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Shorter or longer anticoagulation to prevent recurrent venous thromboembolism: systematic review and meta-analysis - Protocol

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Abstract

Introduction: Venous thromboembolism (VTE) is a major disease associated with both short term and long-term morbidity and mortality. Patients with a VTE provoked by surgery or immobilization are at low risk of recurrence and do not require long term anticoagulation; those with a VTE and metastatic cancer are at high risk of recurrence and require lifetime thromboprophylaxis. In those at intermediate risk of recurrence, it remains controversial whether prolonging anticoagulation and thus incurring treatment burden and bleeding risk is warranted. Methods and Analysis: We will conduct a systematic review and meta-analysis of RCTs enrolling patients with VTE at intermediate risk of recurrence and evaluating short term anticoagulation (12 weeks to 9 months initial therapy) versus longer term anticoagulation (at least 6 months additional anticoagulation beyond the course of treatment in the shorter arm). Anticoagulation could consist of vitamin K antagonists or new oral anticoagulants. Outcomes of interest include recurrent non-fatal thrombosis (deep venous thrombosis and pulmonary embolism), major non-fatal bleeding and mortality. We will systematically search CINAHL, EMBASE, MEDLINE and the Cochrane Central Registry of Controlled Trials. Teams of two reviewers will, independently and in duplicate, screen titles and abstracts and complete full text reviews to determine eligibility, and subsequently abstract data and assess risk of bias in eligible trials. We will conduct meta-analyses to establish the effect of short-term versus long-term anticoagulation on the outcomes of interest and evaluate confidence in estimates (quality of evidence) using the GRADE approach.
Ethics and dissemination: Our review will facilitate evidence-based management of patients with unprovoked or recurrent VTE. For purposes of privacy and confidentiality, the systematic review will be limited to studies with de-identified data. The study will be disseminated by peer-review publication and conference presentation.
Registration: PROSPERO (CRD42014007620

Keywords: VTE. Duration. Vitamin K antagonist. NOAC. RCT. Meta-analysis

ARTICLE FOCUS:

In patients who have suffered a venous thromboembolic event (VTE – deep venous thrombosis or pulmonary embolus) at intermediate risk of recurrence (unprovoked or recurrent VTE but not cancer) what is the relative impact of anticoagulation for 3 to 9 months versus indefinite anticoagulation.

KEY MESSAGE:

We will conduct a systematic review and meta-analysis of RCTs enrolling patients with VTE at intermediate risk of recurrence and evaluating short term anticoagulation (3 to 9 months initial therapy) versus longer term anticoagulation (at least 6 months additional anticoagulation beyond the course of treatment in the shorter arm). Anticoagulation could consist of vitamin K antagonists or new oral anticoagulants. Outcomes of interest will include recurrent non-fatal thrombosis (deep venous thrombosis and pulmonary embolism), major non-fatal bleeding and mortality

STRENGTHS AND LIMITATIONS OF THIS STUDY

The methods of the review are state-of-art, including explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assessing confidence in estimates of effect including independent duplicate assessment of risk of bias, precision, consistency, directness and publication bias. Our protocol represents a model for systematic review methods. Our results are likely to be limited by limitations in the primary studies.

Introduction

Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a major disease that results in considerable morbidity and mortality. Deep venous thrombosis or pulmonary embolism may occur in almost 2 in 1000 people each year and between 5% and 15% of people with untreated DVT may die from pulmonary embolism [1 2]. Thrombosis most commonly affects the deep veins of the lower limbs, but may affect other sites, including the upper limbs. Complications include pulmonary thromboembolism and post-thrombotic syndrome (PTS)[3].

Risk factors for VTE include immobility, surgery (particularly orthopedic), malignancy, pregnancy, older age, estrogen therapy, and inherited or acquired prothrombotic clotting disorders[4]. In many patients, DVT remains asymptomatic and resolves without complications.. DVTs of concern are those that become symptomatic and are responsible for morbidity and mortality[3]. Patients with extensive proximal DVT have a substantial risk of developing the post-thrombotic syndrome, particularly if there is an ipsilateral recurrence with further valve destruction [5]. The average rate of fatal recurrent VTE after anticoagulation is discontinued has been estimated at 0.3 per 100 patient-years[6]. Based on observational data [7 8], authors of the ninth iteration of the American College of Chest Physicians antithrombotic guidelines[9] estimated that in patients with unprovoked proximal DVT or PE the risk of recurrence in the first year after discontinuation of anticoagulation is 10% with a risk of 5% per year thereafter (i.e. 30% at 5 years).

A consensus exists regarding the need for anticoagulant treatment, usually with vitamin K antagonists (VKA) or with novel oral anticoagulants (NOAC) for patients with venous thromboembolism. Whereas clinicians agree on the need for 3 to 6 months of anticoagulation after the diagnosis of venous thromboembolism (VTE), opinions regarding optimal duration of secondary prophylaxis differ. Although the prevention of recurrence is certainly desirable, the risk of major bleeding, together with the burden of therapy and cost, makes long-term treatment potentially problematic.

The risk-to-benefit ratio is highly dependent of the risk of recurrence of VTE which differs according to the presence or absence of reversible predisposing factors, location of the thrombosis, patient age, the presence of comorbid conditions, and intrinsic predispositions to thrombosis (inherited and acquired thrombophilia disorders). Guidelines suggest that the risk of recurrence is sufficiently low after a DVT provoked by temporary immobilization or lower limb fracture that treatment beyond 6 months is not in these patients' best interest. Further, there is agreement that lifelong anticoagulation is warranted patients at highest risk of recurrence (i.e., patients with active metastatic cancer). The controversy regarding treatment beyond 6 months is restricted to those with intermediate risk [10 11]. These patients include those whose VTE was unprovoked or whose VTE, if provoked, has happened more than once (recurrent VTE).

To make optimal decisions, patients and clinicians need best evidence estimates of benefits and harms of short versus long-term anticoagulation. In the trials included in previous systematic reviews of this topic the anticoagulants administered were Vitamin K antagonists [12-15]. Recent randomized trials have evaluated longer and shorter administration of NOACs. Therefore, we will update a systematic review and meta-analysis of the relative benefits and harms of longer versus shorter periods of anticoagulation in patients at intermediate risk of recurrence. Our primary question will be the impact of indefinite anticoagulation versus discontinuing anticoagulation after 3 to 9 months on the outcomes of interest. By indefinite anticoagulation we mean continuing anticoagulation until changes in circumstances would mandate a discontinuation. For many such patients, we would anticipate lifetime anticoagulation.

Methods/design

Protocol and registration

Our protocol is registered on PROSPERO (CRD42014007620), http://www.crd.york.ac.uk/PROSPERO.

Issues in defining trial eligibility

Trials investigating the effect of prolonged anticoagulation on the risk of VTE recurrence vary in terms of the duration of anticoagulation in the shorter and longer duration arms. They also differ in the nature of populations enrolled. These differences create challenges in defining study eligibility criteria.

In defining eligibility criteria any systematic review faces tension between broad eligibility criteria, which enhance precision of effect estimates and generalizability of results, and narrow criteria, which decrease the risks of heterogeneity and of generating pooled estimates that are not applicable to the range of patients and interventions included. A reasonable strategy for dealing with this tension, which we will adopt, is to choose relatively broad but clinically plausible criteria and then explore possible sources of heterogeneity. Therefore, although standard shorter-term anticoagulation is up to 6 months, we are including trials in which the shorter-term arm received anticoagulation up to 9 months. For the longer-term arm, we will accept any trial in which the duration of treatment is at least six months longer than in the shorter-term arm. We will conduct subgroup analyses focusing on the duration of therapy in both the shorter and longer-term arms.

As we described in the background, the controversy regarding duration of anticoagulation is focused on patients in the intermediate risk category. Typically, these are patients with unprovoked VTE or recurrent VTE (provoked and unprovoked), but definitions might differ across trials. Thus, ideally, all patients included in the trials would fall into these risk groups. It would be inappropriate, however, to exclude trials in which most but not all patients fit this description. We will include any study in which, according to the definition used in the study at least 50% of patients fall into one of these risk groups. If there is appreciable heterogeneity in the proportion of patients in these risk categories we will conduct subgroup analyses based on this variability.

Eligibility criteria

Inclusion

Patients: Studies must include patients with DVT and/or PE in whom at least 50% have a first unprovoked (no apparent clinical risk factor [16] VTE, or a second or subsequent VTE (can be provoked or unprovoked) in the absence of cancer.

Intervention shorter duration treatment: Studies must include an arm in which patients are anticoagulated with either vitamin K antagonists or novel anticoagulants for at least 12 weeks, but no longer than 9 months.

Intervention longer duration of treatment: Studies must include an arm in which patients are anticoagulated with either vitamin K antagonists or novel anticoagulants for at least six months longer than in the shorter duration treatment arm.

Outcomes: Trials must report on at least one of the following outcomes: recurrent VTE, DVT, fatal and non-fatal pulmonary embolus confirmed by objective testing (for DVT, venography or ultrasonography; for PE radiological imaging including ventilation/perfusion scanning, CT pulmonary angiography, MRI, conventional angiography, or autopsy), fatal and non-fatal serious/important bleeding episodes, post thrombotic syndrome, quality of life and total mortality.

Type of study and design: We will include only randomized controlled trials (RCT). We will include two types of RCT designs. In one design, patients, at the outset of VTE, are randomized to shorter or longer anticoagulation. In the alternative design all patients undergo the short-course anticoagulation regimen. They are then randomized to stop anticoagulation or to a further period of anticoagulation. We will include studies in which patients undergo shorter-term treatment with an anticoagulant, most often VKA, and then receive a new anticoagulant versus placebo.

Exclusion:

We will exclude studies enrolling only pure populations of high-risk patients, such as those with protein S or C deficiency or pregnancy.

Information sources and search

We will screen all RCTs reviewed in the 9th iteration of the American College of Chest Physicians antithrombotic guidelines and then will conduct additional search from January 2011 forward, six months prior (to account for lag in indexing) to the date the comprehensive search on the topic for the 9th iteration ACCP antithrombotic guidelines. We will search OVID Medline, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL) and CINAHL with no language restriction. An experienced librarian (NB) developed a sensitive search strategy for this (**see Additional file 1**). We will scan the bibliographies of all systematic reviews and meta-analyses as well as all eligible primary studies for additional relevant articles.

Study selection

Following a calibration exercise, reviewers will work in pairs to screen, independently and in duplicate, titles and available abstracts of identified citations. We will acquire the full text publication of any article that either reviewer judges as potentially eligible. The same reviewer teams will, following a second calibration exercise, independently apply eligibility criteria to the full text of potentially eligible trials using standardized forms. They will resolve disagreements by consensus or, if a discrepancy remains, through discussion with an arbitrator (GHG).). We will measure inter-rater agreement for full text eligibility and assessment of risk of bias using the Kappa statistics. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.74 to reflect good agreement and 0.75 or more to reflect excellent agreement [17].

Data collection process and data items

Using pilot tested standardized forms (**see Additional file 2**) and following a calibration exercise, teams of two reviewers will extract data independently and in duplicate from each eligible study. Data abstracted will include details on the study methodology, participants, intervention, control, and all reported patient-important outcomes. For each outcome, we will record number of patients enrolled in each study arm, and the number of patients for whom final follow-up data is available, and the number of events in each study group.

Reviewers will resolve disagreements by discussion, and one arbitrator (GHG) will adjudicate unresolved disagreements. We will contact the authors of each study to clarify any issues of uncertainty in the data abstraction and to ensure that our abstraction is correct.

Reviewers will independently extract details of the anticoagulation regimens in both the shorter and longer duration arms. Outcomes will include death; cause-specific mortality (PE or bleeding); recurrent non-fatal VTE (DVT and pulmonary embolus) and non-fatal serious/important bleeding. We will document definitions of serious/important bleeding in each study.

Risk of bias in individual studies

Reviewers will assess risk of bias within each study with a modified Cochrane risk of bias instrument[18] which assesses the following key domains: randomization sequence generation; allocation concealment; blinding of participants, healthcare professionals, outcome assessors, data collectors, and data analysts; incomplete outcome data; selective outcome reporting; and other sources of bias which will include differential intensity of surveillance for VTE and bleeding in the short and long arms, and premature cessation of follow-up (for instance, no follow-up for bleeding in the short arm after a VTE and resumption of anticoagulation). We will consider as a criterion of risk of bias whether the investigators specify a total surveillance period equal in length for the longer and shorter arms (i.e., same follow-up period from the time of randomization) versus a total surveillance period that is different (e.g., same follow-up period from the time of stopping anticoagulation) or not specified. Reviewers will input response options of 'definitely yes', 'probably yes', 'probably no', and 'definitely no' for each of the domains, with 'definitely yes' and 'probably yes' ultimately assigned low risk of bias and 'definitely no' and 'probably no' assigned high risk of bias[19]. Reviewers will resolve disagreements by discussion, and one arbitrator (GHG) will adjudicate unresolved disagreements.

Meta-analysis and data synthesis

Data regarding VTE, serious/important bleeding, mortality and person-time at risk will be extracted by 2 independent reviewers using a standardized form, with adjudication by a third reviewer in cases of disagreement. Given our primary interest in short term versus indefinite anticoagulation, in studies with follow-up after discontinuation of anticoagulation in the long arm, we will try to identify events that occurred in either arm after the scheduled discontinuation of anticoagulation in the long arm. We will exclude such events in the primary analysis.

For each study, incidence rates in events per person-year at risk will be calculated for the outcomes of recurrent VTE and serious/important bleeding. We have chosen events per person-years rather than number of people with events to account for differential length of follow-up within individual studies and across studies, and the possibility of multiple events in a single

individual. When investigators do not report person-time data (either directly or indirectly through a Kaplan-Meier survival curve), the person-time of the interval will be estimated by multiplying the number of participants present at the beginning of the interval by the duration of the interval and subtracting person-time for events occurring within the interval. For this calculation we will assume that events will be equally likely throughout the interval unless data to the contrary are in the report.

Our estimates of study heterogeneity will be informed using the p-value for Chi^2 for heterogeneity, and the I^2 statistic where 0-40% may be unimportant heterogeneity, 30-60% moderate, 50-90% substantial and 75-100% considerable heterogeneity[44]. We will explore heterogeneity by conducting the five a priori subgroup analyses using a z-test to test for interaction[20].

Assessment of heterogeneity and subgroup analyses

We will explore heterogeneity using sub-group hypotheses, which apply to bleeding and VTE outcomes and mortality and are framed as effects in longer versus shorter duration anticoagulation. We postulate that larger reductions in thrombosis, and larger increases in bleeding, will occur in the following situations: i) when the shorter duration anticoagulation arm is three months or less versus longer than 3 months; ii) when the longer duration anticoagulation arm is more than 12 months longer than the shorter duration arm versus 12 months or less;; iii) studies in which the number of risk of bias domains judged as 'high risk' is greater than the median will have larger effects than studies in which that number is less than the median. iv) when therapy is a NOAC versus warfarin with target INR 2.0 or greater) versus warfarin lower boundary of target INR less than 2.0); v) when anticoagulation was continued until the end of the study or in which we can exclude events that occurred in either arm after timing of cessation of anticoagulation in the long arm versus follow-up continued after anticoagulant stopped and not possible to identify and exclude events that occurred after cessation of anticoagulation in the long arm.

Confidence in pooled estimates of effect

Two reviewers will, independently and in duplicate, assess the confidence in effect estimates for each outcome using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) rating system [21]. In the GRADE system of rating quality of evidence for each outcome, randomized trials begin as high quality evidence, but may be rated down by one or more of five categories of limitations[22]. The GRADE working group has provided detailed guidance regarding judgments for each of these criteria: (1) risk of bias[23], (2) inconsistency[24], (3) indirectness[25], (4) imprecision[26], and (5) publication bias[27].

For assessing the impact of loss to follow-up across studies, we will conduct sensitivity analyses making progressively more stringent assumptions regarding loss to follow-up in intervention and control groups. The extent to which point estimates and confidence intervals differ in these sensitivity analyses will determine whether we rate down for risk of bias[28].

We anticipate that "number of patients enrolled minus number of patients for whom final follow-up is available" may include: i. unexplained losses to follow-up (lost contact), ii. explained losses to follow-up (e.g., followed until patient moved), iii. Followed until they had a recurrent VTE (or lost to follow-up for other complications such as death, or bleeding from restarted anticoagulation).

With respect to precision, the GRADE guidance notes that meta-analyses of small trials can provide evidence of benefit with confidence intervals that appear to convincingly exclude no effect; however, the results of reviews of such studies have often been subsequently refuted by larger trials[26]. To address this potential concern in cases in which our meta-analysis suggests benefit but the sample size is less than the optimal information size (OIS; the number of patients generated by a conventional sample size calculation for a single trial) we will rate down the quality for imprecision. For the purposes of calculating the OIS we will assume, for binary variables a relative risk reduction or increase (delta) of 25%, an alpha of 0.05, and a beta of 0.20, and a median baseline risk from the available studies.

For each outcome we will assess publication bias by visually observing asymmetry of the funnel plot for each outcome. We will follow published guidance and conduct the funnel plot inquiry only for outcomes with 10 or more trials [27].

- After considering these reasons for rating down, reviewers will judge the overall confidence in estimates of effect for each outcome as follows:
- 'high' quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect);
- 'moderate' quality of evidence (we are moderately confident in the effect estimate and 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' quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and
- 'very low' quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) [22].

Again, we will follow GRADE guidance for overall confidence ratings [29].

For both individual domains and overall confidence, if raters disagree they will try to resolve by consensus and, if not successful, the final judgment will be made by an independent reviewer (GHG).

Presentation of Results

We will present the results of our meta-analyses in an Evidence Profile that will provide a succinct, easily digestible presentation of quality of evidence and magnitude of effects [30]. Our Evidence Profile will be constructed to include the following elements:

1. A measure of the typical burden of these outcomes (e.g. control group, estimated risk; if appropriate studies are available we will use the baseline risk for population-based observational studies);
2. A measure of the difference between the risks with and without intervention
3. The relative magnitude of effect;

4. Numbers of participants and studies addressing these outcomes;
5. A rating of the overall confidence in estimate of effect for each outcome and any reasons for rating down the confidence

Discussion

The decision to continue anticoagulant treatment in patients with VTE at moderate risk of recurrence beyond the first few months is based on the patients' and treating physician's perception of the benefits and harms. The risks of recurrent VTE and bleeding associated with different lengths of vitamin K antagonist treatment have been evaluated in several studies that randomly allocated patients with venous thromboembolism to receive different lengths of treatment. These studies, subsequently summarized in systematic reviews, were modest in number and of relatively small sample size. Since these studies were completed, new trials have compared shorter and longer duration of treatment with novel anticoagulants. Since the impact of the these newer agents on both thrombosis and bleeding is similar to that of warfarin, by including these studies in a new systematic review, we will be able to increase precision and narrow confidence intervals, allowing an improved estimate of effects on thrombosis and bleeding.

Our protocol represents a model for systematic review methods. We have planned standard methods that yield credible results, including explicit eligibility criteria, a comprehensive search, and duplicate assessment of eligibility and risk of bias. We have also planned implementation of methods seldom (a priori hypotheses to explain possible effect modification, including specification of direction of effect) or very seldom (use of the GRADE approach to rating confidence in estimates of effect) implemented in current systematic reviews.

Our review presents several unique challenges. One involves the specification of the study question, and the implications of that specification. Relevant studies used two different designs: short versus longer anticoagulation in which patients in the long arm continued anticoagulation until the end of the study, and short versus fixed longer anticoagulation with continued follow-up after anticoagulation was discontinued. We have decided we are interested in the relative impact of short versus indefinite - rather than fixed longer duration - anticoagulation. This will require

exclusion of events in the latter study design that occurred - in both short and long arms - after the end of the longer arm planned anticoagulation.

In conclusion, patients and clinicians choosing between limited and indefinite duration of anticoagulation after VTE deserve access to best estimates of effect derived from the complete current literature. Our review will provide these estimates.

Ethics and dissemination

For purposes of privacy and confidentiality, the systematic review will be limited to studies with de-identified data. The study will be disseminated by peer-review publication and conference presentation.

Competing interests

John Eikelboom has taken the position that anticoagulation should not be used long-term in the patient population of interest and has tested aspirin in this context. Schulman is director of an Anticoagulation Clinic. Clive Kearon led the development of American College of Chest Physicians antithrombotic guidelines addressing anticoagulants use in this population and Gordon Guyatt edited the 9th edition of these guidelines.

Authors' contributions

LCL, GHG, JE, SS, FS, CK and EA conceived the study design. NB and IN designed the database-specific literature search strategies. GHG and LCL completed the first draft of the manuscript. All authors reviewed several drafts of the manuscript and approved the final version.

Acknowledgements

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List of abbreviations

Venous thromboembolism (VTE)

Randomized controlled Trials (RCTs)

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

novel oral anticoagulants (NOAC)

pulmonary embolism (PE)

deep-vein thrombosis (DVT)

vitamin K antagonists (VKA)

optimal information size (OIS)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12, 13

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10, 11, 12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	--
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	---
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	--
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	--
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	--
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	--
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	--
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	--
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	--
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Coumarins/

2 (coumarin$ or chromonar or coumestrol or esculin or isocoumarin$ or psoralen? or pyranocoumarin* or umbelliferone*).mp.

3 warfarin.mp. or Warfarin/ or warfant.mp.

4 (coumadine or warfant or coumadin or marevan or aldocumar or tedicumar).mp.

5 Acenocoumarol/ or acenocoumarol*.mp.

6 (Pradaxa or Dabigatran).mp.

7 (Rivaroxaban or Xarelto).mp.

8 ((vitamin k adj3 antagonis*) or antivitamin K).mp.

9 vitamin k/ai

10 (vk adj2 antagonis*).mp.

11 (endosaban or apixaban).mp.

12 BAY 59-7939.mp.

13 (BMS-562247 or edoxaban or DU-176b or betrixaban).mp.

14 YM150.mp.

15 TAK-442.mp.

16 LY517717.mp.

17 PD0348292.mp.

18 (VKA or VKAs).mp.

19 (NOACs or noac).mp.

20 (DOACs or doac).mp.

21 ((new or novel or direct) adj4 (oral anticoag* or oral anti coag*)).mp.

22 ((novel or new) adj2 (anticoag: or anti coag:)).mp.

23 or/1-22

24 thrombosis.mp. or exp Thrombosis/

25 exp Venous Thromboembolism/ or exp Thromboembolism/ or Thromboembolism*.mp.

26 (pulmonary adj3 embolism*).mp. or exp Pulmonary Embolism/ or (lung adj3 embolism*).mp.

27 (PE or DVT or VTE).mp.

28 ((vein* or ven*) adj2 thromb*).mp.

29 (thrombu* or thrombotic* or thrombolic* or thromboemb* or thrombo* or embol*).mp.

30 or/24-29

31 randomized controlled trial.pt.

32 random allocation/

33 double-blind method/
34 single-blind method/
35 randomi?ed controlled trial$.mp.
36 Randomi?ed clinical trial$.mp.
37 controlled clinical trial.pt.
38 ((singl$ or double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
39 random$.mp.
40 placebo$.mp.
41 cross-over studies.sh.
42 latin square:.tw.
43 or/31-42
44 animals/ not humans/
45 43 not 44
46 23 and 30 and 45
47 (2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014*).em,ed,dc.
48 46 and 47

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BMJ Open

Shorter or longer anticoagulation to prevent recurrent venous thromboembolism: systematic review and meta-analysis - Protocol

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Shorter or longer anticoagulation to prevent recurrent venous thromboembolism: systematic review and meta-analysis - Protocol

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Abstract

Introduction: Venous thromboembolism (VTE) is a major disease associated with both short term and long-term morbidity and mortality. Patients with a VTE provoked by surgery or immobilization are at low risk of recurrence and do not require long term anticoagulation; those with a VTE and metastatic cancer are at high risk of recurrence and require lifetime thromboprophylaxis. In those at intermediate risk of recurrence, it remains controversial whether prolonging anticoagulation and thus incurring treatment burden and bleeding risk is warranted.

Methods and Analysis: We will conduct a systematic review and meta-analysis of RCTs enrolling patients with VTE at intermediate risk of recurrence and evaluating short term anticoagulation (12 weeks to 9 months initial therapy) *versu*s longer term anticoagulation (at least 6 months additional anticoagulation beyond the course of treatment in the shorter arm). Anticoagulation could consist of vitamin K antagonists or new oral anticoagulants. Outcomes of interest include recurrent non-fatal thrombosis (deep venous thrombosis and pulmonary embolism), major non-fatal bleeding and mortality. We will systematically search CINAHL, EMBASE, MEDLINE and the Cochrane Central Registry of Controlled Trials. Teams of two reviewers will, independently and in duplicate, screen titles and abstracts and complete full text reviews to determine eligibility, and subsequently abstract data and assess risk of bias in eligible trials. We will conduct meta-analyses to establish the effect of short-term versus long-term anticoagulation on the outcomes of interest and evaluate confidence in estimates (quality of evidence) using the GRADE approach.

Ethics and dissemination: Our review will facilitate evidence-based management of patients with unprovoked or recurrent VTE. For purposes of privacy and confidentiality, the systematic review will be limited to studies with de-identified data. The study will be disseminated by peer-review publication and conference presentation.

Registration: PROSPERO (CRD42014007620

Keywords: VTE. Duration. Vitamin K antagonist. NOAC. RCT. Meta-analysis

ARTICLE FOCUS:

In patients who have suffered a venous thromboembolic event (VTE – deep venous thrombosis or pulmonary embolus) at intermediate risk of recurrence (unprovoked or recurrent VTE but not cancer) what is the relative impact of anticoagulation for 3 to 9 months versus indefinite anticoagulation.

KEY MESSAGE:

We will conduct a systematic review and meta-analysis of RCTs enrolling patients with VTE at intermediate risk of recurrence and evaluating short term anticoagulation (3 to 9 months initial therapy) versus longer term anticoagulation (at least 6 months additional anticoagulation beyond the course of treatment in the shorter arm). Anticoagulation could consist of vitamin K antagonists or new oral anticoagulants. Outcomes of interest will include recurrent non-fatal thrombosis (deep venous thrombosis and pulmonary embolism), major non-fatal bleeding and mortality

STRENGTHS AND LIMITATIONS OF THIS STUDY

The methods of the review are state-of-art, including explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assessing confidence in estimates of effect including independent duplicate assessment of risk of bias, precision, consistency, directness and publication bias. Our protocol represents a model for systematic review methods. Our results are likely to be limited by limitations in the primary studies.

Introduction

Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a major disease that results in considerable morbidity and mortality. Deep venous thrombosis or pulmonary embolism may occur in almost 2 in 1000 people each year and between 5% and 15% of people with untreated DVT may die from pulmonary embolism [1 2]. Thrombosis most commonly affects the deep veins of the lower limbs, but may affect other sites, including the upper limbs. Complications include pulmonary thromboembolism and post-thrombotic syndrome (PTS)[3].

Risk factors for VTE include immobility, surgery (particularly orthopedic), malignancy, pregnancy, older age, estrogen therapy, and inherited or acquired prothrombotic clotting disorders[4]. In many patients, DVT remains asymptomatic and resolves without complications.. DVTs of concern are those that become symptomatic and are responsible for morbidity and mortality[3]. Patients with extensive proximal DVT have a substantial risk of developing the post-thrombotic syndrome, particularly if there is an ipsilateral recurrence with further valve destruction [5]. The average rate of fatal recurrent VTE after anticoagulation is discontinued has been estimated at 0.3 per 100 patient-years[6]. Based on observational data [7 8], authors of the ninth iteration of the American College of Chest Physicians antithrombotic guidelines[9] estimated that in patients with unprovoked proximal DVT or PE the risk of recurrence in the first year after discontinuation of anticoagulation is 10% with a risk of 5% per year thereafter (i.e. 30% at 5 years).

A consensus exists regarding the need for anticoagulant treatment, usually with vitamin K antagonists (VKA) or with novel oral anticoagulants (NOAC) for patients with venous thromboembolism. Whereas clinicians agree on the need for 3 to 6 months of anticoagulation after the diagnosis of venous thromboembolism (VTE), opinions regarding optimal duration of secondary prophylaxis differ. Although the prevention of recurrence is certainly desirable, the risk of major bleeding, together with the burden of therapy and cost, makes long-term treatment potentially problematic.

The risk-to-benefit ratio is highly dependent of the risk of recurrence of VTE which differs according to the presence or absence of reversible predisposing factors, location of the thrombosis, patient age, the presence of comorbid conditions, and intrinsic predispositions to thrombosis (inherited and acquired thrombophilia disorders). Guidelines suggest that the risk of recurrence is sufficiently low after a DVT provoked by temporary immobilization or lower limb fracture that treatment beyond 6 months is not in these patients' best interest. Further, there is agreement that lifelong anticoagulation is warranted patients at highest risk of recurrence (i.e., patients with active metastatic cancer). The controversy regarding treatment beyond 6 months is restricted to those with intermediate risk [10 11]. These patients include those whose VTE was unprovoked or whose VTE, if provoked, has happened more than once (recurrent VTE).

To make optimal decisions, patients and clinicians need best evidence estimates of benefits and harms of short versus long-term anticoagulation. In the trials included in previous systematic reviews of this topic the anticoagulants administered were Vitamin K antagonists [12-15]. Recent randomized trials have evaluated longer and shorter administration of NOACs. Therefore, we will update a systematic review and meta-analysis of the relative benefits and harms of longer versus shorter periods of anticoagulation in patients at intermediate risk of recurrence. Our primary question will be the impact of indefinite anticoagulation versus discontinuing anticoagulation after 3 to 9 months on the outcomes of interest. By indefinite anticoagulation we mean continuing anticoagulation until changes in circumstances would mandate a discontinuation. For many such patients, we would anticipate lifetime anticoagulation.

Methods/design

Protocol and registration

Our protocol is registered on PROSPERO (CRD42014007620), http://www.crd.york.ac.uk/PROSPERO.

Issues in defining trial eligibility

Trials investigating the effect of prolonged anticoagulation on the risk of VTE recurrence vary in terms of the duration of anticoagulation in the shorter and longer duration arms. They also differ in the nature of populations enrolled. These differences create challenges in defining study eligibility criteria.

In defining eligibility criteria any systematic review faces tension between broad eligibility criteria, which enhance precision of effect estimates and generalizability of results, and narrow criteria, which decrease the risks of heterogeneity and of generating pooled estimates that are not applicable to the range of patients and interventions included. A reasonable strategy for dealing with this tension, which we will adopt, is to choose relatively broad but clinically plausible criteria and then explore possible sources of heterogeneity. Therefore, although standard shorter-term anticoagulation is up to 6 months, we are including trials in which the shorter-term arm received anticoagulation up to 9 months. For the longer-term arm, we will accept any trial in which the duration of treatment is at least six months longer than in the shorter-term arm. We will conduct subgroup analyses focusing on the duration of therapy in both the shorter and longer-term arms.

As we described in the background, the controversy regarding duration of anticoagulation is focused on patients in the intermediate risk category. Typically, these are patients with unprovoked VTE or recurrent VTE (provoked and unprovoked), but definitions might differ across trials. Thus, ideally, all patients included in the trials would fall into these risk groups. It would be inappropriate, however, to exclude trials in which most but not all patients fit this description. We will include any study in which, according to the definition used in the study at least 50% of patients fall into one of these risk groups. If there is appreciable heterogeneity in the proportion of patients in these risk categories we will conduct subgroup analyses based on this variability.

Eligibility criteria

Inclusion

Patients: Studies must include patients with DVT and/or PE in whom at least 50% have a first unprovoked (no apparent clinical risk factor [16] VTE, or a second or subsequent VTE (can be provoked or unprovoked) in the absence of cancer.

Intervention shorter duration treatment: Studies must include an arm in which patients are anticoagulated with either vitamin K antagonists or novel anticoagulants for at least 12 weeks, but no longer than 9 months.

Intervention longer duration of treatment: Studies must include an arm in which patients are anticoagulated with either vitamin K antagonists or novel anticoagulants for at least six months longer than in the shorter duration treatment arm.

Outcomes: Trials must report on at least one of the following outcomes: recurrent VTE, DVT, fatal and non-fatal pulmonary embolus confirmed by objective testing (for DVT, venography or ultrasonography; for PE radiological imaging including ventilation/perfusion scanning, CT pulmonary angiography, MRI, conventional angiography, or autopsy), fatal and non-fatal serious/important bleeding episodes, post thrombotic syndrome, quality of life and total mortality.

Type of study and design: We will include only randomized controlled trials (RCT). We will include two types of RCT designs. In one design, patients, at the outset of VTE, are randomized to shorter or longer anticoagulation. In the alternative design all patients undergo the short-course anticoagulation regimen. They are then randomized to stop anticoagulation or to a further period of anticoagulation. We will include studies in which patients undergo shorter-term treatment with an anticoagulant, most often VKA, and then receive a new anticoagulant versus placebo.

Exclusion:

We will exclude studies enrolling only pure populations of high-risk patients, such as those with protein S or C deficiency or anti-phospholipid antibody or antiphospholipid antibody syndrome.

Information sources and search

We will screen all RCTs reviewed in the 9th iteration of the American College of Chest Physicians antithrombotic guidelines and then will conduct additional search from January 2011 forward, six months prior (to account for lag in indexing) to the date the comprehensive search on the topic for the 9th iteration ACCP antithrombotic guidelines. We will search OVID Medline, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL) and CINAHL with no language restriction. An experienced librarian (NB) developed a sensitive search strategy for this (**see** Appendix 1). We will scan the bibliographies of all systematic reviews and meta-analyses as well as all eligible primary studies for additional relevant articles.

Study selection

Following a calibration exercise, reviewers will work in pairs to screen, independently and in duplicate, titles and available abstracts of identified citations. We will acquire the full text publication of any article that either reviewer judges as potentially eligible. The same reviewer teams will, following a second calibration exercise, independently apply eligibility criteria to the full text of potentially eligible trials using standardized forms. They will resolve disagreements by consensus or, if a discrepancy remains, through discussion with an arbitrator (GHG).). We will measure inter-rater agreement for full text eligibility and assessment of risk of bias using the Kappa statistics. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.74 to reflect good agreement and 0.75 or more to reflect excellent agreement [17].

Data collection process and data items

Using pilot tested standardized forms and following a calibration exercise, teams of two reviewers will extract data independently and in duplicate from each eligible study. Data abstracted will include details on the study methodology, participants, intervention, control, and all reported patient-important outcomes. For each outcome, we will record number of patients enrolled in each study arm, and the number of patients for whom final follow-up data is available, and the number of events in each study group.

Reviewers will resolve disagreements by discussion, and one arbitrator (GHG) will adjudicate unresolved disagreements. We will contact the authors of each study to clarify any issues of uncertainty in the data abstraction and to ensure that our abstraction is correct.

Reviewers will independently extract details of the anticoagulation regimens in both the shorter and longer duration arms. Outcomes will include death; cause-specific mortality (PE or bleeding); recurrent non-fatal VTE (DVT and pulmonary embolus) and non-fatal serious/important bleeding. We will document definitions of serious/important bleeding in each study.

Risk of bias in individual studies

Reviewers will assess risk of bias within each study with a modified Cochrane risk of bias instrument[18] which assesses the following key domains: randomization sequence generation; allocation concealment; blinding of participants, healthcare professionals, outcome assessors, data collectors, and data analysts; incomplete outcome data; selective outcome reporting; and other sources of bias which will include differential intensity of surveillance for VTE and bleeding in the short and long arms, and premature cessation of follow-up (for instance, no follow-up for bleeding in the short arm after a VTE and resumption of anticoagulation). We will consider as a criterion of risk of bias whether the investigators specify a total surveillance period equal in length for the longer and shorter arms (i.e., same follow-up period from the time of randomization) versus a total surveillance period that is different (e.g., same follow-up period from the time of stopping anticoagulation) or not specified. Reviewers will input response options of 'definitely yes', 'probably yes', 'probably no', and 'definitely no' for each of the domains, with 'definitely yes' and 'probably yes' ultimately assigned low risk of bias and 'definitely no' and 'probably no' assigned high risk of bias[19]. Reviewers will resolve disagreements by discussion, and one arbitrator (GHG) will adjudicate unresolved disagreements.

Meta-analysis and data synthesis

Data regarding VTE, serious/important bleeding, mortality and person-time at risk will be extracted by 2 independent reviewers using a standardized form, with adjudication by a third reviewer in cases of disagreement. Given our primary interest in short term versus indefinite anticoagulation, in studies with follow-up after discontinuation of anticoagulation in the long arm, we will try to identify events that occurred in either arm after the scheduled discontinuation of anticoagulation in the long arm. We will exclude such events in the primary analysis.

For each study, incidence rates in events per person-year at risk will be calculated for the outcomes of recurrent VTE and serious/important bleeding. We have chosen events per person-years rather than number of people with events to account for differential length of follow-up within individual studies and across studies, and the possibility of multiple events in a single

individual. When investigators do not report person-time data (either directly or indirectly through a Kaplan-Meier survival curve), the person-time of the interval will be estimated by multiplying the number of participants present at the beginning of the interval by the duration of the interval and subtracting person-time for events occurring within the interval. For this calculation we will assume that events will be equally likely throughout the interval unless data to the contrary are in the report.

Our estimates of study heterogeneity will be informed using the p-value for Chi^2 for heterogeneity, and the I^2 statistic where 0-40% may be unimportant heterogeneity, 30-60% moderate, 50-90% substantial and 75-100% considerable heterogeneity[44]. We will explore heterogeneity by conducting the five a priori subgroup analyses using a z-test to test for interaction[20].

Assessment of heterogeneity and subgroup analyses

We will explore heterogeneity using sub-group hypotheses, which apply to bleeding and VTE outcomes and mortality and are framed as effects in longer versus shorter duration anticoagulation. We postulate that larger reductions in thrombosis, and larger increases in bleeding, will occur in the following situations: i) when the shorter duration anticoagulation arm is three months or less versus longer than 3 months; ii) when the longer duration anticoagulation arm is more than 12 months longer than the shorter duration arm versus 12 months or less;; iii) studies in which the number of risk of bias domains judged as 'high risk' is greater than the median will have larger effects than studies in which that number is less than the median. iv) when therapy is a NOAC versus warfarin with target INR 2.0 or greater) versus warfarin lower boundary of target INR less than 2.0); v) when anticoagulation was continued until the end of the study or in which we can exclude events that occurred in either arm after timing of cessation of anticoagulation in the long arm versus follow-up continued after anticoagulant stopped and not possible to identify and exclude events that occurred after cessation of anticoagulation in the long arm.

Confidence in pooled estimates of effect

Two reviewers will, independently and in duplicate, assess the confidence in effect estimates for each outcome using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) rating system [21]. In the GRADE system of rating quality of evidence for each outcome, randomized trials begin as high quality evidence, but may be rated down by one or more of five categories of limitations[22]. The GRADE working group has provided detailed guidance regarding judgments for each of these criteria: (1) risk of bias[23], (2) inconsistency[24], (3) indirectness[25], (4) imprecision[26], and (5) publication bias[27].

For assessing the impact of loss to follow-up across studies, we will conduct sensitivity analyses making progressively more stringent assumptions regarding loss to follow-up in intervention and control groups. The extent to which point estimates and confidence intervals differ in these sensitivity analyses will determine whether we rate down for risk of bias[28].

We anticipate that "number of patients enrolled minus number of patients for whom final follow-up is available" may include: i. unexplained losses to follow-up (lost contact), ii. explained losses to follow-up (e.g., followed until patient moved), iii. Followed until they had a recurrent VTE (or lost to follow-up for other complications such as death, or bleeding from restarted anticoagulation).

With respect to precision, the GRADE guidance notes that meta-analyses of small trials can provide evidence of benefit with confidence intervals that appear to convincingly exclude no effect; however, the results of reviews of such studies have often been subsequently refuted by larger trials[26]. To address this potential concern in cases in which our meta-analysis suggests benefit but the sample size is less than the optimal information size (OIS; the number of patients generated by a conventional sample size calculation for a single trial) we will rate down the quality for imprecision. For the purposes of calculating the OIS we will assume, for binary variables a relative risk reduction or increase (delta) of 25%, an alpha of 0.05, and a beta of 0.20, and a median baseline risk from the available studies.

For each outcome we will assess publication bias by visually observing asymmetry of the funnel plot for each outcome. We will follow published guidance and conduct the funnel plot inquiry only for outcomes with 10 or more trials [27].

- After considering these reasons for rating down, reviewers will judge the overall confidence in estimates of effect for each outcome as follows:
- 'high' quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect);
- 'moderate' quality of evidence (we are moderately confident in the effect estimate and 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' quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and
- 'very low' quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) [22].

Again, we will follow GRADE guidance for overall confidence ratings [29].

For both individual domains and overall confidence, if raters disagree they will try to resolve by consensus and, if not successful, the final judgment will be made by an independent reviewer (GHG).

Presentation of Results

We will present the results of our meta-analyses in an Evidence Profile that will provide a succinct, easily digestible presentation of quality of evidence and magnitude of effects [30]. Our Evidence Profile will be constructed to include the following elements:

1. A measure of the typical burden of these outcomes (e.g. control group, estimated risk; if appropriate studies are available we will use the baseline risk for population-based observational studies);
2. A measure of the difference between the risks with and without intervention
3. The relative magnitude of effect;

4. Numbers of participants and studies addressing these outcomes;
5. A rating of the overall confidence in estimate of effect for each outcome and any reasons for rating down the confidence

Discussion

The decision to continue anticoagulant treatment in patients with VTE at moderate risk of recurrence beyond the first few months is based on the patients' and treating physician's perception of the benefits and harms. The risks of recurrent VTE and bleeding associated with different lengths of vitamin K antagonist treatment have been evaluated in several studies that randomly allocated patients with venous thromboembolism to receive different lengths of treatment. These studies, subsequently summarized in systematic reviews, were modest in number and of relatively small sample size. Since these studies were completed, new trials have compared shorter and longer duration of treatment with novel anticoagulants. Since the impact of the these newer agents on both thrombosis and bleeding is similar to that of warfarin, by including these studies in a new systematic review, we will be able to increase precision and narrow confidence intervals, allowing an improved estimate of effects on thrombosis and bleeding.

Our protocol represents a model for systematic review methods. We have planned standard methods that yield credible results, including explicit eligibility criteria, a comprehensive search, and duplicate assessment of eligibility and risk of bias. We have also planned implementation of methods seldom (a priori hypotheses to explain possible effect modification, including specification of direction of effect) or very seldom (use of the GRADE approach to rating confidence in estimates of effect) implemented in current systematic reviews.

Our review presents several unique challenges. One involves the specification of the study question, and the implications of that specification. Relevant studies used two different designs: short versus longer anticoagulation in which patients in the long arm continued anticoagulation until the end of the study, and short versus fixed longer anticoagulation with continued follow-up after anticoagulation was discontinued. We have decided we are interested in the relative impact of short versus indefinite - rather than fixed longer duration - anticoagulation. This will require

exclusion of events in the latter study design that occurred - in both short and long arms - after the end of the longer arm planned anticoagulation. Reported data may limit our ability to carry out this exclusion as would be optimal.

Our study is likely to be limited by other aspects of study design and reporting of the primary studies. In particular, though we are interested in the impact of indefinite versus limited anticoagulation, studies will have limited follow-up, often 2 to 3 years. Both bleeding and event rates in the second and third years will, however, provide a useful estimate of what is liable to happen in subsequent years. Another important limitation is that we will not have access to individual patient data and therefore subgroup analysis and inferences will be limited.

In conclusion, patients and clinicians choosing between limited and indefinite duration of anticoagulation after VTE deserve access to best estimates of effect derived from the complete current literature. Our review will provide these estimates.

Acknowledgements

Dr Kearon is supported by the Jack Hirsh Professorship in Thromboembolism and an Investigator Award from the Heart and Stroke Foundation of Ontario.

Competing interests

John Eikelboom has taken the position that anticoagulation should not be used long-term in the patient population of interest and has tested aspirin in this context. Schulman is director of an Anticoagulation Clinic. Clive Kearon led the development of American College of Chest Physicians antithrombotic guidelines addressing anticoagulants use in this population and Gordon Guyatt edited the 9th edition of these guidelines.

Authors' contributions

LCL, GHG, JE, SS, FS, CK and EA conceived the study design. NB and IN designed the database-specific literature search strategies. GHG and LCL completed the first draft of the manuscript. All authors reviewed several drafts of the manuscript and approved the final version.

List of abbreviations

Venous thromboembolism (VTE)

Randomized controlled Trials (RCTs)

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

novel oral anticoagulants (NOAC)

pulmonary embolism (PE)

deep-vein thrombosis (DVT)

vitamin K antagonists (VKA)

optimal information size (OIS)

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Shorter or longer anticoagulation to prevent recurrent venous thromboembolism: systematic review and meta-analysis - Protocol

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Abstract

Introduction: Venous thromboembolism (VTE) is a major disease associated with both short term and long-term morbidity and mortality. Patients with a VTE provoked by surgery or immobilization are at low risk of recurrence and do not require long term anticoagulation; those with a VTE and metastatic cancer are at high risk of recurrence and require lifetime thromboprophylaxis. In those at intermediate risk of recurrence, it remains controversial whether prolonging anticoagulation and thus incurring treatment burden and bleeding risk is warranted.

Methods and Analysis: We will conduct a systematic review and meta-analysis of RCTs enrolling patients with VTE at intermediate risk of recurrence and evaluating short term anticoagulation (12 weeks to 9 months initial therapy) *versu*s longer term anticoagulation (at least 6 months additional anticoagulation beyond the course of treatment in the shorter arm). Anticoagulation could consist of vitamin K antagonists or new oral anticoagulants. Outcomes of interest include recurrent non-fatal thrombosis (deep venous thrombosis and pulmonary embolism), major non-fatal bleeding and mortality. We will systematically search CINAHL, EMBASE, MEDLINE and the Cochrane Central Registry of Controlled Trials. Teams of two reviewers will, independently and in duplicate, screen titles and abstracts and complete full text reviews to determine eligibility, and subsequently abstract data and assess risk of bias in eligible trials. We will conduct meta-analyses to establish the effect of short-term versus long-term anticoagulation on the outcomes of interest and evaluate confidence in estimates (quality of evidence) using the GRADE approach.

Ethics and dissemination: Our review will facilitate evidence-based management of patients with unprovoked or recurrent VTE. For purposes of privacy and confidentiality, the systematic review will be limited to studies with de-identified data. The study will be disseminated by peer-review publication and conference presentation.

Registration: PROSPERO (CRD42014007620

Keywords: VTE. Duration. Vitamin K antagonist. NOAC. RCT. Meta-analysis

ARTICLE FOCUS:

In patients who have suffered a venous thromboembolic event (VTE – deep venous thrombosis or pulmonary embolus) at intermediate risk of recurrence (unprovoked or recurrent VTE but not cancer) what is the relative impact of anticoagulation for 3 to 9 months versus indefinite anticoagulation.

KEY MESSAGE:

We will conduct a systematic review and meta-analysis of RCTs enrolling patients with VTE at intermediate risk of recurrence and evaluating short term anticoagulation (3 to 9 months initial therapy) versus longer term anticoagulation (at least 6 months additional anticoagulation beyond the course of treatment in the shorter arm). Anticoagulation could consist of vitamin K antagonists or new oral anticoagulants. Outcomes of interest will include recurrent non-fatal thrombosis (deep venous thrombosis and pulmonary embolism), major non-fatal bleeding and mortality

STRENGTHS AND LIMITATIONS OF THIS STUDY

The methods of the review are state-of-art, including explicit eligibility criteria, a comprehensive search, independent duplicate assessment of eligibility, and use of the GRADE approach to assessing confidence in estimates of effect including independent duplicate assessment of risk of bias, precision, consistency, directness and publication bias. Our protocol represents a model for systematic review methods. Our results are likely to be limited by limitations in the primary studies.

Introduction

Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a major disease that results in considerable morbidity and mortality. Deep venous thrombosis or pulmonary embolism may occur in almost 2 in 1000 people each year and between 5% and 15% of people with untreated DVT may die from pulmonary embolism [1 2]. Thrombosis most commonly affects the deep veins of the lower limbs, but may affect other sites, including the upper limbs. Complications include pulmonary thromboembolism and post-thrombotic syndrome (PTS)[3].

Risk factors for VTE include immobility, surgery (particularly orthopedic), malignancy, pregnancy, older age, estrogen therapy, and inherited or acquired prothrombotic clotting disorders[4]. In many patients, DVT remains asymptomatic and resolves without complications.. DVTs of concern are those that become symptomatic and are responsible for morbidity and mortality[3]. Patients with extensive proximal DVT have a substantial risk of developing the post-thrombotic syndrome, particularly if there is an ipsilateral recurrence with further valve destruction [5]. The average rate of fatal recurrent VTE after anticoagulation is discontinued has been estimated at 0.3 per 100 patient-years[6]. Based on observational data [7 8], authors of the ninth iteration of the American College of Chest Physicians antithrombotic guidelines[9] estimated that in patients with unprovoked proximal DVT or PE the risk of recurrence in the first year after discontinuation of anticoagulation is 10% with a risk of 5% per year thereafter (i.e. 30% at 5 years).

A consensus exists regarding the need for anticoagulant treatment, usually with vitamin K antagonists (VKA) or with novel oral anticoagulants (NOAC) for patients with venous thromboembolism. Whereas clinicians agree on the need for 3 to 6 months of anticoagulation after the diagnosis of venous thromboembolism (VTE), opinions regarding optimal duration of secondary prophylaxis differ. Although the prevention of recurrence is certainly desirable, the risk of major bleeding, together with the burden of therapy and cost, makes long-term treatment potentially problematic.

The risk-to-benefit ratio is highly dependent of the risk of recurrence of VTE which differs according to the presence or absence of reversible predisposing factors, location of the thrombosis, patient age, the presence of comorbid conditions, and intrinsic predispositions to thrombosis (inherited and acquired thrombophilia disorders). Guidelines suggest that the risk of recurrence is sufficiently low after a DVT provoked by temporary immobilization or lower limb fracture that treatment beyond 6 months is not in these patients' best interest. Further, there is agreement that lifelong anticoagulation is warranted patients at highest risk of recurrence (i.e., patients with active metastatic cancer). The controversy regarding treatment beyond 6 months is restricted to those with intermediate risk [10 11]. These patients include those whose VTE was unprovoked or whose VTE, if provoked, has happened more than once (recurrent VTE).

To make optimal decisions, patients and clinicians need best evidence estimates of benefits and harms of short versus long-term anticoagulation. In the trials included in previous systematic reviews of this topic the anticoagulants administered were Vitamin K antagonists [12-15]. Recent randomized trials have evaluated longer and shorter administration of NOACs. Therefore, we will update a systematic review and meta-analysis of the relative benefits and harms of longer versus shorter periods of anticoagulation in patients at intermediate risk of recurrence. Our primary question will be the impact of indefinite anticoagulation versus discontinuing anticoagulation after 3 to 9 months on the outcomes of interest. By indefinite anticoagulation we mean continuing anticoagulation until changes in circumstances would mandate a discontinuation. For many such patients, we would anticipate lifetime anticoagulation.

Methods/design

Protocol and registration

Our protocol is registered on PROSPERO (CRD42014007620), http://www.crd.york.ac.uk/PROSPERO.

Issues in defining trial eligibility

Trials investigating the effect of prolonged anticoagulation on the risk of VTE recurrence vary in terms of the duration of anticoagulation in the shorter and longer duration arms. They also differ in the nature of populations enrolled. These differences create challenges in defining study eligibility criteria.

In defining eligibility criteria any systematic review faces tension between broad eligibility criteria, which enhance precision of effect estimates and generalizability of results, and narrow criteria, which decrease the risks of heterogeneity and of generating pooled estimates that are not applicable to the range of patients and interventions included. A reasonable strategy for dealing with this tension, which we will adopt, is to choose relatively broad but clinically plausible criteria and then explore possible sources of heterogeneity. Therefore, although standard shorter-term anticoagulation is up to 6 months, we are including trials in which the shorter-term arm received anticoagulation up to 9 months. For the longer-term arm, we will accept any trial in which the duration of treatment is at least six months longer than in the shorter-term arm. We will conduct subgroup analyses focusing on the duration of therapy in both the shorter and longer-term arms.

As we described in the background, the controversy regarding duration of anticoagulation is focused on patients in the intermediate risk category. Typically, these are patients with unprovoked VTE or recurrent VTE (provoked and unprovoked), but definitions might differ across trials. Thus, ideally, all patients included in the trials would fall into these risk groups. It would be inappropriate, however, to exclude trials in which most but not all patients fit this description. We will include any study in which, according to the definition used in the study at least 50% of patients fall into one of these risk groups. If there is appreciable heterogeneity in the proportion of patients in these risk categories we will conduct subgroup analyses based on this variability.

Eligibility criteria

Inclusion

Patients: Studies must include patients with DVT and/or PE in whom at least 50% have a first unprovoked (no apparent clinical risk factor [16] VTE, or a second or subsequent VTE (can be provoked or unprovoked) in the absence of cancer.

Intervention shorter duration treatment: Studies must include an arm in which patients are anticoagulated with either vitamin K antagonists or novel anticoagulants for at least 12 weeks, but no longer than 9 months.

Intervention longer duration of treatment: Studies must include an arm in which patients are anticoagulated with either vitamin K antagonists or novel anticoagulants for at least six months longer than in the shorter duration treatment arm.

Outcomes: Trials must report on at least one of the following outcomes: recurrent VTE, DVT, fatal and non-fatal pulmonary embolus confirmed by objective testing (for DVT, venography or ultrasonography; for PE radiological imaging including ventilation/perfusion scanning, CT pulmonary angiography, MRI, conventional angiography, or autopsy), fatal and non-fatal serious/important bleeding episodes, post thrombotic syndrome, quality of life and total mortality.

Type of study and design: We will include only randomized controlled trials (RCT). We will include two types of RCT designs. In one design, patients, at the outset of VTE, are randomized to shorter or longer anticoagulation. In the alternative design all patients undergo the short-course anticoagulation regimen. They are then randomized to stop anticoagulation or to a further period of anticoagulation. We will include studies in which patients undergo shorter-term treatment with an anticoagulant, most often VKA, and then receive a new anticoagulant versus placebo.

Exclusion:

We will exclude studies enrolling only pure populations of high-risk patients, such as those with protein S or C deficiency or anti-phospholipid antibody or antiphospholipid antibody syndrome~~pregnancy~~.

Information sources and search

We will screen all RCTs reviewed in the 9th iteration of the American College of Chest Physicians antithrombotic guidelines and then will conduct additional search from January 2011 forward, six months prior (to account for lag in indexing) to the date the comprehensive search on the topic for the 9th iteration ACCP antithrombotic guidelines. We will search OVID Medline, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL) and CINAHL with no language restriction. An experienced librarian (NB) developed a sensitive search strategy for this (**see ~~Additional file~~** ~~anticoag vte.medline strategy~~ Appendix 1). We will scan the bibliographies

of all systematic reviews and meta-analyses as well as all eligible primary studies for additional relevant articles.

Study selection

Following a calibration exercise, reviewers will work in pairs to screen, independently and in duplicate, titles and available abstracts of identified citations. We will acquire the full text publication of any article that either reviewer judges as potentially eligible. The same reviewer teams will, following a second calibration exercise, independently apply eligibility criteria to the full text of potentially eligible trials using standardized forms. They will resolve disagreements by consensus or, if a discrepancy remains, through discussion with an arbitrator (GHG).). We will measure inter-rater agreement for full text eligibility and assessment of risk of bias using the Kappa statistics. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.74 to reflect good agreement and 0.75 or more to reflect excellent agreement [17].

Data collection process and data items

Using pilot tested standardized forms and following a calibration exercise, teams of two reviewers will extract data independently and in duplicate from each eligible study. Data abstracted will include details on the study methodology, participants, intervention, control, and all reported patient-important outcomes. For each outcome, we will record number of patients enrolled in each study arm, and the number of patients for whom final follow-up data is available, and the number of events in each study group.

Reviewers will resolve disagreements by discussion, and one arbitrator (GHG) will adjudicate unresolved disagreements. We will contact the authors of each study to clarify any issues of uncertainty in the data abstraction and to ensure that our abstraction is correct.

Reviewers will independently extract details of the anticoagulation regimens in both the shorter and longer duration arms. Outcomes will include death; cause-specific mortality (PE or bleeding); recurrent non-fatal VTE (DVT and pulmonary embolus) and non-fatal

serious/important bleeding. We will document definitions of serious/important bleeding in each study.

Risk of bias in individual studies

Reviewers will assess risk of bias within each study with a modified Cochrane risk of bias instrument[18] which assesses the following key domains: randomization sequence generation; allocation concealment; blinding of participants, healthcare professionals, outcome assessors, data collectors, and data analysts; incomplete outcome data; selective outcome reporting; and other sources of bias which will include differential intensity of surveillance for VTE and bleeding in the short and long arms, and premature cessation of follow-up (for instance, no follow-up for bleeding in the short arm after a VTE and resumption of anticoagulation). We will consider as a criterion of risk of bias whether the investigators specify a total surveillance period equal in length for the longer and shorter arms (i.e., same follow-up period from the time of randomization) versus a total surveillance period that is different (e.g., same follow-up period from the time of stopping anticoagulation) or not specified. Reviewers will input response options of 'definitely yes', 'probably yes', 'probably no', and 'definitely no' for each of the domains, with 'definitely yes' and 'probably yes' ultimately assigned low risk of bias and 'definitely no' and 'probably no' assigned high risk of bias[19]. Reviewers will resolve disagreements by discussion, and one arbitrator (GHG) will adjudicate unresolved disagreements.

Meta-analysis and data synthesis

Data regarding VTE, serious/important bleeding, mortality and person-time at risk will be extracted by 2 independent reviewers using a standardized form, with adjudication by a third reviewer in cases of disagreement. Given our primary interest in short term versus indefinite anticoagulation, in studies with follow-up after discontinuation of anticoagulation in the long arm, we will try to identify events that occurred in either arm after the scheduled discontinuation of anticoagulation in the long arm. We will exclude such events in the primary analysis.

For each study, incidence rates in events per person-year at risk will be calculated for the outcomes of recurrent VTE and serious/important bleeding. We have chosen events per person-years rather than number of people with events to account for differential length of follow-up within individual studies and across studies, and the possibility of multiple events in a single individual. When investigators do not report person-time data (either directly or indirectly through a Kaplan-Meier survival curve), the person-time of the interval will be estimated by multiplying the number of participants present at the beginning of the interval by the duration of the interval and subtracting person-time for events occurring within the interval. For this calculation we will assume that events will be equally likely throughout the interval unless data to the contrary are in the report.

Our estimates of study heterogeneity will be informed using the p-value for Chi^2 for heterogeneity, and the I^2 statistic where 0-40% may be unimportant heterogeneity, 30-60% moderate, 50-90% substantial and 75-100% considerable heterogeneity[44]. We will explore heterogeneity by conducting the five a priori subgroup analyses using a z-test to test for interaction[20].

Assessment of heterogeneity and subgroup analyses

We will explore heterogeneity using sub-group hypotheses, which apply to bleeding and VTE outcomes and mortality and are framed as effects in longer versus shorter duration anticoagulation. We postulate that larger reductions in thrombosis, and larger increases in bleeding, will occur in the following situations: i) when the shorter duration anticoagulation arm is three months or less versus longer than 3 months; ii) when the longer duration anticoagulation arm is more than 12 months longer than the shorter duration arm versus 12 months or less;; iii) studies in which the number of risk of bias domains judged as 'high risk' is greater than the median will have larger effects than studies in which that number is less than the median. iv) when therapy is a NOAC versus warfarin with target INR 2.0 or greater) versus warfarin lower boundary of target INR less than 2.0); v) when anticoagulation was continued until the end of the study or in which we can exclude events that occurred in either arm after timing of cessation of anticoagulation in the long arm versus follow-up continued after anticoagulant stopped and not

possible to identify and exclude events that occurred after cessation of anticoagulation in the long arm.

Confidence in pooled estimates of effect

Two reviewers will, independently and in duplicate, assess the confidence in effect estimates for each outcome using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) rating system [21]. In the GRADE system of rating quality of evidence for each outcome, randomized trials begin as high quality evidence, but may be rated down by one or more of five categories of limitations[22]. The GRADE working group has provided detailed guidance regarding judgments for each of these criteria: (1) risk of bias[23], (2) inconsistency[24], (3) indirectness[25], (4) imprecision[26], and (5) publication bias[27].

For assessing the impact of loss to follow-up across studies, we will conduct sensitivity analyses making progressively more stringent assumptions regarding loss to follow-up in intervention and control groups. The extent to which point estimates and confidence intervals differ in these sensitivity analyses will determine whether we rate down for risk of bias[28].

We anticipate that "number of patients enrolled minus number of patients for whom final follow-up is available" may include: i. unexplained losses to follow-up (lost contact), ii. explained losses to follow-up (e.g., followed until patient moved), iii. Followed until they had a recurrent VTE (or lost to follow-up for other complications such as death, or bleeding from restarted anticoagulation).

With respect to precision, the GRADE guidance notes that meta-analyses of small trials can provide evidence of benefit with confidence intervals that appear to convincingly exclude no effect; however, the results of reviews of such studies have often been subsequently refuted by larger trials[26]. To address this potential concern in cases in which our meta-analysis suggests benefit but the sample size is less than the optimal information size (OIS; the number of patients generated by a conventional sample size calculation for a single trial) we will rate down the quality for imprecision. For the purposes of calculating the OIS we will assume, for binary

variables a relative risk reduction or increase (delta) of 25%, an alpha of 0.05, and a beta of 0.20, and a median baseline risk from the available studies.

For each outcome we will assess publication bias by visually observing asymmetry of the funnel plot for each outcome. We will follow published guidance and conduct the funnel plot inquiry only for outcomes with 10 or more trials [27].

- After considering these reasons for rating down, reviewers will judge the overall confidence in estimates of effect for each outcome as follows:
- 'high' quality of evidence (we are very confident that the true effect lies close to that of the estimate of the effect);
- 'moderate' quality of evidence (we are moderately confident in the effect estimate and 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' quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and
- 'very low' quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) [22].

Again, we will follow GRADE guidance for overall confidence ratings [29].

For both individual domains and overall confidence, if raters disagree they will try to resolve by consensus and, if not successful, the final judgment will be made by an independent reviewer (GHG).

Presentation of Results

We will present the results of our meta-analyses in an Evidence Profile that will provide a succinct, easily digestible presentation of quality of evidence and magnitude of effects [30]. Our Evidence Profile will be constructed to include the following elements:

1. A measure of the typical burden of these outcomes (e.g. control group, estimated risk; if appropriate studies are available we will use the baseline risk for population-based observational studies);
2. A measure of the difference between the risks with and without intervention
3. The relative magnitude of effect;
4. Numbers of participants and studies addressing these outcomes;
5. A rating of the overall confidence in estimate of effect for each outcome and any reasons for rating down the confidence

Discussion

The decision to continue anticoagulant treatment in patients with VTE at moderate risk of recurrence beyond the first few months is based on the patients' and treating physician's perception of the benefits and harms. The risks of recurrent VTE and bleeding associated with different lengths of vitamin K antagonist treatment have been evaluated in several studies that randomly allocated patients with venous thromboembolism to receive different lengths of treatment. These studies, subsequently summarized in systematic reviews, were modest in number and of relatively small sample size. Since these studies were completed, new trials have compared shorter and longer duration of treatment with novel anticoagulants. Since the impact of the these newer agents on both thrombosis and bleeding is similar to that of warfarin, by including these studies in a new systematic review, we will be able to increase precision and narrow confidence intervals, allowing an improved estimate of effects on thrombosis and bleeding.

Our protocol represents a model for systematic review methods. We have planned standard methods that yield credible results, including explicit eligibility criteria, a comprehensive search, and duplicate assessment of eligibility and risk of bias. We have also planned implementation of methods seldom (a priori hypotheses to explain possible effect modification, including specification of direction of effect) or very seldom (use of the GRADE approach to rating confidence in estimates of effect) implemented in current systematic reviews.

Our review presents several unique challenges. One involves the specification of the study

question, and the implications of that specification. Relevant studies used two different designs: short versus longer anticoagulation in which patients in the long arm continued anticoagulation until the end of the study, and short versus fixed longer anticoagulation with continued follow-up after anticoagulation was discontinued. We have decided we are interested in the relative impact of short versus indefinite - rather than fixed longer duration - anticoagulation. This will require exclusion of events in the latter study design that occurred - in both short and long arms - after the end of the longer arm planned anticoagulation. Reported data may limit our ability to carry out this exclusion as would be optimal.

Our study is likely to be limited by other aspects of study design and reporting of the primary studies. In particular, though we are interested in the impact of indefinite versus limited anticoagulation, studies will have limited follow-up, often 2 to 3 years. Both bleeding and event rates in the second and third years will, however, provide a useful estimate of what is liable to happen in subsequent years. Another important limitation is that we will not have access to individual patient data and therefore subgroup analysis and inferences will be limited.

In conclusion, patients and clinicians choosing between limited and indefinite duration of anticoagulation after VTE deserve access to best estimates of effect derived from the complete current literature. Our review will provide these estimates.

Competing interests

John Eikelboom has taken the position that anticoagulation should not be used long-term in the patient population of interest and has tested aspirin in this context. Schulman is director of an Anticoagulation Clinic. Clive Kearon led the development of American College of Chest Physicians antithrombotic guidelines addressing anticoagulants use in this population and Gordon Guyatt edited the 9th edition of these guidelines.

Authors' contributions

LCL, GHG, JE, SS, FS, CK and EA conceived the study design. NB and IN designed the database-specific literature search strategies. GHG and LCL completed the first draft of the manuscript. All authors reviewed several drafts of the manuscript and approved the final version.

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List of abbreviations

Venous thromboembolism (VTE)

Randomized controlled Trials (RCTs)

Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

novel oral anticoagulants (NOAC)

pulmonary embolism (PE)

deep-vein thrombosis (DVT)

vitamin K antagonists (VKA)

optimal information size (OIS)

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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Coumarins/

2 (coumarin$ or chromonar or coumestrol or esculin or isocoumarin$ or psoralens or pyranocoumarins or umbelliferones).mp.

3 warfarin.mp. or Warfarin/ or warfant.mp.

4 (coumadine or warfant or coumadin or marevan or aldocumar or tedicumar).mp.

5 Acenocoumarol/ or acenocoumarol*.mp.

6 (Pradaxa or Dabigatran).mp.

7 (Rivaroxaban or Xarelto).mp.

8 (vitamin k adj3 antagonis*).mp.

9 vitamin k/ai

10 (vk adj2 antagonis*).mp.

11 (endosaban or apixaban).mp.

12 BAY 59-7939.mp.

13 (BMS-562247 or edoxaban or DU-176b or betrixaban).mp.

14 YM150.mp.

15 TAK-442.mp.

16 LY517717.mp.

17 PD0348292.mp.

18 (VKA or VKAs).mp.

19 (NOACs or noac).mp.

20 (DOACs or doac).mp.

21 ((new or novel or direct) adj4 (oral anticoag* or oral anti coag*)).mp.

22 ((novel or new) adj2 (anticoag: or anti coag:)).mp.

23 or/1-22

24 thrombosis.mp. or exp Thrombosis/

25 exp Venous Thromboembolism/ or exp Thromboembolism/ or Thromboembolism.mp.

26 pulmonary embolism.mp. or exp Pulmonary Embolism/

27 (PE or DVT or VTE).mp.

28 ((vein* or ven*) adj2 thromb*).mp.

29 (thrombu* or thrombotic* or thrombolic* or thromboemb* or thrombo* or embol*).mp.

30 or/24-29

31 randomized controlled trial.pt.

32 random allocation/

33 double-blind method/
34 single-blind method/
35 randomi?ed controlled trial$.mp.
36 Randomi?ed clinical trial$.mp.
37 controlled clinical trial.pt.
38 ((singl$ or double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
39 random$.mp.
40 placebo$.mp.
41 cross-over studies.sh.
42 latin square:.tw.
43 or/31-42
44 animals/ not humans/
45 43 not 44
46 23 and 30 and 45
47 (2008* or 2009* or 2010* or 2011* or 2012* or 2013*).em,ed,dc.
48 46 and 47

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12, 13

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10, 11, 12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	--
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	---
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	--
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	--
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	--
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	--
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	--
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	--
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	--
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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