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Original Article

Association between hospitalization for acute medical illness and VTE risk: A lower efficacy of thromboprophylaxis in elderly patients? Results from the EDITH case-control study

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ABSTRACT

Introduction: Whether the association between hospitalization and venous thromboembolism (VTE) is modified by the use of thromboprophylaxis in older patients remains insufficiently evaluated. Our objective was to estimate VTE risk associated with hospitalization for acute medical illness depending on prescription of pharmacological thromboprophylaxis, in two different age categories using a 75 years cutoff.

Methods: Using a case-control design, we estimated the risk for symptomatic VTE associated with hospitalization for acute medical illness depending on prescription of pharmacological thromboprophylaxis in two different age categories using a 75 years cut-off.

Results: 750 symptomatic VTE cases and their 750 age and sex-matched controls were analyzed. A total of 145 cases (19.3%) and 91 controls (12.1%) were hospitalized for acute medical illness in the preceding 3 months prior to inclusion in the study ($p < 0.001$). Hospitalization for acute medical illness was associated with a 75% increase in VTE risk: OR 1.75 (95% CI: 1.32–2.33). In patients <75 years, there was a 2-fold increase in VTE risk associated with hospitalization when thromboprophylaxis was not prescribed: OR 2.01 (95% CI: 1.11–3.62), whereas no association was found when thromboprophylaxis was prescribed: OR 0.93 (95% CI: 0.44–1.95). In patients ≥ 75 years, VTE risk associated with hospitalization remained significant whether or not thromboprophylaxis was prescribed: OR 2.69 (95% CI 1.28–5.66) and OR 2.02 (95% CI: 1.01–4.03) respectively.

Conclusion: Our results suggest that VTE prevention in acutely ill medical patients may be less effective in patients ≥ 75 years. This finding needs to be addressed in further studies.

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Venous thromboembolism (VTE), that is pulmonary embolism (PE) and deep vein thrombosis (DVT) of the lower limbs, is a frequent and potentially life-threatening disease. It is estimated that almost 20% of VTE patients have been hospitalized for an acute medical illness in the three months preceding VTE [1–3]. Pharmacological thromboprophylaxis policies using low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or fondaparinux, have been largely implemented over the last 25 years. Without pharmacological prevention, the three-month incidence of VTE in acutely ill medical patients ranges from 0.3% to 11% depending on intrinsic and extrinsic VTE risk factors [4]. Based on evidence from randomized controlled trials, current guidelines recommend the prescription of low-dose parenteral anticoagulants in

high-risk hospitalized acutely ill medical patients to prevent VTE [5]. However, there is a gap between guidelines and daily clinical practice as regards prescription of pharmacological thromboprophylaxis that is likely due to the complexity for the identification of high-risk patients.

Markedly, older age is associated with an increased VTE risk regardless of the reason for admission to hospital [6]. Elderly patients also carry other VTE risk factors such as heart failure or chronic respiratory diseases that clearly lead to an increased VTE risk [7]. Strikingly, results from randomized controlled trials suggested that patients ≥ 75 years benefit more from pharmacological thromboprophylaxis than younger patients [8,9]. Hence, using age as a single indicator to identify high-risk patients might improve prescription rate of pharmacological thromboprophylaxis during admission for an acute medical illness. However, a major limitation to the aforementioned trials is that outcomes mostly consist of asymptomatic VTE events diagnosed by systematic screening at the end of thromboprophylaxis. Therefore, whether or not exposure to pharmacological thromboprophylaxis is associated with a

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reduced incidence of symptomatic VTE in older patients needs further evaluation.

In this case-control study, we aimed to estimate the risk for symptomatic VTE associated with hospitalization for acute medical illness depending on prescription of pharmacological thromboprophylaxis in two different age categories using a 75 years cutoff.

1. Design and methods

1.1. Design and setting

The EDITH study is a hospital-based case-control study designed to test interactions between genetic and environmental risk factors of VTE. Methods were described in details elsewhere [10]. Briefly, all consecutive unselected patients seen in Brest University Hospital for symptomatic VTE (DVT and/or PE) were asked to participate in the study. Diagnosis of DVT was done by the absence of full compressibility of a proximal or distal vein of the deep lower limb on compression ultrasonography (CUS). Diagnosis of PE was done by 1) a segmental or larger artery filling defect on chest computed tomography (CT) scan; or 2) the combination of high pre-test clinical probability of PE with high probability ventilation–perfusion (V/Q) lung scan according to the PIOPED criteria [11]; or 3) proximal DVT on CUS in a patient with suspected PE.

For this report, we analyzed data of patients, older than 18 years, with a symptomatic VTE event that occurred between May 2000 and November 2008 and not related to known active malignancy, surgery, pregnancy, delivery, or immobilization for a lower limb trauma in the preceding three months.

Daily screening of admission lists was performed for selection of control subjects. Cases were matched in a 1:1 ratio to controls for the following factors: sex, age (± 5 years), hospital unit, and absence of major risk factor for VTE (active malignancy, surgery, pregnancy, delivery, or immobilization for a lower limb trauma in the preceding three months). Controls were selected from the roster of patients hospitalized in the same ward in the following 12 months after the case's event date. Controls were not included if they had a past history of VTE or if they were receiving long-term anticoagulant therapy. Controls were followed up to three months to ensure they did not experience a VTE event. In that instance they were discarded from the list of eligible controls.

The protocol was approved by our hospital's scientific and ethics board. A written informed consent was obtained from all included patients.

1.2. Assessment of clinical data

Cases and controls were interviewed during their hospital stay, using an individual standardized questionnaire, by investigators or research nurses. At the time of inclusion, all demographic data, general characteristics, medication use as well as patient-related risk factors for VTE were recorded. All patients were asked whether they were admitted to hospital in the preceding three months. Although controls were included during a hospital stay, only admission to hospital for an acute medical illness in the three months prior to current admission was considered as an exposure factor. Admissions database of our institution was also interrogated in order to double check accuracy of the information.

We retrospectively reviewed charts of cases and controls who were hospitalized for an acute medical illness for at least three days within three months prior to inclusion in the EDITH study (AD, FH, FF). Patients were considered *a priori* at high VTE risk if they fulfilled the MEDENOX trial inclusion criteria, stroke with lower limb paralysis, or myocardial infarction (see Appendix 1) and at low risk if they did not [12]. Type and duration of prescription of pharmacological thromboprophylaxis was also recorded, regardless of *a priori* VTE risk assessment. We considered that patients received adequate pharmacological thromboprophylaxis during

hospitalization if they were prescribed either: 1) LMWH at an approved preventive dose; 2) low dose unfractionated heparin (5000 units bid or tid); or 3) fondaparinux 2.5 mg once daily, for at least 6 days. Enoxaparin 20 mg once daily and/or aspirin alone were not classified as adequate thromboprophylaxis.

1.3. Statistical methods

Baseline summary statistics were reported as number (%) for categorical variables, and as mean and standard deviation (SD) for continuous variables. Comparisons of cases and controls were made by chi-square test or Fisher's exact test for qualitative variables. Conditional logistic regression taking into account the matching factors was carried out to estimate odds ratios (OR) and 95% confidence intervals (CI) for VTE risk associated with admission to hospital for acute medical illness and use of pharmacological thromboprophylaxis. With the aim of stratifying the analyses in patients according to age categories, we added an interaction term (age category X each parameter) in the conditional logistic regression model in addition to the main effect variables. Thus, we were able to provide an adjusted estimation of the association between admission to hospital and VTE in patients aged 75 or more included in the EDITH study, without modifying the matching design of the study. We subsequently repeated the analyses in order to consider risk stratification according to MEDENOX criteria as a potential confounder of the association between admission to hospital for an acute medical illness, use of pharmacological thromboprophylaxis and VTE.

2. Results

Between May 2000 and November 2008, 1848 patients with a well-documented VTE event agreed to participate in the EDITH study. Of these, we excluded 537 patients with a provoked VTE event (*i.e.* associated with known active malignancy, surgery, pregnancy, delivery, or immobilization for a lower limb trauma in the preceding 3 months) and 516 unmatched unprovoked VTE patients. Of the 795 remaining pairs, an additional 45 pairs were excluded due to missing data. In total, 750 well-matched pairs were analyzed.

2.1. Patients' characteristics

As shown in Table 1 the mean age of the patients was 67.2 $\pm$ 17.1 years, and 664 (44.3%) were men. The 750 VTE cases were 151 symptomatic isolated PE, 324 symptomatic isolated DVT of the lower limb and 275 DVT associated with symptomatic PE. Among the 1500 cases and controls, 313 cases (41.7%) and 316 controls (42.1%) were 75 years and older.

A total of 145 cases (19.3%) and 91 controls (12.1%) were hospitalized for an acute medical illness at least once in the preceding 3 months prior to inclusion in the study ($p < 0.001$); 67 out of the 145 cases (46.2%) received a pharmacological thromboprophylaxis as compared to 47 of the 91 controls (51.6%) ($p = 0.49$). Sixteen of the 145 cases (11.0%) did not receive pharmacological thromboprophylaxis due to recent or active bleeding as compared to one of the 91 controls (1.1%) ($p = 0.003$). In total, 95 cases (65.5%) and 61 controls (67.0%) were identified to be at higher VTE risk according to the MEDENOX criteria ($p = 0.92$). Prescription rates of pharmacological thromboprophylaxis were not different between cases and controls regardless of *a priori* VTE risk established by the MEDENOX criteria (Table 1). Reason for admission to hospital in patients needing for pharmacological thromboprophylaxis is shown in Table 2.

2.2. VTE risk associated with admission to hospital for acute medical illness

Hospitalization for acute medical illness in the preceding three months was associated with a 75% increase in VTE risk: OR 1.75 (95% CI: 1.32–2.33) (Table 3), whether or not patients were classified at

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