

Men had greater risk for recurrent venous thromboembolism than women

Kyrle PA, Minar E, Bialonczyk C, et al. **The risk of recurrent venous thromboembolism in men and women.** *N Engl J Med.* 2004;350:2558-63.

QUESTION

Does the risk for recurrent venous thromboembolism (VTE) differ between men and women?

METHODS

Design: Inception cohort followed for a median of 26 months (Austrian Study on Recurrent Venous Thromboembolism).

Setting: 4 thrombosis centers in Vienna.

Patients: 826 patients > 18 years of age (mean age 48 y, 55% women) who had a first episode of VTE and had been treated with oral anticoagulants for ≥ 3 months. Patients had received standard heparin at doses designed to keep the activated partial thromboplastin time 1.5 to 2.0 times that of the control value or had received subcutaneous low-molecular-weight heparin at therapeutic doses. Exclusion criteria were surgery, trauma, or pregnancy in the previous 3 months; known deficiency of antithrombin, protein C, or protein S; lupus anticoagulant; cancer; or need for long-term treatment with antithrombotic drugs. Women were discouraged from using oral contraceptives or hormone replacement therapy.

Prognostic factors: Sex; age; presence or absence of symptomatic pulmonary embolism at the time of first VTE; duration of anticoagulation; and presence or absence of factor V Leiden, factor II G20210A, and elevated levels of factors VIII and IX.

Outcomes: Recurrence of symptomatic VTE. The diagnosis of deep venous thrombosis was confirmed by venography or color-coded duplex sonography. The diagnosis of pulmonary embolism was confirmed by ventilation-perfusion lung scanning.

MAIN RESULTS

102 patients (12%) had recurrent VTE: 74 men (73%) and 28 women (27%). Men had a greater risk for recurrence than did women (5-y cumulative recurrence 30.7% vs 8.5%) (Table). For men and women, risk for recurrent VTE was associated with an elevated level of factor VIII (≥ 234 IU/dL [23.4 U/L]), presence of factor II G20210A, and

having symptomatic pulmonary embolism vs deep venous thrombosis as the first VTE event (Table).

CONCLUSION

After a first episode of venous thromboembolism, men were at greater risk than women for a recurrent episode.

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Prognostic factors for recurrent venous thromboembolism*

Prognostic factors	Relative risk (95% CI)
Male sex (vs female sex)	3.6 (2.3 to 5.5)
Age (per 10-y increase)	1.1 (0.9 to 1.3)†
Symptomatic pulmonary embolism (vs deep venous thrombosis)	1.7 (1.1 to 2.5)
Factor V Leiden (vs absence)	1.2 (0.8 to 1.8)†
Factor II G20210A (vs absence)	2.1 (1.1 to 3.8)
Factor VIII ≥ 234 IU/dL (vs < 234 IU/dL [23.4 U/L])	2.9 (1.6 to 5.1)
Factor IX ≥ 138 IU/dL (vs < 138 IU/dL [13.8 U/L])	1.3 (0.8 to 2.0)†
Duration of anticoagulation (per 3-mo increase)	1.02 (0.98 to 1.05)†

*Relative risks were adjusted for age, presence or absence of a first symptomatic pulmonary embolism, factor V Leiden, factor II G20210A, elevated factor VIII or factor IX levels, and duration of anticoagulation.

†Not significant.

COMMENTARY

Kyrle and colleagues compared the incidence of recurrent VTE among men and women with incident unprovoked VTE (e.g., no previous surgery or trauma) after a mean of 8 to 9 months of oral anticoagulant therapy. After excluding patients with high-risk thrombophilic disorders (deficiencies of protein C, protein S, and antithrombin, or presence of lupus anticoagulant), they found that men with unprovoked VTE had a > 3-fold higher incidence of recurrence than women. This result was surprising and unforeseen and did not appear to occur because women with unprovoked VTE taking oral contraceptives or hormone replacement therapy simply stopped taking these hormones. In a stratified multivariate analysis, women with incident VTE who were not taking any hormones still had a 3-fold lower incidence of recurrent VTE than men.

Why do women have such a strikingly lower incidence of VTE when the incidence of first-time VTE is the same between men and women? Possibilities include the following: 1) Men may not lyse a thrombus as readily as women, leading to more residual changes in the veins and a higher recurrence rate; 2) men might develop more comorbid conditions after the initial VTE event (e.g., more hospitalizations or worse heart failure); and 3) men might have more underlying occult malig-

nancies. The finding may also be due to chance or bias. This last possibility seems unlikely because another large study also found that women with unprovoked VTE had a significantly lower incidence of recurrent VTE than men (Baglin T. Personal communication), although this finding was not stated in the report of the study (1).

A pressing need exists for prospective studies that more precisely define the risk factors associated with recurrent VTE, particularly among men and women with unprovoked VTE. The ultimate goal is to determine which patients receive more benefit than harm when prescribed long-term anticoagulant therapy. Based on this study, it is still not clear exactly which women and which men are at such high risk for recurrent thromboembolism that they are appropriate candidates for extended anticoagulant treatment.

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Reference

1. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet.* 2003;362:523-6.