# Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation (Review)

**Akl EA, van Doormaal FF, Barba M, Kamath G, Kim SY, Kuipers S, Middeldorp S, Yosuico VED, Dickinson HO, Schünemann H**


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[Intervention Review]

# Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

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## ABSTRACT

### Background

Basic research and clinical studies have generated the hypothesis that anticoagulation may improve survival in patients with cancer through an antitumour effect in addition to the antithrombotic effect.

### Objectives

To evaluate the efficacy and safety of heparin (including unfractionated heparin (UFH) and low molecular weight heparin (LMWH)) and fondaparinux to improve survival of patients with cancer.

### Search strategy

A comprehensive search for studies of anticoagulation in cancer patients including (1) A January 2007 electronic search of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and ISI the Web of Science; (2) Hand search of the American Society of Clinical Oncology and of the American Society of Hematology; (3) Checking of references of included studies; and (4) Use of "related article" feature in PubMed.

### Selection criteria

Randomized controlled trials (RCTs) in cancer patients without clinical evidence of venous thromboembolism comparing UFH, LMWH or fondaparinux to no intervention or placebo and RCTs comparing two of the three agents of interest.

### Data collection and analysis

Using a standardized form we extracted in duplicate data on methodological quality, participants, interventions and outcomes of interest including all cause mortality, venous thrombosis, symptomatic pulmonary embolism, major bleeding and minor bleeding.

### Main results

Of 3986 identified citations five RCTs fulfilled the inclusion criteria. In all included RCTs the intervention consisted of heparin ( either UFH or LMWH). The quality of evidence was high for survival, low for major and minor bleeding, and very low for DVT. Overall, heparin therapy was associated with a statistically and clinically significant survival benefit (hazard ratio (HR) = 0.77; 95% CI: 0.65 to 0.91). In subgroup analyses, patients with limited small cell lung cancer experienced a clear survival benefit (HR = 0.56; 95% CI: 0.38 to 0.83). The survival benefit was not statistically significant for either patients with extensive small cell lung cancer (HR = 0.80; 95% CI: 0.60 to 1.06) or patients with advanced cancer (HR = 0.84; 95%: 0.68 to 1.03). The increased risk of bleeding with heparin was not statistically significant (RR = 1.78; 95% CI: 0.73 to 4.38).

**Authors' conclusions**

This review suggests a survival benefit of heparin in cancer patients in general, and in patients with small cell lung cancer in particular. Heparin might be particularly beneficial in cancer patients with limited cancer or a longer life expectancy. Future research should investigate the survival benefit of different types of anticoagulants (in different dosing, schedules and duration of therapy) in patients with different types and stages of cancers.

## PLAIN LANGUAGE SUMMARY

**Injectable blood thinners to prolong the survival of patients with cancer**

Research evidence suggests that blood thinners improve the survival of patients with cancer. This benefit could be related to a direct anti-tumour effect in addition to preventing blood clots. In this systematic review, data from five trials and 1189 participants show that injectable blood thinners increase the survival of patients with cancer. The survival benefit is more evident in patients with a particular type of lung cancer, the limited small cell lung cancer. However, injectable blood thinners increase the risk of bleeding. The main limitations of this systematic review are the relatively small number of included trials and the inclusion of different types of cancer in a same study.

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

| **Parenteral anticoagulation for prolonging survival of patients with cancer** | | | | | |
|---|---|---|---|---|---|
| **Patient or population:** prolonging survival of patients with cancer<br>**Settings:** Outpatient<br>**Intervention:** parenteral anticoagulation | | | | | |
| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No of Participants (studies)** | **Quality of the evidence (GRADE)** Comments |
| | **Assumed risk** | **Corresponding risk** | | | |
| | **Control** | **parenteral anticoagulation** | | | |
| **Survival at 12 months**<br>study follow up | **Low risk population**[1] | | **RR 0.87**<br>(0.8 to 0.95) | 1174<br>(5) | ⊕⊕⊕⊕<br>**high**[2,3] |
| | **600 per 1000** | **522 per 1000**<br>(480 to 570) | | | |
| | **High risk population**[1] | | | | |
| | **714 per 1000** | **621 per 1000**<br>(571 to 678) | | | |
| **Survival (overall)**<br>study follow up at 24 to 84 months | **Medium risk population** | | **HR 0.77**<br>(0.65 to 0.91) | 1174<br>(5) | ⊕⊕⊕⊕<br>**high**[2] |
| | **850 per 1000** | **768 per 1000**<br>(709 to 822) | | | |
| **DVT** | **Low risk population** | | **RR 0.61**<br>(0.08 to 4.91) | 458<br>(2) | ⊕◯◯◯<br>**very low**[2,4,5] |
| | **10 per 1000** | **6 per 1000**<br>(1 to 49) | | | |
| | **High risk population** | | | | |
| | **40 per 1000** | **24 per 1000**<br>(3 to 196) | | | |
| **Major bleeding** | **Low risk population** | | **RR 1.50**<br>(0.26 to 8.8) | 814<br>(3) | ⊕⊕◯◯<br>**low**[2,4,6] |

| | | | | | |
|---|---|---|---|---|---|
| | **15 per 1000** | **22 per 1000** (4 to 132) | | | |
| | **High risk population** | | | | |
| | **100 per 1000** | **150 per 1000** (26 to 880) | | | |
| **Minor bleeding** | **Low risk population** | | **RR 2.07** (0.78 to 5.51) | 760 (3) | ⊕⊕◯◯ **low**[2,4,6] |
| | **13 per 1000** | **27 per 1000** (10 to 72) | | | |
| | **High risk population** | | | | |
| | **50 per 1000** | **103 per 1000** (39 to 276) | | | |

*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; HR: Hazard ratio;

GRADE Working Group grades of evidance

**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 control group risk in the five studies at 12 months was: 71.4% 69.8 59.2% 73.2% and 60%. We used the second lowest and second highest for the low and high estimate.
[2] Unclear concealment in one of the five trials did not lead to downgrading the quality of evidence.
[3] The studies used different LMWHs but indirectness is not likely given the similiarity in results across studies.
[4] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm
[5] Out of 5 included studies, only 2 reported DVT. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.
[6] Out of 5 included studies, only 3 reported major bleeding. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.

## BACKGROUND

Please refer to the glossary for the definitions of technical terms (
Table 1).

**Table 1. Glossary**

**Table 1. Glossary**

| Term | Definition |
|---|---|
| Adjuvant therapy: | assisting in the amelioration, or cure of disease |
| Anticoagulation: | the process of hindering the clotting of blood especially by treatment with an anticoagulant |
| Antithrombotic: | used against or tending to prevent thrombosis (clotting) |
| Bacteremia: | the presence of bacteria in the blood. |
| Central venous line: | synthetic tube that is inserted into a central (large) vein of a patient to provide temporary intravenous access for the administration of fluid, medication, or nutrients |
| Coagulation: | clotting |
| Deep vein thrombosis (DVT): | a condition marked by the formation of a thrombus within a deep vein (as of the leg or pelvis) that may be asymptomatic or be accompanied by symptoms (as swelling and pain) and that is potentially life threatening if dislodgment of the thrombus results in pulmonary embolism |
| Fibrin: | a white insoluble fibrous protein formed from fibrinogen by the action of thrombin especially in the clotting of blood |
| Fondaparinux: | an anticoagulant medication |
| Haemostatic system: | the system that shortens the clotting time of blood and stops bleeding |
| Heparin: | an enzyme occurring especially in the liver and lungs that prolongs the clotting time of blood by preventing the formation of fibrin. Two forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low molecular weight heparins (LMWH) |
| Impedance plethysmography: | a technique that measures the change in blood volume (venous blood volume as well as the pulsation of the arteries) for a specific body segment. |
| Kappa statistics: | a measure of degree of nonrandom agreement between observers and/or measurements of a specific categorical variable. |
| Metastasis: | the spread of a cancer cells from the initial or primary site of disease to another part of the body |
| Oncogene: | a gene having the potential to cause a normal cell to become cancerous |
| Osteoporosis: | a condition that affects especially older women and is characterized by decrease in bone mass with decreased density and enlargement of bone spaces producing porosity and brittleness |
| Parenteral nutrition: | the practice of feeding a patient intravenously, circumventing the gut. |

**Table 1. Glossary** (*Continued*)

| | |
|---|---|
| Pulmonary embolism (PE): | embolism of a pulmonary artery or one of its branches that is produced by foreign matter and most often a blood clot originating in a vein of the leg or pelvis and that is marked by labored breathing, chest pain, fainting, rapid heart rate, cyanosis, shock, and sometimes death |
| Stroma: | the supporting framework of an organ typically consisting of connective tissue |
| Thrombin: | a proteolytic enzyme formed from prothrombin that facilitates the clotting of blood by catalyzing conversion of fibrinogen to fibrin |
| Thrombocytopenia: | persistent decrease in the number of blood platelets that is often associated with hemorrhagic conditions |
| Thrombosis: | the formation or presence of a blood clot within a blood vessel |
| Vitamin K antagonists: | anticoagulant medications that are used for anticoagulation. Warfarin is a vitamin K antagonist |
| Warfarin: | an anticoagulant medication that is a vitamin K antagonist that is used for anticoagulation |
| Ximelagatran: | an anticoagulant medication<br><br>Ximelagatran: an anticoagulant medication<br><br>Ximelagatran: an anticoagulant medication |

Since the 1930s, basic scientists have been exploring the effects of anticoagulation on cancer (Smorenburg 2001). Studies have implicated the tumour-mediated activation of the haemostatic system in both the formation of tumour stroma and in tumour metastasis (Dvorak 1986; Francis 1998; Levine 2003). There is also evidence that heparin inhibits expression of oncogenes and formation of thrombin and fibrin induced by cancer cells (Smorenburg 2001). In addition, heparin potentially inhibits intravascular arrest of cancer cells and thus metastasis (Smorenburg 2001).

In this context, researchers have hypothesized that heparin may improve outcomes in cancer patients through an antitumour effect in addition to its antithrombotic effect (Thodiyil 2002). In a 1992 clinical trial comparing nadroparin, a low molecular weight heparin (LMWH), to unfractionated heparin (UFH) in patients with proven deep vein thrombosis (DVT), nadroparin unexpectedly reduced mortality in the subgroup of patients with cancer ( Prandoni 1992). At the same time, anticoagulants increase the risk for bleeding. This risk is higher in cancer patients compared to those without cancer. In fact, in patients with venous thrombosis on anticoagulation the risk of bleeding was higher if patients had cancer and correlated with the extent of cancer (Prandoni 2002). Heparins are also known to cause thrombocytopenia and heparin-induced thrombocytopenia (HIT) syndrome (Girolami 2006).

In 1999, Smorenburg et al conducted a systematic review of the effects of UFH on survival in patients with malignancy (Smorenburg 1999). They found three trials of high methodological quality but with conflicting results. Since 1999 reports on several randomized controlled trials (RCTs) on this subject have been published ( Kakkar 2004; Klerk 2005). Therefore, we systematically reviewed the literature to assess both efficacy and safety outcomes of parenteral anticoagulation to prolong survival of patients with cancer.

## OBJECTIVES

To evaluate the effectiveness and safety of heparin (including UFH and LMWH) and fondaparinux in improving the survival of patients with cancer

## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs. We did not include trials with inadequate methods of treatment allocation (i.e. inadequate randomization such as allocation of treatment based on date of birth, clinic identification number or surname).

### Types of participants

Study participants were any patients with cancer. Participants had to have no indication for prophylactic anticoagulation (e.g. for acute illness, central venous line placement, perioperative) or for therapeutic anticoagulation (e.g. for treatment of DVT or pulmonary embolism).

### Types of interventions

Main intervention: UFH or LMWH or fondaparinux
Comparison: placebo or no intervention.
We also considered studies comparing two of the three agents being considered as the main intervention. Investigators had to have the intention to give all other co-interventions (e.g. chemotherapy) similarly.

### Types of outcome measures

Events during the scheduled follow-up period:
(a)

**Primary outcomes**

- Survival

**Secondary outcomes**

- Symptomatic DVT; events had to be diagnosed using one of the following objective diagnostic tests: venography, 125I-fibrinogen-uptake test, impedance plethysmography or compression ultrasound;
- Symptomatic pulmonary embolism; events had to be diagnosed using one of the following objective diagnostic tests: pulmonary perfusion/ventilation scans, computed tomography, pulmonary angiography or autopsy;
- Major bleeding;
- Minor bleeding; for bleeding complications, we accepted the authors' definitions of major and minor bleeding and excluded data from studies where definitions were not provided or unclear.
- Thrombocytopenia;
- Withdrawal from treatment (as a surrogate for tolerability of treatment).

## Search methods for identification of studies

### Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in cancer patients. We electronically searched in January 2007 the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL, 1st Quarter 2007), MEDLINE (1966 onwards; accessed via OVID), EMBASE (1980 onwards; accessed via OVID) and ISI the Web of Science. The search strategies combined terms relating to the anticoagulants, to cancer and to study design. We list the search strategies in an additional table (Table 2).

**Table 2. Search strategies used for the electronic databases**

| Database | Strategy |
|---|---|
| MEDLINE | #1 Heparin/<br>#2 Heparin.tw<br>#3 Heparin, Low-Molecular-Weight/<br>#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<br>#5 1 OR 2 OR 3 OR 4<br>#6 Coumarins/<br>#7 Warfarin/<br>#8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw<br>#9 6 OR 7 OR 8 |

**Table 2. Search strategies used for the electronic databases** (*Continued*)

| | |
|---|---|
| | #10 (fondaparinux OR Arixtra).tw<br>#11 (ximelagatran OR Exanta).tw<br>#12 5 OR 9 OR 10 OR 11<br>#13 Neoplasms/<br>#14 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw<br>#15 13 OR 14<br>#16 clinical trial.pt. OR random:.tw. OR tu.xs.<br>#17 animals/ NOT human/<br>#18 16 NOT 17<br>#25 12 AND 15 AND 18 |
| EMBASE | #1 Heparin/<br>#2 heparin.tw<br>#3 Low Molecular Weight Heparin/<br>#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<br>#5 1 OR 2 OR 3 OR 4<br>#6 Coumarin derivative/<br>#7 Warfarin/<br>#8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw<br>#9 6 OR 7 OR 8<br>#10 fondaparinux/<br>#11 (fondaparinux OR Arixtra).tw<br>#12 ximelagatran/<br>#13 (ximelagatran OR Exanta).tw<br>#14 5 OR 9 OR 10 OR 11 OR 12 OR 13<br>#15 Neoplasm/<br>#16 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw<br>#17 15 OR 16<br>#18 Random:.tw. OR clinical trial:.mp. OR exp health care quality<br>#19 animals/ NOT human/<br>#20 18 NOT 19<br>#21 14 AND 17 AND 20 |
| 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 |

**Table 2. Search strategies used for the electronic databases** (*Continued*)

| | |
|---|---|
| | certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran<br>#2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA<br>#3 fondaparinux OR Arixtra<br>#4 ximelagatran OR Exanta<br>#5 1 OR 2 OR 3 OR 4<br>#6 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor<br>#7 random$ OR placebo$ OR versus OR vs OR double blind OR double-blind OR compar$ OR controlled<br>#8 5 AND 6 AND 7 |
| 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<br>#2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA<br>#3 fondaparinux OR Arixtra<br>#4 ximelagatran OR Exanta<br>#5 1 OR 2 OR 3 OR 4<br>#6 malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor<br>#7 5 AND 6 |

### Searching other resources

In addition to the electronic search we used a number of supplemental search strategies. We hand searched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982) and of the American Society of Hematology (ASH, starting with its 2003 issue). We reviewed the reference lists of papers resulting from the above searches and used the related article feature in PubMed to identify additional articles. We used no language restrictions.

## Data collection and analysis

### Selection of studies

Two review authors independently screened the titles and abstracts of identified articles for eligibility. We retrieved the full text of articles judged by at least one review author as potentially eligible. Two review authors then independently screened the full text articles for eligibility using a standardized form with explicit inclusion and exclusion criteria. The two review authors resolved their disagreements by discussion or by consulting a third review author.

### Data extraction and management

Two review authors independently assessed the methodological quality of each included study and resolved their disagreements by discussion. Methodological criteria included:

- Allocation concealment: Adequate (A), unclear (B), inadequate (C) or not used (D).
- Patient blinding
- Provider blinding
- Outcome assessor blinding
- Analyst blinding
- Percentage of follow-up
- Whether the analysis followed the intention-to-treat (ITT) principle
- Whether the study was stopped early for benefit.

We assessed validity by reporting how each trial scored on each criterion. We considered the following types of allocation concealment as adequate: centralised (e.g. allocation by a central office or

pharmacy-controlled randomisation; on-site web-based or computerized allocation with assignment that is accessible only after the characteristics of an enrolled participant have been entered; pre-numbered or coded identical containers which are administered serially to participants; and sequentially numbered, sealed, opaque envelopes). We considered the following types of allocation concealment as inadequate: alternation; the use of case record numbers or dates of birth or day of the week; and any other procedure that would be entirely transparent before allocation, such as an open list of random numbers. We considered allocation concealment as unclear when studies did not report any concealment approach. Otherwise we classified the allocation as "not used".

#### Data collection

We developed and used a standardized data extraction form. Two authors independently extracted the data from each included study and resolved their disagreements by discussion. We aimed at collecting data related to:

#### Participants

- Number of patients randomized to each treatment arm
- Number of patients followed-up in each treatment arm
- Number of withdrawals from treatment in each treatment arm
- Population characteristics (age, gender, co-morbidity)
- History of VTE
- Type of cancer
- Stage of cancer
- Time since diagnosis
- Co-interventions including radiotherapy, chemotherapy, and hormonal therapy (type and duration)
- Use of indwelling central venous catheters

#### Interventions

- Type of anticoagulant: UFH, LMWH, or fondaparinux
- Dose: prophylactic versus therapeutic (Table 3)

**Table 3. LMWH definitions of prophylactic and therapeutic dosages**

| LMWH | Generic name | Prophlyactic dose | Therapeutic dose |
|---|---|---|---|
| Lovenox | Enoxaparin | 40 mg q 24 h | 1 mg/kg q 12 h |
| Fragmin | Dalteparin | 2,500-5,000 U q 24 h | 200 U/kg q 24 h or<br>100 U/kg q 12 h |

**Table 3. LMWH definitions of prophylactic and therapeutic dosages** (*Continued*)

| | | | |
|---|---|---|---|
| Innohep | Tinzaparin, Logiparin | 4,500 U q 24 h | 90 U/kg q 12 h |
| Fraxiparine | Nadroparin | 35 -75 anti-Xa int. units/kg/day | 175 anti-Xa int. units/kg/day |
| Certoparin | Sandoparin | 3000 anti-Xa int. units qd | |

- Duration of treatment
- Control: placebo or no intervention

### Outcomes

We extracted both time to event data (for the survival outcome) and categorical data (for all outcomes).

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

For categorical data, we extracted data necessary to conduct intention-to-treat (ITT) analyses. We collected all cause mortality at one year (time point defined a priori in the protocol) and at two years (time point defined post hoc based upon results reported in the individual RCTs). When we could not obtain the number of events at the time points of interest from the paper or from the authors, two reviewers calculated these numbers independently and in duplicate from survival curves, if available. We used the mean of the two estimates when they differed. We assessed agreement between the two authors for each estimated value by calculating the percentage difference, which is the difference between the two estimates divided by the denominator (number of subjects at risk for the event) and multiplied by 100.

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.

### Data synthesis

We calculated the agreement between the two independent review authors for the assessment of eligibility using kappa statistic. We created an inverted funnel plot for the primary outcome of survival in order to check for possible publication bias.

For time to event data, we pooled the log (HRs) using a random-effects model and the generic inverse variance facility of RevMan 4.2. We created funnel plots for all analyses.

For categorical data, we calculated the relative risk (RR) separately for each study for the incidence of outcomes by treatment arm. We then pooled the results of the different studies using a random-effects model. We created funnel plots for all analyses.

We tested results for homogeneity across studies using the $I^2$ test ( Higgins 2003). We considered the following classification of heterogeneity based on the value of $I^2$: 0-30 = low; 30 to 60 = moderate and worthy of investigation; 60 to 90 = severe and worthy of understanding; 90 to 100 = allowing aggregation only with major caution (Julian Higgins, personal communication). We planned to explore heterogeneity by conducting subgroup analyses based on the type of intervention (LMWH versus UFH) and the characteristics of participants (type, location, severity and stage of cancer, and whether patients were on cancer treatment or not). We also planned for sensitivity analysis excluding poor quality trials

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

### Results of the search

The search strategy identified 3986 citations, including 322 duplicates. The title and abstract screening of the 3664 unique citations identified 51 as potentially eligible for this review. The full text screening of the 51 citations identified five eligible RCTs published as full reports (Altinbas 2004; Kakkar 2004; Klerk 2005; Lebeau 1994; Sideras 2006). We identified four earlier published abstracts for three of the five included RCTs (Altynbas 2000; Altynbas 2001; Kakkar 2002; Sideras 2005). We also identified seven eligible studies published as abstracts but for which we were not able to obtain the needed data from the authors (Barkagan 1997; Freund 2003; Gatzemeier 2005; Graf 1994; Graf 1996; Salat 1990; Chazouilleres 1994). Agreement between authors for study eligibility was excellent (kappa = 0.94).

### Included studies

The five included studies recruited a total of 1189 participants and reported follow-up data on 1175 (Altinbas 2004; Kakkar 2004;

Klerk 2005; Lebeau 1994; Sideras 2006). One study used UFH as the intervention (Lebeau 1994) while the other four used LMWH as the intervention (Altinbas 2004; Kakkar 2004; Klerk 2005; Sideras 2006). We did not identify any study using fondaparinux as the intervention.

Lebeau et al. recruited 277 patients with both limited and extensive SCLC 78% of which had a Karnofsky Performance Scale Index >80 (Lebeau 1994). The Karnofsky Performance Scale Index ranges from 0 (dead) to 100 (normal) (Karnofsky 1948). Patients were randomized to receive along with their chemotherapy either a prophylactic dose of UFH for five weeks or no intervention. The study outcome was mortality (at one, two and three years). Follow up was complete (100%). The minimum duration of follow-up was not reported. The maximum duration of follow-up was 59 months. HRs were estimated from published survival curves, assuming all patients were followed up for 59 months.

Kakkar et al. (the FAMOUS trial) recruited 385 patients with advanced stage III or IV malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus and a minimum life expectancy of three months (Kakkar 2004). Patients were randomized to receive either a prophylactic dose of a LMWH (dalteparin) or placebo for 12 months with no restriction on concomitant chemotherapy or radiotherapy. The study outcomes included mortality (at one, two and three years), pulmonary embolism, DVT, major bleeding, and minor bleeding. Follow-up data were available for 374 patients (97%). The minimum duration of follow-up was not reported. The maximum duration of follow-up was 77 months. HRs were estimated from published survival curves, assuming all patients were followed up for 77 months.

Klerk et al. (MALT trial) recruited 302 patients with different types of solid malignant tumours that could not be treated curatively and a minimum life expectancy of one month (Klerk 2005). Cancer types included: colorectal, breast, lung, gastric, oesophageal, liver, gallbladder, Katskin, prostate, pancreatic, cervical, urothelial, renal, ovarian, melanoma, endometrial and other cancers. Patients were randomized to receive either a LMWH (nadroparin; two weeks therapeutic dose followed by four weeks of a prophylactic dose) or a placebo for six weeks without any concomitant chemotherapy or radiotherapy. Study outcomes included mortality (at six, months, one year and two years), major bleeding, and major or minor bleeding. Follow up was complete (100%). The minimum duration of follow-up was not reported. The maximum duration of follow-up was 84 months. The HR and its standard error were reported.

Altinbas et al. recruited 84 patients with both limited and extensive SCLC and an Eastern Cooperative Oncology Group (ECOG) state<3 (Altinbas 2004). The ECOG Performance Status scale ranges from 0 (fully active) to 5 (dead) (Oken 1982). Patients were randomized to receive either a prophylactic dose of a LMWH (dalteparin) or placebo for 18 weeks or less in combination with chemotherapy in case of disease progression. Study outcomes included mortality (at one and two years), DVT, and minor bleeding. Follow up was complete (100%). The minimum and maximum duration of follow-up were 2 and 33 months respectively. HRs were estimated from published survival curves.

Sideras et al. recruited 141 patients with different types of advanced cancer and a minimum life expectancy of 12 weeks and ECOG state 0 to 2 (Sideras 2006). Patients were randomized either to a prophylactic dose of a LMWH (dalteparin) or to placebo or no intervention. Study outcomes included mortality (at one, two and three years), VTE, and major bleeding. Follow-up data were available for 138 patients (98%). The minimum duration of follow-up was not reported. The maximum duration of follow-up was 24 months. The authors supplied us with unpublished data giving the HR and its standard error.

### Excluded studies

We excluded 35 articles from this review for the following reasons: intervention was topical heparin (1) or intraportal infusion of heparin (2); studies included no cancer patients (2); no survival outcome (1); study design was not a RCT (16); letter to the editor or editorial (9); publication was a review (4).

## Risk of bias in included studies

Allocation was adequately concealed (using central allocation procedures) in four of the five studies (Kakkar 2004; Klerk 2005; Lebeau 1994; Sideras 2006) and it was unclear whether it was adequately concealed in the fifth study (Altinbas 2004). While two studies blinded participants, caregivers, and outcome assessors ( Klerk 2005; Sideras 2006), one study blinded patients and care givers (Kakkar 2004), one study blinded outcome assessors and data analysts (Lebeau 1994), and one study blinded only outcome assessors (Altinbas 2004). The lowest percentage of follow up in the five studies was 97%. Only one study did not use the ITT analysis principle (Sideras 2006). Only one study was stopped early by patient monitoring committee for insufficient accrual (Sideras 2006). We judged that in the study by Lebeau et al. (Lebeau 1994) patients received similar co-interventions although brain and thoracic irradiation depended on response to treatment. In that study 11% and 7% respectively of patients randomized to heparin and control groups received radiotherapy. The quality of evidence was high for survival, low for major and minor bleeding, and very low for DVT Summary of findings table 1.

## Effects of interventions

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

Agreement between the two authors who extracted data from survival curves was high with an average percentage difference of 2.5%. The data were not heterogeneous ($I^2$ statistic less than 50%) for the review outcomes at one year (the time point defined a priori). The data however showed severe heterogeneity for mortality at 24 months for SCLC, limited SCLC, and extensive SCLC. The

included studies used different definitions for major and minor bleeding. The relatively small number of trials permitted subgroup analyses only for the subgroups of patients with small cell lung cancer (SCLC) and with "advanced cancer" (as defined in individual studies).

### All cause mortality

Based on a pooled estimate from the five RCTs, heparin was associated with a statistically significant survival benefit (HR = 0.77; 95% CI: 0.65 to 0.91) (comparison 01:01) Figure 1. The meta-analysis indicated moderate heterogeneity between trials ($I^2$ = 47 %). We conducted a sensitivity analysis excluding the study by Lebeau et al. (Lebeau 1994) (the only study using UFH) then the study by Altinbas et al. (Altinbas 2004) (in which the allocation was not clearly concealed). This yielded similar estimates of the treatment effect to that found in the primary meta-analysis. The inverted funnel plot for the primary outcome of mortality at one year did not suggest publication bias (Figure 2).

**Figure 1. Forest plot of comparison: 1 Heparin vs placebo, outcome: 1.1 Mortality over duration of study.**

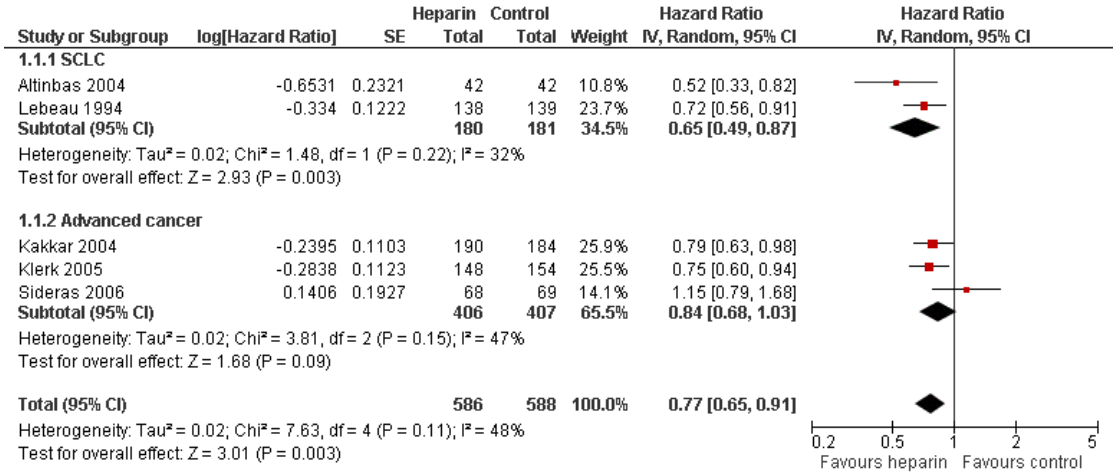
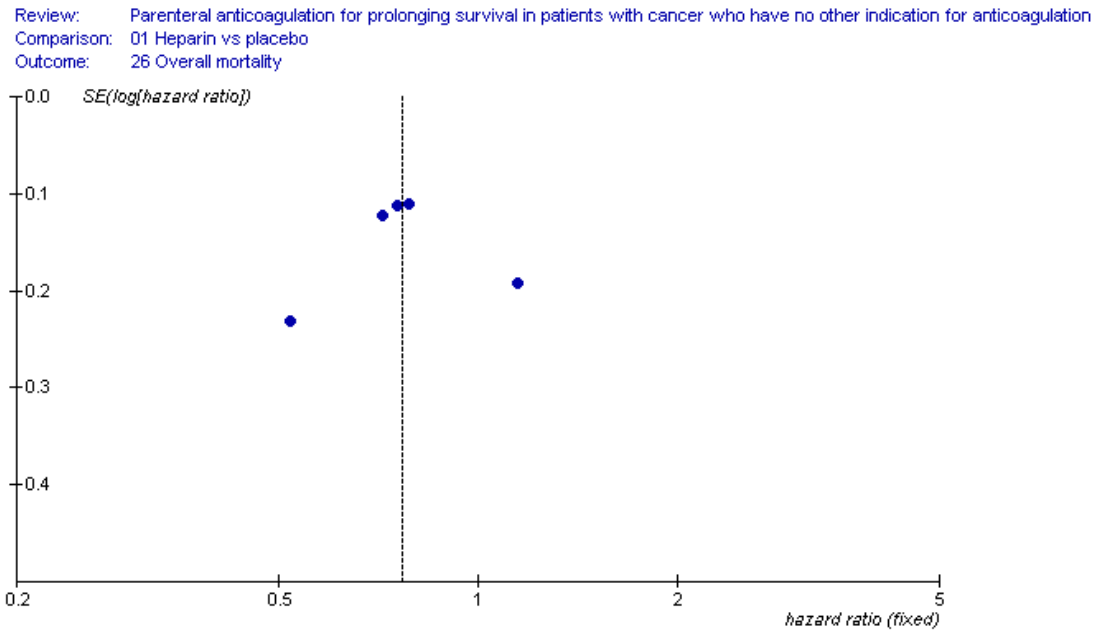


**Figure 2. Inverted funnel plot for the survival outcome in randomized controlled trials of parenteral anticoagulation in cancer patients**



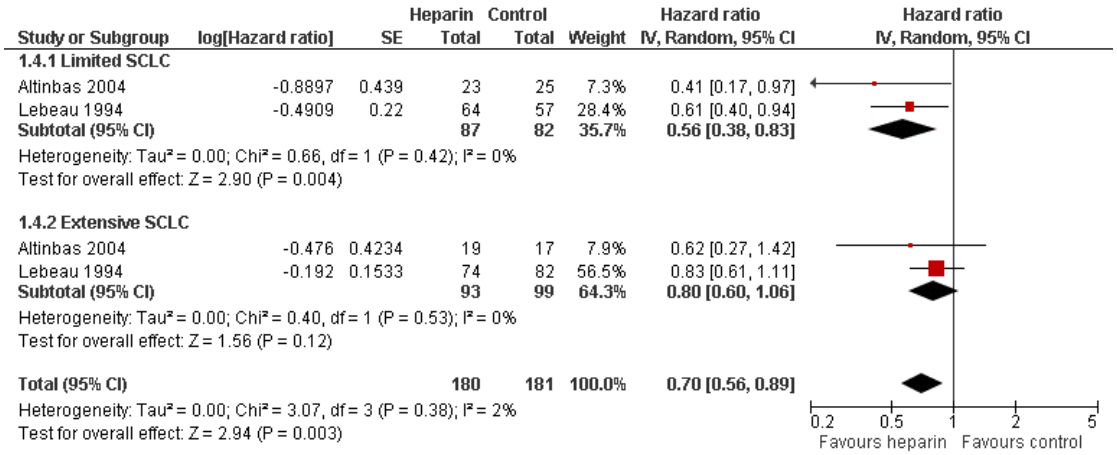
The categorical analysis confirmed the results of the time to event analysis with a statistically significant reduction of mortality at 12 months (RR = 0.87; 95% CI: 0.80 to 0.95; number of participants n = 1174) (comparison 01:02) and at 24 months (RR = 0.92; 95% CI: 0.86 to 0.99: n = 1174) (comparison 01:03).

In order to investigate heterogeneity, we also conducted subgroup analyses for subgroups of patients with SCLC (extensive and limited separately) (Altinbas 2004; Lebeau 1994) and patients with advanced cancer (Kakkar 2004; Klerk 2005; Sideras 2006).

### Small cell lung cancer

In patients with limited SCLC, heparin was associated with a statistically significant survival benefit (HR = 0.56; 95% CI: 0.38 to 0.83), with no heterogeneity between trials ($I^2$ = 0) (comparison 01:04) Figure 3. In the categorical analysis, heparin was associated with a statistically significant reduction of mortality at 12 months (RR = 0.60; 95% CI: 0.42 to 0.87; n =169) (comparison 01:05) but not at 24 months (RR = 0.90; 95% CI: 0.71 to 1.14; n = 169) (comparison 01:06). Excluding the study by Altinbas et al. did not change the results in terms of statistical significance.

**Figure 3. Forest plot of comparison: 1 Heparin vs placebo, outcome: 1.4 Mortality SCLC, over duration of study.**




For extensive SCLC, heparin was associated with a non statistically significant survival benefit (HR = 0.80; 95% CI: 0.60 to 1.06) (comparison 01:04) Figure 3, with no heterogeneity between trials ($I^2$ = 0). The results were similarly non-statistically significant in the categorical analysis at 12 months (RR = 0.93; 95% CI 0.76 to 1.15; n = 192) (comparison 01:05) and 24 months (RR = 0.88; 95% CI 0.65 to 1.18; n = 192) (comparison 01:06).

### Advanced cancer

Based on a pooled estimate from studies including patients with advanced cancer (Kakkar 2004, Klerk 2005, Sideras 2006), heparin was associated with a non statistically significant survival benefit (HR = 0.84; 95% CI: 0.68 to 1.03) (comparison 01:01), with moderate heterogeneity between trials ($I^2$ = 47%). The effect of heparin on mortality was borderline significant at 12 months (RR = 0.89; 95% CI 0.80 to 1.00; n = 813) (comparison 01:02) and 24 months (RR = 0.92; 95% CI 0.85 to 1.00; n = 813) (comparison 01:03)

Klerk et al (Klerk 2005) defined a priori two subgroups of patients with life expectancy less and greater than 6 months respectively. The hazard ratio for survival was 0.64 (95% CI 0.45 to 0.90) for patients with longer life expectancy and 0.88 (95% CI 0.62 to 1.25) for patients with shorter life expectancy)

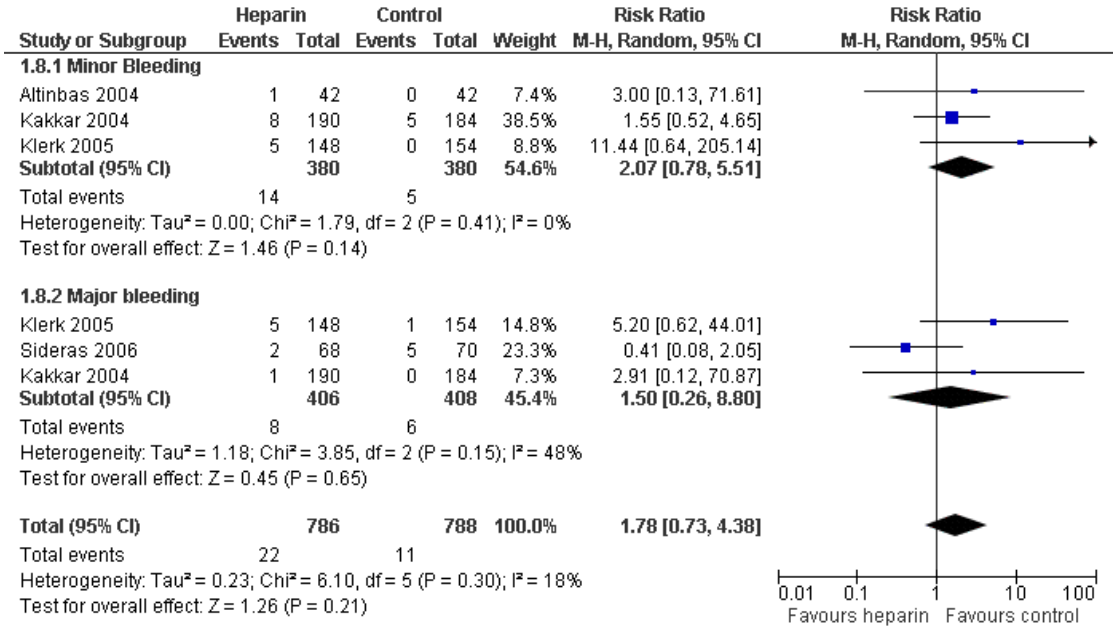
### Venous thromboembolism

Based on pooled estimates from two RCTs (Kakkar 2004, Altinbas 2004), heparin therapy was associated with a non-statistically significant reduction in DVT (RR = 0.61; 95% CI 0.08 to 4.91; n = 458) (comparison 01:07).

### Major and minor bleeding

Pooled estimates showed that heparin therapy was associated with increased bleeding that was non-statistically significant for minor bleeding (RR = 2.07; 95% CI 0.78 to 5.51; n = 760), or major bleeding (RR = 1.50; 95% CI 0.26 to 8.80; n = 814) or any bleeding (RR = 1.78; 95% CI 0.73 to 4.38; n = 1574) (comparison 01:08) Figure 4. After excluding the study by Altinbas et al. the results remained non-statistically significant.

**Figure 4. Forest plot of comparison: 1 Heparin vs placebo, outcome: 1.8 Any bleeding.**




Three studies assessed thrombocytopenia as an outcome but reported no events (Altinbas 2004; Klerk 2005; Lebeau 1994). None of the studies reported participants withdrawing from treatment.

## DISCUSSION

Heparin therapy (with either UFH or LMWH) was associated with a statistically and clinically significant survival benefit in cancer patients who had no indication for parenteral anticoagulation. In subgroup analyses, patients with limited SCLC experienced a clear survival benefit. The survival benefit was not statistically significant for either patients with extensive SCLC or patients with advanced cancer. Heparin therapy may increase the risk of bleeding as high as 4 to 5 folds. We did not identify any study using fondaparinux as the anticoagulant.

Our systematic approach to searching, study selection and data extraction should have minimized the likelihood of missing relevant studies. The overall methodological quality of the included studies was moderate; all included studies were RCTs with high percentages of follow-up and allocation was clearly adequate in all but one included study. Our systematic approach, the high methodological quality for survival, and the low likelihood of publication bias increase the confidence in the internal validity of our findings.

The non-significant findings may be due to the small number of RCTs, of participants and of events. For example, overall mortality at 36 months, with non-significant results, is based on only four studies whereas mortality at all other points is based on five studies. In addition, compared with the data at 12 months, the results at six months tended to be non-significant; the latter could be explained by a smaller number of events in the early follow up period.

Interpretation of the findings of this review is limited by the moderate heterogeneity between the results of different trials, which was not completely explained by subgroup analyses based on type of cancer. The heterogeneity could be related to variety in the stages of cancers, and in the types, dosing, schedules and duration of heparin therapy. The relatively small number of studies and the inclusion of different types of cancer in the same study precluded us from conducting the necessary subgroup analyses to explore all of these factors. The interpretation of findings is also limited by not including data from the 7 trials published as abstracts only.

The statistically significant survival benefit of heparin in the subgroup of patients with limited SCLC in this review and in the subgroup of patients with life expectancy greater than six months in the study by Klerk et al (Klerk 2005) suggests that the less ill patients get greater benefit from Heparin.. The CLOT trial (Lee 2003) supports these findings indirectly; in that study, patients with solid tumours and an acute venous thromboembolic event had improved survival if they did not have a metastatic disease at the time of study entry.

The beneficial effect of heparin on survival of patients with SCLC is not consistent with the effect of warfarin on survival in this patient population. In a systematic review of the use of oral anticoagulation for prolonging survival in patients with cancer, warfarin improved early survival in patients with SCLC (Akl 2007). The reason for this discrepancy is unclear.

Lazo-Lannger et al. conducted a systematic review addressing the same question as this review (Lazlo-Langner 2007). Although that review had different inclusion criteria from our review (in particular, it excluded the trial of Lebeau) and obtained slightly different estimates of HRs using Parmar's methods, it reported similar results: a hazard rate comparing mortality in the heparin and control arms of 0.83 (95% CI: 0.70 to 0.99). This consistency of results from independent reviews confirms the robustness of the findings. Lazo-Langner et al. did not report any subgroup analysis in patients with small cell lung cancer.

# AUTHORS' CONCLUSIONS

## Implications for practice

This systematic review supports a survival benefit from heparin therapy in cancer patients in general, and in patients with limited SCLC in particular. It also suggests a higher benefit in patients with limited cancer or a longer life expectancy.

The decision for a patient with cancer to start heparin therapy for survival benefit should balance the benefits and downsides and integrate the patient's values and preferences (Haynes 2002). Patients with a high preference for a short survival prolongation and limited aversion to bleeding who do not consider heparin therapy a burden may opt to use heparin, while those with aversion to bleeding may not.

## Implications for research

Future research should investigate the effects of heparin (including UFH and LMWH) and other anticoagulants in patients with different types and stages of cancers using different types, dosing, schedules and duration of therapy (Alifano 2004).

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Kakkar AK, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, et al.Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *Journal of Clinical Oncology* 2004;**22** (10):1944–48.

**Karnofsky 1948**

Karnofsky D. The use of nitrogen mustard in the palliative treatment of cancer. *Cancer* 1948;**1**:634–56.

**Lazlo-Langner 2007**

Lazo-Langner A, Goss GD, Spaans JN, Rodger MA. The effect of low-molecular-weight heparin on cancer survival. A systematic review and meta-analysis of randomized trials. *Journal of Thrombosis and Haemostasis* 2007;**5**(4):729–37.

**Lee 2003**

Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al.Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *New England Journal of Medicine* 2003;**349**(2):146–53.

**Levine 2003**

Levine MN, Lee AY, Kakkar AK. From Trousseau to targeted therapy: new insights and innovations in thrombosis and cancer. *Journal of Thrombosis and Haemostasis* 2003;**1**(7):1456–63.

**Oken 1982**

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al.Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* 1982;**5** (6):649–55.

**Parmar 1998**

Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815–34.

**Prandoni 1992**

Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992; **339**:441–5.

**Prandoni 2002**

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

**Salat 1990**

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

**Sideras 2005**

Sideras K, Schaefer PL, Okuno SH, Sloan JA, Kutteh L, Dakhil SR, et al.Phase III clinical trial evaluating low-molecular weight heparin (LMWH) in patients with advanced cancer: A North Central Cancer Treatment Group study.. Journal Of Clinical Oncology. 2005; Vol. 23, issue 16:775S.

**Smorenburg 1999**

Smorenburg SM, Hettiarachchi RJ, Vink R, Buller HR. The effects of unfractionated heparin on survival in patients with malignancy-a systematic review. *Thrombosis and Haemostasis* 1999;**82**(6):1600–4.

**Smorenburg 2001**

Smorenburg SM, Van Noorden CJ. The complex effects of heparins on cancer progression and metastasis in experimental studies. *Pharmacological Reviews* 2001;**53**(1):93–105.

**Thodiyil 2002**

Thodiyil P, Kakkar AK. Can low-molecular-weight heparins improve outcomes in patients with cancer?. *Cancer treatment Reviews* 2002; **28**:151–5.

* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

**Altinbas 2004**

**Altinbas 2004**

| | |
|---|---|
| Methods | Blinded:outcome assessors<br>ITT analysis: yes<br>Study stopped early: no |
| Participants | Small cell lung cancer both limited and extensive, ECOG state<3; 84 patients randomized, 84 patients followed up (100%); median age 58 |
| Interventions | LMWH (Dalteparin; prophylactic dose) vs. placebo for 18 weeks or less if disease progressed; in combination with chemotherapy |
| Outcomes | Outcomes: mortality (at 12 and 24 months) , DVT, and minor bleeding<br>Screening and diagnostic testing for DVT: not reported |
| Notes | Funding: not reported; maximum follow up: 33 months |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Kakkar 2004**

| | |
|---|---|
| Methods | Blinded: patients, care givers<br>ITT analysis: no (investigators excluded patients who did not have at least one injection of study drug or placebo)<br>Study stopped early: no |
| Participants | Different types with advanced stage III or IV malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary , or uterus; minimum life expectancy 3 months; 385 randomized, 374 followed up (97%); no withdrawal from treatment; median age 61 IOR [53-68] |
| Interventions | LMWH (Dalteparin; prophylactic dose) vs. placebo for 12 months; no restriction on concomitant chemotherapy or radiotherapy |
| Outcomes | Outcomes: mortality (at 12, 24, and 36 months), PE, DVT, major bleeding, and minor bleeding<br>Screening testing for DVT/PE: None<br>Diagnostic testing for DVT/PE: not reported |
| Notes | Funding: Pharmacia Corp, NY; maximum follow up: 77 months |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Kakkar 2004** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Klerk 2005**

| | |
|---|---|
| Methods | Blinded: patients, care givers, outcome assessors<br>ITT analysis: yes<br>Study stopped early: no |
| Participants | Different types of solid malignant tumours, "that could not be treated curatively" inclulding: colorectal, breast, lung gastric, oesophageal, liver, gallbladder, Katskin, prostate, pancreatic, cervical, urothelial, renal, ovarian, melanoma, endometrial and other cancers; minimum life expectancy 1 month, stratified according to life expectancy (< or > 6 months); 302 patients randomized, 302 followed up (100%); median age 64 |
| Interventions | LMWH (Nadroparin) vs. placebo for 6 weeks; 2 weeks therapeutic dose then 4 weeks prophylactic dose; no concomitant chemotherapy or radiotherapy |
| Outcomes | Outcomes: mortality (at 6, 12, and 24 months), major bleeding, and major or minor bleeding |
| Notes | Funding: Sanofi provided study medication; maximum follow up: 84 months |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Lebeau 1994**

| | |
|---|---|
| Methods | Blinded: outcome assessors, data analyst<br>ITT analysis: yes<br>Study stopped early: no |
| Participants | Small cell lung cancer both limited and extensive; 78% had Karnofsky>80; 277 randomized and 277 followed up. (100%);85% older than 50 |
| Interventions | UFH (prophylactic dose) vs. no intervention for 5 weeks; in combination with chemotherapy |
| Outcomes | Outcomes: mortality (at 12, 24, and 36 months) |
| Notes | Funding: None; maximum follow up: 84 months |

***Risk of bias***

**Lebeau 1994** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Sideras 2006**

| | |
|---|---|
| Methods | Blinded: patients, care givers, outcome assessors (first 37% of the randomized patients)<br>ITT analysis: no<br>Study stopped early for insufficient accrual |
| Participants | Different types of advanced cancer with minimum life expectancy 12 weeks; ECOG state 0-2; 141 randomized, 138 followed up (98%); no withdrawal from treatment; median age 67 |
| Interventions | LMWH (Dalteparin; prophylactic dose) vs. placebo for unclear duration or no intervention |
| Outcomes | Outcomes: mortality (at 12, 24, and 36 months), VTE, and major bleed,<br>Screening testing for DVT/PE: None<br>Diagnostic testing for DVT: decided by the primary clinician |
| Notes | Funding: governmentally funded, pharmaceutical company supplied drug and placebo; maximum follow up: 24 months |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

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

| | |
|---|---|
| Alifano 2005 | Letter to the editor |
| Arbit 2005 | Letter to the editor |
| Barberi-Heyob 1995 | Letter to the editor |
| Bitsch 1990 | Topical heparin |
| Blaszczyk 1970 | Not randomized |
| Buckman 2005 | No control group |

(*Continued*)

| | |
|---|---|
| Craven 2001 | Letter to editor |
| Di Nisio 2005 | Review |
| Edlis 1976 | No control group |
| Elias 1972 | Case series |
| Elias 1973a | Not randomized |
| Elias 1973b | Case series |
| Elias 1973c | Not randomized |
| Elias 1974 | Case series |
| Elias 1975 | Not randomized |
| Fielding 1992 | Intraportal infusion with heparin |
| Green 1992 | Letter to the editor |
| Guimbretiere 1982 | Not randomized |
| Jorgensen 2001 | No control group |
| Kohanna 1983 | Retrospective study |
| Lecumberri 2005 | Review |
| Levine 2005 | Treatment for DVT/PE; Letter |
| Loynes 2002 | Case report |
| Lykke 2003 | Review |
| Mammen 2004 | Preface |
| Mousa 2001 | No cancer patients in the study |
| Nash 2000 | Letter to editor |
| Nitti 1997 | Intraportal infusion with heparin |
| Retik 1962 | No cancer patients in the study |

(*Continued*)

| | |
|---|---|
| Rohwedder 1977 | No control group |
| Siragusa 1999 | Letter to the editor |
| Spigel 2005 | Review |
| Von Hugo 1981 | No survival outcome |
| Wojtukiewicz 2003 | No control group |
| Zacharski 2003 | Editorial |

## DATA AND ANALYSES

### Comparison 1. Heparin vs placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality over duration of study | 5 | 1174 | Hazard Ratio (Random, 95% CI) | 0.77 [0.65, 0.91] |
| 1.1 SCLC | 2 | 361 | Hazard Ratio (Random, 95% CI) | 0.65 [0.49, 0.87] |
| 1.2 Advanced cancer | 3 | 813 | Hazard Ratio (Random, 95% CI) | 0.84 [0.68, 1.03] |
| 2 Mortality at 12 months | 5 | 1174 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.80, 0.95] |
| 2.1 SCLC | 2 | 361 | Risk Ratio (M-H, Random, 95% CI) | 0.83 [0.70, 0.97] |
| 2.2 Advanced Cancer | 3 | 813 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.80, 1.00] |
| 3 Mortality at 24 months | 5 | 1174 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.86, 0.99] |
| 3.1 SCLC | 2 | 361 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.78, 1.07] |
| 3.2 Advanced Cancer | 3 | 813 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.85, 1.00] |
| 4 Mortality SCLC, over duration of study | 2 | 361 | Hazard ratio (Random, 95% CI) | 0.70 [0.56, 0.89] |
| 4.1 Limited SCLC | 2 | 169 | Hazard ratio (Random, 95% CI) | 0.56 [0.38, 0.83] |
| 4.2 Extensive SCLC | 2 | 192 | Hazard ratio (Random, 95% CI) | 0.80 [0.60, 1.06] |
| 5 Mortality at 12 months SCLC | 2 | 361 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.56, 1.05] |
| 5.1 Limited SCLC | 2 | 169 | Risk Ratio (M-H, Random, 95% CI) | 0.60 [0.42, 0.87] |
| 5.2 Extensive SCLC | 2 | 192 | Risk Ratio (M-H, Random, 95% CI) | 0.93 [0.76, 1.15] |
| 6 Mortality at 24 months SCLC | 2 | 361 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.80, 1.04] |
| 6.1 Limited SCLC | 2 | 169 | Risk Ratio (M-H, Random, 95% CI) | 0.90 [0.71, 1.14] |
| 6.2 Extensive SCLC | 2 | 192 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.65, 1.18] |
| 7 DVT | 2 | 458 | Risk Ratio (M-H, Random, 95% CI) | 0.61 [0.08, 4.91] |
| 8 Any bleeding | 4 | 1574 | Risk Ratio (M-H, Random, 95% CI) | 1.78 [0.73, 4.38] |
| 8.1 Minor Bleeding | 3 | 760 | Risk Ratio (M-H, Random, 95% CI) | 2.07 [0.78, 5.51] |
| 8.2 Major bleeding | 3 | 814 | Risk Ratio (M-H, Random, 95% CI) | 1.50 [0.26, 8.80] |

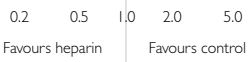
## Analysis 1.1. Comparison 1 Heparin vs placebo, Outcome 1 Mortality over duration of study.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 1 Mortality over duration of study

| Study or subgroup | Heparin N | Control N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 SCLC | | | | | | |
| Altinbas 2004 | 42 | 42 | -0.6531 (0.2321) | | 10.8 % | 0.52 [ 0.33, 0.82 ] |
| Lebeau 1994 | 138 | 139 | -0.334 (0.1222) | | 23.7 % | 0.72 [ 0.56, 0.91 ] |
| **Subtotal (95% CI)** | | | | | **34.5 %** | **0.65 [ 0.49, 0.87 ]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.48$, df = 1 (P = 0.22); $I^2 = 32\%$ | | | | | | |
| Test for overall effect: Z = 2.93 (P = 0.0033) | | | | | | |
| 2 Advanced cancer | | | | | | |
| Kakkar 2004 | 190 | 184 | -0.2395 (0.1103) | | 25.9 % | 0.79 [ 0.63, 0.98 ] |
| Klerk 2005 | 148 | 154 | -0.2838 (0.1123) | | 25.5 % | 0.75 [ 0.60, 0.94 ] |
| Sideras 2006 | 68 | 69 | 0.1406 (0.1927) | | 14.1 % | 1.15 [ 0.79, 1.68 ] |
| **Subtotal (95% CI)** | | | | | **65.5 %** | **0.84 [ 0.68, 1.03 ]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.81$, df = 2 (P = 0.15); $I^2 = 47\%$ | | | | | | |
| Test for overall effect: Z = 1.68 (P = 0.093) | | | | | | |
| **Total (95% CI)** | | | | | **100.0 %** | **0.77 [ 0.65, 0.91 ]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.63$, df = 4 (P = 0.11); $I^2 = 48\%$ | | | | | | |
| Test for overall effect: Z = 3.01 (P = 0.0026) | | | | | | |



Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 1 Mortality over duration of study

| Study or subgroup | Heparin N | Control N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 SCLC | | | | | | |
| Altinbas 2004 | 42 | 42 | -0.6531 (0.2321) | | 10.8 % | 0.52 [ 0.33, 0.82 ] |
| Lebeau 1994 | 138 | 139 | -0.334 (0.1222) | | 23.7 % | 0.72 [ 0.56, 0.91 ] |
| **Subtotal (95% CI)** | | | | | **34.5 %** | **0.65 [ 0.49, 0.87 ]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.48$, df = 1 (P = 0.22); $I^2 = 32\%$ | | | | | | |
| Test for overall effect: Z = 2.93 (P = 0.0033) | | | | | | |


Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 1 Mortality over duration of study

| Study or subgroup | Heparin N | Control N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 2 Advanced cancer | | | | | | |
| Kakkar 2004 | 190 | 184 | -0.2395 (0.1103) | | 25.9 % | 0.79 [ 0.63, 0.98 ] |
| Klerk 2005 | 148 | 154 | -0.2838 (0.1123) | | 25.5 % | 0.75 [ 0.60, 0.94 ] |
| Sideras 2006 | 68 | 69 | 0.1406 (0.1927) | | 14.1 % | 1.15 [ 0.79, 1.68 ] |
| **Subtotal (95% CI)** | | | | | **65.5 %** | **0.84 [ 0.68, 1.03 ]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.81$, df = 2 (P = 0.15); $I^2 = 47\%$ | | | | | | |
| Test for overall effect: Z = 1.68 (P = 0.093) | | | | | | |

## Analysis 1.2. Comparison 1 Heparin vs placebo, Outcome 2 Mortality at 12 months.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

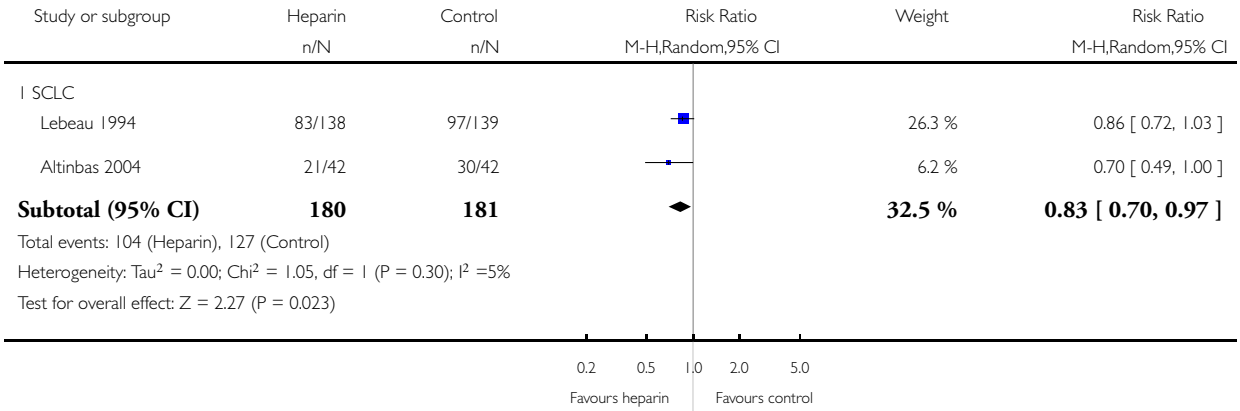
Outcome: 2 Mortality at 12 months

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 SCLC | | | | | |
| Lebeau 1994 | 83/138 | 97/139 | | 26.3 % | 0.86 [ 0.72, 1.03 ] |
| Altinbas 2004 | 21/42 | 30/42 | | 6.2 % | 0.70 [ 0.49, 1.00 ] |
| **Subtotal (95% CI)** | **180** | **181** | | **32.5 %** | **0.83 [ 0.70, 0.97 ]** |
| Total events: 104 (Heparin), 127 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.05$, df = 1 (P = 0.30); $I^2 = 5\%$ | | | | | |
| Test for overall effect: Z = 2.27 (P = 0.023) | | | | | |
| 2 Advanced Cancer | | | | | |
| Kakkar 2004 | 103/190 | 109/184 | | 25.4 % | 0.92 [ 0.77, 1.09 ] |
| Klerk 2005 | 90/148 | 112/153 | | 30.9 % | 0.83 [ 0.71, 0.98 ] |
| Sideras 2006 | 42/68 | 42/70 | | 11.2 % | 1.03 [ 0.79, 1.35 ] |
| **Subtotal (95% CI)** | **406** | **407** | | **67.5 %** | **0.89 [ 0.80, 1.00 ]** |
| Total events: 235 (Heparin), 263 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.94$, df = 2 (P = 0.38); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 2.04 (P = 0.041) | | | | | |
| **Total (95% CI)** | **586** | **588** | | **100.0 %** | **0.87 [ 0.80, 0.95 ]** |
| Total events: 339 (Heparin), 390 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.58$, df = 4 (P = 0.47); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 3.02 (P = 0.0025) | | | | | |

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

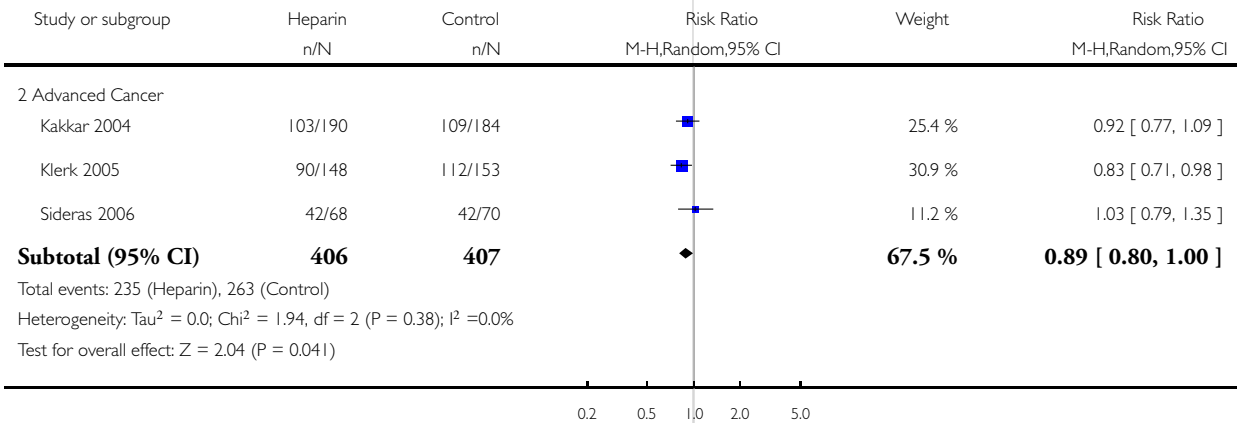
Outcome: 2 Mortality at 12 months




Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 2 Mortality at 12 months



## Analysis 1.3. Comparison 1 Heparin vs placebo, Outcome 3 Mortality at 24 months.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

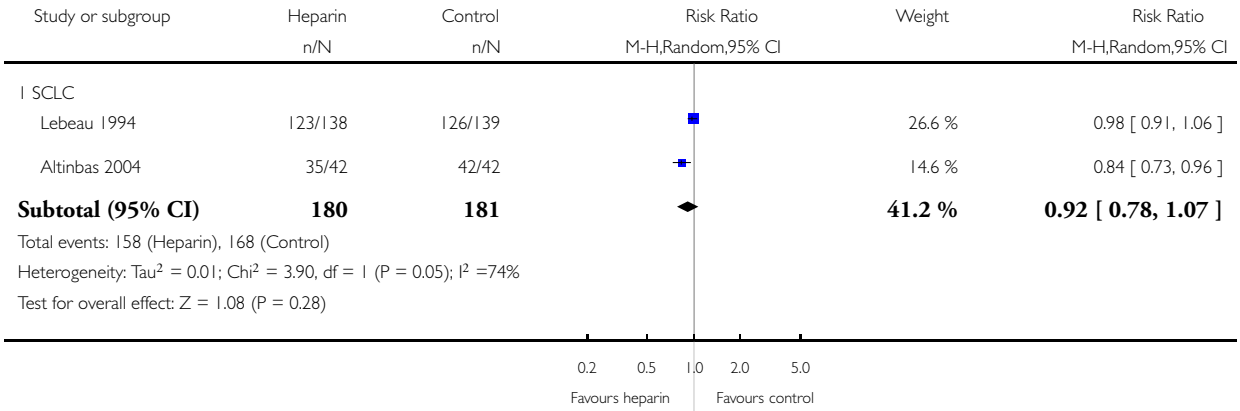
Outcome: 3 Mortality at 24 months

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 SCLC | | | | | |
| Lebeau 1994 | 123/138 | 126/139 | | 26.6 % | 0.98 [ 0.91, 1.06 ] |
| Altinbas 2004 | 35/42 | 42/42 | | 14.6 % | 0.84 [ 0.73, 0.96 ] |
| **Subtotal (95% CI)** | **180** | **181** | | **41.2 %** | **0.92 [ 0.78, 1.07 ]** |
| Total events: 158 (Heparin), 168 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.90$, df = 1 (P = 0.05); $I^2 = 74\%$ | | | | | |
| Test for overall effect: Z = 1.08 (P = 0.28) | | | | | |
| 2 Advanced Cancer | | | | | |
| Kakkar 2004 | 139/190 | 151/184 | | 19.8 % | 0.89 [ 0.80, 0.99 ] |
| Klerk 2005 | 117/148 | 137/153 | | 21.9 % | 0.88 [ 0.80, 0.97 ] |
| Sideras 2006 | 60/68 | 61/70 | | 17.1 % | 1.01 [ 0.89, 1.15 ] |
| **Subtotal (95% CI)** | **406** | **407** | | **58.8 %** | **0.92 [ 0.85, 1.00 ]** |
| Total events: 316 (Heparin), 349 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.31$, df = 2 (P = 0.19); $I^2 = 40\%$ | | | | | |
| Test for overall effect: Z = 1.96 (P = 0.050) | | | | | |
| **Total (95% CI)** | **586** | **588** | | **100.0 %** | **0.92 [ 0.86, 0.99 ]** |
| Total events: 474 (Heparin), 517 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.72$, df = 4 (P = 0.10); $I^2 = 48\%$ | | | | | |
| Test for overall effect: Z = 2.31 (P = 0.021) | | | | | |

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

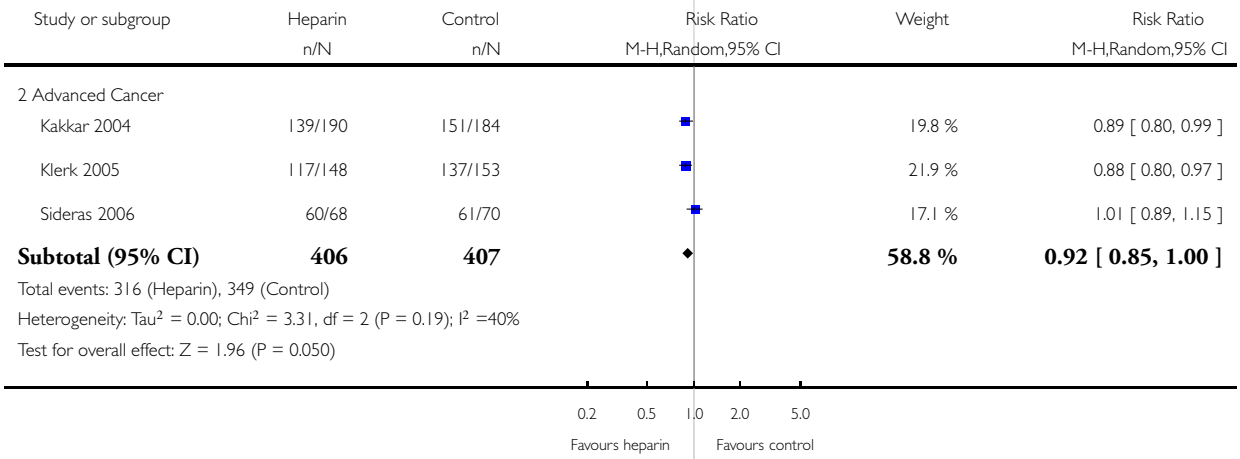
Outcome: 3 Mortality at 24 months




Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 3 Mortality at 24 months



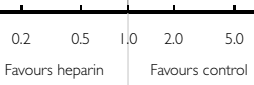
### Analysis 1.4. Comparison 1 Heparin vs placebo, Outcome 4 Mortality SCLC, over duration of study.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 4 Mortality SCLC, over duration of study

| Study or subgroup | Heparin N | Control N | log [Hazard ratio] (SE) | Hazard ratio IV,Random,95% CI | Weight | Hazard ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 Limited SCLC | | | | | | |
| Altinbas 2004 | 23 | 25 | -0.8897 (0.439) | | 7.3 % | 0.41 [ 0.17, 0.97 ] |
| Lebeau 1994 | 64 | 57 | -0.4909 (0.22) | | 28.4 % | 0.61 [ 0.40, 0.94 ] |
| **Subtotal (95% CI)** | | | | | **35.7 %** | **0.56 [ 0.38, 0.83 ]** |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.66, df = 1 (P = 0.42); $I^2$ =0.0% | | | | | | |
| Test for overall effect: Z = 2.90 (P = 0.0037) | | | | | | |
| 2 Extensive SCLC | | | | | | |
| Altinbas 2004 | 19 | 17 | -0.476 (0.4234) | | 7.9 % | 0.62 [ 0.27, 1.42 ] |
| Lebeau 1994 | 74 | 82 | -0.192 (0.1533) | | 56.5 % | 0.83 [ 0.61, 1.11 ] |
| **Subtotal (95% CI)** | | | | | **64.3 %** | **0.80 [ 0.60, 1.06 ]** |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.40, df = 1 (P = 0.53); $I^2$ =0.0% | | | | | | |
| Test for overall effect: Z = 1.56 (P = 0.12) | | | | | | |
| **Total (95% CI)** | | | | | **100.0 %** | **0.70 [ 0.56, 0.89 ]** |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 3.07, df = 3 (P = 0.38); $I^2$ =2% | | | | | | |
| Test for overall effect: Z = 2.94 (P = 0.0033) | | | | | | |



Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 4 Mortality SCLC, over duration of study

| Study or subgroup | Heparin N | Control N | log [Hazard ratio] (SE) | Hazard ratio IV,Random,95% CI | Weight | Hazard ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 Limited SCLC | | | | | | |
| Altinbas 2004 | 23 | 25 | -0.8897 (0.439) | | 7.3 % | 0.41 [ 0.17, 0.97 ] |
| Lebeau 1994 | 64 | 57 | -0.4909 (0.22) | | 28.4 % | 0.61 [ 0.40, 0.94 ] |
| **Subtotal (95% CI)** | | | | | **35.7 %** | **0.56 [ 0.38, 0.83 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.66$, df = 1 (P = 0.42); $I^2 = 0.0\%$

Test for overall effect: Z = 2.90 (P = 0.0037)


Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 4 Mortality SCLC, over duration of study

| Study or subgroup | Heparin N | Control N | log [Hazard ratio] (SE) | Hazard ratio IV,Random,95% CI | Weight | Hazard ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 2 Extensive SCLC | | | | | | |
| Altinbas 2004 | 19 | 17 | -0.476 (0.4234) | | 7.9 % | 0.62 [ 0.27, 1.42 ] |
| Lebeau 1994 | 74 | 82 | -0.192 (0.1533) | | 56.5 % | 0.83 [ 0.61, 1.11 ] |
| **Subtotal (95% CI)** | | | | | **64.3 %** | **0.80 [ 0.60, 1.06 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 1.56 (P = 0.12)

### Analysis 1.5. Comparison 1 Heparin vs placebo, Outcome 5 Mortality at 12 months SCLC.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

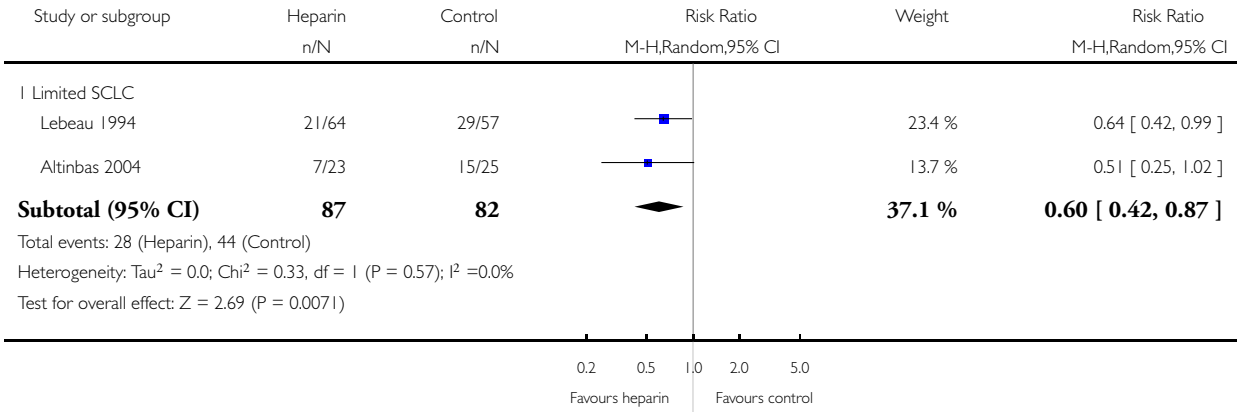
Outcome: 5 Mortality at 12 months SCLC

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Limited SCLC | | | | | |
| Lebeau 1994 | 21/64 | 29/57 | | 23.4 % | 0.64 [ 0.42, 0.99 ] |
| Altinbas 2004 | 7/23 | 15/25 | | 13.7 % | 0.51 [ 0.25, 1.02 ] |
| **Subtotal (95% CI)** | **87** | **82** | | **37.1 %** | **0.60 [ 0.42, 0.87 ]** |
| Total events: 28 (Heparin), 44 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.33$, df = 1 (P = 0.57); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 2.69 (P = 0.0071) | | | | | |
| 2 Extensive SCLC | | | | | |
| Lebeau 1994 | 57/74 | 64/82 | | 38.2 % | 0.99 [ 0.83, 1.17 ] |
| Altinbas 2004 | 12/19 | 14/17 | | 24.7 % | 0.77 [ 0.51, 1.15 ] |
| **Subtotal (95% CI)** | **93** | **99** | | **62.9 %** | **0.93 [ 0.76, 1.15 ]** |
| Total events: 69 (Heparin), 78 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.26$, df = 1 (P = 0.26); $I^2 = 21\%$ | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | |
| **Total (95% CI)** | **180** | **181** | | **100.0 %** | **0.77 [ 0.56, 1.05 ]** |
| Total events: 97 (Heparin), 122 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 7.87$, df = 3 (P = 0.05); $I^2 = 62\%$ | | | | | |
| Test for overall effect: Z = 1.68 (P = 0.094) | | | | | |

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

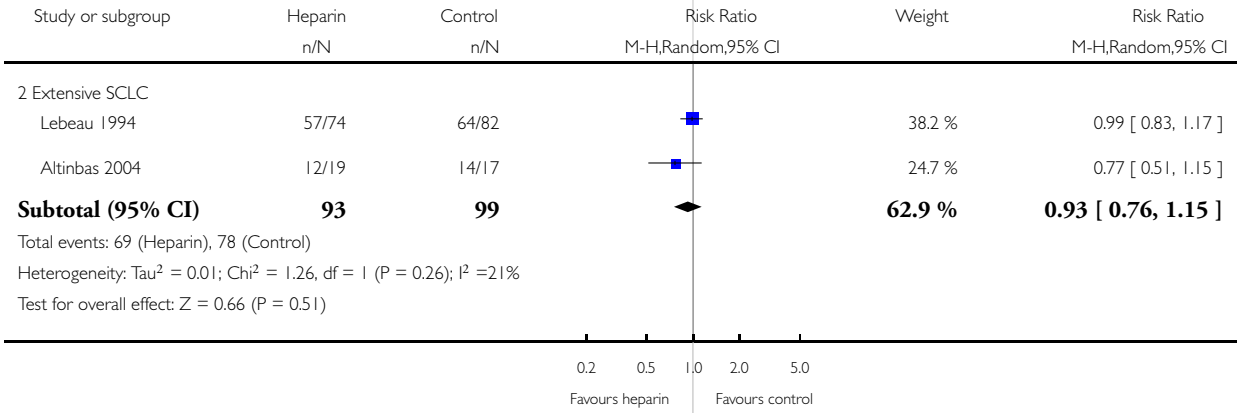
Outcome: 5 Mortality at 12 months SCLC




Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 5 Mortality at 12 months SCLC



### Analysis 1.6. Comparison 1 Heparin vs placebo, Outcome 6 Mortality at 24 months SCLC.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

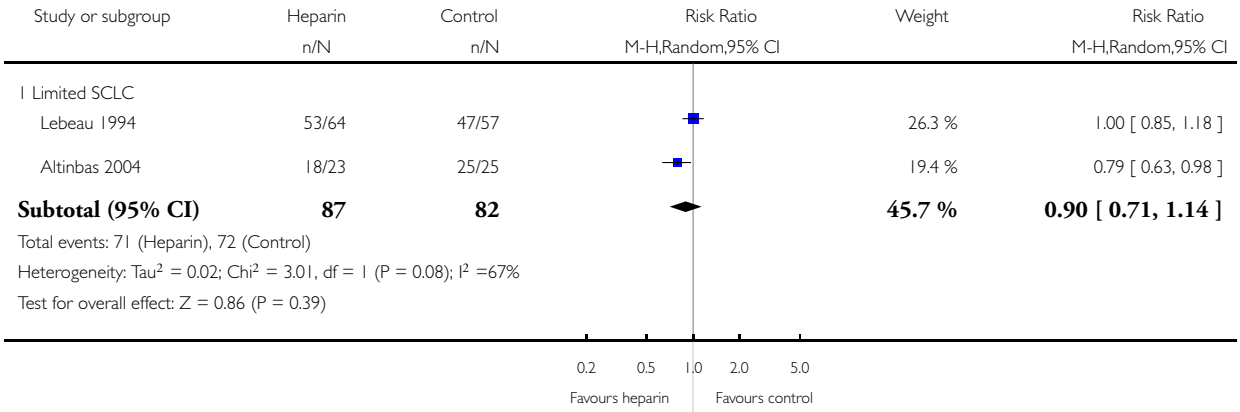
Outcome: 6 Mortality at 24 months SCLC

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Limited SCLC | | | | | |
| Lebeau 1994 | 53/64 | 47/57 | | 26.3 % | 1.00 [ 0.85, 1.18 ] |
| Altinbas 2004 | 18/23 | 25/25 | | 19.4 % | 0.79 [ 0.63, 0.98 ] |
| **Subtotal (95% CI)** | **87** | **82** | | **45.7 %** | **0.90 [ 0.71, 1.14 ]** |
| Total events: 71 (Heparin), 72 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.01$, df = 1 (P = 0.08); $I^2 = 67\%$ | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | |
| 2 Extensive SCLC | | | | | |
| Lebeau 1994 | 70/74 | 79/82 | | 39.6 % | 0.98 [ 0.92, 1.05 ] |
| Altinbas 2004 | 14/19 | 17/17 | | 14.7 % | 0.75 [ 0.56, 0.99 ] |
| **Subtotal (95% CI)** | **93** | **99** | | **54.3 %** | **0.88 [ 0.65, 1.18 ]** |
| Total events: 84 (Heparin), 96 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.41$, df = 1 (P = 0.04); $I^2 = 77\%$ | | | | | |
| Test for overall effect: Z = 0.84 (P = 0.40) | | | | | |
| **Total (95% CI)** | **180** | **181** | | **100.0 %** | **0.91 [ 0.80, 1.04 ]** |
| Total events: 155 (Heparin), 168 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.51$, df = 3 (P = 0.06); $I^2 = 60\%$ | | | | | |
| Test for overall effect: Z = 1.43 (P = 0.15) | | | | | |

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

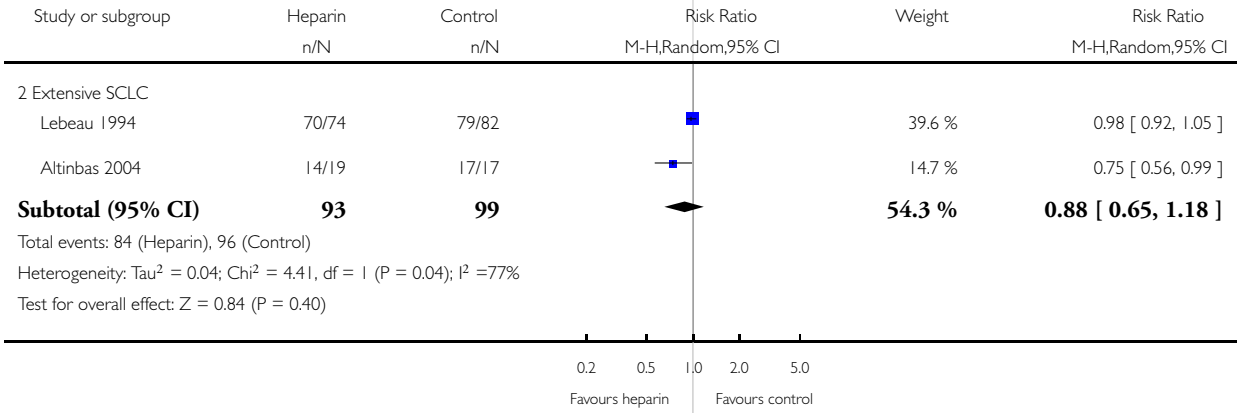
Outcome: 6 Mortality at 24 months SCLC




Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 6 Mortality at 24 months SCLC



### Analysis 1.7. Comparison 1 Heparin vs placebo, Outcome 7 DVT.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 7 DVT

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Altinbas 2004 | 0/42 | 1/42 | | 43.2 % | 0.33 [ 0.01, 7.96 ] |
| Kakkar 2004 | 1/190 | 1/184 | | 56.8 % | 0.97 [ 0.06, 15.37 ] |
| **Total (95% CI)** | **232** | **226** | | **100.0 %** | **0.61 [ 0.08, 4.91 ]** |

Total events: 1 (Heparin), 2 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.46 (P = 0.64)


### Analysis 1.8. Comparison 1 Heparin vs placebo, Outcome 8 Any bleeding.

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 8 Any bleeding

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Minor Bleeding | | | | | |
| Altinbas 2004 | 1/42 | 0/42 | | 7.4 % | 3.00 [ 0.13, 71.61 ] |
| Kakkar 2004 | 8/190 | 5/184 | | 38.5 % | 1.55 [ 0.52, 4.65 ] |
| Klerk 2005 | 5/148 | 0/154 | | 8.8 % | 11.44 [ 0.64, 205.14 ] |
| **Subtotal (95% CI)** | **380** | **380** | | **54.6 %** | **2.07 [ 0.78, 5.51 ]** |
| Total events: 14 (Heparin), 5 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.79$, df = 2 (P = 0.41); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 1.46 (P = 0.14) | | | | | |
| 2 Major bleeding | | | | | |
| Klerk 2005 | 5/148 | 1/154 | | 14.8 % | 5.20 [ 0.62, 44.01 ] |
| Sideras 2006 | 2/68 | 5/70 | | 23.3 % | 0.41 [ 0.08, 2.05 ] |


(*Continued . . .*)

(. . . *Continued*)

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Kakkar 2004 | 1/190 | 0/184 | | 7.3 % | 2.91 [ 0.12, 70.87 ] |
| **Subtotal (95% CI)** | **406** | **408** | | **45.4 %** | **1.50 [ 0.26, 8.80 ]** |
| Total events: 8 (Heparin), 6 (Control) | | | | | |
| Heterogeneity: $Tau^2$ = 1.18; $Chi^2$ = 3.85, df = 2 (P = 0.15); $I^2$ =48% | | | | | |
| Test for overall effect: Z = 0.45 (P = 0.65) | | | | | |
| **Total (95% CI)** | **786** | **788** | | **100.0 %** | **1.78 [ 0.73, 4.38 ]** |
| Total events: 22 (Heparin), 11 (Control) | | | | | |
| Heterogeneity: $Tau^2$ = 0.23; $Chi^2$ = 6.10, df = 5 (P = 0.30); $I^2$ =18% | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | |


Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

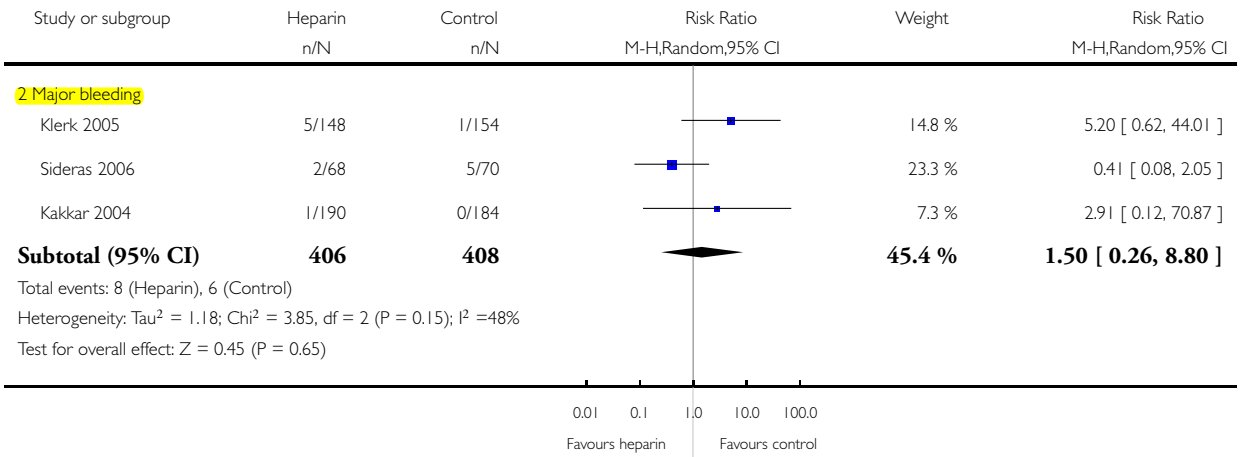
Outcome: 8 Any bleeding

| Study or subgroup | Heparin n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Minor Bleeding | | | | | |
| Altinbas 2004 | 1/42 | 0/42 | | 7.4 % | 3.00 [ 0.13, 71.61 ] |
| Kakkar 2004 | 8/190 | 5/184 | | 38.5 % | 1.55 [ 0.52, 4.65 ] |
| Klerk 2005 | 5/148 | 0/154 | | 8.8 % | 11.44 [ 0.64, 205.14 ] |
| **Subtotal (95% CI)** | **380** | **380** | | **54.6 %** | **2.07 [ 0.78, 5.51 ]** |
| Total events: 14 (Heparin), 5 (Control) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 1.79, df = 2 (P = 0.41); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.46 (P = 0.14) | | | | | |

Review: Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation

Comparison: 1 Heparin vs placebo

Outcome: 8 Any bleeding




## FEEDBACK

### Feedback from Dr D Cundiff

#### Summary

Date of Submission: 13-Sep-2007
Name: David K. Cundiff, MD
Email Address: dkcundiff3@verizon.net
Personal Description: Occupation Physician
Feedback: The major conclusions of the review depend on the statistically significant mortality benefit reported in the ?FAMOUS? RCT lead by AK Kakkar.1 However, same AK Kakkar was a co-author2 of one of the seven review-eligible studies for which data was not available.2-8 Consequently, since 12 RCTs were eligible and only five included, potentially biased selection of trials makes the interpretation of this data?favorable to heparin?highly suspect.
Regarding bleeding, the discussion mentioned, ?Heparin therapy may increase the risk of bleeding as high as 4 to 5 folds.? Given the amount of missing data, the finding that major bleeding was not significantly increased with heparins 8/406 versus 6/408 without offers no consolation or assurance that bleeding is not a major problem. The exclusion of observational studies from consideration in the safety analysis means the risks of bleeding and heparin induced thrombocytopenia with thrombosis (HITT) were almost certainly understated. Fatal bleeding and intracranial bleeding should have been included separately in the primary or secondary endpoints because of the vital importance of these events to physicians and patients.
Rebound hypercoagulability with heparins has been reported.9-13 Given the high rate of discontinuation of anticoagulation treatment in this patient population, the incidence of thrombotic events occurring within two months of discontinuing heparin or LMWH should have been assessed.
Consequently, the authors' conclusions, ?Heparin has a survival benefit in cancer patients in general, and in patients with limited SCLC in particular? are not valid.
Conflict of Interest Issues:
In addition to the relatively minor potential conflict of interest acknowledged by Dr. Holger J. Sch?nemann regarding quality of life instruments for chronic respiratory diseases, there are more serious ones. He was co-author of six articles from the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.14-19 AstraZeneca LP; Aventis Pharmaceuticals; Bristol-Myers Squibb/Sanofi-Syntholabo Partnership; GlaxoSmithKline; Organon Sanofi-Synthelabo LLC supported this anticoagulant-guideline producing conference.20

It should be stated whether the sources of support for this review (State University of New York at Buffalo, Department of Medicine USA, Italian National Cancer Institute Regina Elena, Rome ITALY, Academic Medical Center, Department of Vascular Medicine NETHERLANDS) have or have not received funding directly or indirectly from anticoagulant producing pharmaceutical companies.
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

### Reply

We thank Dr. Cundiff for the feedback
In fact, in addition to the Famous trial, the trials by Lebeau 1994,Altinbas 2004 and Klerk 2005 reported a statistically significant mortality benefit.
We agree that it would have been ideal to include data from the trials published as abstracts. It is relatively reassuring that the inverted funnel plot does not suggest publication bias; the distribution of results in these abstracts is likely similar to the studies included in this review.
Our current "Implications for practice" statement is cautious:
"This systematic review supports a survival benefit… It also suggests a higher benefit".
We will rephrase the abstract conclusion as follows:
"This review suggests a survival benefit of heparin in cancer patients in general, and in patients with limited small cell lung cancer in particular."
We will also the following to the 4th paragraph of the discussion ("Interpretation of the findings of this review is limited by the moderate heterogeneity…"):
"The interpretation of findings is also limited by not including data from the 7 trials published as abstracts only."
We agree that the absence of a statistically significant effect is not equivalent to true absence of an effect. This is exactly why we stated that the risk of bleeding may be as high as 4 to 5 folds. Our systematic review was not designed to include data from observational study and we adequately state this.
Unfortunately, the included trials do not report bleeding events in a detailed or standardized way allowing the analysis proposed by Dr. Cundiff. Both outcomes that we state above are devastating to patients and their family and grouping probably appropriate.
Dr. Cundiff raises an interesting question, whether the incidence of thrombotic events increases within two months of discontinuing heparin therapy. Unfortunately, the studies do not report whether the timing of the events relatively to discontinuing heparin and no individual patient data is available to explore this hypothesis.
Whether this hypothesis is true or not, in all but one trial (in which the duration of treatment was not reported), the mortality benefit extended well beyond the 2 months after heparin discontinuation. This fact makes our conclusion (which is now more cautious, as above) valid.
This is the second letter in which Dr. Cundiff refers to our COI statement. We previously described that our declarations were accurate, conform with and more exhaustive than the policy of the Cochrane Collaboration and refer the reader to that response:
EA Akl, G Kamath, SY Kim, V Yosuico, M Barba, I Terrenato, F Sperati, HJ Schünemann. Oral anticoagulation for prolonging survival in patients with cancer. Cochrane Database of Systematic Reviews. 2007 (2):CD006466 http://dx.doi.org/10.1002/14651858.CD006466
The statement for Dr. Schünemann reads:
"Schünemann: no personal payments from for-profit sponsors, but he received research grants and honoraria that were deposited into research accounts or received by a research group that he belongs to from AstraZeneca, Amgen, Chiesi Foundation, Lily, and Pfizer, Roche and UnitedBioSource for development or consulting regarding quality of life instruments for chronic respiratory diseases and as lecture fees related to the methodology of evidence based practice guideline development and research methodology. Institutions or organizations that Dr. Schünemann is affiliated with likely receive funding from for-profit sponsors that are supporting infrastructure and research that may serve to advance his work."

### Contributors

Elie A Akl
Holger Schunemann

## WHAT'S NEW

Last assessed as up-to-date: 14 May 2007.

| | | |
|---|---|---|
| 15 July 2008 | Amended | Converted to new review format. |

## HISTORY

Review first published: Issue 3, 2007

| | | |
|---|---|---|
| 15 May 2007 | New citation required and conclusions have changed | Substantive amendment<br>We updated the classification of heterogeneity:<br>We considered the following classification of heterogeneity based on the value of I2: 0-30 = low; 30-60 = moderate and worthy of investigation; 60-90 = severe and worthy of understanding; 90-100 = allowing aggregation only with major caution (Julian Higgins, personal communication.<br><br>We rephrased the abstract conclusion as follows:<br>"This review suggests a survival benefit of heparin in cancer patients in general, and in patients with small cell lung cancer in particular."<br><br>We also added the following to the 4th paragraph of the discussion ("Interpretation of the findings of this review is limited by the moderate heterogeneity…"):<br>"The interpretation of findings is also limited by not including data from the 7 trials published as abstracts only." |

## CONTRIBUTIONS OF AUTHORS

EAA: protocol development, search for trials, screening, data extraction, data analysis, manuscript drafting, review coordination. FFvD: data extraction, data analysis. MB: screening.GK: screening, search for trials, full text retrieval, data extraction. SYK: search for trials, screening. SK: data extraction, data analysis. SM: data extraction, data analysis. VY: full text retrieval, data extraction. HJS: protocol development, search for trials, data analysis, methodological advice. HOD: statistical analysis and methodological advice.

## DECLARATIONS OF INTEREST

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

## SOURCES OF SUPPORT

### Internal sources

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

### External sources

- Research Grants, Not specified.

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

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anticoagulants [*administration & dosage; adverse effects]; Carcinoma, Small Cell [mortality]; Hemorrhage [chemically induced]; Heparin [*administration & dosage; adverse effects]; Heparin, Low-Molecular-Weight [administration & dosage]; Lung Neoplasms [mortality]; Neoplasms [*mortality]; Randomized Controlled Trials as Topic; Survival Analysis; Warfarin [administration & dosage]

### MeSH check words

Humans