Venous thromboembolism, coagulation and cancer
van Doormaal, F.F.

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CHAPTER

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


As adapted from Cochrane Database Syst Rev. 2007;18:CD006652
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 as interventions to improve survival of patients with cancer.

Search strategy
A comprehensive search for studies of anticoagulation in cancer patients including (1) a January 2006 electronic search of the following databases: MEDLINE, EMBASE, ISI the Web of Science, and CENTRAL; (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
We included randomized clinical trials (RCT) comparing UFH, LMWH or fondaparinux to no intervention or placebo and RCTs comparing two of the three agents of interest in cancer patients without clinical evidence of venous thromboembolism.

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 15,572 identified citations 5 RCTs fulfilled the inclusion criteria. In all included RCTs the intervention consisted of heparin. The overall methodological quality of the included studies was acceptable. Heparin therapy (with either UFH or LMWH) was associated with a statistically and clinically significant reduction in mortality at 12 months (relative risk 0.87, 95% CI; 0.80-0.95) and 24 months (relative risk 0.92, 95% CI; 0.86-0.99). In subgroup analyses, the reduction was not statistically significant for patients with extensive small cell lung cancer (SCLC), but patients with limited SCLC experienced a survival benefit at 6 months (relative risk 0.27; 95% CI; 0.10-0.69) and 12 months (relative risk 0.60, 95% CI; 0.42-0.87). Heparin exerted a borderline statistically significant survival benefit in patients with advanced cancer showed at 12 months (relative risk 0.89, 95% CI; 0.80-1.00).
and 24 months (relative risk 0.92, 95% CI; 0.85-1.00). However, heparin at least doubled the risk of all bleeding (relative risk 2.21, 95% CI; 1.02-4.78).

Reviewers’ conclusions
Heparin has a survival benefit in cancer patients in general, and in patients with limited SCLC 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.

BACKGROUND
Since the 1930s, basic scientists have been exploring the effects of anticoagulation on cancer [1]. Studies have implicated the tumour-mediated activation of the haemostatic system in both the formation of tumour stroma and in tumour metastasis [2-4]. There is also evidence that heparin inhibits expression of oncogenes and formation of thrombin and fibrin induced by cancer cells. In addition, heparin potentially inhibits intravascular arrest of cancer cells and thus metastasis [1].

In this context, researchers have hypothesized that heparin may improve outcomes in cancer patients through an antitumour effect in addition to their antithrombotic effect [5]. 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 [6]. In 1999, Smorenburg et al conducted a systematic review of the effects of UFH on survival in patients with malignancy [7]. They found three trials of high methodological quality but with conflicting results.

Since 1999 several randomized controlled trials (RCTs) appeared on this subject [8;9] and, therefore, we systematically reviewed the literature and to assess both efficacy and safety outcomes of parenteral anticoagulation to prolong survival of cancer patients.
OBJECTIVES
To evaluate the effectiveness and safety of heparin (including UFH and LMWH) and fondaparinux in improving the survival of patients with cancer

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW
Types of studies
We included only randomized clinical trials (RCT).

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

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) All cause mortality;
(b) Symptomatic DVT;
(c) Symptomatic PE;
(d) Major bleeding;
(e) Minor bleeding

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES
The search was part of a comprehensive search for studies of anticoagulation in cancer patients. We electronically searched the following databases: MEDLINE (1966 onwards), EMBASE (1980 onwards), ISI the Web of Science, and The Cochrane Central Register of
Controlled Trials (CENTRAL). The search date was January 2006. We used the following search strategy:
1- (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)
2- (heparin)
3- (warfarin or coumarin)
4- (Fondaparinux or Arixtra)
5- (Ximelagatran or Exanta)
6- (Malignan$ OR Neoplas$ OR Cancer OR Carcinoma OR adenocarcinoma OR tumour OR tumor)
7- (1 OR 2 OR 3 OR 4 OR 5) AND 6

In addition, 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.

METHODS OF THE REVIEW
Selection of trials
Two reviewers independently screened the titles and abstracts of identified articles for eligibility. We retrieved the full text of articles judged by at least one reviewer as potentially eligible. Two reviewers then independently screened the full text articles for eligibility using a standardized form with explicit inclusion and exclusion criteria. The two reviewers resolved their disagreements by discussion or by consulting a third reviewer.
Methodological quality
Two reviewers 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, harm or insufficient accrual

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.

Data collection
We developed and used a standardized data extraction form. Two reviewers 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 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 vs. therapeutic
- Duration of treatment
- Control: placebo or no intervention

Outcomes
We extracted the outcome data necessary to conduct intention-to-treat (ITT) analyses. We collected all cause mortality at one year (time point defined a priori) and at 6 months, 2 years and 3 years (time points 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 reviewers 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.

DVT events had to be diagnosed using one of the following objective diagnostic tests: venography, 125I-fibrinogen-uptake test, impedance plethysmography or compression ultrasound. PE events had to be diagnosed using one of the following objective diagnostic tests: pulmonary perfusion/ventilation scans, computed tomography, pulmonary angiography or autopsy. For the evaluation of bleeding complications, we accepted the
authors’ definitions of major and minor bleeding and excluded data from studies where definitions were not provided or unclear.

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.

**Analysis**

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

Using the ITT principle, we calculated the relative risk 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 tested results for homogeneity across studies using the I² test [10] and considered substantial heterogeneity present if I² was greater than 50%. We created inverted funnel plots of individual study results plotted against the inverse of the variance in order to check for possible publication bias. We created the funnel plots for the primary outcome of death at 1 year as the other outcomes were reported by four or less number of studies.

To explain heterogeneity we conducted subgroup analyses based on the characteristics of participants, whenever data was available.

**DESCRIPTION OF STUDIES**

**Search yield**

The comprehensive search strategy identified 15,572 citations, including 4,852 duplicates. The title and abstract screening of the 10,720 unique citations identified 51 as potentially eligible for this review. The full text screening of the 51 citations identified 5 eligible RCTs published as full reports [8;9;11-13]. Agreement between reviewers for study eligibility was excellent (kappa = 0.94). The inverted funnel plot for the primary outcome of mortality at 1 year did not suggest publication bias (Figure 1).
Included studies

The five included studies, recruited a total of 1189 participants and reported follow-up data on 1175 [8;9;11-13] (Table). One study used UFH as the intervention [12] while the other four used LMWH as the intervention [8;9;11;13]. 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 [12]. The Karnofsky Performance Scale Index ranges from 0 (dead) to 100 (normal) [14]. Patients were randomized to receive along with their chemotherapy which was given in both arms either a prophylactic dose of UFH for 5 weeks or no intervention. The study outcome was mortality (at 1, 2 and 3 years). Follow up was complete.
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Intervention</th>
<th>Participants</th>
<th>Outcome assessment</th>
<th>Notes</th>
<th>Allocation Concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebeau 1994</td>
<td>Blinded: outcome assessors, data analyst ITT analysis: yes Study stopped early: no</td>
<td>UFH (prophylactic dose) vs. no intervention for 5 weeks; in combination with chemotherapy</td>
<td>Small cell lung cancer both limited and extensive; 78% had Karnofsky&gt;80; 277 randomized and 277 followed up.</td>
<td>Outcomes: mortality (at 12, 24, and 36 months)</td>
<td>Funding: None</td>
<td>Adequate</td>
</tr>
<tr>
<td>Kakkar 2004</td>
<td>Blinded; patients, care givers ITT analysis: yes Study stopped early: no</td>
<td>LMWH (Dalteparin; prophylactic dose) vs. placebo for 12 months; no restriction on concomitant chemotherapy or radiotherapy</td>
<td>Different types of advanced cancer (stage III or IV); minimum life expectancy 3 months; 385 randomized, 374 followed up</td>
<td>Outcomes: mortality (at 12, 24, and 36 months), PE, DVT, major bleed, and minor bleed Screening testing for DVT/PE: None Diagnostic testing for DVT/PE: not reported</td>
<td>Funding: Pharmacia Corp, NY</td>
<td>Adequate</td>
</tr>
<tr>
<td>Klerk 2005</td>
<td>Blinded; patients, care givers, outcome assessors ITT analysis: yes Study stopped early: no</td>
<td>LMWH (Nadroparin) vs. placebo for 6 weeks; 2 weeks therapeutic dose then 4 weeks prophylactic dose; no concomitant chemotherapy or radiotherapy</td>
<td>Different types of advanced cancer “that could not be treated curatively”; minimum life expectancy 1 month, stratified according to life expectancy (&lt; or &gt; 6 months); 302 patients randomized, 302 followed up</td>
<td>Outcomes: mortality (at 6, 12, and 24 months), major bleeding, and major or minor bleeding</td>
<td>Funding: Sanofi provided study medication</td>
<td>Adequate</td>
</tr>
<tr>
<td>Altinbas 2004</td>
<td>Blinded: outcome assessors ITT analysis: yes Study stopped early: no</td>
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<tr>
<td></td>
<td>LMWH (Dalteparin; prophylactic dose) vs. placebo for 18 weeks or less if disease progressed; in combination with chemotherapy</td>
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<tr>
<td></td>
<td>Small cell lung cancer both limited and extensive, ECOG state&lt;3; 84 patients randomized, 84 patients followed up</td>
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<tr>
<td></td>
<td>Outcomes: mortality (at 12 and 24 months), DVT, and minor bleeding</td>
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<tr>
<td></td>
<td>Screening and diagnostic testing for DVT: not reported</td>
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<tr>
<td></td>
<td>Funding: not reported</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Sideras 2006</th>
<th>Blinded: patients, care givers, outcome assessors (1* 37% of randomized patients) ITT analysis: no Study stopped early for insufficient accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMWH (Dalteparin; prophylactic dose) for unclear duration vs. placebo or no intervention</td>
</tr>
<tr>
<td></td>
<td>Different types of advanced cancer with minimum life expectancy 12 weeks; ECOG state 0-2; 141 randomized, 138 followed up</td>
</tr>
<tr>
<td></td>
<td>Outcomes: mortality (at 12, 24, and 36 months), VTE, and major bleed, Screening testing for DVT/PE: None Diagnostic testing for DVT: decided by the primary clinician</td>
</tr>
<tr>
<td></td>
<td>Funding: governmentally funded, pharmaceutical company supplied drug and placebo</td>
</tr>
<tr>
<td></td>
<td>Adequate</td>
</tr>
</tbody>
</table>
Kakkar et al. (the FAMOUS trial) recruited 385 patients with different types of advanced cancer (stage III or IV) and a minimum life expectancy of 3 months [8]. 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 1, 2 and 3 years), PE, DVT, major bleeding, and minor bleeding. Follow-up data were available for 374 patients.

Klerk et al. (MALT trial) recruited 302 patients with different types of advanced cancer that could not be treated curatively and a minimum life expectancy of 1 month [9]. Patients were randomized to receive either a LMWH (nadroparin; 2 weeks therapeutic dose followed by 4 weeks of a prophylactic dose) or a placebo for 6 weeks without any concomitant chemotherapy or radiotherapy. Study outcomes included mortality (at 6 months, 1 year and 2 years), major bleeding, and major or minor bleeding. Follow up was complete.

Altinbas et al. recruited 84 patients with both limited and extensive SCLC and an Eastern Cooperative Oncology Group (ECOG) state<3 [11]. The ECOG Performance Status scale ranges from 0 (fully active) to 5 (dead) [15]. 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 1 and 2 years), DVT, and minor bleeding. Follow up was complete.

Sideras et al. recruited 141 patients with different types of advanced cancer and a minimum life expectancy of 12 weeks and ECOG state 0-2 [13]. Patients were randomized either to a prophylactic dose of a LMWH (dalteparin) or to placebo or no intervention. Study outcomes included mortality (at 1, 2 and 3 years), VTE, and major bleeding. Follow-up data were available for 138 patients.

We excluded 46 articles from this review for the following reasons: studies published as abstracts for which we were not able to obtain data from authors (n=6); abstracts later published in full and included in this review (n=4); intervention was topical heparin (n=1) or intraportal infusion of heparin (n=2); studies included no cancer patients (n=2); no survival outcome (n=2); study design was not a RCT (n=16); letter to the editor or editorial (n=8); publication was a review (n=5).
METHODOLOGICAL QUALITY OF INCLUDED STUDIES
Allocation was adequately concealed in four of the five studies [8;9;12;13] and it was unclear whether it was adequately concealed in the fifth study [11]. While two studies blinded participants, caregivers, and outcome assessors [9;13], one study blinded patients and care givers [8], one study blinded outcome assessors and data analysts [12], and one study blinded only outcome assessors [11]. The lowest percentage of follow up in the five studies was 97.1%. Only one study did not use the ITT analysis principle [13]. Only one study was stopped early by patient monitoring committee for insufficient accrual [13]. We judged that in the study by Lebeau et al. [12] patients enrolled in the study received similar co-interventions although brain and thoracic irradiation depended on response to treatment. 11% and 6.5% respectively of patients randomized to heparin and control groups received radiotherapy.

RESULTS
Agreement between the two reviewers who extracted data from survival curves was high with an average percentage difference of 2.5%. The data were not heterogeneous (I2 statistic less than 50%) for the review outcomes at 1 year (the time point defined a priori). The data however showed substantial heterogeneity (I2 statistic higher than 50%) for overall mortality at 6 and 36 months, mortality for advanced cancer at 6, 24 and 36 months, mortality for limited SCLC at 24 months, and mortality for extensive SCLC at 24 months. 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 pooled estimate from the 5 RCTs, heparin therapy was associated with a reduction of mortality that was statistically significant at 12 months (relative risk 0.87, 95% CI; 0.80-0.95) (Figure 2) and at 24 months (relative risk 0.92, 95% CI; 0.86-0.99) but not at 6 months (relative risk 0.93, 95% CI; 0.68-1.28) or 36 months (relative risk 0.97, 95% CI; 0.89-1.05). We conducted a sensitivity analysis excluding the study by Lebeau et al. [12] because it is the only study using UFH. The results of this latter analysis did not change in terms of effect and statistical significance.
Chapter 4

### Review: Parenteral anticoagulation for prolonging survival in patients with cancer (Version 01)

**Comparison:** 01 Heparin vs placebo  
**Outcome:** 02 Overall mortality at 12 months

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitner 1994</td>
<td>93/128</td>
<td>97/139</td>
<td>26.29, 0.04 [0.72, 1.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allbrooke 2004</td>
<td>23/42</td>
<td>20/42</td>
<td>6.25, 0.75 [0.49, 1.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kivel 2005</td>
<td>25/88</td>
<td>133/133</td>
<td>25.13, 0.04 [0.77, 1.29]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nides 2005</td>
<td>42/49</td>
<td>47/70</td>
<td>25.10, 0.04 [0.77, 1.29]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>586</td>
<td>589</td>
<td>100.00, 0.07 [0.66, 0.69]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for heterogeneity: CHI² = 3.58, df = 4 (P = 0.47), I² = 0%  
Test for overall effect: Z = 3.12 (P = 0.002) |

**Fig. 2.** The effect of heparin therapy (either low molecular weight heparin or unfractionated heparin) on all cause mortality at 1 year in patients with cancer

In order to explain heterogeneity, we also conducted subgroup analyses for subgroups of patients with SCLC (extensive and limited separately) [11;12] and patients with advanced cancer [8;9;13].

### Small cell lung cancer

For limited SCLC, heparin therapy was associated with a reduction of mortality that was statistically significant at 6 months (relative risk 0.27, 95% CI; 0.10-0.69), 12 months (relative risk 0.60, 95% CI; 0.42-0.87) (Figure 3) but not at 24 months (relative risk 0.90, 95% CI; 0.71-1.14). For extensive SCLC, heparin effect on mortality was not statistically significant at 6 months (relative risk 0.86, 95% CI; 0.58-1.29), 12 months (relative risk 0.93, 95% CI; 0.76-1.15) (Figure 4) or 24 months (relative risk 0.88, 95% CI; 0.65-1.18).

### Review: Parenteral anticoagulation for prolonging survival in patients with cancer (Version 01)  
**Outcome:** 03 Mortality at 12 months limited SCLC

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitner 1994</td>
<td>31/64</td>
<td>26/67</td>
<td>72.03, 0.66 [0.43, 0.91]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allbrooke 2004</td>
<td>1/33</td>
<td>15/25</td>
<td>27.97, 0.51 [0.29, 1.02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>87</td>
<td>82</td>
<td>100.00, 0.60 [0.42, 0.87]</td>
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</tr>
</tbody>
</table>
| Test for heterogeneity: CHI² = 0.33, df = 1 (P = 0.57); I² = 0%  
Test for overall effect: Z = 2.69 (P = 0.007) |

**Fig. 3.** The effect of heparin therapy on all cause mortality at 1 year in patients with limited small cell lung cancer
Fig. 4. The effect of heparin therapy on all cause mortality at 1 year in patients with extensive small cell lung cancer

**Advanced cancer**

Pooling data from studies including patients with advanced cancer [8;9;13] did not show a statistically significant effect of heparin therapy on mortality at 6 months (relative risk 1.12, 95% CI: 0.78-1.62) or at 36 months (relative risk 0.96, 95% CI; 0.85-1.09) but a borderline significant effects at 12 months (relative risk 0.89, 95% CI; 0.80-1.00) (Figure 5) and at 24 months (relative risk 0.92, 95% CI; 0.85-1.00).

Fig. 5. The effect of heparin therapy on all cause mortality at 1 year in patients with advanced cancer

Klerk et al [9] 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 0.45-0.90) for patients with longer life expectancy and 0.88 (95% CI 0.62-1.25) for patients with shorter life expectancy.
Venous thromboembolism
Based on pooled estimates from two RCTs [8;11], heparin therapy was associated with a non-statistically significant reduction in DVT (relative risk 0.61, 95% CI 0.08-4.91).

Major and minor bleeding
Pooled estimates showed that heparin therapy was associated with increased bleeding that was non-statistically significant for minor bleeding (relative risk 1.66, 95% CI 0.59-4.70) or major bleeding (relative risk 1.50, 95% CI 0.26-8.80) but statistically significant for all bleeding (relative risk 2.21, 95% CI 1.02-4.78) (Figure 6).

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lelloux 1994</td>
<td>2/138</td>
<td>2/139</td>
<td>10.78</td>
<td>1.01</td>
<td>[0.14, 7.03]</td>
</tr>
<tr>
<td>Alibas 2004</td>
<td>1/43</td>
<td>0/43</td>
<td>5.94</td>
<td>3.00</td>
<td>[0.13, 7.41]</td>
</tr>
<tr>
<td>Kalb 2004</td>
<td>9/130</td>
<td>6/134</td>
<td>55.78</td>
<td>1.16</td>
<td>[0.24, 9.18]</td>
</tr>
<tr>
<td>Kies 2005</td>
<td>10/148</td>
<td>2/134</td>
<td>60.31</td>
<td>5.20</td>
<td>[1.14, 22.30]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>518</td>
<td>519</td>
<td>100.00</td>
<td>2.31</td>
<td>[1.02, 4.78]</td>
</tr>
<tr>
<td>Total events (22 Treatment, 9 Control)</td>
<td></td>
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<tr>
<td>Test for heterogeneity: Chi² = 2.13, df = 5 (P = 0.65); P = 0%</td>
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<tr>
<td>Test for overall effect: Z = 2.07 (P = 0.04)</td>
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**Fig. 6.** The effect of heparin therapy on all bleeding in patients with cancer

**DISCUSSION**
Heparin therapy (with either UFH or LMWH) was associated with a statistically and clinically significant reduction of mortality in cancer patients who had no indication for parenteral anticoagulation at 12 and 24 months. In patients with extensive small cell lung cancer there was no statistically significant reduction in mortality at any of the time-points we analysed, but in patient with limited small cell lung cancer, there was a clinically and statistically significant reduction in mortality at 6 and after 12 months. For patients with advanced cancer, there was a borderline statistically significant reduction in mortality at 12 and 24 months. Heparin therapy doubled the risk of bleeding. 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 or relevant data. The overall
methodological quality of the included studies was acceptable; 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 acceptable overall methodological quality, and the low likelihood of publication bias increase the confidence in the internal validity of our findings.

A limitation of this study is that the ‘no difference’ findings can be related to the small number of RCTs, of studied patients and of events. Although the results were homogeneous for the a priori defined outcome (i.e. overall mortality at 12 months), they were heterogeneous for a number of the other outcomes. The heterogeneity could have been related to factors such as the different types and stages of cancers, and the different 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 all of the necessary subgroup analyses to explore all these factors. The subgroup analyses based on type of cancer did not completely explain the heterogeneity.

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 6 months in the study by Klerk et al [9] are important to note. The CLOT trial [16] 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 extensive SCLC but not in patients with limited SCLC [17]. The reason for this discrepancy is unclear.
REVIEWERS’ 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 [18]. 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 [19].

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