Clinical presentation and mortality in pulmonary embolism: The Optimev study

Présentation clinique et mortalité de l’embolie pulmonaire : les données de l’étude Optimev

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Received 30 March 2010; accepted 7 May 2010
Available online 2 July 2010

KEYWORDS
Venous thrombosis; Pulmonary embolism; Mortality; Diagnosis

Summary
Aims. — To describe the clinical presentation and 3-month mortality in recognized forms of venous thromboembolism (VTE).
Methods. — All 8256 patients referred to 359 vascular physicians for clinical suspicion of VTE were included over a 15-month period in France. Subjects without a confirmed diagnosis of VTE served as controls. Risk factors, clinical presentation and estimated 3-month survival for each form of VTE were evaluated.
Results. — Of 5889 patients, 426 had pulmonary embolism (PE) with deep vein thrombosis (DVT), 148 had PE without DVT, and 5315 had no VTE. 2350 patients with other VTE events (DVT and superficial vein thrombosis) and 17 other patients were excluded of the analysis. PE without DVT patients presented differently for risk factors in the univariate analysis. Three-month mortality was 4.0% for controls, 12.9% for PE with DVT, and 4.6% for PE without DVT. Compared with controls, only PE with DVT patients (adjusted hazard ratio: 2.6 95% CI [1.4—4.7]) were at increased risk of mortality.
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Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common clinical problem associated with significant mortality and life-long morbidity among hospitalized patients and outpatients [1–3]. The diagnosis of VTE is challenging because of the non-specific signs and symptoms of this disease [4,5]. Moreover, anticoagulant treatment has its own risks although it decreases the risk of recurrent VTE [6]. Many epidemiologic studies have focused on VTE, contributing to a better understanding and improving its management. Demonstrated risk factors for VTE have been included in clinical prediction rules derived to help physicians identify patients that should be referred for objective diagnostic tests [4,5]. Other studies have provided accurate estimates of 3-month mortality rates for PE (17%) and have identified prognostic factors that may guide the physician’s initial treatment strategy [7]. Over the past decade, clinical practices regarding VTE prophylaxis, diagnosis, and treatment have changed together with the literature. Primary prophylaxis has dramatically improved for surgical patients and consequently the relative frequency of surgical patients among patients with confirmed VTE has decreased [8]. The use of diagnostic tests combined with advances in imaging technology has resulted in more frequent diagnosis and treatment of atypical presentations of VTE, including isolated distal DVT and PE without DVT [9–13]. The clinical significance and prognosis of these forms of VTE are unknown and warrant clarification. The aim of this study was to investigate the clinical presentation and 3-month mortality associated with some forms of VTE: PE with DVT, and PE without DVT [14]. We conducted the Optimev study in two ways: a cross-sectional study of the prevalence of VTE, and a longitudinal study for the estimate of 3-month mortality.

Methods

Patients

VTE prevalence and analysis of clinical presentation

Inclusion criteria. We carried out a prospective study of patients 18 years of age or older referred for clinically suspected VTE to 359 board-certified vascular medicine physicians evenly distributed geographically throughout France. Depending on the physician and according to a defined plan, the enrolment period consisted of one or several consecutive days during each of the four seasons between November 2004 and January 2006, to avoid a seasonal bias [15]. Participating physicians enrolled all consecutive patients referred for clinically suspected VTE during their specific enrolment period. Clinically suspected VTE was defined as acute onset or worsening of dyspnea or sudden onset of chest pain for PE, and upper or lower limb pain, redness, or edema for DVT.

Exclusion criteria. Hemodynamically unstable patients were not included in the study. Patients with isolated superficial thrombophlebitis or upper limb DVT were diagnosed but not included in the analysis.

Data collection. Vascular medicine physicians prospectively collected baseline demographic characteristics, clinical data at presentation, diagnostic test results, and treatments (including anticoagulant therapy) using an electronic case-report form. Standardized definitions were used for the assessment of transient and chronic VTE clinical risk factors including personal history of VTE, family history of VTE, immobilization, surgery within the previous 45 days, active malignant neoplasm, congestive heart failure, respiratory insufficiency, infectious disease, varicose veins, obesity, pregnancy or early post-partum, hormone replacement therapy, and hormonal contraception.

Conclusions. — PE without DVT is not associated with a higher 3-month mortality compared to controls, in contrast to PE with DVT. When diagnosing PE in patients, the clinical significance of an associated DVT is important.

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**Objective testing of VTE.** Positive cases of VTE were categorized as isolated distal DVT, proximal DVT, PE with DVT, or PE without DVT based on the results of objective diagnostic tests. Patients without confirmed VTE were used as controls. All enrolled patients underwent bilateral B-mode complete compression ultrasound (CUS) of the lower extremities performed by a board-certified vascular medicine physician using a standardized examination protocol [16]. The proximal veins were examined with the patient in the supine position by distally moving the transducer and applying gentle compression along the deep venous system from the common femoral vein in the groin area to the trifurcation of the popliteal vein. The calf veins were evaluated down to ankle level by using CUS in a similar fashion to that of the proximal veins, with the patient in a sitting position with legs hanging down. The calf veins studied were the posterior tibial and fibular veins as well as the gastrocnemius muscular and soleal veins. When these calf veins were occluded they were considered as distal DVT; other thromboses accounted as proximal thromboses. The diagnostic criterion for a first episode of DVT was the non-compressibility of the vein in the transverse plane. Doppler analysis was used for the examination of iliac veins or inferior vena cava in cases of clinically suspected iliac or vena cava thrombosis which was not visible in the common femoral vein [16]. The diagnostic criterion for recurrent DVT was the non-compressibility of a previously normal venous segment in patients with previous history of DVT. Clinical suspicion of PE was confirmed based on findings from multidetector computed tomography, ventilation-perfusion scanning, pulmonary angiography, or in the presence of proximal DVT on ultrasound examination with PE clinical symptoms [17–19]. Multidetector computed tomography consisted of an evaluation of the main and lobar pulmonary arteries as well as the segmental and subsegmental branches of pulmonary arteries. The diagnostic criterion for PE by multidetector computed tomography was the presence of an intraluminal defect outlined by contrast material or the total occlusion of a vessel by low-attenuated material on at least two adjacent slices. In accordance with the PIOPED study, PE was confirmed in the case of a ventilation-perfusion scan showing a high probability of PE [18]. All cases of PE were validated by an independent expert committee.

**Population for longitudinal study follow-up**

**Inclusion criteria.** According to the study protocol, patients were selected for follow-up if they were positive cases of VTE (including patients with superficial thrombophlebitis and upper limb DVT) along with a random sample of controls that was matched by season and enrolling physician [14].

**Exclusion criteria.** For practical reasons, patients who were enrolled in overseas territories, resided outside of France, were homeless, or for whom case-report form completion was delayed could not be eligible for follow-up.

**Methodology of follow-up.** Clinical research assistants conducted structured telephone follow-up interviews with the patients, their relatives, or their primary care physicians 3 months after enrolment. Medical charts were reviewed whenever a patient was hospitalized or referred to a vascular medicine physician during the follow-up period. If follow-up data could not be obtained, the patient’s vital status was ascertained by using his birthplace vital record. All clinical outcomes and causes of death were adjudicated by an independent expert committee (based on the analysis of medical records).

**Statistical analysis**

Categorical variables were expressed as frequency and percentage and continuous variables as median and interquartile range (IQR). For qualitative variables, comparison between different types of VTE and controls was performed using a Chi² test when validation conditions were met (otherwise Fisher’s exact test was used). A Mann-Whitney test was used for continuous variables. Survival curves were established for controls and each form of VTE using Kaplan-Meier estimates. Hazard ratios for 3-month all-cause mortality for each form of VTE were estimated using the Cox proportional hazard model adjusting for sex, age, Charlson index class (0/1/2), theoretical duration of anticoagulant treatment, inpatient versus outpatient status, surgery within the previous 45 days, active malignant neoplasm, bedridden status, acute infectious disease, bone and joint disease, neurological disease, obesity, liver disease, congestive heart failure, respiratory insufficiency, renal failure, hypertension, diabetes, atherosclerosis, dyslipidemia, smoking status, history of digestive bleeding, and use of antiplatelet agents. The Charlson index is a score that allows an estimation of mortality based on comorbid conditions [20]. Two-sided P values of less than 0.05 were considered statistically significant. Statistical analyses were performed using Stata software (version 9.0; Stata Corp, College Station, Texas).

**Ethical and regulatory considerations**

All patients received written information explaining the study objectives and that they could decline telephone follow-up and could consult their data. The study protocol was approved by the Ethics Committee of the French Agency for data treatment in research in the health sector (Comité consultatif sur le traitement de l’information en matière de recherche dans la domaine de la santé) and the French Data protection agency (Commission nationale de l’informatique et libertés). Before starting the study, objectives and methodology were described and data are also available on: http://clinicaltrials.gov/, number: NCT00670540 [14].

**Results**

During the 15-month study period, 8256 patients were enrolled. A total of 2367 patients were excluded from this analysis because of discovery of an exclusion criterion after enrolment (n = 17), a positive diagnosis of isolated upper limb DVT (n = 78), a positive diagnosis of isolated superficial thrombophlebitis (n = 599), a positive diagnosis of distal DVT (n = 933), a positive diagnosis of proximal DVT (n = 710), an early clinical VTE event during follow-up (i.e., false negative cases, n = 16), and technical failure to either confirm or rule out the diagnosis of VTE (n = 14) (Fig. 1). Therefore, the study population for analysis of risk factors for PE consisted...
of 5889 patients, with a median of six patients enrolled per physician (IQR, 2 to 19). Results for DVT have been published previously [21].

The median age was 65 years (IQR, 50—77 years), 2194 (37%) were men, 2495 were inpatients (42%), and 1369 (23%) had a previous history of VTE (Table 1). Diagnosis of VTE was ruled out in 5315 patients (90.3%). A total of 574 patients (9.7%) were positive cases of PE including, 426 PE with DVT (7.2%), and 148 PE without DVT (2.5%). Suspected PE was objectively confirmed by positive multidetector computed tomography in 283 cases, ventilation-perfusion lung scan in 148 cases, and pulmonary angiography in three cases. Positive diagnosis of PE for the remaining 140 patients was based on the presence of proximal DVT on ultrasound examination with a clinical suspicion of PE. Of the 426 cases of PE with DVT, 264 had proximal DVT, 150 had distal DVT, six had upper limb DVT, and six had saphenofemoral junction thrombosis. Of the 429 patients for whom PE topography could be interpreted, 35 (15/287 [5%] patients with PE with DVT and 20/142 [14%] patients with PE without DVT, P < 0.01) had isolated sub-segmental emboli.

We looked at the patients’ clinical profiles and noticed that inpatients, acute respiratory failure or COPD exacerbation or NYHA class III or IV CHF, malignant neoplasm were significant risk factors for all forms of PE while age, men, personal history of DVT or PE and bed confinement were significantly associated with PE with DVT and not for PE without DVT. In PE, without DVT, patients were mostly inpatients but without being bedridden. The patient profile was similar for patients with a first or a recurrent episode of VTE. Overall, of the 5889 patients included in the transversal study, 2905 patients were followed up at 3 months (Fig. 1).

Kaplan-Meier survival estimates were 96% (CI, 95—97) for controls as compared with 87% (CI, 83—90) for PE with DVT, and 95% ( CI, 90—98) for PE without DVT (Fig. 2). In multivariate analysis, adjusting for all prognostic factors and duration of anticoagulant therapy, PE with DVT were independently associated with an increased hazard of death, while PE without DVT were not (Table 2).

Discussion

This study describes the actual prevalence of the different recognized forms of VTE, especially in PE and PE without DVT for which there is little available data. It shows heterogeneity in clinical presentation and mortality for VTE encountered in daily practice, providing new insight into the epidemiology of this disease. Our study defines the actual clinical circumstances of diagnosis and suggests the need to better evaluate PE with and without DVT.

As shown in previous studies, distal DVT accounted for a substantial proportion (56%) of positive cases of DVT confirmed by CUS [12]. In the Optimev cohort, we have previously demonstrated that isolated distal DVT and proximal DVT have similar risk factor pro-
Table 1  Baseline characteristics of patients enrolled in the Optimev study.  
*Caractéristiques des patients inclus dans l’étude Optimev.*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control</th>
<th>PE with DVT</th>
<th>PE without DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>5315 (90.3)</td>
<td>426 (7.2)</td>
<td>148 (2.5)</td>
</tr>
<tr>
<td>Age (median, IQR) (years)</td>
<td>64 (49—77)</td>
<td>73 (59—80)</td>
<td>65 (51—76) NS</td>
</tr>
<tr>
<td></td>
<td>65 (51—76) NS</td>
<td>64 (43) NS</td>
<td>65 (51—76) NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1931 (36)</td>
<td>199 (47) P &lt; 0.01</td>
<td>64 (43) NS</td>
</tr>
<tr>
<td>Inpatients</td>
<td>2103 (40)</td>
<td>274 (64) P &lt; 0.01</td>
<td>118 (80) P &lt; 0.01</td>
</tr>
<tr>
<td><strong>Transient risk factors for venous thromboembolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed confinement</td>
<td>842 (16)</td>
<td>83 (19) P = 0.049</td>
<td>21 (14) NS</td>
</tr>
<tr>
<td>Surgery ≤ 45 days</td>
<td>744 (14)</td>
<td>51 (12) NS</td>
<td>22 (15) NS</td>
</tr>
<tr>
<td>Acute respiratory failure or COPD exacerbation or NYHA class III or IV CHF</td>
<td>238 (4)</td>
<td>48 (11) P &lt; 0.01</td>
<td>14 (9) P &lt; 0.01</td>
</tr>
<tr>
<td><strong>Chronic risk factors for venous thromboembolism, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal history of DVT or PE</td>
<td>1201 (23)</td>
<td>132 (31) P &lt; 0.01</td>
<td>36 (24) NS</td>
</tr>
<tr>
<td>Family history of DVT or PE</td>
<td>745 (14)</td>
<td>64 (15) NS</td>
<td>12 (8) P = 0.040</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>537 (10)</td>
<td>76 (18) P &lt; 0.01</td>
<td>32 (22) P &lt; 0.01</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>1253 (24)</td>
<td>84 (20) NS</td>
<td>19 (13) P &lt; 0.01</td>
</tr>
<tr>
<td>Hormonal contraception</td>
<td>125 (2)</td>
<td>9 (2) NS</td>
<td>10 (7) P &lt; 0.01</td>
</tr>
<tr>
<td>Obesity</td>
<td>811 (15)</td>
<td>66 (15) NS</td>
<td>27 (18) NS</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>83 (1.6)</td>
<td>4 (0.9) NS</td>
<td>0 (0) NS</td>
</tr>
<tr>
<td>No risk factor (idiopathic situation)</td>
<td>2709 (51)</td>
<td>168 (39.4) P &lt; 0.01</td>
<td>53 (35.8) P &lt; 0.01</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise indicated. Each *P*-value relies to the comparison between different types of VTE to controls. COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; DVT: deep vein thrombosis; PE: pulmonary embolism; NS: non-statistically significant comparison.

files, except for recent surgery, that is more frequently associated with distal thrombosis; survival estimates for distal and proximal DVT are also discussed in this paper [21].

Although the prevalence of DVT among patients with confirmed PE has been previously estimated, our study was the second to distinguish between PE with or without DVT but the first one to adjust the results on patient’s comorbid con-
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Table 2  Three-month mortality for different forms of VTE.

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Control group (Deaths/total (%))</th>
<th>PE with DVT (Deaths/total (%))</th>
<th>PE without DVT (Deaths/total (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>4/95 (4.2%)</td>
<td>14/48 (29.2%)</td>
<td>3/6 (50.0%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>43/95 (45.3%)</td>
<td>19/48 (39.6%)</td>
<td>1/6 (16.7%)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2/95 (2.1%)</td>
<td>3/48 (6.2%)</td>
<td>/</td>
</tr>
<tr>
<td>Cardio</td>
<td>25/95 (26.3%)</td>
<td>2/48 (4.2%)</td>
<td>/</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5/95 (5.3%)</td>
<td>3/48 (6.2%)</td>
<td>/</td>
</tr>
<tr>
<td>Other</td>
<td>16/95 (16.8%)</td>
<td>7/48 (14.6%)</td>
<td>2/6 (33.3%)</td>
</tr>
</tbody>
</table>

CI: confidence interval. Hazard ratios were adjusted for sex, age, Charlson index class (0/1/≥2), theoretical duration of anticoagulant treatment, inpatient versus outpatient status, surgery within the previous 45 days, active malignant neoplasm, bedridden status, acute infectious disease, joint and bone disease, neurological disease, obesity, liver disease, congestive heart failure, respiratory insufficiency, renal insufficiency, hypertension, diabetes, atherosclerosis, dyslipidemia, smoking status, history of digestive bleeding, and antiplatelet agents.

ditions [22,23]. Our findings suggest that, in contrast to PE with DVT, PE without DVT occurs mostly in younger inpatients who undergo explorations, without immobilization or bed confinement, even if they share permanent risk factors like cancer with the PE with DVT patient group. Some of these patients may have incidental PE. In addition, our study showed that PE without DVT was significantly associated with a lower 3-month mortality than PE with DVT (4.6% versus 12.9%; P < 0.01) and than proximal DVT 8.0%, in accordance with the findings of Girard et al. whose data did not reach significance for all-cause mortality rates among 281 outpatients presenting with non-severe PE without or with DVT (2.7 and 4.7%) [21,24]. On the opposite, PE without DVT patients have the same 3-month mortality that controls and distal DVT patients. Taken together, these findings raise questions about the natural course and pathophysiology of PE without DVT. Firstly, PE without DVT is usually considered to be PE with an undetectable thrombus in the limb because the thrombus has resolved, migrated, or was overlooked during the examination (i.e. a false negative of lower limb CUS especially in asymptomatic patients). This is unlikely since the clinical presentation of PE without DVT differs from other forms of VTE, suggesting that it does not apply to the same patients. Moreover, none of these patients in our study presented with clinical suspicion of DVT during the early follow-up period, nor did they not receive anticoagulant therapy during this time. Patients with PE and upper-limb DVT at baseline or during follow-up were identified and considered as PE with DVT. Although we cannot exclude the possibility of DVT located in ovarian or renal veins, this feature is rare even when routine abdominal or pelvic CT is performed.

Secondly, in our study, PE without DVT cases were unlikely to be false positives since they were confirmed by abnormal findings on the multidetector CT or a high probability pattern on the ventilation-perfusion scan. These are validated criteria assessed by the adjudication committee, for the positive diagnosis of PE with a proven low rate of false positives [11,13,18].

Thirdly, PE without DVT may be an in situ thrombus and its clinical significance would be determined by long term follow-up.

Fourthly, some of the PE without DVT cases may result from recent improvements in diagnostic technology and more frequent use of non-invasive diagnostic tests. Indeed, patients with PE without DVT in our study were more likely to have subsegmental clots for which treatment is controversial even in patients with pulmonary symptoms [25,26]. Other studies have reported a 5% prevalence of thrombi discovered incidentally on CT performed for other reasons than suspicion of PE and for which evolving VTE could not be found.
Another possible explanation might be that these PE without DVT cases were late diagnoses of PE or an early form of VTE. The population of patients with PE without DVT resumes all these hypotheses. The possibility of overlooking PE in patients with a low probability could explain the low 3-month mortality rate in this population.

Our results suggest that detection of the origin of the clot is important to better understand the natural course of PE and avoid over-diagnosis. These data are supported by guidelines on PE that raise the question of the clinical significance of isolated, symptomatic PE [28].

The strengths of our study include its prospective design, patient enrolment in both outpatient and inpatient settings, data collection performed by vascular medicine physicians using standardized definitions, and confirmation of VTE by objective tests. The laudable participation rate up to 3-month follow-up (99.6% of patients included in the longitudinal study), the external data evaluation by clinical research assistants and adjudication of clinical outcomes by an expert committee limit evaluation bias according to VTE type and bias of subjectivity in data collection of adverse events. Data about mortality have been adjusted on major criteria; the prediction model is excellent and less likely to contain hidden variables. This reinforces the interest that we should take in PE without DVT patients, symptomatic, with proven PE.

We acknowledge the limitations of our study. Firstly, we did not analyze D-dimers levels because most patients with negative D-dimers are not referred to vascular medicine physicians and therefore were less likely to be enrolled in our study. Secondly, patients for whom VTE was ruled out by objective tests served as controls in statistical comparisons, with a risk of false negative cases. Nevertheless, the rate of clinical VTE in our cohort, during the follow-up, is low [29, 30]. Thirdly, we did not enroll hemodynamically unstable patients in our study and thus, mortality rates may have been underestimated. The high mortality rate in our study is explained by the characteristics of our population that included many inpatients with severe and multiple comorbidities. This is consistent with a higher mortality rate observed in provoked VTE compared to idiopathic VTE. However, these data are unlikely to explain the heterogeneity in mortality among the different types of VTE since all patients were enrolled before performing CUS.

Along with the use of state of the art diagnostic tools and thromboprophylaxis, we have shown in this nationwide prospective cohort study that VTE is a heterogeneous disease with regards to clinical profile and short-term prognosis. Proximal DVT and PE with DVT remain severe diseases with substantial 3-month mortality. In contrast, PE without DVT do not modify 3-month mortality and deserve further study to improve understanding of their physiopathology and to determine appropriate management strategies.

**Optimev study sites (France)**


**Funding**

This study was funded by a hospital clinical research program grant (French Ministry of Health) and a grant from Sanofi Aventis France. This study was supported by the French Society of Vascular Medicine.


**Authorship responsibility**

The authors had full access to the data and take the responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Contributors**

MA Sevestre, JL Bosson, I Quéré developed the study protocol, and all of the authors except C. Rolland and C. Genty participated in the study as clinical investigators. C. Genty and J.L. Bosson did all the statistical analyses.

**Conflict of interest statement**

MA Sevestre, JL Bosson have received honoraria from Sanofi Aventis.

**Acknowledgments**

We thank members of the Scientific Advisory Board and participating Regional Vascular Medicine Associations for study design. All contributors have been cited in the work.

We thank Drs Anna Arslanian, Sophie Blaise, Pierre Casez, Sandra David-Tchouda, Michèle Fontaine, José Labarère, Mario Maufus, Marie-Agnès Ningres, Gilles Pernod, Olivier Pichot, Muriel Salvat, Bernadette Satger, Christophe Seinturier, Élodie Sellier, Jacqueline Yver for being members of the expert committee.

We thank C. Blanie, M. Blanc, M. Proust, S. Massicot, L. Delhomme, C. Maillard, C. Bonnet (Grenoble Clinical Research Center) for data monitoring and follow-up of the study participants and a foote for editing the manuscript.

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