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Mortality and recurrence after treatment of VTE: Long term follow-up of patients with good life-expectancy

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ABSTRACT

Introduction: After completed anticoagulant treatment for acute VTE, both the subsequent mortality and risk of recurrent VTE are high, probably related to the frequent presence of serious disease in these patients. The aim of the study was to determine survival and recurrence in selected patients with good life-expectancy, and to evaluate risk factors.

Methods: The 323 patients were followed for median 7.4 years (range 4.1-11.9) after cessation of anticoagulation. Survival analysis and Cox-regression were used for univariate and multivariate analysis.

Results: The cumulative incidence of survival after 5 years was 93.4%. Standardised mortality ratio was 1.42 for men and 1.28 for women. Patients without a transient risk factor prior to the index VTE were associated with higher risk of mortality compared to risk of mortality in patients with a transient risk factor (hazard ratio (HR) 2.81; 95% CI 1.40-5.62). Recurrence of VTE after 5 years was 19.0%. A persistent risk factor or a spontaneous VTE was associated with higher risk of recurrence compared to a transient risk factor (HR 2.39; 95% CI 1.44-3.95). Elevated D-dimer levels increased the risk, and immobilisation prior to the index VTE reduced the risk of recurrence. Sex, age and thrombophilia were not independent risk factors for recurrence.

Conclusions: Despite a low mortality rate in this selected cohort, the recurrence rate and risk factors for recurrence were similar to findings reported in unselected populations. VTE unrelated to a transient risk factor was associated with increased mortality compared to mortality in patients with a transient risk factor.

Introduction

There is a considerable risk of recurrence, post-thrombotic syndrome and death after an episode of venous thromboembolism (VTE) [1]. Mortality one year after a venous thrombotic episode has been reported to be 17-22% [1,2] and 20-25% after 2 years [1,3]. The risk of dying has been shown to be highest shortly after the VTE event, and usually related to concomitant disease.

Moreover, the long-term mortality has also been demonstrated to be high, but available data are limited. In a cohort study, mortality after 8 years was reported to be 13% for patients who survived the first year after an initial deep venous thrombosis (DVT) [1].

Most recurrent events occur within the first months after a thrombotic episode, but the risk of recurrence declines over time [4].

Recurrence of VTE has been estimated to occur in 11-18% of the patients after 2 years [1,4,5], increasing to 22-29% after 5 years [1,5,6]. The risk of recurrence depends on the clinical condition of the patient and on the possible presence of risk factors. VTE provoked by a transient risk factor, such as surgery or trauma is associated with a low tendency to recurrence compared with recurrence in cancer or chronic diseases that persist over time and which are associated with a higher risk [7]. An elevated D-dimer level measured after cessation of anticoagulant treatment is known to be associated with an increased rate of recurrent VTE [8].

Patients with acute VTE are usually treated with low molecular weight heparin or unfractioned heparin for 5–10 days and thereafter with oral anticoagulation (OA) for 3–12 months [9]. Recurrence is rare under OA. A short period of anticoagulant treatment increases markedly the risk of recurrence [10]. The optimal duration of anticoagulation however, is uncertain, as prolonged treatment with OA increases the risk of major bleeding which is 1-3% per year [11]. Moreover, the beneficial effect of prolonged anticoagulation is possibly not maintained after the treatment is completed [12]. It is

Abbreviations: AT, antithrombin; DVT, deep venous thrombosis; FV, factor V; HR, hazard ratio; INR, international normalised ratio; OA, oral anticoagulation; PE, pulmonary embolism; PC, protein C; PS, protein S; SMR, standardised mortality ratio; VTE, venous thromboembolism.

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uncertain whether thrombophilia, age and gender are associated with an increased risk of recurrence [6,7].

In this prospective cohort study, we followed 323 patients for median 7.4 years (range 4.1-11.9) after anticoagulant treatment was discontinued. The purpose was to determine survival and recurrence in the cohort of selected patients with assumed good life-expectancy, and to estimate the roles of risk factors registered at inclusion.

Materials and methods

Study design

A prospective cohort study of 323 patients with objectively confirmed venous thromboembolism (VTE) recruited from the Thrombosis Clinic, Oslo University Hospital Aker, serving a source population of 130 000 in Oslo.

The patients were included between March 25th 1996 and December 10th 2003. During this period, the inclusion of patients was temporarily suspended about 15 months, due to the absence of the senior physician at the Thrombosis Clinic. The net inclusion period was 79 months. The patients were screened and entered the study on the day OA treatment was stopped. The closing date for follow-up was February 1st 2008, or earlier for those patients who died. The endpoints were incidence of recurrent VTE and total mortality. The patients who obtained the endpoint recurrent VTE were followed further to closing date or death.

Participants

The eligibility criterion was a completed anticoagulation treatment period with Warfarin (target INR 2.0-3.0) after a sustained VTE episode according to the hospital's guidelines for duration of OA after VTE. OA was used for 6 months in the majority of patients, but 3 months in case of distal thrombosis triggered by a transient risk factor. OA was used for at least 12 months in most patients with previous thrombosis, unprovoked thrombosis, proximal VTE with prolonged symptoms or symptomatic PE. With some of these patients, OA was cessated after about 12 months because of suspected increased risk of bleeding or lack of cooperation. With 37 included patients, OA had been continued for more than 12 months, with most of them, due to the existence of more than one of these indications for prolonged treatment. The ethical committee had no objections to the study. At the time of entry data information on specified risk factors (Table 2) were recorded and the patients were informed about the study. Written informed consent was obtained from all participants.

The patients met to scheduled follow-up visits at the Thrombosis Clinic 6 and 12 months after inclusion. They were advised to get in touch with the Thrombosis Clinic in case of new symptoms from the lower extremity, chestpain or dyspnoea. Additional patients were referred directly to the hospital by private physicians. All patients with a suspicion of recurrence, had it confirmed by ultrasound or X-ray analysis and were registered with the endpoint recurrence. The majority were treated at Oslo University Hospital, Aker, but three patients were treated at Akershus University Hospital due to a change of the uptake areas. In order to detect all recurrences, medical records of all included patients were screened, as was the hospital's Diagnosis Discharge Registry. Suspected VTE which was not confirmed by objective testing was not registered. Deceased patients were identified by consulting the Statistics Norway. Reliable cause of death was not established in all cases, mainly because autopsy was performed in only about one fourth of the fatalities.

Diagnosis of VTE (index and recurrence of VTE)

DVT was objectively verified by compression ultrasonography or venography. Pulmonary embolism (PE) was verified by spiral computed tomography.

Variables

Our strategy was pragmatic which means we were interested in pinpointing independent risk factors of predictors of recurrent VTE and mortality. The clinical profile included the demographic variables age and sex and other clinical variables which were classified as persistent or transient risk factors. Additionally, the plasma marker D-dimer was included.

Bias

One potential bias is misclassification of the endpoint recurrent VTE (information bias). This means there is a possibility that small events not necessitating hospitalisation were considered as a none event. The other, selection bias in this cohort will come from lost to follow-up where recurrent VTE which might have developed and treated outside Oslo would be missed.

Laboratory analysis

Blood samples were drawn one and three months after cessation of Warfarin. CRP and D-dimer were measured on fresh samples. Citrated plasma was stored at −70 °C until analysis. The laboratory tests were performed on all samples. When available, test results obtained after one month were used in the analyses. Screening for thrombophilia included testing for AT, PC, Protein S (PS), factor V (FV) Leiden mutation (R506Q) and Prothrombin gene mutation (G20210A). AT, PC and PS were measured by standard methods [13–15]. FV Leiden mutation and Prothrombin gene mutation were detected by DNA analysis [16]. Lupus anticoagulant was determined by the lupus ratio test [17]. D-dimer antigen was measured using Tina-quant D-dimer [18].

Epidemiological and statistical methods

For each postulated prognostic factor a preliminary analysis was performed with univariate methods using survival analysis curves [19]. Comparison of univariate survival curves was done with Breslow [20] and log-rank [21] test statistics, and Tarone-Ware test statistic was estimated when having more than two levels of survival curves.

Independent risk factors of total mortality were analysed by the Cox-regression model [22]. The essential check of the proportional effect was done by plotting the logarithm of the integrated hazard [23]. Multifactorial analysis was done by a manual backward elimination procedure.

Multivariate analyses were preceded by estimation of correlation between risk factors. Continuous variables were tested for trend before they were introduced in the model as such.

Another analysis was done considering outcome recurrent VTE events. This analysis led to coding multiple competing risk failure events. The time of death from other causes than the one considered were treated as censored.

The observed mortality in our cohort of VTE patients was compared to the expected total mortality of the Norwegian population stratified on age and gender. This permitted estimation of a standardised mortality ratio (SMR) with 95% confidence interval limits. The method consists of comparing age and gender specific rates of death (expected deaths, E) of a standard population, the total Norwegian population, to the observed deaths (O) in the population of interest, the present cohort. Tables giving the incidents of deaths per 100 000 inhabitants per year among woman and men in different age groups were used. SMR was estimated as $SMR = \sum Oi / \sum Ei$ at age and gender strata [24].

The 95% confidence interval ($SMR \pm 1.96$ x $SE(SMR)$, where $SE(SMR) = SMR/\sqrt{\sum Oi}$), E*i* the summation of expected deaths, and O*i* the summation of the observed deaths.