect estimate remained statistically significant even when using the most stringent plausible assumption (RR 0.68; 95% CI 0.50 to 0.93).

The quality of evidence was moderate (Summary of findings for the main comparison).

Reoperation for bleeding

Meta-analysis of two trials reporting data on 358 patients did not conclusively rule out a reduction or increase with LMWH compared with UFH (RR 0.72; 95% CI 0.06 to 8.48); the percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) represented some heterogeneity (I^2 = 43%) (Heilmann 1998; Onarheim 1986). The quality of evidence was low (Summary of findings for the main comparison).

Intraoperative transfusion

One trial reporting data on 84 patients found that the intraoperative transfusion volume was higher with LMWH compared with UFH (MD 74 mL; 95% CI 47 to 102) (Dahan 1990). Since all participants who were randomized were followed, we did not conduct a sensitivity analysis.

Postoperative transfusion

One trial assessing 81 patients found no difference in effect with LMWH compared with UFH (MD 79mL; 95% CI -54 to 211) (Dahan 1990).

Intraoperative blood loss

Meta-analysis of four trials reporting data on 761 patients found no difference in effect with LMWH compared with UFH (MD -6mL; 95% CI to -85 to 72) (Baykal 2001; Dahan 1990; Gallus 1993; Onarheim 1986).

Postoperative drain volume

Meta-analysis of two trials reporting data on 806 patients found no difference in effect with LMWH compared with UFH (MD 27mL; 95% CI -44 to 98) (Baykal 2001; EFS 1988).

Thrombocytopenia

Meta-analysis of four trials reporting data on 1911 patients did not conclusively rule out a thrombocytopenia reduction or increase with LMWH compared to UFH (RR 1.33; 95% CI 0.59 to 3.00) (Enoxacan 1997; Godwin 1993; Heilmann 1998; Onarheim 1986). The quality of evidence was low (Summary of findings for the main comparison).

Heparin-induced thrombocytopenia

We found no trials reporting the effects of LMWH or UFH on HIT.

DISCUSSION

Summary of main results

The meta-analysis of 16 trials with 12,890 patients did not conclusively rule out either beneficial or harmful effects of LMWH compared with UFH relative to mortality, symptomatic DVT, PE, minor bleeding, and major bleeding. LMWH was associated with lower incidence of wound hematoma (based on four trials) while LMWH was associated with higher volume of intraoperative transfusion (based on one trial). None of the trials reported on HIT. The overall quality of evidence was moderate.

Overall completeness and applicability of evidence

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

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

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

Quality of the evidence

The quality of evidence was moderate for mortality, PE, symptomatic DVT, major bleeding, and wound hematoma, and was low for reoperation for bleeding and thrombocytopenia. The overall quality of evidence was moderate.

Screening patients for DVT may have biased the results of 10 included trials. If screening detects thromboses, patients are typically therapeutically anticoagulated. Some of the patients with asymptomatic events may have developed symptomatic VTE, had screening testing not been undertaken and anticoagulant therapy not been administered. As a result, the number of symptomatic VTE events in this review, and the differential effect of LMWH versus UFH on symptomatic events, may be underestimated.

Potential biases in the review process

Our systematic approach to searching, study selection, and data extraction should have minimized the likelihood of missing relevant trials. We excluded 12 trials that included patients with cancer as subgroups but did not report on their outcome data. The cancer subgroups in these trials included 3185 participants compared with 12,890 participants included in the current analysis. This may have introduced bias.

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

Agreements and disagreements with other studies or reviews

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

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

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

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Baykal 2001

Methods	Randomized double-blind trial
Participants	102 patients undergoing surgery for gynecologic malignancy Mean age 57 years, previous VTE: not reported
Interventions	Intervention: enoxaparin 2500 U 2 h preoperatively then once daily (a LMWH) Control: UFH 5000 U 3 times daily Discontinued treatment: not clear
Outcomes	Duration of follow-up: not clear • Mortality • DVT • PE • Intraoperative bleeding • Catheter drainage Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none
Notes	Funding: Eczacibasi-Rhône Poulenc, Turkey

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	According to author contact: random number table
Allocation concealment (selection bias)	Low risk	According to author contact: "sequentially numbered sealed envelopes"
Blinding of the patients?	Low risk	According to author contact: yes
Blinding of the providers?	Low risk	Quote: "randomised double blind trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "randomised double blind trial" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "the surgical team and those collecting laboratory and clinical data were not informed about the prophylactic anticoagulation being used"
Blinding of the data analysis?	Low risk	According to author contact: yes

Baykal 2001 (*Continued*)

Incomplete data outcome reported?	Low risk	Follow-up 100%
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-treatment analysis?	Low risk	Comment: probably yes; no inappropriate post randomizations exclusions; 100% follow-up

Bergqvist 1990

Methods	Randomized double-blind trial
Participants	637 patients with cancer undergoing elective general abdominal surgery (study subgroup) from 7 centers Mean age 71 years, males 52% (329/637), previous VTE 6% (40/637)
Interventions	Intervention: dalteparin 5000 U 22.00 h preoperatively then daily x 5-8 days (a LMWH) Control: UFH 5000 U 2 h preoperatively then twice daily x 5-8 days Discontinued treatment: not clear
Outcomes	Duration of follow-up: 30 days • DVT • PE • Hemorrhage • Mortality Screening testing for DVT: radiolabeled fibrinogen uptake test for 7 days Diagnostic test for PE: scintigraphy
Notes	Funding: Swedish Medical Research Council

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "a total of 1040 patients were randomised"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "randomised double blind multicenter trial" Comment: probably yes

Bergqvist 1990 (*Continued*)

Blinding of the providers?	Low risk	Quote: "randomised double blind multicenter trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "randomised double blind multicenter trial" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Comment: probably yes
Blinding of the data analysis?	High risk	Comment: probably no
Incomplete data outcome reported?	Low risk	Follow-up 96%
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-treatment analysis?	High risk	Quote: "After randomizations, 38 patients were excluded; 27 because of cancelled operations, four owing to withdrawal of consent after randomizations but before the first injection, and seven for various other reasons"

Boncinelli 2001

Methods	Randomized trial
Participants	50 patient were undergoing prostatectomy for prostate cancer Mean age 60 years, , previous VTE: not reported
Interventions	Intervention: 0.3 mL of calcium nadroparin given as single daily subcutaneous injection (a LMWH) Control: UFH 5000 U subcutaneous 3 times daily In both groups, prophylaxis began preoperatively and maintained throughout the hospital stay (mean 15 days) Discontinued treatment: 0
Outcomes	Duration of follow-up: 15 days • DVT • PE • Major bleeding • Hematoma in the postoperative period Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none

Boncinelli 2001 (*Continued*)

Notes	Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Unclear risk	Comment: not reported
Blinding of the providers?	High risk	Quote: "treatment was continued or interrupted at home under the decision of the general practitioner" Comment: probably no as no placebo used
Blinding of the outcome data collectors?	High risk	Comment: probably no as no placebo used
Blinding of the outcome adjudicators?	Unclear risk	Comment: not reported
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 100%
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-treatment analysis?	Unclear risk	Comment: not reported

Dahan 1990

Methods	Randomized trial
Participants	100 patients undergoing thoracic surgery for cancer; aged > 18 years Mean age 59 years, 92% men, previous VTE: not reported
Interventions	Intervention: nadroparin 7500 U 12 h preoperatively and 12 h postoperatively until the second postoperative day then 10,000 U once daily on postoperative days 3-7 Control: UFH 5000 U 2 h preoperatively and 12 h postoperatively then 3 times daily until the second postoperative day then a dose adjusted to activated partial thromboplastin time on postoperative days 3-7 twice daily Discontinued treatment: 0

Dahan 1990 (*Continued*)

Outcomes	Duration of follow-up: not clear • DVT • PE • Perioperative bleeding and postoperative bleeding Screening testing for DVT/PE: patients were screened with ^{125}I-fibrinogen uptake test Diagnostic testing for DVT/PE: none
Notes	Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised study"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "partially double blind"; "first phase conducted double blind"; "second open phase was conducted" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "partially double blind"; "first phase conducted double blind"; "second open phase was conducted" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "partially double blind"; "first phase conducted double blind"; "second open phase was conducted" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "partially double blind"; "first phase conducted double blind"; "second open phase was conducted" Comment: probably yes
Blinding of the data analysis?	High risk	Quote: "partially double blind"; "first phase conducted double blind"; "second open phase was conducted" Comment: probably no
Incomplete data outcome reported?	Low risk	Follow-up 100%
Free of selective reporting?	Unclear risk	Study not registered. No published protocol. No outcomes listed in the methods section Comment: unclear

Dahan 1990 (*Continued*)

Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention-to-treatment analysis?	Unclear risk	Comment: not reported

EFS 1988

Methods	Randomized trial
Participants	704 patients with cancer (study subgroup) scheduled for elective abdominal surgery Mean age 61 years, 52% males, previous VTE: not reported
Interventions	Intervention: fraxiparin 7500 anti-Xa U given subcutaneously (a LMWH) Control: calcium heparin 5000 U 3 times daily Treatment was initiated 2 h before surgery, the second injection was given 8 h after surgery. Subsequent injections were given every 24 h between 07.00 and 10.00 h from the first to the seventh postoperative day Discontinuation treatment: not clear
Outcomes	Duration of follow-up: 7 days • DVT • Asymptomatic DVT • PE • Hemorrhage • Mortality Screening testing for DVT/PE: not reported Diagnostic testing for DVT/PE: the patients had radiolabeled iodine fibrinogen leg scanning on the day of the surgery and then daily for 7 consecutive days
Notes	Funding: Sanofi Labaz, GmbH, Pharmzeutische Praparate

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the patients were assigned to treatment with either Fraxiparin or calcium heparin following randomised schedule "
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	High risk	Quote: "the trial was not performed in double blind manner" Comment: no
Blinding of the providers?	High risk	Quote: "the trial was not performed in double blind manner" Comment: no
Blinding of the outcome data collectors?	High risk	Quote: "the trial was not performed in double blind manner" Comment: no

EFS 1988 (*Continued*)

Blinding of the outcome adjudicators?	High risk	Quote: "the trial was not performed in double blind manner" Comment: probably no
Blinding of the data analysis?	High risk	Quote: "the trial was not performed in double blind manner" Comment: probably no
Incomplete data outcome reported?	Low risk	Follow-up 99%
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-treatment analysis?	Unclear risk	Comment: not reported

Enoxacan 1997

Methods	Randomized double-blind trial
Participants	1115 patients undergoing planned curative abdominal or pelvic surgery for cancer (study subgroup) were randomized in to the study. Venograms were inadequate in 460 (41.3%) leaving "631 evaluable patients" Minimum age 40 years. Mean age 68.5 years, 53% men, previous DVT 3% (20/631)
Interventions	Intervention: enoxaparin 40 mg once daily started 2 h before surgery (a LMWH) Control: low dose of UFH 3 times daily Discontinuation treatment: 243/556 participants randomized to LMWH and 241/560 participants randomized to UFH
Outcomes	Duration of follow-up: 3 months • DVT • Asymptomatic DVT • PE plus DVT • Minor bleeding • Major bleeding • Thrombocytopenia • Mortality Screening testing for DVT/PE: none Diagnostic test for DVT: venography; "Scheduled bilateral ascending venography was performed 24 hours after the last injection of the trial substance" Diagnostic test for PE: scintigraphy
Notes	Funding: Swedish Medical Research Council grant
Risk of bias	

Enoxacan 1997 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "separate randomisation were made per country and per hospital to one of two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "Double blind randomised trial" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "Double blind randomised trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "Double blind randomised trial" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "the venographic results were evaluated and agreed on by an independent panel before the code was broken" Comment: yes
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	High risk	Of 1115 patients randomized, venograms were inadequate in 460 leaving "631 evaluable patients". 56.6% follow-up Quote: "At the 3-month follow-up, 13 patients were lost or information was missing" Comment: yes
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-treatment analysis?	High risk	Quote: "Efficacy analysis was made on all treated patients basis as well as on the basis of the evaluable patients"; "safety analysis was made on all treated patients"; "these patients were included in the analysis as they have been randomised" Comment: probably no

Fricker 1988

Methods	Randomized trial
Participants	80 patients undergoing surgery for abdominal and pelvic malignancy Mean age 57.6 years, 93% female, previous VTE 13.7%
Interventions	Intervention: 2500 anti-Xa U 2 h before surgery and 12 h after the first injection and then 5000 anti-Xa U fragmin injection every morning for 10 days Control: 5000 IU of calcium heparin injection 2 h before the surgery and then at 8-h intervals for the next 10 days Discontinuation of treatment: 0
Outcomes	Follow-up: 10 days • DVT • Asymptomatic DVT • PE Screening testing for DVT/PE: radio-labeled fibrinogen tests was used for postoperative screening of DVT Diagnostic testing for DVT/PE: none
Notes	Kabivitrum, France

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "eighty patients undergoing pelvic or abdominal surgery for cancer were randomised in two groups"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	High risk	Quote: "we have undertaken a prospective open randomised trial" Comment: probably no
Blinding of the providers?	High risk	Quote: "we have undertaken a prospective open randomised trial" Comment: probably no
Blinding of the outcome data collectors?	High risk	Quote: "we have undertaken a prospective open randomised trial " Comment: probably no
Blinding of the outcome adjudicators?	Unclear risk	Comment: not reported
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Unclear risk	Follow-up 100% Comment: probably yes

Fricker 1988 (*Continued*)

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-treatment analysis?	Unclear risk	Comment: not reported

Gallus 1993

Methods	Randomized double-blind trial
Participants	514 patients undergoing abdominal or thoracic surgery for cancer at the Royal Melbourne and Austin Hospitals (Melbourne, Australia), the Middlemore Hospital (Auckland, New Zealand), and the Flinders Medical Centre (Adelaide, Australia) Mean age 65 years, 62% males, previous VTE 2.5%
Interventions	Intervention: orgaran 750 U 1-2 h preoperatively then at 12-h intervals x 6 days (a LMWH) Control: UFH 5000 U 1-2 h preoperatively then at 12-h intervals x 6 days Discontinued treatment: 16/241 randomized to LMWH and 7/249 randomized to UFH
Outcomes	Duration of follow-up: 4-6 weeks after discharge from hospital. The follow-up period was defined as starting 2 days after the end of trial therapy • DVT • PE • Bleeding • Mortality Screening test for DVT: radio-labeled fibrinogen tests was used for screening of postoperative DVT every second day on the week days Diagnostic test for DVT: ascending contrast medium venography
Notes	Funding: Organon International, Oss, The Netherlands.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "using predetermined randomisation sequences for each trial center"
Allocation concealment (selection bias)	Low risk	Quote: "coded ampoules of Orgaran and Na heparin were supplied by Organon International B.V and dispensed in numbered boxes by hospital pharmacies using predetermined randomisation sequences for each trial center"

Gallus 1993 (*Continued*)

		Comment: yes
Blinding of the patients?	Low risk	Quote: "double blind multicenter trial" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "double blind multicenter trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "double blind multicenter trial" Comment: probably yes
Blinding of the outcome adjudicators?	Unclear risk	Comment: not reported
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 95.5%
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-treatment analysis?	Low risk	Quote: "intent to treat analysis showed statistically non-significant toward trend towards less VT during Orgaran prophylaxis" Quote: "A more restricted "compliant patients" analysis (which excluded significant protocol violators, and, for VT, patients where treatment was discontinued before 6 days for any reason other than onset of VT, e.g. because of bleeding) gave essentially similar results" Comment: probably yes

Godwin 1993

Methods	Randomized double-blind trial
Participants	904 patients undergoing abdominal or pelvic surgery for cancer Mean age not reported, % males not reported, previous VTE % not reported
Interventions	Intervention: RDH (Normiflo) 50 U 2 h preoperatively and then 90 U once or twice daily (a LMWH) Control: UFH 5000 U 2 h preoperatively and then 5000 U twice daily Discontinued treatment: 0

Godwin 1993 (*Continued*)

Outcomes	Duration of follow-up: not clear • DVT • PE • Bleeding • Mortality Screening testing for DVT: preoperatively by non-invasive venous tests, either impedence plethysmography or duplex ultrasound scan Diagnostic testing for DVT/PE: none	
Notes	Funding: KabiVitrum	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "a total of 904 patients were randomised into three groups"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the outcome adjudicators?	Unclear risk	Comment: not reported
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 89%
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-treatment analysis?	Unclear risk	Comment: not reported

Haas 2005

Methods	Randomized double-blind controlled trial
Participants	6124 patient undergoing surgery for cancer at 67 centers in Germany, Austria, and the Czech Republic Minimum age 40 years, mean age 62 years, % males not reported, previous VTE % not reported
Interventions	Intervention: LMWH certoparin 3000 anti-Xa IU, subcutaneously, once daily Control: UFH 5000 IU, administered subcutaneously 3 times daily Discontinued treatment: not applicable
Outcomes	Duration of follow-up: 14 days • Mortality • PE • Bleeding complications (wound hematoma; postoperative wound bleeding; gastric bleeding) Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none
Notes	Funding: Novartis Pharma GmbH, Nürnberg, Germany

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to one of two treatment groups using a centralised computer generated randomizations list"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised to one of two treatment groups using a centralised computer generated randomizations list"
Blinding of the patients?	Low risk	Quote: "double-blind clinical trial"; "Placebo injections were given to Certoparin patients to conform to the double blind trial design" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "double-blind clinical trial"; "Placebo injections were given to Certoparin patients to conform to the double blind trial design" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "double-blind clinical trial"; "Placebo injections were given to Certoparin patients to conform to the double blind trial design"

Haas 2005 (*Continued*)

		Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: " double-blind clinical trial"; "Placebo injections were given to Certoparin patients to conform to the double blind trial design" Comment: probably yes
Blinding of the data analysis?	Unclear risk	Quote: "The statistical analysis was performed by an independent statistician and under the guidance of the Steering Committee" Comment: unclear
Incomplete data outcome reported?	Low risk	Follow-up 100% for mortality; 70% for fatal PE
Free of selective reporting?	Unclear 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	Quote: "the decision was taken to end the study prematurely as the study would not be sufficiently powered to show superiority of Certoparin over UFH" Comment: probably no
Intention-to-treatment analysis?	Low risk	Quote: "The analyses included all randomised patients (intention-to-treat)" Comment: yes

Heilmann 1998

Methods	Randomized double-blind trial
Participants	358 patients undergoing breast and pelvic cancer surgery Minimum age 40 years, mean age not reported, % males not reported, previous DVT 8%
Interventions	Intervention: certoparin 3000 U 2-5 h preoperatively then once daily x 7 days Control: UFH 5000 U 2-5 h preoperatively then 3 times daily x 7 days Discontinued treatment: not clear
Outcomes	Duration of follow-up: 20 months • DVT • PE • Major bleeding • Minor bleeding

	• Wound hematoma • Reoperation for hematoma Screening test for DVT/PE: none Diagnostic test for DVT/PE: scheduled impedence plethysmography on postoperative days 1, 3, 5, 7, and 10
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated to the two treatment groups" Comment: probably yes, particularly given the method of allocation concealment used
Allocation concealment (selection bias)	Low risk	Quote: "prefilled ampoules, prepared by NOVARTIS GmbH, Nuneberg were identical in appearance. Boxes were labeled with trial code number and contained sufficient drug for 10 days"
Blinding of the patients?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "double blind randomised trial" Comment: probably yes
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 91%
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-treatment analysis?	High risk	Quote: "a total of 358 patients were entered into the trial of whom 34 (9.5%) were exclude after randomisa-

Heilmann 1998 (*Continued*)

		tion because written informed consent was withdrawn by the patient or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before seventh postoperative day" Comment: no

Kakkar 1997

Methods	Randomized double-blind trial
Participants	706 patients with an underlying malignancy (out of a total of 1351 patients (52%)) undergoing surgery Minimum age 40 years, mean age 59.6 years, % males not reported, previous VTE % not reported
Interventions	Intervention: LMWH 1750 anti-Xa IU administered subcutaneously once daily with a second injection of saline (placebo) 12 h later Control: UFH 5000 IU subcutaneously every 12 h Treatment commenced 2 h prior to surgery followed by a second injection 8 h postoperatively and continued for at least 5 days (longer if the patient was still confined to bed) Discontinued treatment: 0
Outcomes	Duration of follow-up: not clear • Mortality • DVT • PE • Bleeding complications • Wound hematoma • Wound complications (hematoma, oozing, bruising) • Injection site complications (hemorrhage; hypersensitivity; inflammation; pain) Screening testing for DVT/PE: scheduled radioactive fibrinogen uptake test was done daily for DVT screening Diagnostic testing for DVT/PE: none
Notes	Funding: Knoll AG, Germany

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "double-blind multicenter trial" Comment: probably yes

Kakkar 1997 (*Continued*)

Blinding of the providers?	Low risk	Quote: "double-blind multicenter trial" Comment: probably yes
Blinding of the outcome data collectors?	Unclear risk	Quote: "double-blind multicenter trial" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "The final diagnosis of DVT or PE was based on the assessment of a blinded expert committee" Comment: probably yes
Blinding of the data analysis?	High risk	Comment: not reported; probably not
Incomplete data outcome reported?	Low risk	Quote: "The number of patients who could not be analysed for efficacy was similar in the two groups: 24 (3.6%) with LMWH and 16 (2.4%) with UFH" Comment: most likely relate to the outcome of asymptomatic DVT
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-treatment analysis?	Low risk	Quote: "The study was analysed in accordance with the intention-to-treat principle" Comment: yes

McLeod 2001

Methods	Randomized double-blind trial
Participants	475 patients undergoing surgery for colorectal cancer Mean age 51 years
Interventions	Intervention: enoxaparin 40 mg (100 antifactor Xa U/mg) subcutaneously once daily in the morning plus 2 placebo injections Control: calcium heparin 5000 U every 8 h Prophylaxis was initiated 2 h before the surgery and 1 further injection (heparin or placebo) at 20.00 h on the day of the surgery. Thereafter, patients received 3 injections daily for up to 10 days
Outcomes	Duration of follow-up: not clear • DVT • Asymptomatic DVT • PE

	• Major bleeding • Minor bleeding Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: scheduled bilateral ascending contrast venography was done on or before postoperative day 9
Notes	Funding: Rhône-Poulenc Rorer Canada Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to receive either calcium heparin or enoxaparin" Comment: probably yes, particularly given the method of allocation concealment used
Allocation concealment (selection bias)	Low risk	Quote: "a central computer-generated randomisation scheme in blocks of four was used to prepare numbered kits of study medication that were provided to the pharmacy departments of study centers"; "the study injections were prepared as 0.2-ml preloaded, consecutively numbered syringes"
Blinding of the patients?	Low risk	Quote: "randomised double blind trial" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "randomised double blind trial" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "randomised double blind trial" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "all the venograms and other imaging studies for venous thromboembolism were reviewed by central adjudication committee which was unaware of the treatment allocation and used detailed coding form with prespecified criteria" Comment: yes
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 94% Comment: probably yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on

McLeod 2001 (*Continued*)

		Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention-to-treatment analysis?	Low risk	Quote: "all randomised patients, except those who did not fulfil the entry criteria, were included in the analysis of blood loss and bleeding events" Comment: probably yes

Onarheim 1986

Methods	Randomized double-blind trial
Participants	52 patients undergoing surgery for abdominal malignancy Mean age 70.35 years, % males not reported, previous VTE 5.8%
Interventions	Intervention: dalteparin 5000 U 2 h preoperatively then once daily x 6 days Control: heparin Kabi 2165 5000 U 2 h preoperatively then twice daily x 6 days Discontinued treatment: not clear
Outcomes	Duration of follow-up: 30 days • Mortality • DVT • PE • Major bleeding • Wound hematoma • Thrombocytopenia Screening testing for DVT/PE: radioactive fibrinogen uptake test was used for DVT screening and was performed preoperatively and then daily or every second day for at least 7 postoperative days Diagnostic testing for DVT/PE: none
Notes	Funding: Kabivitrum

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated to receive conventional heparin (heparin group) or LMWH KABI 2165 (LMWH group)"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported

Onarheim 1986 (*Continued*)

Blinding of the patients?	Low risk	Quote: "double blind trial"; "A placebo injection was given each evening, in order in order to keep the study completely blind" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "double blind trial"; "A placebo injection was given each evening, in order in order to keep the study completely blind" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "double blind trial"; "A placebo injection was given each evening, in order in order to keep the study completely blind" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "double blind trial"; "A placebo injection was given each evening, in order in order to keep the study completely blind" Comment: probably yes
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up: 100%
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-treatment analysis?	Low risk	Quote: "the data collected from 52 patients were therefore uniformly analysed on an "intention to treat" basis" Comment: probably yes

von Tempelhoff 1997

Methods	Randomized trial
Participants	60 patients with ovarian cancer undergoing surgery and chemotherapy Mean age 56.7 years, previous VTE 3.3%
Interventions	Intervention: 3000 anti-Xa U/day of LMWH plus 2 placebo injections Control: 5000 IU/day of UFH 3 times a day. Prophylaxis was begun 2 h before operation and continued until the 7th postoperative

von Tempelhoff 1997 (*Continued*)

	day Discontinuation treatment: 0
Outcomes	Duration of follow-up: 7 days • DVT • Asymptomatic DVT Diagnostic testing for DVT/PE: impedance plethysmography was used for DVT screening on days 1, 3, 5, 7, and10
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "all patients were eligible for surgery and randomised to receive either daily LMWH or UFH"
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "All 60 patients were randomised in double blind manner to receive either LMWH or UFH" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "All 60 patients were randomised in double blind manner to receive either LMWH or UFH" Comment: probably yes
Blinding of the outcome data collectors?	Low risk	Quote: "All 60 patients were randomised in double blind manner to receive either LMWH or UFH" Comment: probably yes
Blinding of the outcome adjudicators?	Low risk	Quote: "All 60 patients were randomised in double blind manner to receive either LMWH or UFH" Comment: probably yes
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 100% Comment: probably yes
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

von Tempelhoff 1997 (*Continued*)

Intention-to-treatment analysis?	Unclear risk	Comment: not reported

von Tempelhoff 2000

Methods	Randomized double-blind trial
Participants	350 patients with either histologically confirmed carcinoma of the breast, endometrium, vulva, or vagina, or with suspected ovarian malignancy Minimum age 40 years, mean age 61 years
Interventions	Intervention: certoparin 3000 anti-Xa U subcutaneously once daily in combination with 2 placebo injections (0.9% saline) Control: UFH 5000 IU subcutaneously 3 times daily Initial injection was given 2 h before the surgery always contained active drug. In both treatment arms study medication was given at 8-h intervals until 7th postoperative day Discontinuation treatment: not clear
Outcomes	Duration of follow-up: median of 1849 days in LMWH group and 1954 days in UFH group • Mortality (the 1 relevant outcome listed in the methods section is reported on) Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none
Notes	Funding: Novartis, Germany

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patient who randomly received LMW heparin (certoparin) compared to patients given UF heparin for thrombosis prophylaxis during primary surgery" Comment: probably yes, particularly given the method of allocation concealment used
Allocation concealment (selection bias)	Low risk	Quote: "the boxes and ampoules of both heparins were labelled with a trial code number but were identical in appearance so neither the patient nor the staff were aware of the kind of heparin administered"
Blinding of the patients?	Low risk	Quote: "Randomised double blind trial" Comment: probably yes
Blinding of the providers?	Low risk	Quote: "Randomised double blind trial" Comment: probably yes

von Tempelhoff 2000 (*Continued*)

Blinding of the outcome data collectors?	Low risk	Quote: "Randomised double blind trial" Comment: probably yes
Blinding of the outcome adjudicators?	Unclear risk	Quote: "Randomised double blind trial" Comment: probably yes
Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	Follow-up 100% Comment: probably yes
Free of selective reporting?	High risk	Study appears to have collected data on VTE outcomes but do not report them Comment: probably no
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention-to-treatment analysis?	High risk	Quote: "patients were not randomised according to intention to treat principle" Comment: probably no

DVT: deep venous thrombosis; h: hour; IU: international units; LMWH: low molecular weight heparin; PE: pulmonary embolism; VTE: venous thromboembolism; U: unit; UFH: unfractionated heparin.

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

Study	Reason for exclusion
Arbeit 1981	Comparison was not of interest: UFH vs. no anticoagulant
Attaran 2010	Comparison was not of interest: different doses of LMWH
Azorin 1997	Comparison was not of interest: LMWH vs. no anticoagulant
Bergqvist 1986	Study included patients with cancer as a subgroup for which outcome data were not available
Bergqvist 1988	Study included patients with cancer as a subgroup for which outcome data were not available
Bergqvist 2002	Comparison was not of interest: LMWH (4 weeks) vs. LMWH (1 week)
Boneu 1993	Study included patients with cancer as a subgroup for which outcome data were not available

(*Continued*)

Borstad 1988	Study included patients with cancer as a subgroup for which outcome data were not available
Borstad 1992	Study included patients with cancer as a subgroup for which outcome data were not available
Bricchi 1991	Comparison was not of interest: UFH vs. no anticoagulant
Cade 1983	Comparison was not of interest: the study compared the efficacy of a higher dose of heparin (7500 U twice daily) with the commonly used dose of 5000 U
Caprini 2003	Comparison was not of interest: LMWH vs. no anticoagulant
Clark-Pearson 1990a	Comparison was not of interest: UFH vs. no anticoagulant
Clark-Pearson 1990b	Comparison was not of interest: comparison between 2 doses of UFH
Clarke-Pearson 1983	Comparison was not of interest: UFH vs. no anticoagulant
Clarke-Pearson 1984	Comparison was not of interest: LMWH vs. no anticoagulant
Dickinson 1998	Comparison was not of interest: LMWH vs. no anticoagulant
Gondret 1995	Comparison was not of interest: LMWH vs. no anticoagulant
Ho 1999	Comparison was not interest: LMWH vs. no anticoagulant
Kakkar 1989	Study included patients with cancer as a subgroup for which outcome data were not available
Kakkar 1985	Study included patients with cancer as a subgroup for which outcome data were not available
Kakkar 2009	Comparison was not of interest: time limited vs. extended thromboprophylaxis
Kakkar 2010a	Comparison was not of interest: time limited vs. extended thromboprophylaxis
Kakkar 2010b	Comparison was not of interest: different types of LMWH
Liezorovicz 1991	Study included patients with cancer as a subgroup for which outcome data were not available
Limmer 1994	Study included patients with cancer as a subgroup for which outcome data were not available
Macdonald 2003	Study included patients with cancer as a subgroup for which outcome data were not available
Marassi 1993	Comparison was not interest: LMWH vs. no anticoagulant
Maxwell 2001	Comparison was not of interest: LMWH vs. external pneumatic compression
Nurmohamed 1995	Data for the outcome of interest not available from report or author

(*Continued*)

Rasmussen 2003	Comparison was not of interest: LMWH (4 weeks) vs. LMWH (1 week)
Sakon 2010	Comparison was not of interest: LMWH vs. intermittent pneumatic compression
Samama 1988	Study included patients with cancer as a subgroup for which outcome data were not available
Shukla 2008	Comparison was not interest: LMWH vs. no anticoagulant
Simonneau 2006	Comparison was not of interest: different types of LMWH
Tang 2012	Comparison was not of interest: LMWH vs. no anticoagulant
Ward 1998	Study included patients with cancer as a subgroup for which outcome data were not available

LMWH: low molecular weight heparin; UFH: unfractionated heparin.

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

Safi 2011

Trial name or title	A Randomized, Controlled, Open Label Study of the Efficacy and Safety of the Low Molecular Weight Heparin (LMWH), LovenoxTM (Enoxaparin) Versus HeparinTM (Unfractionated Heparin) for Prevention of Venous Thromboembolism (VTE) in Gynecologic Oncology Patients
Methods	Phase IIIB, randomized, open-label, noncomparative controlled trial
Participants	150 gynecologic oncology patients with diagnosis of malignancy or suspension of malignancy In the Kingdom of Saudi Arabia who required major surgery or admission for the prevention of VTE, aged > 18 years
Interventions	Intervention: enoxaparin (LMWH) Control: unfractionated heparin (UFH)
Outcomes	• Any thromboembolic events • Mortality • Major bleeding • Time to thromboembolic event • Adverse events Diagnostic test for thromboembolic events: spiral computed tomography or V/Q scan, Doppler ultrasound, and coagulation profile parameter
Starting date	October 2009
Contact information	Faisal Safi, MD Gynecology

Safi 2011 (*Continued*)

Notes	Funded by National Guard Health Affairs

DATA AND ANALYSES

Comparison 1. Low molecular weight heparin versus unfractionated heparin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9	9938	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.08]
2 Pulmonary embolism	13	5825	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.34, 1.54]
3 Deep venous thrombosis (DVT) (symptomatic)	8	3233	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.28]
4 DVT (asymptomatic)	11	5418	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 1.01]
5 Major bleeding	8	3533	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.52, 1.37]
6 Minor bleeding	3	1914	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.47, 1.79]
7 Wound hematoma	6	2442	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.52, 0.88]
8 Reoperation for bleeding	2	358	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.06, 8.48]
9 Intraoperative transfusion	1	84	Mean Difference (IV, Random, 95% CI)	74.30 [47.01, 101.59]
10 Postoperative transfusion	1	81	Mean Difference (IV, Random, 95% CI)	78.6 [-53.58, 210.78]
11 Intraoperative blood loss	4	761	Mean Difference (IV, Random, 95% CI)	-6.75 [-85.49, 71.99]
12 Postoperative drain volume	2	806	Mean Difference (IV, Random, 95% CI)	27.26 [-43.89, 98.41]
13 Thrombocytopenia	4	1911	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.59, 3.00]

Analysis 1.1. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 1 Mortality.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 1 Mortality

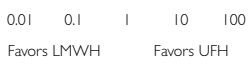
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baykal 2001	0/42	0/51			Not estimable
Bergqvist 1990	5/292	8/307		3.0 %	0.66 [0.22, 1.99]
Enoxacan 1997	26/312	34/319		15.4 %	0.78 [0.48, 1.27]
Gallus 1993	22/241	16/249		9.5 %	1.42 [0.76, 2.64]
Haas 2005	94/3091	98/3033		46.8 %	0.94 [0.71, 1.24]
Heilmann 1998	5/160	3/164		1.8 %	1.71 [0.42, 7.03]
Kakkar 1997	3/665	5/677		1.8 %	0.61 [0.15, 2.55]
Onarheim 1986	0/16	0/18			Not estimable
von Tempelhoff 2000	30/147	43/154		21.8 %	0.73 [0.49, 1.10]
Total (95% CI)	**4966**	**4972**		**100.0 %**	**0.89 [0.74, 1.08]**

Total events: 185 (LMWH), 207 (UFH)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.89$, df = 6 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable

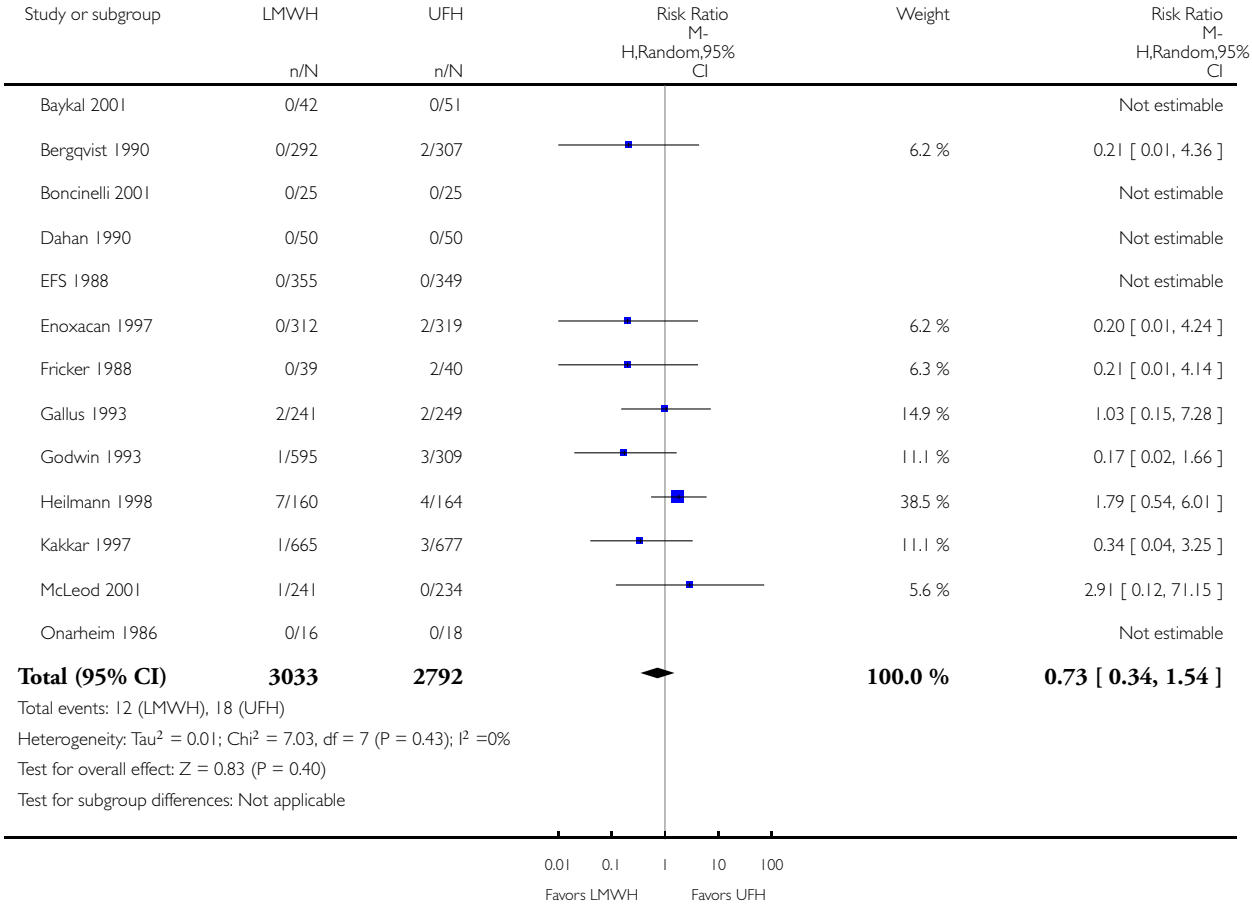


Analysis 1.2. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 2 Pulmonary embolism.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 2 Pulmonary embolism



Analysis 1.3. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 3 Deep venous thrombosis (DVT) (symptomatic).

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 3 Deep venous thrombosis (DVT) (symptomatic)

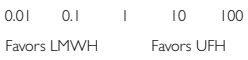
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baykal 2001	0/42	0/51			Not estimable
Boncinelli 2001	0/25	0/25			Not estimable
Dahan 1990	0/50	0/50			Not estimable
Enoxacan 1997	4/312	6/319		54.7 %	0.68 [0.19, 2.39]
Fricker 1988	1/39	1/40		11.5 %	1.03 [0.07, 15.83]
Godwin 1993	1/595	3/309		16.9 %	0.17 [0.02, 1.66]
Kakkar 1997	1/665	3/677		16.9 %	0.34 [0.04, 3.25]
Onarheim 1986	0/16	0/18			Not estimable
Total (95% CI)	**1744**	**1489**		**100.0 %**	**0.50 [0.20, 1.28]**

Total events: 7 (LMWH), 13 (UFH)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.46$, df = 3 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable



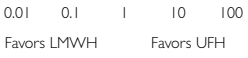
Analysis 1.4. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 4 DVT (asymptomatic).

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 4 DVT (asymptomatic)

Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bergqvist 1990	22/292	34/307		16.0 %	0.68 [0.41, 1.13]
Dahan 1990	0/50	0/50			Not estimable
EFS 1988	15/355	19/349		9.8 %	0.78 [0.40, 1.50]
Enoxacan 1997	41/312	50/319		27.3 %	0.84 [0.57, 1.23]
Fricker 1988	2/39	0/40		0.5 %	5.13 [0.25, 103.45]
Gallus 1993	19/241	28/249		13.7 %	0.70 [0.40, 1.22]
Godwin 1993	0/595	3/309		0.5 %	0.07 [0.00, 1.43]
Kakkar 1997	30/665	28/677		16.4 %	1.09 [0.66, 1.81]
McLeod 2001	20/241	27/234		14.0 %	0.72 [0.42, 1.25]
Onarheim 1986	2/16	2/18		1.3 %	1.13 [0.18, 7.09]
von Tempelhoff 1997	4/28	0/32		0.5 %	10.24 [0.58, 182.23]
Total (95% CI)	**2834**	**2584**		**100.0 %**	**0.81 [0.66, 1.01]**
Total events: 155 (LMWH), 191 (UFH)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.34$, df = 9 (P = 0.41); $I^2 = 4\%$					
Test for overall effect: Z = 1.91 (P = 0.056)					
Test for subgroup differences: Not applicable					



Analysis 1.5. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 5 Major bleeding.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 5 Major bleeding

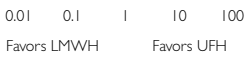
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baykal 2001	0/42	0/51			Not estimable
Boncinelli 2001	0/25	1/25		2.2 %	0.33 [0.01, 7.81]
Dahan 1990	2/50	3/50		6.6 %	0.67 [0.12, 3.82]
Enoxacan 1997	23/555	16/560		27.0 %	1.45 [0.77, 2.72]
Heilmann 1998	27/160	47/164		36.0 %	0.59 [0.39, 0.90]
Kakkar 1997	9/665	15/677		20.4 %	0.61 [0.27, 1.39]
McLeod 2001	5/241	1/234		4.6 %	4.85 [0.57, 41.24]
Onarheim 1986	1/16	1/18		3.0 %	1.13 [0.08, 16.55]
Total (95% CI)	**1754**	**1779**		**100.0 %**	**0.85 [0.52, 1.37]**

Total events: 67 (LMWH), 84 (UFH)

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 9.10$, df = 6 (P = 0.17); $I^2 = 34\%$

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 6 Minor bleeding.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 6 Minor bleeding

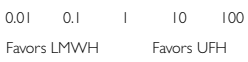
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Enoxacan 1997	81/555	80/560		41.1 %	1.02 [0.77, 1.36]
Heilmann 1998	12/160	28/164		31.5 %	0.44 [0.23, 0.83]
McLeod 2001	17/241	9/234		27.4 %	1.83 [0.83, 4.03]
Total (95% CI)	**956**	**958**		**100.0 %**	**0.92 [0.47, 1.79]**

Total events: 110 (LMWH), 117 (UFH)

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 8.51$, df = 2 (P = 0.01); $I^2 = 76\%$

Test for overall effect: Z = 0.25 (P = 0.80)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 7 Wound hematoma.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 7 Wound hematoma

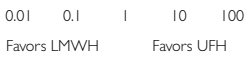
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baykal 2001	0/42	0/51			Not estimable
Bergqvist 1990	36/292	47/307		40.9 %	0.81 [0.54, 1.21]
Boncinelli 2001	2/25	2/25		1.9 %	1.00 [0.15, 6.55]
Heilmann 1998	18/160	29/164		22.3 %	0.64 [0.37, 1.10]
Kakkar 1997	29/665	52/677		34.2 %	0.57 [0.37, 0.88]
Onarheim 1986	0/16	1/18		0.7 %	0.37 [0.02, 8.55]
Total (95% CI)	**1200**	**1242**		**100.0 %**	**0.68 [0.52, 0.88]**

Total events: 85 (LMWH), 131 (UFH)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.68$, df = 4 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 2.96 (P = 0.0031)

Test for subgroup differences: Not applicable

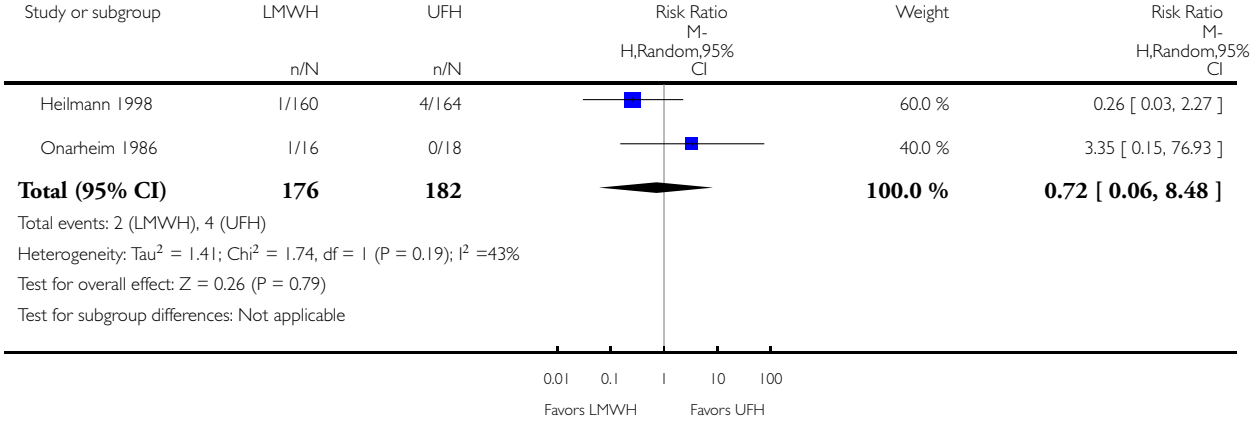


Analysis 1.8. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 8 Reoperation for bleeding.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 8 Reoperation for bleeding

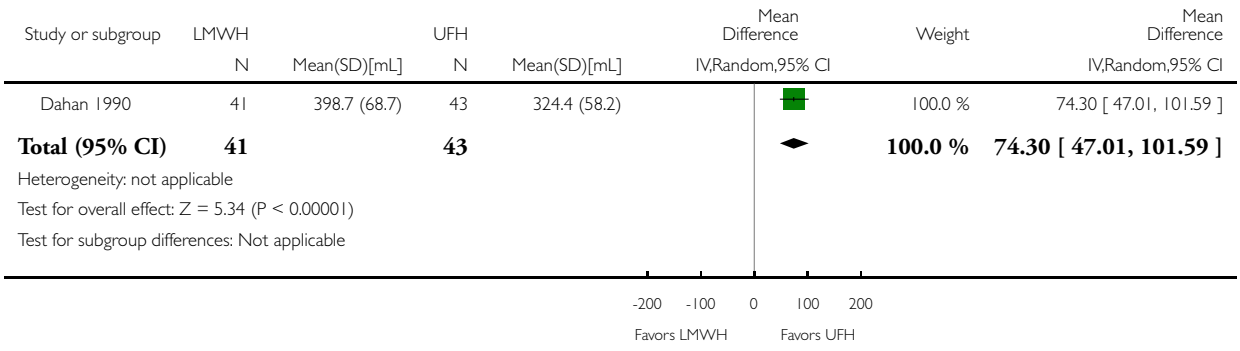


Analysis 1.9. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 9 Intraoperative transfusion.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 9 Intraoperative transfusion



Analysis 1.10. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 10 Postoperative transfusion.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

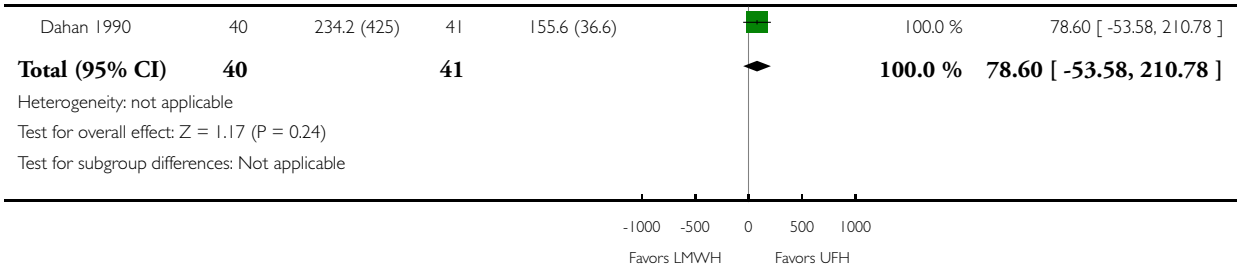
Outcome: 10 Postoperative transfusion

Study or subgroup	LMWH N	Mean(SD)[mL]	UFH N	Mean(SD)[mL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Dahan 1990	40	234.2 (425)	41	155.6 (36.6)		100.0 %	78.60 [-53.58, 210.78]
Total (95% CI)	**40**		**41**			**100.0 %**	**78.60 [-53.58, 210.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 11 Intraoperative blood loss.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

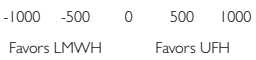
Outcome: 11 Intraoperative blood loss

Study or subgroup	LMWH N	Mean(SD)[mL]	UFH N	Mean(SD)[mL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Baykal 2001	47	915.5 (399.9)	55	798.4 (535.3)		18.7 %	117.10 [-64.79, 298.99]
Dahan 1990	48	290.8 (333.9)	46	307.5 (346.37)		32.7 %	-16.70 [-154.33, 120.93]
Gallus 1993	257	573 (644)	256	615 (714)		44.8 %	-42.00 [-159.68, 75.68]
Onarheim 1986	25	528 (479)	27	646 (956)		3.8 %	-118.00 [-524.55, 288.55]
Total (95% CI)	**377**		**384**			**100.0 %**	**-6.75 [-85.49, 71.99]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.43$, df = 3 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 12 Postoperative drain volume.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

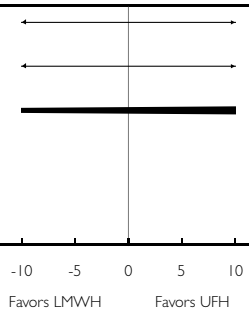
Outcome: 12 Postoperative drain volume

Study or subgroup	LMWH N	Mean(SD)[mL]	UFH N	Mean(SD)[mL]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Baykal 2001	47	836.8 (533.2)	55	723.2 (543.7)		11.5 %	113.60 [-95.88, 323.08]
EFS 1988	355	478 (522)	349	462 (502)		88.5 %	16.00 [-59.65, 91.65]
Total (95% CI)	**402**		**404**			**100.0 %**	**27.26 [-43.89, 98.41]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.74$, df = 1 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable

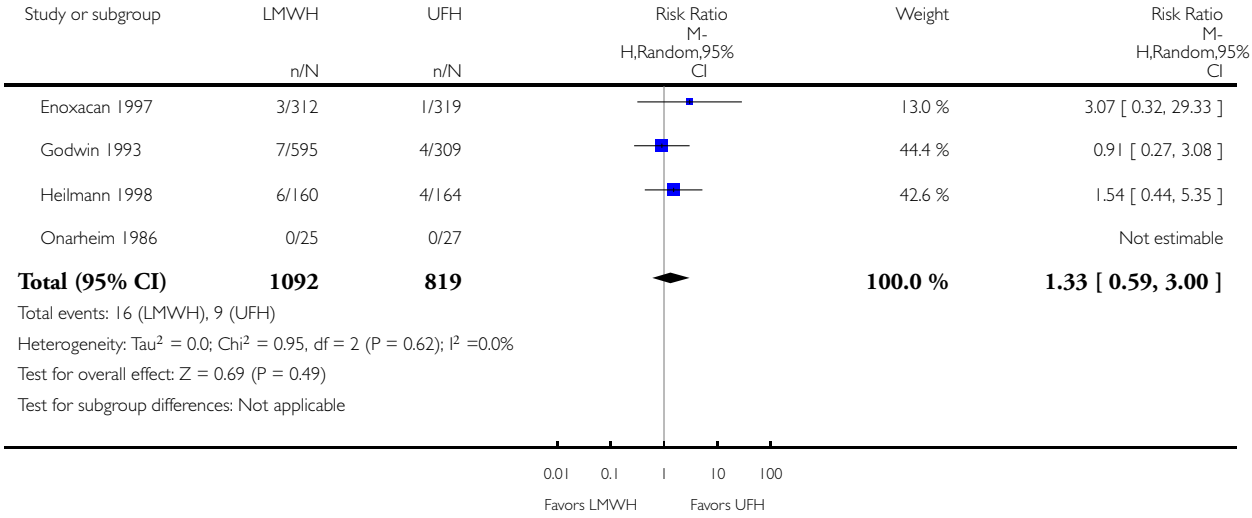


Analysis 1.13. Comparison 1 Low molecular weight heparin versus unfractionated heparin, Outcome 13 Thrombocytopenia.

Review: Low molecular weight heparin versus unfractionated heparin for perioperative thromboprophylaxis in patients with cancer

Comparison: 1 Low molecular weight heparin versus unfractionated heparin

Outcome: 13 Thrombocytopenia



APPENDICES

Appendix 1. Search strategies for the electronic databases - update 2010

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/

(*Continued*)

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

(*Continued*)

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
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 #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor #8 6 AND 7

Appendix 2. Search strategies for the electronic databases - update 2013

Database	Strategy
MEDLINE	#1 exp Heparin/ #2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw

(*Continued*)

	#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
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.

(*Continued*)

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

Appendix 3. Detailed statistical data abstraction

Outcome: All-cause mortality										
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	Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for

(*Continued*)

						CCA) [2]						CCA)
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt		
Baykal 2001	0	47	0	Not clear 9/2[5]	0	47-9/2=42	0	55	0	Not clear 9/2	0	55-9/2=51
Bergqvist 1990	5	311	0	Not clear 38/2[6]	0	311-38/2=292	8	326	0	Not clear 38/2	0	326-38/2=307
Enoxacan 1997	26	556	1	243[7]	0	556-1-243=312	34	560	0	241	0	560-241=319
Gallus 1993	22	257	0	16[8]	0	257-16=241	16	256	0	7	0	256-7=249
Haas 2005	94 [9]	3091	0	0	0	3091	98	3033	0	0	0	3033
Heilmann 1998	5	179	0	19[10]	0	179-19=160	3	179	0	15	0	179-15=164
Kakkar 1997	3	672	7	0	0	671-7=665	5	679	2	0	0	679-2=677
Onarhein 1986	0	25	0	Not clear 18/2	0	25-18/2=16	0	27	0	Not clear 18/2	0	27-18/2=18
Von Tempelhoff 2000	24 +6[11] =30	160+6[12	0	19[13]	0	160+6-19=147	38+5=43	164+5	0	15	0	164+5-15=154

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]"9 patients were excluded from the study (5 for HRT, 2 for Chronic liver disease, 2 had mobilization restrictions" (applies for both arms).

[6]"38 excluded after randomization: 27 because of canceled operations, 4 withdrawal, 7 various other reasons" (applies for both arms).

[7]"560 were randomized to receive UFH and 556 enoxaparin. 1 patients randomized to enoxaparin did not receive any study medication at all and was excluded from further analysis. Adequate endpoint evaluation was not available in 460 patients. 6 received insufficient prophylaxis according to the protocol and 18 received prohibited concomitant medication. The remainder had inadequate venograms. The evaluable patients population was 631 patients, 319 who received UFH and 312 enoxaparin." (Applies for both arms).
[8]"Deaths in hospital or during follow-up were evenly distributed: 22/257, or 8.6%, of Orgaran treated patients died (4 during trial therapy and 18 underfollow up), compared with 16/256 (6.3%) of those given heparin (3 during trial therapy and 13 later)" (applies for both arms)
[9]"A total of 192 patients (3.1%) had died at 14 days after the end of prophylactic treatment, 94 in the certoparin group, and 98 in the UFH-treated group" From Haas 2000 (abstract) (applies for both arms)
[10]"34 (19 LMWH and 15 UFH) were excluded from the study after randomization because written informed consent was withdrawn by the patients (n=20) or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before the seventh postoperative day." (Applies for both arms)
[11]"Patients who died post-operatively and patients who died of other than cancer during follow-up" from table 1 p 817 ((applies for both arms)
[12]"Patients who died post-operatively and patients who died of other than cancer during follow-up" from table 1 p 817 (applies for both arms)
[13]"Of 358 remaining patients, 34 were excluded from the study after randomization (19 in LMWH and 15 in UFH). 14 discontinuation after randomization and 37 excluded from survival analysis." For survival analysis, 37 of the 324 patients were excluded leaving 287 of whom 140 patients were of the LMW heparin group and 147 of the UF heparin group" (applies for both arms)

Outcome: Symptomatic deep vein thrombosis-DVT

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 [					Pre-trt	Post-trt		
Baykal 2001	0[5]	47	0	Not clear 9/2[6]	0	**47-9/2=42**	0	55	0	Not clear 9/2	0	**55-9/2=51**
Boncinel 2001	0	25	0	0	0	**25**	0	25	0	0	0	**25**
Dahan 1990	0	50	0	0	0	**50**	0	50	0	0	0	**50**

(*Continued*)

Enoxacan 1997	4[7]	556	1	243[8]	0	**556-1-243=312**	6	560	0	241	0	**560-241=319**	
Fricker 1988	1	40	0	1	0	**40-1=39**	1	40	0	0	0	**40**	
Onarhei 1986	0	25	0	Not clear	0	**25-18/2=16**	0	27	0	Not clear	0	**27-18/2=18**	
Godwin 1993	1	595	0	0	0	**595**	3	309	0	0	0	**309**	
Kakkar 1997	1	672	7	0	0	**671-7=665**	3	679	2	0	0	**679-2=677**	

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]"There were no demonstrated DVT, PTE, wound hematoma or postop hemorrhage in either group" (Applies to both arms)
[6]"9 patients were excluded from the study (5 for HRT, 2 for Chronic liver disease, 2 had mobilization restrictions" (applies for both arms).
[7]"Of the 101 DVTs, ten were symptomatic (six and four in UFH and enoxaparin groups respectively)." (Applies to both arms)
[8]"560 were randomized to receive UFH and 556 enoxaparin. 1 patients randomized to enoxaparin did not receive any study medication at all and was excluded from further analysis. Adequate endpoint evaluation was not available in 460 patients. 6 received insufficient prophylaxis according to the protocol and 18 received prohibited concomitant medication. The remainder had inadequate venograms. The evaluable patients population was 631 patients, 319 who received UFH and 312 enoxaparin." (Applies for both arms).

Outcome: Asymptomatic deep vein thrombosis-DVT											
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	Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data	

(*Continued*)

						CCA) [2]						(for CCA)	
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt			
Bergqvis 1990	22	311	0	Not clear 38/ 2[5]	0	311-38/2= 292	34	326	0	Not clear 38/2	0	326-38/2= 307	
Dahan 1990	0	50	0	0	0	50	0	50	0	0	0	50	
EFS 1988	15	355	0	0	0	355	19	349	0	0	0	349	
Enoxa-can 1997	41[6]	556	1	243[7]	0	556-1-243= 312	50	560	0	241	0	560-241= 319	
Fricker 1988	2	40	0	1	0	40-1= 39	0	40	0	0	0	40	
Gallus 1993	19[8]	257	0	16[9]	0	257-16= 241	28	256	0	7	0	256-7=249	
God-win 1993	0	595	0	0	0	595	3	309	0	0	0	309	
Kakkar 1997	30	672	7	0	0	671-7=665	28	679	2	0	0	679-2=677	
McLeod 2001	20	241	0	0	0	241	27	234	0	0	0	234	
Onarhei 1986	2	25	0	Not clear	0	25-18/ 2=16	2	27	0	Not clear	0	27-18/ 2=18	
Von Tem-pelhoff 1997	4	28	0	0	0	28	0	32	0	0	0	32	

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]"38 excluded after randomization: 27 because of canceled operations, 4 withdrawal, 7 various other reasons" (applies for both arms).
[6]"Of the 101 DVTs, ten were symptomatic (six and four in UFH and enoxaparin groups respectively)."
From table 2 p1101: total number of "DVT only" is 56 and 45 for UFH and LMWH respectively. Thus the number of asymptomatic DVT is 56-6 for the UFH and 45-4 for the LMWH (Applies to both arms)
[7]"560 were randomized to receive UFH and 556 enoxaparin. 1 patients randomized to enoxaparin did not receive any study medication at all and was excluded from further analysis. Adequate endpoint evaluation was not available in 460 patients. 6 received insufficient prophylaxis according to the protocol and 18 received prohibited concomitant medication. The remainder had inadequate venograms. The evaluable patients population was 631 patients, 319 who received UFH and 312 enoxaparin." (Applies for both arms).
[8]Positive fibrinogen leg scan results for VT. (Applies to both arms)
[9]"Deaths in hospital or during follow-up were evenly distributed: 22/257, or 8.6%, of Orgaran treated patients died (4 during trial therapy and 18 underfollow up), compared with 16/256 (6.3%) of those given heparin (3 during trial therapy and 13 later)" (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		
Baykal 2001	0	47	0	Not clear 9/2[5]	0	47-9/2=42	0	55	0	Not clear 9/2	0	55-9/2=51
Boncinell 2001	0	25	0	0	0	25	1	25	0	0	0	25
Dahan 1990	2	50	0	0	0	50	3	50	0	0	0	50
Enoxacan 1997	23[6]	556	1	0	243	556-1=555	16	560	0	0	241	560

(*Continued*)

Kakkar 1997	9	672	7	0	0	671-7=665	15	679	2	0	0	679-2=677
Heilmann 1998	27	179	0	19[7]	0	179-19=160	47	179	0	15	0	179-15=164
McLeod 2001	5	241	0	0	0	241	1	234	0	0	0	234
Onarhein 1986	1	25	0	Not clear	0	25-18/2=16	1	27	0	Not clear	0	27-18/2=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]"9 patients were excluded from the study (5 for HRT, 2 for Chronic liver disease, 2 had mobilization restrictions" (applies for both arms).
[6]"Major haemorrhage was seen in 2.9 per cent (16 of 560) of patients receiving UFH and in 4.1 per cent (23 of 555) of those having enoxaparin" (applies for both arms)
[7]"34 (19 LMWH and 15 UFH) were excluded from the study after randomization because written informed consent was withdrawn by the patients (n=20) or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before the seventh postoperative day." (Applies for 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)	

(*Continued*)

			Pre-trt[3]	Post-trt [4]					Pre-trt	Post-trt			
Enoxacan 1997	81[5]	556	1	0	243	556-1=555	80	560	0	0	241	560	
Heilmann 1998	12	179	0	19[6]	0	179-19=160	28	179	0	15	0	179-15=164	
McLeod 2001	17	241	0	0	0	241	9	234	0	0	0	234	

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]"The incidence of haemorrhage was 17.1 per cent (96 of 560 patients) in the UFH group. Major haemorrhage was seen in 2.9 per cent (16 of 560) of patients receiving UFH" (Table 3 PAGE 1101) (Applies to both arms)
[6]"34 (19 LMWH and 15 UFH) were excluded from the study after randomization because written informed consent was withdrawn by the patients (n=20) or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before the seventh postoperative day." (Applies for both arms)

Outcome: Wound hematoma

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		

(*Continued*)

Baykal 2001	0	47	0	Not clear 9/2[5]	0	47-9/2=42	0	55	0	Not clear 9/2	0	55-9/2=51
Boncinel 2001	2	25	0	0	0	25	2	25	0	0	0	25
Heilmann 1998	18	179	0	19[6]	0	179-19=160	29	179	0	15	0	179-15=164
Kakkar 1997	29	672	7	0	0	672-7=665	52	679	2	0	0	679-2=677
Onarhei 1986	0	25	0	Not clear 18/2	0	25-18/2=16	1	27	0	Not clear 18/2	0	27-18/2=18
Bergqvis 1990	36	311	0	Not clear 38/2[7]	0	311-38/2=292	47	326	0	Not clear 38/2	0	326-38/2=307

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]"9 patients were excluded from the study (5 for HRT, 2 for Chronic liver disease, 2 had mobilization restrictions" (applies for both arms).
[6]"34 (19 LMWH and 15 UFH) were excluded from the study after randomization because written informed consent was withdrawn by the patients (n=20) or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before the seventh postoperative day." (Applies for both arms)
[7]"38 excluded after randomization: 27 because of canceled operations, 4 withdrawal, 7 various other reasons" (applies for both arms).

Outcome: Reoperation for bleeding											
Study Name	**LMWH**					**UFH**					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available	Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available	

(*Continued*)

						out-come data (for CCA) [2]						out-come data (for CCA)	
			Pre-trt[3]	Post-trt[4]					Pre-trt	Post-trt			
Heil-mann 1998	1	179	0	19[5]	0	**179-19= 160**	4	179	0	15	0	**179-15= 164**	
Onarhei 1986	1	25	0	Not clear	0	**25-18/ 2=16**	0	27	0	Not clear	0	**27-18/ 2=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] [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]"34 (19 LMWH and 15 UFH) were excluded from the study after randomization because written informed consent was withdrawn by the patients (n=20) or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before the seventh postoperative day." (Applies for both arms).

Outcome: Intra-operative blood loss

Study Name	**LMWH**							**UFH**						
	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD[1]	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD
					Pre-trt[2]	Post-trt[3]						Pre-trt	Post-trt	
Baykal 2001	915.5	399.9	47	47	0	0	0	798.4	535.3	55	55	0	0	0

(*Continued*)

Dahan 1990	290.8	48.2	48	50	0	0	0	307.5	56.7	46	50	0	0	0
Gallus 1993	573	644	257	257	0	0	0	615	714	256	257	0	1	0
Onarhei 1986	528	479	25	25	0	0	Not clear	646	956	27	27	0	0	Not clear

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]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[3]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

Outcome: Intra-operative transfusion

Study Name	**LMWH**							**UFH**						
	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD[1]	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD
					Pre-trt[2]	Post-trt[3]						Pre-trt	Post-trt	
Dahan 1990	398.7	68.7	41	50	0	0	0	324.4	58.2	43	50	0	0	0

[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]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[3]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

Outcome: Postoperative drain volume

Study Name	LMWH							UFH						
	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD[1]	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD
					Pre-trt[2]	Post-trt[3]						Pre-trt	Post-trt	
Baykal 2001	836.8	533.2	47	47	0	0	0	723.2	543.7	55	55	0	0	0
EFS 1988	478	522	355	355	0	0	0	462	502	349	349	0	0	0

[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]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[3]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

Outcome: Postoperative transfusion

Study Name	**LMWH**							**UFH**						
	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD[1]	mean	SD	Total	No Rand	No most likely to have MPD		No less likely to have MPD
					Pre-trt[2]	Post-trt[3]						Pre-trt	Post-trt	
Da-han 1990	234.2	425	40	50	0	0	0	155.6	36.6	41	50	0	0	0

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]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
[3]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

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		
Enoxacan 1997	3[5]	556	1	243[6]	0	556-1-243= 312	1	560	0	241	0	560-241= 319
Godwin 1993	7	595	0	0	0	595	4	309	0	0	0	309
Heilmann 1998	6	179	0	19[7]	0	179-19=160	4	179	0	15	0	179-15=164
Onarhein 1986	0	25	0	Not clear	0	25-18/2=16	0	27	0	Not clear	0	27-18/2=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] [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]"In three patients receiving UFH and in one receiving enoxaparin, platelet count fell below 70 000 per m1".

[6]"560 were randomized to receive UFH and 556 enoxaparin. 1 patients randomized to enoxaparin did not receive any study medication at all and was excluded from further analysis. Adequate endpoint evaluation was not available in 460 patients. 6 received insufficient prophylaxis according to the protocol and 18 received prohibited concomitant medication. The remainder had inadequate venograms. The evaluable patients population was 631 patients, 319 who received UFH and 312 enoxaparin." (Applies for both arms).
[7]"34 (19 LMWH and 15 UFH) were excluded from the study after randomization because written informed consent was withdrawn by the patients (n=20) or medication errors such as late or no injection of heparin or discontinuation of prophylaxis before the seventh postoperative day." (Applies for both arms)

WHAT'S NEW

Date	Event	Description
25 March 2015	Amended	Standard deviations of intra-operative blood loss outcome for trial Dahan 1990 are corrected.

HISTORY

Review first published: Issue 11, 2011

Date	Event	Description
3 March 2014	New citation required but conclusions have not changed	Data abstraction verified and detailed statistical data included as appendix
3 March 2014	Amended	Data reanalyzed by using a complete case analysis approach for the primary meta-analysis
9 February 2013	New search has been performed	Search updated

CONTRIBUTIONS OF AUTHORS

EAA: protocol development, search for trials, data extraction, data analysis, manuscript drafting, review coordination, funding.LK: screening, data extraction, data analysis.FS: data extraction.IN: screening.NL: data extraction, manuscript drafting.IT: data extraction, data analysis.MB: screening, data extraction.ES: screening, data extraction.PM: data analysis and interpretation, funding.DJC: data analysis and interpretation, methodologic advice.HJS: protocol development, search for trials, screening, data analysis, methodologic advice, funding.

DECLARATIONS OF INTEREST

HJS: no personal payments from for-profit sponsors related to the subject matter since 2011. DJC conducted a peer-review funded trial comparing LMWH with UFH in critically ill patients and received donated study medication (LMWH) from Pfizer.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cochrane Gynaecological Cancer Review Group Update Incentive Award, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans