Cochrane Library

Cochrane Database of Systematic Reviews

Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation (Review)

Kahale LA, Hakoum MB, Tsolakian IG, Matar CF, Barba M, Yosuico VED, Terrenato I, Sperati F, Schünemann H, Akl EA

Kahale LA, Hakoum MB, Tsolakian IG, Matar CF, Barba M, Yosuico VED, Terrenato I, Sperati F, Schünemann H, Akl EA.
Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation.
Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD006466.
DOI: 10.1002/14651858.CD006466.pub6.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Lara A Kahale[1], Maram B Hakoum[2], Ibrahim G Tsolakian[1], Charbel F Matar[3], Maddalena Barba[4], Victor ED Yosuico[5], Irene Terrenato[6], Francesca Sperati[7], Holger Schünemann[8], Elie A Akl[3]

[1]Faculty of Medicine, American University of Beirut, Beirut, Lebanon. [2]Family Medicine, American University of Beirut, Beirut, Lebanon. [3]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon. [4]Division of Medical Oncology 2 - Scientific Direction, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [5]Buffalo Medical Group, Buffalo, New York, USA. [6]Biostatistics-Scientific Direction, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [7]Biostatistics-Scientific Direction, Regina Elena National Cancer Institute, Rome, Italy. [8]Departments of Health Research Methods, Evidence, and Impact and of Medicine, McMaster University, Hamilton, Canada

Contact address: Elie A Akl, ea32@aub.edu.lb.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2021.

Citation: Kahale LA, Hakoum MB, Tsolakian IG, Matar CF, Barba M, Yosuico VED, Terrenato I, Sperati F, Schünemann H, Akl EA. Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD006466. DOI: 10.1002/14651858.CD006466.pub6.

A B S T R A C T

Background

Oral anticoagulants may improve the survival of people with cancer through both an antitumor effect and antithrombotic effect, yet increase the risk of bleeding.

Objectives

To evaluate the efficacy and safety of oral anticoagulants in ambulatory people with cancer undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.

Search methods

We conducted a comprehensive literature search in February 2016 that included a major electronic search of Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 1), MEDLINE (Ovid) and Embase (Ovid); handsearching of conference proceedings; checking of references of included studies; a search for ongoing studies; and using the 'related citation' feature in PubMed. As part of the living systematic review approach, we are running continual searches and will incorporate new evidence rapidly after it is identified. This update of the systematic review is based on the findings of a literature search conducted on 14 December 2017.

Selection criteria

Randomized controlled trials (RCTs) assessing the benefits and harms of vitamin K antagonist (VKA) or direct oral anticoagulants (DOAC) in ambulatory people with cancer. These participants are typically undergoing systemic anticancer therapy, possibly including chemotherapy, target therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.

Data collection and analysis

Using a standardized form, we extracted data in duplicate on study design, participants, intervention outcomes of interest and risk of bias. Outcomes of interest included all-cause mortality, symptomatic venous thromboembolism (VTE), symptomatic deep vein thrombosis

(DVT), pulmonary embolism (PE), major bleeding, minor bleeding and health-related quality of life (HRQoL). We assessed the certainty of evidence for each outcome using the GRADE approach (GRADE Handbook).

Main results

Of 8545 identified citations, including 7668 unique citations, 16 papers reporting on 7 RCTs fulfilled the inclusion criteria. These trials enrolled 1486 participants. 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 meta-analysis of the studies comparing VKA to no VKA did not rule out a clinically significant increase or decrease in mortality at one year (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.87 to 1.03; risk difference (RD) 29 fewer per 1000, 95% CI 75 fewer to 17 more; moderate certainty evidence). One study assessed the effect of VKA on thrombotic outcomes. The study did not rule out a clinically significant increase or decrease in PE when comparing VKA to no VKA (RR 1.05, 95% CI 0.07 to 16.58; RD 0 fewer per 1000, 95% CI 6 fewer to 98 more; very low certainty evidence), but found that VKA compared to no VKA likely decreases the incidence of DVT (RR 0.08, 95% CI 0.00 to 1.42; RD 35 fewer per 1000, 95% CI 38 fewer to 16 more; low certainty evidence). VKA increased both major bleeding (RR 2.93, 95% CI 1.86 to 4.62; RD 107 more per 1000, 95% CI 48 more to 201 more; moderate certainty evidence) and minor bleeding (RR 3.14, 95% CI 1.85 to 5.32; RD 167 more per 1000, 95% CI 66 more to 337 more; moderate certainty evidence).

The study assessing the effect of DOAC compared to no DOAC did not rule out a clinically significant increase or decrease in mortality at three months (RR 0.24, 95% CI 0.02 to 2.56; RD 51 fewer per 1000, 95% CI 65 fewer to 104 more; low certainty evidence), PE (RR 0.16, 95% CI 0.01 to 3.91; RD 28 fewer per 1000, 95% CI 33 fewer to 97 more; low certainty evidence), symptomatic DVT (RR 0.07, 95% CI 0.00 to 1.32; RD 93 fewer per 1000, 95% CI 100 fewer to 32 more; low certainty evidence), major bleeding (RR 0.16, 95% CI 0.01 to 3.91; RD 28 fewer per 1000, 95% CI 33 fewer to 97 more; low certainty evidence); and minor bleeding (RR 4.43, 95% CI 0.25 to 79.68; RD 0 fewer per 1000, 95% CI 0 fewer to 8 more; low certainty evidence).

Authors' conclusions

The existing evidence does not show a mortality benefit from oral anticoagulation in people with cancer but suggests an increased risk for bleeding.

Editorial note: this is a living systematic review. Living systematic reviews offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence, as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

PLAIN LANGUAGE SUMMARY

Oral blood thinners in people with cancer

Background
Research evidence suggests that blood thinners (called anticoagulants) may not only prevent life-threatening blood clots, but also have a direct anticancer effect. However, blood thinners can also increase the risk of serious and fatal bleeding. Therefore, it is important to understand the pros and cons of treatment to allow people and their doctors to be aware of the balance of risks and benefits.

Study characteristics
We searched the scientific literature for studies of anticoagulants in people with cancer. The evidence is current to December 2017.

Key results
We included seven trials including 1486 participants with cancer. Most trials included participants with various types of cancer especially lung and pancreatic cancer. We found six studies using warfarin and one study using apixaban. When considering people with cancer in general, warfarin had no effect on mortality (death rate) or the risk of blood clots. However, it increased the risk of major bleeding in 107 more people per 1000 population and minor bleeding in 167 more people per 1000 population. Apixaban had no effect on mortality, recurrence of blood clots in blood vessels, major bleeding or minor bleeding; however, these findings were based on only one study.

Certainty of the evidence
When comparing warfarin to no warfarin, we judged the certainty of the evidence (how sure and confident we are of the findings) to be moderate for mortality at one year and major and minor bleeding, low for symptomatic deep vein thrombosis (blood clot within a deep vein, most commonly the legs) and very low for pulmonary embolism (blood clot in the blood vessels of the lungs).

When comparing apixaban to no apixaban, we judged the certainty of evidence to be low for mortality at three months, major and minor bleeding, pulmonary embolism and symptomatic deep vein thrombosis.

Editorial note: this is a living systematic review. Living systematic reviews offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

SUMMARY OF FINDINGS

Summary of findings 1. VKA prophylaxis compared to No prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy

VKA prophylaxis compared to No prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy

Patient or population: ambulatory people with cancer without VTE receiving systemic therapy

Setting: outpatient

Intervention: VKA prophylaxis

Control: no prophylaxis

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with No prophylaxis	Risk difference with VKA prophylaxis
Mortality follow up: 12 months	1281 (5 RCTs)	⊕⊕⊕⊝ MODERATE [1]	RR 0.95 (0.87 to 1.03)	Study population	
				574 per 1,000	29 fewer per 1,000 (75 fewer to 17 more)
PE follow up: 12 months	311 (1 RCT)	⊕⊝⊝⊝ VERY LOW [2,3]	RR 1.05 (0.07 to 16.58)	Study population	
				6 per 1,000	0 fewer per 1,000 (6 fewer to 98 more)
Symptomatic DVT follow up: 12 months	311 (1 RCT)	⊕⊕⊝⊝ LOW [4,5]	RR 0.08 (0.00 to 1.42)	Study population	
				38 per 1,000	35 fewer per 1,000 (38 fewer to 16 more)
Major bleeding follow up: 12 months	1281 (5 RCTs)	⊕⊕⊕⊝ MODERATE [6]	RR 2.93 (1.86 to 4.62)	Study population	
				55 per 1,000	107 more per 1,000 (48 more to 201 more)
Minor bleeding follow up: 12 months	863 (4 RCTs)	⊕⊕⊕⊝ MODERATE [7]	RR 3.14 (1.85 to 5.32)	Study population	
				78 per 1,000	167 more per 1,000 (66 more to 337 more)

HRQoL - not reported	-	-	-

*__The risk in the intervention group__ (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; **DVT:** deep vein thrombosis; **HRQoL:** health-related quality of life; **PE:** pulmonary embolism; **RCT:** randomized controlled trial; **RR:** risk ratio; **VKA:** vitamin K antagonist.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one level due to concern about both risk of bias (lack of blinding in patients and personnel and unclear allocation concealment in 4 out of 5 studies) and imprecision (95% CI is consistent with the possibility for important benefit (75 per 1000 absolute reduction) and the possibility of important harm (17 per 1000 absolute increase), large event rate)
[2] Downgraded by one level due to indirectness. Levine 1994 used fixed dose of VKA instead of adjusted dose which is not representative of the current practice. This study was the only trial that reported on PE and symptomatic DVT.
[3] Downgraded by two levels due to very serious imprecision. 95% CI is consistent with the possibility for important benefit (6 per 1000 absolute reduction) and the possibility of important harm (98 per 1000 absolute increase), including only 2 events.
[4] Levine 1994 used fixed dose of VKA instead of adjusted dose which is not representative of the current practice. This study was the only trial that reported on PE and symptomatic DVT. We do not think that this indirectness has underestimated the effect on symptomatic DVT (RR 0.08)
[5] Downgraded by two levels due to very serious imprecision. Only 6 events among 311 participants.
[6] Downgraded by one level due to concern about risk of bias (lack of blinding in patients and personnel and unclear allocation concealment in 4 out of 5 studies)
[7] Downgraded by one level due to concern about risk of bias (lack of blinding in patients and personnel and unclear allocation concealment in 3 out of 4 studies)

Summary of findings 2. DOAC prophylaxis compared to No prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy (Q6b- Oral)

DOAC prophylaxis compared to No prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy

Patient or population: ambulatory people with cancer without VTE receiving systemic therapy

Setting: outpatient

Intervention: DOAC prophylaxis

Control: no prophylaxis

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)

	Follow up			Risk with No prophylaxis	Risk difference with DOAC prophylaxis
Mortality follow up: 3 months	92 (1 RCT)	⊕⊕⊝⊝ LOW [1,2]	RR 0.24 (0.02 to 2.56)	Study population	
				67 per 1,000	51 fewer per 1,000 (65 fewer to 104 more)
PE follow up: 3 months	92 (1 RCT)	⊕⊕⊝⊝ LOW [1,3]	RR 0.16 (0.01 to 3.91)	Study population	
				33 per 1,000	28 fewer per 1,000 (33 fewer to 97 more)
Symptomatic DVT follow up: 3 months	92 (1 RCT)	⊕⊕⊝⊝ LOW [1,4]	RR 0.07 (0.00 to 1.32)	Study population	
				100 per 1,000	93 fewer per 1,000 (100 fewer to 32 more)
Major bleeding follow up: 3 months	92 (1 RCT)	⊕⊕⊝⊝ LOW [1,3]	RR 0.16 (0.01 to 3.91)	Study population	
				33 per 1,000	28 fewer per 1,000 (33 fewer to 97 more)
Minor bleeding follow up: 3 months	92 (1 RCT)	⊕⊕⊝⊝ LOW [1,5]	RR 4.43 (0.25 to 79.68)	Low	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 8 more)
HRQoL - not reported	-	-	-		

*__The risk in the intervention group__ (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; **DOAC:** direct oral anticoagulant; **DVT:** deep vein thrombosis; **HRQoL:** health-related quality of life; **PE:** pulmonary embolism; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Concern due to unclear allocation concealment

[2] Downgraded by two levels due to very serious imprecision: 95% CI is consistent with the possibility for important benefit (65 per 1000 absolute reduction) and the possibility of important harm (104 per 1000 absolute increase), including only 3 events among 92 participants.

[3] Downgraded by two levels due to very serious imprecision: 95% CI is consistent with the possibility for important benefit (33 per 1000 absolute reduction) and the possibility of important harm (97 per 1000 absolute increase), including only 1 events among 92 participants.

[4] Downgraded by two levels due to very serious imprecision: Including only 3 events among 92 participants.

[5] Downgraded by two levels due to very serious imprecision: Including only 4 events among 92 participants.

BACKGROUND

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

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 participants with 15 years' follow-up, cancer mortality was three times more common in participants who were hypercoagulable at baseline than in participants 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, scientists 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 people 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 people 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 favourably 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 people with SCLC receiving chemotherapy and radiotherapy (Maurer 1997). The last update of this Cochrane systematic review, published in 2014, identified six trials enrolling 1770 participants (Chahinian 1989; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984), concluded that the existing evidence did not suggest a mortality benefit from oral anticoagulation in people with cancer, while the risk for bleeding was increased (Akl 2014a). There have also been publications on the use of newer oral anticoagulants in people with cancer (Levine 2012). See Table 1 for glossary.

Living review approach: following the publication of this current 2017 update of the review, we will maintain it as a living systematic review: we will be continually running the searches and incorporating newly identified studies (for more information about the living systematic review approach being piloted by Cochrane, see Appendix 1). We consider that a living systematic review approach is appropriate for this review for four reasons. First, the review addresses an important subject for clinical practice; people with cancer have a high rate of VTE, up to 17.7% (Ay 2010). In addition, VTE is associated with a 2.3 times increased risk of death in people with non-small cell lung cancer (NSCLC) and breast cancer, 2.5 times lengthening of hospital stay among people with lung cancer, and 50% increased total costs for people with lung cancer (Chew 2007; Chew 2008; Connolly 2012). Second, there is uncertainty in the existing evidence; the 2014 update of this systematic review did not provide definitive results about suspected subgroup effects on all-cause mortality. Third, there are several ongoing trials in this area that will be important to incorporate in a timely manner. Fourth, we are planning to use this living systematic review as the basis of a living recommendation in a clinical practice guideline with the American Society of Hematology (Akl 2017). For more information about the living systematic review approach being piloted by Cochrane, see Appendix 2.

OBJECTIVES

To evaluate the efficacy and safety of oral anticoagulants in ambulatory people with cancer undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Participants of any age (including children) with cancer with no standard 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 vein thrombosis (DVT) or pulmonary embolism (PE)). Typically, these participants are undergoing chemotherapy, target therapy, immunotherapy or radiotherapy.

Types of interventions

Intervention:

- oral pharmacological thromboprophylaxis with VKA;
- oral pharmacological thromboprophylaxis with DOAC.

Control:

- no pharmacological thromboprophylaxis.

We included any comparison of a combination of the three management options listed above. 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: events had to be suspected clinically, and diagnosed using an objective diagnostic test such as: venography, ^{125}I-fibrinogen-uptake test, impedance plethysmography or compression ultrasound.
- PE: events had to be suspected clinically, and diagnosed using an objective diagnostic test such as: pulmonary perfusion/ventilation scans, computed tomography, pulmonary angiography or autopsy.
- Major bleeding: we accepted the authors' definitions of major bleeding.
- Minor bleeding: we accepted the authors' definitions of minor bleeding.
- Health-related quality of life (HRQoL): had to be measured using a validated tool.

Search methods for identification of studies

Electronic searches

The search was part of a comprehensive search for studies of anticoagulation in people with cancer. We did not use language restrictions. We conducted comprehensive searches on 14 December 2017, following the original electronic searches performed in January 2007, February 2010, February 2013 and February 2016 (last major search). We electronically searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (starting 1946) and Embase (starting 1980; accessed via Ovid). For each database, the search strategies combined terms for anticoagulants, terms for cancer and a search filter for RCTs. We list the full search strategies for each of the electronic databases in Appendix 3, Appendix 4, and Appendix 5.

Living review approach: since the last major search in February 2016, we have been running searches monthly, using auto-alerts to deliver the monthly yield by email. We will incorporate new evidence rapidly after it is identified. This update of the systematic review is based on the findings of a literature search conducted on 14 December 2017. We will review search methods and strategies approximately yearly, to ensure they reflect any terminology changes in the topic area, or in the databases.

Searching other resources

We handsearched the conference proceedings of the American Society of Clinical Oncology (ASCO, starting with its first volume, 1982 up to November 2017) and of the American Society of Hematology (ASH, starting with its 2003 issue up to November 2017). We also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies. We reviewed the reference lists of papers included in this review and of other relevant systematic reviews. We used the 'related citation' feature in PubMed to identify additional articles and 'citation tracking' of included studies in Web of Science Core Collection. In addition, we contacted experts in the field to check for unpublished and ongoing trials.

Living systematic review approach: we will search on a monthly basis the conference proceedings of ASCO and ASH soon after their publications, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform. As an additional step, we will contact corresponding authors of ongoing studies as they are identified and ask them to advise when results are available. We will continue to review the reference lists for any prospectively identified studies, with running the 'related citation' feature for all included studies on a monthly basis. Also, we will contact the corresponding authors of any newly included studies for advice as to other relevant studies. Using citation alerts, we will conduct citation tracking of included studies in Web of Science Core Collection on an ongoing basis.

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.

Living systematic review approach: for the monthly searches, we will immediately screen any new citations retrieved each month. As the first step of monthly screening, we will apply the machine learning classifier (RCT model) available in the Cochrane Register of Studies (CSR-Web; Wallace 2017). The classifier assigns a probability (from 0 to 100) to each citation for being a true RCT. For citations that are assigned a probability score of less than 10, the machine learning classifier currently has a specificity/recall of 99.987% (Wallace 2017). For citations assigned a score from 10 to 100, we will screen them in duplicate and independently. Citations that score nine or less will be screened by Cochrane Crowd (Cochrane Crowd). Any citations that are deemed to be potential RCTs by Cochrane Crowd will be returned to the authors for screening.

Data extraction and management

Two review authors independently extracted data from each included study and resolved any disagreements by discussion. We aimed at collecting data related to the following.

Participants

- Number of participants randomized to each study arm.
- Number of participants followed up in each study arm.
- Number of withdrawals from each study arm.
- Population characteristics (e.g. age, gender, co morbidities, co interventions).
- History of VTE.
- Type of cancer.
- Stage of cancer.
- Time since cancer diagnosis.

Interventions

- Type of anticoagulant: VKA, DOAC, other.
- Intensity of VKA therapy (international normalized ratio (INR) target) or dose.
- Duration of treatment.
- Control: placebo or no intervention.
- Cointerventions including chemotherapy, target therapy, immunotherapy or radiotherapy (type and duration).

Outcomes

For dichotomous variables, we extracted data necessary to conduct complete case analysis as the primary analysis. We collected all-cause mortality at one year (time point defined a priori in the protocol), six months, two years and five years (time point defined post hoc based upon results reported in the individual RCTs). When we could not obtain the number of events at the time points of interest from the paper or from the authors, two review authors calculated these numbers in duplicate and independently from survival curves, if available (Zacharski 1984). We used the mean of the two estimates when they differed. We assessed agreement between the two review authors for each estimated value by calculating the percentage difference, which is the difference between the two estimates divided by the denominator (number of people at risk for the event) and multiplied by 100. For some studies, where VTE was not reported as a separate outcome, we added the number of events of DVT and PE.

We attempted to contact study authors for incompletely reported data. We decided a priori to consider abstracts in the main analysis only if study authors supplied us with full reports of their methods and results; otherwise abstracts were included only in the sensitivity analysis.

Other

- Source of funding.
- Ethical approval.
- Conflict of interest.

Assessment of risk of bias in included studies

We assessed risk of bias at the study level using Cochrane'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;
- blinding of participants and personnel;
- blinding of outcome assessment;
- percentage of follow-up and whether incomplete outcome data were addressed;
- whether the study was free of selective reporting;
- whether the study was stopped early for benefit.

See Dealing with missing data section for information on assessing risk of bias associated with participants with missing data per outcome and across studies.

Measures of treatment effect

We collected and analyzed risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous data. None of the outcomes of interest was meta-analyzed as a continuous variable.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

Determining participants with missing data

It was unclear whether certain participant categories (e.g. those described as 'withdrew consent' or 'experienced adverse events') were followed up by the trial authors (versus had missing participant data) (Akl 2016). 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', 'lost to follow-up' (LTFU) and 'outcome not assessable' participant categories and any other category explicitly reported as not being followed up, which are defined after the initiation of the study intervention, most likely have missing participant data;
- 'dead,' 'experienced adverse events,' 'non-compliant' 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 (Guyatt 2017).

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 follow-up time).

For continuous data, we planned to use for each study arm, the reported mean and standard deviation (SD) for participants followed up by the trial authors.

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 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 participants with missing data (LTFU) compared to participants with available data (followed up, 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, pre intervention 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 planned to use the four strategies suggested by Ebrahim and colleagues (Ebrahim 2013). The strategies imputed the means for participants with missing data based on the means of participants 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). If there was evidence of substantial heterogeneity, we attempted to investigate the possible reasons for this (see Subgroup analysis and investigation of heterogeneity).

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 in the published paper. We planned to create funnel plots for outcomes including 10 or more trials.

Data synthesis

For dichotomous data, we calculated the RR separately for each study (DerSimonian 1986; RevMan 2014). When analyzing data related to participants who were reported as not compliant, we attempted to adhere to the principles of intention-to-treat (ITT) analysis. We approached the issue of non-compliance independently from that of missing data (Alshurafa 2012). We then pooled the results of the different studies using a random-effects model. We assessed the certainty of evidence at the outcome level using the GRADE approach (GRADE handbook).

Living systematic review approach: whenever new evidence (studies, data or information) that meets the review inclusion criteria is identified, we will immediately assess risk of bias and extract the data and incorporate it in the synthesis, as appropriate. We will not adjust the meta-analyses to account for multiple testing given the methods related to frequent updating of meta-analyses are under development (Simmonds 2017).

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 and stage of cancer, and whether participants were on cancer treatment or not). In particular, we conducted subgroup analyses for participants with lung cancer (either SCLC or NSCLC) versus participants with non-lung cancer. We included in the lung versus non-lung subgroup analysis data from:

- studies that recruited only participants with lung cancer (either SCLC or NSCLC) and studies that recruited only participants with non-lung cancer;
- studies that recruited both lung and non-lung cancer if they provided data for subgroups of participants with lung cancer AND data for subgroups of participants with non-lung cancer;
- studies that recruited both participants with lung and non-lung cancer but did not provide subgroup data, if more than 75% of participants had lung cancer or more than 75% of participants had non-lung cancer.

Sensitivity analysis

Unlike the 2014 update of this review, we included in the sensitivity analysis the studies published as abstracts only. As described above, we also planned for sensitivity meta-analyses to assess the risk of bias associated with missing participant data when the primary meta-analysis of a specific outcome found a statistically significant effect.

RESULTS

Description of studies

Results of the search

Figure 1 shows the study flow diagram. As of November 2017, the search strategy identified 7668 unique citations. The title and abstract screening identified 155 potentially eligible citations. The full-text screening of the full texts of these 155 citations identified six eligible RCTs published as full reports (Chahinian 1989; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984). We had also identified one eligible study published as an abstract but for which we were unable to obtain the necessary data from the authors (Ciftci 2012). In addition, we identified three ongoing studies (Bristol-Myers Squibb 2006; Janssen Research & Development, LLC 2015; Rodriguez 2015).

Figure 1. Study flow diagram.

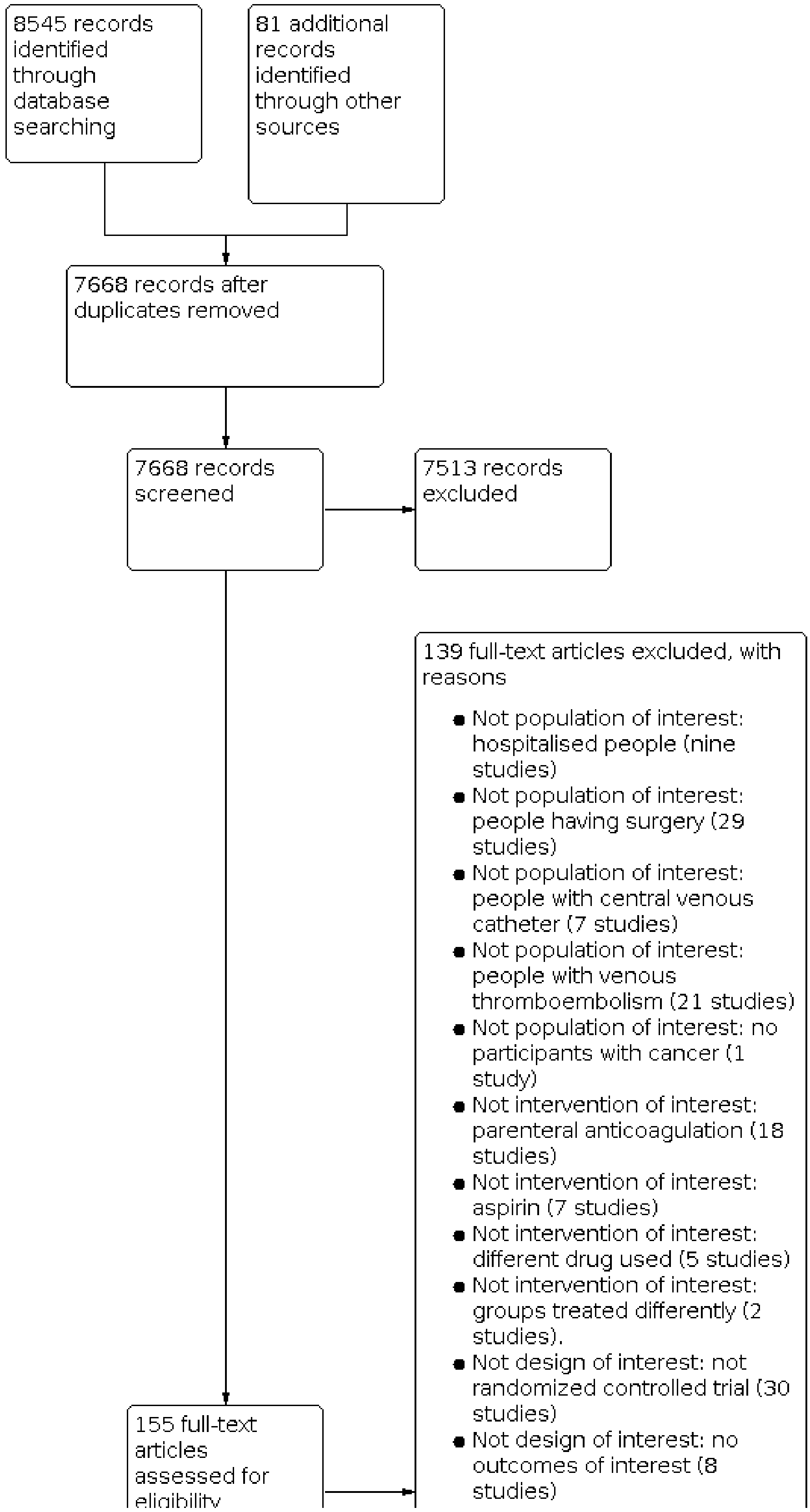
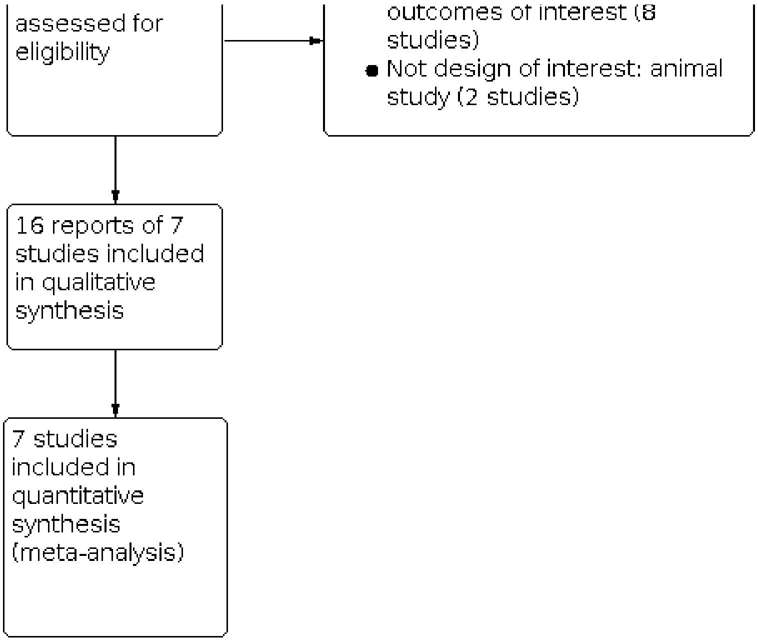


Figure 1. (Continued)



Included studies

Six included RCTs used warfarin as the intervention and one RCT used apixaban as the intervention (Levine 2012). A total of 1486 participants were recruited and follow-up data were available for 1464 participants (Chahinian 1989; Ciftci 2012; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984).

Chahinian and colleagues recruited 189 participants with extensive SCLC undergoing chemotherapy and with a Cancer and Leukemia Group B (CALGB) performance status of 0 to 3 (Chahinian 1989). Participants were randomized to receive either warfarin (to maintain prothrombin time (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. Follow-up rate was 97.3%.

Ciftci and colleagues recruited 91 participants with lung cancer undergoing chemotherapy (Ciftci 2012). Participants were randomized to receive warfarin 5 mg daily or no warfarin starting day one of chemotherapy. Assessed outcomes included mortality and bleeding. Participants were followed up for six months. Information about the follow-up of participants was not reported.

Levine and colleagues recruited 315 participants 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 (Levine 1994). Participants 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. Follow-up rate was 99%.

Levine and colleagues recruited 125 participants 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 (CVC) (VTE risk factor) (Levine 2012). Participants were recruited from six sites in Canada and eight sites in the USA. Participants 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 non-major bleed, VTE, symptomatic DVT and symptomatic PE. For this review, we only included the dosages 5 mg and 10 mg. The study reported complete follow-up.

Maurer and colleagues recruited 369 participants with limited-stage SCLC undergoing chemotherapy and radiotherapy, with a minimum life expectancy of two months and a CALGB performance status less than 3 (Maurer 1997). Participants 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 and minor bleeding. The study reported complete follow-up.

Stanford and colleagues recruited 24 participants 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 (Stanford 1979). 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. The study reported complete follow-up.

Zacharski and colleagues recruited 431 participants with different types of cancer undergoing chemotherapy and with a minimum life expectancy of two months (Zacharski 1984). Participants were randomized to receive either warfarin (to approximately double 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 participants omitting 13 participants 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 participants with SCLC (Zacharski 1981). Study reported 97% follow-up.

Excluded studies

We excluded 139 studies for the following reasons: not population of interest: hospitalized people (nine studies); people having surgery (29 studies); people with CVC (seven studies); people with VTE (21 studies); no participants with cancer (one study); not intervention of interest: parenteral anticoagulation (18 studies); aspirin (seven studies); different drug used (five studies). Groups treated differently (two studies). Not design of interest: not RCT (30 studies); no outcomes of interest (eight studies), animal study (two studies).

Risk of bias in included studies

The judgments for the risk of bias are summarized in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

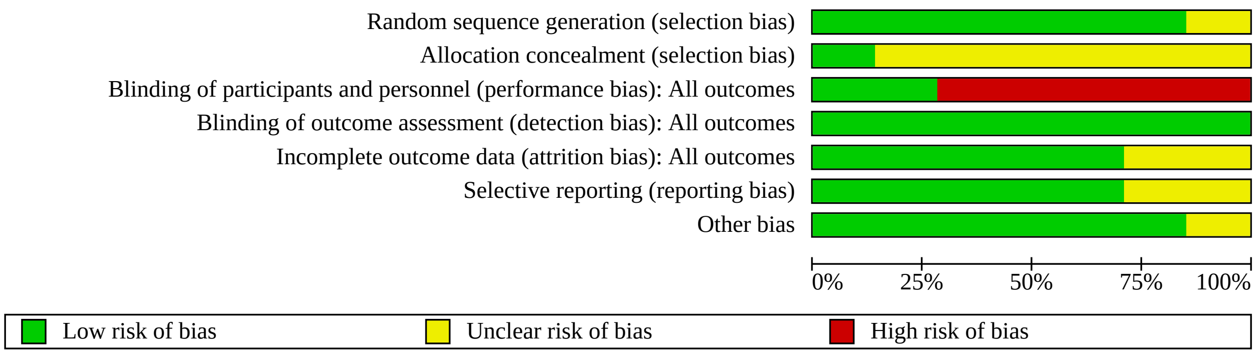


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Chahinian 1989	?	?	-	+	+	+	+
Ciftci 2012	+	?	-	+	?	?	?
Levine 1994	+	?	+	+	+	+	+
Levine 2012	+	?	+	+	+	+	+
Maurer 1997	+	+	-	+	?	+	+
Stanford 1979	+	?	-	+	+	?	+
Zacharski 1984	+	?	-	+	+	+	+

Allocation

The method of sequence generation was unclear for one study (Chahinian 1989), but adequate for the remaining six (Ciftci 2012; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984). Allocation was adequately concealed in one of the seven included studies (Maurer 1997). It was unclear whether it was adequately concealed in six studies (Chahinian 1989; Ciftci 2012; Levine 1994 ; Levine 2012; Stanford 1979; Zacharski 1984).

Blinding

Blinding of participants and personnel (performance bias)

We judged participants and personnel to be blinded in two studies (Levine 1994; Levine 2012), and not blinded in five studies (Chahinian 1989; Ciftci 2012; Maurer 1997; Stanford 1979; Zacharski 1984).

Blinding of outcome assessment (detection bias)

We judged outcome assessors to be blinded in two studies (Levine 1994; Levine 2012), and probably not blinded in five studies (Chahinian 1989; Ciftci 2012; Maurer 1997; Stanford 1979; Zacharski 1984).

Incomplete outcome data

Two studies reported a complete follow-up rate (Levine 2012; Stanford 1979). Only one study reported follow-up data per outcome and not per participant (Chahinian 1989); the follow-up rate for mortality was 97.4% and major bleeding was 97.3%. Levine 1994 reported a follow-up rate of 97% and Zacharski 1984 reported a follow-up rate of 98.7%. Two studies, Maurer 1997 and Ciftci 2012, did not report on follow-up rates.

Selective reporting

None of the seven studies was registered or had a published protocol. Six studies reported the outcomes listed in the methods section in the results section (Chahinian 1989; Levine 1994; Levine 2012; Maurer 1997; Stanford 1979; Zacharski 1984). Reporting bias was unclear in one study (Ciftci 2012).

Other potential sources of bias

None noted.

Effects of interventions

See: **Summary of findings 1** VKA prophylaxis compared to No prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy; **Summary of findings 2** DOAC prophylaxis compared to No prophylaxis in ambulatory patients with cancer without VTE receiving systemic therapy (Q6b- Oral)

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: vitamin K antagonist versus no vitamin K antagonist

All-cause mortality

Mortality at six months: meta-analysis of three RCTs, including 964 participants, and comparing VKA to no VKA, did not rule out a clinically significant increase or decrease in mortality at six months (RR 0.93, 95% CI 0.77 to 1.13) (Analysis 1.1) (Chahinian 1989; Maurer 1997; Zacharski 1984). The I^2 value indicated that the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance) was low ($I^2 = 6\%$).

Mortality at one year: meta-analysis of five RCTs including 1281 participants, and comparing VKA to no VKA, did not rule out a clinically significant increase or decrease in mortality at one year (RR 0.95, 95% CI 0.87 to 1.03; risk difference (RD) 29 fewer per 1000, 95% CI 75 fewer to 17 more; moderate certainty evidence) (Analysis 1.3) (Chahinian 1989; Levine 1994; Maurer 1997; Stanford 1979: Zacharski 1984). The I^2 value indicated that the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance) was absent ($I^2 = 0\%$). The certainty of evidence for mortality at one year was moderate due to imprecision (Summary of findings table 1). Appendix 6 includes the Evidence Profile (a more detailed version of the Summary of findings table 1).

Mortality at two years: meta-analysis of two RCTs including 528 participants, and comparing VKA to no VKA, did not rule out a clinically significant increase or decrease in mortality at two years (RR 0.95, 95% CI 0.70 to 1.30) (Analysis 1.5) (Chahinian 1989; Maurer 1997). The I^2 value indicated that the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance) was high ($I^2 = 93\%$).

Mortality at five years: one RCT including 344 participants, and comparing VKA to no VKA did not rule out a clinically significant increase or decrease in mortality at five years (RR 0.93, 95% CI 0.83 to 1.03) (Analysis 1.6) (Maurer 1997).

Inverted funnel plot was not done due to the relatively few trials to permit an accurate assessment.

In a subgroup analysis of participants with lung cancer (SCLC and NSCLC) versus non-lung cancer, the test for subgroup effect was not statistically significant for mortality at any follow-up time (six months: P = 0.14 (Analysis 1.2); one year: P = 1.00 (see Analysis 1.4)) (Chahinian 1989; Maurer 1997; Zacharski 1984). Of note, Maurer 1997 recruited participants with limited SCLC, while Chahinian 1989 recruited participants with extensive SCLC.

Symptomatic venous thromboembolism

One study reported on the incidence of DVT and PE (Levine 1994). The study found that the use of VKA compared to no VKA likely decreased the incidence of DVT (RR 0.08, 95% CI 0.00 to 1.42; RD 35 fewer per 1000, 95% CI 38 fewer to 16 more; low certainty evidence) and did not rule out a clinically significant increase or decrease in PE (RR 1.05, 95% CI 0.07 to 16.58; RD 0 fewer per 1000, 95% CI 6 fewer to 98 more; low certainty evidence). The certainty of evidence for symptomatic DVT due to imprecision and very low for PE due to indirectness and imprecision (see Summary of findings table 1). Appendix 6 includes the Evidence Profile (a more detailed version of the Summary of findings table 1).

Major bleeding

Meta-analysis of five RCTs including 1281 participants showed that VKA increased the risk of major bleeding compared to no VKA (RR 2.93, 95% CI 1.86 to 4.62; RD 107 more per 1000, 95% CI 48 more to 201 more; moderate certainty evidence) (Analysis 1.9) (Chahinian 1989; Levine 1994; Maurer 1997; Stanford 1979; Zacharsky 1985). The I^2 value indicated that the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance) was low (I^2 = 6%). 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 using the a priori plausible assumptions detailed in the Methods section. The effect estimate remained statistically significant even when using the most stringent plausible assumption (RR 2.70. 95% CI 1.92 to 3.79). We judged the quality of evidence as moderate (Summary of findings table 1). These results did not change in a meta-analysis including the study published as an abstract (RR 2.89, CI 2.07 to 4.04; RD 1.06 more per 1000, 95% CI 60 more to 170 more) (Ciftci 2012).

In subgroup analyses of participants with lung cancer (SCLC and NSCLC) versus non-lung cancer, the test for subgroup effect was not statistically significant (P = 0.16) (Analysis 1.10) (Chahinian 1989; Maurer 1997; Stanford 1979; Zacharski 1984). Of note, Maurer 1997 recruited participants with limited SCLC while Chahinian 1989 recruited participants with extensive SCLC.

Minor bleeding

Meta-analysis of four RCTs including 863 participants showed that VKA increased the risk of minor bleeding compared to no VKA (RR 3.14, 95% CI 1.85 to 5.32; RD 167 more per 1000, 95% CI 66 more to 337 more; moderate certainty evidence) (Analysis 1.11) (Chahinian 1989; Levine 1994; Maurer 1997; Stanford 1979). The I^2 value indicated that the percentage of the variability in effect estimates that was due to heterogeneity rather than sampling error (chance) may represent low heterogeneity (I^2 = 21%). 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 using the a priori plausible assumptions detailed in the Methods section. The effect estimate remained statistically significant even when using the most stringent plausible assumption (RR 2.89, 95% CI 1.96 to 4.27). We judged the quality of evidence as moderate (see Summary of findings table 1).

In subgroup analyses of participants with lung cancer (SCLC and NSCLC) versus non-lung cancer the test for subgroup effect was not statistically significant (P = 0.59) (Analysis 1.12) (Chahinian 1989; Maurer 1997; Stanford 1979; Zacharski 1984). Of note, Maurer 1997 recruited participants with limited SCLC, while Chahinian 1989 recruited participants with extensive SCLC.

Health-related quality of life

We found no data for health-related QoL.

Comparison 2: direct oral anticoagulant versus no direct oral anticoagulant

Mortality

One study with 92 participants comparing apixaban with placebo did not rule out a clinically significant decrease or increase in mortality at three months (RR 0.24, 95% CI 0.02 to 2.56; RD 51 fewer per 1000, 95% CI 65 fewer to 104 more; low certainty evidence) (Levine 2012). The certainty of evidence was low due to imprecision.

Symptomatic venous thromboembolism

One study with 92 participants comparing apixaban with placebo did not rule out a clinically significant decrease or increase in rate of symptomatic DVT (RR 0.07, 95% CI 0.00 to 1.32; RD 93 fewer per 1000, 95% CI 100 fewer to 32 more; low certainty evidence) or rate of PE (RR 0.16, 95% CI 0.01 to 3.91; RD 28 fewer per 1000, 95% CI 33 fewer to 97 more; low certainty evidence) (Levine 2012). There were no missing participant data for this outcome. The certainty of evidence was low due to imprecision (see Summary of findings table 2).

Major bleeding

One study with 92 participants comparing apixaban with placebo did not rule out a clinically significant decrease or increase in major bleeding (RR 0.16, 95% CI 0.01 to 3.91; RD 28 fewer per 1000, 95% CI 33 fewer to 97 more; low certainty evidence) (Levine 2012). The certainty of evidence was low due to imprecision (see Summary of findings table 2).

Minor bleeding

One study with 92 participants comparing apixaban with placebo did not rule out a clinically significant decrease or increase in minor bleeding (RR 4.43, 95% CI 0.25 to 79.68; RD 0 fewer per 1000, 95% CI 0 fewer to 8 more; low certainty evidence) (Levine 2012). The certainty of evidence was low due to imprecision (see Summary of findings table 2).

Health-related quality of life

We found no data for health-related QoL.

DISCUSSION

Summary of main results

VKA appear to have no effect on mortality and VTE in people with cancer who have no therapeutic or prophylactic indication for anticoagulation; however, VKA increase major bleeding and minor bleeding. A subgroup analysis suggested no difference in mortality or risk of bleeding in people with lung cancer compared to people with non-lung cancer.

The systematic review identified only one trial comparing apixaban with placebo. The study did not confirm or exclude a clinically important effect of apixaban on mortality, symptomatic DVT and PE, major bleeding and minor bleeding.

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 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 people with a requirement for long-term oral anticoagulation without indicating how many such participants were excluded (Levine 1994); this could potentially limit the generalizability of the findings to similar populations. In fact, people 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 VKA versus no VKA, we judged the quality of the evidence as moderate for mortality at one year, and for major and minor bleeding, very low for PE and low for symptomatic DVT. We downgraded the quality of evidence for mortality due to imprecision, and for bleeding outcomes due to risk of bias (study limitations). We downgraded the quality of evidence for PE due to indirectness (the study used fixed-dose VKA which is not representative of current practice) and for imprecision (low number of events) and DVT due to imprecision.

For the comparison of DOAC versus no DOAC, 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. The inclusion of different types of cancer in the same study precluded us from conducting the subgroup analyses to explore effect modifiers such as stage of cancer. The interpretation of findings was also limited by not including data from the trials published as abstracts. We had to calculate the number of mortality events at six, 12 and 24 months from the survival curves for only one study (Zacharski 1984). Also, there might be potential bias associated with multiple testing in the planned meta-analyses and currently there are no plans to adjust meta-analyses for multiple testing.

Agreements and disagreements with other studies or reviews

One systematic review by Zhang and colleagues assessed the effects of anticoagulants on the health outcomes of people 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 as the intervention. The meta-analysis found a long-term survival benefit and a reduction in the incidence of VTE, in addition to a significant increase in risk of bleeding. This analysis had the problem of clinical heterogeneity, something we tried to avoid by separating the analysis of oral and parenteral anticoagulation (Akl 2011a).

The systematic review performed by Di Nisio and colleagues assessed the efficacy of primary VTE thromboprophylaxis in ambulatory people with cancer receiving chemotherapy (Di Nisio 2016). Consistent with our findings, their study found no effect on mortality, or incidence of DVT and PE when comparing VKA to no VKA. They found a four-fold increase in major bleeding episodes in participants given VKA versus no VKA (RR 3.82, 95% CI 0.97 to 15.04) compared to a three-fold increase in our study (RR 2.93, 95% CI 1.86 to 4.62). This might be due to the different reports from which the data were abstracted. Di Nisio and colleagues abstracted data from an older version of Zacharsky's study that included 50 participants (Zacharski 1981), while in our study, we used data from a newer report that included 418 participants (Zacharsky 1985).

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review does not provide evidence for a mortality benefit from oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation. 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 vitamin K antagonist treatment (e.g. periodically checking international normalized ratio levels).

Implications for research

Future research should investigate the effects of oral anticoagulation in people with different cancer subtypes (e.g. small cell lung cancer, non-small cell lung cancer) and different cancer stages. While the last clinical trial on this topic was published in 2014, there are still ongoing studies discussing oral anticoagulation in people with cancer. There is also a need to investigate the effects of other anticoagulants (e.g. low-molecular-weight heparins, fondaparinux) in people with different types and stages of cancer (Akl 2014a).

ACKNOWLEDGEMENTS

We thank Dr Daly, Dr Levine, Dr Maurer and Dr Zacharski for providing us with available data. We thank Ms Ann Grifasi for her administrative support. We also thank Dr Assem Khamis for his help with conducting the sensitivity analysis. We thank Dr Paola Muti, Dr Rami A Ballout and Dr Ignacio Neumann for their contributions to previous versions of this systematic review. We thank Ms Anneliese Synnot for the methodological expertise related to the living systematic review approach.

We thank Jo Morrison, Co-ordinating Editor for the Cochrane Gynaecological Neuro-oncology and Orphan Cancers Group. We also thank Gail Quinn, Managing Editor of the Cochrane Gynaecological Neuro-oncology and Orphan Cancers Group for her exceptional support. We thank Joanne Platt, the information specialist of the Cochrane Gynaecological Neuro-oncology and Orphan Cancers Group, for setting up and managing the monthly alerts.

As described under “Sources of Support” this update was supported in part by the American Society of Hematology to inform ASH guidelines on the topic. We thank the ASH guideline panel for prioritizing questions previously addressed by our review and for critically reviewing our work, including Drs. Pablo Alonso, Waleed Alhazanni, Marc Carrier, Cihan Ay, Marcello DiNisio, Lisa Hicks, Alok Khorana, Andrew Leavitt, Agnes Lee, Gary Lyman, Fergus Macbeth, Rebecca Morgan, Simon Noble, and David Stenehjem and patient representatives Jackie Cook and Elizabeth Sexton. Their input was

valuable in validating some of the review related decisions such as eligibility of included studies and the analytical approach.

For our update of these reviews, we followed Cochrane methods using the same eligibility criteria and outcomes used previously. The ASH guidelines group used slightly different methods that generated slightly different results. For example, the ASH guideline panel agreed to prioritize different outcomes; include unpublished data; include abstracts; use different definitions for duration of treatment; and rate certainty of evidence slightly differently for some outcomes, for instance because of imprecision or indirectness. These differences are not described in this publication. Instead, they will be described in the ASH guideline publication.

This project was supported by the National Institute for Health Research(NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.

REFERENCES

References to studies included in this review

Chahinian 1989 *{published data only}*

* Chahinian AP, Propert KJ, Ware JH, Zimmer B, Perry MC, Hirsh V, et al. A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the Cancer and Leukemia Group B. *Journal of Clinical Oncology* 1989;**7**(8):993-1002.

Chahinian AP, Ware JH, Zimmer B, Comis R, Perry MC, Hirsch V, et al. Evaluation of anticoagulation with warfarin and of alternating chemotherapy in extensive small cell cancer of the lung. In: Proceedings of the American Society of Clinical Oncology. Vol. 3. 1984:225.

Chahinian AP, Ware JH, Zimmer B, Comis RI, Perry MC, Hirsh V, et al. Update on anticoagulation with warfarin and alternating chemotherapy in extensive small cell carcinoma of the lung (SCCL). American Society of Clinical Oncology 1985;**4**:191.

Ciftci 2012 *{published data only}*

Ciftci A, Altiay G. The effect of warfarin on survival in patients with lung cancer. *Journal of Thoracic Oncology* 2012;**7**(7):S122.

Levine 1994 *{published data only}*

Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al. A double-blind randomized trial of low-dose warfarin for the prevention of thromboembolism (TE) in patients with stage IV breast cancer. *Proceedings of the American Society of Clinical Oncology* 1993;**15**:59.

Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al. A double-blind randomized trial of mini-dose warfarin for the prevention of thromboembolism (TE) in patients with stage-IV breast-cancer. *Thrombosis and Haemostasis* 1993;**343**(6):981.

* Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet* 1994;**343**(8902):886-9.

Levine 2012 *{published data only}*

Levine MN, Deitchman D, Julian J, Liebman H, Escalante C, O'Brien MC, et al. A randomized phase II trial of a new anticoagulant, apixaban, in metastatic cancer. *Journal of Clinical Oncology* 2009;**27**(15S):e20514.

* Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D, et al. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *Journal of Thrombosis and Haemostasis* 2012;**10**:807-14.

Levine MN, Liebman HA, Esclanate CP, Julian JA, Deitchman D, O'Brien MC, et al. Randomized phase II trial of an oral factor Xa inhibitor in patients with metastatic cancer on chemotherapy. *5th ICTHIC Abstracts: Oral Communications / Thrombosis Research* 2010;**125**:S161-5.

Liebman H, Levine MN, Deitchman D, Julian J, Escalante CP, O'Brien MC, et al. Apixaban in patients with metastatic cancer: a randomized phase II feasibility study. XXII Congress of the International Society on Thrombosis and Haemostasis; 2009 Jul 11-16; Boston (MA) 2009:PP-WE-489.

Maurer 1997 *{published data only}*

Maurer LH, Herndon IJ, Hollis DR, Aisner J, Carey RW, Skarin AT, et al. Randomized trial of chemotherapy and radiation therapy with or without warfarin for limited-stage small-cell lung cancer: a Cancer and Leukemia Group B study. *Journal of Clinical Oncology* 1997;**15**(11):3378-87.

Stanford 1979 *{published data only}*

* Stanford CF. Anticoagulants in the treatment of small cell carcinoma of the bronchus. *Thorax* 1979;**34**:113-6.

Zacharski 1984 *{published data only}*

Zacharski LR, Henderson WG, Forman WB, Edwards RL, Cornell CJ, Forcier RJ, et al. Bleeding complications from warfarin anticoagulation in patients with malignancy. *Journal of Medicine* 1985;**16**:535-61.

* Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ Jr, Forcier RJ, et al. Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. Final report of VA Cooperative Study #75. *Cancer* 1984;**53**(10):2046-52.

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.

Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ, Forcier RJ, et al. Effect of warfarin therapy on survival in cancer - final report of VA Cooperative Study #75. *Circulation* 1982;**66**(4):302.

References to studies excluded from this review

Agnelli 1998 *{published data only}*

Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *New England Journal of Medicine* 1998;**339**:80-5.

Agnelli 2005 *{published data only}*

Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *British Journal of Surgery* 2005;**92**(10):1212-20.

Agnelli 2015 (AMPLIFY) *{published data only}*

Agnelli G, Buller HR, Cohen A, Gallus AS, Lee TC, Pak R, et al. Apixaban for the treatment of venous thromboembolism in cancer patients: data from the amplify trial. *Canadian Journal of Cardiology* 2014;**30**:S278.

* Agnelli G, Buller HR, Cohen A, Gallus AS, Lee TC, Pak R, et al. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *Journal of Thrombosis and Haemostasis* 2015;**13**(12):2187-91.

Aisner 1987 *{published data only}*

Aisner J, Propert K. Aggressive combination chemotherapy, chest and brain irradiation and warfarin for the treatment of limited disease of small cell lung cancer (SCLC). *Proceedings of the American Society of Clinical Oncology* 1987;**6**:179.

Aisner 1992 *{published data only}*

Aisner J, Goutsou M, Maurer LH, Cooper R, Chahinian P, Carey R, et al. Intensive combination chemotherapy, concurrent chest irradiation, and warfarin for the treatment of limited-disease small-cell lung cancer: a Cancer and Leukemia Group B pilot study. *Journal of Clinical Oncology* 1992;**10**(8):1230-6.

Alikhan 2003 (MEDENOX) *{published data only}*

* Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. *Blood Coagulation & Fibrinolysis* 2003;**14**(4):341-6.

Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *New England Journal of Medicine* 1999;**341**(11):793-800.

Anonymous 1994 *{published data only}*

Anonymous. Coumarin (1,2-benzopyrone) - new findings for tumor therapy. *Medizinische Welt* 1994;**45**(5):62-3.

Auer 2011 *{published data only}*

Auer R, Scheer A, Wells PS, Boushey R, Asmis T, Jonker D, et al. The use of extended perioperative low molecular weight heparin (tinzaparin) to improve disease-free survival following surgical resection of colon cancer: a pilot randomized controlled trial. *Blood Coagulation & Fibrinolysis* 2011;**22**(8):760-2.

Bigg 1992 *{published data only}*

Bigg SW, Catalona WJ. Prophylactic mini-dose heparin in patients undergoing radical retropubic prostatectomy: a prospective trial. *Urology* 1992;**39**(4):309-13.

Cahan 2000 *{published data only}*

Cahan MA, Hanna DJ, Wiley LA, Cox DK, Killewich LA. External pneumatic compression and fibrinolysis in abdominal surgery. *Journal of Vascular Surgery* 2000;**32**(3):537-43.

Carpi 1995 *{published data only}*

Carpi A, Sagripanti A, Poddighe R, Gherarducci G, Nicolini A. Cancer incidence and mortality in patients with heart disease. Effect of oral anticoagulant therapy. *American Journal of Clinical Oncology* 1995;**18**(1):15-8.

Chlebowski 1982 *{published data only}*

Chlebowski RT, Gota CH, Chan KK, Weiner JM, Block JB, Bateman JR. Clinical and pharmacokinetic effects of combined warfarin and 5-fluorouracil in advanced colon cancer. *Cancer Research* 1982;**42**(11):4827-30.

Clarke-Pearson 1993 *{published data only}*

Clarke-Pearson DL, Synan IS, Dodge R, Soper JT, Berchuck A, Coleman E. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. *American Journal of Obstetrics and Gynecology* 1993;**168**(4):1146-54.

Cohen 1997 *{published data only}*

Cohen AT, Wagner MB, Mohamed MS. Risk factors for bleeding in major abdominal surgery using heparin thromboprophylaxis. *American Journal of Surgery* 1997;**174**(1):1-5.

Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Das SK, Maher KT, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. *Lancet* 1993;**341**(8840):259-65.

Cohen 2006 *{published data only}*

Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006;**332**(7537):325-9.

Cohen 2007 (PREVENT) *{published data only}*

Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006;**332**(7537):325-9.

* Cohen AT, Turpie AG, Leizorovicz A, Olsson CG, Vaitkus PT, Goldhaber SZ. Thromboprophylaxis with dalteparin in medical patients: which patients benefit? *Vascular Medicine* 2007;**12**(2):123-7.

Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ, PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004;**110**(7):874-9.

Couban 2005 *{published data only}*

Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. A randomized double-blind placebo controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer. *Journal of Thrombosis and Haemostasis : JTH* 2005;**18**:4063-9.

Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. A randomized double-blind placebo-controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer. 44th Annual Meeting of the American Society of Hematology; 2002 Dec 6-10; Philadelphia (PA); abstract No. 2769 2002.

* Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. *Journal of Clinical Oncology* 2005;**23**(18):4063-9.

D'Souza 1980a *{published data only}*

D'Souza DP, Daly L, Thornes RD. Low dosage chemo immunotherapy plus warfarin in metastatic breast cancer. *Irish Journal of Medical Science* 1980;**149**(4):172-3.

D'Souza 1980b *{published data only}*

D'Souza DP, Daly L, Thornes RD. Cyclophosphamide, prednisone, staphage lysate and warfarin in disseminated breast cancer. *Irish Medical Journal* 1980;**73**(10):385-7.

Daly 1991 *{published data only}*

Daly L. The first international urokinase/warfarin trial in colorectal cancer. *Clinical & Experimental Metastasis* 1991;**9**(1):3-11.

Demir 2006 *{published data only}*

Demir M, Hoppensteadt DA, Cunanan J, Iqbal O, Fareed J. Increased levels of inflammatory mediators in lung cancer and their modulation by oral anticoagulant treatment. *Journal of Clinical Oncology* 2006;**24**(18):17050.

Demir 2007 *{published data only}*

Demir M, Ciftci A, Hoppensteadt D, Altiay G, Tobu M, Iqbal O, et al. Protein chip array profiling and markers of inflammation and thrombin generation in plasma samples from lung cancer patients and their modulation by chemotherapy with or without warfarin anticoagulation. American Society of Clinical Oncology (ASCO) 43rd Annual Meeting; 2007 Jun 1-5; Chicago (IL) 2007.

Dickinson 1998 *{published data only}*

Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* 1998;**43**(5):1074-81.

Goldhaber 2002 *{published data only}*

Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *CHEST Journal* 2002;**122**(6):1933-7.

Haas 2011 *{published data only}*

Bauersachs R, Schellong SM, Haas S, Tebbe U, Gerlach HE, Abletshauser C, et al. CERTIFY: prophylaxis of venous thromboembolism in patients with severe renal insufficiency. *Thrombosis and Haemostasis* 2011;**105**(6):981-8.

Haas S, Schellong SM, Tebbe U, Gerlach HE, Bauersachs R, Abletshauser C, et al. CERTIFY: Certoparin versus UFH to prevent venous thromboembolic events in the patients with cancer. *Hämostaseologie* 2011;**31**(1):A10.

* Haas S, Schellong SM, Tebbe U, Gerlach HE, Bauersachs R, Melzer N, et al. Heparin based prophylaxis to prevent venous thromboembolic events and death in patients with cancer - a subgroup analysis of CERTIFY. *BMC Cancer* 2011;**11**:1.

Harenberg 1996 *{published data only}*

* Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. *Pathophysiology of Haemostasis and Thrombosis* 1996;**26**(3):127-39.

Harenberg J, Roebruck P, Stehle G, Habscheid W, Biegholdt M, Heene DL. Heparin Study in Internal Medicine (HESIM): design and preliminary results. *Thrombosis Research* 1992;**68**(1):33-43.

Hata 2016 *{published data only}*

Hata K, Kimura T, Tsuzuki S, Ishii G, Kido M, Yamamoto T, et al. Safety of fondaparinux for prevention of postoperative venous thromboembolism in urological malignancy: a prospective randomized clinical trial. *International Journal of Urology* 2016;**23**(11):923-8.

Herrmann 1988 *{published data only}*

Herrmann R. Coumarin and cimetidine in the treatment of metastatic renal cell carcinoma. *Proceedings of the American Society of Clinical Oncology* 1988;**7**:131.

Herrmann 1990 *{published data only}*

Herrmann R, Manegold C, Maurer B, Hennig FW, Matthiessen W. Phase II trial of coumarin and cimetidine in advanced renal cell carcinoma. *Annals of Oncology* 1990;**1**(6):445-6.

Higashi 1971 *{published data only}*

Higashi H, Heidelberger C. Lack of effect of warfarin (NSC-59813) alone or in combination with 5-fluorouracil (NSC-19893) on primary and metastatic L1210 leukemia and adenocarcinoma 755. *Cancer Chemotherapy Reports - Part 1* 1971;**55**(1):29-33.

Hoppensteadt 2011 *{published data only}*

Hoppensteadt D, Khan H, Thethi I, Demir M, Adiguzel C, Rahman S, et al. Inflammatory and thrombotic mediators in small cell lung carcinoma: potential role in thromboembolic complications. American Society of Hematology (ASH), Annual Meetings and Exposition. 53rd Annual Meeting; 2011 Dec 10-13; San Diego (CA). 2011.

Huber 1993 *{published data only}*

Huber MH, Hong WK. Warfarin and small-cell lung cancer. *Journal of Clinical Oncology* 1993;**11**(2):383.

Hutchins 1984 *{published data only}*

Hutchins LF, Cash DK, Lang NP, Neilan BA. Coumarin and cimetidine as active agents in melanoma and renal-cell carcinoma. *Clinical Research* 1984;**32**(5):A873.

Kakkar 2010 (CANBESURE) *{published data only}*

* Kakkar VV, Balibrea JL, Martinez-Gonzalez J, Prandoni P. Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study. *Journal of Thrombosis and Haemostasis* 2010;**8**:6.

Kakkar VV, Balibrea JL, Martinez-Gonzalez J, Prandoni P. Late breaking clinical trial: a randomised double blind trial to evaluate the efficacy and safety of prolonging the thromboprophylaxis with bemiparin in patients undergoing cancer abdominal or pelvic surgery (the CANBESURE study). *International Society on Thrombosis and Haemostasis* 2009;**7**(Suppl 2):1202, LB-MO-002.

Kakkar 2014 (SAVE-ABDO) *{published data only}*

* Kakkar AK, Agnelli G, Fisher WD, George D, Mouret P, Lassen MR, et al and SAVE-ABDO Investigators. Preoperative enoxaparin versus postoperative semuloparin thromboprophylaxis in major abdominal surgery: a randomized controlled trial. *Annals of Surgery* 2014;**259**(6):1073-9.

Kakkar AK, Agnelli G, Fisher WD, George D, Mouret P, Lassen MR, et al. The ultra-low-molecular-weight heparin semuloparin for prevention of venous thromboembolism in patients undergoing major abdominal surgery. *Blood* 2010;**116**(21):188.

Khan 2012 *{published data only}*

Khan H, Thethi I, Hoppensteadt D, Demir M, Adiguzel C, Rahman S, et al. Inflammatory and thrombotic mediators in small cell lung carcinoma: potential role in thromboembolic complications. Hamostaseologie 2012:P10-2.

Khorana 2017 (PHACS) *{published data only}*

Khorana AA, Francis CW, Kuderer NM, Carrier M, Ortel TL, Wun T, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. *Blood* 2015;**126**(23):427.

* Khorana AA, Francis CW, Kuderer NM, Carrier M, Ortel TL, Wun T, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. *Thrombosis Research* 2017;**151**:89-95. [DOI: http://dx.doi.org/10.1016/j.thromres.2017.01.009]

Kokron 1990 *{published data only}*

Kokron O, Baumgartner G, Theyer G, Maca S, Gasser G, Schmidt PR, et al. Cimetidine and coumarin treatment of metastatic renal cell carcinoma. *Journal of Cancer Research & Clinical Oncology* 1990;**116**(Suppl):971.

Kokron 1993 *{published data only}*

Kokron O, Baumgartner G, Theyer G, Maca S, Gasser G, Schmidt PR, et al. Randomised study in metastatic renal cell cancer: coumarin versus coumarin and cimetidine. *Journal of the Irish Colleges of Physicians & Surgeons* 1993;**22 Suppl 1**:10-1.

Koppenhagen 1992 *{published data only}*

Koppenhagen K, Adolf J, Matthes M, Tröster E, Roder JD, Hass S, et al. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. *Thrombosis and Haemostasis* 1992;**67**(6):627-30.

Larocca 2012 *{published data only}*

Larocca A, Cavallo F, Bringhen S, Raimondo FD, Falanga A, Evangelista A, et al. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. *Blood* 2012;**119**:933-9.

Lebeau 1993 *{published data only}*

Lebeau B, Chastang C, Muir JF, Vincent J, Massin F, Fabre C. No effect of an antiaggregant treatment with aspirin in small-cell lung-cancer treated with Ccavp16 chemotherapy - results from a randomized clinical-trial of 303 patients. *Cancer* 1993;**71**(5):1741-5.

Lecumberri 2005 *{published data only}*

Lecumberri R, Paramo JA, Rocha E. Anticoagulant treatment and survival in cancer patients. The evidence from clinical studies. *Haematologica* 2005;**90**(9):1258-66.

Lee 2015 (CATCH) *{published data only}*

Bauersachs R, Lee AYY, Kamphuisen PW, Meyer G, Janas MS, Jarner MF, et al. Long-term tinzaparin versus warfarin for treatment of venous thromboembolism (VTE) in cancer patients-analysis of renal impairment (RI) in the CATCH study. *Journal of Thrombosis and Haemostasis* 2015;**13**:76.

Bauersachs R. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. In: Hematology Reports. Vol. 3. 2011:13.

Kamphuisen PW, Lee AYY, Meyer G, Bauersachs R, Janas MS, Jarner MF, et al. Characteristics and risk factors of major and clinically relevant non-major bleeding in cancer patients receiving anticoagulant treatment for acute venous thromboembolism-the CATCH study. *Journal of Thrombosis and Haemostasis : JTH* 2015;**13**:182-3.

Khorana AA, Bauersachs R, Kamphuisen PW, Meyer G, Janas MS, Jarner MF, et al. Clinical predictors of recurrent venous thromboembolism (VTE) in cancer patients from a randomized trial of long-term tinzaparin versus warfarin for treatment: the CATCH study. *Journal of Clinical Oncology* 2015;**33**(15):9621.

Lee AY, Bauersachs R, Janas MS, Jarner MF, Kamphuisen PW, Meyer G et al. CATCH: a randomized trial comparing tinzaparin versus warfarin for treatment of acute venous thromboembolism (VTE) in cancer patients. ASCO Annual Meeting. *Journal of Clinical Oncology* 2012;**30**(15S):TPS9149.

Lee AY, Bauersachs R, Janas MS, Jarner MF, Kamphuisen PW, Meyer G, Khorana AA. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. *BMC cancer* 2013;**13**:284.

Lee AY, Bauersachs R, Janas MS, Jarner MF, Kamphuisen PW, Meyer G, et al. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. *BMC Cancer* 2013;**13**(1):284. [NCT01130025]

Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, et al. A randomized trial of long-term tinzaparin, a low molecular weight Heparin (LMWH), versus warfarin for treatment of acute venous thromboembolism (VTE) in cancer patients - the CATCH study. *Blood Conference: 56th Annual Meeting of the American Society of Hematology* 2014;**124**:21.

* Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015;**314**:677.

Loprinzi 1999 *{published data only}*

Loprinzi C, Kugler J, Sloan J, Rooke T, Quella S, Novotny P, et al. Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *New England Journal of Medicine* 1999;**340**:346-50.

Macareo 2001 *{published data only}*

Macareo LR, Ford SM, Crocker JD, Coleman TA. Low dose warfarin decreases central line thrombosis and tissue plasminogen activator (TPA) utilization in cancer patients but does not improve overall survival. *Blood* 2001;**98**(11):94B-5B.

Macbeth 2016 (FRAGMATIC) *{published data only}*

Griffiths GO, Burns S, Noble SI, Macbeth FR, Cohen D, Maughan TS. FRAGMATIC: a randomised phase III clinical trial investigating the effect of Fragmin® added to standard therapy in patients with lung cancer. *BMC Cancer* 2009;**9**:1.

* Macbeth F, Noble S, Evans J, Ahmed S, Cohen D, Hood K, et al. Randomized phase III trial of standard therapy plus low molecular weight heparin in patients with lung cancer: FRAGMATIC trial. *Journal of Clinical Oncology* 2016;**34**(5):488-94.

Macbeth F, Noble S, Griffiths G, Chowdhury R, Rolfe C, Hood K, et al. Preliminary results from the fragmatic trial: a randomised phase III clinical trial investigating the effect of Fragmin (R) added to standard therapy in patients with lung cancer. *Journal of Thoracic Oncology* 2013;**8**:S243.

Noble S, Robbins A, Alikhan R, Hood K, Macbeth F. Prediction of venous thromboembolism in lung cancer patients receiving chemotherapy. *Journal of Thrombosis and Haemostasis* 2015;**13**:143.

Marshall 1987 *{published data only}*

Marshall ME, Mendelsohn L, Butler K, Cantrell J, Harvey J, Macdonald J. Treatment of non-small cell lung cancer with coumarin and cimetidine. *Cancer Treatment Reports* 1987;**71**(1):91-2.

Marshall 1989 *{published data only}*

Marshall ME, Butler K, Cantrell J, Wiseman C, Mendelsohn L. Treatment of advanced malignant melanoma with coumarin and cimetidine: a pilot study. *Cancer Chemotherapy & Pharmacology* 1989;**24**(1):65-6.

Marshall 1990 *{published data only}*

Marshall FF. Phase II study of coumarin and cimetidine in patients with metastatic renal cell carcinoma: editorial comment. *Journal of Urology* 1990;**144**(5):1317.

Maxwell 2001 *{published data only}*

Maxwell GL, Synan I, Dodge R, Carroll B, Clarke-Pearson DL. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *American College of Obstetricians and Gynecologists* 2001;**98**(6):989-95.

McCulloch 1987 *{published data only}*

McCulloch P, George WD. Warfarin inhibition of metastasis: the role of anticoagulation. *British Journal of Surgery* 1987;**74**(10):879-83.

Moazzam 2003 *{published data only}*

Moazzam N, Potti A. Survival and outcome data in patients with adenocarcinoma of the prostate receiving warfarin therapy. *Blood* 2003;**102**(11):325A.

Mohler 1993 *{published data only}*

Mohler JL, Williams B, Thompson I, Marshall ME. Coumarin (1,2-benzopyrone) for the treatment of prostatic carcinoma. *Journal of the Irish Colleges of Physicians & Surgeons* 1993;**22 Suppl 1**:12-6.

Mohler 1994 *{published data only}*

Mohler JL, Williams BT, Thompson IM, Marshall ME. Coumarin (1,2-benzopyrone) for the treatment of prostatic carcinoma. *Journal of Cancer Research & Clinical Oncology* 1994;**120 Suppl**:S35-8.

Murakami 2002 *{published data only}*

Murakami M, Wiley LA, Cindrick-Pounds L, Hunter GC, Uchida T, Killewich LA. External pneumatic compression does not increase urokinase plasminogen activator after abdominal surgery. *Journal of Vascular Surgery* 2002;**36**(5):917-21.

Nagata 2015 *{published data only}*

Nagata C, Tanabe H, Takakura S, Narui C, Saito M, Yanaihara N, et al. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. *Journal of Obstetrics and Gynaecology Research* 2015;**41**(9):1440-8.

Nurmohamed 1996 *{published data only}*

Nurmohamed MT, van Riel AM, Henkens CM, Koopman MM, Que GT, d'Azemar P, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thrombosis Haemostasis* 1996;**75**:233-8.

Palumbo 2011 *{published data only}*

Cavo M, Palumbo A, Bringhen S, Di Raimondo F, Patriarca F, Rossi D, et al. Phase III study of enoxaparin versus aspirin versus low-dose warfarin as thromboprophylaxis for patients with newly diagnosed multiple myeloma treated upfront with thalidomide-containing regimens. *Haematologica* 2010;**95**:391.

Cavo M, Palumbo A, Bringhen S, Falcone A, Musto P, Ciceri F, et al. A phase III study of enoxaparin versus low-dose warfarin versus aspirin as thromboprophylaxis for patients with newly diagnosed multiple myeloma treated up-front with thalidomide-containing regimens. *Blood* 2008;**112**(11):3017.

Cavo M, Palumbo A, Bringhen S, Falcone A, Musto P, Ciceri F, et al. A phase III study of enoxaparin versus low-dose warfarin versus aspirin as thromboprophylaxis for patients with newly diagnosed multiple myeloma treated up-front with thalidomide-containing regimens. *Haematologica* 2009;**94**:s4.

Magarotto V, Brioli A, Patriarca F, Rossi D, Petrucci MT, Nozzoli C, et al. Enoxaparin, aspirin, or warfarin for the thromboprophylaxis in newly diagnosed myeloma patients receiving thalidomide: a randomized controlled trial. *Haematologica* 2010;**95**:C027.

Palumbo A, Cavo M, Bringhen S, Zaccaria A, Spadano A, Palmieri S, et al. Enoxaparin versus aspirin versus low-fixed-dose of warfarin in newly diagnosed myeloma patients treated with thalidomide-containing regimens: a randomized, controlled trial (meeting abstract 0910). *Haematologica* 2008;**93**:362.

* Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *Journal of Clinical Oncology* 2011;**29**:986-93.

Pelzer 2015 (CONKO-004) *{published data only}***02140505**

Pelzer U, Deutschinoff G, Opitz B, Stauch M, Reitzig P, Hahnfeld S, et al. A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy - first results of the CONKO 004 trial. In: DGHO-Meeting; Mannheim (Germany). 2011.

Pelzer U, Hilbig A, Stieler J, Roll L, Riess H, Dorken B, et al. A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy (PROSPECT - CONKO 004). *Onkologie* 2005;**28**(Suppl 3):54 (Abstract 151).

Pelzer U, Hilbig A, Stieler J, Roll L, Stauch M, Opitz B, et al. A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy (PROSPECT-CONKO 004). *Journal of Clinical Oncology* 2006;**24**(18):4110.

Pelzer U, Hilbig A, Stieler JM, Bahra M, Sinn M, Gebauer B, et al. Intensified chemotherapy and simultaneous treatment with heparin in outpatients with pancreatic cancer - the CONKO 004 pilot trial. *BMC Cancer* 2014;**14**:204.

Pelzer U, Oettle H, Stauch M, Opitz B, Stieler J, Scholten T, et al. Prospective, randomized open trial of enoxaparin in patients with advanced pancreatic cancer undergoing first-line chemotherapy. XXIst Congress of the International Society on Thrombosis and Haemostasis; 2007 Jul 6-12; Geneva (Switzerland) 2007:P-T-488.

* Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *Journal of Clinical Oncology* 2015;**33**(18):2028-34.

Riess H, Pelzer U, Deutschinoff G, Opitz B, Stauch M, Reitzig P, et al. A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): results of the CONKO 004 trial. *Journal of Clinical Oncology* 2009;**27**(18S):LBA4506.

Riess H, Pelzer U, Hilbig A, Stieler J, Opitz B, Scholten T, et al. Rationale and design of PROSPECT-CONKO 004: a prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy). *BMC Cancer* 2008;**8**:361.

Riess H, Pelzer U, Opitz B, Stauch M, Reitzig P, Hahnfeld S, et al. A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy: final results of the CONKO-004 trial. *Journal of Clinical Oncology* 2010;**28**(15 Suppl):4033.

Riess HB, Pelzer U, Opitz B, Hilbig A, Strauch M, Hahnfeld S, et al. Late breaking clinical trial: a prospective, randomized trial of chemotherapy with and without the low molecular weight heparin (LMWH) enoxaparin in advanced pancreatic cancer patients. *International Society on Thrombosis and Haemostasis* 2009;**7**(Suppl 2):1-1204.

Prins 2014 (EINSTEIN) *{published data only}*

Prins MH, Lensing AWA, Brighton TA, Lyons RM, Rehm J, Trajanovic M, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematology* 2014;**1**(1):e37-e46.

Raskob 2016 (HOKUSAI) *{published data only}*

Raskob GE, van Es N, Segers A, Angchaisuksiri P, Oh D, Boda Z, et al. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematology* 2016;**3**(8):e379-87.

Sagaster 1995 *{published data only}*

Sagaster P, Micksche M, Flamm J, Ludwig H. Randomised study using IFN-alpha versus IFN-alpha plus coumarin and cimetidine for treatment of advanced renal cell cancer. *Annals of Oncology* 1995;**6**(10):999-1003.

Sakon 2010 *{published data only}*

Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. *Thrombosis Research* 2010;**125**(3):e65-70.

Schulman 2003 *{published data only}*

Schulman S, Wahlander K, Lundstrom T, Clason SB, Eriksson H, Investigators TI , et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *New England Journal of Medicine* 2003;**349**(18):1713-21.

Schulman 2013 (RE-MEDY) *{published data only}*

Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *New England Journal of Medicine* 2013;**368**(8):709-18.

Schulman 2015 (RECOVER) *{published data only}*

Schulman S, Goldhaber SZ, Kearon C, Kakkar AK, Schellong S, Eriksson H, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thrombosis and Haemostasis* 2015;**114**(1):150-7.

Smorenburg 2001 *{published data only}*

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

Song 2014 *{published data only}*

Song KY, Yoo HM, Kim EY, Kim JI, Yim HW, Jeon HM, et al. Optimal prophylactic method of venous thromboembolism for gastrectomy in Korean patients: an interim analysis of prospective randomized trial. *Annals of Surgical Oncology* 2014;**21**(13):4232-8.

Taliani 2003 *{published data only}*

Taliani MR, Agnelli G, Prandoni P, Becattini C, Moia M, Bazzan M, et al. Incidence of cancer after a first episode of idiopathic venous thromboembolism treated with 3 months or 1 year of oral anticoagulation. *Journal of Thrombosis and Haemostasis* 2003;**1**(8):1730-3.

Taliani 2004 *{published data only}*

Taliani MR, Agnelli G, Prandoni P. Vitamin K antagonists and cancer: reply to rebuttal. *Journal of Thrombosis and Haemostasis* 2004;**2**(2):378-9.

Thethi 2011 *{published data only}*

Thethi I, Hoppensteadt D, Khan H, Demir M, Adiguzel C, Litinas E, et al. Procoagulant and inflammatory mediators in small cell lung carcinoma: potential role in thromboembolic complications. *Journal of Clinical Oncology* 2011;**29**(15S):2553.

Thornes 1972 *{published data only}*

Thornes RD. Warfarin as maintenance therapy for cancer. *Journal of the Irish Colleges of Physicians and Surgeons* 1972;**29**(2):41-2.

Thornes 1974 *{published data only}*

Thornes RD. Oral anticoagulant therapy of human cancer. *Journal of Medicine* 1974;**5**(1):83-91.

Thornes 1975 *{published data only}*

Thornes RD. Adjuvant therapy of cancer via the cellular immune mechanism or fibrin by induced fibrinolysis and oral anticoagulants. *Cancer* 1975;**35**(1):91-7.

Thornes 1984 *{published data only}*

Thornes RD. Prevention of recurrence of kaposis sarcoma, breast-cancer and melanoma by coumarin. *Irish Journal of Medical Science* 1984;**153**(5):187.

Thornes 1989 *{published data only}*

Thornes D, Daly L, Lynch G, Browne H, Tanner A, Keane F, et al. Prevention of early recurrence of high risk malignant melanoma by coumarin. *European Journal of Surgical Oncology* 1989;**15**(5):431-5.

Thornes 1993 *{published data only}*

Thornes RD. Prevention of recurrence of malignant melanoma by coumarin (1,2-benzopyrone). *Journal of the Irish Colleges of Physicians & Surgeons* 1993;**22 Suppl 1**:17-9.

Thornes 1994 *{published data only}*

Thornes RD, Daly L, Lynch G, Breslin B, Browne H, Browne HY, et al. Treatment with coumarin to prevent or delay recurrence of malignant melanoma. *Journal of Cancer Research & Clinical Oncology* 1994;**120 Suppl**:S32-4.

Tiska-Rudman 2001 *{published data only}*

Tiska-Rudman L, Stamenic V, Rudman F Jr, Zekaj S, Sabol R. Ten-year survival in patients receiving anticoagulant therapy for breast cancer. *Libri Oncologici* 2001;**29**(2):99-108.

Vedovati 2014 *{published data only}*

Becattini C, Rondelli F, Vedovati MC, Camporese G, Giustozzi M, Boncompagni M, et al. Incidence and risk factors for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Haematologica* 2014;**100**(1):e35-8.

Becattini C, Rondelli F, Vedovati MC, Camporese G, Giustozzi M, Boncompagni M, et al. Incidence and risk factors for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Haematologica* 2015;**100**(1):e35-8.

Becattini C, Vedovati MC, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, et al. One week vs. four week heparin prophylaxis after laparoscopic surgery for colorectal cancer. The pro-laps pilot feasibility study. *International Society on Thrombosis and Haemostasis* 2013;**11**(Suppl. 3):ATT05.

Vedovati MC, Becattini C, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, et al. A randomized study on 1 vs. 4 weeks prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Journal of Thrombosis and Haemostasis* 2013;**11**:214.

* Vedovati MC, Becattini C, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Annals of Surgery* 2014;**259**(4):665-9.

Venook 1989 *{published data only}*

Venook AP, Davenport Y, Tseng A Jr. Activity of coumarin and cimetidine in metastatic renal cell carcinoma. *Journal of Clinical Oncology* 1989;**7**(3):402-3.

Verso 2008 *{published data only}*

Agnelli G, Verso M, Bertoglio S, Ageno W, Bazzan M, Parise P, et al. A double-blind placebo-controlled randomized study on the efficacy and safety of enoxaparin for the prevention of upper limb deep vein thrombosis in cancer patients with central vein catheter. *Journal of Clinical Oncology* 2004;**22**:734S.

Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *Journal of Clinical Oncology* 2005;**23**(18):4057-62.

Verso M, Agnelli G, Kamphuisen PW, Ageno W, Bazzan M, Lazzaro A, et al. A double-blind placebo-controlled randomized study on the efficacy and safety of enoxaparin for the prevention of upper limb deep vein thrombosis in cancer patients with central vein catheter. In: 2003. Vol. [abstract: no P0825]: JTH 1. Journal of Thrombosis and Haemostasis:8021.

* Verso M, Agnelli G, Kamphuisen PW, Ageno W, Bazzan M, Lazzaro A, et al. Risk factors for upper limb deep vein thrombosis associated with the use of central vein catheter in cancer patients. *Internal and Emergency Medicine* 2008;**3**(2):117-22.

Ward 1998 *{published data only}*

Ward B, Pradhan S. Comparison of low molecular weight heparin (Fragmin) with sodium heparin for prophylaxis against postoperative thrombosis in women undergoing major gynaecological surgery. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 1998;**38**(1):91-2.

Wester 1996 *{published data only}*

* Wester JP, de Valk HW, Nieuwenhuis HK, Brouwer CB, van der Graaf Y, Meuwissen OJ, et al. Risk factors for bleeding during treatment of acute venous thromboembolism. *Thrombosis and Haemostasis* 1996;**76**(5):682-8.

de Valk HW, Banga JD, Wester JW, Brouwer CB, van Hessen MW, Meuwissen OJ, et al. Comparing subcutaneous danaparoid with intravenous unfractionated heparin for the treatment of venous thromboembolism. A randomized controlled trial. *Annals of Internal Medicine* 1995;**123**(1):1-9.

Zacharski 1979 *{published data only}*

Zacharski LR. Clinical trial of warfarin in cancer. *Thrombosis & Haemostasis* 1979;**42**(1):xx.

Zacharski 1982b *{published data only}*

Zacharski LR. Warfarin and cancer. *Annals of Internal Medicine* 1982;**97**(5):784.

Zacharski 1990 *{published data only}*

Zacharski LR, Henderson WG. Warfarin for small-cell lung cancer: why not? *Journal of Clinical Oncology* 1990;**8**(7):1282-3.

Zacharski 1993 *{published data only}*

Zacharski LR. Warfarin therapy for cancer. *Journal of the Irish Colleges of Physicians & Surgeons* 1993;**22 Suppl 1**:20-3.

Zacharski 2002 *{published data only}*

Zacharski LR, Henderson WG. A rebuttal: vitamin K antagonists and cancer survival. *Thrombosis & Haemostasis* 2002;**88**(1):173-5.

Zheng 2014 *{published data only}*

Zheng H, Gao Y, Yan X, Gao M, Gao W. Prophylactic use of low molecular weight heparin in combination with graduated compression stockings in post-operative patients with gynecologic cancer. *Zhonghua Zhong Liu za Zhi [Chinese Journal of Oncology]* 2014;**36**(1):39-42.

Zwicker 2013 (MICRO TEC) *{published data only}*

Zwicker J, Liebman HA, Bauer KA, Caughey T, Rosovsky R, Mantha S, et al. A randomized-controlled phase II trial of primary thromboprophylaxis with enoxaparin in cancer patients with elevated tissue factor bearing microparticles (the microtec study). *Journal of Thrombosis and Haemostasis* 2013;**11**:6.

* Zwicker JI, Liebman HA, Bauer KA, Caughey T, Campigotto F, Rosovsky R, et al. Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). *British Journal of Haematology* 2013;**160**(4):530-7.

References to ongoing studies

Janssen Research & Development, LLC 2015 *{published data only}*

A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism (VTE) Prophylaxis in Ambulatory Cancer Participants.. Ongoing study. 11 September 2015.. Contact author for more information.

Rodriguez 2015 *{published data only}*

Rodriguez V, O'Brien S, Sung L, Ramirez D Li, Mitchell LG. Rationale and design of AESOP: apixaban for prevention of deep vein thrombosis in pediatric patients with acute lymphoblastic leukemia or lymphoma treated with l-asparaginase. *Thrombosis and Haemostasis* 2014;**13**:425.

Additional references

Akl 2011a

Akl EA, Gunukula S, Barba M, Yosuico VE, van Doormaal FF, Kuipers S, et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No: CD006652. [DOI: 10.1002/14651858.CD006652.pub3]

Akl 2013

Akl EA, Johnston BC, Alonso-Coello P, Neumann I, Ebrahim S, Briel M, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. *PloS One* 2013;**8**(2):e57132.

Akl 2016

Akl EA, Kahale LA, Ebrahim S, Alonso-Coello P, Schünemann HJ, Guyatt GH. Three challenges described for identifying participants with missing data in trials reports, and potential solutions suggested to systematic reviewers. *Journal of Clinical Epidemiology* 2016;**76**:147-54.

Akl 2017

Akl EA, Meerpohl JJ, Elliott JH, Kahale LA, Schünemann HJ, on behalf of the Living Systematic Review Network. Living systematic reviews: 4. living guideline recommendations. Journal of Clinical Epidemiology 2017 Sep 1 [Epub ahead of print]. [DOI: 10.1016/j.jclinepi.2017.08.009]

Alshurafa 2012

Alshurafa M, Briel M, Akl EA, Haines T, Moayyedi P, Gentles SJ, et al. Inconsistent definitions for intention-to-treat in relation to missing outcome data: systematic review of the methods literature. *PloS One* 2012;**7**(11):e49163.

Ansell 2008

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G, American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;**133**(6 Suppl):160S-98S.

Ay 2010

Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010;**116**(24):5377-82.

Chew 2007

Chew HK, Wun T, Harvey DJ, Zhou H, White RH. Incidence of venous thromboembolism and the impact on survival in breast cancer patients. *Journal of Clinical Oncology* 2007;**25**:70-6.

Chew 2008

Chew HK, Davies AM, Wun T, Harvey D, Zhou H, White RH. The incidence of venous thromboembolism among patients with primary lung cancer. *Journal of Thrombosis Haemostasis* 2008;**6**:601-8.

Cochrane Crowd

Cochrane Crowd. crowd.cochrane.org (accessed 3 November 2017).

Connolly 2012

Connolly GC, Dalal M, Lin J, Khorana AA. Incidence and predictors of venous thromboembolism (VTE) among ambulatory patients with lung cancer. *Lung Cancer* 2012;**78**:253-8.

CSR-Web

CSR-Web. CRS (Cochrane Register of Studies). community.cochrane.org/tools/data-management-tools/crs (accessed 3 November 2017).

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, editors(s). Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd edition. London (UK): BMJ Publication Group, 2001.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Di Nisio 2016

Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AWS. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No: CD008500. [DOI: 10.1002/14651858.CD008500.pub4]

Dvorak 1986

Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *New England Journal of Medicine* 1986;**315**(26):1650-9.

Ebrahim 2013

Ebrahim S, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell D, et al. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. *Journal of Clinical Epidemiology* 2013;**66**(9):1014-21.

Elliott 2017

Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al on behalf of the Living systematic review Network. Living systematic reviews: 1. Introduction - the why, what, when and how. *Journal of Clinical Epidemiology* 2017;**91**:23-30.

Francis 1998

Francis JL, Biggerstaff J, Amirkhosravi A. Hemostasis and malignancy. *Seminars in Thrombosis & Hemostasis* 1998;**24**(2):93-109.

GRADE handbook

Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook, Updated October 2013. gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed prior to 3 November 2017).

Guyatt 2017

Guyatt GH, Ebrahim S, Alonso-Coello P, Johnston BC, Mathioudakis AG, Briel M, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. Journal of Clinical Epidemiology 2017;**87**:14-22.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557-60.

King 2013

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.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

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.

Simmonds 2017

Simmonds ME, Salanti G, Higgins JE, McKenzie J, Elliott JE on behalf of the Living Systematic Review Network. Living Systematic Reviews: 3. Statistical methods for updating meta-analyses. *Journal of Clinical Epidemiology* 2017 Sep 11;**91**:38-46. [DOI: org/10.1016/j.jclinepi.2017.08.008]

Synnot 2017

Synnot A, Turner T, Elliott J, Akl E, MacLehose H and the Living Systematic Review Network. Cochrane Living Systematic Reviews Interim guidance for pilots (Version 0.3, 21 April 2017). community.cochrane.org/review-production/production-resources/living-systematic-reviews (accessed prior to 3 November 2017).

Wallace 2017

Wallace BC, Noel-Storr A, Marshall IJ, Cohen AM, Smalheiser NR, Thomas J. Identifying reports of randomized controlled trials (RCTs) via a hybrid machine learning and crowdsourcing approach. *Journal of the American Medical Informatics Association* 2017;**0**(0):1-4.

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.

Zacharsky 1985

Zacharski LR, Henderson WG, Forman WB, Edwards RL, Cornell CJ, Forcier RJ, et al. Bleeding complications from warfarin anticoagulation in patients with malignancy. *Journal of Medicine* 1985;**16**:535-61.

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.

References to other published versions of this review

Akl 2007

Akl EA, Kamath G, Kim SY, Yosuico V, Barba M, Terrenato I, et al. Oral anticoagulation for prolonging survival in patients with cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No: CD006466. [DOI: 10.1002/14651858.CD006466]

Akl 2010

Akl EA, Vasireddi SR, Gunukula S, Yosuico VED, Barba M, Terrenato I, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews* 2010, Issue 12. Art. No: CD006466. [DOI: 10.1002/14651858.CD006466.pub2]

Akl 2011b

Akl EA, Vasireddi SR, Gunukula S, Yosuico VED, Barba M, Terrenato I, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No: CD006466. [DOI: 10.1002/14651858.CD006466.pub3]

Akl 2014a

Akl EA, Kahale L, Terrenato I, Neumann I, Yosuico VED, Barba M, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No: CD006466. [DOI: 10.1002/14651858.CD006466.pub5]

Akl 2014b

Akl EA, Kahale L, Terrenato I, Neumann I, Yosuico VED, Barba M, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No: CD006466. [DOI: 10.1002/14651858.CD006466.pub5]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Chahinian 1989

Study characteristics	
Methods	Randomized controlled trial.
Participants	189 participants with small cell lung cancer undergoing chemotherapy (CALBG 0-3). Mean age 60 years, 70% male.

Chahinian 1989 *(Continued)*

Interventions	Intervention: warfarin (PT 1.5-2). Control: no intervention. Cointervention: both arms received chemotherapy. Discontinued treatment: none.
Outcomes	Duration of follow-up: not reported. • Major bleeding. • Mortality (6 months, 1 year, 2 years and 5 years). **Screening test for DVT/PE**: none. **Diagnostic test for DVT/PE**: none.
Notes	• Funding: TJ Martell Foundation. • Ethical approval: not reported. • Conflict of interest: not reported. • Intention-to-treat analysis: not reported.

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 participants and personnel (performance bias) All outcomes	High risk	No placebo used. Comment: not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of co interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used. Comment: probably not blinded; knowledge of the assigned intervention may not have impacted on the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison between MPD rate (mortality 5/189 (2.6%), major bleeding 8/294 (2.7%)) and event rate (mortality 61/186 (32.8%), major bleeding 7/186 (3.7%)).
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on. Probably free of selective reporting.
Other bias	Low risk	Study not stopped early.

Ciftci 2012

Study characteristics

Ciftci 2012 *(Continued)*

Methods	Randomized controlled trial.
Participants	91 participants with lung cancer undergoing chemotherapy.
Interventions	Intervention: warfarin starting day 1 of chemotherapy at a dose of 5 mg daily to achieve a target INR of 1.5-2.5. Control: no warfarin. Cointervention: both arms received chemotherapy. Discontinued treatment: not reported.
Outcomes	Duration of follow-up: 6 months. • Mortality. • Bleeding. **Diagnostic test for DVT/PE**: not reported.
Notes	• Funding: not reported. • Ethical approval: not reported. • Conflict of interest: "No significant relationship." • Intention-to-treat analysis: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients with lung cancer were randomly assigned." Comment: yes.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. No placebo used. Comment: not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention, or differential administration of co interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Comment: probably not blinded; knowledge of the assigned intervention may not have impacted on the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Not reported.
Other bias	Unclear risk	Not reported.

Levine 1994

Study characteristics	
Methods	Randomized controlled trial.
Participants	315 participants with breast cancer undergoing chemotherapy; minimum life expectancy 3 months; good performance status (ECOG < 3).
Interventions	Intervention: very-low-dose warfarin 1 mg daily for 6 weeks (INR 1.3-1.9) started within 4 weeks of chemotherapy until 1 week after termination of chemotherapy. Control: placebo. Cointervention: both arms received chemotherapy. 2 participants in the warfarin group and 2 in the control group did not receive chemotherapy and they were not considered in the analysis. No surveillance tests used. Discontinued treatment: 27 participants in each arm discontinued treatment.
Outcomes	Duration of follow-up: not reported. • Thromboembolic events. • Mortality (1 year). • Bleeding. **Diagnostic test for DVT**: venography, impedance plethysmography or Doppler. **Diagnostic test for PE**: ventilation/perfusion scan or angiography.
Notes	• Funding: National Cancer Institute, Canada. • Ethical approval: "The protocol was approved by the institutional review boards for the participating centres." • Conflict of interest: ML is a scientist of the Medical Research Council of Canada, JH is a distinguished professor of the Heart & Stroke Foundation of Ontario and PG is a career scientist of the Ontario Ministry of Health. • Intention-to-treat analysis: not reported.

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 participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither patients nor doctors were aware of treatment allocation." Comment: definitely blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The manager relayed the INR (actual value for patients on active drug, sham value for patients on placebo) to the study nurse and investigator."

Levine 1994 *(Continued)*

		Comment: Definitely blinded; knowledge of the assigned intervention may not have impacted on impact the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Jjudgment based on comparison between MPD rate in study population (4/315= (1.3%)) and event rate (mortality at 1 year 186/311= (60%), DVT 6/311= (1.9%)).
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on. Probably free of selective reporting.
Other bias	Low risk	Study not stopped early for benefit.

Levine 2012

Study characteristics	
Methods	Randomized, phase II, double blind trial.
Participants	125 participants 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%, with 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. Cointervention: either first-line or second-line chemotherapy (expected course ≥ 90 days). Discontinued treatment: none.
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. • Mortality. • Major bleeding. • Clinically relevant non-major bleeding. • Higher adverse events (≥ 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. • Ethical approval: "The study protocol was approved by the Institutional Review Board of each participating center." • Conflict of interest: not reported.

Levine 2012 *(Continued)*

	• Intention-to-treat analysis: not reported. • 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."

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 participants and personnel (performance bias) All outcomes	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: blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All bleeding and VTE events were adjudicated by a committee unaware of treatment allocation." Comment: blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.
Selective reporting (reporting bias)	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.
Other bias	Low risk	No other bias suspected.

Maurer 1997

Study characteristics

Methods	Randomized controlled study.
Participants	369 participants aged > 18 years with small cell lung cancer undergoing chemotherapy and radiotherapy from 27 CALBG main member institutions and their affiliates. Mean age 48 years, 65% male, 55% performance status 0, minimum life expectancy 2 months; CALGB < 3.

Maurer 1997 *(Continued)*

Interventions	Intervention: warfarin (PT 1.4-1.6) started with chemotherapy at 10 mg daily for 3 days and continued for 3 weeks after last cycle of chemotherapy and radiotherapy. Control: no warfarin. Cointervention: both arms received 3 cycles of chemotherapy. 3 participants were randomized but excluded pretreatment because they did not receive protocol treatment (unclear in which group). Discontinued treatment: not reported.
Outcomes	Duration of follow-up: not reported. • Mortality (6 months, 1 year, 2 years, 5 years). • Bleeding. **Diagnostic tests for PE**: not reported. **Diagnostic tests for DVT**: not reported.
Notes	• Funding: National Cancer Institute, USA. • Ethical approval: "Each patient provided signed informed consent, which included a discussion of alternative therapies and which was approved by the institutional review board." • Conflict of interest: not reported. • Intention-to-treat analysis: "Ineligible patients and patients who did not receive protocol treatment are excluded from subsequent analyses."

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." Comment: yes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used. Comment: not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of co interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Comment: probably not blinded; knowledge of the assigned intervention may not have impacted on the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up rate: not reported.

Maurer 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were reported on. Probably free of selective reporting.
Other bias	Low risk	Study not stopped early for benefit.

Stanford 1979

Study characteristics	
Methods	Randomized controlled trial.
Participants	24 participants 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 daily for 6 days. During the first 24 hours of anticoagulants, participants also received 1 L of dextran (Rheomacrodex). A loading dose of warfarin 25 mg was given on the 4th 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 4 hours. Control: no anticoagulant. Cointervention: "Both groups received two induction courses of chemotherapy at three weekly intervals followed by maintenance drugs given three times weekly." Discontinued treatment: none.
Outcomes	Duration of follow-up: 16 months. • Mortality (12 months). • Minor bleeding (4 months). **Diagnostic tests for PE**: not reported. **Diagnostic tests for DVT**: not reported.
Notes	• Funding: not reported. • Ethical approval: not reported. • Conflict of interest: not reported. • Intention-to-treat analysis: not reported. "All the 24 patients enrolled in the study completed the follow-up and their data had been analyzed."

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 participants and personnel (performance bias)	High risk	No placebo used.

Stanford 1979 *(Continued)*

All outcomes		Comment: not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of co interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used Comment: probably not blinded; knowledge of the assigned intervention may not have impacted on the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.
Selective reporting (reporting bias)	Unclear risk	Study not registered. No published protocol. No listing of outcomes in the methods section.
Other bias	Low risk	Study not reported as stopped early for benefit. No other bias suspected.

Zacharski 1984

Study characteristics	
Methods	Randomized controlled trial.
Participants	431 participants 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: warfarin (therapeutic range). Control: no intervention. Cointervention: not reported. 13 randomized participants were excluded from survival analyses (unclear in which group). Discontinued treatment: 0 participants.
Outcomes	Duration of follow-up: 4 years followed for an additional 12 months. • Major bleeding. • Mortality (6 months, 1 year). **Diagnostic tests for PE**: not reported. **Diagnostic tests for DVT**: not reported.
Notes	• Funding: Department of Veterans Affairs Medical Research Service. • Ethical approval: not reported. • Conflict of interest: not reported. • Intention-to-treat analysis: probably not. "patients randomized to receive warfarin were excluded if they did not receive at least 2 weeks of anticoagulant therapy following randomization."

Zacharski 1984 *(Continued)*

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.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used. Comment: not blinded; knowledge of the assigned intervention may have led to differential behaviors across intervention groups (e.g. differential dropout, differential cross-over to an alternative intervention or differential administration of co-interventions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo used. Comment: probably not blinded; knowledge of the assigned intervention may not have impacted on the assessment of the physiological outcomes (mortality, DVT, PE, bleeding, etc.).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: judgment based on comparison between MPD rate (13/431 (3%)) and event rate (mortality in warfarin group 136/215 (63.3%) in warfarin group; mortality in control group 138/216 (63.9%) in control group).
Selective reporting (reporting bias)	Low risk	Study not registered. No published protocol. All outcomes listed in the methods section were not reported. Probably free of selective reporting.
Other bias	Low risk	Study not stopped early for benefit.

CALBG: Cancer and Leukemia Group B; DVT: deep vein thrombosis; ECOG: Eastern Cooperative Oncology Group; INR: international normalized ratio; IU: international unit; MPD: missing patient data; 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
Agnelli 1998	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Agnelli 2005	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Agnelli 2015 (AMPLIFY)	Not population of interest (people with cancer with VTE); included 2 reports.
Aisner 1987	Different drug/agent studied.
Aisner 1992	No control group.
Alikhan 2003 (MEDENOX)	Not population of interest (people with cancer without VTE undergoing a surgical procedure); included 2 reports.
Anonymous 1994	Letter to editor.

Study	Reason for exclusion
Auer 2011	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Bigg 1992	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Cahan 2000	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Carpi 1995	Observational study.
Chlebowski 1982	No control group.
Clarke-Pearson 1993	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Cohen 1997	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Cohen 2006	Not population of interest (hospitalized).
Cohen 2007 (PREVENT)	Not population of interest (hospitalized people with cancer); included 3 reports.
Couban 2005	Not population of interest (people with cancer with CVC without VTE); included 3 reports.
D'Souza 1980a	Groups treated differently.
D'Souza 1980b	Groups treated differently.
Daly 1991	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Demir 2006	No reporting outcome of interest.
Demir 2007	No reporting outcome of interest.
Dickinson 1998	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Goldhaber 2002	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Haas 2011	Not population of interest (hospitalized people with cancer); included 3 reports.
Harenberg 1996	Not population of interest (hospitalized people with cancer); included 2 reports.
Hata 2016	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
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 editor.
Hutchins 1984	No control group.
Kakkar 2010 (CANBESURE)	Not population of interest (people with cancer who had a surgical procedure); included 2 reports.
Kakkar 2014 (SAVE-ABDO)	Not population of interest (people with cancer without VTE undergoing a surgical procedure).

Study	Reason for exclusion
Khan 2012	No reporting outcome of interest.
Khorana 2017 (PHACS)	Not comparison of interest (parenteral anticoagulant); included 2 reports.
Kokron 1990	Different drug/agent studied.
Kokron 1993	Different drug/agent studied.
Koppenhagen 1992	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Larocca 2012	Not comparison of interest (LMWH vs aspirin).
Lebeau 1993	Different drug/agent studied.
Lecumberri 2005	Review.
Lee 2015 (CATCH)	Not population of interest (people with cancer with VTE); included 9 reports.
Loprinzi 1999	Not population of interest, no people with cancer.
Macareo 2001	Observational study: retrospective.
Macbeth 2016 (FRAGMATIC)	Not comparison of interest (parenteral anticoagulant); included 4 reports.
Marshall 1987	No control group.
Marshall 1989	No control group.
Marshall 1990	No control group.
Maxwell 2001	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
McCulloch 1987	Animal study.
Moazzam 2003	No control group.
Mohler 1993	No control group.
Mohler 1994	No control group.
Murakami 2002	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Nagata 2015	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Nurmohamed 1996	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Palumbo 2011	Not comparison of interest (aspirin versus warfarin); included 6 reports.
Pelzer 2015 (CONKO-004)	Not comparison of interest (parenteral anticoagulant); included 10 reports.
Prins 2014 (EINSTEIN)	Not population of interest (people with cancer with VTE); included 2 reports.
Raskob 2016 (HOKUSAI)	Not population of interest (people with cancer with VTE); included 3 reports.
Sagaster 1995	Different drug/agent studied.

Study	Reason for exclusion
Sakon 2010	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Schulman 2003	Not population of interest (people with VTE).
Schulman 2013 (RE-MEDY)	Not population of interest (people with cancer with VTE).
Schulman 2015 (RECOVER)	Not population of interest (people with cancer with VTE).
Smorenburg 2001	Review.
Song 2014	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Taliani 2003	Letter to editor.
Taliani 2004	Letter to editor.
Thethi 2011	No reporting outcome of interest.
Thornes 1972	Controlled clinical trial, inadequate randomization.
Thornes 1974	Controlled clinical trial, inadequate randomization.
Thornes 1975	Controlled clinical trial, inadequate randomization (each alternate person 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.
Vedovati 2014	Not population of interest (people with cancer who had a surgical procedure); included 5 reports.
Venook 1989	Letter to editor.
Verso 2008	Not population of interest (people with cancer with CVC without VTE); included 4 reports.
Ward 1998	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Wester 1996	Not population of interest (people with cancer with VTE); included 2 reports.
Zacharski 1979	Protocol.
Zacharski 1982b	Letter to editor.
Zacharski 1990	Letter to editor.
Zacharski 1993	Review.
Zacharski 2002	Letter to editor.

Study	Reason for exclusion
Zheng 2014	Not population of interest (people with cancer without VTE undergoing a surgical procedure).
Zwicker 2013 (MICRO TEC)	Not comparison of interest (parenteral anticoagulant); included 2 reports.

CVC: central venous catheter; LMWH: low-molecular-weight heparin; VTE: venous thromboembolism.

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

Janssen Research & Development, LLC 2015

Study name	A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism (VTE) Prophylaxis in Ambulatory Cancer Participants.
Methods	Randomized, parallel assignment, double-blind, placebo-controlled trial.
Participants	People aged ≥ 18 years with histologically confirmed solid malignancy, and a plan to initiate systemic cancer therapy within ± 1 week of receiving first dose of study drug.
Interventions	Rivaroxaban: 10 mg tablet orally once daily for 180 days. Placebo: tablet orally once daily for 180 days.
Outcomes	• Time to first objectively confirmed symptomatic and asymptomatic lower extremity proximal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, VTE-related death. • Major bleeding.
Starting date	11 September 2015.
Contact information	Janssen Research & Development, LLC. JNJ.CT@sylogent.com.
Notes	NCT02555878 Status as of November 2017: currently recruiting participants.

Rodriguez 2015

Study name	Rationale and Design of AESOP: APIXABAN for Prevention of Deep Vein Thrombosis in Pediatric Patients with Acute Lymphoblastic Leukemia or Lymphoma Treated with L-Asparaginase
Methods	Phase III trial, randomized, open-label, control: no anticoagulation.
Participants	Children and adolescents aged 1 to < 18 years with newly diagnosed acute lymphoblastic leukemia or lymphoma and a central venous catheter in place.
Interventions	Apixaban.
Outcomes	DVT prevention in children and adolescents during induction chemotherapy including l-asparaginase.
Starting date	March 2015.
Contact information	Vilmarie Rodriguez, MD, Mayo Clinic.
Notes	NCT02369653

Rodriguez 2015 *(Continued)*

	Status as of November 2017: currently recruiting participants

DVT: deep vein thrombosis; PE: pulmonary embolism.

DATA AND ANALYSES

Comparison 1. Vitamin K antagonist (VKA) versus no VKA

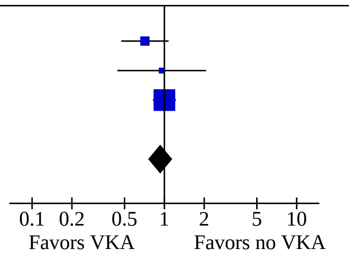
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality at 6 months: main analysis	3	946	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.13]
1.2 Mortality at 6 months: subgroup analysis (lung cancer)	3	946	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.14]
1.2.1 Lung cancer (small cell and non-small cell)	3	813	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
1.2.2 Non-lung cancer	1	133	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.82, 1.82]
1.3 Mortality at 12 months: main analysis	5	1281	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
1.4 Mortality at 12 months: subgroup analysis (lung cancer)	5	1281	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
1.4.1 Lung cancer (small cell and non-small cell)	4	837	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.05]
1.4.2 Non-lung cancer	2	444	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.81, 1.10]
1.5 Mortality at 2 years	2	528	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.70, 1.30]
1.6 Mortality at 5 years	1	344	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.03]
1.7 Symptomatic deep vein thrombosis	1	311	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.42]
1.8 Pulmonary embolism	1	311	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.07, 16.58]
1.9 Major bleeding: main analysis	5	1281	Risk Ratio (M-H, Random, 95% CI)	2.93 [1.86, 4.62]
1.10 Major bleeding: subgroup analysis (lung cancer)	5	1281	Risk Ratio (M-H, Random, 95% CI)	2.85 [1.76, 4.62]
1.10.1 Lung cancer (small cell and non-small cell)	4	837	Risk Ratio (M-H, Random, 95% CI)	3.95 [2.38, 6.55]
1.10.2 Non-lung cancer	2	444	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.63, 4.89]
1.11 Minor bleeding: main analysis	4	863	Risk Ratio (M-H, Random, 95% CI)	3.14 [1.85, 5.32]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.12 Minor bleeding: subgroup analysis (lung cancer)	4	865	Risk Ratio (M-H, Random, 95% CI)	3.19 [1.83, 5.55]
1.12.1 Lung cancer (small cell and non-small cell)	3	554	Risk Ratio (M-H, Random, 95% CI)	3.79 [1.55, 9.24]
1.12.2 Non-lung cancer	1	311	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.64, 9.27]

Analysis 1.1. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 1: Mortality at 6 months: main analysis

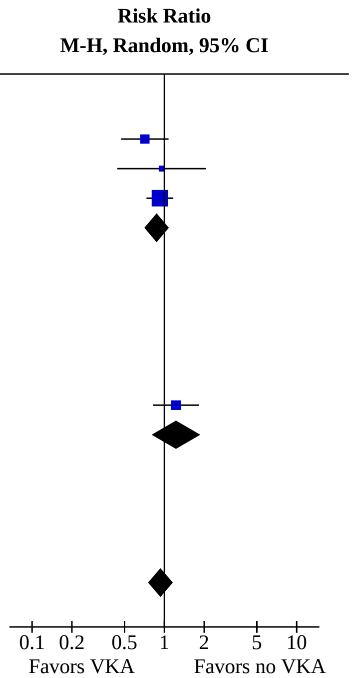
Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Chahinian 1989	28	100	33	84	20.7%	0.71 [0.47 , 1.08]
Maurer 1997	12	176	12	168	6.1%	0.95 [0.44 , 2.07]
Zacharski 1984	100	210	99	208	73.2%	1.00 [0.82 , 1.22]
Total (95% CI)		**486**		**460**	**100.0%**	**0.93 [0.77 , 1.13]**
Total events:	140		144			

Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 2 (P = 0.35); I² = 6%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



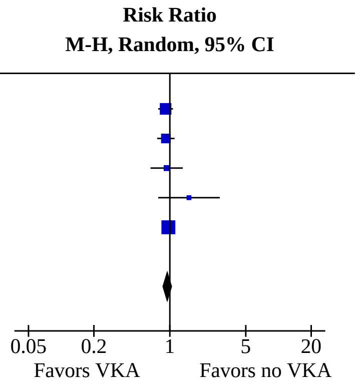
Analysis 1.2. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 2: Mortality at 6 months: subgroup analysis (lung cancer)

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Lung cancer (small cell and non-small cell)						
Chahinian 1989	28	100	33	84	20.6%	0.71 [0.47 , 1.08]
Maurer 1997	12	176	12	168	6.4%	0.95 [0.44 , 2.07]
Zacharski 1984	68	142	74	143	51.2%	0.93 [0.73 , 1.17]
Subtotal (95% CI)		**418**		**395**	**78.1%**	**0.87 [0.72 , 1.06]**
Total events:	108		119			
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.35 (P = 0.18)						
1.2.2 Non-lung cancer						
Zacharski 1984	32	68	25	65	21.9%	1.22 [0.82 , 1.82]
Subtotal (95% CI)		**68**		**65**	**21.9%**	**1.22 [0.82 , 1.82]**
Total events:	32		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**486**		**460**	**100.0%**	**0.93 [0.77 , 1.14]**
Total events:	140		144			
Heterogeneity: Tau² = 0.01; Chi² = 3.44, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 2.21, df = 1 (P = 0.14), I² = 54.8%						



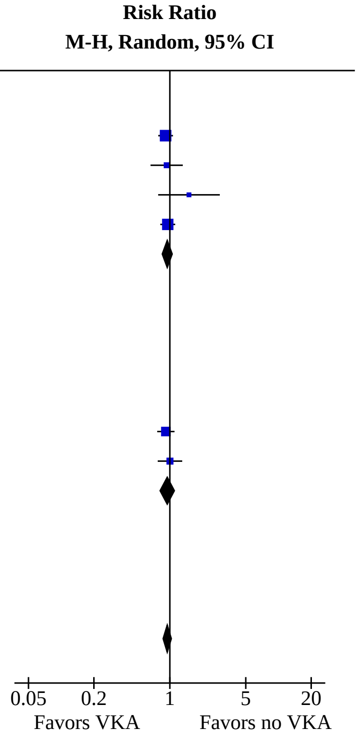
Analysis 1.3. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 3: Mortality at 12 months: main analysis

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Chahinian 1989	74	100	68	84	30.2%	0.91 [0.78 , 1.07]
Levine 1994	87	152	99	159	21.8%	0.92 [0.77 , 1.10]
Maurer 1997	47	176	48	168	6.3%	0.93 [0.66 , 1.32]
Stanford 1979	9	12	6	12	1.7%	1.50 [0.78 , 2.88]
Zacharski 1984	138	210	141	208	40.0%	0.97 [0.85 , 1.11]
Total (95% CI)		**650**		**631**	**100.0%**	**0.95 [0.87 , 1.03]**
Total events:	355		362			
Heterogeneity: Tau² = 0.00; Chi² = 2.33, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Not applicable						



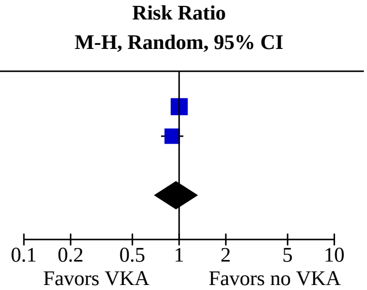
Analysis 1.4. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 4: Mortality at 12 months: subgroup analysis (lung cancer)

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Lung cancer (small cell and non-small cell)						
Chahinian 1989	74	100	68	84	30.1%	0.91 [0.78 , 1.07]
Maurer 1997	47	176	48	168	6.2%	0.93 [0.66 , 1.32]
Stanford 1979	9	12	6	12	1.7%	1.50 [0.78 , 2.88]
Zacharski 1984	95	142	100	143	29.3%	0.96 [0.82 , 1.12]
Subtotal (95% CI)		**430**		**407**	**67.4%**	**0.95 [0.85 , 1.05]**
Total events:	225		222			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.4.2 Non-lung cancer						
Levine 1994	87	152	99	159	21.8%	0.92 [0.77 , 1.10]
Zacharski 1984	43	68	41	65	10.8%	1.00 [0.77 , 1.30]
Subtotal (95% CI)		**220**		**224**	**32.6%**	**0.95 [0.81 , 1.10]**
Total events:	130		140			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Total (95% CI)		**650**		**631**	**100.0%**	**0.95 [0.87 , 1.03]**
Total events:	355		362			
Heterogeneity: Tau² = 0.00; Chi² = 2.42, df = 5 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.27 (P = 0.20)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



Analysis 1.5. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 5: Mortality at 2 years

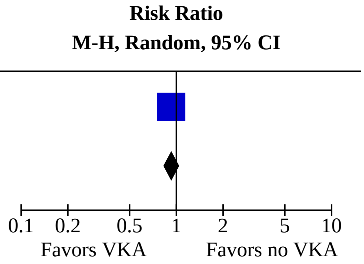
Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Chahinian 1989	99	100	83	84	53.5%	1.00 [0.97 , 1.03]
Maurer 1997	104	176	110	168	46.5%	0.90 [0.77 , 1.06]
Total (95% CI)		**276**		**252**	**100.0%**	**0.95 [0.70 , 1.30]**
Total events:	203		193			
Heterogeneity: Tau² = 0.05; Chi² = 13.46, df = 1 (P = 0.0002); I² = 93%						
Test for overall effect: Z = 0.30 (P = 0.77)						
Test for subgroup differences: Not applicable						



Analysis 1.6. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 6: Mortality at 5 years

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Maurer 1997	136	176	140	168	100.0%	0.93 [0.83 , 1.03]
Total (95% CI)		**176**		**168**	**100.0%**	**0.93 [0.83 , 1.03]**
Total events:	136		140			

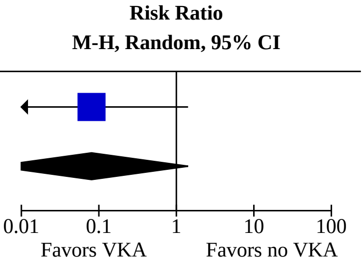
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 7: Symptomatic deep vein thrombosis

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Levine 1994	0	152	6	159	100.0%	0.08 [0.00 , 1.42]
Total (95% CI)		**152**		**159**	**100.0%**	**0.08 [0.00 , 1.42]**
Total events:	0		6			

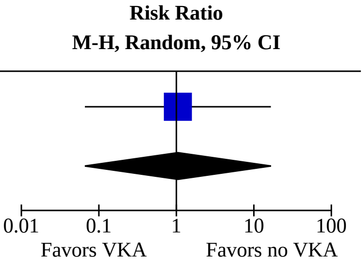
Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 8: Pulmonary embolism

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Levine 1994	1	152	1	159	100.0%	1.05 [0.07 , 16.58]
Total (95% CI)		**152**		**159**	**100.0%**	**1.05 [0.07 , 16.58]**
Total events:	1		1			

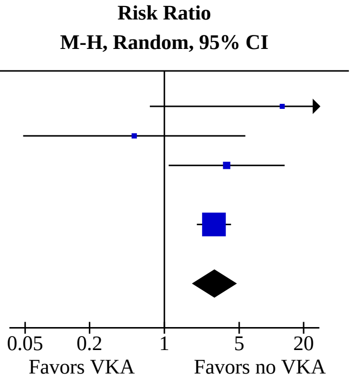
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 9: Major bleeding: main analysis

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Chahinian 1989	7	100	0	84	2.5%	12.62 [0.73 , 217.83]
Levine 1994	1	152	2	159	3.5%	0.52 [0.05 , 5.71]
Maurer 1997	12	176	3	168	12.3%	3.82 [1.10 , 13.29]
Stanford 1979	0	12	0	12		Not estimable
Zacharski 1984	88	210	30	208	81.6%	2.91 [2.01 , 4.20]
Total (95% CI)		**650**		**631**	**100.0%**	**2.93 [1.86 , 4.62]**
Total events:	108		35			

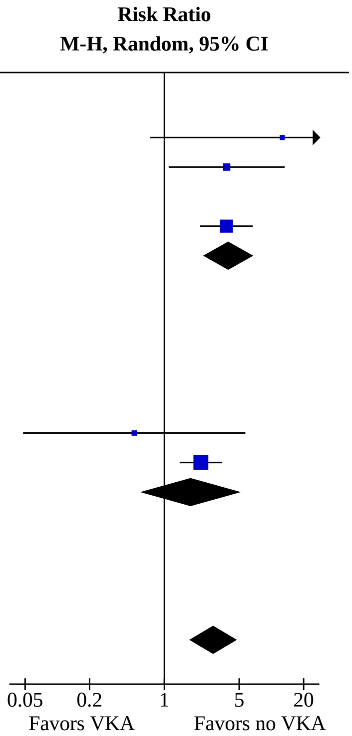
Heterogeneity: Tau² = 0.03; Chi² = 3.20, df = 3 (P = 0.36); I² = 6%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 10: Major bleeding: subgroup analysis (lung cancer)

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Lung cancer (small cell and non-small cell)						
Chahinian 1989	7	100	0	84	2.8%	12.62 [0.73 , 217.83]
Maurer 1997	12	176	3	168	12.4%	3.82 [1.10 , 13.29]
Stanford 1979	0	12	0	12		Not estimable
Zacharski 1984	49	142	13	143	36.6%	3.80 [2.16 , 6.68]
Subtotal (95% CI)		**430**		**407**	**51.8%**	**3.95 [2.38 , 6.55]**
Total events:	68		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 5.31 (P < 0.00001)						
1.10.2 Non-lung cancer						
Levine 1994	1	152	2	159	3.8%	0.52 [0.05 , 5.71]
Zacharski 1984	39	68	17	65	44.4%	2.19 [1.39 , 3.46]
Subtotal (95% CI)		**220**		**224**	**48.2%**	**1.75 [0.63 , 4.89]**
Total events:	40		19			
Heterogeneity: Tau² = 0.27; Chi² = 1.35, df = 1 (P = 0.25); I² = 26%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Total (95% CI)		**650**		**631**	**100.0%**	**2.85 [1.76 , 4.62]**
Total events:	108		35			

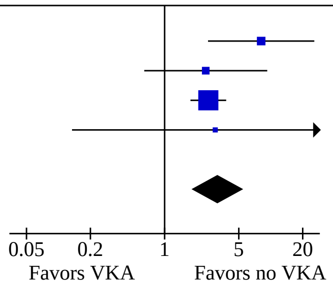
Heterogeneity: Tau² = 0.08; Chi² = 5.60, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 4.26 (P < 0.0001)
Test for subgroup differences: Chi² = 1.93, df = 1 (P = 0.16), I² = 48.2%



Analysis 1.11. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 11: Minor bleeding: main analysis

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
Chahinian 1989	29	100	3	84	17.4%	8.12 [2.56 , 25.71]
Levine 1994	7	152	3	159	13.6%	2.44 [0.64 , 9.27]
Maurer 1997	73	176	27	168	66.3%	2.58 [1.75 , 3.80]
Stanford 1979	1	12	0	12	2.8%	3.00 [0.13 , 67.06]
Total (95% CI)		**440**		**423**	**100.0%**	**3.14 [1.85 , 5.32]**
Total events:	110		33			

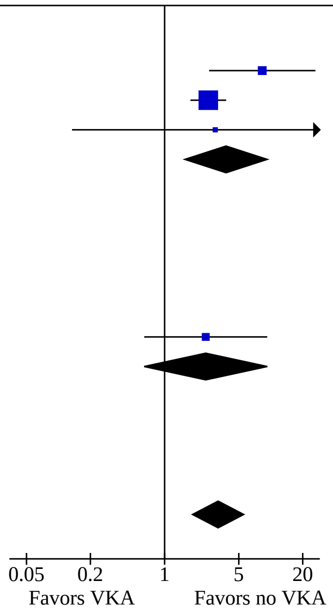
Heterogeneity: Tau² = 0.07; Chi² = 3.67, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 4.26 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Vitamin K antagonist (VKA) versus no VKA, Outcome 12: Minor bleeding: subgroup analysis (lung cancer)

Study or Subgroup	VKA Events	VKA Total	No VKA Events	No VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Lung cancer (small cell and non-small cell)						
Chahinian 1989	29	100	3	86	18.5%	8.31 [2.62 , 26.34]
Maurer 1997	73	176	27	168	63.9%	2.58 [1.75 , 3.80]
Stanford 1979	1	12	0	12	3.1%	3.00 [0.13 , 67.06]
Subtotal (95% CI)		**288**		**266**	**85.5%**	**3.79 [1.55 , 9.24]**
Total events:	103		30			
Heterogeneity: Tau² = 0.30; Chi² = 3.78, df = 2 (P = 0.15); I² = 47%						
Test for overall effect: Z = 2.93 (P = 0.003)						
1.12.2 Non-lung cancer						
Levine 1994	7	152	3	159	14.5%	2.44 [0.64 , 9.27]
Subtotal (95% CI)		**152**		**159**	**14.5%**	**2.44 [0.64 , 9.27]**
Total events:	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)		**440**		**425**	**100.0%**	**3.19 [1.83 , 5.55]**
Total events:	110		33			

Heterogeneity: Tau² = 0.09; Chi² = 3.82, df = 3 (P = 0.28); I² = 21%
Test for overall effect: Z = 4.11 (P < 0.0001)
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%



Comparison 2. Direct oral anticoagulants (DOAC) versus no DOAC

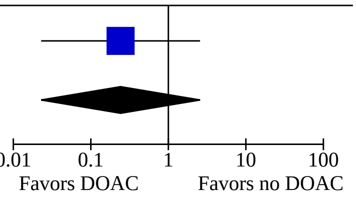
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mortality at 3 months	1	92	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.02, 2.56]
2.2 Symptomatic deep vein thrombosis	1	92	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.32]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.3 Pulmonary embolism	1	92	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 3.91]
2.4 Major bleeding	1	92	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 3.91]
2.5 Minor bleeding	1	92	Risk Ratio (M-H, Random, 95% CI)	4.43 [0.25, 79.68]

Analysis 2.1. Comparison 2: Direct oral anticoagulants (DOAC) versus no DOAC, Outcome 1: Mortality at 3 months

	DOAC		No DOAC			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Levine 2012	1	62	2	30	100.0%	0.24 [0.02 , 2.56]
Total (95% CI)		**62**		**30**	**100.0%**	**0.24 [0.02 , 2.56]**
Total events:	1		2			

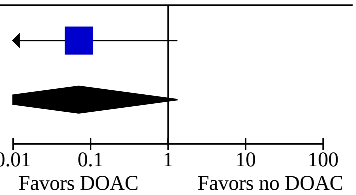
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Direct oral anticoagulants (DOAC) versus no DOAC, Outcome 2: Symptomatic deep vein thrombosis

	DOAC		No DOAC			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Levine 2012	0	62	3	30	100.0%	0.07 [0.00 , 1.32]
Total (95% CI)		**62**		**30**	**100.0%**	**0.07 [0.00 , 1.32]**
Total events:	0		3			

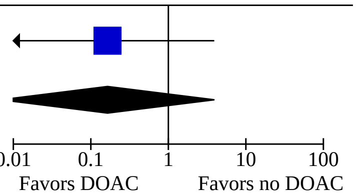
Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Direct oral anticoagulants (DOAC) versus no DOAC, Outcome 3: Pulmonary embolism

	DOAC		No DOAC			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Levine 2012	0	62	1	30	100.0%	0.16 [0.01 , 3.91]
Total (95% CI)		**62**		**30**	**100.0%**	**0.16 [0.01 , 3.91]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable

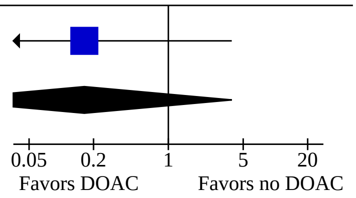


Analysis 2.4. Comparison 2: Direct oral anticoagulants (DOAC) versus no DOAC, Outcome 4: Major bleeding

Study or Subgroup	DOAC Events	DOAC Total	No DOAC Events	No DOAC Total	Weight	Risk Ratio M-H, Random, 95% CI
Levine 2012	0	62	1	30	100.0%	0.16 [0.01 , 3.91]
Total (95% CI)		**62**		**30**	**100.0%**	**0.16 [0.01 , 3.91]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI

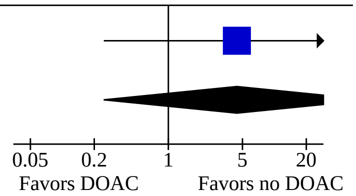


Analysis 2.5. Comparison 2: Direct oral anticoagulants (DOAC) versus no DOAC, Outcome 5: Minor bleeding

Study or Subgroup	DOAC Events	DOAC Total	No DOAC Events	No DOAC Total	Weight	Risk Ratio M-H, Random, 95% CI
Levine 2012	4	62	0	30	100.0%	4.43 [0.25 , 79.68]
Total (95% CI)		**62**		**30**	**100.0%**	**4.43 [0.25 , 79.68]**
Total events:	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Random, 95% CI



ADDITIONAL TABLES

Table 1. Glossary

Term	Meaning
Adjuvant therapy	Assisting in the amelioration or cure of disease.
Anticoagulation	Process of hindering the clotting of blood especially by treatment with an anticoagulant.
Antithrombotic	Used against or tending to prevent thrombosis (clotting).
Apixaban	Oral direct factor Xa inhibitor used for anticoagulation.
Coagulation	Clotting.
Direct factor Xa inhibitor	Anticoagulant medications used for anticoagulation. Apixaban is an oral direct factor Xa inhibitor.
Deep vein thrombosis (DVT)	Condition marked by the formation of a thrombus within a deep vein (e.g. leg or pelvis) that may be asymptomatic or symptomatic (as swelling and pain) and that is potentially life-threatening if dislodgment of the thrombus results in pulmonary embolism.
Fibrin	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.

Table 1. Glossary *(Continued)*

Heparin	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).
Major bleeding	Bleeding that is intracranial or retroperitoneal, if it leads directly to death, or if results in hospitalization or transfusion.
Metastasis	Spread of a cancer cells from the initial or primary site of disease to another part of the body.
Minor bleeding	Any bleeding not classified as major bleeding.
Oncogene	Gene having the potential to cause a normal cell to become cancerous.
Osteoporosis	Condition that affects mainly 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	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 (VKA)	Anticoagulant medications. Warfarin is a vitamin K antagonist.
Warfarin	Anticoagulant medication that is a vitamin K antagonist.
Ximelagatran	Anticoagulant medication.

APPENDICES

Appendix 1. Living systematic review protocol

The methods outlined below are specific to maintaining the review as a living systematic review on the Cochrane Library (Synnot 2017). They will be implemented immediately upon publication of this update. Core review methods, such as the criteria for considering studies in the review and assessment of risk of bias, are unchanged. As such, below we outline only those areas of the methods for which additional or different activities are planned or rules apply.

Search methods for identification of studies

We will rerun the majority of searches monthly. For electronic databases and other electronic sources (CENTRAL, MEDLINE, Embase), we have set up auto-alerts to deliver a monthly search yield by email. We will search the remaining resources (conference proceedings of the American Society of Clinical Oncology (ASCO), the American Society of Haematology (ASH) and clinicaltrials.gov) on a monthly basis. For that purpose, we will note when these conference proceedings are published.

As additional steps to inform the living systematic review, we will contact corresponding authors of ongoing studies as they are identified and ask them to advise when results are available, and to share early or unpublished data. We will contact the corresponding authors of any newly included studies for advice as to other relevant studies. We will conduct citation tracking of included studies in Web of Science Core Collection on an ongoing basis. For that purpose, we have set up citation alerts in Web of Science Core Collection. We will manually screen the reference list of any newly included studies, and identified relevant guidelines and systematic reviews. In addition, we will use the 'related citation' feature in PubMed to identify additional articles.

We will review search methods and strategies approximately yearly, to ensure they reflect any terminology changes in the topic area, or in the databases.

Selection of studies

We will immediately screen any new citations retrieved by the monthly searches. As the first step of monthly screening, we will apply the machine learning classifier (RCT model) available in the Cochrane Register of Studies (CSR-Web; Wallace 2017). The classifier assigns a probability (from 0 to 100) to each citation for being a true RCT. For citations that are assigned a probability score of less than 10, the machine learning classifier currently has a specificity/recall of 99.987% (Wallace 2017). For citations assigned a score from 10 to 100, we will screen them in duplicate and independently. Citations that score 9 or less will be screened by Cochrane Crowd (Cochrane Crowd). Any citations that are deemed to be potential RCTs by Cochrane Crowd will be returned to the authors for screening.

Data synthesis

Whenever new evidence (studies, data or information) that meets the review inclusion criteria is identified, we will immediately assess risk of bias and extract the data and incorporate it in the synthesis, as appropriate. We will not adjust the meta-analyses to account for multiple testing given the methods related to frequent updating of meta-analyses are under development (Simmonds 2017).

Other

We will review the review scope and methods approximately yearly, or more frequently if appropriate, given potential changes in the topic area, or the evidence being included in the review (e.g. additional comparisons, interventions or outcomes or new review methods available).

Appendix 2. Cochrane's living systematic review pilots

Living systematic reviews offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available (Elliott 2017). Cochrane is exploring the feasibility of preparing and publishing living systematic reviews in a series of pilots (which includes this review). For the Cochrane pilots, searching is being conducted monthly, and new relevant evidence (studies, data or other information) will be incorporated into the review in a timely manner, so that the findings of the review remain current.

For the most up-to-date information about the review, the results of the searches and any new evidence being incorporated, readers are encouraged to check the update status information. The update status information will be updated whenever the searches are rerun. The review will be updated with a new citation whenever a new study is found.

Appendix 3. Full search strategies for the electronic databases - update 2010

Database	Strategy
CENTRAL (the Cochrane Library, latest issue)	#1 heparin OR low molecular weight heparin OR LMWH OR low-molecular-weight-heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran #2 Coumarins OR Warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA #3 fondaparinux OR Arixtra #4 ximelagatran OR Exanta #5 Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban #6 1 OR 2 OR 3 OR 4 OR 5 #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/ #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 organ).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/

(Continued)

	#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 organ).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 #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

(Continued)

	#9 6 AND 7 AND 8

Appendix 4. Full search strategies for the electronic databases - update 2013

Database	Strategy
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Heparin] explode all trees #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) #3 MeSH descriptor: [Coumarins] explode all trees #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA) #5 (fondaparinux or arixtra) #6 (ximelagatran or exanta) #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban) #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Neoplasms] explode all trees #10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) #11 #9 or #10 #12 #8 and #10
MEDLINE	#1 exp Heparin/ #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. #3 exp Coumarins/ #4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw. #5 (fondaparinux or arixtra).tw. #6 (ximelagatran or exanta).tw. #7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw. #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.

(Continued)

	#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 organan 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 anticoagulant 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 #14 crossover procedure/ #15 double-blind procedure/ #16 randomized controlled trial/ #17 single-blind procedure/

(Continued)

	#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 5. Full search strategies for the electronic databases - update 2017

Database	Strategy
CENTRAL (the Cochrane Library, latest issue)	#1 MeSH descriptor: [Anticoagulants] explode all trees
	#2 (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane 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 danaparoid or organ or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or organ or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock)
	#3 FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216
	#4 MeSH descriptor: [Coumarins] explode all trees
	#5 (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-bis-coumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl)
	#6 (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix)
	#7 thrombin near inhibitor*
	#8 factor Xa inhibitor* or antithrombin* or anticoagul*

(Continued)

	#9 (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. #10 MeSH descriptor: [Rivaroxaban] this term only #11 MeSH descriptor: [Dabigatran] this term only #12 target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC* #13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #14 MeSH descriptor: [Neoplasms] explode all trees #15 malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma* #16 #14 or #15 #17 #13 and #16
MEDLINE	**RCT search strategy:** 1. exp Anticoagulants/ 2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane 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 danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp. 3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp. 4. exp Coumarins/ 5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp. 6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp. 7. (thrombin adj inhibitor*).mp. 8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp. 9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

(Continued)

10. RIVAROXABAN/

11. DABIGATRAN/

12. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp Neoplasms/

15. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

16. 14 or 15

17. 13 and 16

18. randomized controlled trial.pt.

19. controlled clinical trial.pt.

20. randomized.ab.

21. placebo.ab.

22. clinical trials as topic.sh.

23. randomly.ab.

24. trial.ti.

25. 18 or 19 or 20 or 21 or 22 or 23 or 24

26. (animals not (humans and animals)).sh.

27. 25 not 26

28. 17 and 27

Systematic Review search strategy:

1. exp Anticoagulants/

2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane 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 danaparoid or organ or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

4. exp Coumarins/

5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or

(Continued)

Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.

6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

7. (thrombin adj inhibitor*).mp.

8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. RIVAROXABAN/

11. DABIGATRAN/

12. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp Neoplasms/

15. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

16. 14 or 15

17. 13 and 16

18. (review or review,tutorial or review, academic).pt.

19. (medline or medlars or embase or pubmed or cochrane).tw,sh.

20. (scisearch or psychinfo or psycinfo).tw,sh.

21. (psychlit or psyclit).tw,sh.

22. cinahl.tw,sh.

23. ((hand adj2 search*) or (manual* adj2 search*)).tw,sh.

24. (electronic database* or bibliographic database* or computeri?ed database* or online database*).tw,sh.

25. (pooling or pooled or mantel haenszel).tw,sh.

26. (peto or dersimonian or der simonian or fixed effect).tw,sh.

27. (retraction of publication or retracted publication).pt.

28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. 18 and 28

30. meta-analysis.pt.

31. meta-analysis.sh.

32. (meta-analys* or meta analys* or metaanalys*).tw,sh.

(Continued)

	33. (systematic* adj5 review*).tw,sh. 34. (systematic* adj5 overview*).tw,sh. 35. (quantitativ* adj5 review*).tw,sh. 36. (quantitativ* adj5 overview*).tw,sh. 37. (methodologic* adj5 review*).tw,sh. 38. (methodologic* adj5 overview*).tw,sh. 39. (integrative research review* or research integration).tw. 40. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 41. 29 or 40 42. 17 and 41
Embase	**RCT search strategy:** 1. exp anticoagulant agent/ 2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane 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 danaparoid or orgaran or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp. 3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp. 4. exp coumarin derivative/ 5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp. 6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp. 7. (thrombin adj inhibitor*).mp. 8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp. 9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp. 10. rivaroxaban/ 11. dabigatran/

(Continued)

12. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp neoplasm/

15. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

16. 14 or 15

17. 13 and 16

18. crossover procedure/

19. double-blind procedure/

20. randomized controlled trial/

21. single-blind procedure/

22. random*.mp.

23. factorial*.mp.

24. (crossover* or cross over* or cross-over*).mp.

25. placebo*.mp.

26. (double* adj blind*).mp.

27. (singl* adj blind*).mp.

28. assign*.mp.

29. allocat*.mp.

30. volunteer*.mp.

31. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32. 17 and 31

Systematic Review search strategy:

1. exp anticoagulant agent/

2. (LMWH* or heparin* or nadroparin* or frixiparin* or enoxaparin* or clexane or klexane 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 danaparoid or organ or antixarin or bemiparin* or hibor or zibor or ivor or badyket or semuloparin or parnaparin or tedelparin or fluxum or lohepa or lowhepa or parvoparin or seleparin* or tedelgliparin or lomoparan or orgaran or sulodexide or zivor or embolex or xaparin or clivarine or fondaparinux or Arixtra or UFH or Hepalean or Calcilean or Calciparine or Liquaemin or Liquemin or Multiparin or Novoheparin or Eparina or Hep-lock or Heparinate or Heparinic acid or Panheprin or Hepalean or Heparin Leo or Heparin Lock).mp.

3. (FR-860 or FR 860 or FR860 or PK-10,169 or PK 10,169 or PK10,169 or PK-10169 or PK 10169 or PK10169 or EMT-967 or EMT 967 or EMT967 or EMT-966 or EMT 966 or EMT966 or CY 216 or CY-216 or CY216 or LMF CY-216 or LMF CY 216 or LMF CY216).mp.

4. exp coumarin derivative/

(Continued)

5. (4-Hydroxycoumarin* or warfarin* or acenocoumarol or nicoumalone or sinthrome or Sintrom or phenindione or dicoumarol or coumadin or phenprocoumon or phepromaron or ethyl-biscoumacetate or phenindione or Diphenadione or Tioclomarol or Racumi or Marcoumar or Marcumar or Falithrom or Jantoven or vitamin K antagonist* or VKA or fluindione or difenacoum or coumatetralyl).mp.

6. (Dermatan Sulfate or (Chondroitin Sulfate adj B) or Dermatan Sulfphate or DS 435 or MF-701 or OP-370 or b-Heparin or Mistral or Venorix).mp.

7. (thrombin adj inhibitor*).mp.

8. (factor Xa inhibitor* or antithrombin* or anticoagul*).mp.

9. (rivaroxaban or Xarelto or apixaban or Eliquis or dabigatran etexilate or Edoxaban or Savaysa or Betrixaban or ximelagatran or pradaxa or lixiana or exanta or Darexaban or Otamixaban* or Razaxaban or Bivalirudin or Desirudin or Lepirudin or Melagatran or YM 150 or Iprivask or argatrovan or pradax* or Xarelto or BIBR-953 or BIBR-953ZW or BAY 59-7939 or BMS-562247 or DU-176 or DU-176b).mp.

10. rivaroxaban/

11. dabigatran/

12. (target specific oral anticoagulant* or target-specific oral anticoagulant* or TSOAC* or new oral anticoagulant* or novel oral anticoagulant* or NOAC* or direct-acting oral anticoagulant* or direct acting oral anticoagulant* or direct oral anticoagulant* or DOAC*).ti,ab,kw.

13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14. exp neoplasm/

15. (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or glioma* or myeloma* or lymphoma* or leukemia* or leukaemia* or epithelioma* or adenoma*).tw.

16. 14 or 15

17. 13 and 16

18. exp review/

19. (literature adj3 review*).ti,ab.

20. exp meta analysis/

21. exp "Systematic Review"/

22. 18 or 19 or 20 or 21

23. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.

24. RETRACTED ARTICLE/

25. 23 or 24

26. 22 and 25

27. (systematic* adj2 (review* or overview)).ti,ab.

28. (meta?anal* or meta anal* or meta-anal* or metaanal* or metanal*).ti,ab.

29. 26 or 27 or 28

30. 17 and 29

Appendix 6. GRADE evidence profile: VKA versus no prophylaxis

Question: VKA prophylaxis compared to no prophylaxis in ambulatory people with cancer without VTE receiving systemic therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VKA prophylaxis	No prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 12 months)												
5	randomised trials	not serious	not serious	not serious	serious [a]	none	355/650 (54.6%)	362/631 (57.4%)	**RR 0.95** (0.87 to 1.03)	**29 fewer per 1,000** (from 17 more to 75 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
PE (follow up: 12 months)												
1	randomised trials	not serious	not serious	serious [b]	very serious [c]	none	1/152 (0.7%)	1/159 (0.6%)	**RR 1.05** (0.07 to 16.58)	**0 fewer per 1,000** (from 6 fewer to 98 more)	⊕◯◯◯ VERY LOW	CRITICAL
Symptomatic DVT (follow up: 12 months)												
1	randomised trials	not serious	not serious	not serious [d]	very serious [e]	none	0/152 (0.0%)	6/159 (3.8%)	**RR 0.08** (0.00 to 1.42)	**35 fewer per 1,000** (from -- to 16 more)	⊕⊕◯◯ LOW	CRITICAL
Major bleeding (follow up: 12 months)												
5	randomised trials	serious [f]	not serious	not serious	not serious	none	108/650 (16.6%)	35/631 (5.5%)	**RR 2.93** (1.86 to 4.62)	**107 more per 1,000** (from 48 more to 201 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Minor bleeding (follow up: 12 months)												
4	randomised trials	serious [g]	not serious	not serious	not serious	none	110/440 (25.0%)	33/423 (7.8%)	**RR 3.14** (1.85 to 5.32)	**167 more per 1,000** (from 66 more to 337 more)	⊕⊕⊕◯ MODERATE	CRITICAL
HRQoL - not reported												
-	-	-	-	-	-	-		-	CRITICAL			

CI: confidence interval; **DVT:** deep vein thrombosis; **HRQoL:** health-related quality of life; **PE:** pulmonary embolism; **RR:** risk ratio; **VKA:** vitamin K antagonist; **VTE:** venous thromboembolism.

Explanations

[a]Downgraded by one level due to concern about both risk of bias (lack of blinding in patients and personnel and unclear allocation concealment in 4 out of 5 studies) and imprecision (95% CI is consistent with the possibility for important benefit (75 per 1000 absolute reduction) and the possibility of important harm (17 per 1000 absolute increase), large event rate)

[b]Downgraded by one level due to indirectness. Levine 1994 used fixed dose of VKA instead of adjusted dose which is not representative of the current practice. This study was the only trial that reported on PE and symptomatic DVT.

[c]Downgraded by two levels due to very serious imprecision. 95% CI is consistent with the possibility for important benefit (6 per 1000 absolute reduction) and the possibility of important harm (98 per 1000 absolute increase), including only 2 events.

[d]Levine 1994 used fixed dose of VKA instead of adjusted dose which is not representative of the current practice. This study was the only trial that reported on PE and symptomatic DVT. We do not think that this indirectness has underestimated the effect on symptomatic DVT (RR 0.08)

[e]Downgraded by two levels due to very serious imprecision. Only 6 events among 311 participants.

[f]Downgraded by one level due to concern about risk of bias (lack of blinding in patients and personnel and unclear allocation concealment in 4 out of 5 studies)

[g]Downgraded by one level due to concern about risk of bias (lack of blinding in patients and personnel and unclear allocation concealment in 3 out of 4 studies)

Appendix 7. GRADE evidence profile: DOAC versus no prophylaxis

Question: DOAC prophylaxis compared to no prophylaxis in ambulatory people with cancer without VTE receiving systemic therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOAC prophylaxis	No prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 3 months)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	1/62 (1.6%)	2/30 (6.7%)	**RR 0.24** (0.02 to 2.56)	**51 fewer per 1,000** (from 65 fewer to 104 more)	⊕⊕◯◯ LOW	CRITICAL
PE (follow up: 3 months)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [c]	none	0/62 (0.0%)	1/30 (3.3%)	**RR 0.16** (0.01 to 3.91)	**28 fewer per 1,000** (from 33 fewer to 97 more)	⊕⊕◯◯ LOW	CRITICAL
Symptomatic DVT (follow up: 3 months)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [d]	none	0/62 (0.0%)	3/30 (10.0%)	**RR 0.07** (0.00 to 1.32)	**93 fewer per 1,000** (from -- to 32 more)	⊕⊕◯◯ LOW	CRITICAL
Major bleeding (follow up: 3 months)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [c]	none	0/62 (0.0%)	1/30 (3.3%)	**RR 0.16** (0.01 to 3.91)	**28 fewer per 1,000** (from 33 fewer to 97 more)	⊕⊕◯◯ LOW	CRITICAL
Minor bleeding (follow up: 3 months)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [e]	none	4/62 (6.5%)	0.0%	**RR 4.43** (0.25 to 79.68)	**0 fewer per 1,000** (from 0 fewer to 8 more)	⊕⊕◯◯ LOW	CRITICAL
HRQoL - not reported												
-	-	-	-	-	-	-		-	CRITICAL			

CI: confidence interval; **DOAC**: Direct Oral AntiCoagulant; **DVT:** deep vein thrombosis; **HRQoL:** health-related quality of life; **PE:** pulmonary embolism; **RR:** risk ratio; **VTE:** venous thromboembolism.

Explanations

[a]Concern due to unclear allocation concealment

[b]Downgraded by two levels due to very serious imprecision: 95% CI is consistent with the possibility for important benefit (65 per 1000 absolute reduction) and the possibility of important harm (104 per 1000 absolute increase), including only 3 events among 92 participants.

[c]Downgraded by two levels due to very serious imprecision: 95% CI is consistent with the possibility for important benefit (33 per 1000 absolute reduction) and the possibility of important harm (97 per 1000 absolute increase), including only 1 events among 92 participants.

[d]Downgraded by two levels due to very serious imprecision: Including only 3 events among 92 participants.

[e]Downgraded by two levels due to very serious imprecision: Including only 4 events among 92 participants.

Appendix 8. Detailed results of sensitivity analyses

Outcome	**Major bleeding** **VKA vs no VKA**
CCA effect estimate	RR 2.93 (95% CI 1.86 to 4.62)
Sensitivity analysis	
RI 1.5 $_{\text{intervention}}$ 1 $_{\text{control}}$	RR 2.86 (95% CI 2.03 to 4.04)
RI 2 $_{\text{intervention}}$ 1 $_{\text{control}}$	RR 2.83 (95% CI 2.00 to 3.99)
RI 3 $_{\text{intervention}}$ 1 $_{\text{control}}$	RR 2.77 (95% CI 1.97 to 3.90)
RI 5 $_{\text{intervention}}$ 1 $_{\text{control}}$	RR 2.70 (95% CI 1.92 to 3.79)

Outcome	**Minor bleeding** **VKA vs no VKA**
CCA effect estimate	RR 3.14 (95% CI 1.85 to 5.32)
Sensitivity analysis	
RI 1 $_{\text{intervention}}$ 1.5 $_{\text{control}}$	RR 3.05 (95% CI 1.90 to 4.91)
RI 1 $_{\text{intervention}}$ 2 $_{\text{control}}$	RR 3.02 (95% CI 1.91 to 4.80)
RI 1 $_{\text{intervention}}$ 3 $_{\text{control}}$	RR 2.97 (95% CI 1.92 to 4.61)
RI 1 $_{\text{intervention}}$ 5 $_{\text{control}}$	RR 2.89 (95% CI 1.96 to 4.27)
CCA: complete case analysis; CI: confidence interval; RI: relative incidence; RR: risk ratio; VKA: vitamin K antagonist.	

Appendix 9. Study eligibility for subgroup analysis

Study	Lung cancer			Non-lung cancer		
	Included people only with lung cancer	Included people with lung and non-lung cancer AND provided subgroup data for people with lung cancer	Included people with lung and non-lung cancer AND > 75% of people had lung cancer	Included people only with non-lung cancer	Included people with lung and non-lung cancer AND provided subgroup data for people with non-lung cancer	Included people with lung and non-lung cancer AND > 75% of people had non-lung cancer
Chahinian 1989	x	-	-	-	-	-
Levine 1994	-	-	-	x	-	-
Levine 2012	-	-	-	-	-	x
Maurer 1997	x	-	-	-	-	-
Stanford 1979	x	-	-	-	-	-
Zacharski 1984	-	x	-	-	x	-

WHAT'S NEW

Date	Event	Description
17 February 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2021 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.

HISTORY

Protocol first published: Issue 2, 2006
Review first published: Issue 2, 2007

Date	Event	Description
29 October 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 October 2020 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.

Date	Event	Description
17 June 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2020 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 March 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2020 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
2 January 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 November 2019 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
7 October 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 August 2019 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
9 July 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 June 2019 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
9 May 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 24 April 2019 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
25 February 2019	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 February 2019 (two potentially relevant studies identified but not yet completed). As such, results of all available included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date
29 November 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 November 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
2 October 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 September 2018 (no new studies found). As such, results of all included studies identified

Date	Event	Description
		have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
9 August 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 July 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
28 June 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 May 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
28 June 2018	Amended	Declaration of interest updated.
23 April 2018	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 14 March 2018 (no new studies found). As such, results of all included studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
14 December 2017	New citation required but conclusions have not changed	New citation, conclusions not changed.
14 December 2017	New search has been performed	Search updated to December 2017. One new study identified. Following Living Systematic Review approach.

CONTRIBUTIONS OF AUTHORS

LAK: searching for trials, full-text retrieval, screening, data extraction, data analysis, data interpretation, manuscript drafting, review co-ordination. MBH: full-text retrieval, screening, data extraction, manuscript drafting. IGT: screening, data extraction, manuscript drafting. CM: screening. MB: screening. VY: screening. IT: screening. FS: screening. HJS: protocol development, data interpretation, methodological expertise.EAA: protocol development, data analysis, data interpretation, manuscript drafting, methodological expertise, review co-ordination.

DECLARATIONS OF INTEREST

LAK: none known. MBH: none known. IGT: none known. CM: none known. MB: none known. VY: none known. IT: none known. FS: none known. HJS: panel member of the ASH VTE in cancer patients, Vice-Chair of the ASH VTE guidelines and played various leadership roles from 1999 until 2014 with ACCP VTE guidelines. EAA: served on the executive committee the American College of Clinical Pharmacy Antithrombotic Therapy Guidelines published in 2016.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK

  This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group

- American Society of Hematology, USA

  This project was supported by the American Society of Hematology

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update includes new sections relevant to living systematic reviews, which are included in the Methods and described in Appendix 1 and Appendix 2.

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