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Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis

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ABSTRACT

Objective To assess the risk of venous thromboembolism in women using hormone replacement therapy by study design, characteristics of the therapy and venous thromboembolism, and clinical background.

Design Systematic review and meta-analysis.

Data sources Medline.

Studies reviewed Eight observational studies and nine randomised controlled trials.

Inclusion criteria Studies on hormone replacement therapy that reported venous thromboembolism.

Review measures Homogeneity between studies was analysed using χ^2 and I^2 statistics. Overall risk of venous thromboembolism was assessed from a fixed effects or random effects model.

Results Meta-analysis of observational studies showed that oral oestrogen but not transdermal oestrogen increased the risk of venous thromboembolism. Compared with non-users of oestrogen, the odds ratio of first time venous thromboembolism in current users of oral oestrogen was 2.5 (95% confidence interval 1.9 to 3.4) and in current users of transdermal oestrogen was 1.2 (0.9 to 1.7). Past users of oral oestrogen had a similar risk of venous thromboembolism to never users. The risk of venous thromboembolism in women using oral oestrogen was higher in the first year of treatment (4.0, 2.9 to 5.7) compared with treatment for more than one year (2.1, 1.3 to 3.8; $P < 0.05$). No noticeable difference in the risk of venous thromboembolism was observed between unopposed oral oestrogen (2.2, 1.6 to 3.0) and opposed oral oestrogen (2.6, 2.0 to 3.2). Results from nine randomised controlled trials confirmed the increased risk of venous thromboembolism among women using oral oestrogen (2.1, 1.4 to 3.1). The combination of oral oestrogen and thrombogenic mutations or obesity further enhanced the risk of venous thromboembolism, whereas transdermal oestrogen did not

seem to confer additional risk in women at high risk of venous thromboembolism.

Conclusion Oral oestrogen increases the risk of venous thromboembolism, especially during the first year of treatment. Transdermal oestrogen may be safer with respect to thrombotic risk. More data are required to investigate differences in risk across the wide variety of hormone regimens, especially the different types of progestogens.

INTRODUCTION

Recent observational studies have shown consistent associations between hormone replacement therapy use and risk of venous thromboembolism in postmenopausal women.^{1w1-w11} These findings were confirmed by randomised controlled trials.^{1w12-w20} We systematically reviewed the risk of venous thromboembolism among users of hormone replacement therapy.

METHODS

We searched Medline from 1974 to 2007 using keywords related to hormone replacement therapy and venous thromboembolism (see bmj.com) and we also back referenced from reviews published after 1970. The quality of the randomised controlled trials was assessed according to several criteria, and the quality of the observational studies was assessed as recommended by the Meta-analysis Of Observational Studies in Epidemiology group.²

We extracted data on route of oestrogen administration, type of oestrogens, unopposed or opposed hormone regimen, duration of treatment and type of venous thromboembolism (idiopathic or secondary, deep vein thrombosis or pulmonary embolism).

Statistical analysis

For each study we used the most adjusted relative risks or odds ratios, with 95% confidence intervals. We

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analysed homogeneity between studies using the χ^2 and I^2 statistics.^{3,4} The results of homogenous studies were pooled and an overall estimate of relative risk was obtained from a fixed effects model.⁵ For each study we estimated the variance of relative risk from the 95% confidence interval. When we detected heterogeneity between studies, we used a random effects model.⁵

RESULTS

Nine randomised controlled trials,^{w12-w20} 12 case-control studies,^{w1-w3 w5-w7 w9-w11 w21-w23} and three prospective cohort studies^{w4 w24 w25} were assessed for quality. Seven case-control studies^{w1 w3 w5 w9-w11 w21} and one cohort study^{w4} were eligible for inclusion. All investigated the risk of venous thromboembolism in relation to oral oestrogen^{w1 w3-w5 w9-w11 w21} and four evaluated the risk in relation to transdermal oestrogen.^{w1 w5 w10 w11} Treatments were 17- β -oestradiol,^{w1 w3 w5 w11} conjugated equine oestrogens,^{w1 w3-w5 w9 w11 w21} or esterified oestrogen.^{w3 w9} In most of the studies the clinical end point was first time idiopathic venous thromboembolism⁶—deep venous thrombosis or pulmonary embolism.

The PEPI trial^{w12} examined the effects of hormone replacement therapy on risk factors for heart disease among 875 healthy postmenopausal women (see bmj.com). Intervention was placebo or conjugated equine oestrogens alone or combined with cyclic medroxyprogesterone acetate, consecutive medroxyprogesterone acetate, or cyclic micronised progesterone. During three years of follow-up venous thromboembolism occurred in four women among pooled treated groups and in none among the placebo group.

HERS^{w13} investigated the effect of hormone replacement therapy on recurrence of coronary heart disease in 2763 postmenopausal women with an intact uterus. Intervention was conjugated equine oestrogens plus medroxyprogesterone acetate or placebo. Venous thromboembolism occurred in 34 women in the therapy group and 12 in the placebo group.

EVTET^{w14} compared estradiol plus norethisterone acetate with placebo in postmenopausal women with previous venous thromboembolism. The study was stopped prematurely after a mean of 16 months. More women experienced recurrent venous thromboembolism in the therapy group ($n=8$) than in the placebo group ($n=1$).

The ERA trial^{w15} examined the effects of hormone replacement therapy on the progression of coronary atherosclerosis in 309 postmenopausal women. Intervention was conjugated equine oestrogens alone or combined with medroxyprogesterone acetate, or placebo. During 3.2 years of follow-up, venous thromboembolism occurred in five, two, and one of the women, respectively.

WEST^{w16} investigated hormone replacement therapy for the secondary prevention of cerebrovascular disease in 664 postmenopausal women with a recent ischaemic stroke or transient ischaemic attack. Intervention was 17- β -oestradiol or placebo. Venous thromboembolism occurred in three women in the therapy group and four in the placebo group.

ESPRIT^{w17} assessed the effect of unopposed estradiol valerate on the risk of coronary heart disease in 1017

postmenopausal women after a first myocardial infarction. Intervention was estradiol valerate or placebo for two years. Venous thromboembolism occurred in two women in the therapy group and one in the placebo group.

The women's health initiative^{w18 w19 w26 w27} enrolled 161 809 postmenopausal women into a set of clinical trials, two of postmenopausal hormone replacement therapy. The oestrogen plus progestogen trial was a primary prevention trial in 16 608 postmenopausal women with an intact uterus. Intervention was conjugated equine oestrogens plus medroxyprogesterone acetate or placebo.^{w18} Venous thromboembolism occurred in 151 women in the therapy group and 67 in the placebo group. The oestrogen alone trial was a primary prevention trial in 10 739 postmenopausal women with previous hysterectomy. Intervention was conjugated equine oestrogens or placebo.^{w19} Venous thromboembolism occurred in 167 women in the oestrogen group and 76 in the placebo group.

The WISDOM trial^{w20} assessed the long term risk and benefits of hormone replacement therapy in 5692 women without arterial disease within the past six months. Intervention was conjugated equine oestrogens alone or combined with medroxyprogesterone acetate or placebo. The study was stopped prematurely because of results from the women's health initiative. After a mean 11.9 months, venous thromboembolism occurred in 22 women in the combined therapy group and three in the placebo group.

Risk of venous thromboembolism by characteristics of hormone replacement therapy

All but one of the observational studies^{w21} consistently reported an association between oral oestrogen and an increased risk of venous thromboembolism (figure).^{w1 w3-w5 w9-w11} Four of the studies investigated the effect of transdermal oestrogen on risk of a first episode of venous thromboembolism (figure)^{w1 w5 w10 w11}; pooled odds ratio for oral oestrogen 2.5 (95% confidence interval 1.9 to 3.4) and for transdermal oestrogen 1.2 (0.9 to 1.7). The association between venous thromboembolism and oral oestrogen was confirmed by results from randomised controlled trials: pooled odds ratio 2.1 (1.4 to 3.1). The combined odds ratio from both trials and observational studies in oral oestrogen users was 2.4 (1.9 to 3.0) and was higher than the summary risk among women using transdermal oestrogen ($P<0.001$).

One study suggested that conjugated equine oestrogen was associated with an increased risk of venous thromboembolism whereas esterified oestrogen was not.^{w9}

Data from four observational studies showed that previous use of hormone replacement therapy was not associated with an increased risk of venous thromboembolism: pooled odds ratio 1.2 (0.9 to 1.7; see bmj.com).^{w1 w4 w10 w11}

Six observational studies investigated the impact of unopposed and opposed oral oestrogens on the risk of venous thromboembolism.^{w1 w3 w5 w9-w11} No significant difference in risk was observed between users of oral

oestrogen alone (pooled odds ratio 2.2, 1.6 to 3.0) and oral oestrogen plus progestogen (2.6, 2.0 to 3.2).

Information on duration of oral oestrogen use was available in only five case-control studies.^{w1 w3 w5 w10 w11} The risk of venous thromboembolism was significantly higher for treatment within the first year (pooled odds ratio 4.0, 2.9 to 5.7) than for treatment of more than a year (2.1, 1.3 to 3.8; $P < 0.05$; see bmj.com).

Risk of venous thromboembolism by type of diagnosis

When analysis was restricted to the first episode of idiopathic events,^{w1 w3-w5 w10 w11 w21} the risk of venous thromboembolism in relation to oral oestrogen use substantially increased (pooled odds ratio 3.1, 2.3 to 4.1), whereas results for transdermal oestrogen remained unchanged.

Analysis by type of venous thromboembolism showed no significant difference in risk between deep vein thrombosis and pulmonary embolism in relation to oral oestrogen use. From observational studies, the pooled odds ratio was 2.8 (1.9 to 4.0) for deep vein thrombosis and 2.7 (1.1 to 2.5) for pulmonary embolism.

Women at high risk of venous thromboembolism

The effect of prothrombotic mutations^{7 8} on risk of venous thromboembolism, with or without hormone replacement therapy, was investigated in four case-control studies^{w28-w31} and both clinical trials of the women's health initiative.^{w26 w27} Overall, the presence of the factor V Leiden mutation or prothrombin G20210A mutation increased the risk of venous thromboembolism by more than threefold (pooled odds ratio 3.3, 2.6 to 4.1). The combination of thrombogenic mutations and oral oestrogen use, especially conjugated equine oestrogens with or without progestogen, further enhanced the risk (odds ratio 8.0, 5.4 to 11.9) compared with women without mutations who did not use any treatment. In one study, however, no significant difference was observed in risk of venous thromboembolism between women with either mutation who used transdermal oestrogen and those who did not use oestrogen (odds ratio 4.4, 2.0 to 9.9; see bmj.com).^{w30}

The association between venous thromboembolism and hormone replacement therapy with high body mass index was investigated in the women's health initiative^{w26 w27} and in one case-control study.^{w32} Being overweight or obese increased the risk of venous thromboembolism (pooled odds ratio 2.6, 2.1 to 3.3). In addition, the combination of current oral oestrogen use and an increased body mass index resulted in a further increase in the risk of venous thromboembolism (pooled odds ratio 5.4, 2.9 to 10.0 compared with non-users with a body mass index less than 25 kg/m²). In one study, however, current use of transdermal oestrogen did not confer an additional risk on women who were overweight or obese (see bmj.com).^{w32}

DISCUSSION

This meta-analysis of observational studies and randomised controlled trials showed that current use of oral oestrogen increases the risk of venous thromboembolism by twofold to threefold. This increased risk was higher within the first year of treatment and more pronounced for women at higher risk of venous thromboembolism. Overall, with a baseline risk for venous thromboembolism of about 1 per 1000 woman years,^{9 10} an additional 1.5 events per 1000 women each year would be expected. Combined analysis of observational studies showed no significant increase in the risk of venous thromboembolism among women using transdermal oestrogen.

Strengths and weaknesses of the study

Previous reviews and meta-analyses on hormone replacement therapy and risk of venous thromboembolism focused on oral oestrogen and did not consider the route of oestrogen administration.¹¹⁻¹⁴ This report provides a separate quantitative assessment of the thrombotic risk among users of oral and transdermal oestrogen. Moreover, the present meta-analysis investigated the impact of hormone replacement therapy by route of oestrogen administration among women at high risk of venous thromboembolism. In two previous reviews^{13 14} the risk of venous

Observational studies

Oral oestrogen

Boston CDSP 1974 ^{w21}	1.9 (0.4 to 7.8)
Daly 1996 ^{w1}	4.6 (2.1 to 10.1)
Jick 1996 ^{w3}	3.6 (1.6 to 7.8)
Nurses' health study 1996 ^{w4}	2.4 (1.2 to 4.6)
Perez-Gutthann 1997 ^{w5}	2.1 (1.3 to 3.6)
Smith 2004 ^{w9}	1.7 (1.2 to 2.2)
Douketis 2005 ^{w10}	1.9 (1.2 to 3.2)
ESTHER 2007 ^{w11}	4.5 (2.6 to 7.5)
Pooled odds ratio	2.5 (1.9 to 3.4)
Test for homogeneity: $\chi^2=14.99$, $P=0.03$, $I^2=53.3\%$	

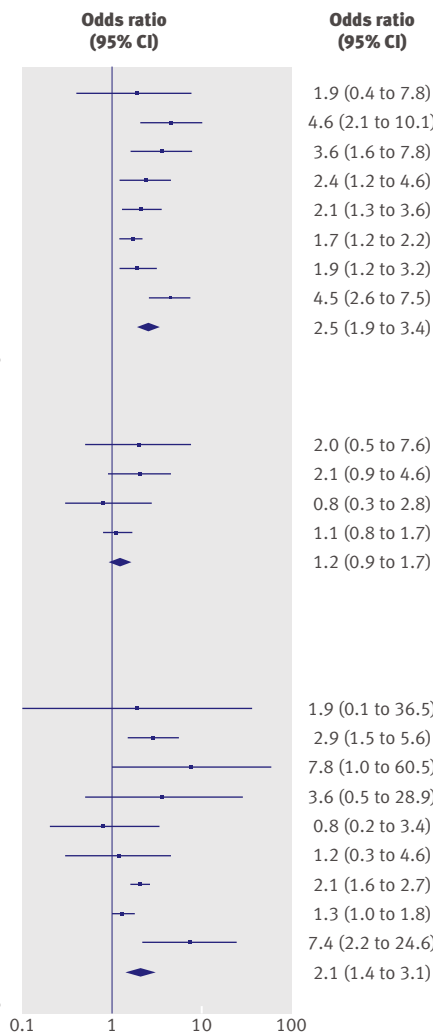
Transdermal oestrogen

Daly 1996 ^{w1}	2.0 (0.5 to 7.6)
Perez-Gutthann 1997 ^{w5}	2.1 (0.9 to 4.6)
Douketis 2005 ^{w10}	0.8 (0.3 to 2.8)
ESTHER 2007 ^{w11}	1.1 (0.8 to 1.7)
Pooled odds ratio	1.2 (0.9 to 1.7)
Test for homogeneity: $\chi^2=2.92$, $P=0.40$, $I^2=0\%$	

Randomised controlled trials

Oral oestrogen

PEPI 1995 ^{w12}	1.9 (0.1 to 36.5)
HERS 1998 ^{w13}	2.9 (1.5 to 5.6)
EVTET 2000 ^{w14}	7.8 (1.0 to 60.5)
ERA 2000 ^{w15}	3.6 (0.5 to 28.9)
WEST 2001 ^{w16}	0.8 (0.2 to 3.4)
ESPRIT 2002 ^{w17}	1.2 (0.3 to 4.6)
WHI I 2002 ^{w18}	2.1 (1.6 to 2.7)
WHI II 2004 ^{w19}	1.3 (1.0 to 1.8)
WISDOM 2007 ^{w20}	7.4 (2.2 to 24.6)
Pooled odds ratio	2.1 (1.4 to 3.1)
Test for homogeneity: $\chi^2=17.01$, $P=0.03$, $I^2=58.9\%$	



Risk of first episode of venous thromboembolism by study design and route of oestrogen administration

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hormone replacement therapy improves the quality of life for women

The risk of venous thromboembolism is known to be increased with hormone replacement therapy

WHAT THIS STUDY ADDS

Transdermal oestrogen decreases the risk of venous thromboembolism compared with oral oestrogen and seems safe with respect to thrombotic risk

Women with prothrombotic mutations or a high body mass index should avoid oral oestrogens

thromboembolism among oral oestrogen users with prothrombotic mutations was assessed from two case-control studies.^{w28 w29} We updated this meta-analysis by adding data from four other studies.^{w26 w27 w30 w31} Our meta-analysis shows a substantial increase in the risk of venous thromboembolism among oral oestrogen users who are overweight or obese.^{w26 w27 w32}

In the present meta-analysis, assessment of the risk of venous thromboembolism among users of transdermal oestrogen was based on relatively few data and results should be interpreted cautiously.^{w1 w5 w10 w11} Another limitation of our report is the lack of data on the impact of progestogens. Although this meta-analysis showed a similar risk of venous thromboembolism among users of oral oestrogen alone and opposed oral oestrogen, progestogens have emerged as a determinant of the risk of venous thromboembolism. Finally, recent data from one case-control study showed that norpregnane derivatives might increase the risk of venous thromboembolism whereas there was no association between venous thromboembolism and micronised progesterone and pregnane derivatives.^{w11}

Our meta-analysis of observational studies and randomised controlled trials showed heterogeneity between studies among oral oestrogen users. An important source of heterogeneity between trials may arise from differences in duration of treatment. The WISDOM trial—stopped after a median of 11.2 months—reported an odds ratio for venous thromboembolism higher than those from other randomised controlled trials.^{w20} When analysis was restricted to randomised trials with a longer follow-up, heterogeneity between studies disappeared. Explanations for heterogeneity between observational studies include differences in type of venous thrombotic event. Two studies included women with non-idiopathic venous thromboembolism.^{w4 w9} If analysis was restricted to idiopathic venous thromboembolism, heterogeneity between observational studies disappeared. Differences were also found in results by study design. The association of venous thromboembolism with oral oestrogen use was lower in the randomised controlled trials.

Biological explanations for results

Oral oestrogen administration results in a hepatic first-pass effect and may impair the balance between procoagulant factors and antithrombotic mechanisms.¹⁵ Oral but not transdermal oestrogen increases plasma concentrations of prothrombin

fragment 1+2,^{16 17} which is a marker for in vivo thrombin generation and increases the fibrinolytic potential in postmenopausal women. A lower anti-thrombin concentration has also been shown in women using oral oestrogen but not in those using transdermal oestrogens.¹⁸ In addition, an acquired resistance to activated protein C has been found in users of oral oestrogen,^{19 20} but two recent randomised trials indicated that these results did not apply to users of transdermal oestrogen.^{17 21} Thus transdermal oestrogen seems to have little or no effect on haemostasis.

Clinical implications

The findings of the present meta-analysis of studies by route of oestrogen administration may have important clinical implications. Pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events associated with long term hormone replacement therapy.²² Therefore the risk of venous thromboembolism is an important determinant of the benefit and risk profile of hormone replacement therapy, and differences in the risk of venous thromboembolism between types of hormone replacement therapy may have important clinical implications. In addition, since guidelines recommend that women are prescribed the lowest effective dose of hormone replacement therapy for the shortest time possible,²³ pulmonary embolism becomes a main adverse effect owing to oral oestrogen therapy within the first year of treatment. In contrast, there is little increase in the risk of stroke and breast cancer within the first year of treatment. Therefore reducing the risk of venous thromboembolism by using transdermal oestrogen could improve the benefit and risk profile of hormone replacement therapy, especially among women at high risk of venous thromboembolism.

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Increasing antituberculosis drug resistance in the United Kingdom: analysis of national surveillance data

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ABSTRACT

Objective To identify recent trends in, and factors associated with, resistance to antituberculosis drugs in England, Wales, and Northern Ireland.

Design Cohort of tuberculosis cases reported to the enhanced tuberculosis surveillance system matched to data on drug susceptibility and national strain typing data.

Setting England, Wales, and Northern Ireland 1998-2005.

Main outcome measures Unadjusted and adjusted odds ratios for drug resistance and associated factors.

Proportion of multidrug resistant tuberculosis cases clustered.

Results 28 620 culture confirmed cases were available for analysis. The proportion of cases resistant to isoniazid increased from 5% to 7%. Rifampicin resistance increased from 1.0% to 1.2% and multidrug resistance from 0.8% to 0.9%. Ethambutol and pyrazinamide resistance remained stable at around 0.4% and 0.6%, respectively. Regression analyses showed a significant increase in isoniazid resistance outside London (odds ratio 1.04, 95% confidence interval 1.01 to 1.07, a year, associated with changes in age (0.98, 0.98 to 0.99, a year), place of birth (1.49, 1.16 to 1.92), and ethnicity ($P < 0.05$). In London, the rise (1.05, 1.02 to 1.08, a year) was related mainly to an ongoing outbreak. Increases in rifampicin resistance (1.06, 1.01 to 1.11, a year) and multidrug resistance (1.06, 1.00 to 1.12, a year) were small. A fifth of patients with multidrug resistant tuberculosis in 2004-5 had

indistinguishable strain types, and one case was identified as extensively drug resistant.

Conclusions The rise in isoniazid resistance reflects increasing numbers of patients from sub-Saharan Africa and the Indian subcontinent, who might have acquired resistance abroad, and inadequate control of transmission in London. The observed increases highlight the need for early case detection, rapid testing of susceptibility to drugs, and improved treatment completion.

INTRODUCTION

Resistance to antituberculosis drugs is increasing globally, and transmission of drug resistant tuberculosis has been shown among marginalised groups in urban areas, such as London.^{1,2} Data on drug susceptibility have been routinely collected in the UK since 1993. Drug resistance, including multidrug resistance, remained stable from 1993 to 1999.^{3,4} We examined recent trends in resistance to antituberculosis drugs among cases reported in England, Wales, and Northern Ireland from 1998 to 2005 and investigated factors associated with resistance.

METHODS

Data on drug susceptibility for initial isolates were available from the UK Mycobacterial Surveillance Network (MycobNet), which collates information from all UK mycobacterial reference laboratories on first