BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023939
Article Type:	Protocol
Date Submitted by the Author:	01-May-2018
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Keywords:	pulmonary embolism, lung scintigraphy, recurrent venous thromboembolism, residual pulmonary vascular obstruction

Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism: protocol for a systematic review and meta-analysis of individual participant data

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Total word count: 3378

Abstract

Background: In patients with a first, unprovoked venous thromboembolism (VTE), the optimal duration of oral anticoagulant therapy (OAT) is controversial due to tightly balanced risks and benefits of indefinite anticoagulation. The objective of this study is to assess among patients with a first acute pulmonary embolism (PE) who received ≥ 3 months of OAT and thereafter had a planar lung scan, whether residual pulmonary vascular obstruction (RPVO) is associated with VTE recurrence after discontinuation of OAT.

Methods and analysis: We will conduct a systematic review with a meta-analysis of individual participant data (IPDMA) of contemporary studies evaluating the prognostic significance of RPVO in patients with a first acute PE. We will search from inception to January 24th, 2018, PubMed, Medline, Embase, and Cochrane's Central Registry for Randomized Controlled Trials, CENTRAL for randomized controlled trials and prospective cohort studies. Two reviewers will conduct all screening and data collection independently. The methodological quality and risk of bias of eligible studies will be carefully and rigorously assessed using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. The primary objective will be to assess the relationship between RPVO on V/Q scan after completion of at least 3 months of anticoagulant therapy after an acute PE event, and the risk of an objectively confirmed symptomatic recurrent VTE (including DVT or PE) or death due to PE. The secondary objectives will include the assessment of the optimal RPVO cut-off and the risk of recurrent VTE, as well as the relationship between the relative change in RPVO between PE diagnosis and at discontinuation of OAT (≥ 3 months) and risk of recurrent VTE.

Ethics and dissemination: This study of secondary data does not require ethics approval. It will be presented internationally and published in the peer reviewed literature.

PROSPERO registration number: CRD42017081080.

Keywords: pulmonary embolism; lung scintigraphy; recurrent venous thromboembolism, residual pulmonary vascular obstruction

Strengths and Limitations of this study

- A better prediction of the risk of recurrent VTE after oral anticoagulant therapy discontinuation is necessary.
- Whether residual pulmonary vascular obstruction (RPVO) improves the stratification of the risk of recurrence after PE, and could influence decisions about OAT duration especially for unprovoked VTE, is still unknown.
- Various studies have reported different results regarding the prognostic significance of RPVO in patients with a first acute PE.
- This present individual patient data meta-analysis will allow to provide precise estimates for the relationship between RPVO on planar lung scan after completion of OAT after acute PE, and the risk of recurrent VTE.

Introduction

The risk of recurrence after a first episode of venous thromboembolism (VTE) is high, especially in patients with unprovoked VTE (1-4). Indeed, these patients carry a risk of recurrence of approximately 10% one year after discontinuing anticoagulant therapy. Current clinical practice guidelines recommend at least three months of oral anticoagulation therapy (OAT) after a first provoked VTE (5). In patients with a first, unprovoked VTE, characterized by the absence of major transient risk factors, the optimal duration of OAT is controversial. Although OAT is very effective for reducing the risk of recurrent VTE during therapy, this benefit disappears after discontinuation of treatment (6). Extending OAT indefinitely after an unprovoked VTE may not be the most appropriate management strategy for every patient because the treatment benefit needs to be balanced against the risk of major bleeding, the main adverse effect of OAT (7). A better prediction of the risk of recurrent VTE after OAT discontinuation is necessary to determine the optimal, individualized treatment plan.

Stratification of the recurrence risk after a first episode of VTE is an important topic of research. Various predictors have been described to identify subgroups of patients whose risk of recurrent VTE is low enough that they could safely stop OAT (8). Indeed, patient age, patient sex, location of the VTE, and D-dimer levels may inform decisions about the duration of AT in patients with unprovoked VTE (9). Moreover, some studies have suggested that residual vein obstruction (RVO) identified on venous compression ultrasonography of the lower limbs in patients with deep vein thrombosis after 3-6 months of anticoagulant therapy, may be associated with higher risk of recurrent VTE (10-13). The role of residual pulmonary artery thrombis has been much less studied. Whether residual pulmonary vascular obstruction (RPVO) improves the stratification of the risk of recurrence after PE, and could influence decisions about OAT duration especially for unprovoked VTE, is still unknown. Results from clinical studies are conflicting. Two single-centre prospective cohort studies designed to evaluate the association between residual pulmonary embolism detected on ventilation-perfusion (V/Q) scan and risk of recurrent VTE were published recently and they showed inconsistent results (14,15). One study found no significant association between

residual perfusion defect on lung scintigraphy and VTE recurrence (14), whereas the results of the other study suggested that RPVO > 10% was an independant risk factor of recurrent VTE after a first acute PE (15).

To address this knowledge gap, we sought to perform a systematic review and individual patient data meta-analysis (IPDMA) of contemporary studies evaluating the prognostic significance of RPVO in patients with a first acute PE. The objective of this study is to assess among patients with a first acute pulmonary embolism who received ≥ 3 months of anticoagulant therapy and thereafter had a planar lung V/Q scan, whether residual pulmonary vascular obstruction is associated with VTE recurrence after discontinuation of oral anticoagulant therapy at one year.

METHODS

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P; see Appendix 1) (16). For the IPDMA, we will adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) (17). In accordance with the guidelines, this systematic review was registered with the International Prospective Register of Systematic Reviews on 5 December 2017 (registration number: CRD42017081080)

Eligibility criteria

Studies will be selected according to the criteria specified below.

Study designs

We will include randomized controlled trials, and prospective cohort studies. Retrospective cohort studies, case-control studies, cross-sectional studies, and cases reports will be excluded.

Participants

The study population will include adult patients (18 years or older) who had experienced and survived a first episode of objectively confirmed acute PE, that is either unprovoked or provoked by a transient and/or persistent risk factor (18), had completed at least 3 months of anticoagulant therapy, and did not have any recurrence during this period.

Interventions

Patients had to receive a planar ventilation/perfusion (V/Q) lung scintigraphy at discontinuation of anticoagulation therapy (i.e. ≥ 3 months of anticoagulation therapy), with an assessment of the pulmonary vascular obstruction.

Timing

Patients had to be followed prospectively for recurrent symptomatic VTE (PE or DVT) after discontinuation of anticoagulation therapy. All events occurring during follow-up had to be documented by an adjudication committee, or by an investigator blinded to the planar V/Q scan results.

Objectives

Primary objective:

- Relationship between residual pulmonary vascular obstruction (RPVO) on V/Q scan after completion of at least 3 months of oral anticoagulant therapy after acute PE, and risk of recurrent VTE at one year.

Secondary objectives*:*

- Association between the percentage of RPVO using different cut-off (>0%, ≥5%, ≥10%), and the risk of recurrent VTE.
- Relationship between the relative change in RPVO between PE diagnosis and at discontinuation of OAT (≥ 3 months), and risk of recurrent VTE.
- Recurrence rate per patient-year following a provoked or an unprovoked PE.
- Type/site (number of isolated proximal DVT, isolated PE, PE + DVT, fatal PE) of recurrence and median time to recurrence (in months).
- Risk factors of RPVO in patient's baseline characteristics.
- Independence of RPVO as a predictor for recurrent VTE.
- Percentage of RPVO/ change in RPVO and risk of developing Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Information sources and search strategy

The following databases will be accessed during the electronic component of the systematic review: PubMed, Medline and Medline in Process (via OVID), Embase Classic + Embase (via OVID), and Cochrane's Central Registry for Randomized Controlled Trials, CENTRAL

(via OVID). The specific search strategies will be created by a Health Sciences Librarian with expertise in the design of systematic review searching. A Peer Review of Electronic Search Strategy (PRESS) will be performed by a second librarian. A search strategy will be developed to define keywords for all searches (see Appendix 1 for Medline searches). After the MEDLINE strategy will be finalized, it will be adapted to the syntax of the other databases. There will be no beginning date identified, while the cutoff date will be January 24, 2018. There will be no language exclusion criteria, nor any other publication restrictions.

Study selection process

Literature search results will be imported into EndNote v17.3.1.8614, de-duplicated, and then uploaded to the Covidence platform (www.covidence.org) to facilitate collaboration among the reviewers during the study selection process. Two reviewers (PR and ME) will independently screen titles and abstracts, and will independently assess the full-text articles for eligibility, using a pre-defined list of exclusion criteria. Disagreements will be resolved by consensus or by a third person (GLG). None of the review authors will be blind to the journal titles or to the study authors or institutions.

Search results and study selection will be illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (19), with reasons specified for excluding articles during full-text screening. In accordance with the guidelines, this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on December 5th, 2017 (registration number CRD42017081080).

Included studies and data collection process

For the studies that will be included in the review, corresponding authors will be invited by e-mail to participate in the project. Investigators who agreed to participate will be requested to provide a copy of their dataset. Each dataset will be carefully checked for the quality of the data in collaboration with the investigator. Data from each participant in the relevant studies

will be re-analysed and recoded to make them compatible and standardized in related studies.

The common dataset will include whenever possible:

- *Participant characteristics*: Demographics characteristics (age, gender, height, weight, BMI), medical history (previous VTE), comorbid conditions (chronic lung disease, tobacco use (current or past smoker vs. never smoked)), thrombophilia,
- *Index event (i.e. acute PE)*: date of acute PE, definition of VTE that is provoked or unprovoked [(transient major risk factors, prolonged immobility, recent trauma or surgery, hormonal therapy (oral contraceptive pill or hormone replacement therapy), active cancer, thrombophilia (V Leiden mutation, ATIII/Protein C/Protein S deficiency, APL)],
- *Treatment of index event*: Type of treatment, duration of therapy before stopping AT (date of starting OAT and date of OAT discontinuation),
- *Initial PVO assessment at the time of index event*: Date and type of initial PVO assessment at the time of acute PE diagnosis,
- *Residual pulmonary vascular obstruction at OAT discontinuation*: date of RPVO assessment at OAT discontinuation, definition of RPVO (normal lung V/Q scan vs. abnormal V/Q scan or >0%, ≥5%, ≥10%), extent of RPVO, D-dimer level just before OAT discontinuation, antiplatelet use at OAT discontinuation, post-thrombotic syndrome at OAT discontinuation,
- *Follow-up information*:, date and type of objectively confirmed recurrent VTE (total number of isolated proximal DVT, isolated PE, PE + DVT, Fatal PE), CTEPH diagnosis, date of end of follow-up (i.e. date and cause of death, or date of lost to follow-up).

Once the individual patient data from all primary studies will be homogenized and merged, descriptive statistics will be used to check consistency of the data. Using the provided datasets, the baseline tables and primary analysis will be replicated. Any inconsistencies or discrepancies will be resolved by contacting the investigators.

Risk of bias of individual studies

RCTs will be appraised using the Cochrane Collaboration Risk of Bias tool (20). For studies that have used a cohort design, the ROBINS-1 tool will be used (21). Signaling questions for each domain will be adapted or omitted, and we will add questions, if needed. Two reviewers (PR and ME) will independently assess the studies for risks of bias on a study level. A judgment as to the possible risk of bias on each item in the domains ('low risk', 'moderate risk', or 'high risk') will be made from study-level data and, if needed, from a summary of the obtained individual patient data. Results will be compared and disagreements resolved by discussion or, if needed, with the help of a third reviewer.

Research questions

Research question 1:

What is the clinical/prognostic significance of residual pulmonary vascular obstruction (RPVO) in patients with treated pulmonary embolism?

The primary objective will be to assess the relationship between RPVO on V/Q scan after completion of at least 3 months of anticoagulant therapy after an acute PE event, and the risk of an objectively confirmed symptomatic recurrent VTE (including deep vein thrombosis or pulmonary embolism) or death due to PE.

Proximal deep vein thrombosis recurrence will have to be defined as a symptomatic objectively confirmed lower limb deep vein thrombosis involving the popliteal or more proximal veins by compression ultrasonography. A diagnosis of pulmonary embolism recurrence will have to be based on a new finding of intravascular filling defect in a different segmental area than for the initial PE on CTPA, or a new segmental perfusion defect on planar V/Q lung scan. Sudden unexplained deaths will have to be considered to be related with PE. All events occurring during follow-up will have to be adjudicated.

Research question 2:

What is the most clinically relevant definition of residual PE (RPVO) for the prediction of recurrent VTE?

A RPVO is defined as the persistence of a perfusion defect on planar V/Q lung scan after discontinuation of anticoagulant therapy. However, the definition of residual PE varies among studies, using different perfusion defect cut-off values. Residual PE should be considered in case of an abnormal V/Q scan whatever the extent of the perfusion defects is, or residual PE should be considered above a certain amount of perfusion defect (e.g. more than 5 or 10%, or more than one segmental, more than two sub-segmental or two segmental perfusion defects). A ROC curve analysis will be performed in order to find the most appropriate predictor of VTE recurrence in patients with treated acute PE.

Research question 3:

What are the risk factors for RPVO?

We will try to identify factors in patient's history or physical exam at presentation that could affect RPVO. Some concomitant diseases or exposures (e.g. chronic obstructive pulmonary disease (COPD), pneumonia, and tobacco use) are known to induce lung parenchymal alteration and thus lung scan abnormalities. We will perform univariate analyses of the association between each of the predictors in patient's baseline characteristics and RPVO, using chi-2 test or Fischer exact test when appropriate for categorical variables and Student t-test for continuous variables. Multivariate analyses will be performed using Cox proportional hazard models that included all variables that achieved a p value of ≤ 0.20 in univariate analyses.

Research question 4:

What is the independence of RPVO as a predictor for recurrent VTE?

When examining the relationship between an explanatory factor and an outcome, we are interested in identifying factors that may modify the factor's effect on the outcome. A confounding factor corresponds to a situation in which the association between an exposure

(i.e. RPVO) and outcome (i.e. risk of recurrent VTE) is distorted by the presence of another variable (i.e. COPD).

Research question 5:

Is change in RPVO between PE diagnosis and at discontinuation of OAT (≥ 3 months), predictive of recurrent VTE or the development of CTEPH?

We know that more than 50% of patients with PE will still have perfusion defects after 6 months of OAT, which may persist for several months. Some patients will recover their lung perfusion after OAT, some patients not. We would like to know if the change of RPVO between diagnosis and after OAT discontinuation is predictive of recurrent VTE or development of CTEPH: are patients with no change in PVO more likely to present a recurrence or CTEPH than those who recover partially or totally their lung perfusion?

Data synthesis

Meta-analysis

Characteristics of eligible studies will be summarized and presented in a table in the final report. One of the main objectives of this systematic review is to combine individual participant data from pertinent studies to generate a pooled estimate of the rate of recurrent VTE in patient with RPVO diagnosed on planar V/Q scan after discontinuation of at least 3 month of OAT for an acute PE. Prior to pooling results, the research team will assess studies for clinical and methodological heterogeneity through comparison of important study characteristics. The degree of statistical heterogeneity will be measured and interpreted using a combination of Cochrane's Q (statistically significant at $p<0.10$) and the I2 statistic (>50% considered substantial). An I2 value >75% is indicative of a very high degree of heterogeneity, and if encountered the data will not be pooled. If homogeneity among studies is judged as satisfactory, then the results from studies will be pooled using standard meta-analysis procedures.

Statistical analysis

Data will be quantitatively synthesized as follows. A two-stage meta-analysis will be performed using the complete case database for all outcomes to generate forest plots, enabling results across studies to be compared visually, illustrate heterogeneity and differences across subgroups (22).

General characteristics of participants will be assessed using mean and standard deviation for quantitative variables, number and proportion of total participants for qualitative variables. ROC curve analysis will be performed in order to find the most appropriate cut-off for RPVO to predict VTE recurrence in patients with treated acute PE. Incidence rates of recurrent VTE will be calculated as the number of recurrent VTE over the number of person-years of follow-up. Univariate analyses of the association between each of the predictors in patient's baseline characteristics and RPVO will be performed using chi-2 test or Fischer exact test when appropriate for categorical variables and Student t-test for continuous variables. Multivariate analyses will be performed using Cox proportional hazard models that included all variables that achieved a p value of ≤ 0.20 in univariate analyses.

Management of missing data

If data are not directly reported, they will be requested from the primary investigator of the study. Analysis will be conducted on the final data available, and the potential impact of the missing data will be discussed as a limitation. Patients in whom the PVO was not assessed will be excluded from the analysis.

Limitations and challenges

IPDMA is a powerful method to address questions, since combining individual data from multiple studies allows for greater precision of estimates, analysis of clinically relevant subgroups and the evaluation of narrower outcomes. In addition, an IPDMA enables exploration of methodological and statistical heterogeneity between the studies.

However, IPDMA also have limitations that need to be highlighted. Pooling of data may be biased due to differences across the studies with respect to inclusion criteria. Although all investigators will provide their datasets, we acknowledge that it will be difficult, even impossible for some studies to retrieve additional information from the medical records. As a consequence, analyses may be restricted to subgroups of studies which can provide the required information.

Conclusion

The present IPDMA will aim to address several unanswered questions about the relationship between residual perfusion vascular obstruction on planar lung scan after completion of at least 3 months of OAT after acute PE, and the risk of recurrent VTE. Thus, identification of patients with low enough risk of recurrent VTE using RPVO on lung scintigraphy might help physicians to justify safely stopping OAT in patients with VTE.

Ethics and dissemination

Ethical approval and patient consent are not required since this is a systematic review on published studies. The results of this study will be submitted for presentation at relevant national and international conferences, and for publication in a peer-reviewed journal.

List of abbreviations:

COPD: Chronic obstructive pulmonary disease

CTEPH: Chronic Thromboembolic Pulmonary Hypertension

DVT: Deep Vein Thrombosis

IPD: Individual Patient Data

IPDMA: Individual Patient Data Meta-Analysis

OAT: Oral Anticoagulant Therapy

PE: Pulmonary Embolism

PRISMA: Preferred Reporting Items for Systematic Review

PROSPERO: Prospective Register of Systematic Reviews

RCT: Randomized Controlled Trial

RPVO: Residual Pulmonary Vascular Obstruction

RVO: Residual Vein Obstruction

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

VTE: Venous Thromboembolism

Declarations

Ethics approval and consent to participate: Ethical approval and patient consent are not required since this is a meta-analysis based on published studies.

Consent for publication: Not applicable.

Availability of data and material: Not applicable.

Competing interests: None of the authors have competing interests to declare.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contributions:

Drs Carrier, Le Gal, Robin, and Salaun developed the methodology for the protocol. Drs Le Gal, Robin, and Salaun drafted the manuscript with input from all members of the authorship team. Ms Sikora developed the search strategy. All authors read, provided feedback, and approved the final manuscript.

Acknowledgements: Nathalie Leclair for her search strategy contribution.

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Appendix 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			**Page**
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	18
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-8 & 11-13
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	22-23

1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11-14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism: protocol for a systematic review and meta-analysis of individual participant data

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023939.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Oct-2018
Complete List of Authors:	Robin, Philippe; CHRU de Brest, Eddy, Maggie; Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Thrombosis Research Group, Ottawa, Canada Sikora, Lindsey; University of Ottawa, Health Sciences Library Le Roux, Pierre-Yves; CHRU de Brest, Médecine Nucléaire Carrier, Marc; Ottawa Hospital Research Institute Couturaud, F.; CHU Cavale Blanche Planquette, Benjamin; Hôpital Européen Georges Pompidou, AP-HP Pesavento, Raffaele; University of Padua Rodger, Marc; Ottawa Hospital Research Institute Salaun, Pierre-Yves; CHRU de Brest Le Gal, G; Ottawa Hospital Research Institute, University of Ottawa
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	pulmonary embolism, lung scintigraphy, recurrent venous thromboembolism, residual pulmonary vascular obstruction

Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism: protocol for a systematic review and meta-analysis of individual participant data

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Total word count: 3378

Abstract

Background: In patients with a first, unprovoked venous thromboembolism (VTE), the optimal duration of anticoagulant therapy (AT) is controversial due to tightly balanced risks and benefits of indefinite anticoagulation. The objective of this study is to assess among patients with a first acute pulmonary embolism (PE) who received ≥ 3 months of AT and thereafter had a planar lung scan, whether residual pulmonary vascular obstruction (RPVO) is associated with VTE recurrence after discontinuation of AT.

Methods and analysis: We will conduct a systematic review with a meta-analysis of individual participant data (IPDMA) of contemporary studies evaluating the prognostic significance of RPVO in patients with a first acute PE. We will search from inception to January 24th, 2018, PubMed, Medline, Embase, and Cochrane's Central Registry for Randomized Controlled Trials, CENTRAL for randomized controlled trials and prospective cohort studies. Two reviewers will conduct all screening and data collection independently. The methodological quality and risk of bias of eligible studies will be carefully and rigorously assessed using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. The primary objective will be to assess the relationship between RPVO on V/Q scan after completion of at least 3 months of anticoagulant therapy after an acute PE event, and the risk of an objectively confirmed symptomatic recurrent VTE (including DVT or PE) or death due to PE. The secondary objectives will include the assessment of the optimal RPVO cut-off and the risk of recurrent VTE, as well as the relationship between the relative change in RPVO between PE diagnosis and at discontinuation of AT (≥ 3 months) and risk of recurrent VTE.

Ethics and dissemination: This study of secondary data does not require ethics approval. It will be presented internationally and published in the peer reviewed literature.

PROSPERO registration number: CRD42017081080.

Keywords: pulmonary embolism; lung scintigraphy; recurrent venous thromboembolism, residual pulmonary vascular obstruction

Strengths and Limitations of this study

- This will be the first systematic review and individual patient data meta-analysis (IPDMA) to provide precise estimates for the relationship between residual pulmonary vascular obstruction (RPVO) on planar lung scan after completion of anticoagulation therapy (AT) after acute pulmonary embolism (PE), and the risk of recurrent venous thromboembolism (VTE).
- Electronic databases will be consulted following a rigorous selection process, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements. A Peer Review of Electronic Search Strategy (PRESS) will be performed by a second librarian.
- The quality of included studies will be evaluated using validated tools specifically developed to assess the risk of bias of randomized controlled trials (Cochrane Collaboration Risk of Bias tool) and cohort studies (ROBINS-1 tool).
- A two-stage meta-analysis will be performed using the complete case database for all outcomes.
- Conclusions will be limited by the numbers and the quality of included studies.

Introduction

The risk of recurrence after a first episode of venous thromboembolism (VTE) is high, especially in patients with unprovoked VTE (1-4). Indeed, these patients carry a risk of recurrence of approximately 10% one year after discontinuing anticoagulant therapy. Current clinical practice guidelines recommend at least three months of oral anticoagulation therapy (AT) after a first provoked VTE (5). In patients with a first, unprovoked VTE, characterized by the absence of major transient risk factors, the optimal duration of AT is controversial. Although AT is very effective for reducing the risk of recurrent VTE during therapy, this benefit disappears after discontinuation of treatment (6). Extending AT indefinitely after an unprovoked VTE may not be the most appropriate management strategy for every patient because the treatment benefit needs to be balanced against the risk of major bleeding, the main adverse effect of AT (7). A better prediction of the risk of recurrent VTE after AT discontinuation is necessary to determine the optimal, individualized treatment plan.

Stratification of the recurrence risk after a first episode of VTE is an important topic of research. Various predictors have been described to identify subgroups of patients whose risk of recurrent VTE is low enough that they could safely stop AT (8). Indeed, patient age, patient sex, location of the VTE, and D-dimer levels may inform decisions about the duration of AT in patients with unprovoked VTE (9). Moreover, some studies have suggested that residual vein obstruction (RVO) identified on venous compression ultrasonography of the lower limbs in patients with deep vein thrombosis after 3-6 months of anticoagulant therapy, may be associated with higher risk of recurrent VTE (10-13). The role of residual pulmonary artery obstruction has been much less studied. Whether residual pulmonary vascular obstruction (RPVO) improves the stratification of the risk of recurrence after PE, and could influence decisions about AT duration especially for unprovoked VTE, is still unknown. Results from clinical studies are conflicting. Two single-centre prospective cohort studies designed to evaluate the association between residual pulmonary embolism detected on ventilation-perfusion (V/Q) scan and risk of recurrent VTE were published

recently and they showed inconsistent results (14,15). One study found no significant association between residual perfusion defect on lung scintigraphy and VTE recurrence (14), whereas the results of the other study suggested that RPVO > 10% was an independant risk factor of recurrent VTE after a first acute PE (15).

To address this knowledge gap, we sought to perform a systematic review and individual patient data meta-analysis (IPDMA) of contemporary studies evaluating the prognostic significance of RPVO in patients with a first acute PE. The objective of this study is to assess among patients with a first acute pulmonary embolism who received ≥ 3 months of anticoagulant therapy and thereafter had a planar lung V/Q scan, whether residual pulmonary vascular obstruction is associated with VTE recurrence after discontinuation of anticoagulant therapy at one year.

METHODS

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P; see Appendix 1) (16). For the IPDMA, we will adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) (17). In accordance with the guidelines, this systematic review was registered with the International Prospective Register of Systematic Reviews on 5 December 2017 (registration number: CRD42017081080)

Eligibility criteria

Studies will be selected according to the criteria specified below.

Study designs

We will include randomized controlled trials, and prospective cohort studies. Retrospective cohort studies, case-control studies, cross-sectional studies, and cases reports will be excluded.

Participants

The study population will include adult patients (18 years or older) who had experienced and survived a first episode of objectively confirmed acute PE, that is either unprovoked or provoked by a transient and/or persistent risk factor (18), had completed at least 3 months of anticoagulant therapy, and did not have any recurrence during this period.

Interventions

Patients had to receive a planar ventilation/perfusion (V/Q) lung scintigraphy at discontinuation of anticoagulation therapy (i.e. ≥ 3 months of anticoagulation therapy), with an assessment of the pulmonary vascular obstruction.

Timing

Patients had to be followed prospectively for recurrent symptomatic VTE (PE or DVT) after discontinuation of anticoagulation therapy. All events occurring during follow-up had to be documented by an adjudication committee, or by an investigator blinded to the planar V/Q scan results.

Objectives

Primary objective:

- Relationship between residual pulmonary vascular obstruction (RPVO) on V/Q scan after completion of at least 3 months of anticoagulant therapy after acute PE, and risk of recurrent VTE at one year.

Secondary objectives*:*

- Association between the percentage of RPVO using different cut-off (>0%, ≥5%, ≥10%), and the risk of recurrent VTE.
- Relationship between the relative change in RPVO between PE diagnosis and at discontinuation of AT (≥ 3 months), and risk of recurrent VTE.
- Recurrence rate per patient-year following a provoked or an unprovoked PE.
- Type/site (number of isolated proximal DVT, isolated PE, PE + DVT, fatal PE) of recurrence and median time to recurrence (in months).
- Risk factors of RPVO in patient's baseline characteristics.
- Independence of RPVO as a predictor for recurrent VTE.
- Percentage of RPVO/ change in RPVO and risk of developing Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Information sources and search strategy

The following databases will be accessed during the electronic component of the systematic review: PubMed, Medline and Medline in Process (via OVID), Embase Classic + Embase (via OVID), and Cochrane's Central Registry for Randomized Controlled Trials, CENTRAL (via OVID). The specific search strategies will be created by a Health Sciences Librarian with expertise in the design of systematic review searching. A Peer Review of Electronic Search Strategy (PRESS) will be performed by a second librarian. A search strategy will be developed to define keywords for all searches (see Appendix 2 for Medline searches). After the MEDLINE strategy will be finalized, it will be adapted to the syntax of the other databases. There will be no beginning date identified, while the cutoff date will be January 24, 2018. There will be no language exclusion criteria, nor any other publication restrictions.

Study selection process

Literature search results will be imported into EndNote v17.3.1.8614, de-duplicated, and then uploaded to the Covidence platform (www.covidence.org) to facilitate collaboration among the reviewers during the study selection process. Two reviewers (PR and ME) will independently screen titles and abstracts, and will independently assess the full-text articles for eligibility, using a pre-defined list of exclusion criteria. Disagreements will be resolved by consensus or by a third person (GLG). None of the review authors will be blind to the journal titles or to the study authors or institutions.

Search results and study selection will be illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (19), with reasons specified for excluding articles during full-text screening.

Included studies and data collection process

For the studies that will be included in the review, corresponding authors will be invited by e-mail to participate in the project. Investigators who agreed to participate will be requested to provide a

copy of their dataset. Each dataset will be carefully checked for the quality of the data in collaboration with the investigator. Data from each participant in the relevant studies will be re-analysed and recoded to make them compatible and standardized in related studies.

The common dataset will include whenever possible:

- *Participant characteristics*: Demographics characteristics (age, gender, height, weight, BMI), medical history (previous VTE), comorbid conditions (chronic lung disease, tobacco use (current or past smoker vs. never smoked)), thrombophilia,
- *Index event (i.e. acute PE)*: date of acute PE, definition of VTE that is provoked or unprovoked [(transient major risk factors, prolonged immobility, recent trauma or surgery, hormonal therapy (oral contraceptive pill or hormone replacement therapy), active cancer, thrombophilia (V Leiden mutation, ATIII/Protein C/Protein S deficiency, APL)],
- *Treatment of index event*: Type of treatment, duration of therapy before stopping AT (date of starting AT and date of AT discontinuation),
- *Initial PVO assessment at the time of index event*: Date and type of initial PVO assessment at the time of acute PE diagnosis,
- *Residual pulmonary vascular obstruction at AT discontinuation*: date of RPVO assessment at AT discontinuation, definition of RPVO (normal lung V/Q scan vs. abnormal V/Q scan or >0%, ≥5%, ≥10%), extent of RPVO, D-dimer level just before AT discontinuation, antiplatelet use at AT discontinuation, post-thrombotic syndrome at AT discontinuation,
- *Follow-up information*:, date and type of objectively confirmed recurrent VTE (total number of isolated proximal DVT, isolated PE, PE + DVT, Fatal PE), CTEPH diagnosis, date of end of follow-up (i.e. date and cause of death, or date of lost to follow-up).

Once the individual patient data from all primary studies will be homogenized and merged, descriptive statistics will be used to check consistency of the data. Using the provided datasets,

the baseline tables and primary analysis will be replicated. Any inconsistencies or discrepancies will be resolved by contacting the investigators.

Risk of bias of individual studies

RCTs will be appraised using the Cochrane Collaboration Risk of Bias tool (20). For studies that have used a cohort design, the ROBINS-1 tool will be used (21). Signaling questions for each domain will be adapted or omitted, and we will add questions, if needed. Two reviewers (PR and ME) will independently assess the studies for risks of bias on a study level. A judgment as to the possible risk of bias on each item in the domains ('low risk', 'moderate risk', or 'high risk') will be made from study-level data and, if needed, from a summary of the obtained individual patient data. Results will be compared and disagreements resolved by discussion or, if needed, with the help of a third reviewer.

Research questions

Research question 1:

What is the clinical/prognostic significance of residual pulmonary vascular obstruction (RPVO) in patients with treated pulmonary embolism?

The primary objective will be to assess the relationship between RPVO on V/Q scan after completion of at least 3 months of anticoagulant therapy after an acute PE event, and the risk of an objectively confirmed symptomatic recurrent VTE (including deep vein thrombosis or pulmonary embolism) or death due to PE.

Proximal deep vein thrombosis recurrence will have to be defined as a symptomatic objectively confirmed lower limb deep vein thrombosis involving the popliteal or more proximal veins by compression ultrasonography. A diagnosis of pulmonary embolism recurrence will have to be based on a new finding of intravascular filling defect in a different segmental area than for the initial PE on CTPA, or a new segmental perfusion defect on planar V/Q lung scan. Sudden

unexplained deaths will have to be considered to be related with PE. All events occurring during follow-up will have to be adjudicated.

Research question 2:

What is the most clinically relevant definition of residual PE (RPVO) for the prediction of recurrent VTE?

A RPVO is defined as the persistence of a perfusion defect on planar V/Q lung scan after discontinuation of anticoagulant therapy. However, the definition of residual PE varies among studies, using different perfusion defect cut-off values. Residual PE should be considered in case of an abnormal V/Q scan whatever the extent of the perfusion defects is, or residual PE should be considered above a certain amount of perfusion defect (e.g. more than 5 or 10%, or more than one segmental, more than two sub-segmental or two segmental perfusion defects). A ROC curve analysis will be performed in order to find the most appropriate predictor of VTE recurrence in patients with treated acute PE.

Research question 3:

What are the risk factors for RPVO?

We will try to identify factors in patient's history or physical exam at presentation that could affect RPVO. Some concomitant diseases or exposures (e.g. chronic obstructive pulmonary disease (COPD), pneumonia, and tobacco use) are known to induce lung parenchymal alteration and thus lung scan abnormalities. We will perform univariate analyses of the association between each of the predictors in patient's baseline characteristics and RPVO, using chi-2 test or Fischer exact test when appropriate for categorical variables and Student t-test for continuous variables. Multivariate analyses will be performed using Cox proportional hazard models that included all variables that achieved a p value of ≤ 0.20 in univariate analyses.

Research question 4:

What is the independence of RPVO as a predictor for recurrent VTE?

When examining the relationship between an explanatory factor and an outcome, we are interested in identifying factors that may modify the factor's effect on the outcome. A confounding factor corresponds to a situation in which the association between an exposure (i.e. RPVO) and outcome (i.e. risk of recurrent VTE) is distorted by the presence of another variable (i.e. COPD).

Research question 5:

Is change in RPVO between PE diagnosis and at discontinuation of AT (≥ 3 months), predictive of recurrent VTE or the development of CTEPH?

We know that more than 50% of patients with PE will still have perfusion defects after 6 months of AT, which may persist for several months. Some patients will recover their lung perfusion after AT, some patients not. We would like to know if the change of RPVO between diagnosis and after AT discontinuation is predictive of recurrent VTE or development of CTEPH: are patients with no change in PVO more likely to present a recurrence or CTEPH than those who recover partially or totally their lung perfusion?

Data synthesis

Meta-analysis

Characteristics of eligible studies will be summarized and presented in a table in the final report. One of the main objectives of this systematic review is to combine individual participant data from pertinent studies to generate a pooled estimate of the rate of recurrent VTE in patient with RPVO diagnosed on planar V/Q scan after discontinuation of at least 3 month of AT for an acute PE. Prior to pooling results, the research team will assess studies for clinical and methodological

heterogeneity through comparison of important study characteristics. The degree of statistical heterogeneity will be measured and interpreted using a combination of Cochrane's Q (statistically significant at p<0.10) and the I2 statistic (>50% considered substantial). An I2 value >75% is indicative of a very high degree of heterogeneity, and if encountered the data will not be pooled. If homogeneity among studies is judged as satisfactory, then the results from studies will be pooled using standard meta-analysis procedures.

Statistical analysis

Data will be quantitatively synthesized as follows. A two-stage meta-analysis will be performed using the complete case database for all outcomes to generate forest plots, enabling results across studies to be compared visually, illustrate heterogeneity and differences across subgroups (22).

General characteristics of participants will be assessed using mean and standard deviation for quantitative variables, number and proportion of total participants for qualitative variables. A sensitivity analysis, in which patients with provoked and cancer-associated VTE will be excluded, will be performed. ROC curve analysis will be performed in order to find the most appropriate cut-off for RPVO to predict VTE recurrence in patients with treated acute PE. Incidence rates of recurrent VTE will be calculated as the number of recurrent VTE over the number of person-years of follow-up. Univariate analyses of the association between each of the predictors in patient's baseline characteristics and RPVO will be performed using chi-2 test or Fischer exact test when appropriate for categorical variables and Student t-test for continuous variables. Multivariate analyses will be performed using Cox proportional hazard models that included all variables that achieved a p value of ≤ 0.20 in univariate analyses.

Management of missing data

If data are not directly reported, they will be requested from the primary investigator of the study. Patients in whom the PVO was not assessed will be excluded from the analysis. We will not use imputation techniques or consider missing data to be normal or abnormal. Number of missing values will be reported. If a variable was not collected in one of the studies, the study will be excluded from the corresponding analysis. As a consequence, analyses may be restricted to subgroups of studies which can provide the required information. Analysis will be conducted on the final data available, and the potential impact of the missing data will be discussed as a limitation.

Limitations and challenges

IPDMA is a powerful method to address questions, since combining individual data from multiple studies allows for greater precision of estimates, analysis of clinically relevant subgroups and the evaluation of narrower outcomes. In addition, an IPDMA enables exploration of methodological and statistical heterogeneity between the studies.

However, IPDMA also have limitations that need to be highlighted. Pooling of data may be biased due to differences across the studies with respect to inclusion criteria. Although all investigators will provide their datasets, we acknowledge that it will be difficult, even impossible for some studies to retrieve additional information from the medical records. As a consequence, analyses may be restricted to subgroups of studies which can provide the required information.

The present IPDMA will aim to address several unanswered questions about the relationship between residual perfusion vascular obstruction on planar lung scan after completion of at least 3 months of AT after acute PE, and the risk of recurrent VTE. Thus, identification of patients with low enough risk of recurrent VTE using RPVO on lung scintigraphy might help physicians to justify safely stopping AT in patients with VTE.

Ethics and dissemination

Ethical approval and patient consent are not required since this is a systematic review on published studies. The results of this study will be submitted for presentation at relevant national and international conferences, and for publication in a peer-reviewed journal.

Patient and Public Involvement

Patients and or public were not involved in this study.

List of abbreviations:

AT: Anticoagulant Therapy

COPD: Chronic obstructive pulmonary disease

CTEPH: Chronic Thromboembolic Pulmonary Hypertension

DVT: Deep Vein Thrombosis

IPD: Individual Patient Data

IPDMA: Individual Patient Data Meta-Analysis

PE: Pulmonary Embolism

PRISMA: Preferred Reporting Items for Systematic Review

PROSPERO: Prospective Register of Systematic Reviews

RCT: Randomized Controlled Trial

RPVO: Residual Pulmonary Vascular Obstruction

RVO: Residual Vein Obstruction

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

VTE: Venous Thromboembolism

Declarations

Ethics approval and consent to participate: Ethical approval and patient consent are not required since this is a meta-analysis based on published studies.

Consent for publication: Not applicable.

Availability of data and material: Not applicable.

Competing interests: None of the authors have competing interests to declare.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contributions:

MC, GLG, PR, and PYS developed the methodology for the protocol.

LS developed the search strategy.

GLG, PR, and PYS drafted the manuscript with input from all members of the authorship team.

The manuscript was reviewed by FC, ME, PYLR, RP, BP, and MR for important intellectuel content.

All authors (PR, GLG, MC, PYS, FC, ME, PYLR, RP, BP, MR and LS) read, provided feedback, and approved the final manuscript.

Acknowledgements: Nathalie Leclair for her search strategy contribution.

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Appendix 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			**Page**
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	19
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	19
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-10 & 12-14
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10-11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14-15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2

MEDLINE search strategy

1. Venous Thrombosis/
2. exp Pulmonary Embolism/
3. (pulmonary adj3 (embolism* or thrombo-embolism or thromboembolism* or infarct*)).tw
4. ((venous or deep vein) adj2 thrombos*).tw.
5. phlebothrombos*.tw.
6. or/1-5
7. Ventilation-Perfusion Ratio/
8. Lung/dg [Diagnostic Imaging]
9. Perfusion Imaging/
10. (planar adj3 ventilation adj2 perfusion adj3 (scan* or scintigraph*)).tw.
11. (planar adj3 v?q adj4 (scan* or scintigraph*)).tw.
12. or/7-11
13. Anticoagulants/
14. Antithrombins/
15. (anticoagulant* or anti-coagulant* or antithrombin* or anti-thrombin*).tw.
16. (thrombin adj3 inhibit*).tw.
17. (Factor Xa adj2 (antagonist? or inhibit* or block*)).tw.
18. heparin/ or exp heparin, low-molecular-weight/
19. (heparin* or beparine or clarin or contusol or disebrin or eleparon or elheparin or elheparon or epiheparin or gag 98 or helberina or hepaflex or hepalean or heparitin* or hepcon or hepsal or inhepar or inviclot or lipo-hepin or lipohepin or liquemin or liquemine or menaven or monoparin or mucoitin or multiparin or nevparin or noparin or panheparin or panhepin or panheprin or parinix or praecivenin or pularin or thromb*or niparin or vetren or vaster).tw.
20. liquaemin.tw.
21. dalteparin*.tw.
22. fragmin*.tw.
23. enoxaprin*.tw.
24. clexane.tw.
25. lovenox.tw.
26. fraxiparin*.tw.
27. nadroparin*.tw.
28. Warfarin/
29. (warfarin or warfant or tedicumar or savaysa or endoxaban or befarin or adoisine or carfin or circuvit or coumadan or coumafene or coumaphene or dagonal or tintorane or uniwarfin or waran or warfar or warnerin or farin or jantoven or kumatox or maforan or orfarin or panwarfarin or panwarfin or prothromadin or warfil* or sofarin).tw.
30. coumadin*.tw.
31. aldocumar.tw.
32. marevan.tw.
33. exp Vitamin K/ai
34. (Vitamin K adj2 (antagonist? or inhibit* or block*)).tw.
35. Dabigatran/
36. dabigatran.tw.
37. pradaxa.tw.
38. Rivaroxaban/
39. rivaroxaban.tw.
40. eliquis.tw.
41. xarelto.tw.
42. Factor Xa Inhibitors/

43. edoxaban.tw.
44. lixiana.tw.
45. or/13-44
46. 6 and 12 and 45
47. 46 not (Animals/ not (Animals/ and Humans/))