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Full Length Article

History of deep vein thrombosis is a discriminator for concomitant atrial fibrillation in pulmonary embolism☆,★

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ABSTRACT

Background: Pulmonary embolism (PE) is the consequence of deep vein thrombosis (DVT) in 70% of all cases. Although, PE and DVT are commonly related to risk factors of Virchow's triad, both entities are linked to cardiovascular risk factors, but risk factors seem differently important in both entities.
Objectives: We aimed to investigate clinical profile and outcome of patients with PE history stratified by concomitant DVT.
Patients/Methods: Data from the observational multi-center thrombEVAL-study were analyzed.
Results: The sample (N = 2,318) comprised 295 PE patients, of whom 69.2% (N = 204) had DVT. Individuals without DVT were older and had higher prevalence of concomitant atrial fibrillation (AF), chronic lung diseases, coronary artery disease, heart failure and hypertension. Multivariable regression revealed an independent association of AF (Odds Ratio (OR) 3.17, 95% CI 1.63–6.18, P < 0.001) and coronary artery disease (OR 2.31, 95% CI 1.15–4.66, P = 0.019) with PE without DVT. There was higher frequency of permanent AF in individuals without DVT, whereas paroxysmal AF was more prevalent in individuals with DVT. All AF subtypes were independently associated with PE without DVT with increasing ORs from paroxysmal to permanent AF. PE patients with and without DVT did not differ in survival (P = 0.32) and cost-relevant clinical outcome (P = 0.26) during follow-up. AF in PE patients was associated with cost-relevant clinical outcome (Hazard Ratio (HR) 1.78, 95% CI 1.03–3.09, P = 0.040), but no significant difference in survival (HR 0.93, 95% CI 0.35–2.50, P = 0.88) was observed.
Conclusions: History of DVT is a significant discriminator for clinical profile of PE patients. Individuals without DVT had more often cardiac and pulmonary disease with strongest association with AF. Data advocate a potential link between AF and PE.
Clinical Trial Registration: URL: http://www.clinicaltrials.gov, Unique identifier NCT01809015.

1. Introduction

Acute pulmonary embolism (PE) is a cardiovascular emergency with high morbidity and mortality [1–3]. Annual incidence of PE ranges between 23 and 69 cases per 100,000 people in the general population [1].

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and PE. As Virchow postulated in 1856, the triad of venous stasis, vessel wall abnormalities such as endothelial dysfunction, flow abnormalities in combination with hypercoagulability are the main causes of venous thrombus formation [4]. Hence, VTE is commonly related to risk factors like trauma, immobilization, surgery, high age, pregnancy, myocardial infarction, congestive heart failure, hormone replacement therapy, thrombophilia and cancer [5–12]. However, a cumulating body of evidence suggests that VTE risk factors may not be equally important for both, DVT and PE. Cancer and factor V Leiden are more common in DVT, whereas PE is primarily associated with major surgery and trauma, high age, myocardial infarction and heart failure [11]. In about 70% of all cases, PE is the consequence of DVT rather than a separate

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; eCRF, electronic case report form; PE, pulmonary embolism; VTE, venous thromboembolism.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

★ Summary conflict of interest statement: Nothing to declare.

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clinical entity [13]. For PE without underlying DVT, data from clinical studies suggest an important role of co-morbidities like cancer [14], atrial fibrillation (AF) [15], myocardial infarction [15] and heart failure [15] in the pathogenesis of thrombus formation.

We hypothesized that PE in patients without a history of DVT might have a different underlying pathomechanism and, therefore, we investigated whether these patients differ with respect to their cardiovascular and clinical profile, the strength of the associations and their outcomes.

2. Materials and methods

2.1. Study design

The thrombEVAL study program (registered at: http://clinicaltrials.gov, unique identifier: NCT01809015) was designed to compare the quality of oral anticoagulation with vitamin K antagonists between general medical care and a specialized telemedicine-based coagulation service [16–18]. The project comprises an observational, multi-center cohort study of patients with oral anticoagulation in regular medical care and a single-center cohort study of patients being treated by a telemedicine-based coagulation service, both located in Rhineland-Palatinate, Mid-west Germany. For the current analysis, data of individuals with history of venous thromboembolism, i.e. history of pulmonary embolism and/or deep vein thrombosis, from both cohorts were included.

2.2. Study sample

Between January 2011 and April 2013 a total number of 2318 patients were enrolled in 21 study-center hospitals.

Patients ≥18 years of age with indication for treatment with vitamin K antagonist were eligible for participation. All participants gave informed written consent prior to study enrolment. The local ethics boards and the local data safety commissioner have approved the study protocol. The investigation conforms to Good Clinical Practice and Good Epidemiological Practice and the principles outlined in the Declaration of Helsinki. The rationale and design of the thrombEVAL study have been recently described in detailed [16].

2.3. Assessment of study data

At the baseline visit, clinical data were obtained by a standardized clinical visit, from medical records and laboratory data and documented in an electronic case report file (eCRF) with predefined checks for plausibility according to standard operating procedures in both cohorts. Diagnosis and history of PE as well as DVT were assessed of medical report and patients' anamnesis. PE and DVT events were confirmed in former medical consultations.

Outcome (i.e., cost-relevant clinical outcome and survival under treatment with vitamin K antagonists) was measured via regular endpoint assessment through computer-assisted telephone interview and clinical visits. All information on study endpoints was validated by medical records and adjudicated by an independent review panel. In order to minimize loss to follow-up, checks with registration offices on mortality were performed on a regular basis. Study monitoring was carried out by an independent institution. All data underwent a detailed quality control before analysis.

2.4. Study groups

For this analysis, all patients of the thrombEVAL study program with a history of PE at baseline were included and categorized according to the presence of a concomitant history of DVT. Therefore, main premise for inclusion in one of the two study groups was a PE event at any time of life before acquisition and assessment for the thrombEVAL study. A history of DVT means that there was a DVT at any time of life in the medical history of the patients.

2.5. Definition of outcome parameters

Mortality under treatment with vitamin K antagonists comprises death of all causes in the one year of follow-up. Cost-relevant clinical outcome under treatment with vitamin K antagonists is defined as the composite of all cost-intensive complications, i.e. all thromboembolic events, major and clinically-relevant non-major bleeding and hospitalization during one year of follow-up.

2.6. Statistical analysis

For analysis, participants from the two thrombEVAL cohorts with history VTE were categorized as individuals with history of PE and no history of DVT, and individuals with both, history of PE and history of DVT.

For descriptive analysis, dichotomous variables were presented by absolute and relative frequencies; differences were tested with Fisher's Exact Test. Continuously normally distributed variables were described by mean and standard deviation and in case of a non-normal distribution by median and 25th and 75th percentiles (inter-quartile range, IQR). Statistical comparisons for continuous variables were made by the Mann–Whitney U-test in case of a non-normal distribution; otherwise the *t*-test was applied. Multivariable logistic regression was performed with the independent variable VTE group (i.e. PE with history of DVT versus PE without history of DVT) to assess the association of the subgroups with cardiovascular risk factors and comorbidities. All models were adjusted for age, sex and traditional cardiovascular risk factors, i.e. diabetes, dyslipidemia, family history of myocardial infarction, hypertension, obesity and smoking. Adjusted odds ratios (OR) are provided with 95% confidence interval (CI; denoted in brackets). Alpha level of 5% was chosen as threshold for statistical significance.

For the endpoints (survival and cost-relevant clinical outcome) under vitamin K antagonist treatment Kaplan–Meier curves were computed for 1 year of treatment. Comparison of the curves was tested with the logrank test. Moreover Cox-regressions with adjustment for age, sex and treatment cohort for hazard ratios (HR) with 95% CI (denoted in brackets) were calculated. Beside the comparison of the groups PE with and without concomitant history of DVT, the groups PE with and without concomitant AF were compared (this Cox-regression was additionally adjusted for presence of history of DVT).

A value of $P < 0.05$ was considered as significant clinical association. All tests were carried out two-sided. Analyses were performed with R, Version 3.0.3.

3. Results

The thrombEVAL sample (N = 2,318 of patients with indication for treatment with a Vitamin K antagonist) comprised 295 patients (12.7%) with a history of PE; 69.2% (N = 204) of these PE patients had a concomitant history of DVT. The clinical profile of individuals with history of PE stratified for concomitant history of DVT is presented in Table 1. PE patients without DVT were in median 4 years older than those with DVT ($P = 0.00056$) and suffered more frequently from arterial hypertension ($P = 0.0050$), on the other hand, they had lower values of body mass index ($P = 0.0057$). In multivariable logistic regression adjusting for all traditional cardiovascular risk factors, age and sex and modeling for PE without DVT history, taking PE with DVT history as reference group, age was independently associated with isolated PE (OR for decades of age, 1.26 [1.03–1.54], $P = 0.023$) and hypertension showed a tendency for association (OR, 1.87 [1.00–3.51], $P = 0.051$, see Fig. 1).

Stratification of PE patients for a history of DVT revealed marked differences in cardiac and lung diseases: Patients with isolated PE had