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Epidemiology of venous thromboembolism in the Framingham Heart Study

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ABSTRACT

Background: Reports of the crude incidence of venous thromboembolism (VTE) in Western countries vary widely. Data regarding risk factors, incidence and recurrence of VTE from deeply-phenotyped community-based cohort studies are needed.
Objectives: To study the incidence, associated mortality, and predisposing factors of VTE in the prospective, longitudinal community-based Framingham Heart Study.
Patients/Methods: The study sample consisted of the Framingham Heart Study Original, Offspring, Third Generation, and Omni cohorts (N = 9754). Incidence rates (IR) were standardized to the 2000 US population. Cox proportional hazards regression models were used to study risk factor associations.
Results: During 1995–2014 (total follow-up time 104,091 person-years [median 9.8 (range 0–20) years]), 297 incident VTE events were observed. Age-adjusted IR of VTE was 20.3/10,000 (95% CI 17.9–22.6). Of the events 120 (40%) were pulmonary embolism (PE) and 177 (60%) were deep venous thrombosis (DVT); 29% were unprovoked, 40% provoked, and 31% cancer-related. Cancer-related VTE was associated with high mortality at 30 days (24.2%), 1 year (66.3%), and 5 years (75.6%). In multivariable models, age and obesity, but no other traditional cardiovascular risk factors, were significantly associated with VTE (hazard ratio [HR] per 10-year increase in age 1.69, 95% CI 1.48–1.92; HR for obesity (BMI ≥ 30 kg/m^2) 1.88, 95% CI 1.44–2.45).
Conclusions: We provide data on the epidemiology of VTE. VTE is associated with significant mortality, and prognosis after cancer-related VTE is particularly poor. Traditional cardiovascular risk factors beyond age and obesity are not associated with VTE.

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1. Introduction

Venous thromboembolism (VTE) — comprising pulmonary embolism (PE) and deep venous thrombosis (DVT) — remains a common, preventable disease with high recurrence rate [1]. The incidence of VTE in Western countries has recently been systematically reviewed by a subcommittee of the International Society of Thrombosis and Haemostasis [2]. Unadjusted incidence rates (IR) of VTE range from 8 to 27 per 10, 000 person-years [3–12]. VTE is the cause of major morbidity with an estimated average of 548,000 hospitalizations annually in the US alone [13]. Furthermore, for almost one-quarter of patients experiencing PE, the initial clinical presentation is sudden death [14]. Direct ascertainment of mortality caused by VTE is challenging due to the low rate of autopsies revealing often undiagnosed PE as the immediate cause, but according to one estimate up to over 530,000 annual deaths could be attributed to VTE in the European Union in 2004 [14]. VTE events may be associated with predisposing factors (i.e. provoked), or they may be unprovoked, i.e. idiopathic [15]. Pathophysiologic characteristics of VTE include endothelial dysfunction, inflammation and hypercoagulability [16,17]. VTE also has a strong hereditary component [18,19]. Whether traditional cardiovascular risk factors (e.g. smoking, diabetes, hypertension and hyperlipidemia) predispose individuals to VTE remains controversial with accumulating evidence suggesting no or weak association [20–29].

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We describe the epidemiology of incident VTE over two decades of follow-up, and we examine the role of traditional cardiovascular (CV) risk factors measured at baseline, in a community-based prospective cohort, the Framingham Heart Study (FHS).

2. Methods

2.1. Study sample

The study sample consisted of the Framingham Heart Study Original, Offspring, and Third Generation cohorts [30–32] and the Framingham Heart Study Omni cohort [33]. The Original cohort was recruited in 1948; since then, participants have been examined biennially at the FHS Clinic. In 1971 the Offspring cohort was initiated by recruiting offspring (and their spouses) of the Original cohort; participants have been examined roughly every 4 years. The Third Generation cohort, consisting of children of the Offspring cohort, was recruited in 2002 and has returned for one repeat examination. The Omni cohort was added in 1994 and consists of Framingham residents aged 40 to 75 years who self-identified as minority group members. Written informed consent was provided by all participants and the study has been approved by the Boston University Medical Center Institutional Review Board.

VTE has been a systematically adjudicated endpoint since 1994; therefore, we identified January 1, 1995, as the baseline date for follow-up. The total number of eligible participants across the four cohorts was N = 9874; 109 participants were excluded: 53 had reported prevalent VTE at inclusion and 56 did not attend the baseline examination for this study. The final study sample was N = 9765: 1259 Original cohort, 3914 Offspring cohort, 4089 Third Generation cohort, and 503 Omni cohort. Follow up was from January 1st 1995 to March 24th 2014.

2.2. Baseline characteristics

Baseline characteristics were recorded at the following exams that served as the cohort-specific baseline examination for this study: Exam 24 (1995–1998) for the Original cohort, Exam 6 for (1995–1998) for the Offspring cohort, Exam 1 (2002–2005) for the Third Generation cohort, and Exam 1 (1994–1998) for the OMNI cohort. Baseline characteristics were obtained at a preceding exam or the immediate following exam if the participant did not attend the pre-specified baseline exam or had the first incident VTE after January 1st 1995 but before attending the pre-specified baseline examination (n = 853). Baseline characteristics were always obtained before the VTE event.

2.3. VTE diagnosis and classification

At each examination, participants underwent a medical history and physical examination. Medical records and imaging reports were obtained for each reported physician visit (out-patient) or hospital admission (in-patient) by a participant with symptoms suggestive of VTE. Diagnosis of VTE was based on clinical symptoms and signs suggestive of VTE coupled with objective imaging data obtained from physician office records, hospital records, or autopsy reports. PE was diagnosed using either ventilation perfusion (V/Q) scan or computed tomography angiography, or at autopsy. Isolated subsegmental PE was included. DVT was diagnosed using a venogram, Doppler ultrasound, impedance plethysmography (IPG) (N = 0), 125I fibrinogen leg scan (N = 1), or a combination of the IPG and leg scan (N = 0). DVT located outside the lower or upper extremities, as well as in the superficial veins, or restricted to the calf only, was not included. The final VTE diagnosis was confirmed by a panel of three Framingham Heart Study physicians. Information on predisposing factors was obtained from medical records.

2.4. Predisposing factors to VTE

A supplemental manual review of the Framingham chart and medical records obtained for confirmation of the VTE diagnosis was performed by an experienced physician to abstract information on predisposing factors for VTE in participants with an incident event. Any of the following factors were considered predisposing factors if present within 3 months prior to VTE: Surgery defined as any surgical operation; any fracture/trauma requiring medical attention; hospitalization defined as any admission to a hospital ward; immobilization defined as bed rest ≥2 days; self-reported use of hormone replacement therapy or oral contraceptives. Self-reported travel >4 h within 1 month prior to VTE was counted as a predisposing factor. Pregnancy was defined as a predisposing factor if VTE occurred any time during pregnancy or within 3 months after delivery (puerperium) or miscarriage.

A VTE event was considered provoked if at least one predisposing factor (surgery, fracture, hospitalization, immobilization, HRT/OC use, travel >4 h, pregnancy/puerperium) other than cancer was present; a VTE event was considered cancer-related if there was a diagnosis of active cancer (excluding only non-melanoma skin cancer). Active cancer was defined as new cancer diagnosis within six months prior to event or three months after VTE, any treatment for cancer within the six months prior to event, recurrent cancer, or the presence of metastasis. In the absence of a documented provoking factor or cancer, a VTE event was considered unprovoked. These three VTE groups were mutually exclusive. We further categorized participants with VTE events into the DVT group and the PE group. The DVT group included only deep venous thrombosis events, but the PE group included individuals with PE with or without concomitant DVT.

A recurrent VTE event was defined as a first occurrence of thrombosis in a previously uninvolved lower/upper extremity venous (DVT) or pulmonary (PE) segment. A recurrent event in the same location would be considered only if objective imaging in the interim showed complete resolution of the clot. All recurrences were adjudicated by a panel of three physicians to verify a new event clinically clearly independent of the first event.

2.5. Cardiovascular risk factor definitions

CV risk factors were recorded at baseline exam. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), non-fasting plasma glucose ≥200 mg/dL (11.1 mmol/L) or treatment with hypoglycemic agents [34]. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or current use of antihypertensive treatment. Hypercholesterolemia was defined as total cholesterol ≥200 mg/dL (5.2 mmol/L) or LDL cholesterol ≥130 mg/dL (3.4 mmol/L) or treatment with lipid-lowering medication. Prevalent CVD was defined by an existing diagnosis of myocardial infarction, stroke or peripheral arterial disease (either a history of intermittent claudication or documented lower extremity revascularization). Body mass index was calculated as weight in kilograms divided by height in meters squared. Current cigarette smoking was defined by self-reported regular smoking of cigarettes within 1 year of the examination. Aspirin use was defined as self-reported use of aspirin ≥81 mg at least three pills per week.

2.6. Mortality outcome

All cohorts remain under continuous surveillance and all deaths that occurred prior to January 1, 2014 were included in this study. Deaths were identified using multiple strategies including routine participant contact for research examinations or health history updates, surveillance at the local hospital, search of obituaries in the local newspaper, and if needed through use of the National Death Index. Death certificates were routinely obtained and all hospital and nursing home