

ORIGINAL ARTICLE

Efficacy and safety of adjunctive anticoagulation in patients with lung cancer without indication for anticoagulants: a systematic review and meta-analysis

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ABSTRACT

Background Patients with lung cancer are at high risk of venous thromboembolism (VTE), and VTE predicts a poor prognosis. Anticoagulation therefore might be beneficial for these patients. It is not clear whether anticoagulants could improve survival and other outcomes in patients with lung cancer with no indication for anticoagulation.

Methods We searched the Web of Science, Medline, EMBASE and Cochrane databases for relevant studies. Two reviewers evaluated the studies and extracted data independently. The primary outcomes were 1-year survival and incidence of VTE. Pooled risk ratios (RR) were calculated using control as a reference group and significance was determined by the Z test.

Results Nine eligible studies with 2185 participants were included. Anticoagulation showed significant improvement in survival at 1 year (RR 1.18, 95% CI 1.06 to 1.32; $p=0.004$) and at 2 years (RR 1.27, 95% CI 1.04 to 1.56; $p=0.02$), but not at 6 months. Subgroup analysis showed a survival benefit for patients with small cell lung cancer (SCLC) and those with non-advanced/limited cancer. The incidence of VTE (RR=0.55, 95% CI 0.31 to 0.97; $p=0.04$) and thromboembolic events (RR=0.48, 95% CI 0.28 to 0.82; $p=0.008$) was reduced with anticoagulation. Both vitamin K antagonist (VKA) and subcutaneous heparin increased the risk of haemorrhage, but heparin did not increase the incidence of major bleeding.

Conclusions Anticoagulation showed a survival benefit, especially for those with SCLC and prolonged life expectancy, and reduced the risk of VTE in lung cancer patients with no indication for anticoagulants. Subcutaneous heparin is superior to VKA because of a potentially smaller risk of major bleeding.

INTRODUCTION

It is well-known that malignancy is a common risk factor for venous thromboembolism (VTE).^{1 2} The incidence of VTE in patients with cancer has been reported to be increased by >20-fold compared with the general population,^{2 3} and this risk seems to increase further by 20–30% in patients with advanced cancer who receive chemotherapy.^{4 5} Lung cancer is among the malignant diseases showing the highest incidence of VTE.^{1 6} Many patients with lung cancer have a history of smoking and thus are more likely to have comorbidities which may further increase the risk of thromboembolic events.

Key messages

What is the key question?

► Can anticoagulants improve survival and other outcomes in patients with lung cancer without indication for anticoagulation?

What is the bottom line?

► This meta-analysis revealed a long-term survival benefit in addition to reduced incidence of venous thromboembolism from anticoagulation treatment in patients with lung cancer who have no clinical indication for anticoagulants.

Why read on?

► Patients with small cell lung cancer or prolonged life expectancy might benefit most from adjunctive anticoagulation.

Activation of coagulation can predict a poor prognosis in patients with lung cancer. Previous studies showed that elevated plasma levels of thrombin–antithrombin complex and D-dimer were associated with increased mortality.^{7 8} The presence of VTE is also a significant independent predictor of death.³ Danish registry data indicate that 1-year survival in cancer patients with VTE is three times less than in those without VTE.⁹ A more recent study by Huang *et al*⁵ reported that lung cancer patients with VTE had a twofold shorter time to death.

Anticoagulants have potential antitumour effects by mechanisms of regulating growth, apoptosis and differentiation of neoplastic cells, inhibiting angiogenesis and modulating metastatic processes in addition to their antithrombotic effect.¹⁰ Some small-scale studies have suggested that concomitant treatment with heparin may improve the response rate to chemotherapy and prolong progression-free survival in patients with small cell lung cancer (SCLC).^{11–14} Putting these facts together, it is rational to consider using anticoagulants in patients with lung cancer to achieve a better outcome.

However, individual studies on the survival benefit and safety of anticoagulation in patients with lung cancer were of limited sample size and

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there has been a lack of consistency between various studies due to heterogeneity. We therefore performed a systematic literature review and meta-analysis to investigate the impact of anticoagulants on survival in patients with lung cancer. The impact on the incidence of thromboembolic events and adverse events such as bleeding was also evaluated.

METHODS

Literature search

A literature search was performed using the Web of Knowledge (1990–July 2012) via the library of Fudan University and Medline (1990–July 2012) by PubMed search engines, with the databases being last accessed on 15 August 2012. The Cochrane Central database and EMBASE were also searched for relevant studies published up to July 2012. No language restriction was imposed. The search strategies were as follows: (lung cancer OR SCLC OR non-SCLC (NSCLC)) AND (coagulant* OR anticoagulant* OR coagulation OR heparin OR warfarin OR low-molecular-weight heparin (LMWH) OR vitamin K antagonist (VKA) OR low molecular weight heparin). The reference lists

of relevant publications were manually searched for additional studies. Ethical approval was not required for this meta-analysis.

Study eligibility

Two reviewers independently screened the abstracts of papers generated by the literature search, retrieved potentially relevant studies and determined study eligibility. Included studies had to be randomised controlled trials (RCTs) with at least two comparison groups (ie, anticoagulation treatment and controls) and survival data reported. Anticoagulation therapy could be oral VKA or heparin. In case of studies containing the same datasets as studies that had been published before, only the study with the largest sample size was included. Data published only in abstract form or from website materials were excluded because these studies had not been peer reviewed and their inclusion might introduce bias into the meta-analysis. Case reports, review articles and textbook chapters were also excluded from the analysis.

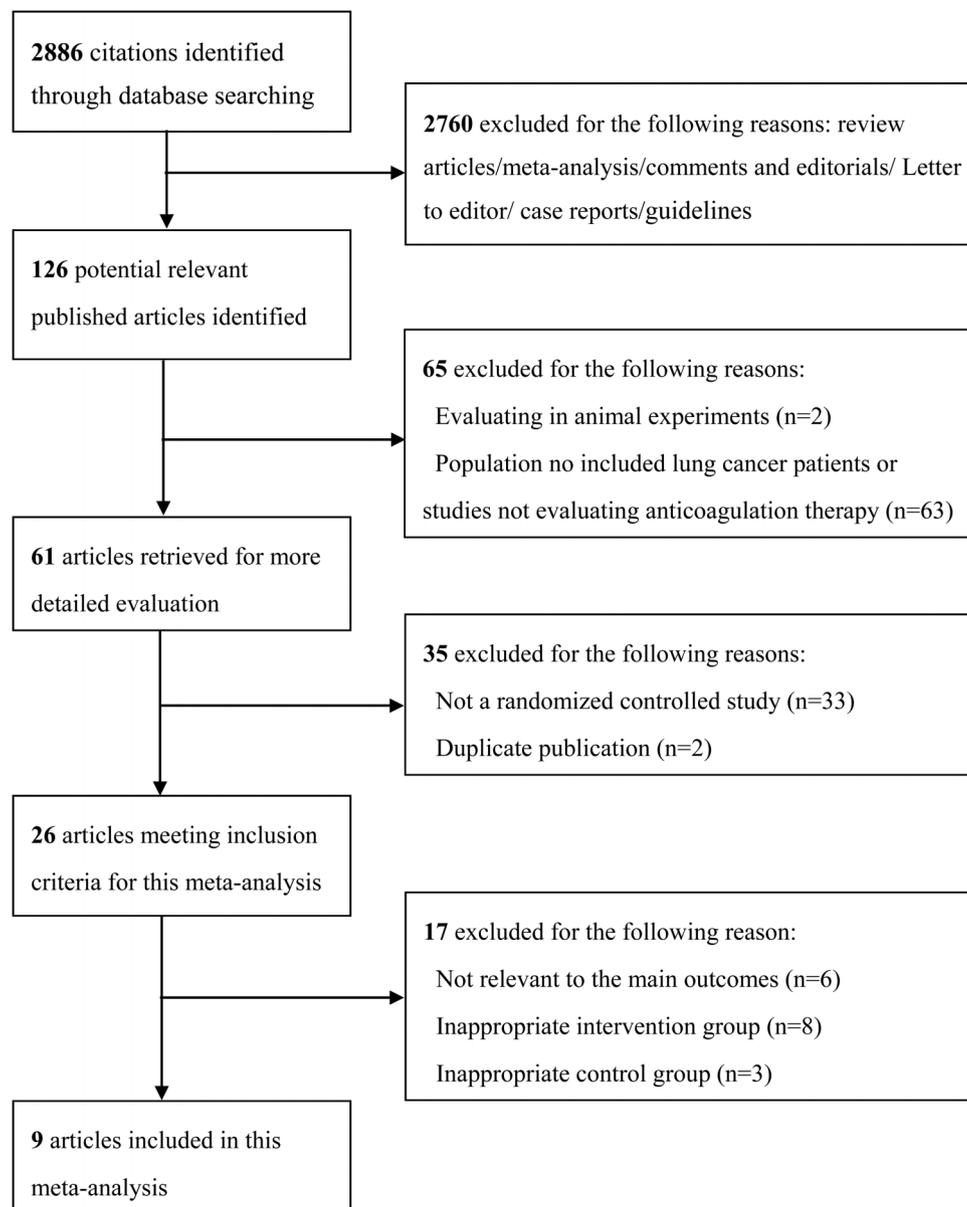


Figure 1 Flow of study selection.

Table 1 Characteristics of studies included in the meta-analysis

Study (year)	Population	Interventions	No. of patients	Quality score
Agnelli (2009)	Subjects extracted from the study with metastatic or locally advanced lung cancer undergoing CT	Intervention: subcutaneous nadroparin 3800 IU anti-Xa once daily. Control: placebo	199/80	5
Altinbas (2004)	Patients with SCLC undergoing chemotherapy	Intervention: dalteparin 5000 IU once daily during 18 weeks of CT. Control: no intervention	42/42	2
Altinbas-1 (2004)	Subjects extracted from the study: limited SCLC		23/25	
Altinbas-2 (2004)	Subjects extracted from the study: extensive SCLC		19/17	
Chahinian (1989)	Patients with extensive SCLC undergoing CT	Intervention: VKA (PT 1.5–2). Control: no intervention	103/85	2
Haas (2012)	Subjects extracted from the study with stage III/IV NSCLC undergoing CT	Intervention: certoparin 3000 IU subcutaneously once daily for 6 months. Control: placebo	273/273	5
Lebeau (1994)	Patients with limited or extensive SCLC undergoing CT	Intervention: subcutaneous heparin for 5 weeks. Control: no intervention	138/139	3
Lebeau-1 (1994)	Subjects extracted from the study: limited SCLC		64/57	
Lebeau-2 (1994)	Subjects extracted from the study: extensive SCLC		74/82	
Maurer (1997)	Patients with limited SCLC undergoing CT and radiotherapy; minimum life expectancy 2 months	Intervention: VKA (PT 1.4–1.6) started with CT and continued for 3 weeks after last cycle of CT. Control: no intervention	178/169	3
Stanford (1979)	Patients with stage III or more SCLC undergoing CT	Intervention: VKA following heparin. Control: no intervention	12/12	2
van Doormaal (2011)	Subjects extracted from the study with stage IIIB NSCLC receiving standard anticancer treatment	Intervention: subcutaneous nadroparin for 6 weeks. Control: no intervention	81/88	3
Zacharski (1984)	Patients with different types of cancer undergoing CT; minimum life expectancy of 2 months	Intervention: VKA (therapeutic range). Control: no intervention		3
Zacharski-1 (1984)	Subjects extracted from the study: advanced NSCLC		96/98	
Zacharski-2 (1984)	Subjects extracted from the study: SCLC		25/25	
Zacharski-3 (1984)	Subjects extracted from the study: NSCLC following potentially curative surgical resection or radiation therapy		21/20	

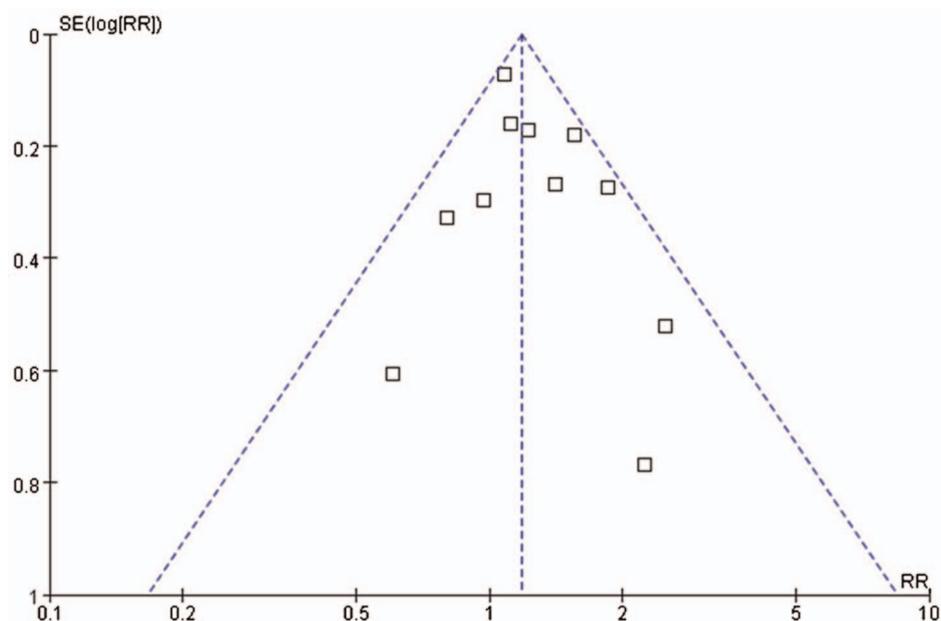
CT, chemotherapy; NSCLC, non-small cell lung cancer; PT, prothrombin time; SCLC, small cell lung cancer; VKA, vitamin K agonist.

Data extraction

The full-text articles of all eligible studies were reviewed and data were extracted by the two authors independently. Any discrepancies were resolved by discussion with a third author to

reach a final consensus. The extracted data included: (1) publication details; (2) sample size; (3) study methodology (eg, eligibility criteria, method of randomisation and blinding); (4) patient characteristics including pathological type and stage

Figure 2 Funnel plot for survival at 1 year showing no evidence of publication bias.



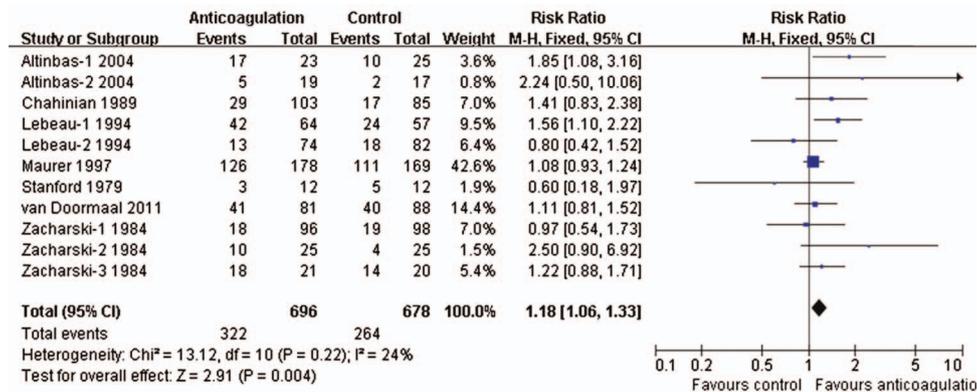


Figure 3 Forest plot showing the effect of anticoagulant treatment on survival at 1 year in patients with lung cancer.

of lung cancer; (5) intervention (eg, type of anticoagulants, dose, route of administration and duration); and (6) clinical outcomes. The authors of the included studies were contacted for additional information if there were insufficient data for analysis.

The primary efficacy outcomes were survival rate at 1 year and incidence of VTE. Other outcomes also evaluated were: (1) symptomatic VTE and all reported thromboembolic events; (2) survival rate at 6 months and at 2 years; (3) adverse effects including haemorrhage events (major and minor bleeding) and thrombocytopenia. Survival data were collected at 6 months, 1 year and 2 years. When we could not obtain the number of survivors at the time points of interest from the paper or from the authors, two authors calculated these numbers independently and in duplicate from survival curves. We used the mean of the two estimates when they differed. VTE was defined as deep vein thrombosis of the lower or upper limbs, pulmonary embolism and visceral venous thrombosis. Thromboembolic events referred to VTE plus other thromboses such as stroke and peripheral thrombosis.^{15 16} Major bleeding was defined as The Cancer and Leukemia Group B (CALGB) toxicity grades 3–5 (grade 3, bleeding causing some functional disability and/or requiring <4 units of blood; grade 4, massive haemorrhage and/or profound functional disability and/or requiring >4 units of blood; grade 5, lethal haemorrhage). Overall haemorrhage events referred to major and minor bleeding.¹⁷

Quality assessment

We assessed the methodological quality of each trial using the Jadad score¹⁸ which incorporates randomisation, blinding and attrition to derive a score of 0–5. Two reviewers independently appraised the quality of the included trials. Studies were considered to be of low quality if the Jadad score was ≤ 2 and of high quality if the score was ≥ 3 .

Statistical analysis

An intervention meta-analysis was conducted using Review Manager Software 5.1.2 (Cochrane Collaboration, Oxford, UK). Pooled risk ratios (RRs) were calculated for all the outcomes. The χ^2 test was used to evaluate the presence of statistically significant heterogeneity across the studies and the inconsistency index (I^2) was used to quantify the amount of heterogeneity.¹⁹ We predefined heterogeneity as low, moderate and high with I^2 values of more than 25%, 50% and 75%, respectively. Study-level data were pooled using a random effects model when I^2 was $>50\%$ or a fixed effects model when I^2 was $<50\%$. The significance of the pooled RR was determined by the Z test, along with 95% CIs. Publication bias was assessed by a funnel plot using 1-year survival as an endpoint. A p value of <0.05 was considered statistically significant.

Subgroup analyses were performed based on the type of anticoagulants (oral VKA vs subcutaneous heparin), histological

Table 2 Impact of additional anticoagulant therapy on survival rate at 1 year for patients with lung cancer

Variables	Number of subjects Anticoagulation/control (number of studies, groups)	Number of events Anticoagulation (%)/control (%)	Anticoagulation vs control effect			Heterogeneity		
			RR (95% CI)	Z	p Value	χ^2	p Value	I^2 (%)
Total	696/678 (7, 11)	322 (46.3)/264 (38.9)	1.18 (1.06 to 1.32)	2.91	0.004	13.12	0.22	24
Anticoagulants								
VKA	435/409 (4, 6)	204 (46.9)/170 (41.6)	1.13 (0.99 to 1.30)	1.80	0.07	5.02	0.41	0
Heparin	261/269 (3, 5)	118 (45.2)/94 (34.9)	1.28 (1.04 to 1.57)	2.37	0.02	6.34	0.18	37
Histological type								
NSCLC	102/108 (2, 3)	77 (38.9)/73 (35.4)	1.10 (0.87 to 1.39)	0.78	0.44	0.60	0.74	0
SCLC	498/472 (6, 8)	245 (49.2)/191 (40.5)	1.21 (1.07 to 1.38)	2.94	0.003	12.75	0.08	45
Stage of lung cancer								
Non-advanced/limited	286/271 (4, 4)	203 (71.0)/159 (58.7)	1.30 (1.03 to 1.65)	2.19	0.03	6.85	0.08	56
Advanced/extensive	385/382 (6, 6)	109 (28.3)/101 (26.4)	1.09 (0.87 to 1.36)	0.71	0.48	3.84	0.57	0

NSCLC, non-small cell lung cancer; RR, risk ratio; SCLC, small cell lung cancer; VKA, vitamin K antagonist.

Table 3 Impact of additional anticoagulant therapy on survival at 2 years for patients with lung cancer

Variables	Number of subjects Anticoagulation/control (number of studies, groups)	Number of events Anticoagulation (%)/ control (%)	Anticoagulation vs control effect			Heterogeneity		
			RR (95% CI)	Z	p Value	χ^2	p Value	I ² (%)
Total	684/ 666 (6, 10)	148 (21.6)/113 (17.0)	1.27 (1.04 to 1.56)	2.34	0.02	4.15	0.90	0
Anticoagulation regimen								
VKA	423/397 (3, 5)	100 (23.6)/77 (19.4)	1.23 (0.97 to 1.57)	1.71	0.09	0.68	0.95	0
Heparin	261/269 (3, 5)	48 (18.4)/36 (13.4)	1.36 (0.93 to 1.99)	1.60	0.11	3.62	0.46	0
Histological type								
NSCLC	198/206 (2, 3)	44 (22.2)/37 (18.0)	1.24 (0.86 to 1.78)	1.14	0.25	0.63	0.73	0
SCLC	486/460 (5, 7)	104 (21.4)/76 (16.5)	1.29 (1.01 to 1.65)	2.05	0.04	3.60	0.73	0
Stage of lung cancer								
Non-advanced/Limited	286/271 (4, 4)	107 (37.4)/76 (28.0)	1.33 (1.05 to 1.68)	2.38	0.02	3.42	0.33	12
Advanced/Extensive	373/370 (5, 5)	40 (10.7)/36 (9.7)	1.16 (0.77 to 1.73)	0.71	0.48	0.59	0.96	0

NSCLC, non-small cell lung cancer; RR, risk ratio; SCLC, small cell lung cancer; VKA, vitamin K antagonist.

type (NSCLC vs SCLC) and stage (non-advanced/limited vs advanced/extensive).

RESULTS

Study description

The initial literature search revealed a total of 2886 articles, from which 2760 were removed due to publishing type. After title and abstract screening, 65 citations were removed because they were not relevant to our study aim. Full-text screening of the remaining articles identified 26 potentially eligible citations. After evaluating these references, 17 articles were excluded for the following reasons: (1) not relevant to the main outcomes; (2) intervention was topical heparin or intraportal infusion of heparin, or the duration of anticoagulation therapy was <5 days or the comparison was between heparin and VKA; (3) concomitant treatments were different between intervention and control groups. In total, nine eligible RCTs of 2185 patients with lung cancer were included in the meta-analysis.^{11–15 17 20 21} A flow-chart of the evaluation of the studies is shown in figure 1.

Five of the included studies recruited patients with lung cancer^{11–14 20}; the others were carried out in patients with different types of cancers.^{15–17 21} According to histological type and disease stage, a total of 13 groups were extracted from the nine studies. The primary outcome of the studies by Agnelli *et al*¹⁵ and Haas *et al*¹⁶ was thrombotic events and VTE events, respectively, and survival data at 1 year and 2 years were not available for these two studies. The average survival rate at 1 year was 42.6%. Two studies of extensive SCLC in 1979 and 1989 reported low survival rates at 1 year of 33.3% and 24.5%, respectively.^{14 20} The 1-year survival reported by Zacharski *et al*²¹ in 1984 was also low at 29.1%. Four studies used VKA^{13 14 20 21} and others used subcutaneous heparin, with unfractionated heparin in one study¹¹ and LMWH in four

studies.^{12 15–17} The characteristics of the included studies are summarised in table 1.

The average Jadad score of these studies was 3.1 (range 2–5). A funnel plot for the primary outcome indicated no evidence of publication bias (figure 2).

Survival and subgroup analyses

Survival at 1 year

The results from seven trials (11 groups, n=1374 patients) were available to examine the effects of anticoagulants on the survival rate at 1 year in patients with lung cancer.^{11–14 17 20 21} No evidence of statistical heterogeneity was found for this outcome (I²=24%; p=0.22). A pooled analysis showed that the use of anticoagulants was associated with a statistically significant improvement in 1-year survival (RR 1.18, 95% CI 1.06 to 1.32; p=0.004; figure 3).

For 1-year survival (table 2), heparin (RR 1.28, 95% CI 1.04 to 1.57; p=0.02) showed a greater improvement than oral VKA (RR 1.13, 95% CI 0.99 to 1.30; p=0.07); anticoagulation treatment showed efficacy in patients with SCLC (RR 1.21, 95% CI 1.07 to 1.38; p=0.003) but not in those with NSCLC (RR 1.10, 95% CI 0.87 to 1.39; p=0.78); and anticoagulants were found to have a beneficial effect in patients with non-advanced or limited lung cancer (RR 1.30, 95% CI 1.03 to 1.65; p=0.03) but, in patients with advanced or extensive disease, the benefit was not statistically significant (RR 1.09, 95% CI 0.87 to 1.36; p=0.48). The test for subgroup effect was not statistically significant for the three subgroup analyses.

Survival at 6 months

Eight studies including 1920 patients from 12 groups reported data on 6-month survival.^{11–14 16 17 20 21} No statistically

**Figure 4** Forest plot showing the effect of anticoagulant treatment on the risk of overall venous thromboembolism.

Table 4 Impact of additional anticoagulant therapy on thromboembolic events for patients with lung cancer

Variables	Number of subjects Anticoagulation/control (Number of studies)	Number of events Anticoagulation (%) / control (%)	Anticoagulation vs Control effect			Heterogeneity		
			RR (95% CI)	Z	p Value	χ^2	p Value	I ² (%)
Overall VTE*	509/386 (3)	20 (3.9)/28 (7.3)	0.55 (0.31 to 0.97)	2.05	0.04	0.18	0.91	0
Symptomatic VTE	509/386 (3)	15 (2.9)/20 (5.2)	0.56 (0.29 to 1.09)	1.70	0.09	0.26	0.88	0
Thromboembolic events	509/386 (3)	20 (3.9)/32 (8.3)	0.48 (0.28 to 0.82)	2.65	0.008	0.06	0.97	0

*Asymptomatic and symptomatic VTE. Thromboembolic events include deep vein thrombosis, pulmonary embolism, visceral venous thrombosis, stroke and peripheral thrombosis. RR, risk ratio; VTE, venous thromboembolism.

significant differences were found for the survival rate at 6 months between patients who received anticoagulants versus controls (RR 1.03, 95% CI 0.94 to 1.13; $p=0.51$). We found evidence of statistical heterogeneity for 6-month survival ($I^2=69\%$; $p=0.0002$; see online supplementary table S1 and supplementary figure S1).

Survival at 2 years

Ten groups from eight trials (1350 patients) contributed to the analysis of 2-year survival.^{11-14 17 21} A meta-analysis found that anticoagulant administration had a beneficial effect on 2-year survival (RR 1.27, 95% CI 1.04 to 1.56; $p=0.02$; table 3 and online supplementary figure S2). No evidence of statistical heterogeneity was found for this outcome ($I^2=0\%$; $p=0.90$).

There was a significant beneficial effect in patients with SCLC (RR 1.29, 95% CI 1.01 to 1.65; $p=0.04$, table 3). As for 1-year survival, a significant benefit on 2-year survival was seen in patients with non-advanced or limited lung cancer (RR 1.33, 95% CI 1.05 to 1.68; $p=0.02$) but not in those with advanced or extensive disease. The test for subgroup effect was not statistically significant for any of the three subgroup analyses.

Thromboembolic events and subgroup analyses

Only three RCTs provided information regarding thromboembolic events.^{12 15 16} All of them used LMWH as anticoagulants. The meta-analysis showed that, compared with control, anticoagulant treatment was associated with a significant reduction in the risk of VTE (RR 0.55, 95% CI 0.31 to 0.97;

$p=0.04$; figure 4) and thromboembolic events (RR 0.48, 95% CI 0.28 to 0.82; $p=0.008$; table 4). Anticoagulation had a marginal effect on risk reduction for symptomatic VTE (RR 0.56, 95% CI 0.29 to 1.09; $p=0.09$).

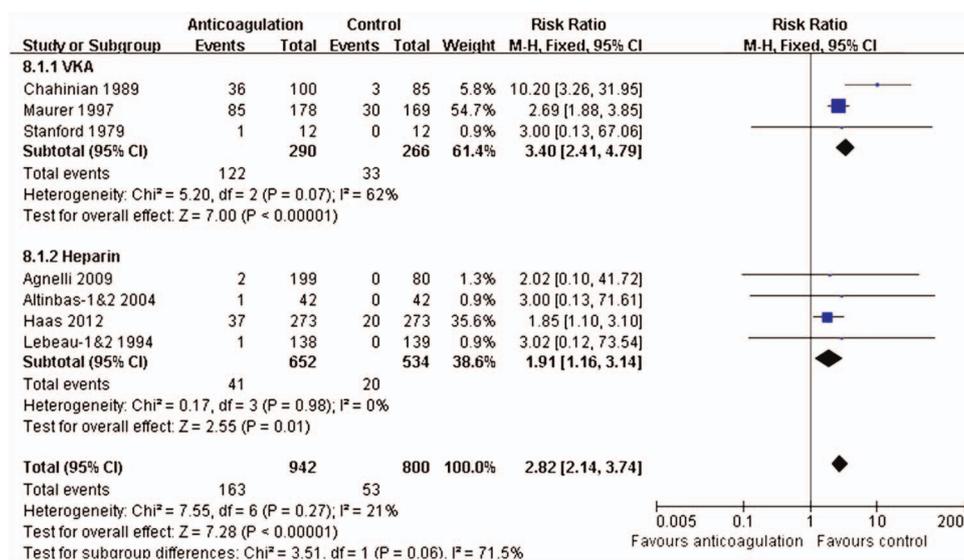
Haemorrhage events and subgroup analyses

The main side effect of anticoagulants is bleeding. In our analysis of seven RCTs,^{11-16 20} anticoagulation was associated with an apparent increase in the risk of overall haemorrhage events (RR 2.82, 95% CI 2.14 to 3.74; $p<10^{-5}$; figure 5), major bleeding (RR 2.91, 95% CI 1.43 to 5.90; $p=0.003$; figure 6) and minor bleeding (RR 2.78, 95% CI 2.04 to 3.80; $p=0.43$; see online supplement table S2) compared with control.

Despite the fact that the test for subgroup effect was not statistically significant for heparin versus oral VKA ($p=0.14$, figure 6), it was noted that the increase in the risk of major bleeding for heparin was not statistically significant (RR 1.70, 95% CI 0.66 to 4.40; $p=0.27$) while VKA conferred a more significant effect (RR 5.14, 95% CI 1.66 to 15.94; $p=0.005$).

DISCUSSION

Our meta-analysis revealed a survival benefit at 1 year and at 2 years from adjunctive anticoagulation in patients with lung cancer without indication for anticoagulants. The most recent analyses in this area were published by Akl *et al* in 2011.^{22 23} They investigated the impact of VKA and heparin on mortality in a mixed population of various cancers in two separate meta-analyses and found that heparin reduced mortality at

**Figure 5** Forest plot showing the effect of anticoagulant treatment on the risk of overall haemorrhage events.

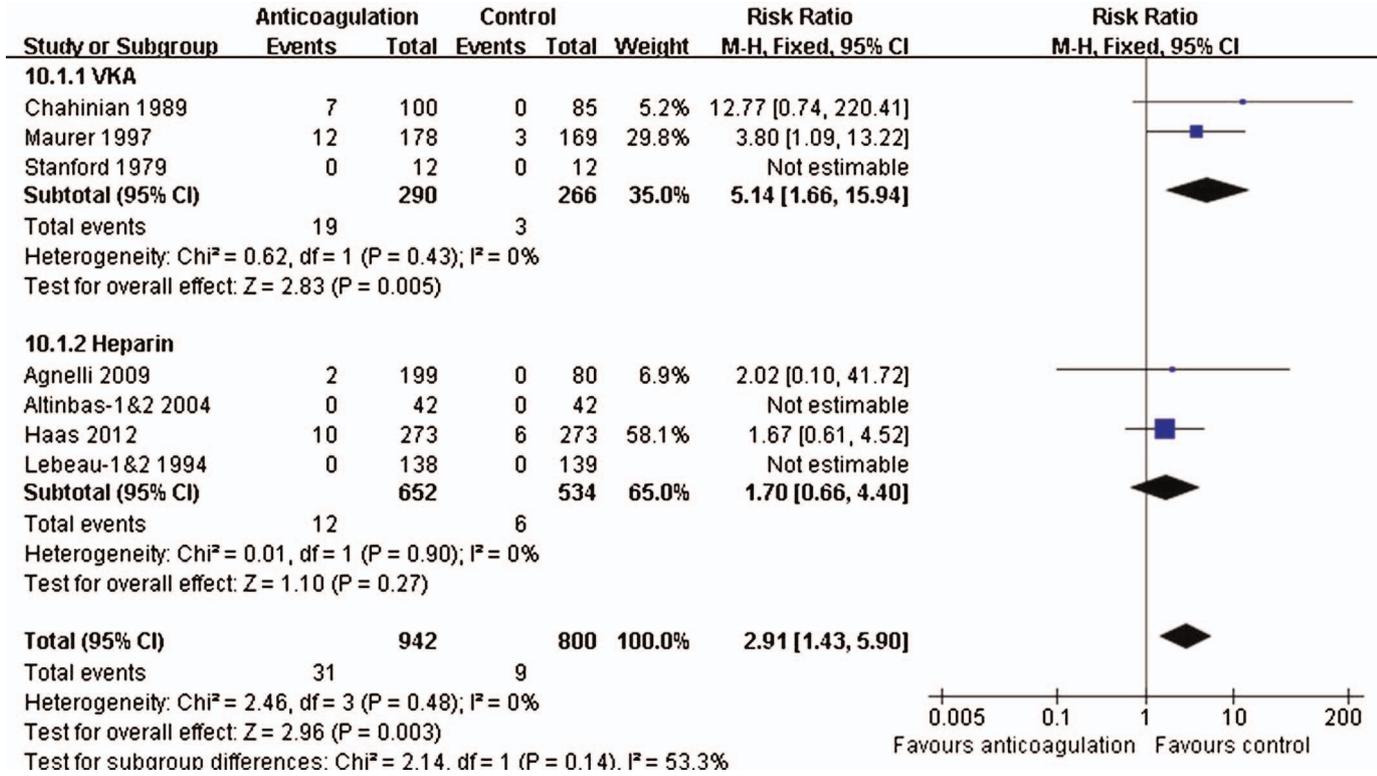


Figure 6 Forest plot showing the effect of anticoagulant treatment on the risk of major bleeding.

2 years but not at 1 year.²² No statistically significant benefit was found when using VKA.²³ They performed a subgroup analysis of patients with SCLC versus other cancer types which suggested a reduction in mortality at 1 year with heparin in patients with SCLC but not in those with other cancers.²² Considering the especially high risk of VTE for lung cancer, we focused on patients with lung cancer and included participants from three additional studies for survival analysis.^{17 20 21} Patients with NSCLC were also included in our analysis.

It is notable that the 1-year and 2-year survival benefit was seen in patients with lung cancer of non-advanced or limited stage but not in those with advanced or extensive cancer, and no statistically significant difference was found regarding survival at 6 months. In a RCT in patients with various types of cancer without underlying thrombosis, Kakkar *et al*²⁴ found that, in a subgroup of patients with a better prognosis, survival rates at 2 and 3 years were significantly improved for patients receiving LMWH versus placebo. In another similar study, Klerk *et al*²⁵ reported that, in a subgroup of patients with a life expectancy of ≥ 6 months, the HR of mortality for LMWH was 0.64 (95% CI 0.45 to 0.90) compared with 0.88 (95% CI 0.62 to 1.25) for patients with a shorter life expectancy. Together with these data, our findings suggest that anticoagulation might not produce an immediate survival benefit and it may be beneficial only in patients with prolonged life expectancy.

The underlying mechanisms of the increased survival from anticoagulation for lung cancer might be explained from two aspects. On one hand, our data—which are consistent with a previous analysis²⁶—suggest that adjunctive anticoagulation treatment can reduce the occurrence of VTE, which has been proved to be a risk factor for mortality.^{3 5 9} On the other hand, an accumulating number of *in vitro* and *in vivo* studies indicate that anticoagulants have an anticancer effect in non-antithrombotic pathways.^{27–30} In clinical studies in patients with SCLC, the use of both VKA and heparin was found to improve significantly the response rate to chemotherapy and progression-free survival.^{11–14}

Our data suggest that anticoagulation has a beneficial effect on 1-year and 2-year survival in patients with SCLC but not in those with NSCLC. Although subgroup analysis for the difference between SCLC and NSCLC was not statistically significant, it indicated a potential divergence in histological type. It should also be noted that only two included studies were eligible for the pooled analysis of NSCLC so the data might be insufficient to reveal a statistically significant potential benefit. Considering the fact that patients with NSCLC had a two-fold higher risk for VTE than those with SCLC,³ further studies are required for this cell type.

Anticoagulation may increase the incidence of bleeding, especially in patients receiving concomitant angiogenesis inhibitors and chemotherapy which might lead to thrombocytopenia. In our analysis we found that administration of anticoagulants can significantly increase the risk of major bleeding, minor bleeding and overall haemorrhage events. It has been shown in a previous study that factors including advanced age (≥ 65 years), low platelet counts, a history of bleeding and the concomitant use of drugs such as angiogenesis inhibitors and high-dose systemic corticosteroids are also associated with a high bleeding rate.³¹ It may therefore be prudent to deliver anticoagulation therapy in patients with these risk factors.

The subgroup analysis, although not statistically significant, suggests that subcutaneous heparin might have a better effect on 1-year survival than oral VKA. Owing to the limited number of studies, we did not compare the effectiveness in reducing the risk of VTE between oral VKA and heparin, but previous studies have

confirmed that LMWH may be superior in this respect.^{32 33} Our data also suggest that oral VKA significantly increases the risk of major bleeding while subcutaneous heparin does not. These results are consistent with results from other studies.^{22 23 26 31–33} Furthermore, in the four trials included in the meta-analysis of adverse events of heparin there were no fatal bleeding events which had been judged to be related to heparin treatment.^{11 12 15 16} Considering efficacy and safety, the potential superiority of subcutaneous heparin to oral VKA makes heparin the preferred choice of anticoagulation treatment in patients with lung cancer. Based on the available evidence, the most recent antithrombotic guideline of the American College of Chest Physicians has recommended against the use of VKA for long-term prophylaxis in patients with cancer,³⁴ and future clinical trials should focus on the use of heparin rather than VKA.

Our study has several limitations. First, due to the differences in study design and protocol, the trials included in this meta-analysis had heterogeneity in two aspects: (1) subjects of each study had different histological types, different stages of disease and different anticancer treatments (chemotherapy or supportive therapy only); (2) a discrepancy in the anticoagulant agents, duration and dosage of anticoagulation treatment (table 1). However, it should be noted that all the included studies were RCTs comparing anticoagulants with controls and the characteristics of the participants in each study were comparable. In addition, data of the same histological type or disease stage were extracted and pooled analysed. Second, the quality of the included studies was not consistent. Only two of the nine included studies used placebo in the control group.^{15 16} The quality of trials can affect the direction and magnitude of treatment effects when undergoing a meta-analysis. Third, to elucidate which population can benefit from additional anticoagulation therapy and the most optimal regimen, three subgroup analyses were performed. However, due to the limited number of available eligible studies, no confirmed conclusions can be made at present.

CONCLUSIONS

The use of anticoagulants was found to have a survival benefit in patients with lung cancer without an indication for anticoagulation, especially those with SCLC or with non-advanced or limited disease. It was also associated with a decrease in thromboembolic events. The use of subcutaneous heparin was safe, showing no significant increase in the risk of major bleeding. Further trials are required to elucidate the efficacy and safety of anticoagulation therapy in diverse populations of lung cancer patients with various disease stages, performance status, life expectancy, cell types and concomitant anticancer drugs including new molecularly-targeted agents. The optimal agents, dose intensity, timing and duration of anticoagulants should also be investigated.

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Contributors JZ participated in the design of the study, carried out database search, performed article evaluation and statistical analysis and drafted the manuscript. Y-LZ carried out database search, article evaluation and data extraction. K-XM participated in data extraction and statistical analysis. J-MQ conceived the idea, participated in study design and coordination and drafted/revised the manuscript. All authors read and approved the final manuscript.

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