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[Intervention Review]

Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation

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ABSTRACT

Background

Several basic research and clinical studies have led to the hypothesis that oral anticoagulants may improve the survival of patients with cancer through an antitumor effect in addition to their antithrombotic effect.

Objectives

To evaluate the efficacy and safety of oral anticoagulants in patients with cancer with no therapeutic or prophylactic indication for anticoagulation.

Search methods

We performed a comprehensive search for studies of anticoagulation in patients with cancer including 1. a February 2013 electronic search of the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE; 2. a handsearch of the American Society of Clinical Oncology (starting with its first volume, 1982) and of the American Society of Hematology (starting with the 2003 issue); 3. checking of references of included studies; 4. use of the 'related citation' feature in PubMed; and 5. searching clinical trials.gov for ongoing studies.

Selection criteria

Randomized controlled trials (RCTs) comparing vitamin K antagonist or other oral anticoagulants with no intervention or placebo in patients with cancer without clinical evidence of venous thromboembolism.

Data collection and analysis

Using a standardized data form, we extracted data on risk of bias, participants, interventions and outcomes of interest that included all-cause mortality, venous thromboembolism, major bleeding, and minor bleeding.

Main results

Of 9559 identified citations, seven RCTs (eight reports) fulfilled the inclusion criteria. The oral anticoagulant was warfarin in six of these RCTs and apixaban in the seventh RCT. The comparator was either placebo or no intervention. The use of warfarin had no effect on mortality at six months (risk ratio (RR) 0.98; 95% confidence interval (CI) 0.82 to 1.22), one year (RR 0.97; 95% CI 0.89 to 1.04), two years (RR 0.98; 95% CI 0.81 to 1.18), or five years (RR 0.92; 95% CI 0.83 to 1.01). One study assessed the effect of warfarin on venous thromboembolism and did not show or exclude a beneficial or detrimental effect (RR 0.15; 95% CI 0.02 to 1.20). Warfarin increased both major bleeding (RR 4.24; 95% CI 1.86 to 9.65) and minor bleeding (RR 3.19; 95% CI 1.83 to 5.55). We judged the quality of evidence as moderate for all outcomes.

The study assessing the effect of apixaban did not show or exclude a beneficial effect or detrimental of apixaban on mortality at six months (RR 0.16; 95% CI 0.01 to 1.66); major bleeding (RR 0.62; 95% CI 0.06 to 6.63); and minor bleeding (RR 2.87; 95% CI 0.16 to 51.82). We judged the quality of evidence as low for all outcomes.

Authors' conclusions

Existing evidence does not suggest a mortality benefit from oral anticoagulation in patients with cancer while the risk for bleeding is increased.

PLAIN LANGUAGE SUMMARY

Oral blood thinners in patients with cancer

Background

This review assessed the effects of oral anticoagulation (blood-thinning drugs) in people with cancer on survival, thromboembolic events, and bleeding outcomes.

Study characteristics

We searched the scientific literature for studies of anticoagulants in people with cancer. The evidence is current to February 2013.

Key results

We found six studies using warfarin and one study using apixaban. When considering people with cancer in general, warfarin did not reduce mortality, but did reduce the risk of venous clots while increasing the risk of minor and major bleeding. Apixaban reduced DVT and had no effect on death, major bleeding, or minor bleeding; however, this was in only one study.

Quality of the evidence

We judged the evidence on warfarin to be moderate quality and the evidence of apixaban as low quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Oral anticoagulation in patients with cancer with no therapeutic or prophylactic indication for anticoagulation

Oral anticoagulation in patients with cancer with no therapeutic or prophylactic indication for anticoagulation

Patient or population: patients with cancer with no therapeutic or prophylactic indication for anticoagulation

Settings: outpatient

Intervention: oral 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	oral anticoagulation				
Mortality Follow-up: median 1 year	483 per 1000	468 per 1000 (429 to 502)	RR 0.97 (0.89 to 1.04)	1539 (6 studies)	⊕⊕⊕⊖ moderate ¹	-
VTE Follow-up: 1 year	44 per 1000	7 per 1000 (1 to 53)	RR 0.15 (0.02 to 1.2)	311 (1 study)	⊕⊕⊕⊖ moderate ²	-
Major bleeding Follow-up: median 1 year	24 per 1000	102 per 1000 (45 to 231)	RR 4.24 (1.86 to 9.65)	1184 (4 studies)	⊕⊕⊕⊖ moderate ³	-
Minor bleeding Follow-up: 1 year	78 per 1000	248 per 1000 (142 to 431)	RR 3.19 (1.83 to 5.55)	865 (4 studies)	⊕⊕⊕⊖ moderate ³	-
Health-related quality of life - not reported	See comment	See comment	Not estimable	-	See comment	-

*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; **VTE** : venous thromboembolism.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 We downgraded because lack of blinding of patients and providers in 4 out of 5 studies; it was unclear whether allocation was concealed in 2 studies; and only 1 study clearly used intention-to-treat analysis.
- 2 We downgraded because the precision of the estimate does not exclude a patient important benefit (the lower limit of RR still suggests a benefit that might be relevant given the high baseline risk).
- 3 We downgraded because lack of blinding of patients and providers in 3 out of 4 studies; it was unclear whether allocation was concealed in 2 studies; and only 1 study clearly used intention-to-treat analysis.

BACKGROUND

Description of the condition

Studies have implicated the tumor-mediated activation of the hemostatic system in both the formation of tumor stroma and in tumor metastasis (Dvorak 1986; Francis 1998; Levine 2003). In one cohort study of over 3000 healthy men with 15 years' follow-up, cancer mortality was three times more common in patients who were hypercoagulable at baseline than in patients who were not (Miller 2004).

Description of the intervention

Vitamin K antagonists (VKA) have been the mainstay of oral anticoagulant therapy since the mid-1950s'. Well-designed clinical trials have shown their effectiveness for the primary and secondary prevention of several venous and arterial thrombotic diseases (Ansell 2008).

Apixaban belongs to the family of oral activated factor X inhibitors, which is currently approved in Europe for venous thromboembolism (VTE) prevention following major orthopedic surgery (King 2013).

How the intervention might work

Since the 1930s, researchers have been exploring the effects of anticoagulation on cancer (Smorenburg 2001), and there is evidence that warfarin has an inhibitory effect on tumor growth and metastasis. Schulman 2000 showed that in patients with a first episode of VTE, cancer incidence was lower when treated with oral anticoagulants for six months rather than for six weeks. These observations led to the hypothesis that the antitumor effect of oral anticoagulants, in addition to their antithrombotic effect, may improve outcomes of patient with cancer.

Why it is important to do this review

In the early 1980s, one large US Veterans Administration Cooperative Study suggested that warfarin, as a single anticoagulant agent, may favorably modify the course of some types of human malignancy such as small cell lung cancer (SCLC) (Zacharski 1981). Conversely, in another trial, warfarin did not improve the outcomes of patients with SCLC receiving chemotherapy and radiation therapy (Maurer 1997). The last update of this Cochrane systematic review concluded that the existing evidence does not suggest a mortality benefit from oral anticoagulation in patients with cancer, while the risk for bleeding is increased (Akl 2010). There have also been publications on the use of newer oral anticoagulants in patients with cancer (Levine 2012). See Table 1 for glossary.

OBJECTIVES

To evaluate the efficacy and safety of oral anticoagulants in patients with cancer with no therapeutic or prophylactic indication for anticoagulation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Patients with cancer with no indication for prophylactic anticoagulation (e.g. for acute illness, for central venous line placement, perioperatively) or for therapeutic anticoagulation (e.g. for the treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE)).

Types of interventions

Main intervention: VKA or other oral anticoagulants.

Comparison: placebo or no intervention.

We also considered studies comparing different oral anticoagulants. The protocol from original studies should have planned to provide all other co-interventions (e.g. chemotherapy) similarly.

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Symptomatic DVT.
- Symptomatic PE.
- VTE.
- Major bleeding: we accepted the authors' definitions of major bleeding.
- Minor bleeding: we accepted the authors' definitions of minor bleeding.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in patients with cancer. We conducted the original electronic search in January 2007 and updated it in February 2010 and February 2013. We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), Issue 12, 2012;
- MEDLINE (1966 onwards; accessed via Ovid);
- EMBASE (1980 onwards; accessed via Ovid);
- ISI the Web of Science.

The search strategies combined terms for anticoagulants, terms for cancer and a search filter for RCTs. We used no language restrictions. We list the full search strategies for each of the electronic databases in Appendix 1 and Appendix 2.

Searching other resources

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

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts of identified articles for eligibility. We retrieved the full text of articles judged as potentially eligible by at least one review author. 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 extracted data from each included study and resolved their disagreements by discussion. We aimed at collecting data related to the following.

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, comorbidity).
- History of VTE.
- Type of cancer.
- Stage of cancer.
- Time since cancer diagnosis.

Interventions

- Type of anticoagulant: VKA, other.
- Intensity of VKA therapy (international normalized ratio (INR) target) or dose.
- Duration of treatment.
- Control: placebo or no intervention.
- Co-interventions including radiation therapy, chemotherapy, and hormonal therapy (type and duration).

Outcomes

We extracted outcome data necessary to conduct intention-to-treat (ITT) analyses. We collected all-cause mortality data at one and five years (time points defined a priori) and at six months and two years (defined post hoc based on results reported in the individual RCTs).

We attempted to contact study authors for incompletely reported data.

When we could not obtain the number of events at the time points of interest from the published paper or from the study authors, two biostatisticians estimated 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 biostatisticians for each estimated value by calculating the percentage difference. That percentage corresponded to the difference between the two estimates divided by the number of participants at risk for the event and multiplied by 100.

We determined a priori to consider abstracts only if study authors supplied us with full reports of their methods and results.

Assessment of risk of bias in included studies

We assessed risk of bias at the study level using The Cochrane Collaboration's 'Risk of bias' tool. Two review authors independently assessed the methodological quality of each included study and resolved their disagreements by discussion. Methodological criteria included:

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

See [Dealing with missing data](#) section about assessing risk of bias associated with participants with missing data.

Measures of treatment effect

We collected risk ratios (RR) and 95% confidence intervals (CI) for categorical data. We did not meta-analyze any of the outcomes of interest as a continuous variable.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Determining participants with missing data

It was not clear whether certain participant categories (e.g. those described as 'withdrew consent' or 'experienced adverse events') were actually followed up by the trialists (versus had missing participant data). To deal with this issue, we made the following considerations:

- 'ineligible participants' and 'did not receive the first dose' participant categories, which are defined prior to the initiation of the study intervention, most likely have missing participant data;
- 'withdrew consent' and 'lost to follow-up' (LTFU) participant categories, which are defined after the initiation of the study intervention, most likely have missing participant data;
- 'dead', 'experienced adverse events', 'noncompliant', and 'discontinued prematurely' (and similarly described) participant categories, less likely have missing participant data.

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

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

For categorical data, we used the following calculations for each study arm:

- denominator: (number of participants randomized) - (number of participants most likely with missing data, both pre- and postintervention initiation);
- numerator: number of participants with observed events (i.e. participants who had at least one event for the outcome of interest during their available FU time).

For continuous data, we used for each study arm, the reported mean and standard deviation (SD) for participants actually followed up by the trialists.

Assessing the risk of bias associated with participants with missing data

When the primary meta-analysis of a specific outcome found a statistically significant effect, we conducted sensitivity meta-analyses to assess the risk of bias associated with missing participant data. Those sensitivity meta-analyses used a priori plausible assumptions about the outcomes of participants considered to have missing data. The assumptions we used in the sensitivity meta-analyses were increasingly stringent in order to challenge the statistical significance of the results of the primary analysis progressively (Akl 2013; Ebrahim 2013).

For categorical data, and for RR showing a reduction in effect (RR less than 1), we used the following increasingly stringent but plausible assumptions (Akl 2013)>

- For the control arm, relative incidence (RI) among those with missing data (LTFU) compared with those with available data (FU) in the same arm ($RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 1.5$;
- For the control arm, $RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 2$;
- For the control arm, $RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 3$;
- For the control arm, $RI_{LTFU/FU} = 1$; for the intervention arm, $RI_{LTFU/FU} = 5$;

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

Specifically, we used the following calculations for each study arm:

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

Assumed events were calculated by applying the a priori plausible assumptions to the participants considered most likely with missing data postintervention initiation.

For continuous data, we used the four strategies suggested by Ebrahim et al. (Ebrahim 2013). The strategies imputed the means for participants with missing data based on the means of participants actually followed up in individual trials included in the systematic review. To impute SD, we used the median SD from the control arms of all included trials (Ebrahim 2013).

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (I^2 test; Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). We considered the following classification of heterogeneity based on the value of I^2 :

- 0 to 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).

Assessment of reporting biases

We assessed selective outcome reporting bias by trying to identify whether the study was included in a trial registry, whether a protocol was available, and whether the methods section provided a list of outcomes. We compared the list of outcomes from those sources to the outcomes reported on in the published paper. We also created an inverted funnel plot for the primary outcome of mortality in order to check for possible publication bias. We did not create funnel plots for the other outcomes due to the low number of included trials for each outcome.

Data synthesis

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

For categorical data, we calculated the 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 assessed the quality of evidence at the outcome level across studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We planned to explore substantial heterogeneity by conducting subgroup analyses based on the type of oral anticoagulant and the characteristics of participants (type, severity and stage of cancer, and whether patients were on cancer treatment or not).

Sensitivity analysis

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

RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow. The February 2013 search strategy identified 9559 citations from which we removed the results of our February 2010 search. We identified two new studies. The title and abstract screening of the results of the 2007 search identified 60 citations as potentially eligible for this review. The full-text screening of the 60 citations identified eight papers reporting

seven eligible RCTs. Agreement between review authors for study eligibility was excellent ($\kappa = 0.94$). The inverted funnel plot for the primary outcome of mortality at one year did not suggest publication bias (Figure 2).

Figure 1. Study flow diagram.

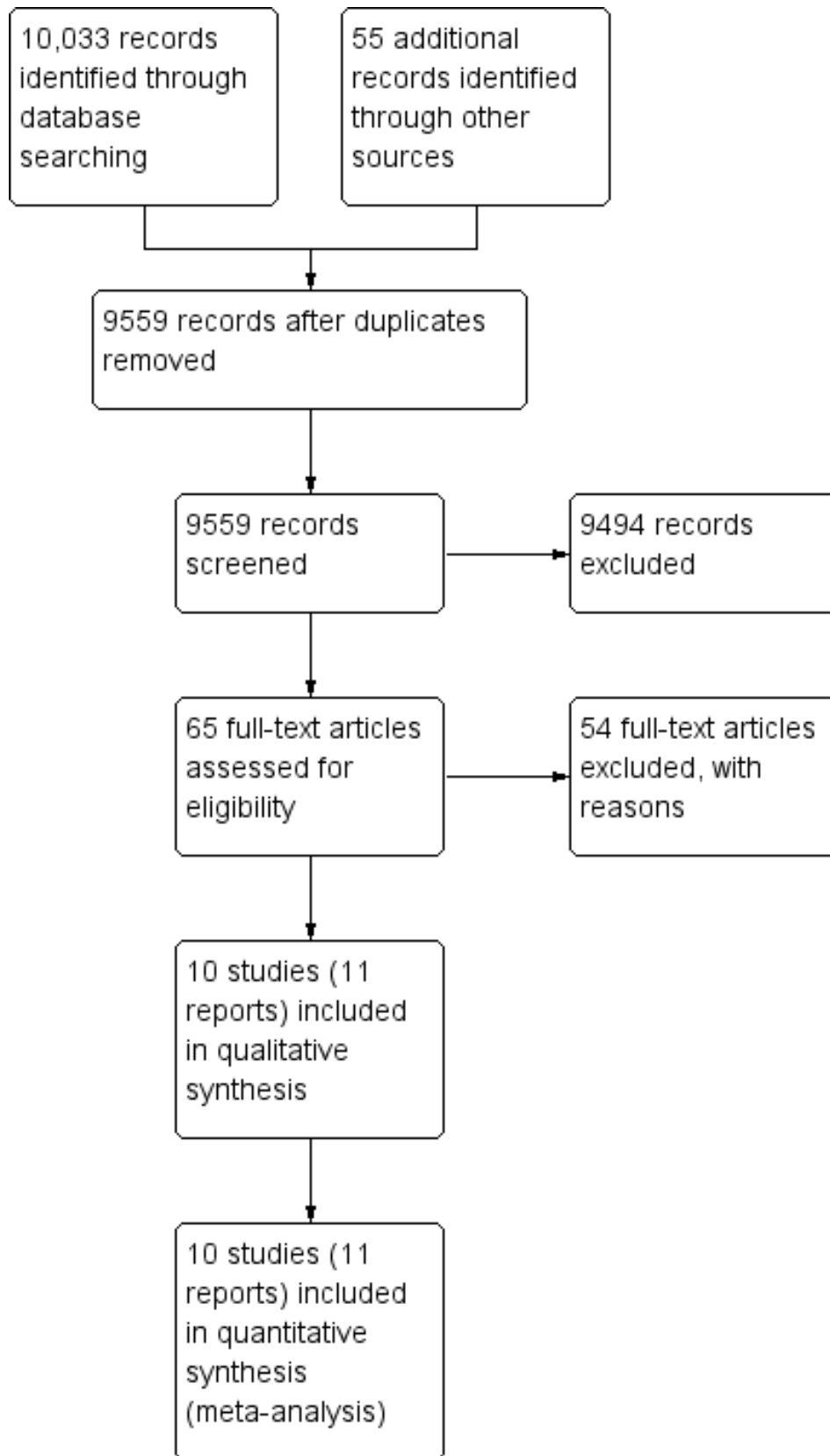
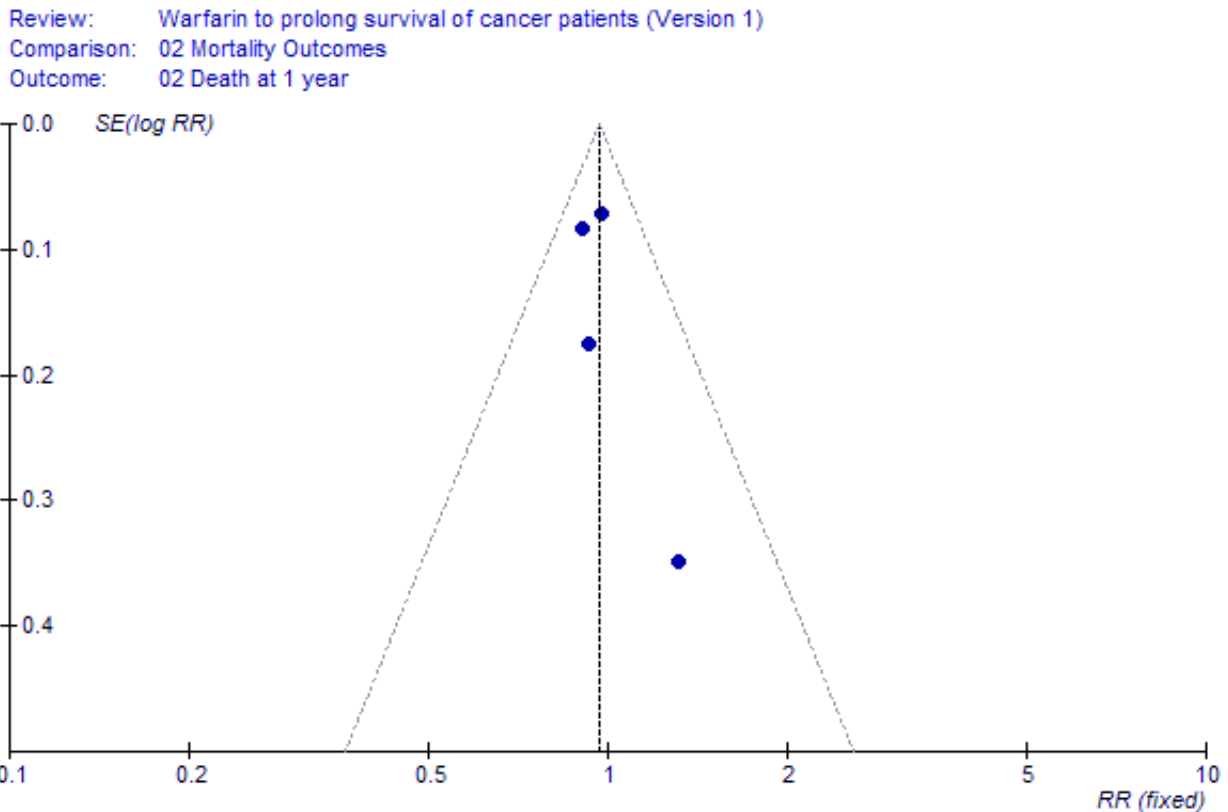


Figure 2. Funnel plot. Inverted funnel plot for studies of warfarin therapy in patients with cancer to improve mortality outcome at 1 year.



Included studies

Six included RCTs used warfarin as the oral anticoagulation agent and one RCT used apixaban as the oral anticoagulant. A total of 1770 participants were recruited and FU data were available for 1669 participants (Chahinian 1989; Daly 1991; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984).

Stanford 1979 recruited 24 patients with a small cell carcinoma (at least stage T3 disease) of the bronchus receiving chemotherapy, 75% of participants were males and 79% had extrathoracic metastases. Participants were randomized to receive heparin or warfarin or dextran at different time intervals during chemotherapy or no anticoagulant. Assessed outcomes were mortality and bleeding. No patients were LTFU.

Zacharski 1984 recruited 431 patients with different types of cancer undergoing chemotherapy and with a minimum life expectancy of two months. Patients were randomized to receive either warfarin (to approximately double prothrombin time (PT)) or no warfarin. Treatment was given until death or the end of the study. Assessed outcomes included mortality and major bleeding. The authors reported data on 418 patients omitting 13 patients who had resection with curative intent for Duke's C carcinoma of the colon because "no conclusions could be reached for this category". The authors had reported earlier on a subgroup of 50 patients with SCLC (Zacharski 1981).

Chahinian 1989 recruited 189 patients with extensive SCLC undergoing chemotherapy and with a Cancer and Leukemia Group B (CALGB) performance status of 0 to 3. Patients were randomized to receive either warfarin (to maintain PT between 1.5 and 2) or no warfarin. Therapy was started on the first day of chemotherapy and continued throughout the chemotherapy course. Assessed outcomes included mortality, major bleeding, and minor bleeding. FU was complete.

Daly 1991 recruited 352 patients with operable colorectal cancer Dukes' stage B or C. Patients were randomized to receive either warfarin (to double PT) or no warfarin for two years. The trial assessed mortality as the unique outcome. FU data were available for 339 patients.

Levine 1994 recruited 315 patients with stage IV breast cancer, undergoing chemotherapy, with a minimum life expectancy of three months and with a good performance status based on the Eastern Cooperative Oncology Group (ECOG less than 3) assessment. Patients were randomized to receive either warfarin at a "therapeutic dose" (to maintain INR between 1.3 and 1.9) or placebo. Treatment began either at the start of chemotherapy or within four weeks and continued until one week after termination of chemotherapy. Assessed outcomes included mortality, DVT, PE, major bleeding, and minor bleeding. FU data were available for 311 patients after excluding four patients who did not start chemotherapy.

Maurer 1997 recruited 369 patients with limited stage SCLC undergoing chemotherapy and radiation therapy, with a minimum life expectancy of two months and a CALGB performance status less than 3. Patients were randomized to receive either warfarin at a "therapeutic dose" (to maintain PT between 1.4 and 1.6) or no warfarin. Treatment was started on the first day of chemotherapy and continued three weeks after the last cycle of chemotherapy. Assessed outcomes included mortality, major bleeding, minor bleeding, and thrombocytopenia. FU data were available for 347 patients after excluding 22 ineligible patients.

Levine 2012 recruited 125 patients with advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian, or prostate cancers; cancer of unknown origin; myeloma; or selected lymphomas receiving either first-line or second-line chemotherapy. Half of the participants had ECOG of 0, and 30% had central venous catheter (VTE risk factor). Participants were recruited from six sites in Canada and eight sites in the USA. Patients were randomized to receive placebo, or apixaban 5 mg, 10 mg, or 20 mg once daily for 12 weeks beginning within four weeks of the date on which the first-line or second-line chemotherapy was begun. Assessed outcomes were mortality, major bleed, clinically relevant nonmajor bleed. VTE, symptomatic DVT, and symptomatic PE.

Excluded studies

We excluded 52 studies for the following reasons: animal studies (N = 2); intervention different to oral anticoagulant (five studies); by protocol, co-interventions were not similar among compared groups (three studies); no outcome of interest reported (eight studies); duplicate publication (one study); study protocol (one study); letter to the editor (eight studies); abstracts later published in full and included in this review (three studies); not an RCT (17 studies); review (three studies); no population of interest, that is, cancer patients (one study).

Risk of bias in included studies

Allocation

The method of sequence generation was unclear for one study (Chahinian 1989), but adequate for the remaining six.

Allocation was adequately concealed in two of the seven included studies (Daly 1991; Maurer 1997). It was unclear whether it was adequately concealed in five studies (Chahinian 1989; Levine 1994; Levine 2012; Stanford 1979; Zacharski 1984).

Blinding

One study blinded participants, caregivers, outcome assessors, and analysts (Levine 1994); one study blinded participants and outcome assessors (Levine 2012); and five studies did not use blinding

(Chahinian 1989; Daly 1991; Maurer 1997; Stanford 1979; Zacharski 1984).

Incomplete outcome data

Although the percentage of follow-up varied across studies, it was distributed as following: 100% in Levine 2012 and Stanford 1979, 96.3% in Daly 1991, 98% in Levine 1994, 98.8% in Zacharski 1984, and 97% in Chahinian 1989. Finally, Maurer 1997 did not report percentage of FU.

Selective reporting

None of the seven studies was registered or had a published protocol. One study did not list outcomes in its methods section (Daly 1991). The remaining six studies did list outcomes in the methods section and reported on them (Chahinian 1989; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984).

Other potential sources of bias

None of the studies was stopped early for benefit. One of the seven studies analyzed data using the ITT principle (Levine 1994); two studies did not use ITT (Maurer 1997; Zacharski 1984); and four studies did not report on the use of ITT (Chahinian 1989; Daly 1991; Levine 2012; Stanford 1979).

The quality of evidence across review outcomes was moderate for all outcomes (Summary of findings for the main comparison).

Effects of interventions

See: [Summary of findings for the main comparison Oral anticoagulation in patients with cancer with no therapeutic or prophylactic indication for anticoagulation](#)

Agreement between the two biostatisticians who extracted data from survival curves was high with a mean percentage difference in measured survival of 1.5%. In a sensitivity analysis using either biostatistician estimates or the mean of their estimates, we noted no difference in the statistical significance of the results. Heterogeneity was low to moderate in all but one analysis.

Comparison 1: warfarin versus no warfarin

All-cause mortality

The pooled estimates did not conclusively rule out increase or reduction in mortality at six months (RR 0.98; 95% CI 0.82 to 1.17), one year (RR 0.97; 95% CI 0.89 to 1.04) (Figure 3), two years (RR 0.98; 95% CI 0.81 to 1.18), and five years (RR 0.92; 95% CI 0.83 to 1.01). Heterogeneity was absent ($I^2 = 0\%$) at one year (6% at six months, 73% at two years, 0% at five years for comparison warfarin versus no warfarin). The associated risk of bias for mortality at one year is presented in Figure 4. We judged the quality of evidence as moderate (Summary of findings for the main comparison).

Figure 3. Forest plot of comparison: 1 Warfarin versus no warfarin, outcome: 1.2 Mortality at 1 year.

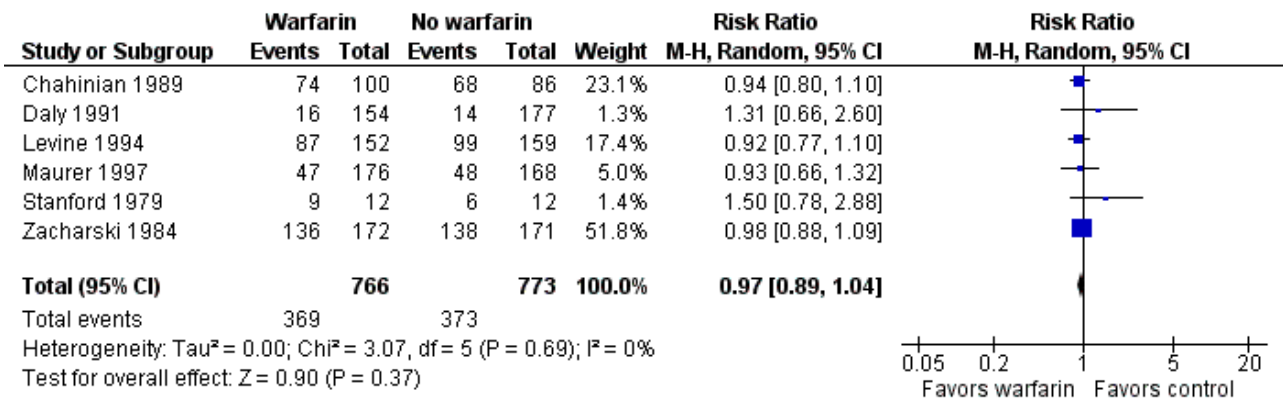


Figure 4. Risk of bias summary for mortality at 1 year: review authors' judgments about each risk of bias item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding of patients?	Blinding of providers?	Blinding of data collectors?	Blinding of outcome adjudicators?	Blinding of data analysts?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Intention to treat analysis
Chahinian 1989	?	?	-	-	+	+	-	+	?	+	?
Daly 1991	+	+	-	-	+	+	-	+	+	+	?
Levine 1994	+	?	+	+	+	+	+	+	+	+	+
Maurer 1997	+	+	-	-	+	+	-	?	+	+	-
Zacharski 1984	+	+	-	-	+	+	-	+	+	+	-

In a subgroup analysis of patients with SCLC versus other types of cancer (Chahinian 1989; Maurer 1997), the test for subgroup effect was not statistically significant at any FU time. Of note, Maurer

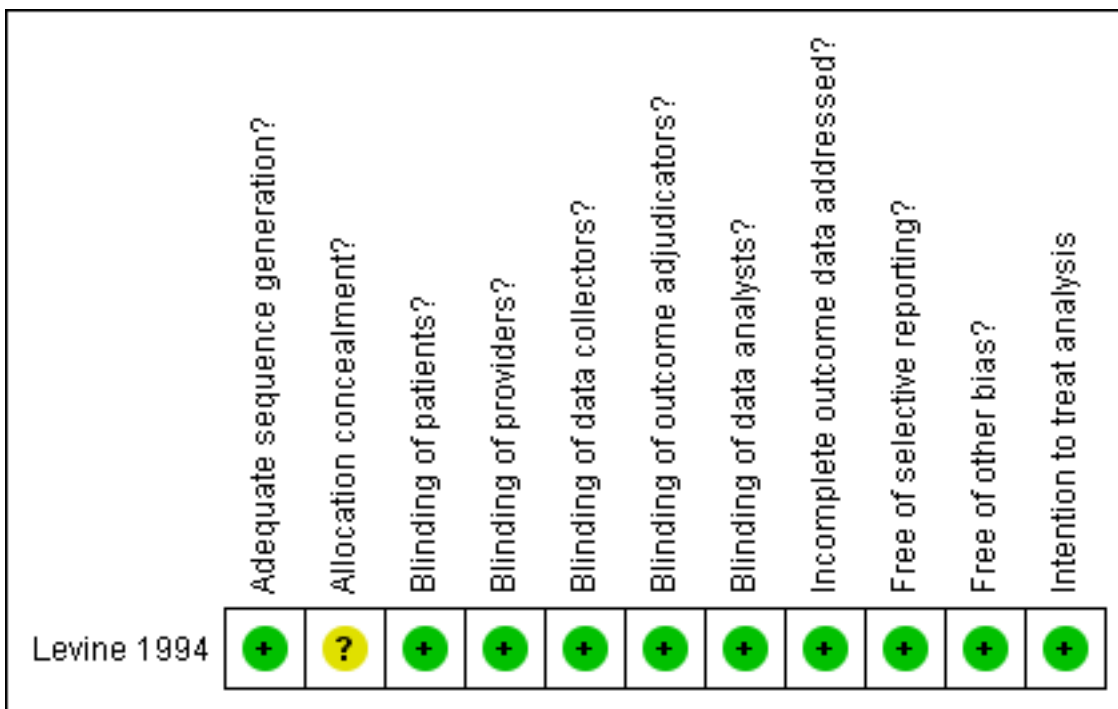
1997 recruited patients with limited SCLC, while Chahinian 1989 recruited patients with extensive SCLC.

Symptomatic venous thromboembolism

Only one study reported on the incidence of DVT and PE (Levine 1994); there was only one PE in the warfarin group, and six DVT

and one PE in the placebo group (RR 0.15; 95% CI 0.02 to 1.20). The associated risk of bias is presented in Figure 5. We judged the quality of evidence as moderate (Summary of findings for the main comparison).

Figure 5. Risk of bias summary for venous thromboembolism: review authors' judgments about each risk of bias item for each included study.



Major bleeding

Four of the included studies comparing warfarin with no warfarin evaluated the occurrence of major bleeding (Chahinian 1989; Levine 1994; Maurer 1997; Zacharski 1984). The pooled estimates showed statistically significant increases (RR 4.24; 95% CI 1.86 to 9.65) (Figure 6). Heterogeneity was low ($I^2 = 28\%$). The associated risk of bias is presented in Figure 7. Since the primary meta-

analysis found a statistically significant effect, and in order to assess the risk of bias associated with missing participant data, we conducted sensitivity meta-analyses used the priori plausible assumptions detailed in the Methods section. The effect estimate remained statistically significant even when using the most stringent plausible assumption (RR 2.79; 95% CI 1.62 to 4.81). We judged the quality of evidence as moderate (Summary of findings for the main comparison).

Figure 6. Forest plot of comparison: 1 Warfarin versus no warfarin, outcome: 1.6 Major bleeding.

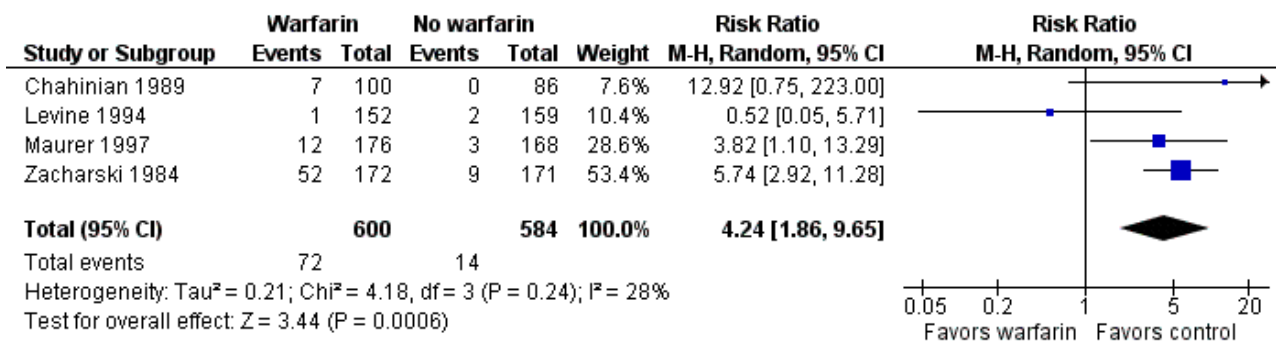


Figure 7. Risk of bias summary for major bleeding: review authors' judgments about each risk of bias item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding of patients?	Blinding of providers?	Blinding of data collectors?	Blinding of outcome adjudicators?	Blinding of data analysts?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Intention to treat analysis
Chahinian 1989	?	?	-	-	-	-	-	+	?	+	?
Levine 1994	+	?	+	+	+	+	+	+	+	+	+
Maurer 1997	+	+	-	-	-	-	-	?	+	+	-
Zacharski 1984	+	+	-	-	-	-	-	+	+	+	-

In subgroup analyses of patients with SCLC versus other types of cancer (Chahinian 1989; Maurer 1997), the test for subgroup effect was not statistically significant.

Minor bleeding

Four of the included studies comparing warfarin with no warfarin evaluated the occurrence of minor bleeding (Chahinian 1989;

Levine 1994; Maurer 1997; Stanford 1979). The pooled estimates showed statistically significant increases for minor bleeding (RR 3.19; 95% CI 1.83 to 5.55) (Figure 8). Heterogeneity was low (I² = 21%). The associated risk of bias is presented in Figure 9. There were no missing participant data for this outcome. We judged the quality of evidence as moderate (Summary of findings for the main comparison).

Figure 8. Forest plot of comparison: 1 Warfarin versus no warfarin, outcome: 1.5 Minor bleeding.

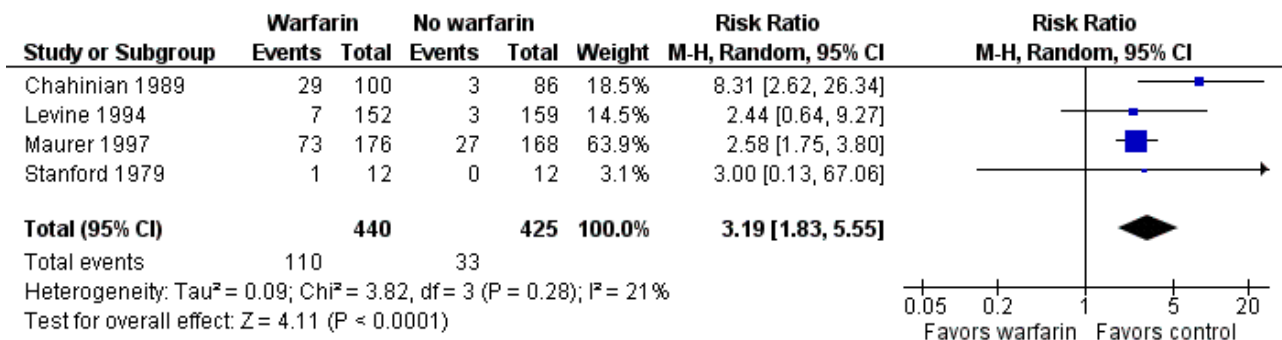


Figure 9. Risk of bias summary for minor bleeding: review authors' judgments about each risk of bias item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding of patients?	Blinding of providers?	Blinding of data collectors?	Blinding of outcome adjudicators?	Blinding of data analysts?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Intention to treat analysis
Chahinian 1989	?	?	-	-	-	-	-	+	?	+	?
Levine 1994	+	?	+	+	+	+	+	+	+	+	+
Maurer 1997	+	+	-	-	-	-	-	?	+	+	-

In subgroup analyses of patients with SCLC versus other types of cancer (Chahinian 1989; Maurer 1997), the test for subgroup effect was not statistically significant.

Comparison 2: apixaban versus no apixaban

Mortality

The one study comparing apixaban with placebo did not rule out a clinically significant decrease or increase in mortality at six months (RR 0.16; 95% CI 0.01 to 1.66) (Levine 2012). We judged the quality of evidence as low due to imprecision.

Symptomatic venous thromboembolism

The one study comparing apixaban with placebo found a statistically significant reduction of symptomatic DVT (RR 0.08; 95% CI 0.01 to 0.67) but did not rule out a clinically significant decrease or increase in PE (RR 0.11; 95% CI 0.00 to 2.54) (Levine 2012). There were no missing participant data for this outcome. We judged the quality of evidence as low due to imprecision.

Major bleeding

The one study comparing apixaban with placebo did not rule out a clinically significant decrease or increase in major bleeding (RR 0.62; 95% CI 0.06 to 6.63) (Levine 2012). We judged the quality of evidence as low due to imprecision.

Minor bleeding

The one study comparing apixaban with placebo did not rule out a clinically significant decrease or increase in minor bleeding (RR 2.87; 95% CI 0.16 to 51.82) (Levine 2012). We judged the quality of evidence as low due to imprecision.

DISCUSSION

Summary of main results

This systematic review neither proved nor excluded a clinically important effect of warfarin on mortality of patients with cancer in general. Warfarin did reduce thromboembolic events but increased major and minor bleeding events. We did not detect any subgroup effect based on type of cancer.

The systematic review identified only one trial comparing apixaban with placebo. While the study showed a statistically significant reduction of symptomatic DVT, it did not prove or exclude a clinically important effect of apixaban on mortality, major bleeding, and minor bleeding. We judged the quality of evidence as low for all outcomes.

Overall completeness and applicability of evidence

Unfortunately, the available data were insufficient to assess the statistical significance of potentially clinically significant benefit in different types of cancer such as SCLC and nonsmall cell lung cancer

(NSCLC). The study results apply directly to the types of cancer the eligible studies have focused on, that is, mostly lung cancer.

Only one included study reported excluding patients with a requirement for long-term oral anticoagulation without indicating how many such patients were excluded (Levine 1994); this could potentially limit the generalizability of the findings to similar populations. In fact, patients with other indications for anticoagulation might experience greater effects on survival compared with the ones included in that study.

Quality of the evidence

For the comparison of warfarin versus no warfarin, we judged the quality of the evidence as moderate for all outcomes. We downgraded the quality of evidence for mortality and bleeding outcomes because of the risk of bias (study limitations). We downgraded the quality of evidence for VTE because of imprecision and concern about publication bias (only one study reporting on this outcome).

For the comparison of apixaban versus no apixaban, we judged the quality of evidence as low for all outcomes due to imprecision related to the small number of events, expressed for most outcomes as very wide CIs including both values suggesting major benefit and values suggesting major harm.

Potential biases in the review process

Our systematic approach to searching, study selection, and data extraction should have minimized the likelihood of missing relevant studies or relevant data.

Agreements and disagreements with other studies or reviews

One systematic review by Zhang et al. assessed the effects of anticoagulants on the health outcomes of patients with lung cancer with no indication for anticoagulation (Zhang 2013). The meta-analysis included nine RCTs: five RCTs assessed VKA as the intervention, while the other four RCTs assessed low molecular

weight heparin (LMWH) as the intervention. The meta-analysis found a long-term survival benefit and a reduction in the incidence of VTE. This analysis had the problem of clinical heterogeneity, something we tried to avoid by separating the analysis of oral and parenteral anticoagulation (Akl 2010; Akl 2011).

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review does not provide evidence for a mortality benefit from oral anticoagulation in patients with cancer in general. In fact, current evidence suggests that there is no mortality benefit from oral anticoagulation therapy. The intervention may be associated with a reduction in venous thromboembolism but also with an increased risk of minor and major bleeding and by the burden of warfarin treatment (e.g. periodically checking international normalized ratio levels).

Implications for research

Future research should investigate the effects of oral anticoagulation in patients with different cancer subtypes (e.g. small cell lung cancer, nonsmall cell lung cancer) and different cancer stages. The last clinical trial on this topic was published in 1997 despite the relevance of the question and the lack of a clear answer. There is also a need to investigate the effects of other anticoagulants (e.g. low molecular weight heparin, fondaparinux) in patients with different types and stages of cancer (Akl 2011).

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King CS, Holley AB, Moores LK. Moving toward a more ideal anticoagulant: the oral direct thrombin and factor Xa inhibitors. *Chest* 2013;**143**(4):1106-16.

Levine 2003

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

Miller 2004

Miller GJ, Bauer KA, Howarth DJ, Cooper JA, Humphries SE, Rosenberg RD. Increased incidence of neoplasia of the digestive tract in men with persistent activation of the coagulant pathway. *Journal of Thrombosis & Haemostasis* 2004;**2**(12):2107-14.

Schulman 2000

Schulman S, Lindmarker P. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism. Duration of Anticoagulation Trial. *New England Journal of Medicine* 2000;**342**(26):1953-8.

Zacharski 1981

Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ Jr, Forcier RJ, et al. Effect of warfarin on survival in small cell carcinoma of the lung. Veterans Administration Study No. 75. 1981 *JAMA*; **245**(8):831-5.

Zhang 2013

Zhang J, Zhang YL, Ma KX, Qu JM. Efficacy and safety of adjunctive anticoagulation in patients with lung cancer without indication for anticoagulants: a systematic review and meta-analysis. *Thorax* 2013;**68**(5):442-50.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Chahinian 1989

Methods	Randomized controlled trial
Participants	189 patients with small cell lung cancer undergoing chemotherapy; (CALBG 0-3) Mean age 60 years, 70% male
Interventions	Intervention: VKA (PT 1.5-2)

Chahinian 1989 (Continued)

Control: no intervention

Co-intervention: both arms received chemotherapy

34 patients were excluded: 15 were ineligible, 9 did not receive the treatment protocol and 10 had inadequate data

Screening testing for DVT/PE: none

Diagnostic testing for DVT/PE: none

Outcomes	Major bleeding and mortality (6 months, 1 year, 2 years, and 5 years)
Notes	Funding: TJ Martell Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of patients?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of providers?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of data collectors?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of outcome adjudicators?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of data analysts?	High risk	Quote: "No placebo used" Comment: probably not
Incomplete outcome data addressed?	Low risk	Follow-up rate: 97% Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on. Probably free of selective reporting
Free of other bias?	Low risk	Study not stopped early
Intention-to-treat analysis	Unclear risk	Not reported

Daly 1991

Methods	Randomized controlled trial; 2 x 2 factorial design
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Daly 1991 (Continued)

Participants	352 patients with colorectal cancer Mean age 65 years, 52% male
Interventions	Intervention: VKA (doubling of PT) for 2 years Control: no intervention Co-intervention: a subgroup of patients in each arm received urokinase: 46% in warfarin group and 47% in non-warfarin group 159 patients were excluded after the first randomization, 5 early died and were excluded from the analysis Screening testing for DVT/PE: none Diagnostic testing for DVT/PE: none
Outcomes	Mortality (6 months, 1 year, 2 years, and 5 years)
Notes	Funding: Abbott Europe, Boehringer-Ingelheim & Serono Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All eligible patients were preoperatively randomized" Comment: no further detailed provided, but probably yes
Allocation concealment (selection bias)	Low risk	Quote: "All eligible patients were preoperatively randomized (by telephoning a trial office) to receive urokinase or not"
Blinding of patients?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of providers?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of data collectors?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of outcome adjudicators?	High risk	Quote: "No placebo used" Comment: probably not
Blinding of data analysts?	High risk	Quote: "No placebo used" Comment: probably not
Incomplete outcome data addressed?	Low risk	Follow-up rate: 96% (352 randomized and 339 followed-up) Comment: definitely yes
Free of selective reporting?	High risk	Study not registered. No published protocol. No listing of outcomes in the methods section Comment: probably no

Daly 1991 (Continued)

Free of other bias?	Low risk	Study not stopped early for benefit
Intention-to-treat analysis	Unclear risk	Not reported

Levine 1994

Methods	Randomized controlled trial
Participants	315 patients with breast cancer undergoing chemotherapy; minimum life expectancy 3 months; good performance status (ECOG < 3)
Interventions	<p>Intervention: VKA (INR 1.3-1.9) started within 4 weeks of chemotherapy until 1 week after termination of chemotherapy</p> <p>Control: placebo</p> <p>Co-intervention: both arms received chemotherapy</p> <p>2 patients in the warfarin group and 2 in the control group did not receive chemotherapy and they were not considered in the analysis</p> <p>DVT diagnostic tests: venography, impedance plethysmography, or Doppler</p> <p>PE diagnostic tests: ventilation/perfusion scan or angiography</p> <p>No surveillance tests used</p>
Outcomes	DVT, PE, arterial thrombosis, and mortality (1 year)
Notes	Funding: National Cancer Institute, Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned warfarin or placebo according to a computer-generated random arrangement"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of patients?	Low risk	Quote: "Neither patients nor doctors were aware of treatment allocation" Comment: definitely yes
Blinding of providers?	Low risk	Quote: "Neither patients nor doctors were aware of treatment allocation" Comment: definitely yes
Blinding of data collectors?	Low risk	Quote: "given control was placebo" Comment: probably yes
Blinding of outcome adjudicators?	Low risk	Quote: "given control was placebo" Comment: probably yes

Levine 1994 (Continued)

Blinding of data analysts?	Low risk	Based on a personal communication with the author
Incomplete outcome data addressed?	Low risk	Follow-up rate: 98% (315 randomized and 311 followed up) Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on. Probably free of selective reporting
Free of other bias?	Low risk	Study not stopped early for benefit
Intention-to-treat analysis	Low risk	All patients randomized and received first dose of chemotherapy were included in the analysis. No reports of cross-over Comment: probably yes

Levine 2012

Methods	Randomized phase II double-blinded trial
Participants	125 patients with advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian or prostate cancers; cancer of unknown origin; myeloma; or selected lymphomas from 6 sites in Canada and 8 in the USA Mean age 60 years, 50% male, ECOG 0 50%, have central venous catheter (VTE risk factor) 30%
Interventions	Intervention: apixaban 5 mg, 10 mg, or 20 mg once daily for 12 weeks beginning within 4 weeks of the date on which the first-line or second-line chemotherapy was begun Control: placebo Co-intervention: either first-line or second-line chemotherapy (expected course \geq 90 days)
Outcomes	Duration of follow-up: 30 days after completion of the 12-week treatment period (114-121 days) or premature discontinuation of study medication or of the study. <ul style="list-style-type: none"> • Mortality • Major bleeding • Clinically relevant nonmajor bleeding • Higher adverse events (\geq grade 3) • VTE • Symptomatic DVT • Symptomatic PE Diagnostic tests for bleeding: "In the absence of visible bleeding, confirmatory imaging techniques that can detect the presence of bleeding (e.g. ultrasound [US], computed tomography [CT], and magnetic resonance imaging) could be used" Diagnostic tests for DVT: compression ultrasound or venography Diagnostic tests for PE: spiral computed tomography or ventilation/perfusion lung scan
Notes	Funding: Bristol-Myers Squibb and Pfizer Inc. Quote: "In September 2008, a decision was made by the Steering Committee and BMS [Bristol-Myers Squibb] to close the trial because of the slow rate of accrual. It was felt that the main study objectives could be met despite not reaching the intended sample size"

Levine 2012 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally by contacting a computerized telephone voice response system provided by Bristol Myers Squibb (BMS)". "Treatment assignments were implemented with a randomization schedule with blocks of size four; blocks were stratified by the presence (or not) of metastatic liver disease and clinical center"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of patients?	Low risk	Quote: "Subjects received blister packs containing a combination of apixaban (2.5-mg or 10-mg tablets) and matching placebo tablets supplied by BMS. All subjects took four tablets orally once daily; these consisted of a combination of apixaban and matching placebo tablets for the apixaban treatment groups, or all placebo tablets for the placebo treatment group, such that the study supplies for subjects in all treatment groups were identical in appearance" Comment: definitely blinded
Blinding of providers?	Unclear risk	Not reported
Blinding of data collectors?	Unclear risk	Not reported
Blinding of outcome adjudicators?	Low risk	Quote: "All bleeding and VTE events were adjudicated by a committee unaware of treatment allocation" Comment: probably blinded
Blinding of data analysts?	Unclear risk	Not reported
Incomplete outcome data addressed?	Low risk	Quote: "The percentages of patients in each group (5 mg, 10 mg and 20 mg of apixaban and placebo) completing the full 12 weeks of study drug were 78%, 80%, 76%, and 63% respectively. No patients were lost to follow-up"
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on Quote: "Study protocol approved by Institutional Review Board of each participating center" Comment: probably free of selective reporting
Free of other bias?	Low risk	No other bias suspected
Intention-to-treat analysis	Unclear risk	Not reported Participants randomized but had not received treatment: 2 of 95 participants randomized to the intervention arms and 1 of 30 participants randomized to the control arm

Maurer 1997

Methods Randomized controlled study

Maurer 1997 (Continued)

Participants	<p>347 patients > 18 years of age with small cell lung cancer undergoing chemotherapy and radiation therapy from 27 CALBG main member institutions and their affiliates</p> <p>Mean age 48 years, 65% male, 55% performance status 0, minimum life expectancy 2 months; CALGB < 3</p>
Interventions	<p>Intervention: VKA (PT 1.4-1.6) started with chemotherapy at a dose of 10 mg/day for 3 days and continued for 3 weeks after last cycle of chemotherapy and radiation therapy</p> <p>Control: no warfarin</p> <p>Co-intervention: both arms received 3 cycles of chemotherapy</p> <p>3 patients were randomized but excluded pretreatment because they did not received protocol treatment (not clear in which group)</p> <p>Diagnostic tests for PE: not reported</p> <p>Diagnostic tests for DVT: not reported</p>
Outcomes	<ul style="list-style-type: none"> • Mortality (6 months, 1 year, 2 years, 5 years) • Bleeding
Notes	Funding: National Cancer Institute, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized to receive warfarin or no warfarin". Communication with author: "allocation by central office" Comment: probably yes given this was done by a central office
Allocation concealment (selection bias)	Low risk	Communication with author: "allocation by central office"
Blinding of patients?	High risk	Quote: "given no placebo was used" Comment: probably not
Blinding of providers?	High risk	Quote: "given no placebo was used" Comment: probably not
Blinding of data collectors?	High risk	Quote: "given no placebo was used" Comment: probably not
Blinding of outcome adjudicators?	High risk	Comment: probably not
Blinding of data analysts?	High risk	Quote: "given no placebo was used" Comment: probably not
Incomplete outcome data addressed?	Unclear risk	Follow-up rate: not reported

Maurer 1997 (Continued)

Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in in the methods section were reported on. Probably free of selective reporting
Free of other bias?	Low risk	Study not stopped early for benefit
Intention-to-treat analysis	High risk	Quote: "Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses" Comment: definitely not

Stanford 1979

Methods	Randomized controlled trial
Participants	24 patients with a small cell carcinoma (at least stage T3 disease) of the bronchus receiving chemotherapy 75% male, 79% extrathoracic metastases
Interventions	Intervention: 48 hours before each induction course of cytotoxic drugs, a loading dose of heparin 5000 IU and then heparin 20,000 IU a day for 6 days. During the first 24 hours of anticoagulants also received 1 L of dextran (Rheomacrodex). A loading dose of warfarin 25 mg was given on the fourth day of heparin treatment. On the day of the intravenous maintenance chemotherapy, each patient of the anticoagulant group also received heparin 5000 IU contained in 500 mL of dextran over a period of 4 hours Control: no anticoagulant Co-intervention: "Both groups received two induction courses of chemotherapy at three weekly intervals followed by maintenance drugs given three times weekly" Diagnostic tests for PE: not reported Diagnostic tests for DVT: not reported
Outcomes	Duration of follow-up: 16 months <ul style="list-style-type: none"> Mortality (12 months) Minor bleeding (4 months)
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were assigned to either the anticoagulant or control treatment groups according to a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of patients?	Unclear risk	Not reported
Blinding of providers?	Unclear risk	Not reported
Blinding of data collectors?	Unclear risk	Not reported

Stanford 1979 (Continued)

Blinding of outcome adjudicators?	Unclear risk	Not reported
Blinding of data analysts?	Unclear risk	Not reported
Incomplete outcome data addressed?	Low risk	No loss to follow-up reported
Free of selective reporting?	Unclear risk	Study not registered. No published protocol. No listing of outcomes in the methods section
Free of other bias?	Unclear risk	Study not reported as stopped early for benefit No other bias suspected
Intention-to-treat analysis	Unclear risk	Not reported Quote: "All the 24 patients enrolled in the study completed the follow up and their data had been analyzed"

Zacharski 1984

Methods	Randomized controlled trial
Participants	431 patients with different types of cancer undergoing chemotherapy; minimum life expectancy of 2 months from 13 different Veterans Affairs Medical Centers over a 4-year period and were followed for an additional 12 months
Interventions	Intervention: VKA (therapeutic range) Control: no intervention Co-intervention: not reported 13 randomized patients were excluded from survival analyses (not clear in which group) Diagnostic tests for PE: not reported Diagnostic tests for DVT: not reported
Outcomes	Study duration: 4 years followed for an additional 12 months <ul style="list-style-type: none"> Major bleeding Mortality (6 months, 1 year)
Notes	Funding: Department of Veterans Affairs Medical Research Service

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients admitted to the study were subjected to computer randomization by hospital, performance status and tumour category to receive standard therapy either with or without warfarin anticoagulation"
Allocation concealment (selection bias)	Unclear risk	Not reported

Zacharski 1984 (Continued)

Blinding of patients?	High risk	Comment: probably not
Blinding of providers?	High risk	Comment: probably not
Blinding of data collectors?	High risk	Comment: probably not
Blinding of outcome adjudicators?	High risk	Comment: probably not
Blinding of data analysts?	High risk	Comment: probably not
Incomplete outcome data addressed?	Low risk	Follow-up rate: 98% (431 randomized and 418 followed up) Comment: definitely yes
Free of selective reporting?	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were not reported. Probably free of selective reporting
Free of other bias?	Low risk	Study not stopped early for benefit
Intention-to-treat analysis	High risk	Quote: "patients randomized to receive warfarin were excluded if they did not receive at least 2 weeks of anticoagulant therapy following randomization" Comment: probably not

CALBG: Cancer and Leukemia Group B; DVT: deep vein thrombosis; ECOG: Eastern Cooperative Oncology Group; INR: international normalized ratio; IU: international unit; PE: pulmonary embolism; PT: prothrombin time; VKA: vitamin K antagonist; VTE: venous thromboembolism.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aisner 1987	Different drug/agent studied
Aisner 1992	No control group
Anonymous 1994	Letter to editor
Carpi 1995	Observational study
Chahinian 1984	Abstract, later published in full text
Chahinian 1985	Abstract, later published in full text
Chlebowski 1982	No control group
D'Souza 1980a	Groups treated differently
D'Souza 1980b	Groups treated differently
Demir 2006	No reporting outcome of interest
Demir 2007	No reporting outcome of interest

Study	Reason for exclusion
Herrmann 1988	No control group
Herrmann 1990	No control group
Higashi 1971	Animal study
Hoppensteadt 2011	No reporting outcome of interest
Huber 1993	Letter to the editor
Hutchins 1984	No control group
Khan 2012	No reporting outcome of interest
Kokron 1990	Different drug/agent studied
Kokron 1993	Different drug/agent studied
Lebeau 1993	Different drug/agent studied
Lecumberri 2005	Review
Loprinzi 1999	Not population of interest, no patients with cancer
Macareo 2001	Observational study: retrospective
Marshall 1987	No control group
Marshall 1989	No control group
Marshall 1990	No control group
McCulloch 1987	Animal study
Moazzam 2003	No control group
Mohler 1993	No control group
Mohler 1994	No control group
Sagaster 1995	Different drug/agent studied
Smorenburg 2001	Review
Taliani 2003	Letter to editor
Taliani 2004	Letter to editor
Thethi 2011	No reporting outcome of interest
Thornes 1972	Controlled clinical trial, not randomized
Thornes 1974	Controlled clinical trial, not randomized

Study	Reason for exclusion
Thornes 1975	Controlled clinical trial, no adequate randomization (each alternate patient with the same histology was given warfarin)
Thornes 1984	No control group
Thornes 1989	No relevant outcomes reported
Thornes 1993	No relevant outcomes reported
Thornes 1994	No relevant outcomes reported
Tiska-Rudman 2001	No control group
Venook 1989	Letter to the editor
Zacharski 1979	Protocol
Zacharski 1982a	Abstract, later published in full text
Zacharski 1982b	Letter to the editor
Zacharski 1990	Letter to the editor
Zacharski 1993	Review
Zacharski 2002	Letter to the editor

Characteristics of ongoing studies [ordered by study ID]

Bristol-Myers Squibb 2006

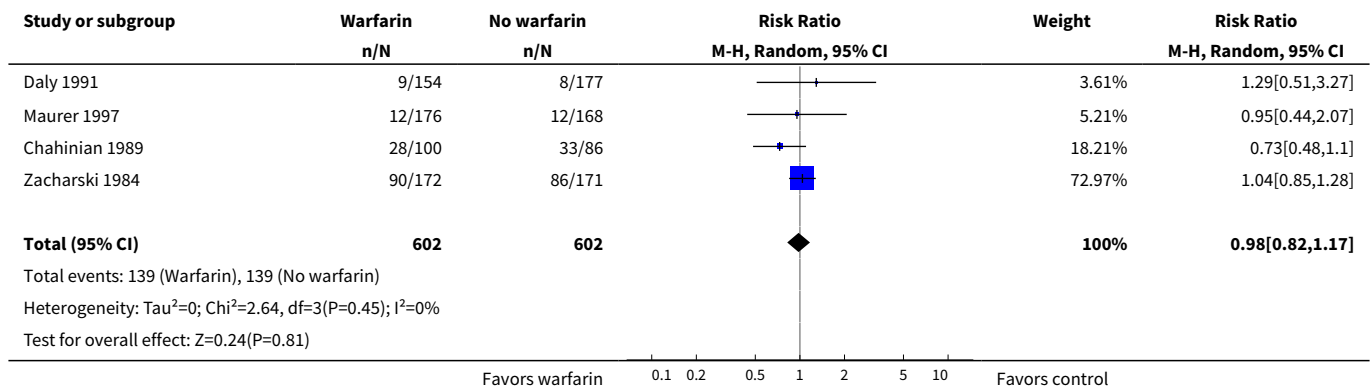
Trial name or title	A Randomized, Double-blind, Placebo-controlled Study of Apixaban for the Prevention of Thromboembolic Events in Patients Undergoing Treatment for Advanced Cancer: a Phase 2 Pilot Study
Methods	Phase 2 pilot study; randomized, double-blind, placebo-controlled study
Participants	Patients undergoing chemotherapy for ≥ 90 days for advanced or metastatic cancer
Interventions	Apixaban: oral, 5 mg once daily for 12 weeks Placebo: oral, 0 mg, once daily for 12 weeks
Outcomes	Major bleeding Clinically relevant nonmajor bleeding Symptoms compatible with venous thromboembolism
Starting date	June 2006
Contact information	Bristol-Myers Squibb, no contact information provided clinicaltrials.gov/ct2/show/NCT00320255
Notes	This study has been completed

DATA AND ANALYSES

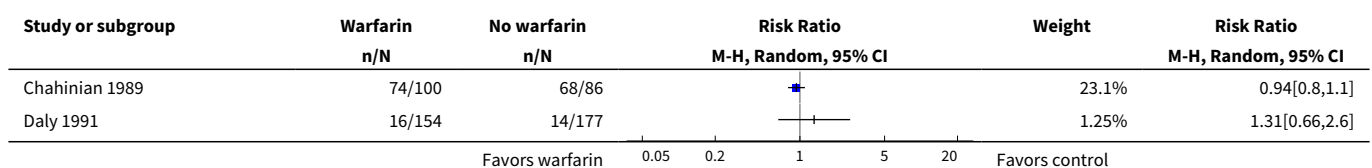
Comparison 1. Warfarin versus no warfarin

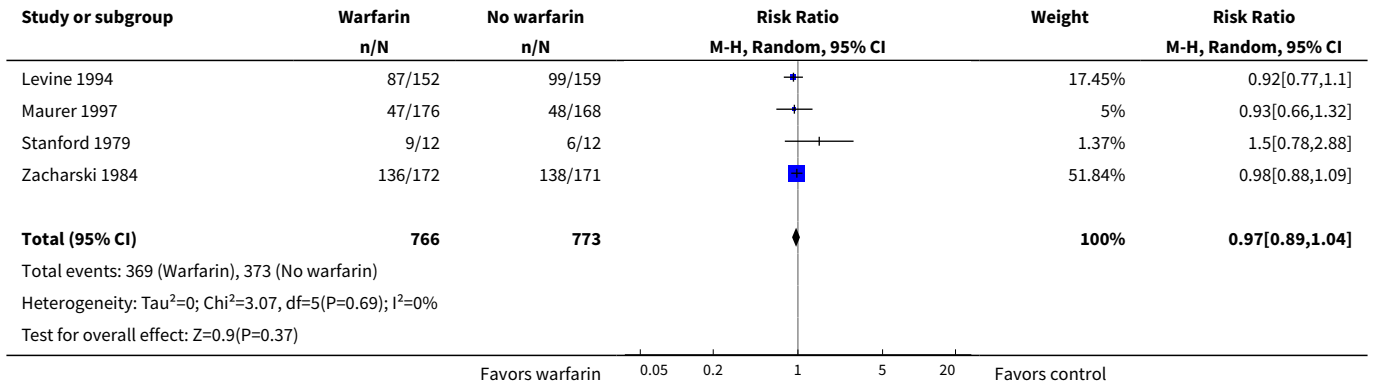
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at 6 months	4	1204	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.17]
2 Mortality at 1 year	6	1539	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.04]
3 Mortality at 2 years	3	861	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.18]
4 Mortality at 5 years	2	675	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.01]
5 Deep vein thrombosis	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.42]
6 Pulmonary embolism	1	311	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.58]
7 Venous thromboembolism	1	311	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.20]
8 Major bleeding	4	1184	Risk Ratio (M-H, Random, 95% CI)	4.24 [1.86, 9.65]
9 Minor bleeding	4	865	Risk Ratio (M-H, Random, 95% CI)	3.19 [1.83, 5.55]

Analysis 1.1. Comparison 1 Warfarin versus no warfarin, Outcome 1 Mortality at 6 months.

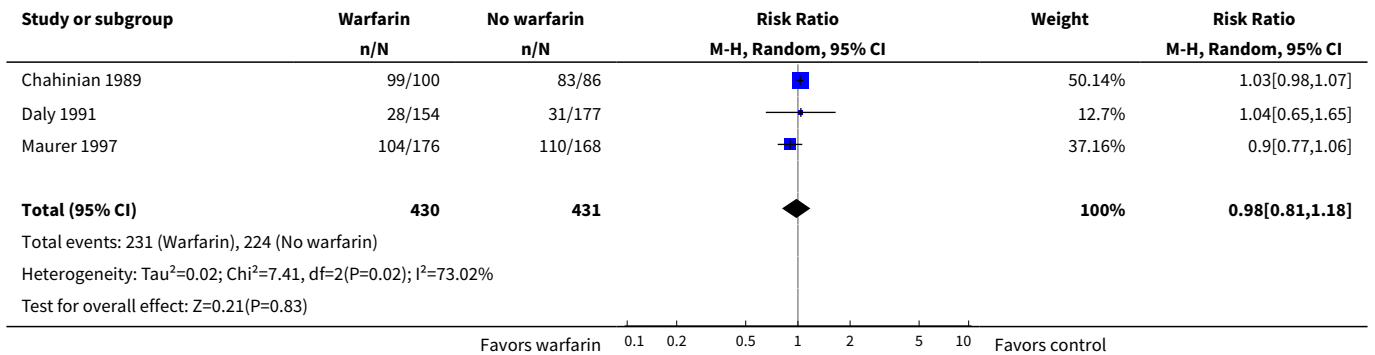


Analysis 1.2. Comparison 1 Warfarin versus no warfarin, Outcome 2 Mortality at 1 year.

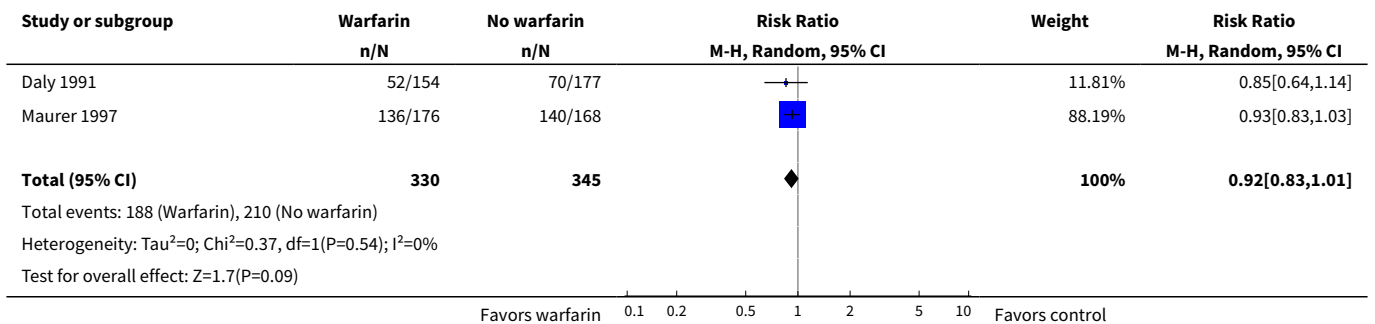




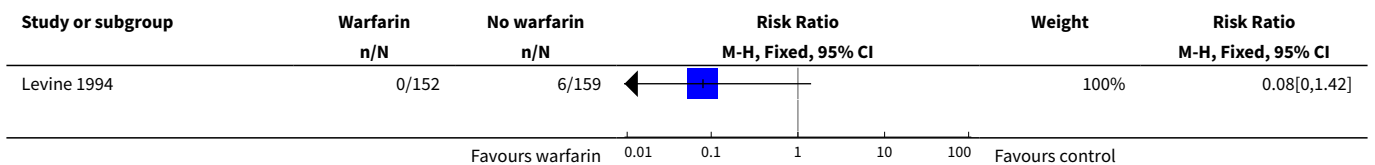
Analysis 1.3. Comparison 1 Warfarin versus no warfarin, Outcome 3 Mortality at 2 years.

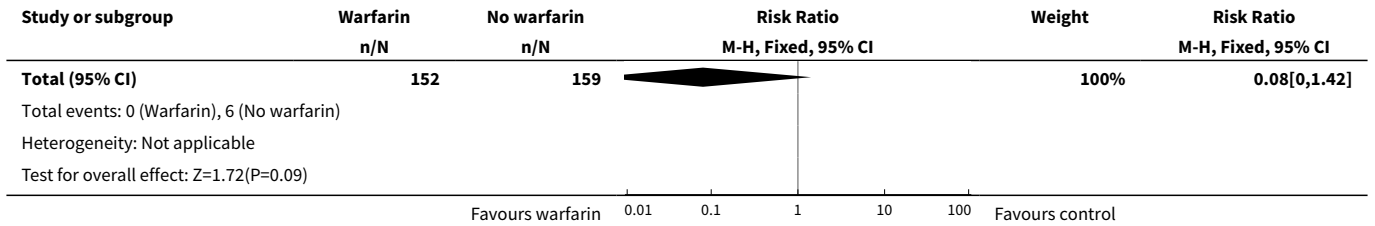


Analysis 1.4. Comparison 1 Warfarin versus no warfarin, Outcome 4 Mortality at 5 years.

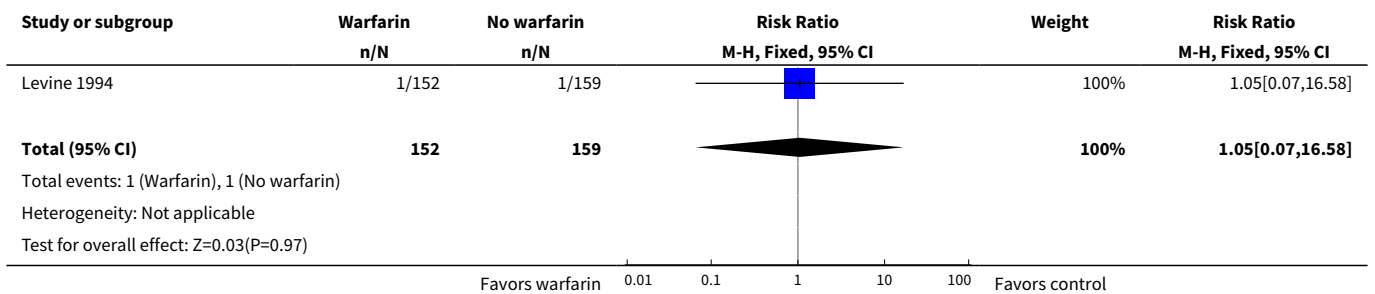


Analysis 1.5. Comparison 1 Warfarin versus no warfarin, Outcome 5 Deep vein thrombosis.

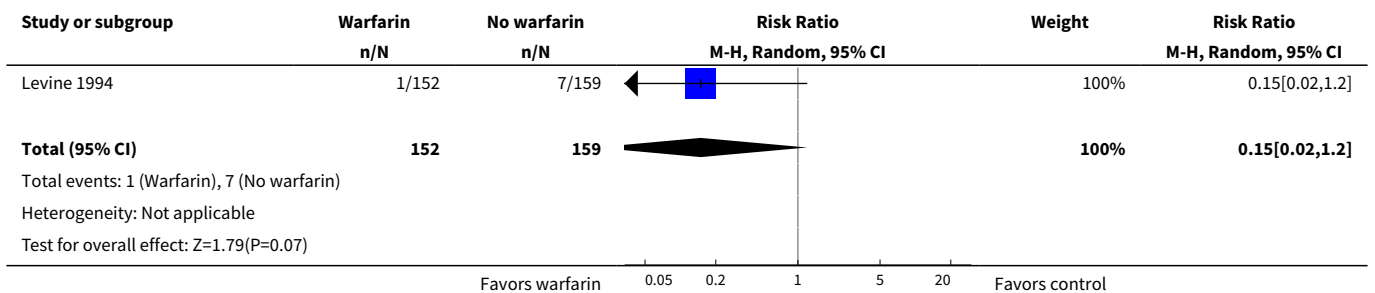




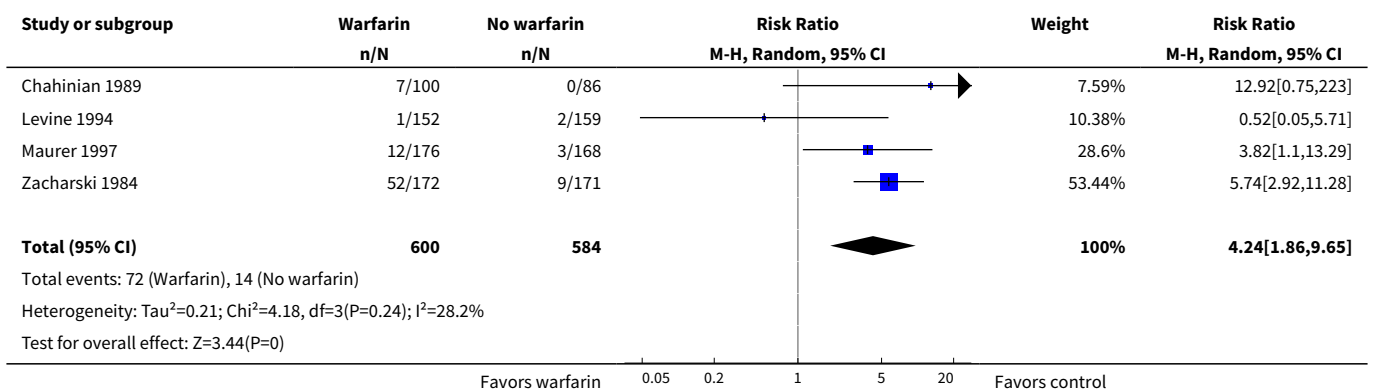
Analysis 1.6. Comparison 1 Warfarin versus no warfarin, Outcome 6 Pulmonary embolism.



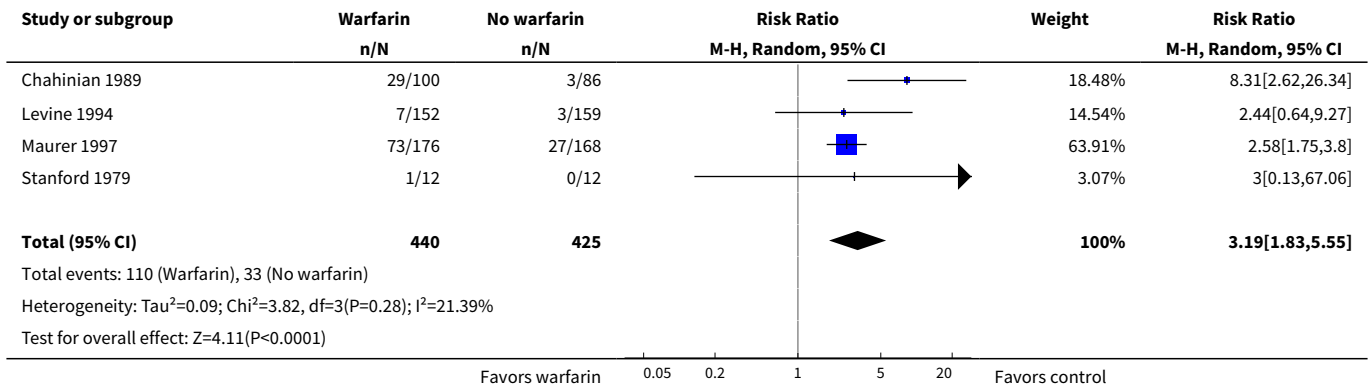
Analysis 1.7. Comparison 1 Warfarin versus no warfarin, Outcome 7 Venous thromboembolism.



Analysis 1.8. Comparison 1 Warfarin versus no warfarin, Outcome 8 Major bleeding.



Analysis 1.9. Comparison 1 Warfarin versus no warfarin, Outcome 9 Minor bleeding.



ADDITIONAL TABLES

Table 1. Glossary

Term	Meaning
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)
Antithrombotic	Used against or tending to prevent thrombosis (clotting)
Apixaban	An anticoagulant medication that is an oral direct factor Xa inhibitor that is used for anticoagulation
Coagulation	Clotting
Direct factor Xa inhibitor	Anticoagulant medications that are used for anticoagulation. Apixaban is an oral direct factor Xa inhibitor
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
Hemostatic 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. 2 forms of heparin that are used as anticoagulant medications are: unfractionated heparin (UFH) and low molecular weight heparins (LMWH)

Table 1. Glossary (Continued)

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
Pulmonary embolism (PE)	Embolism of a pulmonary artery or 1 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
Vitamin K antagonist	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
Major bleeding	A bleeding that is intracranial or retroperitoneal, if it leads directly to death, or if results in hospitalization or transfusion
Minor bleeding	Any bleeding not classified as major bleeding

APPENDICES

Appendix 1. Full search strategies for the electronic databases - update 2010

Database	Strategy
CENTRAL	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #7 malignan\$ OR neoplasm\$ OR cancer OR carcinoma\$ OR adenocarcinoma OR tumour OR tumor #8 6 AND 7
MEDLINE	#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/

(Continued)

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

EMBASE

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

ISI (International Scientific Information) the Web of Science

#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran
 #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA
 #3 fondaparinux OR Arixtra
 #4 ximelagatran OR Exanta
 # 5 Pradaxa OR Dabigatran OR rivaroxaban OR Xarelto OR apixaban

(Continued)

#6 1 OR 2 OR 3 OR 4 OR 5
 #7 malignan\$ OR neoplasm\$ OR cancer OR carcinoma\$ OR adenocarcinoma OR tumour OR tumor
 #8 random\$ OR placebo\$ OR versus OR vs OR double blind OR double-blind OR compar\$ OR controlled
 #9 6 AND 7 AND 8

Appendix 2. Full search strategies for the electronic databases - update 2013

Database	Strategy
CENTRAL	<p>#1 MeSH descriptor: [Heparin] explode all trees</p> <p>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum)</p> <p>#3 MeSH descriptor: [Coumarins] explode all trees</p> <p>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anti-coagulant or vitamin K antagonist or VKA)</p> <p>#5 (fondaparinux or arixtra)</p> <p>#6 (ximelagatran or exanta)</p> <p>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban)</p> <p>#8 #1 or #2 or #3 or #4 or #5 or #6 or #7</p> <p>#9 MeSH descriptor: [Neoplasms] explode all trees</p> <p>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)</p> <p>#11 #9 or #10</p> <p>#12 #8 and #10</p>
MEDLINE	<p>#1 exp Heparin/</p> <p>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.</p> <p>#3 exp Coumarins/</p> <p>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anti-coagulant or vitamin K antagonist or VKA).tw.</p> <p>#5 (fondaparinux or arixtra).tw.</p> <p>#6 (ximelagatran or exanta).tw.</p> <p>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.</p>

(Continued)

- #8 1 or 2 or 3 or 4 or 5 or 6 or 7
- #9 exp Neoplasms/
- #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
- #11 9 or 10
- #12 8 and 11
- #13 randomized controlled trial.pt.
- #14 controlled clinical trial.pt.
- #15 randomized.ab.
- #16 placebo.ab.
- #17 drug therapy.fs.
- #18 randomly.ab.
- #19 trial.ab.
- #20 groups.ab.
- #21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
- #22 12 and 21
- #23 exp animals/ not humans.sh.
- #24 22 not 23

EMBASE

- #1 heparin/
- #2 exp low molecular weight heparin/
- #3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.
- #4 exp coumarin derivative/
- #5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anti-coagulant or vitamin K antagonist or VKA).tw.
- #6 (fondaparinux or arixtra).tw.
- #7 (ximelagatran or exanta).tw.
- #8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
- #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- #10 exp neoplasm/
- #11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
- #12 10 or 11
- #13 9 and 12

(Continued)

- #14 crossover procedure/
 - #15 double-blind procedure/
 - #16 randomized controlled trial/
 - #17 single-blind procedure/
 - #18 random*.mp.
 - #19 factorial*.mp.
 - #20 (crossover* or cross over* or cross-over*).mp.
 - #21 placebo*.mp.
 - #22 (double* adj blind*).mp.
 - #23 (singl* adj blind*).mp.
 - #24 assign*.mp.
 - #25 allocat*.mp.
 - #26 volunteer*.mp.
 - #27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
 - #28 13 and 27
 - #29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
 - #30 28 not 29
-
-

Appendix 3. Detailed statistical data abstraction

Comparison: warfarin versus no warfarin



Outcome: Mortality at 6 months												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA)[2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre- trt[3]	Post-trt [4]					Pre-trt	Post-trt		
CHAHINIAN 1989	28	103	3[5]	0	Not clear 28/2[6]	103-3=100	33	86	0	0	Not clear 28/2	86
DALY 1991	9	163	5	Not clear 8/2[7]	0	163-5-8/2=154	8	181	0	Not clear 8/2	0	181-8/2=177
MAURER 1997	12	178	Not clear 3/2[8]	0	0	178-3/2=176.5	12	169	Not clear 3/2	0	0	169-3/2=167.5
ZACHARSKI 1984	90	215	5	Not clear 5/2[9] 13/2[10] 57/2[11]	Not clear	215-5- (5+13+57)/2 =172.5	86	216	8	Not clear 5/2 13/2 57/2	Not clear	216-8-(5+13+57)/2= 170.5

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5]"3 patients with known brain metastasis were randomized to receive warfarin, never received warfarin because of early progression during brain radiotherapy" (Applies to both arms).

[6]"28 patients die early before evaluation but were included in the denominator for the calculation of response rate." (Applies to both arms).

[7]"The eight withdrawals from the trial after the second randomization were attributed to chemotherapy/radiotherapy treatment or problems with warfarin therapy."

[8]"Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).

[9]"5 (1.2%) of the 431 patients were lost to follow-up" (Applies to both arms).

[10]"Only 13 patients were entered to this study who had had resection with curative intent for Duke's C carcinoma of the colon. Since no conclusions could be reached for this category, these patients were omitted from this analysis. Thus, results obtained in the remaining 418 patients are reported here." (Applies to both arms).

[11]"Patients were excluded if they did not receive at least one course of standard treatment or did not survive at least 2 weeks following randomization. In addition, patients randomized to receive warfarin were excluded if they did not receive at least 2 weeks of anticoagulant therapy following randomization. Application of these criteria resulted in exclusion of 57 patients (13% of the Total)" (Applies to both arms).

Outcome: Mortality at 1 year												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA) [2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre- trt[3]	Post-trt [4]					Pre-trt	Post-trt		
CHAHINIAN 1989	74	103	3[5]	0	Not clear 28/2[6]	103-3=100	68	86	0	0	Not clear 28/2	86
DALY 1991	16	163	5	Not clear 8/2[7]	0	163-5-8/2=154	14	181	0	Not clear 8/2	0	181-8/2=177
LEVINE 1994	87	154	2[8]	0	0	154-2=152	99	161	2	0	0	161-2=159
MAURER 1997	47	178	Not clear 3/2[9]	0	0	178-3/2=176.5	48	169	Not clear 3/2	0	0	169-3/2=167.5
ZACHARSKI 1984	136	215	5	Not clear 5/2[10] 13/2[11] 57/2[12]	Not clear	215-5- (5+13+57)/2 =172.5	138	216	8	Not clear 5/2 13/2 57/2	Not clear	216-8-(5+13+57)/2= 170.5
STANDFORD 1979	9[13]	12	0	0	0	12	6	12	0	0	0	12

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1] Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2] Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3] Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4] Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5] "3 patients with known brain metastasis were randomized to receive warfarin, never received warfarin because of early progression during brain radiotherapy" (Applies to both arms).

[6] "28 patients die early before evaluation but were included in the denominator for the calculation of response rate." (Applies to both arms).

[7] "The eight withdrawals from the trial after the second randomization were attributed to chemotherapy/radiotherapy treatment or problems with warfarin therapy."

[8] "2 patients in each group did not start chemotherapy; thus the analysis is based on 152 warfarin-allocated patients and 159 placebo-allocated patients"

[9] "Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).

[10] "5 (1.2%) of the 431 patients were lost to follow-up" (Applies to both arms).

[11] "Only 13 patients were entered to this study who had had resection with curative intent for Duke's C carcinoma of the colon. Since no conclusions could be reached for this category, these patients were omitted from this analysis. Thus, results obtained in the remaining 418 patients are reported here." (Applies to both arms).

[12] "Patients were excluded if they did not receive at least one course of standard treatment or did not survive at least 2 weeks following randomization. In addition, patients randomized to receive warfarin were excluded if they did not receive at least 2 weeks of anticoagulant therapy following randomization. Application of these criteria resulted in exclusion of 57 patients (13% of the Total)" (Applies to both arms).

[13] From survival curve

Outcome: Mortality at 2 years												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA) [2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre-trt[3]	Post-trt [4]					Pre-trt	Post- trt		
CHAHINIAN 1989	99	103	3[5]	0	Not clear 28/2[6]	103-3=100	83	86	0	0	Not clear 28/2	86
DALY 1991	28	163	5	Not clear 8/2[7]	0	163-5-8/2=154	31	181	0	Not clear 8/2	0	181-8/2=177
MAURER 1997	104	178	Not clear 3/2[8]	0	0	178-3/2=176.5	110	169	Not clear 3/2	0	0	169-3/2=167.5

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1] Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2] Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3] Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4] Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5] "3 patients with known brain metastasis were randomized to receive warfarin, never received warfarin because of early progression during brain radiotherapy" (Applies to both arms).

[6] "28 patients die early before evaluation but were included in the denominator for the calculation of response rate." (Applies to both arms).

[7] "The eight withdrawals from the trial after the second randomization were attributed to chemotherapy/radiotherapy treatment or problems with warfarin therapy."

[8] "Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).

Outcome: Mortality at 5 years												
Study Name	LMWH						UFH					
	Events	No	No most likely to have MPD		No less likely to have MPD[1]	No with available outcome data (for CCA)[2]	Events	No	No more likely to have MPD		No less likely to have MPD	No. with available outcome data (for CCA)
	Rand		Pre-trt[3]	Post-trt [4]			Rand		Pre-trt	Post-trt		
DALY 1991	52	163	5	Not clear	0	163-5-8/2=154	70	181	0	Not clear	0	181-8/2=177
				8/2[5]						8/2		
MAU-RER 1997	136	178	Not clear	0	0	178-3/2=176.5	140	169	Not clear	0	0	169-3/2=167.5
			3/2[6]						3/2			

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5]"The eight withdrawals from the trial after the second randomization were attributed to chemotherapy/radiotherapy treatment or problems with warfarin therapy."

[6]"Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).

Outcome: Deep Vein Thrombosis												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA) [2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available out- come data (for CCA)	
			Pre- trt[3]	Post-trt [4]				Pre-trt	Post- trt			
LEVINE 1994	0	154	2	0	0	154-2=152	6	161	2	0	0	161-2=159

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).



Outcome: Pulmonary Embolism												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA) [2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available out- come data (for CCA)	
			Pre- trt[3]	Post-trt [4]				Pre-trt	Post- trt			
LEVINE 1994	1	154	2	0	0	154-2=152	1	161	2	0	0	161-2=159

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

Outcome: Venous Thromboembolic Events												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA) [2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available out- come data (for CCA)	
			Pre- trt[3]	Post-trt [4]				Pre-trt	Post- trt			
LEVINE 1994	1	154	2	0	0	154-2=152	7	161	2	0	0	161-2=159

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).



Outcome: Major Bleeding												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less likely to have MPD[1]	No with available outcome data (for CCA)[2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre- trt[3]	Post-trt [4]					Pre-trt	Post-trt		
CHAHINIAN 1989	7	103	3[5]	0	Not clear 28/2[6]	103-3=100	0	86	0	0	Not clear 28/2	86
LEVINE 1994	1	154	2	0	0	154-2=152	2	161	2	0	0	161-2=159
MAURER 1997	12	178	Not clear 3/2[7]	0	0	178-3/2=176.53		169	Not clear 3/2	0	0	169-3/2=167.5
ZACHARSKI 1984	52	215	5	Not clear 5/2[8] 13/2[9] 57/2[10]	Not clear	215-5- (5+13+57)/2 =172.5	9	216	8	Not clear 5/2 13/2 57/2	Not clear	216-8-(5+13+57)/2= 170.5

- [1] Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).
- [2] Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).
- [3] Participants categorized as "ineligible" and did not receive first dose (applies for both arms).
- [4] Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).
- [5] "3 patients with known brain metastasis were randomized to receive warfarin, never received warfarin because of early progression during brain radiotherapy" (Applies to both arms).
- [6] "28 patients die early before evaluation but were included in the denominator for the calculation of response rate." (Applies to both arms).
- [7] "Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).
- [8] "5 (1.2%) of the 431 patients were lost to follow-up" (Applies to both arms).
- [9] "Only 13 patients were entered to this study who had had resection with curative intent for Duke's C carcinoma of the colon. Since no conclusions could be reached for this category, these patients were omitted from this analysis. Thus, results obtained in the remaining 418 patients are reported here." (Applies to both arms).
- [10] "Patients were excluded if they did not receive at least one course of standard treatment or did not survive at least 2 weeks following randomization. In addition, patients randomized to receive warfarin were excluded if they did not receive at least 2 weeks of anticoagulant therapy following randomization. Application of these criteria resulted in exclusion of 57 patients (13% of the Total)" (Applies to both arms).

Outcome: Minor Bleeding												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less like- ly to have MPD[1]	No with available outcome data (for CCA)[2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre-trt[3]	Post- trt [4]					Pre-trt	Post- trt		
CHAHINIAN 1989	29	103	3[5]	0	Not clear 28/2[6]	103-3=100	3	86	0	0	Not clear 28/2	86
LEVINE 1994	7	154	2	0	0	154-2=152	3	161	2	0	0	161-2=159
MAURER 1997	73	178	Not clear 3/2[7]	0	0	178-3/2=176.5	27	169	Not clear 3/2	0	0	169-3/2=167.5
STANDFORD 1979	1	12	0	0	0	12	0	12	0	0	0	12

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5]"3 patients with known brain metastasis were randomized to receive warfarin, never received warfarin because of early progression during brain radiotherapy" (Applies to both arms).

[6]"28 patients die early before evaluation but were included in the denominator for the calculation of response rate." (Applies to both arms).

[7]"Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).

Outcome: Minor Bleeding												
Study Name	LMWH						UFH					
	Events	No Rand	No most likely to have MPD	No less like- ly to have MPD[1]	No with available outcome data (for CCA)[2]		Events	No Rand	No more likely to have MPD	No less likely to have MPD	No. with available outcome data (for CCA)	
			Pre-trt[3]	Post- trt [4]					Pre-trt	Post- trt		
CHAHINIAN 1989	29	103	3[5]	0	Not clear 28/2[6]	103-3=100	3	86	0	0	Not clear 28/2	86
LEVINE 1994	7	154	2	0	0	154-2=152	3	161	2	0	0	161-2=159
MAURER 1997	73	178	Not clear 3/2[7]	0	0	178-3/2=176.5	27	169	Not clear 3/2	0	0	169-3/2=167.5
STANDFORD 1979	1	12	0	0	0	12	0	12	0	0	0	12

No: number; Rand: randomized; MPD: missing participant data; CCA: complete case analysis; Pre-trt: pre-treatment; Post-trt: post-treatment; LMWH: low molecular weight heparin; UFH: unfractionated heparin

[1]Participants reported as "non-compliant" (or "discontinued") to treatment for various reasons excluding "loss to follow-up", "withdrawal of consent", and "ineligible participants" (applies for both arms).

[2]Total number randomized - most likely MPD (pretreatment and post-treatment) (applies for both arms).

[3]Participants categorized as "ineligible" and did not receive first dose (applies for both arms).

[4]Participants categorized as "lost to follow-up", "withdrew consent", and "outcome not assessable" (applies for both arms).

[5]"3 patients with known brain metastasis were randomized to receive warfarin, never received warfarin because of early progression during brain radiotherapy" (Applies to both arms).

[6]"28 patients die early before evaluation but were included in the denominator for the calculation of response rate." (Applies to both arms).

[7]"Three additional patients were cancelled immediately after registration and before initiation of protocol treatment as new clinical information indicated the patient to be ineligible to participate in the study. Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses". (Applies to both arms).

FEEDBACK

Cochrane Editorial Unit's report on feedback on anticoagulants reviews, 15 February 2011

Summary

Feedback received on this review, and other reviews and protocols on anticoagulants, is available on the Cochrane Editorial Unit website at www.editorial-unit.cochrane.org/anticoagulants-feedback.

Reply

N/A

Contributors

N/A

WHAT'S NEW

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

CONTRIBUTIONS OF AUTHORS

EAA: protocol development, search for trials, screening, data extraction, data analysis, manuscript drafting, review coordination.LK: screening, data extraction, data analysis.IT: data extraction, data analysis.IN: screening.VY: full-text retrieval, data extraction.MB: screening.FS: data analysis.HJS: protocol development, search for trials, data analysis, methodological advice.

DECLARATIONS OF INTEREST

HJS: no personal payments from for-profit sponsors related to the subject matter in the past three years. EAA is a member of the American College of Chest Physicians (ACCP) Antithrombotic Therapy Guidelines panel.

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- Italian National Cancer Institute Regina Elena, Rome, Italy.

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- Research Grants, Other.

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)

Administration, Oral; Anticoagulants [*administration & dosage] [adverse effects]; Carcinoma, Small Cell [blood] [mortality]; Hemorrhage [chemically induced]; Heparin [*administration & dosage] [adverse effects]; Lung Neoplasms [blood] [mortality]; Neoplasms [blood] [*mortality] [therapy]; Pyrazoles [*administration & dosage] [adverse effects]; Pyridones [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Thromboembolism [*prevention & control]; Time Factors; Warfarin [*administration & dosage] [adverse effects]

MeSH check words

Female; Humans; Male