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Risk factors for recurrent venous thromboembolism in young and middle-aged women

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ABSTRACT

Background: It is a matter of debate whether women with an episode of VTE associated with estrogen have a lower risk of recurrence than women with an unprovoked VTE.
Objectives: To identify risk factors for recurrent VTE in women and to assess the risk of recurrent VTE associated with combined oral contraceptives (CHC) or menopausal hormone treatment (HT), compared to surgery-related and unprovoked VTE.
Patients/Methods: A cohort of 974 women aged 18–64 years with a first episode of VTE were followed-up for a median time of 5.2 years. All women were previously included as cases in the Swedish nation-wide case–control study "Thrombo Embolism Hormone Study" (TEHS). Hazard ratios for recurrence were calculated using univariable and multivariable Cox proportional hazards model.
Results: A total of 102 patients (10%) suffered from recurrent VTE. The annual rate of recurrence was 1.0% in patients with surgery/cast, 2.0% in patients with CHC/HT and 3.2% in patients with unprovoked first VTE. Adjusted hazards ratio (HR_a) for recurrence was 0.35 (95% CI 0.20-0.61) in women with VT provoked by surgery/cast while women with estrogen-associated VTE had a HR_a of 0.70 (95% CI 0.43-1.20) compared to women with unprovoked VTE.
Conclusion: Women 18–64 years are at low risk of recurrent VTE. Women with hormone associated VTE had a lower risk of recurrence than women with unprovoked VTE, but not as low as surgery/cast provoked VTE.

Introduction

After a first episode of venous thromboembolism (VTE), there is a considerable risk of recurrence. The risk is highest within the first year after discontinuation of anticoagulant treatment with a cumulative incidence of 20-25% after 5 years in an unselected population [1,2]. Continuous anticoagulant treatment can prevent most episodes of recurrent VTE but decisions on extended treatment must be balanced against the risk of major bleeding complications [3–5].

The risk of recurrence after an unprovoked VTE is higher than if the VTE was provoked by a transient risk factor like surgery, cast or pregnancy [2,6,7]. The risk of recurrent episodes of VTE is also influenced by gender as several studies have shown that men have at least a two-fold higher risk of recurrence than women [7–12]. A lower risk of recurrent VTE in women where the first episode was associated with estrogen treatment has been suggested as a possible explanation for this difference. Data on this matter is however still conflicting and it is debated whether hormonal treatment with combined oral contraceptives (CHC) or menopausal hormone treatment (HT) should be regarded as a provoking factor or not [9,13–17].

The current international guidelines recommend extended anticoagulant treatment in patients with a high risk of recurrence, such as after unprovoked proximal deep vein thrombosis (DVT) or unprovoked pulmonary embolism (PE) [18]. As women have a lower risk of recurrence than men there is a need to better understand the risk factors for recurrence in female patients, including the risk related to hormone associated VTE.

The overall aim of this study was to assess the risk of recurrent VTE in women with hormone related thrombosis, VTE related to surgery or cast and unprovoked VTE. Furthermore, we wanted to identify the

Abbreviations: VTE, venous thromboembolism; CHC, combined hormonal contraceptives; HT, menopausal hormone treatment; DVT, deep vein thrombosis; PE, pulmonary embolism; TEHS, Thrombo Embolism Hormone Study; ICD, International Classification of Diseases; BMI, body mass index; HR, hazard ratios; CI, confidence intervals.

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most important risk factors for recurrent VTE in young and middle aged women.

Materials and Methods

Population and Study Design

This cohort study called TEHS-follow-up comprised women 18 to 64 years of age. All participants were previously included as cases in the "Thrombo Embolism Hormone Study" (TEHS), a population based case–control study on risk factors for VTE that recruited patients and controls from 43 larger or medium sized hospitals spread geographically in Sweden. In the TEHS- follow up study all cases in TEHS who accepted participation were followed-up concerning recurrent VTE.

TEHS

The methodology of the TEHS has been described elsewhere [19]. Briefly, 1433 women with a first episode of PE or DVT of the lower limb or pelvis were included as cases, from 2003 to 2009. The diagnosis of VTE was based on venography or Doppler ultrasound in DVT and CT-scan or perfusion-ventilation scintigraphy in PE. Patients, who had been pregnant the past three months, had a current malignant disease or a history of malignancy within the past five years were not eligible for the TEHS. Baseline data was obtained through a telephone interview with the participants in a period of three months after the diagnosis of VTE and included information on body weight and height, risk factors for VTE, medical history, use of combined hormonal contraceptives (CHC) or menopausal hormone treatment (HT) and family history of VTE. Blood samples for DNA-analyses were collected from the women at time of inclusion.

TEHS-follow-up

In 2011, all cases included in TEHS who were still living in Sweden were followed-up by a questionnaire sent by mail. The questionnaire covered different medical aspects, as current medication, duration of previous and current anticoagulant treatment, hormone therapy with CHC or HT and recurrent events of VTE. Within one month a reminder was sent if the questionnaire was not returned. Out of the 1435 women included in the TEHS-study, 38 were not alive at the time of follow-up. The cause of death was retrieved from Cause of Death Register in Sweden, held by the National Board of Health and Welfare [20] and none was related to VTE. Thirteen women died from cancer, 11 from cardiovascular disease and the remaining 14 from other causes. Three patients had emigrated from Sweden leaving 1394 patients who were asked to participate in the follow-up study. Women on continuous anticoagulant treatment were not eligible for the analysis of recurrent VTE in the follow-up since they were not considered to be at risk of recurrence. A total of 345 patients rejected participation, 53 were on continuous anticoagulant treatment and 22 patients did not answer the question about current anticoagulant treatment, leaving 974 women to follow-up, Fig. 1.

We obtained information on recurrent VTE both from the questionnaire and from data recorded in the Swedish Patient Register, a nationwide register held by the National Board of Health and Welfare in Sweden. From 1987 the Patient Register includes all hospital-based care in Sweden and from 2001 it also includes outpatient visits. The register cover data on age, sex, national registration number (a unique identification number assigned to every resident in Sweden) and up to 6 diagnoses and 6 surgical procedures including for each patient. Diagnoses are recorded according the current International Classification of Diseases (ICD) version 10 (ICD-10) at each out-clinic visit or hospitalization [21].

To identify potential recurrent events all study participants recorded in the register with diagnose of venous thrombosis according to ICD 10 (I80.1-9, I82.1-9, I26.0, 9, I67.6, O22.3, O22.5) after their initial VTE were reviewed. All events, recorded in the register, were objectively verified by a review of the medical records. To be considered as a recurrent event the diagnosis was required to be confirmed by any of the same objective radiological methods as at inclusion of the TEHS-study. Furthermore, the event had to be regarded, by the treating physician, as having indication for resumed anticoagulant treatment for at least 3 months. The follow-up period started at the time of discontinuation of anticoagulant treatment after the first episode of VTE and patients were censored either at first recurrent VTE or at the date for answering the questionnaire. If information on the duration of anticoagulant treatment was missing, women with an index DVT were assumed to be treated with anticoagulants for 6 months and women with an index PE for 12 months according to the clinical praxis during the time of inclusion in Sweden.

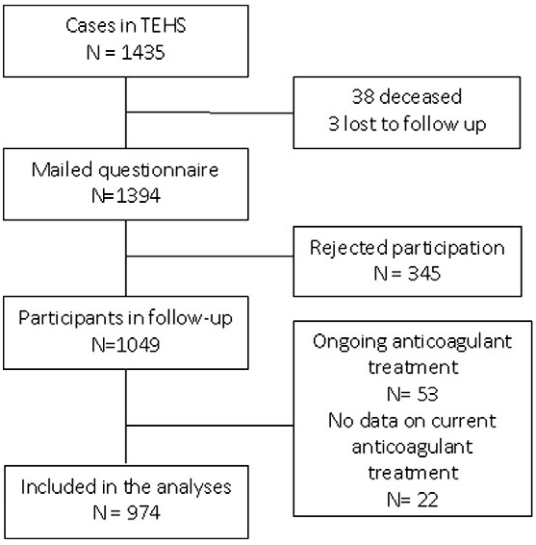

Fig. 1. Flow-chart of the study cohort.

Both the TEHS and the TEHS follow-up study were approved by the research ethics committees in Sweden. All participants in TEHS and the TEHS follow-up study were included after a signed informed consent at inclusion of the study.

Statistical Analyses

Cumulative incidence of recurrent VTE was calculated using Kaplan-Meier survival analysis. All study participants were included with their maximum time available for follow-up and censored at time of recurrent event or end of follow-up. The localization of the VTE was classified as either distal DVT when localized below the popliteal vein, proximal DVT from the popliteal vein and more proximal including pelvic veins, or as PE. Patients with both DVT and PE were classified as having PE. To calculate the risk of recurrence according to characteristics of first VTE we classified patients in three groups according to provoking factor at the first VTE: unprovoked, provoked by surgery and or treatment with cast or provoked by HT/CHC treatment. CHC included oral tablets, dermal patches and intravaginal devices. HT included progestogen opposed and non-opposed oral formulations and dermal patches. Women with both surgery and HT/CHC treatment prior to the first episode of VTE were classified into the surgery/cast group as surgery/cast has been shown to be a stronger risk factor than HT/CHC[19]. Information on weight and length were collected from time of inclusion in TEHS. Obesity was defined as body mass index (BMI) $\geq$ 30 kg/m^2. Groups were compared using log-rank test. Cox proportional hazard model was used to calculate both crude and multivariable adjusted hazard ratios (HR) with their corresponding 95% confidence intervals (CI). The multivariable model included age, presence of factor V