

Increased Risk of Recurrent Venous Thromboembolism during Hormone Replacement Therapy

Results of the Randomized, Double-blind, Placebo-controlled Estrogen in Venous Thromboembolism Trial (EVTET)

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Key words

Clinical trial, venous thromboembolism, hormone replacement therapy, estrogen

Summary

Recent observational studies suggest a 2-4 fold increased risk of venous thromboembolism (VTE) in women taking hormone replacement therapy (HRT). The present study was started before publication of these studies, and the aim was to determine if HRT alters the risk of VTE in high risk women. The study was a randomized, double-blind, and placebo-controlled clinical trial with a double-triangular sequential design. Females with previously verified VTE were randomized to 2 mg estradiol plus 1 mg norethisterone acetate, 1 tablet daily (n = 71) or placebo (n = 69). The primary outcome was recurrent deep venous thrombosis (DVT) or pulmonary embolism (PE). Between 1996 and 1998 a total of 140 women were included. The study was terminated prematurely based on the results of circumstantial evidence emerging during the trial. Eight women in the HRT group and one woman in the placebo group developed VTE. The incidence of VTE was 10.7% in the HRT group and 2.3% in the placebo group. In the HRT group, all events happened within 261 days after inclusion. The sequential design did not stop the study, but strongly indicated a difference between the two groups. Our data strongly suggests that women who have previously suffered a VTE have an increased risk of recurrence on HRT. This treatment should therefore be avoided in this patient group if possible. The results also support those of recent epidemiological studies, which also indicate increased risk of VTE in non-selected female populations during HRT.

Introduction

An increasing number of women are eligible for hormone replacement therapy (HRT), but the evaluation of the benefits and hazards of HRT still needs further investigation. The relief of climacteric symptoms, which improves quality of life, is recognized (1), and also the prevention of osteoporosis (2-4). HRT may on the other hand adversely increase the risk of breast and endometrial cancers (5, 6).

Numerous epidemiological studies strongly suggest that HRT may reduce the risk of arterial vascular thrombosis (7). However, the first randomized trial, the Heart and Estrogen/progestin Replacement Study (HERS), did not confirm a reduction in the overall rate of coronary heart disease events in women with established coronary artery disease (8).

The evidence on the effect of HRT on the risk of venous thromboembolism (VTE) is contradictory. Early epidemiological studies failed to show an increased risk of VTE among users (9-13), but recent studies suggest a 2-4 fold increased risk for current users (14-19). Five recent review articles have re-evaluated the risk associated with HRT use and the authors unanimously conclude that an association may exist, but that further investigations are required and clinical trials warranted (20-24).

The present randomized clinical trial was initiated to test whether estradiol treatment influences the risk of VTE. We chose to study individuals at high risk, since the much higher incidence of VTE in these individuals might help to detect a clinically relevant effect with a much smaller sample size than would have been required for low-risk females. The study was terminated prematurely as several novel epidemiological studies (14-19) and one randomized study published during execution of the study indicated increased risk of VTE (8).

Participants, Materials and Methods

Study Population

Participants were postmenopausal women younger than 70 years who had suffered previous DVT or PE. Previous VTE was verified by objective means, i.e., venography or ultrasound in cases of DVT, and lung-scan, helical computed tomography, or angiography in cases of PE. Women (n = 28) were also accepted for the study without objective testing if they had a typical history and had subsequently been treated for VTE. Postmenopausal was defined as no natural menstruation for at least one year.

Women were excluded for the following reasons: current use or use of anti-coagulants within the last three months; familial antithrombin deficiency; any type of malignant diseases including known, suspected or past history of carcinoma of the breast; acute or chronic liver disease or history of liver disease in which liver function tests had failed to return to normal; porphyria, known drug abuse or alcoholism; life expectancy less than two years; or women who had taken part in other clinical trials within 12 weeks before study entry.

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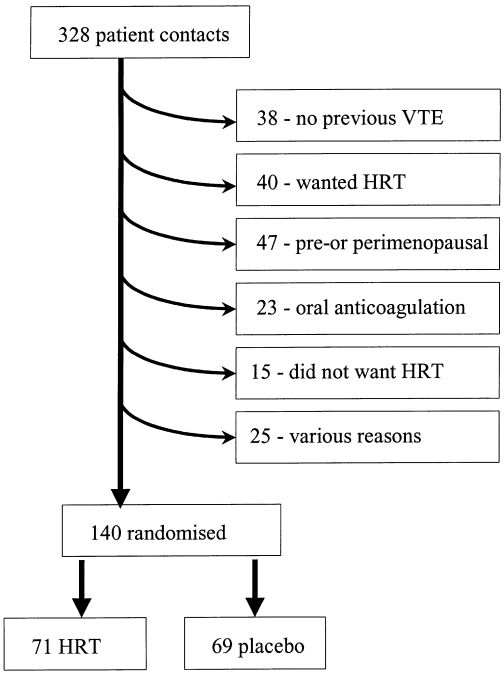

Fig. 1 Flow-chart showing the number of patient contacts and reasons for not being randomized in the study

Recruitment to the study was promoted by letters to family doctors, gynecologists, and hospitals. An invitation to participate was also made through health bulletins and media. The trial profile and reasons for exclusions are shown in Fig. 1.

The study protocol was approved by the Regional Ethical Committee and by the Norwegian Medicines Control Authority. Written, informed consent was obtained from all women. The study was carried out in accordance with the Helsinki Declaration and Good Clinical Practice.

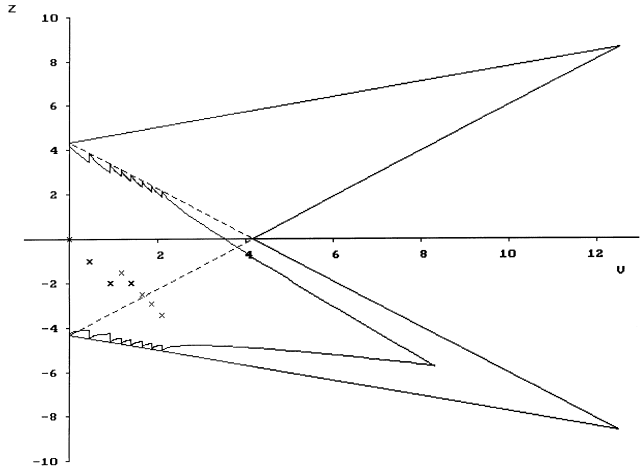

Fig. 2 The sequential design and development of recurrent venous thromboembolism (VTE). The effect of treatment *(z)* was calculated for every 10th patient reaching 3 months of follow-up. For each inspection Christmas tree correction was made, as indicated in the lower triangle. The *v* value is proportional to the sample path. The double triangles indicate the stop boundaries. A *z* value exceeding the upper or lower continuous lines of the triangles indicates a significant result in favor of one of the two treatment groups. The diagram is generated from the Pest 2.1 software (25)

Procedures

At the inclusion visit, data were collected on demographic characteristics, reproductive and health history, risk factors for VTE, and medication use. Participants had a clinical examination, including breast and pelvic examinations with cytological smear test and evaluation of the endometrium with transvaginal ultrasound. A screening mammogram was also performed.

Routine hematological and clinical chemistry screening including blood lipids were performed at baseline and at each follow-up visit. A baseline thrombophilia assessment, i.e., screening for antithrombin, protein C, and protein S deficiencies, activated protein C resistance, lupus anticoagulant and anti-cardiolipin antibodies, and the factor V Leiden mutation and the prothrombin gene 20210 GA allele variation were made.

All women were given detailed instructions on symptoms and signs of DVT and PE, and advised to contact their own physician, local hospital, the investigator, or a 24-h operated telephone number immediately if symptoms occurred.

Scheduled follow-up visits occurred after 3 and 12 months, and an end-of-study visit after 24 months. Women who withdrew their consent to participate were followed until the time of consent withdrawal. Every visit included general physical examination and venipuncture. The end-of study visit also included pelvic examination with cytological smear test and evaluation of the endometrium with transvaginal ultrasound and a screening mammogram. At 6 and 18 months, the women were followed up by postal questionnaires. Adverse events reported by the patient spontaneously, given in response to direct questioning, or observed on clinical examination were evaluated by the investigator.

Assignment

The study was carried out as a randomized, double-blind, and placebo-controlled study combined with a stratified double-triangular sequential design (Fig. 2) (25). The study was stratified for age (first stratum: <60 years of age, second stratum: >60 years of age), as age was considered the most important risk factor for VTE.

Within each of these strata, half the women were allocated to treatment with HRT containing 2 mg estradiol plus 1 mg norethisterone acetate 1 mg (Kliogest®, Novo Nordisk, Gentofte, Denmark) and the other half to equal-looking placebo tablets. Women were allocated to treatment by computer generated 1:1 block randomization with fixed block sizes of 10 women. To avoid early drop-outs due to the known adverse effect of breast tenderness, the dose regimen was one tablet every other day for the first two weeks, then one tablet daily. Every visit provided study medication refill and assessment of drug accountability.

Outcomes

The major outcome parameter was VTE verified by objective tests, i.e., venography or ultrasound in the case of DVT, and lung-scan, angiography, or helical computed tomography, in the case of PE. All primary end-points were independently and blindly examined by a radiologist and/or an internist/hematologist at the patient's local hospital. At the end of the trial all information on end-points including original venograms, CT-scans, and lung scans were independently and blindly evaluated by a radiologist, a specialist of nuclear medicine, and a hematologist not involved in the study. Secondary outcome parameters were acute myocardial infarction, transient ischaemic attacks, or stroke.

Statistical Analysis

For the safety of the women a double triangular sequential design was chosen to allow surveillance of the major end-points throughout the study (25). The expected two-year incidence of VTE was 7.5% in the placebo group (26-28). In case of an excess risk of HRT, we expected most VTEs to occur early. In analogy to the 3-4 fold increased risk of VTE associated with oral contraceptives (29), a three-fold change in the HRT group was assumed

Table 1 Baseline characteristics by treatment groups

	HRT (n=71)		Placebo (n=69)	
	no. or mean (SD)			
Previous/concomitant disease				
Myocardial infarction	0		1	
Angina pectoris	2		2	
Thromboembolic stroke	0		2	
Transient ischemic attack	2		2	
Hypertension	14		10	
Diabetes	3		0	
Smoking habits				
Never	25		29	
Previous	31		19	
1-10 cigarettes daily	9		11	
>10 cigarettes daily	6		9	
Baseline parameters				
Age , years	55.8	(7.0)	55.7	(5.9)
Body mass index (kg/m$^{2)}$	26.8	(4.3)	27.4	(4.0)
Weight (kg)	74.6	(12.8)	76.6	(11.4)
Total cholesterol (mmol/l)	6.5	(1.0)	6.6	(1.2)
HDL cholesterol (mmol/l)	1.7	(0.5)	1.6	(0.4)
LDL cholesterol (mmol/l)	4.2	(1.0)	4.3	(1.1)
Triglycerides (mmol/l)	1.4	(0.6)	1.7	(1.7)
Systolic blood pressure	137	(17)	139	(19)
Diastolic blood pressure	83	(10)	83	(8)

clinically relevant. At a significance level of 5% and a power of 90% the sample size was estimated to a maximum of 240 women (25).

In accordance with the trial plan, a sequential analysis was carried out for every 10th patient completing three months of treatment. For each sequential investigation, Christmas tree corrections of the two boundaries (Fig. 2) were carried out (25). All tests used were carried out two-tailed with a significance level of 5%. Continuously distributed factors and variables were presented by mean values with standard deviations (SD) in brackets. In case of extreme skewness, median with total range was used. Categorized factors and variables were presented in contingency tables. In order to visualize the thrombotic events as a function of time, a Kaplan-Meier plot was used. Comparison of the groups with regard to continuously distributed variables or factors were carried out using analysis of variance. The primary variable was analyzed by simple Binomial sequences and the other categorized factors and variables by contingency table analysis. Version 2.1 of PEST (Planning and Evaluation of Sequential Trials) was used in designing, and monitoring the study. The statistical package SAS(r) version 6.12 and PEST were used to perform the statistical analysis (25, 30-32).

Trial Termination

The first patient was randomized in February 1996. Novel epidemiological studies published during execution of our study (14-19) clearly indicated that HRT might increase the risk of VTE. After publication of the results of the randomized HERS study, which showed as a secondary end-point an increased risk of VTE (8), recruitment of women was discontinued in September 1998, until reviewed by the safety-monitoring committee. The committee was also concerned about a non-significant clustering of end-points in one study group, but without knowing treatment allocation (Fig. 2). The committee advised on premature termination of the study even though formal boundaries showing an excess risk of VTE were not reached. The final decision on termination of the study was made in February 1999, and by the end of March 1999, all the participants had completed a final follow-up visit.

Results

Previous Diseases and Baseline Parameters

Altogether 140 women were enrolled in the study: 71 were allocated to receive HRT and 69 to receive placebo (Fig. 1). Participants ranged in age from 42 to 69 years, with a mean of 55.8 years at baseline. Ninety-eight women were below 60 years old (first stratum), while 42 women were above 60 years old (second stratum). Distribution of demographics including age, body mass index, smoking habits, previous and concomitant illnesses, serum lipid levels, and blood pressure showed no significant differences between the two treatment groups (Table 1).

Before inclusion in the study all women had experienced at least one previous event of VTE. Type of previous VTE(s) and time elapsed since last VTE (Table 2) and risk factors for VTE (Table 3) were similar for HRT and placebo allocated women. A positive screening test for thrombophilia was detected in 28% (20/71) of the HRT women and 22% (15/69) in the placebo group (Table 4). Heterozygous factor V Leiden mutation was the most frequent finding, but no woman had antithrombin deficiency (exclusion criterium), protein C- or protein S deficiency, or lupus anticoagulant.

Adverse Events and Drop-Outs

The HRT group reported 137 adverse events while only 71 adverse events were reported in the placebo group. There was a significantly higher percentage of HRT women experiencing an adverse event from

Table 2 History of venous thromboembolism (VTE) by treatment groups

History of VTE	HRT (n=71)		Placebo (n=69)	
	no. (%) or median (range)			
Family history of VTE	25	(35)	18	(26)
Total number of previous DVT	52		49	
Total number of previous PE	28		29	
Coexisting VTE/PE	3		3	
Previous >1 VTE	6		6	
Years since last DVT	3	(0-32)	5	(0-37)
Years since last PE	4	(1-34)	6	(0-28)

Table 3 Risk factors for first venous thromboembolism by treatment group

Risk factor	HRT		Placebo	
	no. (%)			
Spontaneous	41	(58)	32	(46)
Pregnancy/delivery	6	(8)	11	(16)
Immobilisation/infection	1	(1)	8	(12)
Oral contraception	3	(4)	4	(6)
Surgery	20	(28)	14	(20)
Total	**71**	**(100)**	**69**	**(100)**

Table 4 Baseline thrombophilic states by treatment groups*

Thrombophilia	HRT	Placebo	p
	no. (%)		
Factor V Leiden mutation - homozygous	2 (3)	1 (1)	ns
Factor V Leiden mutation - heterozygous	13 (18)	10 (14)	ns
Prothrombin gene 20211 GA mutation	1 (1)	1 (1)	ns
Anti-cardiolipin antibodies	4 (6)	3 (4)	ns
Total	**20 (28)**	**15 (22)**	ns

*None of the patients had antithrombin, protein C, or protein S deficiencies, or lupus anticoagulant.

first (baseline) visit to second visit ($p < 0.001$) due to vaginal bleeding or breast tenderness, but this difference was not found at later visits. There was no statistically significant difference in the percentage of women with serious adverse events between groups. Excluding the women reaching end-points, a total of 16 women (7 in the HRT and 9 in the placebo group) were examined by venography or a lung-scan because of possible symptoms of VTE. The results of these examinations were normal.

Sixty-one women attended all visits per protocol. Thirty-seven (23 HRT and 14 placebo allocated women) did not attend all visits due to premature termination of the study. Nine women discontinued due to recurrent VTE. Thirty-three women withdrew consent (drop-outs), i.e., 10 women in the HRT group and 23 women in the placebo group. Thirteen of these (2 HRT and 11 placebo allocated women) left the study because they wanted to be certain of being treated with estrogen for their postmenopausal symptoms. In the placebo group, other reasons for withdrawal of consent were hot flushes (n = 5), anxiety (n = 3), chest pain (n = 1), and lack of compliance (n = 1). In the HRT group, the reasons were vaginal bleeds (n = 4), anxiety (n = 1), hypertension (n = 1), hematuria (n = 1), and acne (n = 1).

Primary and Secondary Outcomes

Mean duration of follow-up in the study was 485 days and 483 days in HRT and placebo allocated women, respectively. A total of eight women in the HRT group suffered recurrent VTE (Table 5). Three of these women had their DVT verified by venography, and one by ultrasound scanning. Three women suffered PE verified by lung scan (n = 2) or spiral computed tomography (n = 1). One patient suffered cerebral sinus vein thrombosis verified by magnetic resonance imaging. Only one primary end-point, a PE verified by a lung-scan, occurred in the placebo group. The incidence rates per 100 patient years were 8.5 (95% CI 2.6-14.4) in HRT allocated women and 1.1 (0-3.2) in the placebo group.

After 13 sequential analyses, the study was prematurely terminated without the stopping criteria being reached (Fig. 2). The incidence of VTE was found to be 10.7% in the HRT group and 2.3% in the placebo group. In the sequential analysis, this difference did not reach the level of significance, but is statistically significant ($p = 0.04$) if the sequential design is ignored. In spite of not reaching the stopping boundaries, the results are strongly indicative of significant inferiority of HRT with regard to the incidence of DVT and PE (25).

An early excess risk of VTE associated with HRT is evident from the Kaplan-Meier plot (Fig. 3). In the HRT group, all 8 primary end-points occurred within 261 days of treatment. In contrast, the only primary end-point of the placebo group occurred after 413 days on placebo.

Five of the women reaching a primary end-point, all in the HRT group, tested positive for thrombophilia (Table 5). Thrombophilia was a significant risk factor ($p = 0.04$) for recurrence on HRT with a relative risk (RR) of 2.6 (95% CI 1.3-5.4) as compared with no thrombophilia. Heterozygous factor V Leiden mutation was associated with a non-significant excess risk for recurrence on HRT (RR 1.4, 95% CI 0.4-5.3, as compared with no factor V Leiden). Seven of the 9 women with recurrent VTE had previously suffered spontaneous thrombosis, but all the recurrences occurred without precipitating risk factors. Previous spontaneous thrombosis was associated with a non-significant increased risk of recurrence on HRT (RR 1.4, 95% CI

Table 5 Characteristics of patients with recurrent venous thromboembolism

Type of VTE	Age (years)	Allocation	Time since last VTE (years)	Time to recurrent VTE (days)	Thrombophilia	Transient risk factor	
						First VTE	Recurrent VTE
Deep venous thrombosis	56	HRT	5	56	Factor V Leiden mutation – heterozygous	None	None
Pulmonary embolism	69	HRT	1	64	Factor V Leiden mutation – homozygous	None	None
Deep venous thrombosis	60	HRT	1	82	Factor V Leiden mutation – heterozygous	None	None
Pulmonary embolism	51	HRT	20	102	None detected	Surgery	None
Deep venous thrombosis	64	HRT	1	116	None detected	Surgery	None
Cerebral sinus vein thrombosis	54	HRT	2	170	Anti-cardiolipin antibodies	None	None
Pulmonary embolism	47	HRT	3	220	Anti-cardiolipin antibodies	None	None
Deep venous thrombosis	64	HRT	2	261	None detected	None	None
Pulmonary embolism	40	Placebo	3	413	None detected	None	None

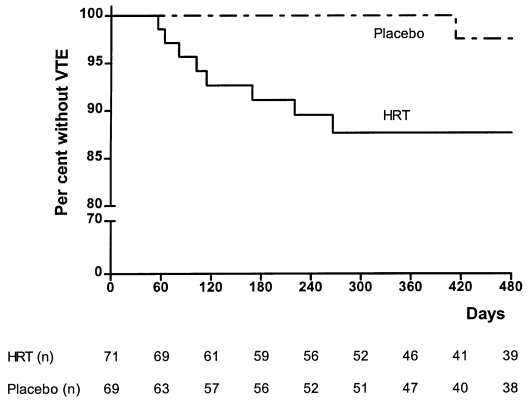

Fig. 3 Kaplan Meier plot indicating the proportion of patients without recurrent venous thromboembolism (VTE) as a function of time from randomization by treatment group, i.e., HRT (continuous line) and placebo

0.9-2.1 as compared with non-spontaneous previous thrombosis). All end points occurred within 5 years of prior VTE, except for one patient who had suffered DVT 20 years earlier (Table 5). The mean age of the women with end-points was 57.1 years compared with the mean age for the rest of the study population being 55.7 years (ns).

Only one patient in the study, allocated to placebo, experienced a secondary end-point. This patient had not experienced acute symptoms, but a cerebral computed tomography scan showed a small cerebral infarction.

Discussion

In this clinical trial, postmenopausal women younger than 70 years of age with prior VTE receiving continuous HRT had an increased risk of recurrent VTE. This is the first-ever randomized trial on the effect of HRT with VTE as a primary end-point. Our results are only valid for women with previous VTE, but they support the evidence of an early excess risk of VTE associated with use of HRT detected in recent epidemiological studies on healthy women (14-19) and with the excess incidence of VTE events observed in the randomized HERS-study (8).

The estimated 2-4 fold relative increased risk for VTE among HRT users is of the same magnitude as the risk associated with oral contraceptive use. Since the baseline incidence of VTE is much higher in postmenopausal women than in women of reproductive age, HRT may lead to a considerably higher number of women developing VTE (absolute risk) than does oral contraceptive use. In populations with high use of HRT, its impact on the overall frequency of VTE could therefore be substantial.

Our study is too small to carry out subgroup analysis, but it is known that two clinical factors appear to be important for the risk of recurrent thrombosis: presence or absence of transient risk factors for VTE (26, 28, 33-35) and the time elapsed since VTE. Our treatment groups were similar with regard to risk factors for VTE. Neither did time from previous VTE to inclusion in the study show statistically significant difference between groups.

The rate of identified thrombophilia was low. Only 35 (25%) had hereditary or acquired thrombophilia, which is lower than that reported in recent studies (27, 36). The reason for this may be due to patient selection. Women with recognized deficiencies or defects may have hesitated to take part in the study. Our study population may therefore represent a group at lower risk than an unselected population with previous VTE. Protein C and protein S deficiencies were not detected, but heterozygous factor V Leiden mutation was identified in 23 (16.5%) of the women. Only 4 of these women had already been identified prior to study entry.

Thrombophilia was associated with an excess risk of recurrent thrombosis, but thrombophilia can not completely explain the increased risk for recurrence in our study. Heterozygous factor V Leiden mutation was only a weak risk factor for recurrence. Three women with homozygous factor V Leiden mutation were included, and two of these were allocated HRT. One of the latter women, a 69-year old woman with severe osteoporosis, developed a PE 64 days after inclusion. Her only previous VTE was a spontaneous DVT 9 months prior to inclusion. The other patient was a 49-year old woman who had had a spontaneous DVT 10 years prior to the study. She completed the two-year period on HRT without adverse events. Homozygosity for the Leiden mutation has been reported to be associated with a 50-100 fold excess risk for VTE (37).

It is probable that estrogen acts in some women as an additional risk factor to generate a hypercoagulable state. In some individuals the pre-existing risk may be high and HRT may act as a trigger of thrombosis at an early stage of treatment. This hypothesis is supported by the early recurrences on estrogen as contrasted to the late recurrence on placebo in our study.

Although the compiled literature prior to 1996 did not give evidence for an increase in the risk of VTE on HRT (9, 10), we carefully considered the ethics of performing a randomized study on high-risk women. Firstly, our experience was that many physicians regularly prescribed estrogens in women with previous thrombosis. This is underlined by the fact that one of the major problems recruiting women to the study was that many women with previous VTE were already established on HRT, or they did not want to enter the study in fear of being allocated placebo (Figure 1). Secondly, it was emphasized that participants were well informed regarding symptoms and signs of VTE and encouraged to contact the investigator at any time during the study. Finally, the statistical model gave an opportunity to assess differences between groups throughout the study.

In conclusion, our study provides evidence, which strongly supports that initiating HRT in women with previous VTE most probably increases the risk of recurrent VTE. The incidence of recurrence was approximately 11% on HRT as compared to 2% on placebo. The increased risk is obviously clinically relevant, and prescribing HRT in such women should be avoided in most cases or only be given with great care. However, the net balance of risk and benefit of HRT use must also consider the potential beneficial health effects of relieving climacteric symptoms (1), reducing the risk of osteoporosis (2, 3), and possibly the risk of coronary heart disease (7). In women with no risk factors for VTE, the excess risk for VTE associated with HRT use would appear to be small as compared with the potentially stronger beneficial effects. Even in women with previous VTE or strong risk factors for VTE, the balance of risk and benefits might still favor the use of HRT in some cases. In such individuals, use of HRT in combination with oral anticoagulant treatment could be another safe approach, but this hypothesis needs confirmation in clinical trials.

Committees

Steering Committee: Dr. Per Morten Sandset (chairman), professor Harald Arnesen, professor Stig Larsen, professor Erik Qvigstad, and Dr. Egil Wickstrøm.

Safety-Monitoring Committee: Professor Ulrich Abildgaard (chairman, Aker Hospital, Department of Medicine, Oslo), professor Britt-Ingjerd Nesheim (Ullevål Hospital, Department of Gynecology), and professor Steinar Tretlie (Cancer Registry, Oslo).

End-Point Adjudication: Professor Nils-Einar Kløw (Ullevål Hospital, Department of Interventional Radiology), Dr. Carl Müller (Ullevål Hospital, Department of Nuclear Medicine), and Dr. Bernt Ly (Aker Hospital, Department of Medicine).

Acknowledgement

We are indepted to all the women who contributed enthusiastically to the trial and to Trine Opstad Andersen, Marie-Christine Mowinckel, Ingebjørg Seljeflot, and Gro Gjønnes for excellent laboratory support. Barry Andrews, Per Asbridge, and Ståle Gautvik were responsible for monitoring the study. Heidi Walsøe was responsible for the statistical report. We are also grateful to Ole-Erik Iversen and Katariina Laine, and to Mette Moen who contributed to randomisation of women in Bergen and Trondheim.

This work was supported by grants from Novo-Nordisk Pharma, Norway, and Research Forum, Ullevål University Hospital, Oslo, Norway.

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Received March 23, 2000 Accepted after revision June 30, 2000