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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 systematically review the evidence for the relative efficacy and safety of LMWH and UFH for perioperative thromboprophylaxis in patients with cancer.

Search methods

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

Selection criteria

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

Data collection and analysis

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

Main results

Of 8187 identified citations, we included 16 RCTs with 11,847 patients in the meta-analyses, all using preoperative prophylactic anticoagulation. The overall quality of evidence was moderate. The meta-analysis did not conclusively rule out either a beneficial or harmful effect of LMWH compared to UFH for the following outcomes: mortality (RR = 0.90; 95% CI 0.73 to 1.10), symptomatic

DVT (RR = 0.73; 95% CI 0.23 to 2.28), PE (RR = 0.59; 95% CI 0.25 to1.41), minor bleeding (RR = 0.88; 95% CI 0.47 to 1.66) and major bleeding (RR = 0.84; 95% CI 0.52 to 1.36). LMWH was associated with lower incidence of wound hematoma (RR = 0.60; 95% CI 0.43, 0.84) while UFH was associated with higher incidence of intra-operative transfusion (RR = 1.16; 95% CI 0.69,1.62).

Authors' conclusions

We found no difference between perioperative thromboprophylaxis with LMWH verus UFH in their effects on mortality and embolic outcomes in patients with cancer. Further trials are needed to more carefully evaluate the benefits and harms of different heparin thromboprophylaxis strategies in this population.

PLAIN LANGUAGE SUMMARY

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

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 or low molecular weight heparin. These two blood thinners may have different efficacies and safety profiles. In this systematic review, data from 16 trials found no difference between the two types of agents.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

LMWH compared to 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				
Death Follow-up: median 2 weeks	**35 per 1000**	**31 per 1000** (26 to 39)	**RR 0.9** (0.73 to 1.1)	10483 (9 studies)	⊕⊕⊕◯ **moderate**[1]	
PE Follow-up: median 2 weeks	**7 per 1000**	**4 per 1000** (2 to 10)	**RR 0.59** (0.25 to 1.41)	5900 (13 studies)	⊕⊕⊕◯ **moderate**[1]	
DVT (symptomatic) Follow-up: median 2 weeks	**14 per 1000**	**10 per 1000** (3 to 32)	**RR 0.73** (0.23 to 2.28)	1015 (6 studies)	⊕⊕⊕◯ **moderate**[1]	
Major bleeding Follow-up: median 2 weeks	**49 per 1000**	**41 per 1000** (25 to 67)	**RR 0.84** (0.52 to 1.36)	3441 (7 studies)	⊕⊕⊕◯ **moderate**[1]	
Wound hematoma Follow-up: median 2 weeks	**94 per 1000**	**56 per 1000** (40 to 79)	**RR 0.6** (0.43 to 0.84)	1777 (4 studies)	⊕⊕⊕◯ **moderate**[2]	

Thrombocytopenia Follow-up: median 2 weeks	**16 per 1000**	**19 per 1000** (8 to 45)	**RR 1.18** (0.49 to 2.81)	1280 (3 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; **RR:** Risk ratio;

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

[1] The 95% CI includes both negligible effect and appreciable benefit or appreciable 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) (venous thrombosis (DVT) and/or pulmonary embolism (PE)) than patients without cancer (Kakkar 1970; Galus 1997; 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; Galus 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 deep venous thrombosis DVT and PE and subsequently reduce the incidence of VTE associated mortality (Barritt 1960). At the same time they increase the risk of bleeding which might be potentiated by the presence of surgical wounds.

Why it is important to do this review

The American College of Chest Physicians (ACCP) recommends that patients with cancer undergoing surgical interventions receive thromboprophylaxis "that is appropriate for their current risk state" which includes the type of surgical intervention (Geerts 2004) Two systematic reviews found that in patients undergoing colorectal or general surgery respectively, heparins are superior to no anticoagulation in the prevention of DVT and PE (Boryl 2005; Mismetti 2001). 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.

OBJECTIVES

To compare 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

Types of interventions

Experimental intervention: Low Molecular Weight Heparin (LMWH)
Comparator intervention: Unfractionated Heparin (UFH)
The protocol should have planned to provide all other co-interventions similarly in the intervention and comparison group.

Types of outcome measures

The outcome measures did not constitute criteria for including studies.

Primary outcomes

- All cause mortality

Secondary outcomes

- Symptomatic PE
- Symptomatic DVT
- Asymptomatic DVT
- Bleeding outcomes:
- Major bleeding
- Minor bleeding
- Wound hematoma
- Reoperation for bleeding
- 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 did not use language restrictions. We electronically searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1), MEDLINE (1966 to February 2010; accessed via Ovid), EMBASE (1980 to February 2010; accessed via Ovid), and ISI Web of Science (February 2010). The search strategies combined terms relating to the anticoagulants, cancer, and study design. We list the search strategies in Appendix 1.

Searching other resources

We hand-searched the conference proceedings of the American Society of Clinical Oncology (ASCO) (starting with its first volume, 1982) and American Society of Hematology (ASH) (starting with its 2003 issue). We reviewed the reference lists of reports included this review and of other relevant systematic reviews. We used the related article feature in PubMed to identify additional articles.

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 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 data related to:

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
- Co-interventions including radiotherapy, chemotherapy, and hormonal therapy (type and duration)
- History of VTE
- Use of indwelling central venous catheters

Interventions

- Type of anticoagulant: UFH or LMWH
- Dose: prophylactic versus therapeutic
- Duration of treatment

Outcomes

We attempted to extract both time to event data (for all cause mortality) and categorical data (for all outcomes). However, none of the reported time to event data for patients with cancer. For categorical data, we extracted the reported outcome data necessary to conduct intention-to-treat analyses. For continuous data we extracted mean and standard deviation separately for each arm. We attempted to contact authors for incompletely reported data. We determined a priori to consider abstracts only if authors supplied us with full reports of their methods and results.

Assessment of risk of bias in included studies

First, we assessed risk of bias at the trial level using the Cochrane risk of bias tool. Two review authors independently assessed the risk of bias for each included trial and resolved their 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 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 intention-to-treat (ITT) principle

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

Measures of treatment effect

We analyzed hazard ratios (HRs) for time to event data, risk ratios (RRs) for categorical data, and standardized mean difference (SMD) for continuous data.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We analyzed the available data assuming that any data that could be missing were missing at random

Assessment of heterogeneity

Heterogeneity among trials was assessed by visual inspection of forest plots, estimation of the percentage heterogeneity among trials which cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (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 meta-analysis of the primary outcome. These plots did not suggest that treatment effects may not have been sampled from a symmetric distribution, as assumed by the random effects model, so further meta-analyses were not performed using fixed effects models.

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 is 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.

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 analysis because of the relatively small number of trials and the inclusion of different types of cancer in the same trial.

Sensitivity analysis

We did not conduct any sensitivity analyses.

RESULTS

Description of studies

Results of the search

The February 2010 search strategy identified a total of 8187 citations. In total, the title and abstract screening identified 32 potentially eligible citations. The full text screening of the 44 citations identified 16 eligible trials.

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; Heilmann 1998; Heilmann 1998; McLeod 2001; Onarheim 1986; von Tempelhoff 1997; von Tempelhoff 2000; Haas 2005; Kakkar 1997). One of these trials was published as an abstract (Godwin 1993).

Design of studies:

All included studies consisted of RCTs.

Patient characteristics:

Trials were conducted in patients with cancer undergoing the following types of surgery: gynaecological (n = 4) (Baykal 2001; Heilmann 1998; von Tempelhoff 1997; von Tempelhoff 2000), abdominal or pelvic (n = 7) (Bergqvist 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Godwin 1993; McLeod 2001; Onarheim 1986), thoracic (n = 1) (Dahan 1990), abdominal or thoracic (n= 1) (Gallus 1993), prostate (n = 1) (Boncinelli 2001), and unspecified (n = 2) (Haas 2005; Kakkar 1997). Mean age of participants varied from 51 to 71 across included trials.

Interventions:

Types of LMWH studied were: exnoxaparin (n = 2: Baykal 2001; Enoxacan 1997); dalteparin (n = 3: Bergqvist 1990; Fricker 1988; Onarheim 1986); nadroxiparin (n = 2: Boncinelli 2001; Dahan 1990); fraxiparin (n = 1: EFS 1988); orgaran (n = 1: Gallus 1993); normiflo (n = 1: Godwin 1993); certoparin (n = 2: Haas 2005; Heilmann 1998); and not specified (n = 4: Kakkar 1997; McLeod 2001; von Tempelhoff 1997; von Tempelhoff 2000). All trials started thromboprophylaxis preoperatively.

Outcomes:

- Nine trials reported on death (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).

- Six trials reported on symptomatic DVT (Baykal 2001; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Fricker 1988; 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).
- Three trials reported on minor bleeding (Enoxacan 1997; Heilmann 1998; McLeod 2001).
- Seven trials reported on major bleeding (Boncinelli 2001; Dahan 1990; Enoxacan 1997; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986).
- Four trials reported on wound hematoma (Boncinelli 2001; Heilmann 1998; Kakkar 1997; Onarheim 1986).
- Two trials reported on re-operation for bleeding (Heilmann 1998; Onarheim 1986).
- Three trials reported on thrombocytopenia (Godwin 1993; Heilmann 1998; Onarheim 1986).
- None of the trials reported on heparin-induced thrombocytopenia (HIT).

Excluded studies

We excluded 28 trials from this review. Of these 28 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 (n = 5); comparison was between UFH and no anticoagulation (n = 6); comparison was between 2 weeks of LMWH and 4 weeks of LMWH (n = 2); comparison of 2 different doses of heparin (n = 2); and data for the outcome of interest not available from report or author (n = 1).

Risk of bias in included studies

Figure 1 presents the risk of bias graph while Figure 2 presents the risk of bias summary associated with the outcomes: death, PE, DVT and major bleeding.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

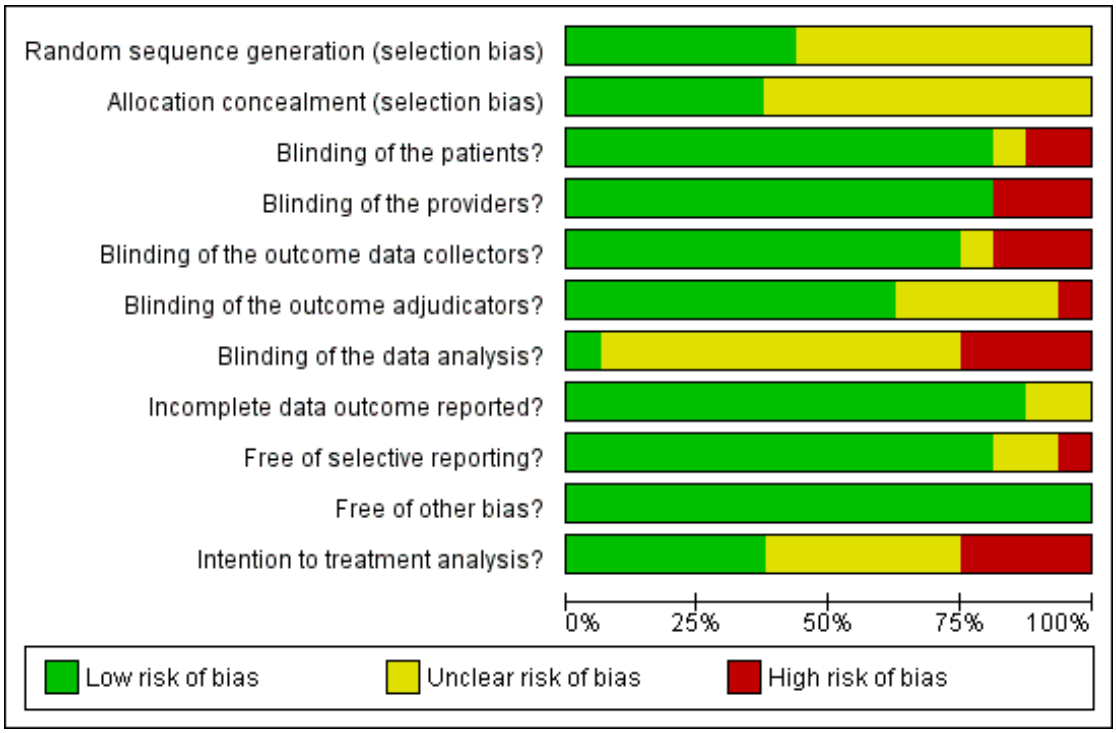
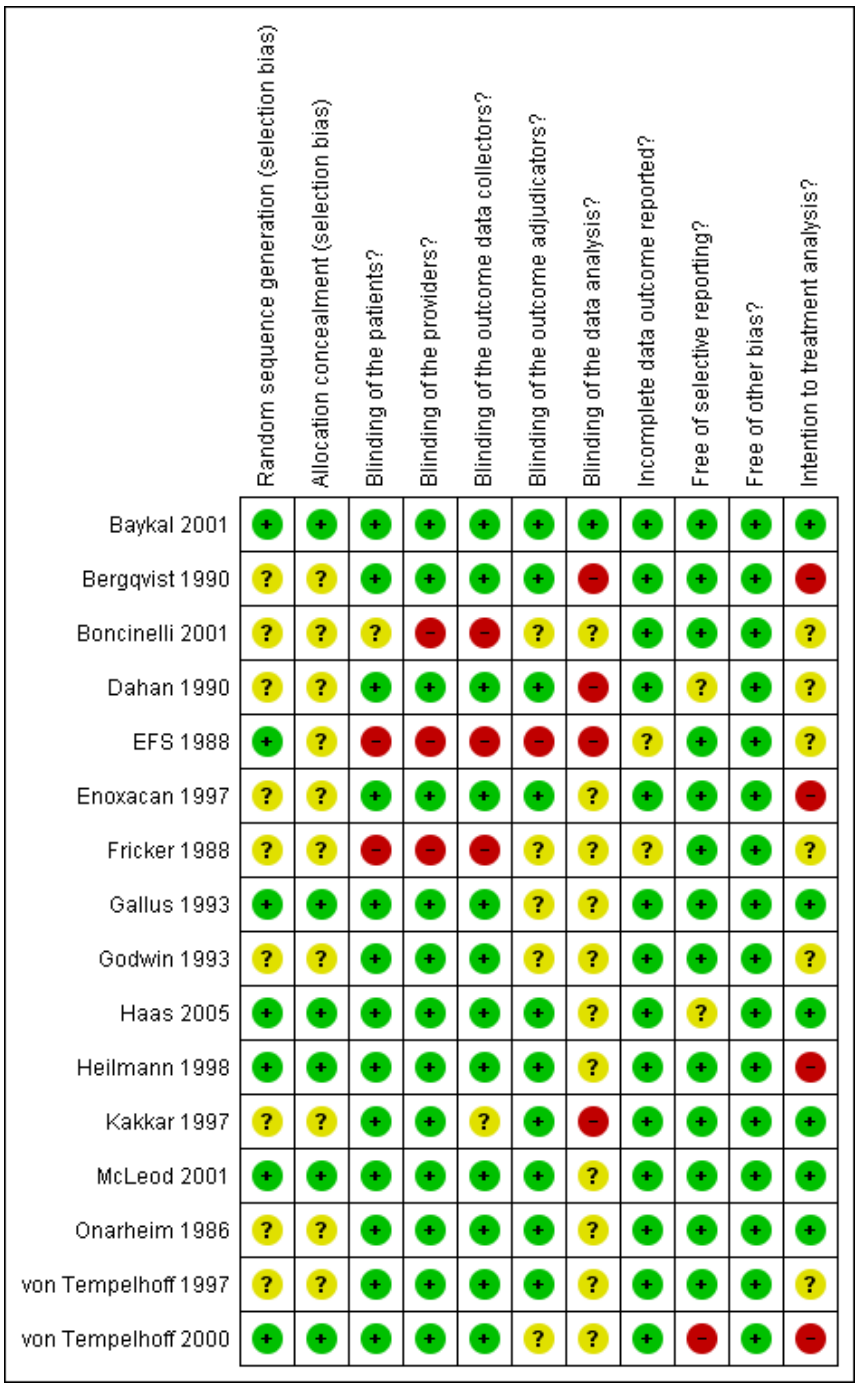


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation was unclear in seven 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, Heilmann 1998, McLeod 2001, von Tempelhoff 2000; Haas 2005). Allocation was not reported in 10 trials (Bergqvist 1990; Boncinelli 2001; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Onarheim 1986; von Tempelhoff 1997; Kakkar 1997; Godwin 1993)

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 (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 (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 (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 rest of trials.

Incomplete outcome data

Follow-up 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 suffered from 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 of insufficient recruitment and not to benefit.

Six trials reported adhering to the ITT principle (Baykal 2001; Gallus 1993; McLeod 2001; Onarheim 1986; Haas 2005; Kakkar 1997); 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 to UFH for perioperative thromboprophylaxis in patients with cancer

Death

Meta-analysis of nine trials (Baykal 2001; Bergqvist 1990; Enoxacan 1997;Gallus 1993; Haas 2005;Heilmann 1998; Kakkar 1997;Onarheim 1986;von Tempelhoff 2000) assessing 10,483 patients did not conclusively rule out a mortality reduction with LMWH compared to UFH (RR = 0.90; 95% CI 0.73 to 1.10): 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%) (Figure 3). The inverted funnel plot suggested no publication bias (Figure 4). The quality of evidence was moderate (Summary of findings for the main comparison).

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

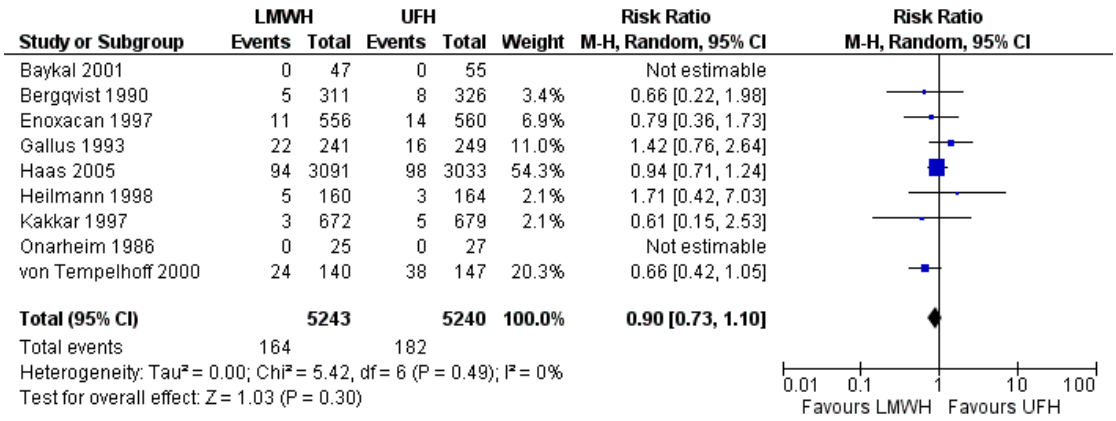
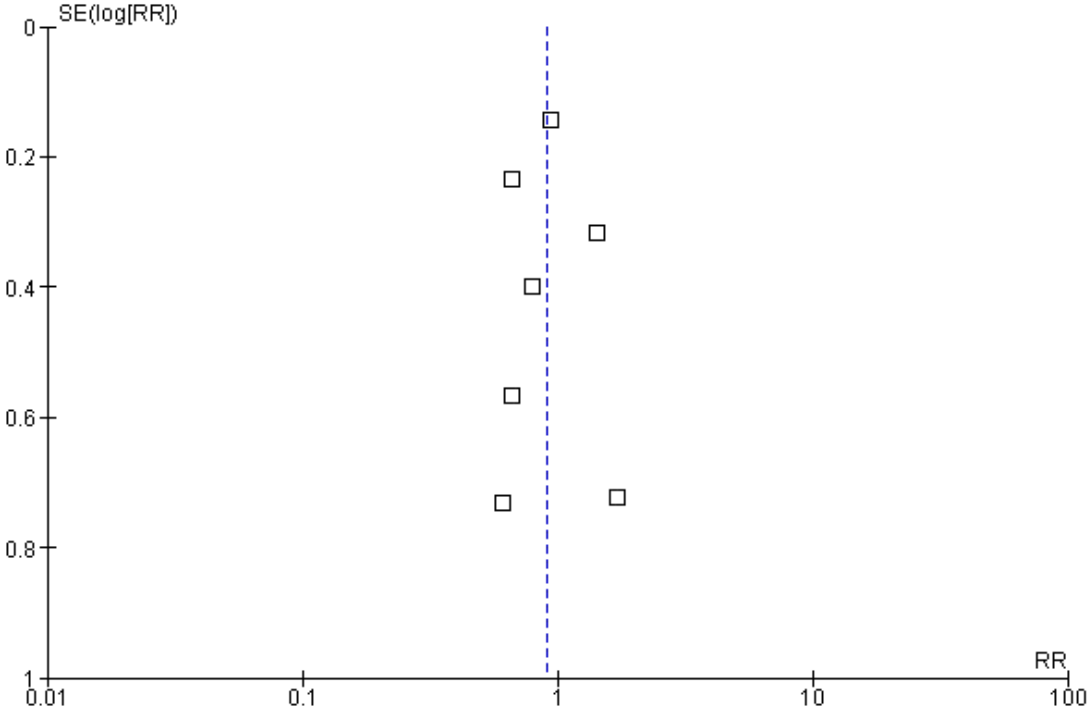


Figure 4. Funnel plot of comparison: 1 LMWH vs UFH, outcome: 1.1 Death.



PE

Meta-analysis of thirteen trials (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) assessing 5,900 patients did not conclusively rule out a decrease in PE or increase with LMWH compared to UFH (RR = 0.59; 95% CI 0.25 to 1.41); the per-

centage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important (I^2 =17%).

Symptomatic DVT

Meta-analysis of six trials reported on this outcome (Baykal 2001; Boncinelli 2001; Dahan 1990; Enoxacan 1997; Fricker 1988; Onarheim 1986) assessing 1,015 patients did not conclusively rule out a symptomatic DVT reduction or increase with LMWH compared to UFH (RR= 0.73; 95% 0.23, 2.28); 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%). The quality of evidence was moderate (Summary of findings for the main comparison).

Asymptomatic DVT

Meta-analysis of eleven trials (Bergqvist 1990; Dahan 1990; EFS 1988; Enoxacan 1997; Fricker 1988; Gallus 1993; Godwin 1993; Kakkar 1997; McLeod 2001; Onarheim 1986; von Tempelhoff 1997) assessing 2333 patients showed a reduction in asymptomatic DVT with LMWH compared to UFH (RR = 0.8; 95% CI 0.65 to 0.99); 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 =2%).

Minor bleeding

Meta-analysis of three trials (Enoxacan 1997; Heilmann 1998; McLeod 2001) assessing 1,888 patients did not conclusively rule out a reduction or increase with LMWH compared to UFH (RR = 0.88; 95% CI 0.47 to 1.66); 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 =75%).

Major bleeding

Meta-analysis of seven trials (Boncinelli 2001; Dahan 1990; Enoxacan 1997; Heilmann 1998; Kakkar 1997; McLeod 2001; Onarheim 1986) assessing 3441 patients did not conclusively rule out a reduction or increase with LMWH compared to UFH (RR = 0.84; 95% CI 0.52 to 1.36); 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 = 34%). The quality of evidence was moderate (Summary of findings for the main comparison).

Would hematoma

Meta-analysis of four trials (Boncinelli 2001;Heilmann 1998; Kakkar 1997; Onarheim 1986)assessing 1777 patients showed a reduction with LMWH compared to UFH (RR = 0.6; 95% CI 0.43 to 0.84); 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%). The quality of evidence was moderate (Summary of findings for the main comparison).

Re-operation for bleeding

Meta-analysis of two trials Heilmann 1998; Onarheim 1986) assessing 376 patients did not conclusively rule out a reduction or increase with LMWH compared to UFH (RR = 0.70; 95% CI 0.06 to 7.89); 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 = 40%). The quality of evidence was low (Summary of findings for the main comparison).

Intra-operative blood loss

Meta-analysis of four trials (Baykal 2001; Dahan 1990; Gallus 1993; Onarheim 1986) assessing 761 patients found no difference in effect with LMWH compared to UFH (MD = -0.16; 95% CI to 0.37 to 5).

Intra-operative transfusion

One trial (Dahan 1990) assessing 84 patients found that the intra-operative transfusion volume was higher with LMWH compared to UFH (MD = 74; 95% CI 47 to 102).

Post-operative drain volume

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

Post-operative transfusion

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

Thrombocytopenia

Meta-analysis of three trials (Godwin 1993; Heilmann 1998; Onarheim 1986) assessing 1280 patients did not conclusively rule out a thrombocytopenia reduction or increase with LMWH compared to UFH (RR = 1.18; 95% CI 0.49 to 2.81). The quality of evidence was low (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

The meta-analysis of 16 trials with 11,847 patients did not conclusively rule out either beneficial or harmful effect of LMWH compared to 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 UFH was associated with higher incidence of intra-operative 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 post-operatively. However, a systematic review did not find statistically significant differences in the amount of blood loss when the first dose of enoxaparin is administered 12 hours before surgery versus post-operatively (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 bias the results of 10 included trial. 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 vs. 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 cancer patients as subgroups but did not report on their outcome data. The cancer subgroups in these trials included 3185 participants, compared to 5822 participants included in the current analysis. This may introduce 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 follow-up periods in the same trials precluded us from conducting the subgroup analyses to explore effect modifiers.

Agreements and disagreements with other studies or reviews

A systematic review of thromboprophylaxis in colorectal surgery found no differences between LMWH and UFH in their effects on preventing DVT and/or PE (odds ratio = 1.01; 95% CI 0.67 to 1.52)(Boryl 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 2 trials prospectively examined HIT and reported a total of 10 events (all in the UFH group). The meta-analysis found an odds ratio (OR) of 0.10 (95% CI, 0.01 to 0.82) for HIT and of 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 agent 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.

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 a number of trials assessed surrogate outcome (asymptomatic DVT) instead of patient important outcomes such as DVT and PE. Researchers can use these results to plan additional number of randomized trials to either exclude or confirm a superiority of one of the 2 agents 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	Randomised double blind trial
Participants	102 patients undergoing surgery for gynaecological malignancy, minimum age of age 40 yrs, mean age 57 years
Interventions	Intervention:Enoxaparin 2500 U 2h preoperatively then once daily Control: UFH 5000 U three times daily
Outcomes	Death, DVT, PE, Intraoperative bleeding, Catheter drainage No screening test was used for diagnosing DVT.
Notes	Funded by Eczacibasi-Rhoune 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
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

Baykal 2001 (*Continued*)

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	Randomised double blind trial
Participants	637 patients with cancer undergoing abdominal surgery (study subgroup); minimum age of 40 years, mean age of 71 years
Interventions	Intervention: Dalteparin 5000 U 10 PM preoperatively then daily x 5-8 days Control: UFH 5000 U 2h preoperatively then twice daily x 5-8 days
Outcomes	DVT, pulmonary embolism, haemorrhage, death Screening of postoperative DVT was done for 7 days with radiolabeled fibrinogen uptake test
Notes	Funded by 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" Comment: unclear
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of the patients?	Low risk	Quote: "randomised double blind multicenter trial" Comment: probably yes
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	96% follow up

Bergqvist 1990 (*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?	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	Randomised trial
Participants	50 patient were undergoing prostatectomy for prostate cancer,minimum age of 40 years, mean age of 60
Interventions	Intervention:0.3ml of calcium nadroparin given as single daily SQ injection Control: UFH given at dose of 5000 units SQ three times daily In both groups prophylaxis began preoperatively and maintained throughout the hospital stay (mean 15 days)
Outcomes	DVT, pulmonary embolism, major bleeding, hematoma, in the postoperative period No scheduled Doppler Ultrasonic surveillance was used
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" Comment: unclear
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

Boncinelli 2001 (*Continued*)

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	100% follow up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention to treatment analysis?	Unclear risk	Comment: not reported

Dahan 1990

Methods	Randomised trial
Participants	100 patients undergoing cancer thoracic surgery; age>18 years,mean age 59 years
Interventions	Intervention: Nadroparin 7500 U 12 h preoperatively and 12 h postoperatively until the 2^{nd} postoperative day then 10,000 U once daily on postoperative days 3 to 7 Control: UFH 5000 U 2 h preoperatively and 12 h postoperatively then thrice daily until the 2^{nd} postoperative day then a dose adjusted to APTT on postoperative days 3 to 7 twice daily
Outcomes	DVT, pulmonary embolism, perioperative bleeding and postoperative bleeding Patients were screened with 125 I-fibrinogen uptake test
Notes	Funding source not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized study" Comment: unclear
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

Dahan 1990 (*Continued*)

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	100% follow up
Free of selective reporting?	Unclear risk	Study not registered. No published protocol. No outcomes listed in the methods section Comment: unclear
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	Randomised trial
Participants	704 patients with cancer (study subgroup) scheduled for elective abdominal surgery, minimum age of 40 years, mean age of 61 years
Interventions	Intervention: Fraxiparin 7500 anti-Xa units given subcutaneously Control: Calcium heparin 5000 units three times daily Treatment was initiated 2 h before surgery, the second injection was given 8hr after surgery. Subsequent injections were given every 24 h between 07.00 and 10.00 hours from the first to the seventh postoperative day
Outcomes	DVT, asymptomatic DVT, pulmonary embolism, haemorrhage, death The patients had radio labelled iodine fibrinogen leg scanning on the day of the surgery and then daily for seven consecutive days

EFS 1988 (*Continued*)

Notes	Funded by Sanofi Labaz, GmbH, Pharmzeutische Praparate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patient were assigned to treatment with either Fraxiparin or calcium heparin following randomised schedule " Comment: yes
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
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?	Unclear risk	99% follow up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention to treatment analysis?	Unclear risk	Comment: not reported

Enoxacan 1997

Methods	Double blind randomised trial
Participants	631 patients undergoing planned curative abdominal or pelvic surgery for cancer (study subgroup). Minimum age of 40 years old. Mean age of 68.5 years
Interventions	Intervention: enoxaparin 40 mg once daily started 2 hours before the surgery Control: low dose of unfractionated heparin three times daily

Enoxacan 1997 (*Continued*)

Outcomes	DVT only, asymptomatic DVT, Pulmonary embolism plus DVT, Haemorrhage, death at 3 months interval Scheduled bilateral ascending venography was performed 24 hours after the last injection of the trial substance
Notes	Funded by Swedish medical research grant

Risk of bias

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" Comment: unclear
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?	Low risk	100% follow up 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
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"

Enoxacan 1997 (*Continued*)

		"these patients were included in the analysis as they have been randomised " Comment: probably no

Fricker 1988

Methods	Randomised trial
Participants	80 patients with cancer undergoing surgery for abdominal and pelvic malignancy, minimum age of 40 years,mean age of 57.6, 93% female
Interventions	Intervention: 2500 anti-Xa Units 2 h before surgery and 12 h after the first injection and then 5000 anti-Xa Units fragmin injection every morning for 10 days Control: patients received a 5000 IU of calcium heparin injection 2 h before the surgery and then at 8-h intervals for the next 10 days
Outcomes	DVT, Asymptomatic DVT, pulmonary embolism, Haemorrhage Radio-labelled fibrinogen tests was used for postoperative screening of DVT
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" Comment: unclear
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

Fricker 1988 (*Continued*)

Incomplete data outcome reported?	Unclear 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
Intention to treatment analysis?	Unclear risk	Comment: not reported

Gallus 1993

Methods	Double blind randomised trial
Participants	514 patients undergoing abdominal or thoracic cancer surgery, minimum age of 40, mean age of 65 years
Interventions	Intervention: Orgaran 750 U 1-2h preoperatively then at 12 h intervals x 6 days Control: UFH 5000 U 1-2h preoperatively then at 12h intervals x 6 days
Outcomes	DVT, pulmonary embolism, Haemorrhage, death Radio -labelled fibrinogen tests was used for screening of postoperative DVT every second day on the week days
Notes	Funded by 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" Comment: yes
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" Comment: yes
Blinding of the patients?	Low risk	Quote: "double blind multicenter trial" Comment: probably yes

Gallus 1993 (*Continued*)

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	95% follow up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention to treatment analysis?	Low risk	Quote: "intent to treat analysis showed statistically non-significant toward trend towards less VT during Orgaran prophylaxis" Comment: probably yes

Godwin 1993

Methods	Double blind randomised trial	
Participants	904 patients undergoing abdominal or pelvic cancer surgery	
Interventions	Intervention: RDH (Normiflo) 50 U 2h preoperatively and then 90 U once or twice daily Control: UFH 5000 U 2h preoperatively and then 5000 U twice daily	
Outcomes	DVT, pulmonary embolism, bleeding, death Patients were screened for DVT preoperatively by non -invasive venous tests, either impedence plethysmography or duplex ultra sound scan	
Notes	KabiVitrum funded the study	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Godwin 1993 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "a total of 904 patients were randomised into three groups" Comment: unclear
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	89% follow up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention to treatment analysis?	Unclear risk	Comment: not reported

Haas 2005

Methods	Double blind randomised control trial
Participants	6124 patient with cancer undergoing cancer surgery, minimum age of 40 years, mean age 62
Interventions	Intervention: LMWH Certoparin 3000 anti- Xa IU, subcutaneously, once-daily Control: UFH (5000 IU), administered subcutaneously three-times daily
Outcomes	Death, pulmonary embolism, bleeding complications (Wound hematoma; Post-operative wound bleeding; Gastric bleeding)
Notes	Funded by: Novartis Pharma GmbH, Nürnberg, Germany
Risk of bias	

Haas 2005 (*Continued*)

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" Comment: yes
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised to one of two treatment groups using a centralised computer generated randomizations list " Comment: yes
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" 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	100% f/u for mortality; 70% f/u 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 power- ed to show superiority of Certoparin over UFH"

Haas 2005 (*Continued*)

		Comment: probably no
Intention to treatment analysis?	Low risk	Quote: "The analyses included all randomised patients (intention-to-treat)" Comment: yes

Heilmann 1998

Methods	Double blind randomised trial
Participants	358 patients undergoing breast and pelvic cancer surgery, minimum age of 40
Interventions	Intervention: Certoparin 3000 U 2-5h preoperatively then once daily x 7 days Control: UFH 5000 U 2-5h preoperatively then thrice daily x 7 days
Outcomes	DVT, pulmonary embolism, major bleeding, minor bleeding, wound hematoma, reoperation for hematoma Patient underwent scheduled impedence plethysmography on postoperative days 1, 3, 5, 7, and 10
Notes	Funding source: 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 labelled with trial code number and contained sufficient drug for 10 days" Comment: yes
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

Heilmann 1998 (*Continued*)

Blinding of the data analysis?	Unclear risk	Comment: not reported
Incomplete data outcome reported?	Low risk	91% follow up
Free of selective reporting?	Low risk	Study not registered. No published protocol. All relevant outcomes listed in the methods section are reported on Comment: probably yes
Free of other bias?	Low risk	Study not reported as stopped early for benefit Comment: probably yes
Intention to treatment analysis?	High risk	Quote: "a total of 358 patients were entered into the trial of whom 34 (9.5%) were exclude after randomisation 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	Double blind randomised trial
Participants	706 patient with an underlying malignancy (out of a total of 1351 patients (52%)) undergoing surgery, minimum age of 40 years, mean age of 59.6
Interventions	Intervention: LMWH 1750 anti-Xa IU administered subcutaneously (SC) once daily with a second injection of saline (placebo) 12 hours later Control: UFH 5000 IU SC every 12 hours Treatment commenced 2 hours prior to surgery followed by a second injection 8 hours postoperatively and continued for at least 5 days (longer if the patient was still confined to bed)
Outcomes	Death, DVT, PE, Bleeding complications, Wound hematoma, wound complications (hematoma; oozing; bruising), Injection site complications (Hemorrhage; Hypersensitivity ;Inflammation ;Pain) Scheduled radioactive fibrinogen uptake test was done daily for DVT screening
Notes	Funded by Knoll AG, Germany

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated" Comment: unclear

Kakkar 1997 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: not reported
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?	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 analyzed 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" Coomment: yes

McLeod 2001

Methods	Randomised double blind trial
Participants	475 patients with cancer undergoing colorectal cancer surgery, mean age of 51 years
Interventions	Intervention: 40mg of LMWH (100 antifactor Xa units per milligram) subcutaneously once daily in the morning plus two placebo injections Control: 5,000 units of calcium heparin every 8 hours Prophylaxis was initiated 2h before the surgery and one further injection (heparin or placebo) at 8pm at the day of the surgery. Thereafter, patients received three injections daily for up to 10 days

Outcomes	DVT, asymptomatic DVT, pulmonary embolism, major bleeding and minor bleeding Scheduled bilateral ascending contrast venography was done on or before post-operative day 9
Notes	Funded by Rhone-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" Comment: yes
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 Comment: probably yes

McLeod 2001 (*Continued*)

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	Randomised double blind trial
Participants	52 patients undergoing surgery for abdominal malignancy, minimum age of 40 years, mean age of 70.35 years
Interventions	Intervention: Dalteparin 5000 U 2h preoperatively then once daily x 6 days Control: Heparin Kabi 2165 5000 U 2h preoperatively then twice daily x 6 days
Outcomes	Death, DVT, pulmonary embolism, major bleeding, wound hematoma thrombocytopenia Radioactive firbrinogen uptake test was used for DVT screening and was performed preoperatively and then daily or every second day for at least 7 postoperative days
Notes	Funded by 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)" Comment: unclear
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
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

Onarheim 1986 (*Continued*)

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	Randomised trial	
Participants	60 patient with ovarian cancer undergoing surgery and chemotherapy, mean age 56.7	
Interventions	Intervention: 3000anti-Xa units/day of LMWH plus 2 placebo injections Control: 5000 IU/day of UFH three times a day. Prohylaxis begins was begun 2 h before operation and continued until the 7th postoperative day	
Outcomes	DVT, asymptomatic DVT. Impedance plethysmography was used for DVT screening on days 1, 3, 5, 7 and10	
Notes	Not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

von Tempelhoff 1997 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "all patients were eligible for surgery and randomised to receive either daily LMWH or UFH" Comment: unclear
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
Intention to treatment analysis?	Unclear risk	Comment: not reported

von Tempelhoff 2000

Methods	Randomised double blind trial
Participants	350 patients with either histologically confirmed carcinoma of the breast, endometrium, vulva or vagina, or with suspected ovarian malignancy were included, minimum age of 40, mean age of 61 years
Interventions	Intervention: LMW heparin given at a dose of 3,000 anti-Xa units subcutaneously once daily in combination with 2 placebo injections (0.9% NaCl) Control: the patient were assigned to thrombosis prophylaxis with UF heparin received

von Tempelhoff 2000 (*Continued*)

	5,000 IU subcutaneously three times daily Intial injection was given 2h before the surgery always contained active drug. In both treatment arms study medication was given at 8h interval until 7th postoperative day
Outcomes	Death. The one relevant outcome listed in the methods section is reported on
Notes	Funded by 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" Comment: yes
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?	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

von Tempelhoff 2000 (*Continued*)

Intention to treatment analysis?	High risk	Quote: "patients were not randomised according to intention to treat principle" Comment: probably no

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

Study	Reason for exclusion
Arbeit 1981	Comparison is not of interest: UFH vs no anticoagulant
Azorin 1997	Comparsion is 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	Comparsion is not of interest: LMWH (4weeks) vs LMWH (1week)
Boneu 1993	Study included patients with cancer as a subgroup for which outcome data were not available
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	Comparisonn is not of interest: UFH vs no anticoagulant
Cade 1983	Comparison is 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	Comparsion is not of interest: LMWH vs no anticoagulant
Clark-Pearson 1990 a	Comparsion is not of interest: UFH vs no anticoagulant
Clark-Pearson 1990 b	Comparison is not of interest: comparison between two doses of UFH
Clarke-Pearson 1983	Comparsion is not of interest: UFH vs no anticoagulant
Dickinson 1998	Comparsion is not of interest: LMWH vs no anticoagulant
Gondret 1995	Comparsion is not of interest: LMWH vs no anticoagulant
Ho 1999	Comparsion is not interest: LMWH vs no anticoagulant
Kakkar 1989	Study included patients with cancer as a subgroup for which outcome data were not available

(*Continued*)

Kakkar 1985	Study included patients with cancer as a subgroup for which outcome data were not available
Liezorovicz A 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	Comparsion is not interest: LMWH vs no anticoagulant
Nurmohamed 1995	Data for the outcome of interest not available from report or author
Rasmussen 2003	Comparsion is not of interest: LMWH (4weeks) vs LMWH (1week)
Samama 1988	Study included patients with cancer as a subgroup for which outcome data were not available
Shukla 2008	Comparsion is not interest: LMWH vs no anticoagulant
Ward 1998	Study included patients with cancer as a subgroup for which outcome data were not available

DATA AND ANALYSES

Comparison 1. LMWH vs UFH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	9	10483	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.10]
2 PE	13	5900	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.25, 1.41]
3 DVT (symptomatic)	6	1015	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.23, 2.28]
4 DVT (asymptomatic)	11	5333	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
5 Minor bleeding	3	1888	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.47, 1.66]
6 Major bleeding	7	3441	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.52, 1.36]
7 Wound hematoma	4	1777	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.43, 0.84]
8 Reoperation for bleeding	2	376	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.06, 7.89]
9 Intra-operative blood loss	4	761	Mean Difference (IV, Random, 95% CI)	-16.01 [-36.82, 4.80]
10 Intra-operative transfusion	1	84	Mean Difference (IV, Random, 95% CI)	74.30 [47.01, 101.59]
11 Postoperative drain volume	2	806	Mean Difference (IV, Random, 95% CI)	27.26 [-43.89, 98.41]
12 Post-operative transfusion	1	81	Mean Difference (IV, Random, 95% CI)	78.6 [-53.58, 210.78]
13 Thrombocytopenia	3	1280	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.49, 2.81]

Analysis 1.1. Comparison 1 LMWH vs UFH, Outcome 1 Death.

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

Comparison: 1 LMWH vs UFH

Outcome: 1 Death

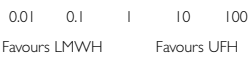
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baykal 2001	0/47	0/55			Not estimable
Bergqvist 1990	5/311	8/326		3.4 %	0.66 [0.22, 1.98]
Enoxacan 1997	11/556	14/560		6.9 %	0.79 [0.36, 1.73]
Gallus 1993	22/241	16/249		11.0 %	1.42 [0.76, 2.64]
Haas 2005	94/3091	98/3033		54.3 %	0.94 [0.71, 1.24]
Heilmann 1998	5/160	3/164		2.1 %	1.71 [0.42, 7.03]
Kakkar 1997	3/672	5/679		2.1 %	0.61 [0.15, 2.53]
Onarheim 1986	0/25	0/27			Not estimable
von Tempelhoff 2000	24/140	38/147		20.3 %	0.66 [0.42, 1.05]
Total (95% CI)	**5243**	**5240**		**100.0 %**	**0.90 [0.73, 1.10]**

Total events: 164 (LMWH), 182 (UFH)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.42$, df = 6 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

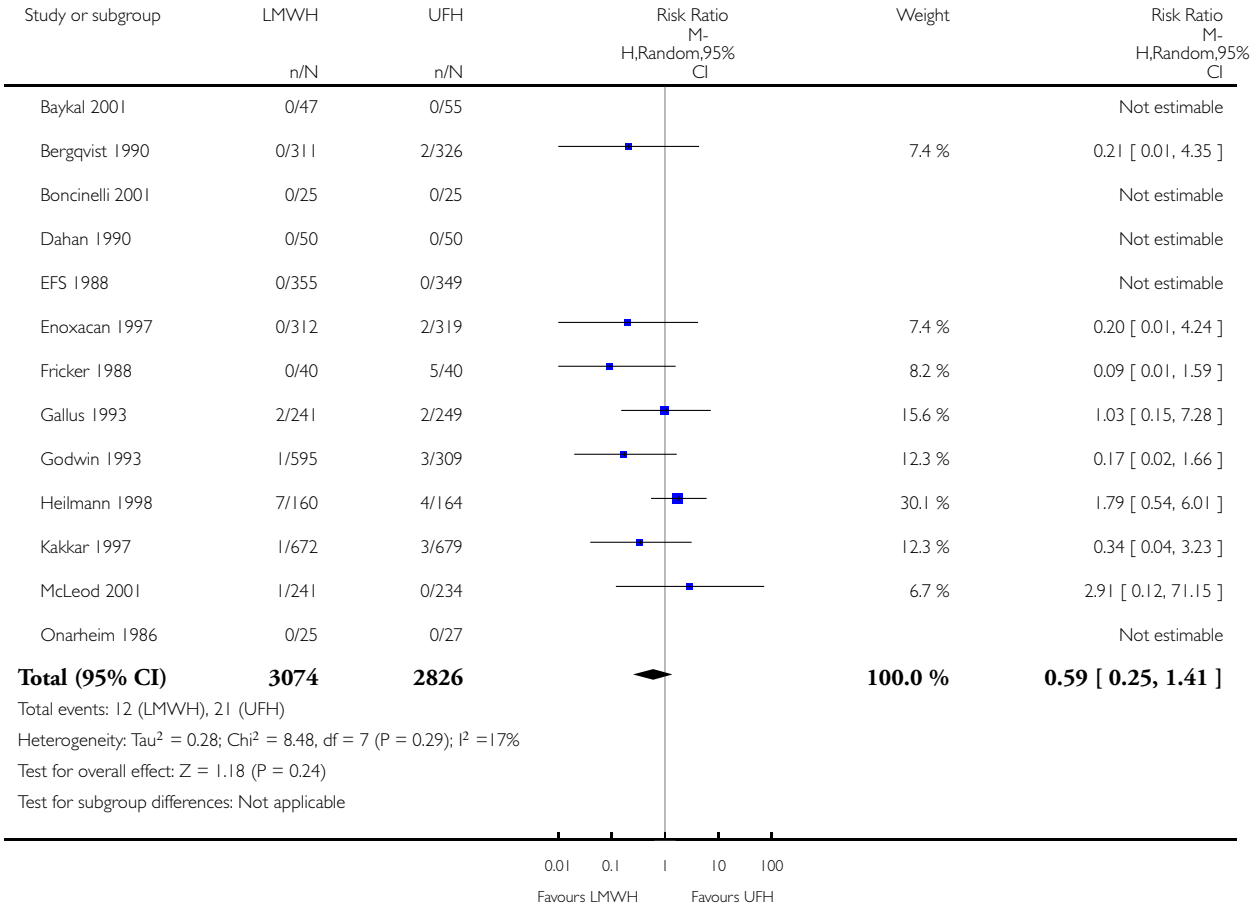


Analysis 1.2. Comparison 1 LMWH vs UFH, Outcome 2 PE.

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

Comparison: 1 LMWH vs UFH

Outcome: 2 PE

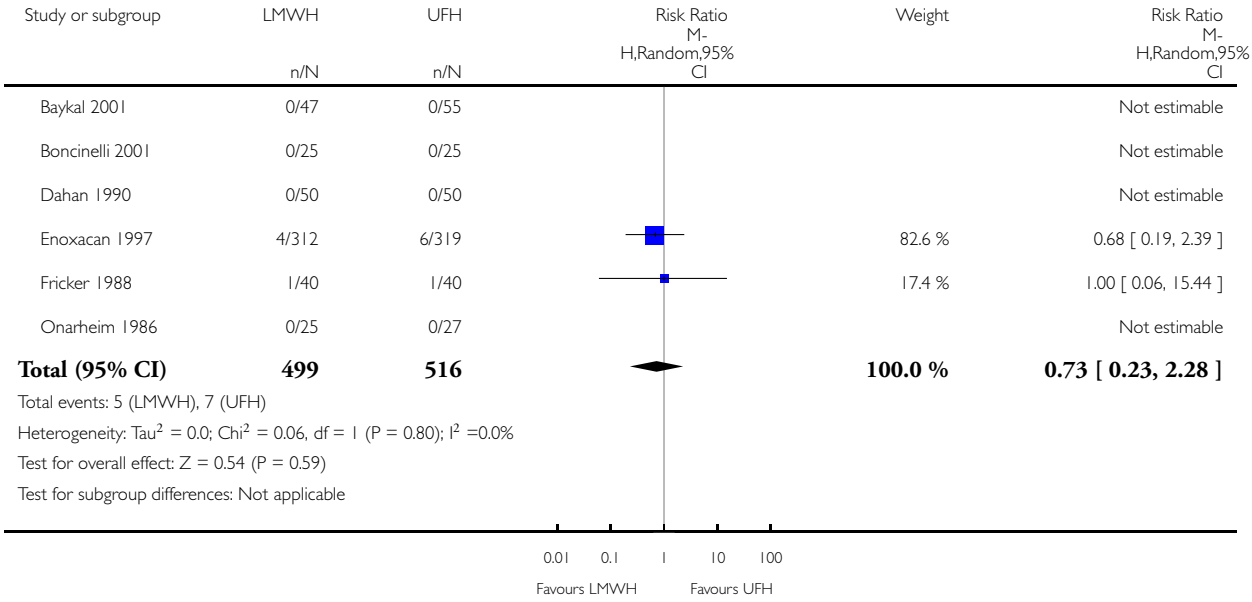


Analysis 1.3. Comparison 1 LMWH vs UFH, Outcome 3 DVT (symptomatic).

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

Comparison: 1 LMWH vs UFH

Outcome: 3 DVT (symptomatic)

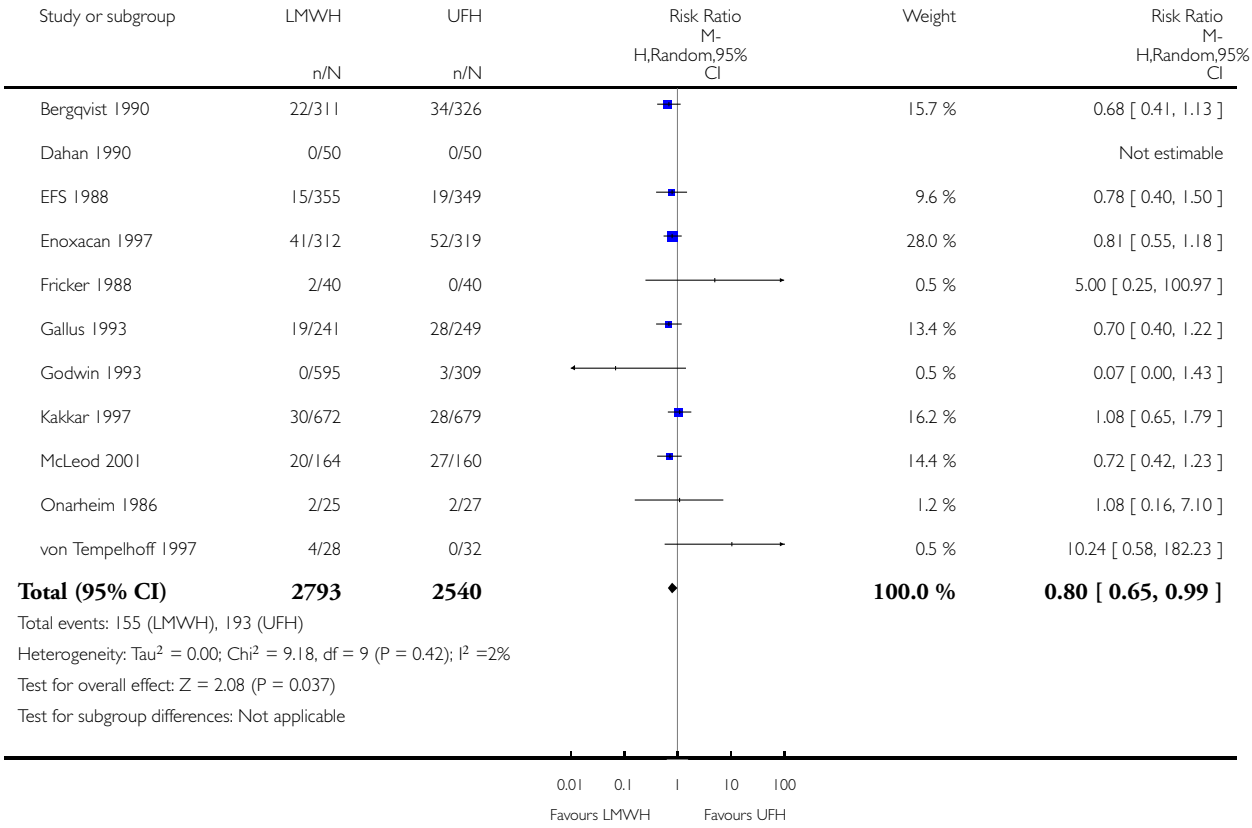


Analysis 1.4. Comparison 1 LMWH vs UFH, Outcome 4 DVT (asymptomatic).

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

Comparison: 1 LMWH vs UFH

Outcome: 4 DVT (asymptomatic)



Analysis 1.5. Comparison 1 LMWH vs UFH, Outcome 5 Minor bleeding.

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

Comparison: 1 LMWH vs UFH

Outcome: 5 Minor bleeding

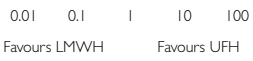
Study or subgroup	LMWH n/N	UFH n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Enoxacan 1997	81/556	88/560		42.0 %	0.93 [0.70, 1.22]
Heilmann 1998	12/160	28/164		31.2 %	0.44 [0.23, 0.83]
McLeod 2001	17/229	9/219		26.8 %	1.81 [0.82, 3.97]
Total (95% CI)	**945**	**943**		**100.0 %**	**0.88 [0.47, 1.66]**

Total events: 110 (LMWH), 125 (UFH)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 7.87$, df = 2 (P = 0.02); $I^2 = 75\%$

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

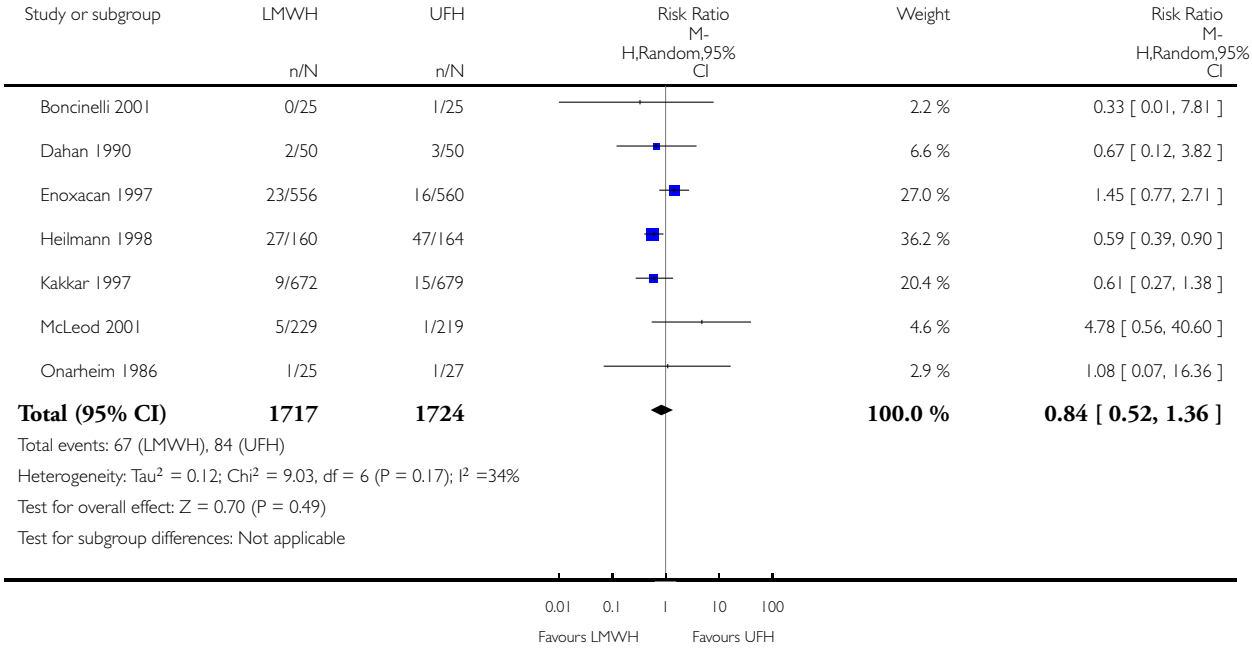


Analysis 1.6. Comparison 1 LMWH vs UFH, Outcome 6 Major bleeding.

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

Comparison: 1 LMWH vs UFH

Outcome: 6 Major bleeding

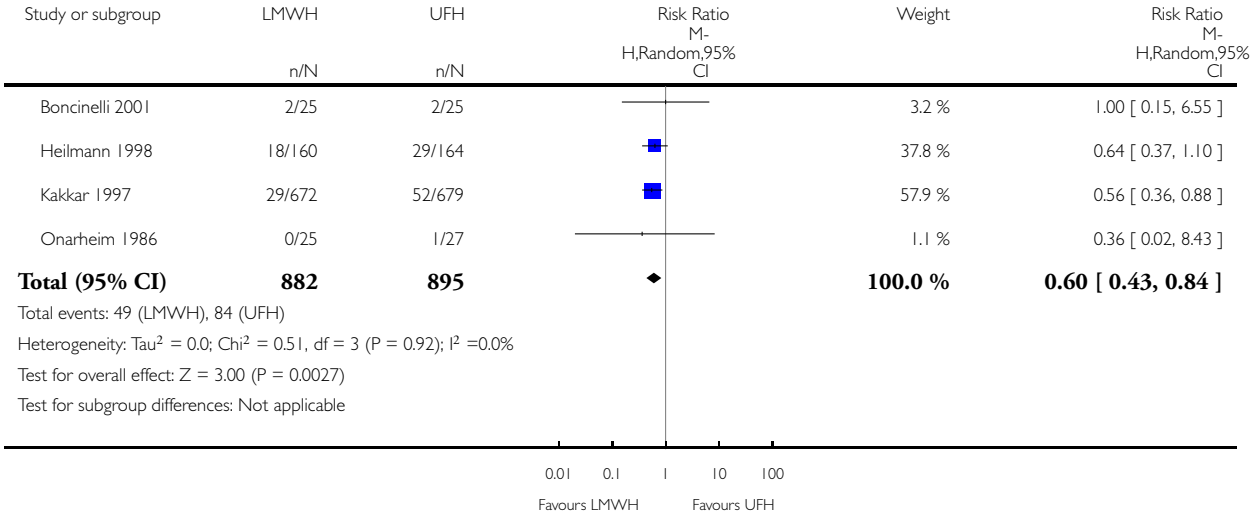


Analysis 1.7. Comparison 1 LMWH vs UFH, Outcome 7 Wound hematoma.

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

Comparison: 1 LMWH vs UFH

Outcome: 7 Wound hematoma

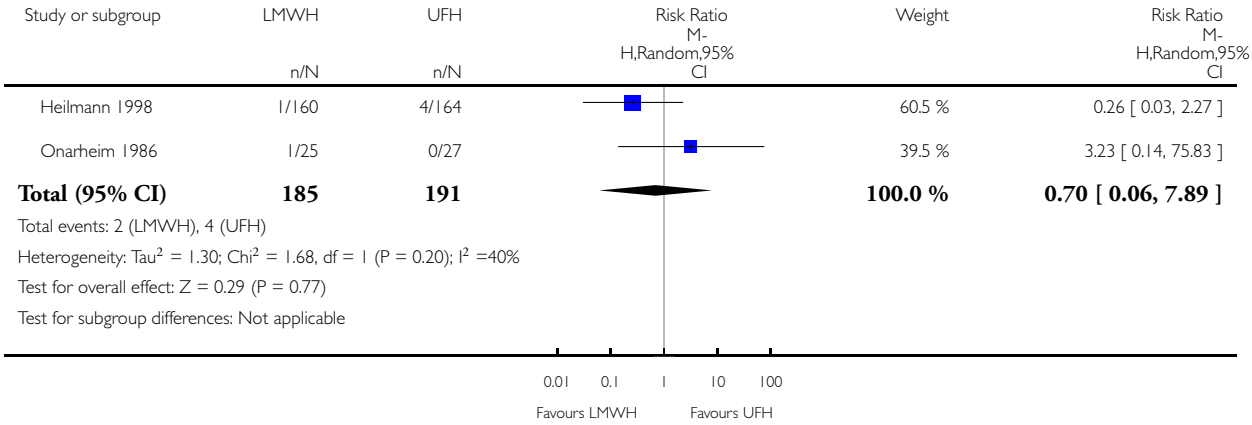


Analysis 1.8. Comparison 1 LMWH vs UFH, Outcome 8 Reoperation for bleeding.

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

Comparison: 1 LMWH vs UFH

Outcome: 8 Reoperation for bleeding



Analysis 1.9. Comparison 1 LMWH vs UFH, Outcome 9 Intra-operative blood loss.

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

Comparison: 1 LMWH vs UFH

Outcome: 9 Intra-operative blood loss

Study or subgroup	Favours LMWH N	Mean(SD)	UFH N	Mean(SD)	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)		1.3 %	117.10 [-64.79, 298.99]
Dahan 1990	48	290.8 (48.2)	46	307.5 (56.7)		95.3 %	-16.70 [-38.02, 4.62]
Gallus 1993	257	573 (644)	256	615 (714)		3.1 %	-42.00 [-159.68, 75.68]
Onarheim 1986	25	528 (479)	27	646 (956)		0.3 %	-118.00 [-524.55, 288.55]
Total (95% CI)	**377**		**384**			**100.0 %**	**-16.01 [-36.82, 4.80]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.49$, df = 3 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 1.51 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 LMWH vs UFH, Outcome 10 Intra-operative transfusion.

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

Comparison: 1 LMWH vs UFH

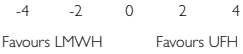
Outcome: 10 Intra-operative transfusion

Study or subgroup	LMWH N	Mean(SD)	UFH N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Dahan 1990	41	398.7 (68.7)	43	324.4 (58.2)		100.0 %	74.30 [47.01, 101.59]
Total (95% CI)	**41**		**43**			**100.0 %**	**74.30 [47.01, 101.59]**

Heterogeneity: not applicable

Test for overall effect: Z = 5.34 (P < 0.00001)

Test for subgroup differences: Not applicable

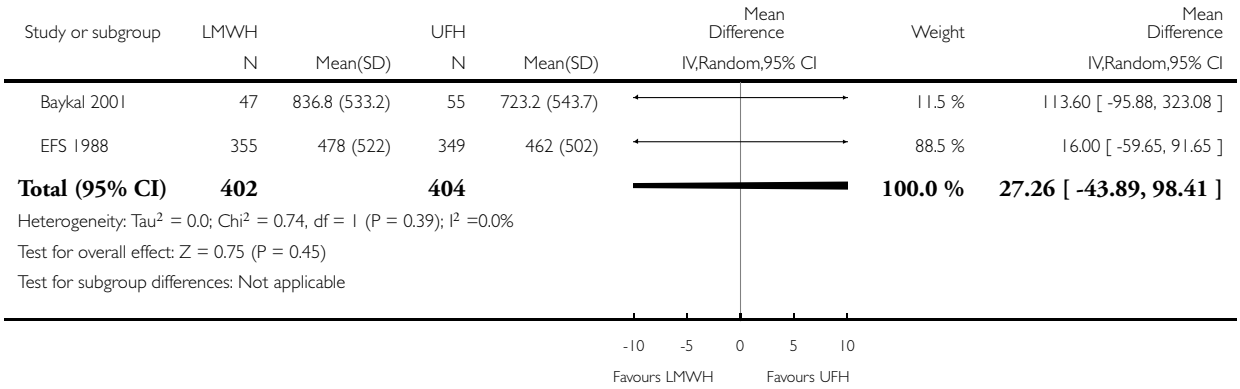


Analysis 1.11. Comparison 1 LMWH vs UFH, Outcome 11 Postoperative drain volume.

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

Comparison: 1 LMWH vs UFH

Outcome: 11 Postoperative drain volume

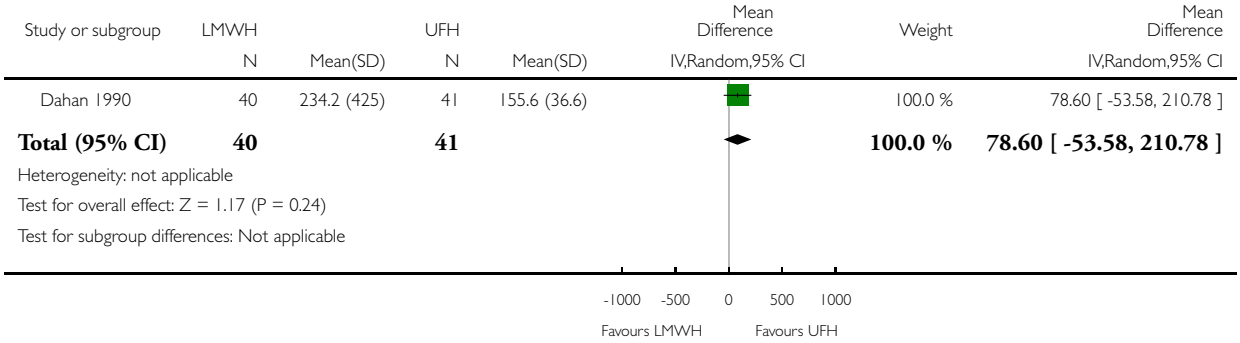


Analysis 1.12. Comparison 1 LMWH vs UFH, Outcome 12 Post-operative transfusion.

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

Comparison: 1 LMWH vs UFH

Outcome: 12 Post-operative transfusion

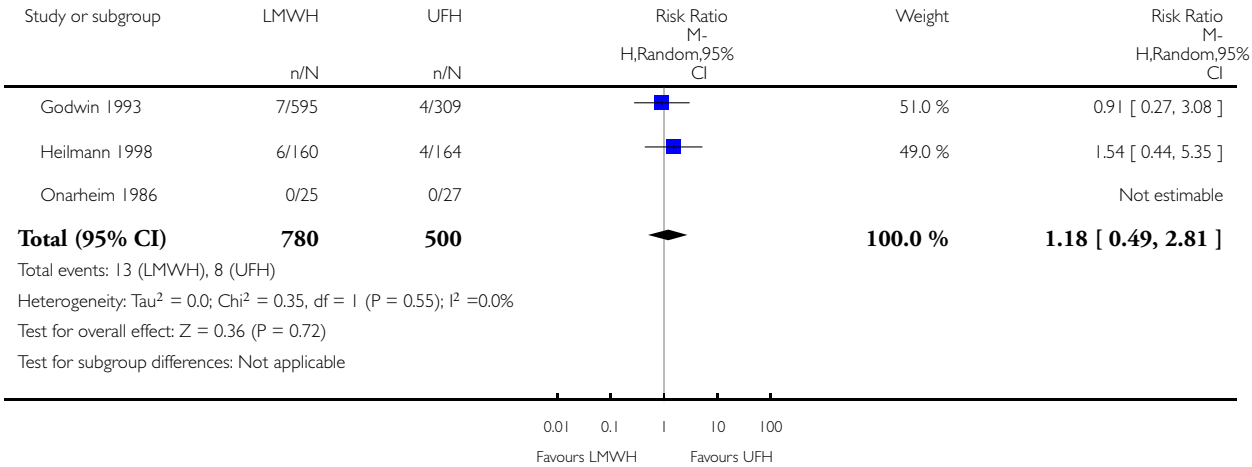


Analysis 1.13. Comparison 1 LMWH vs UFH, Outcome 13 Thrombocytopenia.

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

Comparison: 1 LMWH vs UFH

Outcome: 13 Thrombocytopenia



APPENDICES

Appendix 1. Search strategies for the electronic databases

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

(*Continued*)

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

(*Continued*)

	#7 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor #8 6 AND 7

WHAT'S NEW

Date	Event	Description
28 November 2012	Amended	Author contact details amended

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

HJS: no personal payments from for-profit sponsors related to the subject matter in the past three years. HJS is executive committee member of the ACCP Antithrombotic Therapy Guidelines. DJC conducted a peer-review funded trial comparing LMWH with UFH in critically ill patients and received donated study medication (LMWH) from Pfizer.

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External sources

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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