# Effect of Tamoxifen on Venous Thromboembolic Events in a Breast Cancer Prevention Trial

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***Background***—Tamoxifen, a selective estrogen-receptor modulator, increases venous thromboembolic events (VTE), but the factors explaining this risk are unclear. Atherosclerosis may induce VTE, or the 2 conditions may share common risk factors. We assessed the effect of tamoxifen on VTE in a breast cancer prevention trial and studied its association with risk factors for VTE.

***Methods and Results***—The incidence of VTE was studied in 5408 hysterectomized women randomly assigned to tamoxifen 20 mg/d or placebo for 5 years. There were 28 VTEs on placebo and 44 on tamoxifen therapy (hazard ratio [HR]=1.63; 95% confidence interval [CI], 1.02 to 2.63), 80% of which were superficial phlebitis, accounting for all of the excess due to tamoxifen within 18 months from randomization. Compared with placebo, the risk of VTE on tamoxifen was higher in women aged 55 years or older, women with a body mass index ≥25 kg/m$^2$, elevated blood pressure, total cholesterol ≥250 mg/dL, current smoking, and a family history of coronary heart disease (CHD). Of the 685 women with a CHD risk score ≥5 who entered the trial, 1 in the placebo arm and 13 in the tamoxifen arm developed VTE (log-rank $P$=0.0013). In multivariate regression analysis, age ≥60 years, height ≥165 cm, and diastolic blood pressure ≥90 mm Hg had independent detrimental effects on VTE risk during tamoxifen therapy, whereas transdermal estrogen therapy concomitant with tamoxifen was not associated with any excess of VTE (HR=0.64; 95% CI, 0.23 to 1.82).

***Conclusions***—Women with conventional risk factors for atherosclerosis have a higher risk of VTE during tamoxifen therapy. This information should be incorporated into counseling women on its risk-benefit ratio, particularly in the prevention setting. **(*Circulation*. 2005;111:650-656.)**

**Key Words:** prevention ■ veins ■ thrombosis ■ risk factors ■ trials

Tamoxifen decreases mortality in patients with estrogen receptor–positive breast cancer[1] and breast cancer incidence in at-risk women,[2] but its partial estrogenic activity may limit its use, particularly in the prevention setting. Although the agonistic activity of tamoxifen reduces osteoporotic bone fractures,[3] its use has been associated with an increased risk of endometrial tumors[1,4] and venous thromboembolic events (VTEs).[2]

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Although the development of endometrial cancer is often symptomatic, can be detected by different screening methods, and is rarely life threatening, the onset of VTE is less predictable and may sometimes be lethal. In a recent meta-analysis of 4 major primary prevention trials of tamoxifen involving 28 406 subjects,[2] the use of tamoxifen was associated with 118 serious VTEs versus 62 in the placebo group, with a relative risk of 1.9 (95% confidence interval [CI], 1.4 to 2.6), including 6 versus 2 cases of fatal pulmonary emboli. Moreover, the risk of superficial thrombophlebitis was doubled with tamoxifen relative to placebo (68 versus 30 events).

Assessing the baseline risk of developing VTE and its association with tamoxifen may have important implications in determining the risk-benefit ratio of tamoxifen, both in the

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treatment and particularly in the prevention setting. Insight into the factors associated with VTE risk during tamoxifen use was recently provided by the International Breast Cancer Intervention Study (IBIS), wherein major VTEs increased significantly during tamoxifen therapy within 3 months of major surgery, immobilization, or fracture.[5] In addition, recent studies have suggested that atherosclerosis may induce VTEs or that the 2 conditions share common risk factors.[6] Indeed, studies have found an association between hyperlipidemia, hypertension, and VTEs.[7,8] Also, cholesterol-lowering agents such as statins have been shown to decrease VTE risk in recent trials.[9,10]

In the present study, we assessed the effect of tamoxifen on VTEs in the Italian breast cancer prevention trial in hysterectomized women and studied its association with recognized or putative risk factors for VTEs.

## Methods

The Italian Randomized Trial of Tamoxifen is a primary breast cancer chemoprevention trial conducted in average-risk women aged 35 to 70 who had been hysterectomized for benign disorders. The study characteristics and main results on breast cancer risk have been published elsewhere.[11,12] In brief, between October 1992 and December 1997, a total of 5408 women (median age, 51 years), were randomly assigned to receive tamoxifen 20 mg/d or placebo for 5 years. The participant flow diagram is depicted in Figure 1. Exclusion criteria included personal history of VTE; prior or current cardiovascular events except stable angina; current anticoagulant therapy; moderate to severe alterations of hematologic and biochemical tests; retinal disorders; or active neurological or psychiatric diseases. Use of estrogen replacement therapy (ERT) was allowed during the trial, and a total of 1584 (23.4%) were on ERT either at randomization (n=989) or during the 5-year intervention period. Notably, 83.5% of ERT was transdermal estradiol and 16.5%, oral estradiol or conjugated equine estrogen. At the present analysis, the participating women had a median follow-up of 59.9 months for evaluating adverse events (Figure 1).

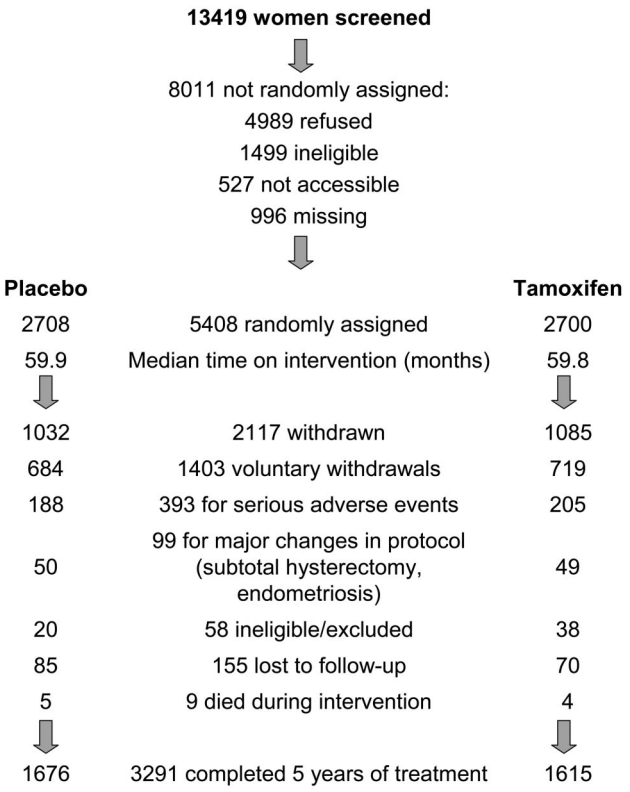


**Figure 1.** Participant flow diagram as of July 1, 2003.

### Study Objectives and Outcomes

The main objectives of the present study were to (1) compare the effect of tamoxifen and placebo on the incidence of VTEs during the 5-year intervention period and (2) determine which factors were associated with an increased risk of VTEs in each arm.

All VTEs were centrally adjudicated by an external committee that reviewed in a blinded fashion all case records of suspicious VTE submitted by the participating centers. Cases had to be confirmed by ultrasonography, Doppler ultrasonography, or hospital admissions records. Selection of the factors that could explain an association between VTEs and tamoxifen treatment was prespecified and included conventional risk factors for VTEs, such as age, body mass index (kg/m$^2$), smoking, current or past use of ERT, trauma, surgery and immobilization, and diabetes mellitus. In addition, we analyzed the association between risk factors for coronary heart disease (CHD) and VTEs and their interaction with tamoxifen, inasmuch as recent data indicate that atherosclerosis may induce VTEs or that the 2 conditions share common risk factors.[6–8] For this purpose, we utilized the CHD score system developed by our group for assessing the eligibility of the women entering the trial, which included the following variables: stable angina (absent/present), 0/5; ischemic cardiopathy (no/yes), 0/3; total cholesterol (<250/250 to 300/>300 mg/dL), 0/1/2; diabetes (no/yes), 0/3; smoking (no/former/current, 5 to 20 cigarettes per day/>20 cigarettes per day), 0/2/2/3; family history of CHD (no/yes), 0/3; obesity (no/yes), 0/1; hypertension on treatment (no/yes), 0/1. This model has not been validated in previous settings. Finally, we utilized the latest version of the Framingham score system,[13] a validated risk assessment model for CHD, which includes age, total cholesterol, HDL cholesterol, blood pressure, diabetes, and smoking. In this model, prediction of CHD risk factors is based on a prospective, single-center study of 2856 women 30 to 74 years old at baseline with 12 years of follow-up. However, as many as 1601 subjects were not assessable with the Framingham risk score in our study because baseline HDL cholesterol was not requested per protocol.

### Statistical Methods

The Cox proportional-hazards regression model was used to assess the association between selected subject characteristics and the development of VTEs in the placebo group, thus identifying risk factors for VTEs in the study sample.[14] The Cox model was also used to assess the effect of tamoxifen on the development of VTEs in the whole study group and in different subsets of subjects according to their baseline characteristics. A stepwise multivariate regression model was used to identify the baseline subject characteristics that were independently associated with the development of VTEs during tamoxifen intervention.

All models were adjusted for age. The Kaplan-Meier method was used to estimate the cumulative incidences of VTEs during intervention, which were compared by the log-rank test.[15] All analyses were conducted according to the intention-to-treat approach and were performed with SAS software. All tests were 2 sided.

## Results

A total of 72 VTEs occurred during the 5-year intervention period, 28 on placebo and 44 on tamoxifen ($P$=0.04, log-rank test). The type and distribution of VTEs by allocated arm are summarized in Table 1. The vast majority of VTEs were superficial phlebitis of the legs, which accounted for all of the excess due to tamoxifen. No case of fatal VTE occurred in either arm. Figure 2 illustrates the cumulative incidence of

**TABLE 1. VTEs During Intervention With Placebo or Tamoxifen**

| | Placebo (n=2708) | Tamoxifen (n=2700) |
|---|---|---|
| Women reporting any VTE | 28 | 44 |
| Superficial phlebitis | 17 | 41*† |
| Deep venous thrombosis | 8 | 9 |
| Pulmonary embolism | 1 | 1† |
| Visceral venous thrombosis | 1 | 0 |
| Retinal venous thrombosis | 1 | 1 |

*Forty-one events in 34 women.
†One subject developed both superficial phlebitis and pulmonary embolism.

VTEs in the 2 treatment arms. The mean (±SD) time to occurrence of VTE was 26.5±14.0 months in the placebo arm and 18.6±13.9 months in the tamoxifen arm. Incidence rates on tamoxifen and placebo were, respectively, 4.4 versus 2.7 per 1000 woman-years (7.5/1000 versus 3.1/1000 in the first 18 months and 2.8/1000 versus 2.5/1000 thereafter). In the tamoxifen arm, 8 women had multiple VTEs (6 women had 2 episodes of superficial phlebitis, 1 woman exhibited 3 episodes of superficial phlebitis, and 1 woman developed both superficial phlebitis and then pulmonary embolism).

The association between baseline risk factors and VTEs in the 2 treatment arms adjusted for age is summarized in Table 2. In the placebo arm, there was a trend toward a higher risk of VTEs with increasing age ($P$ for trend=0.05), whereas baseline weight, use of ERT at randomization, hypertension, total cholesterol, smoking, and family history of CHD were not significantly associated with the development of VTEs. Tamoxifen increased significantly the risk of VTEs relative to placebo (hazard ratio [HR]=1.63; 95% CI, 1.02 to 2.63). The association between tamoxifen and VTE risk was stronger in women with the following characteristics: age 55 years or older (HR=2.03; 95% CI, 1.00 to 4.11), systolic blood pressure ≥140 mm Hg (HR=2.59; 95% CI, 1.28 to 5.22), total cholesterol ≥250 mg/dL (HR=2.81; 95% CI, 1.10 to 7.19), ever smoking (HR=3.78; 95% CI, 1.40 to 10.2), and family history of CHD (HR=3.60; 95% CI, 1.19 to 10.9). Notably, the risk of VTEs during tamoxifen was higher in women not on ERT at randomization (HR=1.87; 95% CI, 1.11 to 3.14), whereas there was no trend toward a higher risk in women who were on ERT at randomization (HR=0.80; 95% CI, 0.22 to 2.83). Among women who had VTEs, there was no significant association between recent surgery, fracture or immobility, and treatment arm (not shown).

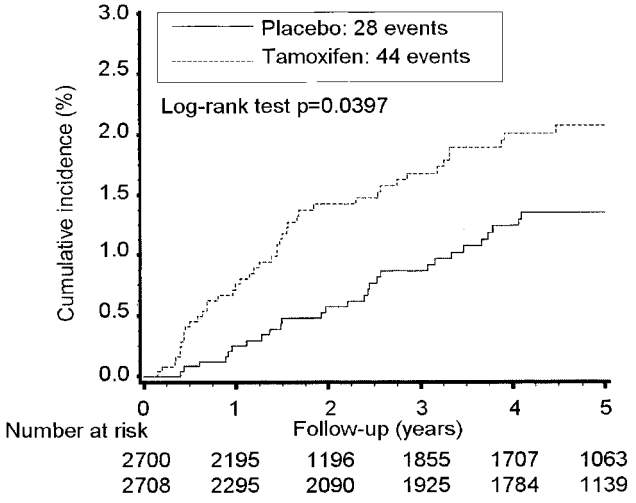


**Figure 2.** Cumulative incidence of VTEs in placebo arm (continuous line) and tamoxifen arm (dotted line). Abbreviations are as defined in text.

The association between treatment and VTEs according to a global cardiovascular risk score is illustrated in Table 3. Whereas women with an elevated CHD risk based on the Italian or the Framingham score showed no increased risk of VTEs in the placebo arm, those allocated to tamoxifen with elevated CHD risk based on the Italian score had a significantly greater risk of VTEs (HR=13.3; 95% CI, 1.73 to 101.6). Of the 685 women with a CHD score ≥5, 1 subject in the placebo arm and 13 subjects in the tamoxifen arm developed VTEs (log-rank $P$=0.0013). A positive association between tamoxifen and the development of VTEs was noted, albeit to a lower extent, also in women with an elevated Framingham score (≥10 points).

When each factor was assessed as an independent predictor of VTEs by the Cox proportional-hazards model, age ≥60 years, height ≥165 cm, and diastolic blood pressure ≥90 mm Hg had an independent effect on VTE risk during tamoxifen treatment at $P<0.05$ (Table 4). Interestingly, ERT at baseline was not associated with any excess VTEs during tamoxifen (HR=0.64, 95% CI, 0.23 to 1.82, $P$=0.40).

## Discussion

The higher risk of VTEs during treatment with tamoxifen or other selective estrogen receptor modulators such as raloxifene is the most important limiting factor for the use of these agents in primary prevention, because this adverse event is often unpredictable and may sometimes be life threatening.[2] However, recent studies have contributed toward shedding light onto the factors that may explain VTE risk during tamoxifen treatment. In IBIS, serious VTEs increased significantly on tamoxifen (odds ratio [OR]=4.7; 95% CI, 2.2 to 10.1) within 3 months of major surgery, fracture, or after immobility.[5] Garber et al[16] have recently shown that the risk of serious VTEs in the National Surgical Adjuvant Breast and Bowel Project-P1 (NSABP-P1) trial was associated with a high body mass index and with a genetic predisposition due to a mutation in factor V Leiden or prothrombin G20210A, although no evidence for a statistically significant gene-by-treatment interaction was noted.

Our study aimed at providing further insight into the factors associated with this risk of developing VTEs on tamoxifen. Our primary prevention trial in healthy women at average risk for breast cancer indicates that tamoxifen induced a borderline significantly higher risk of VTEs (HR=1.63; 95% CI, 1.02 to 2.63). Importantly, the majority of all VTEs were superficial thrombophlebitis, which accounted for all of the excess VTEs attributable to tamoxifen. Also, all VTE excess due to tamoxifen occurred within the

**TABLE 2. Associations of Baseline Risk Factors and VTEs in the Placebo and Tamoxifen Arms**

| Variable | No. of Women With VTEs | | | Effect of Tamoxifen on Risk of VTEs† HR (95% CI) |
|---|---|---|---|---|
| | Placebo (n=2708) | Tamoxifen (n=2700) | Risk of VTE* HR (95% CI) | |
| All subjects (n=5408) | 28 | 44 | ... | 1.63 (1.02–2.63)‡ |
| Age, y | | | | |
| <49 (n=2073) | 5 | 14 | 1.00 | 1.38 (0.72–2.62) |
| 50–54 (n=1649) | 11 | 8 | 2.74 (0.95–7.88) | |
| 55–59 (n=1063) | 8 | 9 | 2.82 (0.92–8.63) | 2.03 (1.00–4.11)‡ |
| ≥60 (n=623) | 4 | 13 | 2.72 (0.73–10.1) | |
| Use of ERT at baseline | | | | |
| No (n=4419) | 22 | 40 | 1.00 | 1.87 (1.11–3.14)‡ |
| Yes (n=989) | 6 | 4 | 1.23 (0.49–3.07) | 0.80 (0.22–2.83) |
| Height, cm | | | | |
| <165 (n=3964) | 17 | 24 | 1.00 | 1.53 (0.82–2.85) |
| ≥165 (n=1428) | 11 | 20 | 1.84 (0.86–3.93) | 1.72 (0.82–3.60) |
| Weight, kg | | | | |
| <65 (n=2616) | 11 | 13 | 1.00 | 1.26 (0.56–2.80) |
| ≥65 (n=2776) | 17 | 31 | 1.49 (0.70–3.17) | 1.87 (1.04–3.39)‡ |
| Body mass index, kg/m$^2$ | | | | |
| <25 (n=2627) | 15 | 16 | 1.00 | 1.12 (0.55–2.26) |
| ≥25 (n=2764) | 13 | 28 | 0.84 (0.40–1.77) | 2.25 (1.17–4.36)‡ |
| Systolic blood pressure, mm Hg | | | | |
| <140 (n=3208) | 17 | 17 | 1.00 | 1.06 (0.54–2.08) |
| ≥140 (n=2105) | 11 | 27 | 0.90 (0.42–1.93) | 2.59 (1.28–5.22)‡ |
| Diastolic blood pressure, mm Hg | | | | |
| <90 (n=3713) | 16 | 20 | 1.00 | 1.29 (0.67–2.48) |
| ≥90 (n=1596) | 12 | 24 | 1.60 (0.75–3.40) | 2.22 (1.11–4.43)‡ |
| Total cholesterol, mg/dL | | | | |
| <250 (n=3765) | 22 | 28 | 1.00 | 1.33 (0.76–2.32) |
| 250–300 (n=1318) | 4 | 10 | 0.42 (0.14–1.22) | 2.81 (1.10–7.19)‡ |
| >300 (n=275) | 2 | 6 | 1.04 (0.24–4.46) | |
| Smoking status | | | | |
| Never (n=3362) | 23 | 26 | 1.00 | 1.18 (0.67–2.07) |
| Ever (n=2047) | 5 | 18 | 0.39 (0.15–1.04) | 3.78 (1.40–10.2)‡ |
| Family history of CHD | | | | |
| No (n=4157) | 24 | 30 | 1.00 | 1.31 (0.77–2.24) |
| Yes (n=1201) | 4 | 14 | 0.56 (0.19–1.61) | 3.60 (1.19–10.9)‡ |
| Angina | | | | |
| No (n=5345) | 28 | 43 | 1.00 | ... |
| Yes (n=14) | 0 | 1 | ... | ... |
| Treatment of hypertension | | | | |
| No (n=4644) | 22 | 31 | 1.00 | 1.47 (0.85–2.54) |
| Yes (n=714) | 6 | 13 | 1.48 (0.59–3.72) | 2.26 (0.86–5.94) |

Abbreviations are as defined in text.
*HRs and 95% CIs were adjusted for age and treatment.
†HRs and 95% CIs were adjusted for age.
‡$P<0.05$.

first 18 months from randomization, a finding that is in line with that observed with ERT, wherein the risk of VTEs is highest in the first year of use.[17] This observation suggests that closer surveillance and preventive measures may be appropriate during this period in at-risk subjects, possibly including use of aspirin or statins.

Although some of the known risk factors associated with VTEs, including age[18,19] and height,[20] explained the risk of

**TABLE 3. Univariate Analysis of CHD Risk Factors and VTEs by Allocated Arm**

| Variable | No. of Women With VTEs | | | Effect of Tamoxifen on Risk of VTEs HR (95% CI)† |
|---|---|---|---|---|
| | Placebo (n=2708) | Tamoxifen (n=2700) | Risk of VTEs HR (95% CI)* | |
| Italian risk score‡ | | | | |
| 0–4 (n=4673) | 27 | 31 | 1.00 | 1.22 (0.73–2.04) |
| 5+ (n=685) | 1 | 13 | 0.25 (0.03–1.84) | 13.3 (1.73–101.6)# |
| Framingham risk score§ | | | | |
| Not assessable (n=1601) | 9 | 12 | 1.21 (0.52–2.81) | 1.41 (0.59–3.34) |
| 0–9 (n=3035) | 14 | 19 | 1.00 | 1.47 (0.74–2.93) |
| 10+ (n=772) | 5 | 13 | 1.16 (0.40–3.35) | 2.40 (0.86–6.78) |

Abbreviations are as defined in text.

*HRs and 95% CIs were adjusted for age and treatment.

†HRs and 95% CIs were adjusted for age.

‡Includes stable angina, total cholesterol level, diabetes mellitus, smoking status, family history of CHD, obesity, and hypertension under treatment (see Methods for details).

§As per Reference 13.

#$P<0.05$.

VTEs in the placebo arm, several risk factors for CHD such as increased diastolic blood pressure and, to a lesser extent, high total cholesterol levels, explained the higher risk of VTEs during tamoxifen. These results support recent hypotheses of a link between atherosclerosis and VTEs[6–8] and suggest that tamoxifen triggers some of these common mechanistic pathways. Likewise, women with prior CHD have a higher risk of VTEs during ERT,[17] presumably as a result of activation of platelets, blood coagulation, and increase in fibrin turnover.[21–23] In our study, the relative risk of VTEs under tamoxifen was substantially lower than in other prevention trials, including the NSABP-P1 trial,[3] IBIS,[5] and the Multiple Outcomes of Raloxifene Evaluation (MORE) trial of raloxifene.[24] More important, the risk of VTEs was limited to superficial thrombophlebitis and, unlike other prevention trials, both deep venous thrombosis and pulmonary emboli were not increased on tamoxifen. Variations in genetic, dietary, and lifestyle components between southern European and northern European or US women may account for these differences, as well as differences in selection criteria. For instance, all women in our trial had been hysterectomized because of benign disorders and may therefore be a selected group at a lower risk of VTEs because they underwent pelvic surgery without VTE complications. Moreover, the majority of our study participants were not at higher risk for breast cancer. Although there is no evidence for a direct link between risk factors for breast cancer and VTEs and the MORE trial has shown no association between circulating estradiol and VTE risk on raloxifene,[25] it is possible that the 2 disorders share common mechanistic pathways and that tamoxifen interacts with some of these factors. For instance, sex-steroid hormones are known to play

**TABLE 4. Multivariate Analysis of Risk Factors for VTEs in Women Taking Tamoxifen**

| Risk Factor at Randomization | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | HR (95% CI)* | *P* | HR (95% CI)* | *P* |
| Age ≥60 years | 2.41 (1.21–4.78) | 0.01 | 2.82 (1.47–5.41) | 0.002 |
| Height ≥165 cm | 1.93 (1.05–3.54) | 0.03 | 2.18 (1.20–3.94) | 0.010 |
| Weight ≥65 kg | 1.83 (0.93–3.63) | 0.08 | ... | ... |
| Diastolic blood pressure ≥90 mm Hg | 1.82 (0.90–3.70) | 0.10 | 2.60 (1.43–4.72) | 0.002 |
| Systolic blood pressure ≥140 mm Hg | 1.26 (0.60–2.61) | 0.37 | ... | ... |
| Total cholesterol >300 mg/dL | 2.18 (0.90–5.29) | 0.09 | ... | ... |
| Current smoker | 1.91 (0.95–3.85) | 0.07 | ... | ... |
| Family history of CHD | 1.22 (0.63–2.36) | 0.55 | ... | ... |
| Angina | 9.65 (1.17–79.5) | 0.04 | ... | ... |
| Hypertension on treatment | 1.70 (0.85–3.40) | 0.13 | ... | ... |
| Use of ERT at baseline | 0.64 (0.23–1.82) | 0.40 | ... | ... |

Abbreviations are as defined in text.

*HRs and 95% CIs were obtained from a stepwise Cox proportional-hazards regression model with all terms fitted simultaneously (model 1). Only statistically significant factors (with *P* values ≤0.05) added stepwise were retained in model 2.

an important role in both diseases, as shown by the association between circulating estradiol and breast cancer risk[26] and between oral contraceptives and VTE risk.[27] Further studies are necessary to clarify this issue.

One important finding in our study is the lack of a detrimental interaction between ERT and tamoxifen on VTEs. Indeed, the positive association between VTEs and use of tamoxifen was restricted to women not on ERT at baseline, whereas women on ERT at baseline experienced no risk of VTEs. The results are consistent with the IBIS trial data,[28] in which a favorable interaction between HRT use and tamoxifen was noted. In that study, among ever-users of HRT, there were 12 cases of VTEs in 1849 women allocated to tamoxifen compared with 9 VTEs in 1783 women allocated to placebo, whereas among never-users of HRT, there were 31 VTEs in 1724 women allocated to tamoxifen versus 8 VTEs in 1783 women allocated to placebo. Likewise, in the NSABP-P1 trial, the risk of VTEs under tamoxifen was lower in women aged 50 or younger (premenopausal) than in older women.[3] In our study, the vast majority of the women received transdermal unopposed estradiol, which is associated with a lower VTE risk compared with both oral estrogen therapy[29] and combined estroprogestins.[30] Taken together, these observations suggest that the prothrombotic estrogenic effect of tamoxifen varies, depending on the woman's endocrine milieu, and tends to be attenuated in premenopausal women or women taking HRT, particularly when administered by the transdermal route. Although a healthier selection bias cannot be excluded in our study, as women who were prescribed ERT for symptomatic relief may be at a lower risk of VTEs, our results suggest that the combination of ERT and tamoxifen is safe and may in fact retain the benefits while reducing the risks of both agents. A phase III trial is currently taking place to address these issues.[31]

In conclusion, our data indicate that tamoxifen slightly increased the risk of VTEs in healthy women at average risk for developing breast cancer. The excess was restricted to superficial thrombophlebitis during the first 18 months. Women at high risk for CHD were at greater risk for VTEs on tamoxifen, whereas use of transdermal ERT was associated with no excess of VTEs. Assessment of the baseline risk of VTEs should become an important component of counseling women on the use of tamoxifen, particularly in the prevention setting.

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## References

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet.* 1998;351: 1451–1467.
2. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P. Overview of the main outcomes in breast-cancer prevention trials. *Lancet*. 2003;361:296–300.
3. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanagh M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90:1371–1388.
4. Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L, Runowicz CD. Association of tamoxifen and uterine sarcoma. *J Clin Oncol.* 2002;20:2758–2760.
5. Duggan C, Marriott K, Edwards R, Cuzick J. Inherited and acquired risk factors for venous thromboembolic disease among women taking tamoxifen to prevent breast cancer. *J Clin Oncol*. 2003;21:3588–3593.
6. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, Prins MH, Girolami A. An association between atherosclerosis and venous thrombosis. *N Engl J Med*. 2003;348:1435–1441.
7. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Willett WC, Hennekens CH. A prospective study of risk factors for pulmonary embolism in women. *JAMA*. 1997;277:642–645.
8. Vaya A, Mira Y, Ferrando F, Contreras M, Estelles A, Espana F, Corella D, Aznar J. Hyperlipidaemia and venous thromboembolism in patients lacking thrombophilic risk factors. *Br J Haematol*. 2002;118:255–259.
9. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, Vittinghoff E, Hulley S. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med*. 2000;132:689–696.
10. Ray JG, Mamdani M, Tsuyuki RT, Anderson DR, Yeo EL, Laupacis A. Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med*. 2001;161:1405–1410.
11. Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N, Boyle P. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet.* 1998;352: 93–97.
12. Veronesi U, Maisonneuve P, Rotmensz N, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Lovison F, Gucciardio G, Muraca MG, Pizzichetta MA, Conforti S, Decensi A, Robertson C, Boyle P; Italian Tamoxifen Study Group. Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. *J Natl Cancer Inst*. 2003;95:160–165.
13. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.
14. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972;34: 187–220.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
16. Garber JE, Costantino JP, Wickerham DL, Berliner N, Wolmark N. Factor V Leiden (FVL) and prothrombin G20210A (PTG) mutations and risk of thromboembolic events (TE) in NSABP P-1, the breast cancer prevention trial (BCPT). Presented at: 25th Annual San Antonio Breast Cancer Symposium; December 11-14, 2002; San Antonio, Tex. Abstract No. 413.
17. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2002;136:680–690.
18. Martinelli I. Risk factors in venous thromboembolism. *Thromb Haemost*. 2001;86:395–403.
19. Heit JA. Venous thromboembolism epidemiology: implications for prevention and management. *Semin Thromb Hemost.* 2002;28(suppl 2):3–13.
20. Lowe GD, Osborne DH, McArdle BM, Smith A, Carter DC, Forbes CD, McLaren D, Prentice CR. Prediction and selective prophylaxis of venous thrombosis in elective gastrointestinal surgery. *Lancet*. 1982;1:409–412.
21. Libby P. Multiple mechanisms of thrombosis complicating atherosclerotic plaques. *Clin Cardiol.* 2000;23(suppl 6):VI-3–VI-7.
22. FitzGerald GA, Tigges J, Barry P, Lawson JA. Markers of platelet activation and oxidant stress in atherothrombotic disease. *Thromb Haemost*. 1997;78:280–284.
23. Koenig W, Rothenbacher D, Hoffmeister A, Griesshammer M, Brenner H. Plasma fibrin D-dimer levels and risk of stable coronary artery disease: results of a large case-control study. *Arterioscler Thromb Vasc Biol*. 2001;21:1701–1705.
24. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjanarson NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA*. 1999; 281:2189–2197.

25. Cummings SR, Duong T, Kenyon E, Cauley JA, Whitehead M, Krueger KA; Multiple Outcomes of Raloxifene Evaluation (MORE) Trial. Serum estradiol level and risk of breast cancer during treatment with raloxifene. *JAMA*. 2002;287:216–220.
26. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson HE Jr, Falk RT, Miller R, Schatzkin A, Allen DS, Fentiman IS, Key TJ, Wang DY, Dowsett M, Thomas HV, Hankinson SE, Toniolo P, Akhmedkhanov A, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Berrino F, Muti P, Micheli A, Krogh V, Sien S, Pala V, Venturelli E, Secreto G, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE, Cauley JA, Kuller LH, Cummings SR, Helzlsouer KJ, Alberg AJ, Bush TL, Comstock GW, Gordon GB, Miller SR, Longcope C; Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003; 95:1218–1226.
27. Kemmeren JM, Algra A. Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ*. 2001;323: 131–134.
28. Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, Hamed A, Howell A, Powell T; IBIS Investigators. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. *Lancet*. 2002;360:817–824.
29. Scarabin PY, Oger E. Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet*. 2003;362:428–432.
30. Poulter NR, Chang CL, Farley TM, Meirick O. Risk of cardiovascular diseases associated with oral progestogen preparations with therapeutic indications. *Lancet*. 1999;354:1610.
31. Decensi A, Galli A. Veronesi U. HRT opposed to low-dose tamoxifen (HOT study): rationale and design. *Recent Results Cancer Res*. 2003;163: 104–111.