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Residual pulmonary embolism as a predictor for recurrence after a first unprovoked episode: Results from the REVERSE cohort study

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ABSTRACT

Background: The optimal duration of oral anticoagulant therapy after a first, unprovoked venous thromboembolism is controversial due to tightly balanced risks and benefits of indefinite anticoagulation. Risk stratification tools may assist in decision making.

Objectives: We sought to determine the relationship between residual pulmonary embolism assessed by baseline ventilation-perfusion scan after completion of 5–7 months of oral anticoagulant therapy and the risk of recurrent venous thromboembolism in patients with the first episode of unprovoked pulmonary embolism.

Methods: We conducted a multicentre prospective cohort study of participants with a first, unprovoked venous thromboembolism enrolled after the completion of 5–7 months of oral anticoagulation therapy. The participants completed a mean 18-month follow-up. Participants with pulmonary embolism had baseline ventilation-perfusion scan before discontinuation of oral anticoagulant therapy and the percentage of vascular obstruction on baseline ventilation-perfusion scan was determined. During follow-up after discontinuation of oral anticoagulant therapy, all episodes of suspected recurrent venous thromboembolism were independently adjudicated with reference to baseline imaging.

Measurements and main results: During follow-up, 24 of 239 (10.0%) participants with an index event of isolated pulmonary embolism or pulmonary embolism associated with deep vein thrombosis and central assessment of percentage of vascular obstruction on baseline ventilation-perfusion scan had confirmed recurrent venous thromboembolism. As compared to participants with no residual pulmonary embolism on baseline ventilation-perfusion scan, the hazard ratio for recurrent venous thromboembolism was 2.0 (95% CI 0.5–7.3) for participants with percentage of vascular obstruction of 0.1%–4.9%, 2.1 (95% CI 0.5–7.8) for participants with percentage vascular obstruction of 5.0%–9.9% and 5.3 (95% CI 1.8–15.4) for participants with percentage vascular obstruction greater than or equal to 10%.

Conclusions: Residual pulmonary embolism assessed by pulmonary vascular obstruction on baseline ventilation-perfusion performed after 5–7 months of oral anticoagulant therapy for the first episode of unprovoked

Abbreviations: CUS, compression ultrasonography; DVT, deep vein thrombosis; FVL, Factor V Leiden; OAT, oral anticoagulant therapy; PE, pulmonary embolism; PGM, prothrombin gene mutation; PVO, percentage of vascular obstruction; RVO, residual vein obstruction; VTE, venous thromboembolism; V/Q, ventilation-perfusion

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pulmonary embolism was associated with a statistically significant higher risk of subsequent recurrent venous thromboembolism. Percentage of pulmonary vascular obstruction assessment by ventilation-perfusion scans maybe a useful tool to help guide the duration of oral anticoagulant therapy after a first unprovoked pulmonary embolism.

Trial registration: Registered at www.clinicaltrials.gov identifier: NCT00261014.

1. Introduction

The optimal duration of oral anticoagulant therapy (OAT) after a first, unprovoked venous thromboembolism (VTE), characterized by the absence of major transient risk factors, is controversial. In patients with unprovoked VTE, the risk of recurrence after discontinuing OAT is high [1–4]. Although OAT is very effective for reducing the risk of recurrent VTE during therapy, this benefit disappears after discontinuation of treatment [4,5]. 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 [6]. In the setting of unprovoked VTE, rate of major bleeding events during OAT is lower than rate of recurrent VTE after OAT discontinuation, but the case-fatality rates of major bleeding events and recurrent VTE, 11.3% versus 3.6% respectively, need to be considered when balancing the risk-benefit ratio of extended duration of OAT [7]. Although current clinical practice guidelines suggest indefinite anticoagulation in most patients with a first, unprovoked VTE [8], better prediction of the risk of recurrent VTE after OAT discontinuation is necessary to determine the optimal, individualized treatment plan.

Ongoing research attempts to identify independent risk factors of recurrent VTE in order to stratify subgroups of patients with a low enough recurrence risk to safety discontinue OAT [9]. Several risk factors, including characteristics of the index thromboembolic event (location of VTE), demographic characteristics (age, sex, ethnicity) and parameters related to haemostasis (thrombophilia, D-dimer levels, thrombin generation assays) have been studied [10]. Several studies suggested that persistent residual venous obstruction (RVO) in leg vein imaging after 3–6 months of OAT for deep vein thrombosis (DVT) may be associated with higher risk of recurrent VTE. Residual vein obstruction may impair venous flow leading to stasis and local activation of coagulation cascade, or may be a surrogate marker for a hypercoagulable state [11–14]. Whether the same applies to residual pulmonary artery occlusion is widely unknown. 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 [15,16]. Therefore, we sought to determine the relationship between residual pulmonary embolism (PE) assessed by percentage of vascular obstruction (PVO) on baseline V/Q scan after completion of 5–7 months of OAT and risk of recurrent VTE among patients with unprovoked pulmonary embolism included in the REVERSE study.

2. Methods

2.1. Study design and selection of participants

The REVERSE study was a prospective cohort study designed to derive a clinical decision rule to identify patients at low risk for recurrent VTE after completion of 5 to 7 months of OAT for a first, unprovoked major VTE [9]. Institutional research ethics board approval was obtained at all participating centres. Between October 2001 and March 2006, consecutive unselected patients seen in clinics by participating physicians for VTE follow-up at 12 tertiary care centres in 4 countries were asked to participate if they had: 1) a first, objectively proven unprovoked VTE (proximal DVT, or segmental or greater PE) 5–7 months before enrollment; 2) received heparin or low-molecular-weight heparin for 5 or more days followed by 5–7 months of OAT (target International Normalized Ratio 2 to 3); and 3) no recurrent VTE during the initial treatment period. Diagnosis of PE required a high-probability V/Q scan or a segmental or larger artery filling defect on CTPA. Diagnosis of DVT required a non-compressible segment on compression ultrasonography (CUS) of the popliteal vein or a more proximal leg veins. Unprovoked VTE was defined as VTE occurring in the absence of a leg fracture or lower extremity plaster cast, immobilization for > 3 days or surgery using a general anesthetic in the 3 months prior to the index event, and without diagnosis of malignancy in the past five years at the time of enrollment. Patients were excluded if they were unable or unwilling to provide written informed consent, were under the age of 18 years, had already discontinued OAT, required ongoing anticoagulation for reasons other than VTE, were geographically inaccessible for follow-up, were being treated for a recurrent unprovoked VTE or a previously known high-risk thrombophilia, defined as known deficiency of protein S, protein C or antithrombin, known persistently positive anticardiolipin antibodies (> 30 U/ml), known persistently positive lupus anticoagulant or 2 or more known thrombophilic defects (e.g. homozygous for Factor V Leiden (FVL) or prothrombin gene mutation (PGM), or compound heterozygous for FVL and PGM). Thrombophilia testing was not systematically conducted prior to enrolment but patients were excluded if high-risk thrombophilia was independently identified prior to enrolment.

2.2. Baseline imaging assessment

After obtaining written informed consent, all participants underwent standardized data collection including demographic characteristics, non-major risk factors for VTE and imaging reports documenting the index (i.e. initial) VTE 5–7 months before enrollment. All participants then underwent baseline imaging including CUS of the leg(s) that had signs or symptoms of DVT at the time of the index event, and/or V/Q scan if the patient had signs or symptoms PE at the time of index event. V/Q scans were locally interpreted in each participating centre and nuclear medicine physicians were asked to classify V/Q scans as normal, abnormal or inadequate.

The PVO on baseline V/Q scan was centrally assessed by a single experienced nuclear medicine physician after completion of the study. In a subset of 65 randomly selected participants, a second nuclear medicine physician independently assessed the PVO. The method previously described by Brochier and Meyer [17,18] was used to assess the PVO on the V/Q scans. Each lobe was assigned a weight based on the regional distribution of pulmonary blood flow in the supine position: right lower lobe 25%, right middle lobe 12%, right upper lobe 18%, left lower lobe 20%, lingula 12% and left upper lobe 13%. Perfusion within each lobe was estimated from the anterior, posterior and oblique views. For each lobe, a semi-quantitative perfusion score from 0 to 1 (0, 0.25, 0.5, 0.75 or 1) was determined based on the size and severity of the perfusion defect. Each lobar perfusion score was then calculated by multiplying the weight by the perfusion score. The overall perfusion score was determined by summing the six separate lobar perfusion scores. The PVO by perfusion scanning was then calculated as (1 − overall perfusion score) × 100. A PVO score of 0% indicates no residual vascular obstruction in the lungs.