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Association between smoking and recurrence of venous thromboembolism and bleeding in elderly patients with past acute venous thromboembolism

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ABSTRACT

Background: While the association between smoking and arterial cardiovascular events has been well established, the association between smoking and venous thromboembolism (VTE) remains controversial.
Objectives: To assess the association between smoking and the risk of recurrent VTE and bleeding in patients who have experienced acute VTE.
Patients/methods: This study is part of a prospective Swiss multicenter cohort that included patients aged ≥65 years with acute VTE. Three groups were defined according to smoking status: never, former and current smokers. The primary outcome was the time to a first symptomatic, objectively confirmed VTE recurrence. Secondary outcomes were the time to a first major and clinically relevant non-major bleeding. Associations between smoking status and outcomes were analysed using proportional hazard models for the subdistribution of a competing risk of death.
Results: Among 988 analysed patients, 509 (52%) had never smoked, 403 (41%) were former smokers, and 76 (8%) current smokers. After a median follow-up of 29.6 months, we observed a VTE recurrence rate of 4.9 (95% confidence interval [CI] 3.7–6.4) per 100 patient-years for never smokers, 6.6 (95% CI 5.1–8.6) for former smokers, and 5.2 (95% CI 2.6–10.5) for current smokers. Compared to never smokers, we found no association between current smoking and VTE recurrence (adjusted sub-hazard ratio [SHR] 1.05, 95% CI 0.49–2.28), major bleeding (adjusted SHR 0.59, 95% CI 0.25–1.39), and clinically relevant non-major bleeding (adjusted SHR 1.21, 95% CI 0.73–2.02).
Conclusions: In this multicentre prospective cohort study, we found no association between smoking status and VTE recurrence or bleeding in elderly patients with VTE.

1. Introduction

Venous thromboembolism (VTE), defined as deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a common disease [1]. The incidence of VTE increases with age, rising from <1 case per 1000 person-years in persons aged <50 years to more than 6 cases per 1000 person-years in persons aged >80 years [2–6]. Overall, 60% of VTE events occur in persons aged ≥65 years [1,2,7].

Several factors induced by smoking could promote the formation of a clot and the subsequent VTE. These mechanisms were often studied in researches on atherosclerosis, and smoking shares common biological consequences on the venous system. Smoking causes endothelial damage that can lead to a reduced capacity for dilatation (by a decreased activity of nitrous oxide) and increased vessel contraction (by stimulation of the release of catecholamines) [8–11]. This endothelial damage can lead to pro-thrombotic and pro-inflammatory states with an increased production of cytokines including IL-6, IL1B and TNFα [8–11]. Those cytokines play major regulatory roles in the hepatic synthesis of acute phase proteins, including fibrinogen. As IL-6 appears to be the principal procoagulant cytokine in humans, it could be an important link to VTE [11,12]. Moreover, there is a clear dose–effect relationship between number of cigarettes smoked per day and raised plasma fibrinogen concentration and conversely a reduction of it with smoking cessation [13].

The association between smoking and VTE remains controversial. While a meta-analysis reported no statistically significant relationship between smoking and first VTE (odds ratio [OR] 1.18, 95% confidence

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interval [CI] 0.95–1.46) [14], a recent meta-analysis demonstrated that cigarette smoking was associated with a slightly increased risk for first VTE (pooled relative risk 1.23, 95% CI 1.14–1.33) in current smokers compared with never smokers [15].

Smoking interacts directly with the metabolism of vitamin K antagonists by increasing the required dosage to achieve and maintain a therapeutic international normalized ratio [16], potentially increasing the risk of VTE recurrence. Pathophysiologically, smoking may increase the clearance of warfarin and in this way reduce its anticoagulant effect. Therefore, smoking cessation or a decrease in smoking may lead to overanticoagulation and an increased risk of bleeding.

Evidence suggests that elderly patients who have experienced an acute VTE may have a higher risk of VTE recurrence, bleeding, and death than younger patients [2,7]. Given that the elderly are a rapidly growing population segment in Western societies and almost half of the elderly population is or has been exposed to smoking [17], it is of interest to examine the possible association between smoking and VTE recurrence and bleeding in this population. In a prospective multicenter cohort study, we aimed to assess the association between smoking status and the risk of recurrent VTE and bleeding in elderly patients with acute VTE.

2. Methods

2.1. Cohort sample

The study was conducted between September 2, 2009 and December 6 2013 as part of Swiss Cohort of Elderly Patients with Venous Thromboembolism (SWITCO65+), a prospective, multicenter cohort study that assessed long-term medical outcomes in elderly patients with acute VTE from all five university and four high-volume non-university hospitals in Switzerland. Consecutive patients aged ≥65 years with acute, objectively confirmed symptomatic VTE were prospectively identified in the inpatient and outpatient services of all participating study sites. Exclusion criteria were catheter-related thrombosis, insufficient German or French-speaking ability, no follow-up possible (i.e., terminal illness), an inability to provide informed consent (i.e., severe dementia), or previous enrollment in the cohort. The detailed methodology of the SWITCO65+ cohort has been described elsewhere [2]. The study has been approved by the Institutional Review Board at each participating center. For the present study, we excluded patients with missing information about their smoking status.

2.2. Baseline data collection

For all enrolled patients, trained study nurses prospectively collected information about baseline demographics (age, gender, insurance status, living status, and educational level), comorbid conditions (active cancer, hepatic, cardiac, lung, renal, and cerebrovascular disease, and history of major bleeding), traditional cardiovascular risk factors (arterial hypertension, diabetes mellitus, hypercholesterolemia, body mass index, physical activity level), risk factors for VTE (active cancer, recent immobilization, major surgery, estrogen therapy), type and localization of the index VTE, VTE-related treatments (oral and parenteral anticoagulants), and concomitant antiplatelet/non-steroidal anti-inflammatory drug therapy using standardized data collection forms.

Smoking habits, including self-reported smoking status, the average number of cigarettes smoked per day and years of smoking were assessed. We defined three possible smoking statuses: current smokers (i.e. patients reporting smoking ≥1 cigarette per day at the time of the interview), former smokers (defined as smokers who had quit for >6 months) and never smokers. Current and former smokers were classified into three subgroups according to the number of pack-years smoked (defined as the number of packs of cigarettes smoked per day multiplied by the duration of smoking in years): ≤20, 21–40, and >40 pack-years.

2.3. Study outcomes

The primary outcome was the time to the recurrence of symptomatic, objectively confirmed VTE during follow-up, defined as new or recurrent PE or DVT based on previously published criteria [18,19]. We defined recurrent symptomatic VTE as acute chest pain, new or worsening dyspnea or cough, acute hemoptysis, or syncope coupled with an objective diagnosis of pulmonary embolism based on spiral computed tomography, pulmonary angiography, or autopsy, or a new unilateral leg pain or swelling coupled with an objective diagnosis of deep vein thrombosis based on ultrasonography or contrast venography.

The secondary outcome was the time to a first bleeding event. We defined major bleeding as fatal bleeding, symptomatic bleeding in a critical organ (intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), bleeding with a reduction of hemoglobin ≥20 g/l, or bleeding leading to the transfusion of 2 units of packed red blood cells or more [2,20]. Non-major bleeding was defined as bleeding leading to a medical consultation or a visit to an emergency center, without fulfilling the criteria for a major bleeding [2].

Follow-up included one telephone interview and two surveillance, face-to-face evaluations during the first year of study participation and then semi-annual contacts, alternating between face-to-face evaluations (clinic visits or home visits in house-bound patients) and telephone calls as well as periodic reviews of the patient's hospital chart. During each visit/contact, study nurses interviewed patients to obtain information about the date and type of clinical events (recurrent VTE, bleeding, and death). If a clinical event had occurred, this information was complemented by reviewing medical charts and interviewing patients' primary care physicians and family members. We assessed outcomes using patient or proxy interviews, interview of the patient's primary care physician, and/or hospital chart review. A committee of three blinded clinical experts adjudicated all outcomes and classified the cause of all deaths as definitely due to PE, possibly due to PE, due to major bleeding, or due to another cause. Final classification was made on the basis of the full consensus of this committee.

2.4. Statistical analysis

We compared baseline and outcome characteristics of never, current, and former smokers using chi-squared test for categorical variables and non-parametric Kruskal–Wallis test for continuous variables. Smoking characteristics of current and former smokers were compared using chi-squared and Wilcoxon rank-sum test as appropriate. We calculated the incidence rate of a first VTE recurrence in each group and compared incidences among groups using the incidence rate ratio. We estimated the cumulative incidence of a first VTE recurrence by the Kaplan–Meier method and compared survivor functions across groups of patients with different smoking status and the quantity of pack-years smoked by the logrank test.

We compared the percentage of time spent within one of three specified INR ranges (<2.0, 2.0–3.0, >3.0) across different smoking levels by analysis of variance (ANOVA), excluding the first seven treatment days and patients with no or only one INR measurement.

Associations between smoking status and the time to the first VTE recurrence were assessed by competing risk regression accounting for death as a competing event, according to the method of Fine and Gray (1999) [21]. The method yields sub-hazard ratios (SHR) with corresponding 95% confidence intervals (CIs). Adjustments were done for