

ORIGINAL ARTICLE

The Risk of Recurrent Venous Thromboembolism in Men and Women

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ABSTRACT

BACKGROUND

Whether a patient's sex is associated with the risk of recurrent venous thromboembolism is unknown.

METHODS

We studied 826 patients for an average of 36 months after a first episode of spontaneous venous thromboembolism and the withdrawal of oral anticoagulants. We excluded pregnant patients and patients with a deficiency of antithrombin, protein C, or protein S; the lupus anticoagulant; cancer; or a requirement for potentially long-term antithrombotic treatment. The end point was objective evidence of a recurrence of symptomatic venous thromboembolism.

RESULTS

Venous thromboembolism recurred in 74 of the 373 men, as compared with 28 of the 453 women (20 percent vs. 6 percent; relative risk of recurrence, 3.6; 95 percent confidence interval, 2.3 to 5.5; $P < 0.001$). The risk remained unchanged after adjustment for age, the duration of anticoagulation, and the presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, or an elevated level of factor VIII or IX. At five years, the likelihood of recurrence was 30.7 percent among men, as compared with 8.5 percent among women ($P < 0.001$). The relative risk of recurrence was similar among women who had had their first thrombosis during oral-contraceptive use or hormone-replacement therapy and women in the same age group in whom the first event was idiopathic.

CONCLUSIONS

The risk of recurrent venous thromboembolism is higher among men than women.

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THE ANNUAL INCIDENCE OF VENOUS thromboembolism is 1 to 2 cases per 1000 persons,^{1,2} and the risk of the disorder rises exponentially with age, from an annual rate of less than 5 per 100,000 children to greater than 400 per 100,000 adults older than 80 years.³ The overall incidence of a first venous thromboembolism seems to be similar among men and women,¹⁻³ but the risk is higher among women of childbearing age than among men in the same age group.^{2,4,5} This difference probably relates to the association of venous thromboembolism with pregnancy or the use of oral contraceptives. By contrast, the risk among older women is substantially lower than that among men in the same age group.^{2,4,5}

Venous thromboembolism has a recurrence rate of 5 to 10 percent per year.⁶⁻⁸ As for a first episode, the pathogenesis of recurrences is multifactorial, with risks that depend on the severity and number of hereditary and circumstantial factors. Whether a patient's sex is associated with the risk of recurrent venous thromboembolism is uncertain. Large prospective studies of the incidence of recurrence did not address sex.^{6,8} In a study in Norway,⁷ proximal deep-vein thrombosis, cancer, and a history of venous thromboembolism, but not the person's sex, predicted an increased risk of recurrent thrombotic events. In this report, we assessed the association of patient sex with the risk of recurrence in 826 patients with a first episode of spontaneous venous thromboembolism.

METHODS

PATIENTS AND STUDY DESIGN

The Austrian Study on Recurrent Venous Thromboembolism is an ongoing prospective study involving four thrombosis centers in Vienna. Between July 1992 and June 2003, 2795 patients older than 18 years of age who had been treated with oral anticoagulants for at least three months after venous thromboembolism were enrolled after providing written informed consent. All patients had been treated with standard heparin at doses designed to keep the activated partial-thromboplastin time 1.5 to 2.0 times that of the control value or with subcutaneous low-molecular-weight heparin at therapeutic doses. A total of 1945 patients were excluded because of the following conditions: previous venous thromboembolism in 451; surgery, trauma, or pregnancy within the previous three months in 527; a known deficiency of antithrombin, protein C, or protein S in 65; the lupus anticoagulant in 43; can-

cer in 423; and the need for long-term treatment with antithrombotic drugs for reasons other than venous thrombosis in 436.

The day of discontinuation of oral anticoagulants was defined as the day of study entry. After three weeks, patients were screened for the presence of a deficiency of antithrombin, protein C, and protein S; the lupus anticoagulant; factor V Leiden; and factor II G20210A. Levels of factors VIII and IX were also determined. The 24 patients who had a deficiency of antithrombin, protein C, or protein S or in whom the lupus anticoagulant was detected were excluded. Patients were observed at three-month intervals for the first year and every six months thereafter. They were provided with detailed written information on the symptoms of venous thromboembolism and were instructed to report to one of the thrombosis centers in case of symptoms. All women were strongly discouraged from using contraceptive pills or hormone-replacement therapy regardless of whether they had a history of an association between the use of these hormones and the initial venous thromboembolism. At each visit, a data form was completed regarding the patient's medical history.

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

The diagnosis of deep-vein thrombosis was established by venography or color-coded duplex sonography (in the case of proximal deep-vein thrombosis). If venography was used, one of the following direct or indirect criteria had to be fulfilled: a constant filling defect was present on two views; there was an abrupt discontinuation of the contrast-filled vessel at a constant point in the vein; and the entire deep-vein system failed to fill without an external compressing process, with or without venous flow through collateral veins. Diagnostic criteria for color-coded duplex sonography were the following: visualization of an intraluminal thrombus in a deep vein, lack of or incomplete compressibility, and lack of flow spontaneously and after distal manipulation. The diagnosis of pulmonary embolism was made by ventilation-perfusion lung scanning according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis.⁹ Patients with both deep-vein thrombosis and pulmonary embolism were categorized as having pulmonary embolism.

OUTCOME MEASURES

The end point of the study was recurrence of symptomatic venous thromboembolism confirmed by

venography, ventilation–perfusion lung scanning, or both, according to the aforementioned criteria. The diagnosis was established by an adjudication committee consisting of independent clinicians and radiologists who were aware of the patient’s sex but unaware of the presence or absence of thrombotic risk factors. Recurrent deep-vein thrombosis was diagnosed if the patient had a thrombus in another deep vein in the leg involved in the previous event, a thrombus in the other leg, or a thrombus in the same venous system involved in the previous event with a proximal extension of the thrombus if the upper limit of the original thrombus had been visible or the presence of a constant filling defect surrounded by contrast medium if it had not.

LABORATORY ANALYSIS

Venous blood was obtained after the patient had fasted overnight, placed in 1/10 volume of 0.11 mmol of trisodium citrate per liter, and centrifuged for 20 minutes at 2000×g. The plasma was stored at –80°C. Routine laboratory methods were used to identify antithrombin, protein C, and protein S. Screening for factor V Leiden and factor II G20210A was carried out on genomic DNA as described previously.^{10,11} Factor VIII and factor IX were measured by one-step clotting assays with the use of factor VIII– or factor IX–deficient plasma (Immuno Baxter) and a Sysmex CA 6000 fully automated coagulation analyzer. The presence of the lupus anticoagulant was established on the basis of the criteria of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis.¹² The technicians were unaware of the patient’s characteristics, including sex, at all times.

STATISTICAL ANALYSIS

Categorical data were compared between groups with use of contingency-table analyses (the chi-square test), and continuous data (presented as means ±SD) were compared with use of Mann–Whitney U tests. All P values were two-tailed. Survival-time methods were used to analyze the time to recurrent venous thromboembolism among patients with a subsequent episode (uncensored observations) or the duration of follow-up among patients without recurrence (censored observations).¹³ The probability of recurrence was estimated according to the method of Kaplan and Meier.¹⁴ Data on patients who left the study because of a require-

ment for potentially long-term antithrombotic treatment, a diagnosis of cancer, or pregnancy, who were lost to follow-up, or who died were censored at the time of withdrawal. To test for homogeneity among the various groups of patients, we used the log-rank test. Univariate and multivariate Cox proportional-hazards models were used to analyze the association of the patient’s sex with the risk of recurrent venous thromboembolism. Analyses were adjusted for age, the presence or absence of symptomatic pulmonary embolism at the time of a first thrombotic event, the duration of anticoagulation, and the presence or absence of factor V Leiden, factor II G20210A, and elevated levels of factors VIII and IX (dichotomized at the 90th percentile [234 IU per deciliter] and at the 75th percentile [138 IU per deciliter] of the patient population, respectively). All computations were performed with the use of SPSS software, version 10.0.

RESULTS

STUDY POPULATION

We studied 826 patients (373 men and 453 women) who had had a first episode of spontaneous venous thromboembolism. The mean ages of these men and women were 51±14 years and 45±18 years, respectively (P<0.001). They were enrolled after the discontinuation of oral anticoagulants and followed for a median of 26 months. The median duration of follow-up was 23 months (interquartile range, 10 to 49) among the men and 28 months (interquartile range, 12 to 57) among the women (P=0.02). A total of 189 patients left the study: 125 required long-term antithrombotic treatment for reasons other than venous thromboembolism (15 women and 10 men received anticoagulants because of atrial fibrillation and 54 women and 46 men were given aspirin for arterial disease), 14 received a diagnosis of cancer, 26 became pregnant and started prophylaxis with low-molecular-weight heparin, and 24 were lost to follow-up. Three patients died of cancer, six of cardiac failure, and one of septicemia.

RECURRENT VENOUS THROMBOEMBOLISM

A total of 102 of the 826 patients (12 percent) had recurrent venous thromboembolism (deep-vein thrombosis in 67 and pulmonary embolism in 35). Of these 102 patients, 74 (73 percent) were men and 28 (27 percent) were women. Table 1 shows the relative risk of a recurrence according to age, the presence of a previous symptomatic pulmonary

embolism, factor V Leiden, factor II G20210A, or an elevated level of factor VIII or IX, and the duration of anticoagulation. When age was analyzed in a Cox proportional-hazards model, the relative risk of recurrent venous thromboembolism was 1.2 (95 percent confidence interval, 1.1 to 1.4; $P=0.001$) for each 10-year increase and 1.1 (95 percent confidence interval, 0.9 to 1.3; $P=0.3$) in the multivariate analysis. An elevated level of factor VIII and a first symptomatic pulmonary embolism were the strongest determinants of recurrence.

RECURRENT VENOUS THROMBOEMBOLISM AND SEX

Venous thromboembolism recurred in 74 of the 373 men, as compared with 28 of the 453 women (20 percent vs. 6 percent, $P<0.001$). Table 2 shows the baseline characteristics of all patients. The men were on average older than the women (51 ± 14 years vs. 45 ± 18 years, $P<0.001$), and they had a shorter duration of follow-up (33 ± 29 months vs. 38 ± 33 months, $P=0.02$). There was no significant difference between men and women with regard to the presence of factor V Leiden (31 percent and 29 percent, respectively), factor II G20210A (7 percent and 8 percent, respectively), elevated levels of factor VIII (8 percent and 10 percent, respectively), elevated levels of factor IX (25 percent and 22 percent, respectively), or the duration of anticoagulation (eight months and nine months, respectively). According to Kaplan–Meier analysis, there was a clear divergence between the rate of recurrence among men and the rate among women throughout the period of observation ($P<0.001$) (Fig. 1). At five years, the cumulative probability of recurrence was 30.7 percent (95 percent confidence interval, 23.8 to 37.6) among men, as compared with 8.5 percent (95 percent confidence interval, 5.0 to 12.0) among women. According to the univariate analysis, male sex conferred a relative risk of recurrence of 3.6 (95 percent confidence interval, 2.3 to 5.5; $P<0.001$). After adjustments for age, the duration of anticoagulation, and the presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, and an elevated level of factor VIII or IX, the risk of recurrence among men, as compared with women, was 3.6 (95 percent confidence interval, 2.3 to 5.8; $P<0.001$).

A first venous thromboembolism occurred during oral-contraceptive use in 175 women. The cumulative probability of recurrence at five years was 5.9 percent (95 percent confidence interval, 0.6 to

Table 1. Relative Risk of Recurrent Venous Thromboembolism According to Baseline Characteristics.*

Characteristic	Univariate Relative Risk (95% CI)	Multivariate Relative Risk (95% CI)†
Age (per 10-yr increase)	1.2 (1.1–1.4)	1.1 (0.9–1.3)
Symptomatic pulmonary embolism (vs. deep-vein thrombosis)	1.7 (1.2–2.5)	1.7 (1.1–2.5)
Factor V Leiden (vs. absence of mutation)	1.0 (0.7–1.6)	1.2 (0.8–1.8)
Factor II G20210A (vs. absence of mutation)	1.7 (0.9–3.1)	2.1 (1.1–3.8)
Factor VIII ≥ 234 IU/dl (vs. <234 IU/dl)	3.4 (2.1–5.6)	2.9 (1.6–5.1)
Factor IX ≥ 138 IU/dl (vs. <138 IU/dl)	1.8 (1.2–2.7)	1.3 (0.8–2.0)
Duration of anticoagulation (per 3-mo increase)	1.03 (0.99–1.07)	1.02 (0.98–1.05)

* CI denotes confidence interval.

† Multivariate relative risks were calculated with adjustment for age; the presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, elevated factor VIII levels, or elevated factor IX levels; and the duration of anticoagulation.

Table 2. Baseline Characteristics of the 826 Patients According to Sex.*

Characteristic	Women (N=453)	Men (N=373)	P Value
Age — yr	45±18	51±14	<0.001
Site of thrombosis — no. (%)			0.09
Distal veins of the leg	102 (23)	58 (16)	
Proximal veins of the leg	150 (33)	135 (36)	
Axillary veins	19 (4)	14 (4)	
Pulmonary embolism	182 (40)	166 (45)	
Duration of anticoagulation — mo	9±12	8±11	0.76
Follow-up — mo	38±33	33±29	0.02
Factor V Leiden — no. (%)	130 (29)	115 (31)	0.5
Factor II G20210A — no. (%)	36 (8)	25 (7)	0.5
Factor VIII ≥ 234 IU/dl — no. (%)	44 (10)	28 (8)	0.5
Factor IX ≥ 138 IU/dl — no. (%)	101 (22)	95 (25)	0.3

* Plus–minus values are means \pm SD.

11.1) among these women and 4.3 percent (95 percent confidence interval, 0 to 10.1; $P=0.8$) among the 60 women in the same age groups in whom the first event was idiopathic (Fig. 2). Among women who were taking oral contraceptives, the relative risk of recurrence was 0.8 (95 percent confidence interval, 0.1 to 4.0; $P=0.8$) and remained unchanged after adjustment for age and other possibly confounding factors.

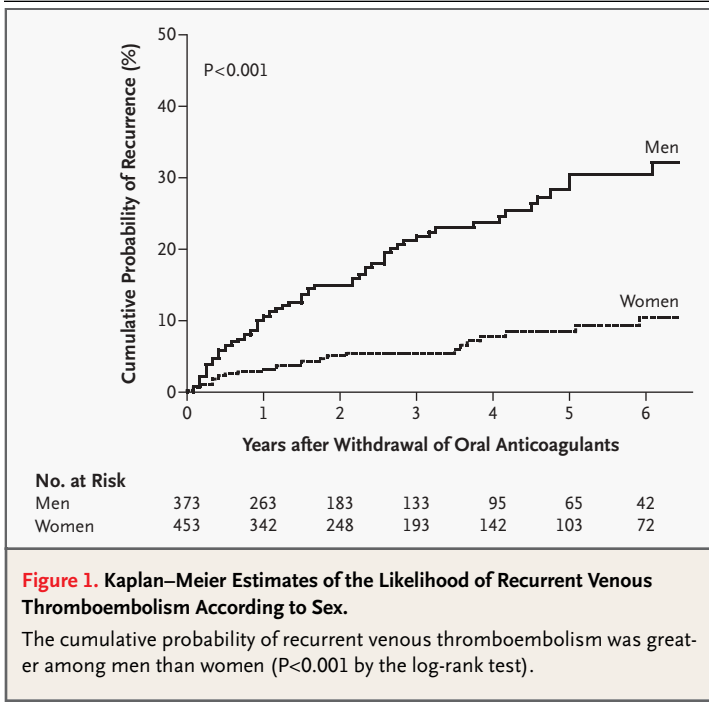


Figure 1. Kaplan–Meier Estimates of the Likelihood of Recurrent Venous Thromboembolism According to Sex.
The cumulative probability of recurrent venous thromboembolism was greater among men than women ($P < 0.001$ by the log-rank test).

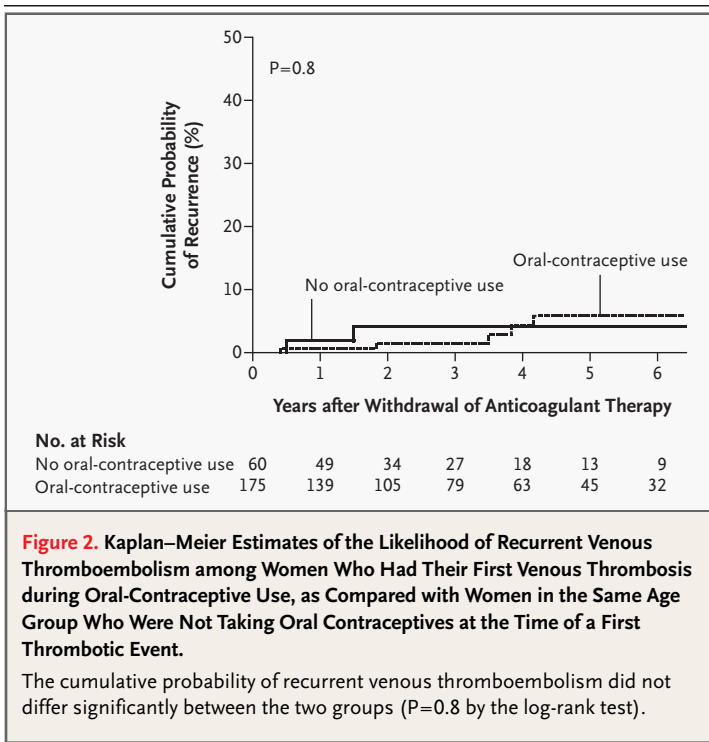


Figure 2. Kaplan–Meier Estimates of the Likelihood of Recurrent Venous Thromboembolism among Women Who Had Their First Venous Thrombosis during Oral-Contraceptive Use, as Compared with Women in the Same Age Group Who Were Not Taking Oral Contraceptives at the Time of a First Thrombotic Event.
The cumulative probability of recurrent venous thromboembolism did not differ significantly between the two groups ($P = 0.8$ by the log-rank test).

replacement therapy had a relative risk of recurrent thromboembolism of 1.6 (95 percent confidence interval, 0.4 to 6.0; $P = 0.5$). In the multivariate analysis, the relative risk of recurrence was 3.4 times as great among men as among women who had not received hormone-replacement therapy (95 percent confidence interval, 2.1 to 5.5; $P < 0.001$).

DISCUSSION

Our study of 826 patients shows that the patient's sex is a major determinant of recurrent venous thromboembolism after an initial episode of spontaneous venous thromboembolism. The risk of recurrence was almost four times as great among men as among women. Five years after the withdrawal of oral anticoagulation, the likelihood of recurrent venous thrombosis was 30.7 percent among men and only 8.5 percent among women (with an upper 95 percent confidence bound of 12.0 percent).

The risk of recurrent venous thrombosis is greatly increased among patients who have had more than one thromboembolic episode¹⁵ and among patients who have cancer,⁶ the lupus anticoagulant,¹⁶ or a hereditary deficiency of an inhibitor of coagulation.¹⁷ Patients with these risk factors receive long-term secondary thromboprophylaxis and were therefore not included in our study. Arterial disease or atrial fibrillation developed in a relatively large number of patients during follow-up, and these patients thus began antithrombotic treatment. Given the evidence that oral anticoagulation and aspirin reduce the risk of venous thrombosis and pulmonary embolism,^{15,18-20} data on these patients were censored at the time antithrombotic therapy was initiated.

We previously reported that a high level of factor VIII or factor IX or a first symptomatic pulmonary embolism increases the risk of recurrent venous thromboembolism.²¹⁻²³ In the current study, however, the proportion of patients with a high level of factor VIII or IX was similar among men and women. In addition, the higher risk of recurrence among men remained unchanged after adjustment for an elevated level of factor VIII or IX and the presence of factor V Leiden, factor II G20210A, and a first symptomatic pulmonary embolism.

Advanced age is an important risk factor for venous thrombosis.³ The men in our study were on average six years older than the women. The difference in age between the two groups, however, does not explain the higher rate of recurrent venous thromboembolism among men, since the likeli-

Sixty-one women had their first venous thromboembolism during hormone-replacement therapy. As compared with these women, the 108 women in the same age groups who did not use hormone-

hood of recurrence among men and women remained unchanged after adjustment for age.

Oral-contraceptive use increases the risk of venous thrombosis.²⁴ At the time of their first venous thrombosis, more than a third of the women were taking oral contraceptives, and they were advised to refrain from further oral contraceptive use. These women might have had a lower risk of recurrence — which could explain the low overall risk of recurrence among women — but the risk was low among users and nonusers of oral contraception, and there was no significant difference between the two groups.

Hormone-replacement therapy more than doubles the risk of venous thrombosis.²⁴ In our study, 61 women had their first thrombotic event while they were taking postmenopausal hormones, but the risk of recurrence among them did not differ significantly from the risk among women who did not use hormone-replacement therapy. Moreover, after these women were excluded from the analysis,

the risk of recurrent venous thrombosis was more than three times as great among men as among women in whom the initial episode of thrombosis was not related to postmenopausal hormone use.

Why the women had a low risk of recurrent venous thrombosis is unknown, but the finding may have clinical implications. First, the sex-related difference in the risk of recurrence has to be taken into account in the interpretation of past studies and the design of future trials. Second, the low risk among women could influence decisions concerning the duration of secondary thromboprophylaxis for women, but independent confirmation of our findings is required before they can be translated into routine clinical practice. Third, future studies are warranted to determine whether there are risk factors specific to men or protective factors specific to women.

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