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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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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 of contemporary studies evaluating the prognostic significance of RPVO in patients with a first acute PE. We will search from inception to 24 January 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 tool. The primary objective will be to assess the relationship between RPVO on ventilation–perfusion scan after completion of at least 3 months of AT after an acute PE event, and the risk of an objectively confirmed symptomatic recurrent VTE (including deep vein thrombosis 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.

Strengths and limitations of this study

- This will be the first systematic review and individual patient data meta-analysis to provide precise estimates for the relationship between residual pulmonary vascular obstruction on planar lung scan after completion of anticoagulation therapy after acute pulmonary embolism and the risk of recurrent venous thromboembolism.
- 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 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 randomised controlled trials (Cochrane Collaboration Risk of Bias tool) and cohort studies (Risk Of Bias In Non-randomised Studies of Interventions 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% 1 year after discontinuing anticoagulant therapy (AT). Current clinical practice guidelines recommend at least 3 months of oral AT after a first provoked VTE.[5] In patients with a first, unprovoked VTE, characterised 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, individualised 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 identified on venous compression ultrasonography of the lower limbs in patients with deep vein thrombosis (DVT) after 3–6 months of AT, 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 pulmonary embolism (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 PE 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 independent 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 PE who received ≥3 months of AT and thereafter had a planar lung V/Q scan, whether RPVO is associated with VTE recurrence after discontinuation of AT at 1 year.

METHODS

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA; see online supplementary appendix 1).[16] For the IPDMA, we will adhere to the PRISMA of individual participant data (IPD).[17]

Eligibility criteria

Studies will be selected according to the criteria specified below.

Study designs

We will include randomised controlled trials (RCTs) 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 AT and did not have any recurrence during this period.

Interventions

Patients had to receive a planar V/Q lung scintigraphy at discontinuation of AT (ie, ≥3 months of AT), 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 AT. 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 RPVO on V/Q scan after completion of at least 3 months of AT after acute PE and risk of recurrent VTE at 1 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 will be performed by a second librarian. A search strategy will be developed to define keywords for all searches (see online supplementary appendix 2 for Medline searches). After the Medline strategy will be finalised, it will be adapted to the syntax of the other databases. There will be no beginning date identified, while the cut-off date will be 24 January 2018. There will be no language exclusion criteria, nor any other publication restrictions.

Study selection process

Literature search results will be imported into EndNote V.17.3.1.8614, 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 predefined 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 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 email 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 reanalysed and recoded to make them compatible and standardised in related studies.

The common dataset will include whenever possible:

- Participant characteristics: Demographics characteristics (age, gender, height, weight, body mass index), medical history (previous VTE), comorbid conditions (chronic lung disease, tobacco use (current or past smoker vs never smoked)), thrombophilia.
- Index event (ie, 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 (contraceptive pill/oral contraceptives or hormone replacement therapy), active cancer, thrombophilia (V Leiden mutation, ATIII/protein C/protein S deficiency, antiphospholipid syndrome (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.
- RPVO 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 (ie, date and cause of death or date of lost to follow-up).

Once the individual patient data from all primary studies will be homogenised 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 Risk Of Bias In Non-randomised Studies of Interventions tool will be used.[21] Signalling 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 judgement 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 RPVO in patients with treated PE?

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

Proximal DVT recurrence will have to be defined as a symptomatic objectively confirmed lower limb DVT involving the popliteal or more proximal veins by compression ultrasonography. A diagnosis of PE 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?

An RPVO is defined as the persistence of a perfusion defect on planar V/Q lung scan after discontinuation of AT. 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 (eg, more than 5% or 10%, or more than one segmental, more than two subsegmental or two segmental perfusion defects). A receiver operating characteristic (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 examination at presentation that could affect RPVO. Some concomitant diseases or exposures (eg, 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 χ^2 test or Fisher's exact test when appropriate for categorical variables and Student's 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 (ie, RPVO) and outcome (ie, risk of recurrent VTE) is distorted by the presence of another variable (ie, 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 summarised and presented in a table in the final report. One of the main objectives of this systematic review is to combine IPD 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 months 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 I^2 statistic (>50% considered substantial). An I^2 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 synthesised 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 SD 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. An 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 χ^2 test or Fisher's exact test when appropriate for categorical variables and Student's 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. The 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, IPDMAs 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

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.

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