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Increased risk and severity of unprovoked venous thromboembolism with clustering cardiovascular risk factors for atherosclerosis: Results of the REMOTEV registry☆

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ABSTRACT

Background: The role of cardiovascular risk factors (CVRF) for atherosclerosis in venous thromboembolic disease (VTE) is controversial. The aim of this study was to evaluate the impact of CVRF and their cumulative effects on the occurrence of unprovoked VTE, severity, recurrence and survival.

Methods and results: This is a prospective cohort from the REMOTEV registry including all consecutively hospitalized patients for acute symptomatic VTE. From November 2013 to December 2016, 515 patients with 6 months follow-up (FU) were selected for the analysis. Events were classified as unprovoked or provoked VTE. In univariate analysis, hypertension (OR 1.44, [95% CI 1.01–2.06]), diabetes (OR 2.07, [95% CI: 1.25–3.55]) and age (OR 1.94, [95% CI: 1.31–2.88]) were significantly associated with the risk of unprovoked VTE. After adjustment, diabetes (OR 1.82, [95% CI: 1.07–3.18]) and age (OR 1.79, [95% CI: 1.15–2.8]) remained associated with the risk of unprovoked VTE. The proportion of unprovoked VTE increased significantly with the number of CVRF adjusted for thrombophilia (1 CVRF: OR 3 [95% CI: 1.44–6.52]) 2 CVRF: OR 4.33 [95% CI: 2.07–9.49] and ≥3 CVRF: OR 4.58 [95% CI: 2.27–9.7]). The severity of pulmonary embolism was significantly associated with CVRF clustering. There were more VTE recurrences and deaths during the 6 months of FU with cumulative CVRF.

Conclusion: The risks of unprovoked VTE and PE severity are associated with clustering CVRF. The role of cumulative CVRF predominates rather than the specific burden of each of the CVRF in the risk of VTE occurrence.

1. Introduction

Venous thromboembolism (VTE) is the third most common cardiovascular disease after coronary artery disease and heart failure. Its annual incidence in Western Europe and North America is estimated to be between 0.6 and 1.83 per thousand people/year [1–3]. The identification of transient or persistent VTE risk factors modulates recurrence frequency and guides the duration of treatment. However, 30–50% of VTE events remain unprovoked, with no clearly identifiable cause [4–6]. The unprovoked nature of the thrombotic episode is an essential marker of the risk of recurrence and determines the decision to treat with long-term anticoagulation [7,8]. In those patients, the presence of potential risk factors, either environmental or constitutional, becomes *de facto* a diagnostic and therapeutic issue, and also upstreams a potential research orientation exploring the pathophysiology of the venous thrombus formation.

Previous research has explored the hypothesis that cardiovascular risk factors (CVRF) for atherosclerosis are involved in the occurrence of VTE. Cohort studies or clinical trials have investigated the association of modifiable conventional CVRF (*i.e.*, smoking, high blood pressure (HBP), diabetes, obesity and dyslipidemia) and the risk of VTE [9–12]. In a trial measuring the prevalence of the subclinical atherosclerosis, Prandoni et al. showed a link between CVRF and unprovoked VTE [9]. Other authors reported an increase in the frequency of cerebrovascular and cardiovascular events after an episode of VTE [13,14]. A meta-analysis of studies connecting CVRF and VTE showed for the first time the existence of an excess risk of VTE associated with standard risk factors for atherosclerosis. However, this study has shown that if the relative risk of each parameter is low, their cumulative effect may explain the causal effect [15]. Thus, the metabolic syndrome, adding by definition at least three among the following: HBP, obesity, diabetes and dyslipidemia is associated with an unprovoked VTE [16,17].

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Indirect evidence of the relationship between CVRF and VTE is provided by previous therapeutic trials. In primary prevention, several observational cohort and case-control studies appear to show that statins reduce the incidence of VTE by about 30% [18]. In the single randomized placebo-controlled clinical trial (JUPITER) conducted, which included 17,000 patients, rosuvastatin reduced the risk of VTE by 43%. In secondary prevention, several observational studies and post-hoc analyses of randomized clinical trials have suggested that statins may prevent the recurrence of VTE [19]. In the WARFASA study, for secondary prevention of VTE in patients with an unprovoked episode, low dose aspirin reduced the frequency of VTE recurrences by 40% [20]. This result was confirmed by the ASPIRE study and the INSPIRE meta-analysis of the individual data [21,22]. The results obtained with statins and aspirin suggest that drugs known for their anti-atherothrombotic properties would also have an effect on the genesis of the venous thrombus.

In this study, our main objective was to measure the impact of CVRF and their cumulative effects on the risk of VTE in a prospective cohort of patients hospitalized for a symptomatic VTE episode. We corroborated the possible role of CVRF by measuring the effect of their accumulation on the severity and prognosis of venous thromboembolic events.

2. Patients and methods

2.1. Study design and patient selection

REMOTEV is an ongoing, prospective, observational registry of all consecutive patients hospitalized in the department of vascular medicine of the University Hospital of Strasbourg for an acute episode of deep vein thrombosis (DVT) or pulmonary embolism (PE) [23]. For this analysis, we defined two groups of patients according to whether the index episode was provoked or not [24]. VTE events were classified as provoked in the presence of the following risk factors: recent surgery, prolonged immobilization (>3 days), recent trip (travelling at least 6 h in the previous 3 weeks), active cancer, pregnancy or postpartum, and estrogen hormone therapy (oral contraception or hormone replacement therapy) [24]. In the absence of any of these risk factors, the thrombotic event was considered as unprovoked. Screening for thrombophilia was performed according to the current guidelines [1]. The presence of a hereditary thrombophilia did not qualify the event as provoked and carriers of thrombophilia were classified as having provoked or unprovoked VTE according to the presence or not of an environmental provoking factor [6]. We analyzed the clinical characteristics of patients, treatments and events occurring within the first 6 months after the diagnosis of VTE in both groups: provoked and unprovoked. Patients with known active cancer or cancer diagnosed during follow-up (FU) were excluded from the analysis because of peculiar cancer-related thrombosis history (*i.e.* higher thrombotic recurrence risk, high mortality rate due to cancer progression, *etc.*) that may represent a significant bias. Patients were informed of the purpose of the registry and gave oral consent to their participation according to the requirements of the local ethics committee. Data were anonymized and stored in a computer database.

2.2. VTE diagnosis

The presence of PE or DVT was confirmed by standardized and validated imaging procedures [1,25]. The episode of PE or DVT (index event) was reported. PE was confirmed by either CT pulmonary angiogram (CTPA) or ventilation perfusion lung scan. Patients with symptomatic PE were routinely screened for DVT. The presence of DVT was assessed by ultrasonography from inferior vena cava to calf veins in both lower limbs. The diagnosis of acute coronary syndrome was excluded for all patients included (gradual use of appropriate complementary examinations if necessary).

2.3. Baseline variables of the study population

Age, sex, height and weight parameters were collected. Renal function was assessed at admission and the estimated glomerular filtration rate (eGFR) was calculated according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation. Cardiac biomarkers, troponin I and BNP, as well as right ventricular dilatation on CTPA and/or transthoracic echocardiography were identified in order to establish PE severity according to the 2014 ESC Guidelines for PE management based on the short-term mortality risk [1].

2.4. Cardiovascular risk factors

Seven major traditional risk factors for atherosclerosis were recorded at hospitalization and included age (>50 years for a man and >60 years for a woman), active smoking, diabetes, HBP, dyslipidemia, obesity (defined by a BMI >30 kg/m^2) or family history of coronary heart disease (CHD), defined as an immediate relative diagnosed with CHD before 55 years of age for men and 65 years for women. These risk factors were identified before and during hospitalization, as documented in the medical record, and were based on patient/family self-report or previous medical records. The combination of risk factors resulted from the summation of individual CVRF.

2.5. Anticoagulant therapy

The type, dosage and duration of anticoagulant therapy were based on current guidelines [1,26,27]. The anticoagulant treatment included either a direct oral anticoagulant (rivaroxaban 15 mg bid for 21 days and then 20 mg od without dose reduction) or unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux at the beginning of hospitalization, relayed by antivitamin K with a target INR between 2 and 3. In case of contraindication to an oral anticoagulant or in exceptional therapeutic situation excluding cancer, a parenteral treatment with LMWH has been established in the long term. Indications of thrombolysis, thromboaspiration, thrombectomy or inferior vena cava filter placement were based on current guidelines [1,27]. All patients received at least 6 months of anticoagulant therapy whether the event was provoked or not.

2.6. Follow-up and outcome assessment

In this study, we monitored patients over a period of 6 months after the occurrence of the index event. All patient data were collected at the initial visit and then by phone interview at 1 month (±5 days), 3 months (±10 days) and 6 months (±15 days). The primary endpoints were recurrence of VTE, major cardiovascular events (MACE), and all-cause mortality. All symptomatic DVT or PE were acknowledged as VTE recurrence when a diagnostic imaging procedure confirmed the presence of new thrombosis (CTPA, ventilation/perfusion lung scan or duplex ultrasound). MACE included myocardial infarction, stroke and non PE-related sudden death.

2.7. Statistical analysis

Variables were described as number of cases (percentages) for categorical variables and as mean (±standard deviation) for continuous variables. Non-normally distributed variables were described as median (10–90th percentiles). Patients were divided according to the number of their cardiovascular risk factors, *i.e.*: 0, 1, 2, 3 or more. The risk of unprovoked VTE associated with each CVRF was assessed by univariate analysis. The Mantel–Haenszel χ^2 test was used for trend in binomial proportions. The proportion of unprovoked episodes based on the number of risk factors was compared using a Chi^2 test, with an alpha level of 0.05 used as the cutoff for significance. Any CVRF having a univariate test with a p value cut-off point of 0.20 was selected as a candidate for the multivariate logistic regression analysis. The Kaplan–Meier estimator was used to compute survival curves over the 6-month FU for deaths and recurrences in each group. MACE were expressed as the number of events over a 6-month FU period.

3. Results

3.1. Baseline characteristics in provoked versus unprovoked VTE groups

Between November 2013 and December 2016, 604 patients were hospitalized for VTE. All cancer patients (known active cancer at the time of the index event or diagnosed during FU) were excluded from the present study (n = 89). Overall, 515 cancer-free patients, followed for 6 months were included in this analysis. Among them, 190 (36.7%) patients suffered from provoked VTE while for 325 patients (63.1%), no causal factor for VTE was identified (unprovoked group) (Table 1). The proportion of males and females differed significantly between the unprovoked and provoked groups (Table 1). This disparity is mainly explained by the high frequency of hormonal therapy including estrogens in the provoked group (55 women in total, corresponding to 28.9% of the provoked VTE). Patients presenting with an unprovoked event were significantly older (respectively: 66.1 years *vs* 59.7 years, p < 0.001). The proportions of HBP and diabetes were significantly different between the two groups (HBP: 56.4% in the unprovoked group *vs* 47.4% in the provoked group, p = 0.05; diabetes: 21.3% in the unprovoked group vs 11.6% in the provoked group, p < 0.01) (Table 1). There was no difference in the proportion of patients with renal insufficiency between the 2 groups (1.9% in the unprovoked group *versus* 2.6%).

In 319 cases (61.9%), the index event was a PE with concomitant DVT. Approximately one-quarter of patients (n = 138) had isolated PE and 11.3% (n = 58) had DVT without symptomatic PE. For patients with PE, the severity of the event was graded: “low risk” in 237 patients (51.9%), “intermediate risk” (low and high) in 210 patients (46%) and “high risk” in 10 patients (2.2%). The overall comparison of the severity between unprovoked and provoked VTE showed no difference between groups. However, in patients with unprovoked VTE, PE was less likely to be at “low risk” than in the case of provoked VTE (49.8% *vs* 56.4%).