Journal of Thrombosis and Haemostasis, **4**: 2199–2203

ORIGINAL ARTICLE

Hormonal factors and risk of recurrent venous thrombosis: the Prevention of Recurrent Venous Thromboembolism trial

M. CUSHMAN,* R. J. GLYNN,† S. Z. GOLDHABER,‡ S. MOLL,§ K. A. BAUER,¶ S. DEITCHER,[1]** S. SHRIVASTAVA†† and P. M. RIDKER‡††

*Department of Medicine, University of Vermont, Burlington, VT; †Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA and Department of Biostatistics, Harvard School of Public Health; ‡Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA; §Division of Hematology-Oncology, University of North Carolina, Chapel Hill, NC; ¶Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Boston, MA; **Section of Hematology and Coagulation Medicine, The Cleveland Clinic Foundation, Cleveland, OH; and ††Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, MA, USA*

To cite this article: Cushman M, Glynn RJ, Goldhaber SZ, Moll S, Bauer KA, Deitcher S, Shrivastava S, Ridker PM. Hormonal factors and risk of recurrent venous thrombosis: the Prevention of Recurrent Venous Thromboembolism trial. *J Thromb Haemost* 2006; **4**: 2199–203.

Summary. *Background:* In some but not all studies, men with venous thrombosis had a higher risk of recurrence than women. Information on women with initial hormone-related thrombosis is scant. *Objective:* We assessed the incidence of recurrent thrombosis by gender, and among women using exogenous hormones or pregnant/postpartum at the time of index thrombosis. *Patients/methods:* A total of 508 men and women with one or more previous venous thrombosis episodes were observed while participating in a randomized trial of low-intensity warfarin or placebo for 2.1 years. Index thrombosis events during treatment with postmenopausal hormones, oral contraceptives, or during pregnancy, or the puerperium were considered to be hormone-related events. *Results:* Among 268 men the 3-year probability of recurrent thrombosis was 18.4% (95% confidence intervals; CI 12.3–24.4). Among 109 women without hormone-related thrombosis, the rate was 15.0% (95% CI 6.3–23.8). Among 129 women with hormone-related thrombosis, the rate was 5.0% (95% CI 1.1–8.9). Adjusting for other risk factors and treatment assignment, women had a 39% lower thrombosis recurrence risk than men: hazard ratio (HR) 0.61 (95% CI 0.34–1.08). Women with hormone-related thrombosis had a 58% lower risk than men: HR 0.42 (95% CI 0.19–0.97); and a 46% lower recurrence risk than other women; HR 0.54 (95% CI 0.19–1.54). Women without hormone-related index events had a recurrence rate similar to men; HR 0.83 (95% CI 0.42–1.66). *Conclusions:* In this trial population, women had a lower risk of recurrent venous thrombosis than men. This difference was explained by a low risk of recurrence among women with hormone-related index thrombosis.

Keywords: gender, hormone therapies, risk factor, venous thrombosis.

Correspondence: Mary Cushman, Department of Medicine, University of Vermont, 208 South Park Drive, Suite 2, Colchester, VT 05446, USA. Tel.: +1 802 656 8968; fax: +1 802 656 8965; e-mail: mary.cushman@uvm.edu

[1]Present address: Department of Medical Sciences, Nuvelo, Inc., Sunnyvale, CA, USA.

Received 24 February 2006, accepted 17 June 2006

Introduction

Oral contraceptives and postmenopausal hormone therapy increase the risk for a first episode of venous thrombosis [1]. In general, patients experiencing thrombosis in association with reversible risk factors have a lower risk of recurrent thrombosis than patients with idiopathic first events, or events related to persistent risk factors such as active cancer [2,3]. Precise information on the risk of recurrent thrombosis among women whose first thrombosis was associated with exogenous hormone use is scant.

After completion of 3–6 months of anticoagulation for venous thrombosis, clinical trials have confirmed the effectiveness of more prolonged anticoagulation of 2–4 years' duration with low (International Normalized Ratio [INR] 1.5–2.0) or standard (INR 2.0–3.0) intensity warfarin or ximelagatran [4–6]. As long-term anticoagulation increases bleeding risk, requires regular laboratory monitoring and dietary discretion, and is not always accepted by patients, it is important to have a full understanding of the risk factors for recurrence. This information might be useful in tailoring the prescription of long-term oral anticoagulation by providing it to those who have the highest risk, and using it less often among those at lower recurrence risk.

We studied the risk of recurrent thrombosis among men and women with one or more previous episodes of thrombosis according to their gender and whether the women were taking exogenous hormones, or were pregnant, or postpartum at the time of their previous thrombosis.

Methods

Participants and study design

Prevention of Recurrent Venous Thromboembolism (PREVENT) was a double blind randomized trial comparing long-term low-intensity warfarin therapy (target INR 1.5–2.0) with placebo in patients with previous idiopathic venous thromboembolism (VTE) [4]. Men and women older than age 30 years with documented idiopathic VTE were eligible if they had completed at least 3 months of warfarin treatment with a target INR of 2.0–3.0. Major exclusion criteria were metastatic cancer, gastrointestinal bleeding, hemorrhagic stroke, life expectancy less than 3 years, or known antiphospholipid syndrome. The study was approved by each participating center's institutional review board and all participants provided informed consent.

Five hundred and eight patients with idiopathic VTE were randomized at 52 centers: 253 to placebo and 255 to low-intensity warfarin. Median duration of standard intensity warfarin prior to randomization was 6.5 months, and the median time from cessation of anticoagulation was 7 weeks (range: 12 days–2 years). At enrollment, blood samples were obtained and shipped to a central laboratory by overnight courier. DNA was analyzed for Factor V Leiden (FVL) and prothrombin 20210A [7,8].

Among 240 women, the index thrombosis defining study eligibility was considered to be hormone-related if it occurred while a participant was pregnant or postpartum ($n = 6$), or taking oral contraceptives ($n = 42$), or postmenopausal hormones ($n = 81$). Two women were missing data for these characteristics.

After randomization, patients were seen approximately every 2 months for blinded determination of the INR to adjust the warfarin dose, and to ascertain occurrence of clinical events. The primary end point was recurrent VTE confirmed by an imaging study such as duplex ultrasonography, computed tomography, or ventilation perfusion scanning. Major hemorrhage was defined as any bleeding that led to hospitalization or transfusion. The Data Safety and Monitoring Board terminated the trial ahead of schedule in December 2002, because of a 65% risk reduction in recurrent thrombosis with low-intensity warfarin. The median duration of follow-up was 2.1 years (interquartile range: 1.0–3.3 years). This report includes one additional recurrent VTE beyond the number reported in the primary publication of the trial results [4]. This event occurred during randomized follow-up but was reported after the close of the database for the initial publication.

Statistical analysis

Initial analyses compared the distribution of baseline characteristics across three groups: men; women with a hormone-related index event; and women with an index event not hormone-related. Comparisons of continuous variables used the non-parametric Kruskal–Wallis test and comparisons of discrete variables used chi-squared tests. The cumulative probability of recurrent VTE was estimated using the method of Kaplan and Meier; intergroup comparisons were tested with a two-sided log-rank test. Annual incidence proportions for recurrent events (%/year) were expressed as incidence rates (events/100 person years). Cox proportional hazard models were used to estimate the hazard ratios (HR) with 95% CI for recurrence, based on sex and hormone exposure or pregnancy at the time of index thrombosis. These HRs were then adjusted for age, treatment assignment, body-mass index, presence of FVL or prothrombin 20210A, and number of pre-enrollment VTE. The hypothesis of varying effect of warfarin treatment among groups was tested in proportional hazards models that included terms for interaction between sex or hormonal exposure and assignment to warfarin. Analyses of treatment classified subjects according to intention to treat. Because few recurrent VTE occurred among women with an index VTE that was hormone-related, we used an exact test to compare recurrence rates between women in this group assigned to placebo vs. warfarin. SAS software version 8 (SAS Institute, Cary, NC, USA) was used, and a P-value of < 0.05 was considered significant.

Results

Baseline characteristics of men and women with and without hormone-related thrombosis are shown in Table 1. Women with hormone-related thrombosis were 4 years younger, on average, than women without hormone-related thrombosis, and they were more likely to be on hormones at enrollment. Women with hormone-related index thrombosis and men, were more likely to have FVL than women whose index thrombosis was not hormone-related. There was no significant difference in randomized allocation to warfarin across groups. Of the 22 women using hormones at enrollment (five oral contraceptives, 17 postmenopausal hormones), one had recurrent thrombosis during follow-up (61-year-old randomized to placebo after 6.4 months of initial warfarin, and with prothrombin 20210A).

Figure 1 shows the cumulative thrombosis recurrence rate by gender (left) and further stratification of women by whether their index thrombosis was hormone-related (right). Among the 268 men, the 1- and 3-year probabilities of recurrent thrombosis were 6.9% (95% CI 3.7–10.1) and 18.4% (95% CI 12.3–24.4). Among the 109 women without hormone-related index thrombosis, these probabilities were 6.4% (95% CI 1.4–11.4) and 15.0% (95% CI 6.3–23.8), respectively. Among the 129 women with hormone-related index thrombosis, these probabilities were 5.0% (95% CI 1.1–8.9) and 5.0% (95% CI 1.1–8.9), with only one recurrence after the first year of follow-up (at 3.7 years of follow-up).

Adjusting for age, number of prior thromboses, body-mass index, presence of FVL or prothrombin 20210A and treatment assignment, women had a 39% lower thrombosis recurrence risk than men: HR 0.61 (95% CI 0.34–1.08). Women with hormone-related thrombosis had a 58% lower

Table 1 Baseline participant characteristics by gender and whether the index thrombosis was hormone-related

Characteristic	Men ($n = 268$)	Women		P-value
		Thrombosis not hormone-related* ($n = 109$)	Hormone-related thrombosis* ($n = 129$)	
Median age, years (IQR)	53 (47–66)	55 (47–67)	51 (44–58)	0.017
Race or ethnic group, %				
Non-Hispanic white	89.2	82.6	87.6	0.17
Non-Hispanic black	7.8	14.7	9.3	
Hispanic	1.9	1.8	0.0	
Other	1.1	0.9	3.1	
Factor V Leiden, %	30.7	12.0	21.7	0.005
Prothrombin 20210A, %	3.4	4.6	7.8	0.16
Median BMI (IQR)	30.1 (27.3–33.5)	30.3 (26.5–36.8)	29.0 (26.1–34.5)	0.27
≥ 2 prior VTE, %	41.8	37.6	31.8	0.16
Median duration of full-dose warfarin, months (IQR)	6.7 (5.8–10.8)	6.3 (5.6–8.2)	6.4 (5.9–10.4)	0.22
History of cancer, %	9.7	10.1	5.4	0.31
Assigned active warfarin, %	50.4	56.0	45.0	0.24
Hormone use at enrollment, %	NA	2.8	14.7	0.001

*Use of hormone replacement therapy, oral contraceptives or pregnant/postpartum at the time of index event; two women have missing data on these characteristics. BMI, body mass index; IQR, interquartile range; VTE, venous thromboembolism.

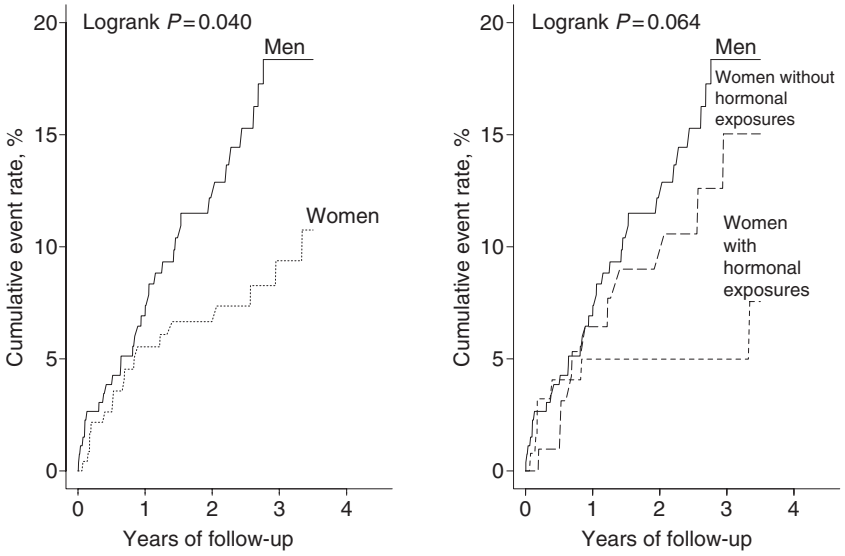

Fig. 1. Kaplan–Meier estimates of the probability of recurrent thrombosis by gender (left panel) and hormonal exposure at the time of the index thrombosis (right panel).

recurrence risk than men: HR 0.42 (95% CI 0.19–0.97). These women had a 46% lower recurrence risk than other women; HR 0.54 (95% CI 0.19–1.54). This HR was similar when women with pregnancy-related thrombosis were excluded from analysis. This HR was also similar for the 42 women with contraceptive-associated thrombosis; 0.43 (95% CI 0.07–2.46; 3-year probability of recurrence 4.8%; 95% CI 0.0–11.3) and for the 81 women with postmenopausal hormone-related thrombosis; 0.62 (95% CI 0.20–1.91; 3-year probability of recurrence 5.5%; 95% CI 0.2–10.7). Women without hormone-related index events were not less likely to experience recurrence than men; HR 0.83 (95% CI 0.42–1.66). With women as the reference group for these analyses, men had a 1.65-fold higher recurrence risk than women (95% CI 0.93–2.95), a 2.35-fold higher risk than women with hormone-related index thrombosis (95% CI 1.03–5.38), and a 1.20-fold higher risk than women without hormone-related index events (95% CI 0.60–2.39).

As shown in Table 2, a clear benefit was present for assignment to warfarin in women and men. Although the 80% reduction in recurrence risk in women was larger than the 55% reduction in men, this apparent difference in the relative effect of warfarin was not statistically significant ($P = 0.25$). Women without a hormone-related index event had a 71% reduction in recurrent thrombosis with warfarin. Among women with hormone-related index events, there were no recurrent thromboses on warfarin, while the recurrence rate on placebo among these women was 4.6% yearly ($P = 0.02$).

Table 2 Rates and hazard ratios (HRs) for recurrent venous thromboembolism according to treatment group

Characteristic	Placebo group		Warfarin group		HR (95% CI)	*P*-value for interaction
	Events (*n*)	Incidence rate (% per year)	Events (*n*)	Incidence rate (% per year)		
Overall	38	7.4	14	2.6	0.35 (0.19–0.65)	
Sex						
Men	23	9.0	11	3.9	0.45 (0.22–0.92)	0.25
Women	15	5.9	3	1.1	0.20 (0.06–0.67)	
Women						
Not hormone-related	8	8.1	3	2.3	0.29 (0.08–1.11)	
Hormone-related	7	4.6	0	0.0	0.0 (0–0.80)*	

*Exact 95% CI based on incidence rate ratios; all other intervals from proportional hazards models.

Discussion

In this randomized trial of low-intensity warfarin for the prevention of recurrent VTE, women had a lower risk of recurrence than men. This difference was largely explained by a low risk of recurrence among women with hormone-related index thromboses. Among women, those with contraceptive-related index thrombosis had a slightly lower risk of recurrence than women with postmenopausal hormone-related events.

Several available studies report slightly different findings in relation to gender, hormones and recurrent thrombosis. Our findings are similar, but the effect size much smaller, than in a study of 826 Austrian men and women with first idiopathic thrombosis [9]. In that study, men had a 5 year cumulative probability of recurrence of 30.7%, compared to only 8.5% among women. There was no difference in recurrence risk comparing women who were or were not using oral contraceptives at the time of their first thrombosis. Among older participants there was a similar gradation of recurrence risk as observed here, with men being at highest risk, followed by women who were not using postmenopausal hormones at the time of their index thrombosis, followed by women who were using hormones at their index thrombosis. Among 570 men and women with first venous thrombosis, Baglin and colleagues reported 2 year cumulative incidences of recurrence of 19.2% among men and 7.7% among women. Women exposed to hormones (primarily oral contraceptives) were not at lower risk of recurrence than other women [10]. Among 474 patients with a first non-cancer related deep vein thrombosis, the Leiden Thrombophilia Study reported a 2.7-fold higher 10 year recurrence risk in men compared to women [11]. Postmenopausal hormone use was not analyzed, but among younger women, recurrence was less likely in those who used oral contraceptives at the time of their initial thrombosis [11]. Differences among studies in participant characteristics may explain slight differences in findings. Our study had a larger number of women exposed to postmenopausal hormones at their index thrombosis ($n = 81$) compared to the above studies ($n = 69$ total for all studies).

Other studies reported different findings on gender and the risk of recurrent thrombosis. In an analysis of registry data from Spain there was a 40% higher risk of recurrence in men compared to women [12]. Large studies from Italy, Sweden, and Olmsted County, MN, USA did not demonstrate differences in recurrence risk by sex [3,13,14].

The limitations of the current study merit discussion. There were low numbers of participants in some groups so not all findings were statistically significant at the $P = 0.05$ level. However, the point estimates of recurrence risk in each group are likely close to the actual risk. It is possible that a longer follow-up time would have allowed better power. We did not have information on type of hormone treatment used at the time of the index thrombosis so could not analyze potential differences in hormone regimens. There were few women with pregnancy-related index thrombosis, a condition with hormonal and non-hormonal influence on thrombosis risk, so conclusions about the natural history of this group could not be made.

In conclusion, in this study, women were at lower risk of recurrence of venous thrombosis than men. Much of this difference was explained by a lower recurrence risk among women with hormone-related thrombosis. This information may be useful when considering cessation of anticoagulation in women with hormone-related thrombosis. Although their recurrence risk is lower, treatment remained effective in these women in this study.

Disclosure of Conflict of Interests

Dr Cushman received an investigator-initiated grant from AstraZeneca and one consultant fee each from Bristol-Myers-Squibb and from GlaxoSmithKline. Dr Ridker has received research grant funding from Bristol-Myers-Squibb. Dr Goldhaber has received research grant funding from Bristol Myers Squibb, Sanofi-Aventis and GlaxoSmithKline, and consulting fees from Emisphere, Bayer, and Duramed.

Acknowledgements

Supported by grants (HL-57951, HL-58036 and HL-71221) from the National Heart Lung and Blood Institute (Bethesda, MD). Dr Shrivastava is supported by an institutional NRSA grant (HL 007575) from the National Heart Lung Blood Institute (Bethesda, MD). We are grateful to the investigators and staff who participated at clinical sites for this study.

References

1 Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. *Arterioscler Thromb Vasc Biol* 2002; **22**: 201–10.

2 Prandoni P, Lensing A, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan A, Polistena P, Bernardi E, Prins M. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; **125**: 1–7.

3 Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000; **160**: 761–8.

4 Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG, Paulson R, Wong T, Bauer KA, Schwartz BA, Miletich JP, Bounameaux H, Glynn RJ. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **348**: 1425–34.

5 Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, MacKinnon B, Weitz JI, Crowther MA, Dolan S, Turpie AG, Geerts W, Solymoss S, van Nguyen P, Demers C, Kahn SR, Kassis J, Rodger M, Hambleton J, Gent M. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; **349**: 631–9.

6 Schulman S, Wahlander K, Lundstrom T, Clason SB, Eriksson H. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003; **349**: 1713–21.

7 Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994; **369**: 64–7.

8 Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variant in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996; **88**: 3698–703.

9 Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med* 2004; **350**: 2558–63.

10 Baglin T, Luddington R, Brown K, Baglin C. High risk of recurrent venous thromboembolism in men. *J Thromb Haemost* 2004; **2**: 2152–5.

11 Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA* 2005; **293**: 2352–61.

12 Nieto JA, Monreal M. Recurrent venous thromboembolism in men and women [letter]. *N Engl J Med* 2004; **351**: 2015–8.

13 Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med* 2000; **160**: 769–74.

14 Agnelli G, Becattini C, Prandoni P. Recurrent venous thromboembolism in men and women [letter]. *N Engl J Med* 2004; **351**: 2015–8.