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

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Postmenopausal hormone therapy and risk of venous thromboembolism: a systematic review and meta-analysis

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Abstract

Objectives. To assess the risk of venous thromboembolism in relation to hormone therapy by study design, characteristics of hormone therapy and venous thromboembolism, and clinical background.

Design. Systematic review and meta-analysis of observational studies and randomized clinical trials identified from Medline.

Studies reviewed. 8 observational studies and 9 randomised controlled trials.

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

Results. Meta-analysis of observational studies showed that oral but not transdermal oestrogen increased the risk of venous thromboembolism. Compared with non-users, odds ratios (95 % confidence interval) of first-time venous thromboembolism in current users of oral and transdermal oestrogen were 2.5(1.9-3.4) and 1.2(0.9-1.7), respectively. Past users of oral oestrogen had similar risk of venous thromboembolism to never users. The risk of venous thromboembolism in relation to oral oestrogen was higher within the first year of treatment [4.0(2.9-5.7)] for a duration less than 1 year, compared to [2.1(1.3-3.8)] for a duration more than 1 year, ($p<0.05$). No striking difference in the risk of venous thromboembolism was observed between unopposed and opposed oral oestrogen [2.2(1.6-3.0) and 2.6(2.0-3.2), respectively]. Results from nine randomised controlled trials have confirmed the increased risk of venous thromboembolism among women using oral oestrogen [2.1(1.4-3.1)]. The combination of oral oestrogen use and either thrombogenic mutations or obesity further enhanced the risk of venous thromboembolism, whereas transdermal oestrogen might not confer additional risk on women at high venous thromboembolism risk.

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

Hormone therapy can improve the quality of life of women with hypo-oestrogenic symptoms [1]. Despite recent data showing that overall health risks may exceed benefits of long-term hormone therapy [2], many women are still prescribed estrogen therapy to treat postmenopausal climacteric symptoms. Hormone therapy is also effective for preventing osteoporotic fractures among current users [2 3]. By contrast, harmful effects of hormone therapy include breast cancer and venous thromboembolism [4]. Furthermore, randomised controlled trials showed that hormone therapy might increase the risk of coronary heart disease and stroke [2 5].

Despite evidence that oral oestrogen activates blood coagulation in postmenopausal women [6], hormone therapy had, until 1996, long been believed to have little effect on the risk of venous thromboembolism [7]. However, observational studies recently showed consistent associations between current use of hormone therapy and an increased risk of venous thromboembolism in postmenopausal women [5 w1-w11]. These findings have been confirmed by randomised controlled trials [5 w12-w20].

Most previous studies of venous thromboembolism in users of hormone therapy were done among women using conjugated equine oestrogens alone or combined with medroxyprogesterone acetate [8 9]. These results cannot be generalized to other regimens of hormone therapy, especially those used in some European countries. Recent data have suggested the importance of the route of oestrogen administration in determining risk of venous thromboembolism [10].

The purpose of this review was to estimate the risk of venous thromboembolism among hormone therapy users. This quantitative assessment takes into account the study design (observational studies or randomized controlled trials) and the characteristics of both hormone therapy (route of oestrogen administration, unopposed or combined with progestogens, duration of treatment) and venous thromboembolism (idiopathic or secondary).

Methods

Literature search

An electronic search of medical literature was carried out on the MEDLINE database from 1974 to 2007. Relevant keywords relating to hormone therapy (eg, "estrogen replacement" or "oestrogen replacement" or "estrogen" or "estrogen therapy" or "oestrogen" or "oestrogen therapy" or "estrogen replacement therapy" or "oestrogen replacement therapy" or "hormone" or "hormone replacement therapy" or "hormone therapy" or "hormonal therapy" or "hormonal replacement therapy") were used in combination with words relating to venous thromboembolism (eg, "venous thrombosis" or "venous thromboembolism" or "thrombosis" or "pulmonary embolism" or "embolism" or "emboli") We also identified original articles by back-referencing from general reviews published after 1970 [7-9 11-17].

Study selection

We screened all articles identified by key words using Medline Database (n=1890). We first excluded publications not in English, not related to the topic, on contraception and biological studies. The selected articles (n=111) were reviewed and we excluded general reviews and articles which did not assess venous thromboembolism risk. Twenty four studies (nine randomised controlled trials [w12-w20], twelve case-control studies [w1-w3 w5-w7 w9-w11 w21-23] and three prospective cohort studies [w4 w24-w25]) were eligible for inclusion in meta-analysis and were assessed for quality.

Quality assessment

We assessed the quality of randomized controlled trials and observational studies separately. Regarding randomized controlled trials, we assessed studies for quality of randomization, blinding, reporting of withdrawals, generation of random numbers and concealment of allocation. Trials scored one point for each area addressed, therefore receiving a score between 0 and 5 (highest level of quality) [18 19]. We included in the meta-analysis trials which had a score higher or equal to 4 [w12-w20] (Table 1). We assessed the quality of observational studies using a specific checklist consistent with the consensus recommendations by the Meta-analysis Of Observational Studies in Epidemiology MOOSE group [20]. Case-control studies received a score between 0

and 6 (highest level of quality) and we included in the meta-analysis studies which had a score higher or equal to 5 [w1 w3 w5 w9-w11 w21] (Table 2). Cohort studies received a score between 0 and 7 (highest level of quality) and we included in the meta-analysis studies which had a score higher or equal to 6 [w4] (Table 3) (see Quality assessment in appendix).

Data extraction

Included studies were independently reviewed by two authors (PYS and MC). Disparities were resolved by discussion.

Study characteristics

Each study was classified according to the design (either observational study or randomised controlled trials). Relevant data on the characteristics of hormone therapy (route of oestrogen administration, type of oestrogens, unopposed or opposed hormone regimen, duration of treatment) as well as the characteristics of venous thromboembolism (idiopathic or secondary, deep vein thrombosis or pulmonary embolism, ascertainment of venous thromboembolism) were extracted and used to provide an overall estimate.

Statistical methods

For each study, the most adjusted relative risks (RR) or odds ratios (OR) and their 95% confidence interval (95% CI) were used. Homogeneity between the studies was analyzed using the χ^2 and I^2 statistics [21 22]. The results of homogenous studies were pooled and an overall estimate of relative risk was obtained from a fixed-effects model [23]. Briefly, a weighted average of relative risks was calculated, with the weights being the inverse of variance of relative risk [24]. For each study, the variance of relative risk was estimated from the 95% confidence interval. When between studies heterogeneity was detected, a random-effects model was used [23]. Statistical analyses were performed using SAS statistical software (version 9.1, SAS Institute Inc, Cary, NC).

Results

Characteristics of the studies

General characteristics of subjects, sample size and types of treatment were studied for each observational study and randomized controlled trial.

- Observational studies

We selected seven case-control studies [w1 w3 w5 w9-w11 w21] and one cohort study [w4] (figure 1 and appendix). Characteristics of included studies are summarized in the table 4.

All the studies have investigated the risk of venous thromboembolism in relation to oral oestrogen use [w1 w3-w5 w9-w11 w21] and four of them have evaluated the risk of venous thromboembolism in relation to transdermal route of oestrogen administration [w1 w5 w10 w11].

With regard to the characteristics of hormone therapy, women were treated by either 17β-oestradiol [w1 w3 w5 w11] or conjugated equine oestrogens [w1 w3-w5 w9 w11 w21] or esterified oestrogen [w3 w9]. Women were generally classified as current users if they had used hormone therapy at any time in the past 1 to 6 months before inclusion date.

In most of the studies, the clinical endpoint was a first-time idiopathic venous thromboembolism (i.e. without provoking risk factors [25]), either deep venous thrombosis or pulmonary embolism. The Nurses' Health Study was restricted to first episode of either idiopathic or non idiopathic pulmonary embolism [w4] and Smith included first-time idiopathic and non idiopathic venous thromboembolism [w9]. The clinical events were mostly validated by ultrasound (deep vein thrombosis) or lung scanning (pulmonary embolism).

- Randomised controlled trials (Table 5)
  - Postmenopausal oEstrogen/Progestin Interventions (PEPI) [w12]

PEPI was a multicenter, randomised, double-blind, placebo-controlled trial which examined the effects of hormone therapy on heart disease risk factors among 875 healthy postmenopausal women. Intervention was placebo or 0.625 mg per day conjugated equine oestrogens alone or combined with either cyclic

medroxyprogesterone acetate or consecutive medroxyprogesterone acetate or cyclic micronised progesterone. During 3 years of follow-up, venous thromboembolism occurred in 4 women among pooled treated groups and none among the placebo group.

- Heart and oEstrogen/progestin Replacement Study (HERS) [w13]

HERS was the first clinical trial designed to investigate the effect of hormone therapy on coronary heart disease recurrence. Starting in 1993, HERS was a multi-centre randomised, double-blind, placebo-controlled trial that enrolled 2763 postmenopausal women (mean age 66.7 years) with an intact uterus. Intervention was 0.625 mg conjugated equine oestrogens plus 2.5 mg medroxyprogesterone acetate or placebo. Venous thromboembolism was used as a secondary outcome in HERS. Venous thromboembolism occurred in 34 women in the hormone therapy group and in 12 women in the placebo group.

- OEstrogen in Venous ThromboEmbolism Trial (EVTET) [w14]

EVTET was a randomised double-blind trial, comparing 2 mg oestradiol plus 1 mg norethisterone acetate to placebo in postmenopausal women with previously documented venous thromboembolism. The study was stopped prematurely after a mean follow-up of 1 year and 4 months. More women experienced recurrent venous thromboembolism in the hormone therapy group than in the placebo group (8 and 1, respectively).

- OEstrogen Replacement and Atherosclerosis trial (ERA) [w15]

The ERA trial examined the effects of hormone therapy on the progression of coronary atherosclerosis in 309 postmenopausal women who had angiographically verified coronary heart disease. Women were randomly assigned to receive conjugated equine oestrogens (0.625 mg per day) alone or conjugated equine oestrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo. During 3.2 years of follow-up, venous thromboembolism occurred in 5 women, 2 women and one woman respectively.

- Women's Oestrogen for Stroke Trial (WEST) [w16]

WEST was started in 1993 as a randomised, placebo-controlled trial of hormone therapy for the secondary prevention of cerebrovascular disease. This trial was conducted in 664 postmenopausal women (mean age, 71 years) who had recently had an ischaemic stroke or transient ischaemic attack. Women were randomly assigned to receive either 1 mg of 17β-oestradiol per day or a placebo. Women were

monitored for venous thromboembolism events. Venous thromboembolism occurred in 3 women in the hormone therapy group and in 4 women in the placebo group.

- OEStrogen in the Prevention of ReInfarction Trial (ESPRIT) [w17]

ESPRIT was set up in United Kingdom to assess the effect of unopposed oestradiol valerate on the risk of coronary heart disease in postmenopausal women who had survived their first myocardial infarction. The study was a randomised, blinded, placebo controlled, secondary prevention trial among 1017 women aged 50-69 years. Women received either oestradiol valerate (2 mg per day) or placebo for 2 years. In this secondary prevention trial after a first myocardial infraction, 2 women in the hormone therapy group and 1 in the placebo group experienced venous thromboembolism.

- Women's Health Initiative (WHI) [w18 w19 w26 w27]

The WHI focuses on strategies which could potentially reduce the incidence of coronary heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and two trials of postmenopausal hormone therapy) and an observational study at 40 clinical centers in the United States.

The oestrogen plus progestin component of the WHI was a randomised controlled primary prevention trial in which 16 608 postmenopausal women with an intact uterus were randomly assigned to receive conjugated equine oestrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo [w18]. A total of 218 venous thromboembolism was enumerated (151 in the hormone therapy group and 67 in the placebo group).

The oestrogen alone component of the WHI was a randomised controlled primary prevention trial in which 10 739 postmenopausal women with prior hysterectomy were randomly assigned to receive conjugated equine oestrogens (0.625 mg per day) or placebo [w19]. Venous thromboembolism occurred in 167 oestrogen treated women and in 76 placebo treated ones.

- The Women's International Study of long Duration Oestrogen after Menopause (WISDOM) [w20]

The WISDOM trial was a randomized, double blinded, placebo controlled trial, set up in United Kingdom, Australia and New Zealand to assess the long term risk and

benefits of hormone therapy in women aged 50 to 69 years without an arterial disease within the past 6 months before inclusion (n=5692). Women were randomly assigned to receive either conjugated equine oestrogens (0.625 mg per day) alone or conjugated equine oestrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo. It was planned to compare conjugated equine oestrogens plus medroxyprogesterone acetate with placebo and conjugated equine oestrogens plus medroxyprogesterone acetate with conjugated equine oestrogens alone. Ten years of treatment were been planned but WISDOM was prematurely closed following publication of the WHI results. After a mean follow-up of 11.9 months, venous thromboembolism occurred in 22 women in the conjugated equine oestrogens plus medroxyprogesterone acetate group and in 3 women in the placebo group. Comparison of conjugated equine oestrogens plus medroxyprogesterone acetate versus conjugated equine oestrogens alone outcomes revealed no significant differences.

Results of the meta-analysis

Pooled risk of venous thromboembolism was assessed from eight observational studies and nine randomized controlled trials. From observational studies, the risk of venous thromboembolism was estimated by route of oestrogen administration. In addition, the risk of venous thromboembolism was estimated according to the characteristics of both treatment (type, duration) and venous thromboembolism (idiopathic or secondary, type of diagnostic).

- Venous thromboembolism risk by characteristics of hormone therapy

Figure 2 shows pooled OR of first-time venous thromboembolism in relation to hormone therapy use by study design and route of oestrogen administration. All but one observational studies [w21] consistently reported an association between oral oestrogen use and an increased risk of venous thromboembolism [w1 w3-w5 w9-w11]. Four of them investigated the impact of transdermal oestrogen use on risk of first episode of venous thromboembolism [w1 w5 w10 w11]. Pooled OR (95% CI) for oral and transdermal oestrogen was 2.5 (1.9-3.4) and 1.2 (0.9-1.7), respectively. The upper 95% CI for transdermal use (1.7) was lower than the lowest 95% CI for oral use (1.9). The association of venous thromboembolism with oral oestrogen use was confirmed by results from randomized controlled trials (pooled OR=2.1; 95%CI: 1.4-3.1). The

combined odds ratio from both trials and observational studies in oral estrogen users was 2.4 (1.9-3.0) and was higher than the summary risk among women using transdermal estrogen (p<0.001). No trials have investigated the effect of transdermal estrogen on the risk of venous thromboembolism.

One study suggested that the type of oestrogen might be an important determinant of the risk of venous thromboembolism. In this study, conjugated equine oestrogen was associated with increased risk, whereas esterified oestrogen was not [w9].

Data on the risk of venous thromboembolism in past users of hormone therapy compared with never users were available in four observational studies [w1 w4 w10 w11] and showed that past use of hormone therapy was not associated with an increased risk of venous thromboembolism (pooled OR=1.2; 95%CI: 0.9-1.7) (Figure 3).

The impact of unopposed and opposed oral oestrogen therapy on the risk of venous thromboembolism has been investigated in six observational studies [w1 w3 w5 w9-w11]. No significant difference in the risk of venous thromboembolism was observed between oral oestrogen alone and oral oestrogen/progestogen therapy (pooled OR=2.2; 95%CI: 1.6-3.0 and pooled OR=2.6; 95% CI: 2.0-3.2, respectively).

Finally, the risk of venous thromboembolism has been assessed according to the duration of treatment. Information on duration of oral oestrogen was available in only five case-control studies [w1 w3 w5 w10 w11]. Results from these studies showed that the risk of venous thromboembolism was significantly higher within the first year of treatment (pooled OR=4.0; 95% CI: 2.9-5.7 for a duration of hormone therapy less than one year and pooled OR=2.1; 95% CI: 1.3-3.8 for a duration of hormone therapy more than one year, p<0.05) (Figure 3).

- 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 OR=3.1; 95% CI: 2.3-4.1), whereas results for transdermal oestrogen use remained unchanged.

Analysis by diagnosis of venous thromboembolism showed no significant difference in the risk of venous thromboembolism between deep vein thrombosis and pulmonary embolism in relation to oral oestrogen use. From observational studies, pooled OR (95% CI) was 2.8 (1.9-4.0) for deep vein thrombosis and 2.7 (1.1-2.5) for

pulmonary embolism. This result was confirmed by data from randomised controlled trials (data not shown).

- Women at high risk for venous thromboembolism

The impact of prothrombotic mutations [26 27] on the risk of venous thromboembolism, with or without hormone therapy, has been investigated in four case-control studies [w28-w31] and in both WHI clinical trials [w26 w27]. Overall the presence of the Factor V Leiden mutation or prothrombin G20210A mutation increased the risk of venous thromboembolism more than 3-fold (pooled OR=3.3; 95%CI: 2.6-4.1). The combination of thrombogenic mutations and oral oestrogen use, especially conjugated equine oestrogen, with or without progestin, further enhanced the risk of venous thromboembolism (OR=8.0; 95% CI: 5.4-11.9) compared with women without mutations who did not use any treatment. However, in one study, there was no significant difference in the risk of venous thromboembolism between women with factor V Leiden mutation or prothrombin G20210A mutation using transdermal oestrogen and women with a mutation but not using oestrogen (OR= 4.4; 95%CI: 2.0-9.9) [w30] (Figure 4).

The association of venous thromboembolism with hormone therapy in relation to elevated body-mass index has been investigated in both the WHI clinical trials [w26 w27] and in a case-control study [w32]. An elevated body-mass index (overweight or obesity) increased the risk of venous thromboembolism (pooled OR=2.6; 95%CI: 2.1-3.3). In addition, the combination of current oral oestrogen use and an increased body-mass index resulted in a further elevation of the risk of venous thromboembolism (pooled OR=5.4; 95%CI: 2.9-10.0). However, in one study, current use of transdermal oestrogen did not confer an additional risk on women with overweight or obesity [w32] (Figure 5).

Discussion

Principal findings

This meta-analysis of both observational studies and randomised controlled trials shows that current use of oral oestrogen increases two to three times the risk of venous thromboembolism. This elevation is higher within the first year of treatment and more pronounced for women at high thrombotic risk. Overall, with a baseline risk for venous thromboembolism of about 1 per 1000 women-years [28 29], an additional 1.5 events per 1000 women each year would be expected. Combined analysis of observational studies shows no significant increase in the risk of venous thromboembolism among transdermal oestrogen users.

Strengths of the study

Previous reviews and meta-analysis regarding hormone therapy and risk of venous thromboembolism focused on oral oestrogen use and failed to take into account the route of oestrogen administration [7 11 13 15]. This report provides the first quantitative assessment of the thrombotic risk among oral and transdermal oestrogen users separately. Moreover, the present meta-analysis investigated the impact of hormone therapy by route of oestrogen administration among women at high thrombotic risk. In two previous reviews [13 15], the risk of venous thromboembolism among oral oestrogen users who carried prothrombotic mutations was assessed from two case-control studies [w28-w29]. We updated this meta-analysis by adding data from four studies [w26 w27 w30 w31]. With regard to women with overweight or obesity, our meta-analysis is the first to show a substantial increase in the risk of venous thromboembolism among oral estrogen users with elevated body-mass index (overweight or obesity) [w26 w27 w32].

Weaknesses of the study

In the present meta-analysis, assessment of the risk of venous thromboembolism among transdermal oestrogen was based on relatively few data [w1 w5 w10 w11]. Therefore, results should be interpreted with caution and further investigation of transdermal oestrogen is needed. Another limitation of the present report is the lack

of data on the impact of progestogens. Although this meta-analysis showed similar risk of venous thromboembolism comparing oral oestrogen alone and opposed oral oestrogen, progestogens have recently emerged as a determinant of the risk of venous thromboembolism. One study reported that the risk of venous thromboembolism was higher in users of opposed oral oestrogen than in users of oral oestrogen alone [w10] and the risk of venous thromboembolism was higher in the WHI oestrogen/progestogen clinical trial [w18] than in the WHI oestrogen alone clinical trial [w19]. In addition, among women recruited in the conjugated equine oestrogens plus medroxyprogesterone acetate versus conjugated equine oestrogens WISDOM trial, there was a suggestion in the opposed oestrogen therapy group of an increase in venous thromboembolism (RR=2.39; 95%CI: 0.62-9.24) [w20]. Finally, recent data from one case-control study showed that norpregnane derivatives might increase the risk of venous thromboembolism whereas there was no association of venous thromboembolism with micronised progesterone and pregnane derivatives [w11].

Our meta-analysis of both 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 the duration of treatment. The WISDOM trial, which was closed after a median follow-up 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 the 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. There were also differences in results by study design. The association of venous thromboembolism with oral oestrogen use was lower in randomized controlled trials than in observational studies. This difference could be explained by inclusion of procedure-related venous thromboembolism in WHI trials, as well as the high degree of nonadherence to study medication in randomized controlled trials, resulting in an underestimation of hormone effects in randomized controlled trials.

Biological explanations for results

Biological evidence lends support to the difference in the risk of venous thromboembolism between oral and transdermal oestrogen. Oral oestrogen administration results in a hepatic first-pass effect and may impair the balance between procoagulant factors and antithrombotic mechanisms [30]. Oral, but not transdermal, oestrogen increases plasma concentrations of prothrombin fragment 1+2 [31 32], which is a marker for in-vivo thrombin generation, and increases the fibrinolytic potential in postmenopausal women. A lower antithrombin concentration has also been shown in women using oral oestrogen but not in those using transdermal oestrogens [33]. In addition, an acquired resistance to activated protein C has been demonstrated in users of oral oestrogen [34 35] but two randomised trials recently indicated that these results did not apply to users of transdermal oestrogen [32 36]. Thus, transdermal oestrogen appears to have little or no effect on haemostasis.

Clinical implications

The findings of the present meta-analysis of studies by route of estrogen administration may have important clinical implications. Pulmonary embolism accounts for about one third of the excess incidence of potentially fatal events due to long-term hormone therapy [4]. Therefore, the risk of venous thromboembolism is an important determinant of the benefit/risk profile of hormone therapy, and differences in the risk of venous thromboembolism between types of hormone therapy may have important clinical implications. In addition, since recent guidelines recommend that women are prescribed the lowest effective dose of hormone therapy for the shortest time possible [37], pulmonary embolism becomes a main adverse effect due to oral oestrogen therapy within the first year of treatment. By contrast, there is little increase risk of stroke and breast cancer within the first year of treatment. Therefore, reducing venous thromboembolism risk by transdermal oestrogen use could improve the benefit/risk profile of hormone therapy, especially among women at high risk of venous thromboembolism (e.g. known prothrombotic mutation, elevated body-mass index).

Future research

Future randomized trials of oral versus transdermal oestrogen will clarify this apparent lower risk. Clinical research should continue into genetic factors influencing the risk associated with hormone therapy, different oestrogen and progestogen formulations, different modes of delivery, lower-dose options and alternative regimens (e.g. selective oestrogen receptor modulators, phytooestrogens). Such research will assist patients and clinicians in making treatment decisions on the basis of an individual's benefits and risks [38].

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“What this study add” box

What is already known on this topic

Hormone therapy improves the quality of life but it is known to increase the risk of venous thromboembolism.

What this study adds

Transdermal oestrogen decreases the risk of venous thromboembolism when compared to oral oestrogen and it appears safe with respect to thrombotic risk.

Women with prothrombotic mutations or elevated body-mass index are at high risk of venous thromboembolism and should be discouraged from using oral oestrogen therapy.

Contributors: MC and PYS reviewed the studies and collected the data. MC, GPB and PYS performed statistical analysis. MC, GPB, GDL and PYS drafted the manuscript. MC, GBP, GDL and PYS revised the paper. PYS is guarantor.

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Competing interests: All authors have declared no conflicts of interest.

Table1- Quality assessment of included randomised controlled trials (Appropriate=1 / No information or no appropriate=0)

Study, *years*	Randomisation	Double-blinding	Dropout and withdrawals	Generation of random numbers	Allocation concealment	Score (0-5)
PEPI [w12],1995	Yes	Yes	3.0% withdrawal and dropout	Computer generated block randomisation	Active drug and placebo prepared in identical forms	5
HERS [w13], *1998*	Yes	Yes	0% dropout 2.1% withdrawal	Computer generated random numbers	Active drug and placebo prepared in identical forms	5
EVTET [w14], *2000*	Yes	Yes	23.6% dropout or withdrawal	Computer generated block randomisation	Active drug and placebo prepared in identical forms	5
ERA [w15], *2000*	Yes	Yes	14.0% dropout 4.0% withdrawal	Permuted block randomisation	Each women received two tablets (active treatment and placebo tablets or 2 placebo tablets)	5
WEST [w16], *2001*	Yes	Yes	0% dropout 1.4% withdrawal	Computer generated block randomisation	?	4
ESPRIT [w17], *2002*	Yes	Yes	?	Computer generated block randomisation	Active drug and placebo prepared in identical forms	4
WHI I [w18], *2002*	Yes	Yes	3.5% dropout	Permuted block randomisation	Active drug and placebo prepared in identical forms	5
WHI II [w19], *2004*	Yes	Yes	2.2% dropout 3.0% withdrawal	Permuted block randomisation	Active drug and placebo prepared in identical forms	5
WISDOM [w20], *2007*	Yes	Yes	0.01% dropout 13.2% withdrawal	Computer generated block randomisation	Active drug and placebo prepared in identical forms	5

Table 2- Quality assessment of included case/control studies (Yes=1 / No=0)

Author or Study, *year*	Appropriate inclusion and exclusion criteria applied equally to cases and controls	Only first episode of venous thromboembolism	Objective diagnostic procedure	Adequate assessment of menopausal status	Accurate assessment of HT including the route of oestrogen administration	Adequate analysis and controlling for confusion (adjustment)	Score (0-6)
Boston CDSP [w21], *1974*	Yes	Yes	No	Yes	Yes	Yes	5
Daly [w1], *1996*	Yes	Yes	No	Yes	Yes	Yes	5
Jick [w3], *1996*	Yes	Yes	Yes	Yes	Yes	Yes	6
Perez-Gutthann [w5], *1997*	Yes	Yes	No	Yes	Yes	Yes	5
Smith [w9], *2004*	Yes	Yes	Yes	Yes	Yes	Yes	6
Douketis [w10], *2005*	Yes	Yes	Yes	Yes	Yes	Yes	6
ESTHER Study [w11], *2007*	Yes	Yes	Yes	Yes	Yes	Yes	6

Table 3- Quality assessment of included cohort studies (Yes =1 / No =0)

Author or Study, *year*	Appropriate method of subject selection	Only first episode of venous thromboembolism	Objectives diagnostic procedure	Adequate assessment of menopausal status	Accurate assessment of HT including the route of oestrogen administration	Overall low loss of follow-up	Adequate analysis and controlling for confusion (adjustment)	Score (0-7)
Nurses' Health Study [w4], *1996*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7

Table 4- Characteristics of included observational studies

Author or Study, *year*	Route of oestrogen administration	Clinical endpoint	Oestrogen type	Current users definition*	Exposed cases (n)	Adjusted risk ratio of VTE (95 % CI)
Boston CDSP [w21], *1974*	Oral	1st episode of idiopathic VTE	Mainly CEE	NA	3	1.9 (1.4-7.8)
Daly [w1], *1996*	Oral	1st episode of idiopathic VTE	E2 / CEO	Less than 1	37	4.6 (2.1-10.1)
	Transdermal		E2		5	2.0 (0.5-7.6)
Jick [w3], *1996*	Oral	1st episode of idiopathic VTE	CEE / EO	Less than 6	21	3.6 (1.6-7.8)
Nurses' Health Study [w4], *1996*	Oral	1st episode of PE	Mainly CEE	NA	68	2.1 (1.2-3.8)
Perez-Gutthann [w5], *1997*	Oral	1st episode of idiopathic VTE	E2 / CEO	Less than 6	20	2.1 (1.3-3.6)
	Transdermal		E2		7	2.1 (0.9-4.6)
Smith [w9], *2004*	Oral	1st episode of VTE	CEO	NA	121	1.7 (1.2-2.2)
			EO		86	0.9 (0.7-1.2)
Douketis [w10], *2005*	Oral	1st episode of idiopathic VTE	NA	Less than 1	36	1.9 (1.2-3.2)
	Transdermal		NA		3	0.8 (0.3- 2.8)
ESTHER Study [w11], *2007*	Oral	1st episode of idiopathic VTE	E2 / CEO	Less than 3	57	4.5 (2.6-7.5)
	Transdermal		E2		67	1.1 (0.8-1.7)

* Time duration between oestrogen use and VTE to be considered as current users (months)
# 90% CI
95 % CI: 95 % confidence interval
VTE: venous thromboembolism
PE: pulmonary embolism
NA: not available
E2: oestradiol or oestradiol valerate
CEO: conjugated equine oestrogen
EO: esterified oestrogen

Table 5- Characteristics of included randomised controlled trials

Study, *years*	Total number of subjects *	Clinical background	Duration of the trial (years)	Number of events HT/placebo	Adjusted risk ratio of VTE (95 % CI)
PEPI [w12],1995	847	"Healthy"	3	4/0 [§]	1.9 (0.1-36.5) [$ #]
HERS [w13], *1998*	2763	History of CHD	4.1	34/12	2.9 (1.5-5.6)
EVTET [w14], *2000*	140	History of VTE	1.3	8/1	7.8 (1.0-60.5)
ERA [w15], *2000*	309	History of CHD	3.2	7/1 [£]	3.6 (0.5-28.9) [$]
WEST [w16], *2001*	664	History of stroke	2.8	3/4	0.8 (0.2-3.4)
ESPRIT [w17], *2002*	1017	History of CHD	2	5/4	1.2 (0.3-4.6)
WHI I [w18], *2002*	16608	"Healthy"	5.2	151/67	2.1 (1.6-2.7)
WHI II [w19], *2004*	10739	"Healthy"	7	77/54	1.3 (1.0-1.8)
WISDOM [w20], *2007*	5692	Possible history of arterial disease	0.99	22/3	7.4 (2.2-24.6)

* Approximately equal number in placebo and active treatment group except in PEPI and ERA trials
[§] HT: n=682 Placebo: n=165
[$] Risk was calculated from data reported in the study
[#] To estimate the RR, number of events in placebo group was considered equal to 0.5
[£] HT: n=204 Placebo: n=105
CHD : coronary heart disease
95 % CI : 95 % confidence interval

Legend of figures

Figure 1.
Results of literature search for randomized controlled trials and observational studies of hormone therapy that reported venous thromboembolism.

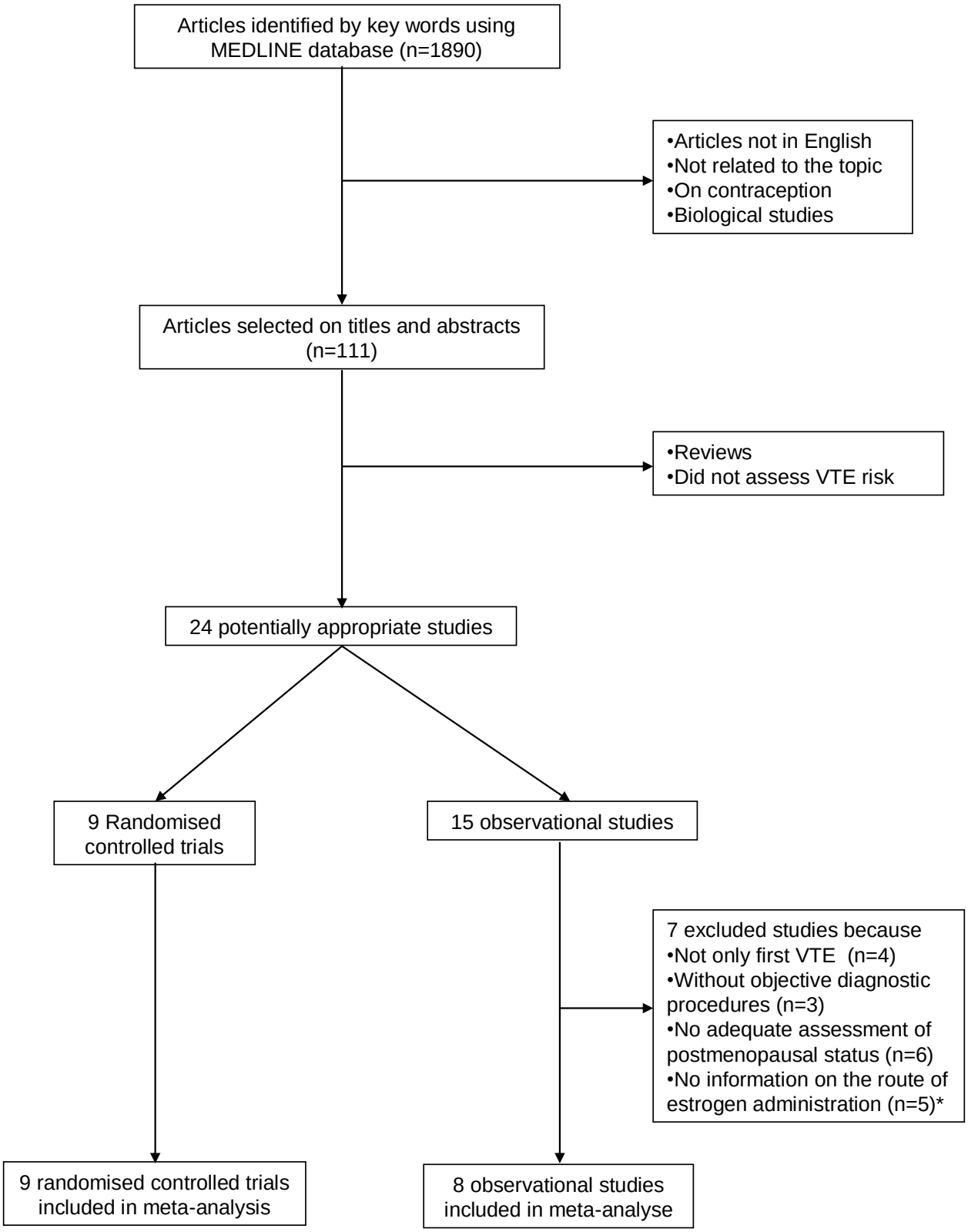
Figure 2.
Risk of first episode of venous thromboembolism by study design and route of oestrogen administration. Values are adjusted odds ratios (95% confidence interval).
(NHS: Nurses' Health Study; Trans: transdermal; RCTs: randomised controlled trials).

Figure 3.
Risk of venous thromboembolism by characteristics of hormone therapy among users of oral oestrogen. Values are odds ratios (95% confidence interval).
(O: oestrogen; O+P: oestrogen and progestogen; HT: hormone therapy).

Figure 4.
Risks of venous thromboembolism among hormone therapy users by route of oestrogen administration and presence of one of two prothrombotic mutations (Factor V Leiden mutation and/or prothrombin G20210A mutation). Values are odds ratios (95% confidence intervals)
(O : oestrogen).

Figure 5.
Risks of venous thromboembolism among hormone therapy users by route of oestrogen administration and presence of an elevated body-mass index (overweight or obesity). Values are odds ratios (95% confidence intervals)
(O : oestrogen).

Figure 1



** n > 7 because excluded studies have more than one defect (low score of quality)*

Figure 2

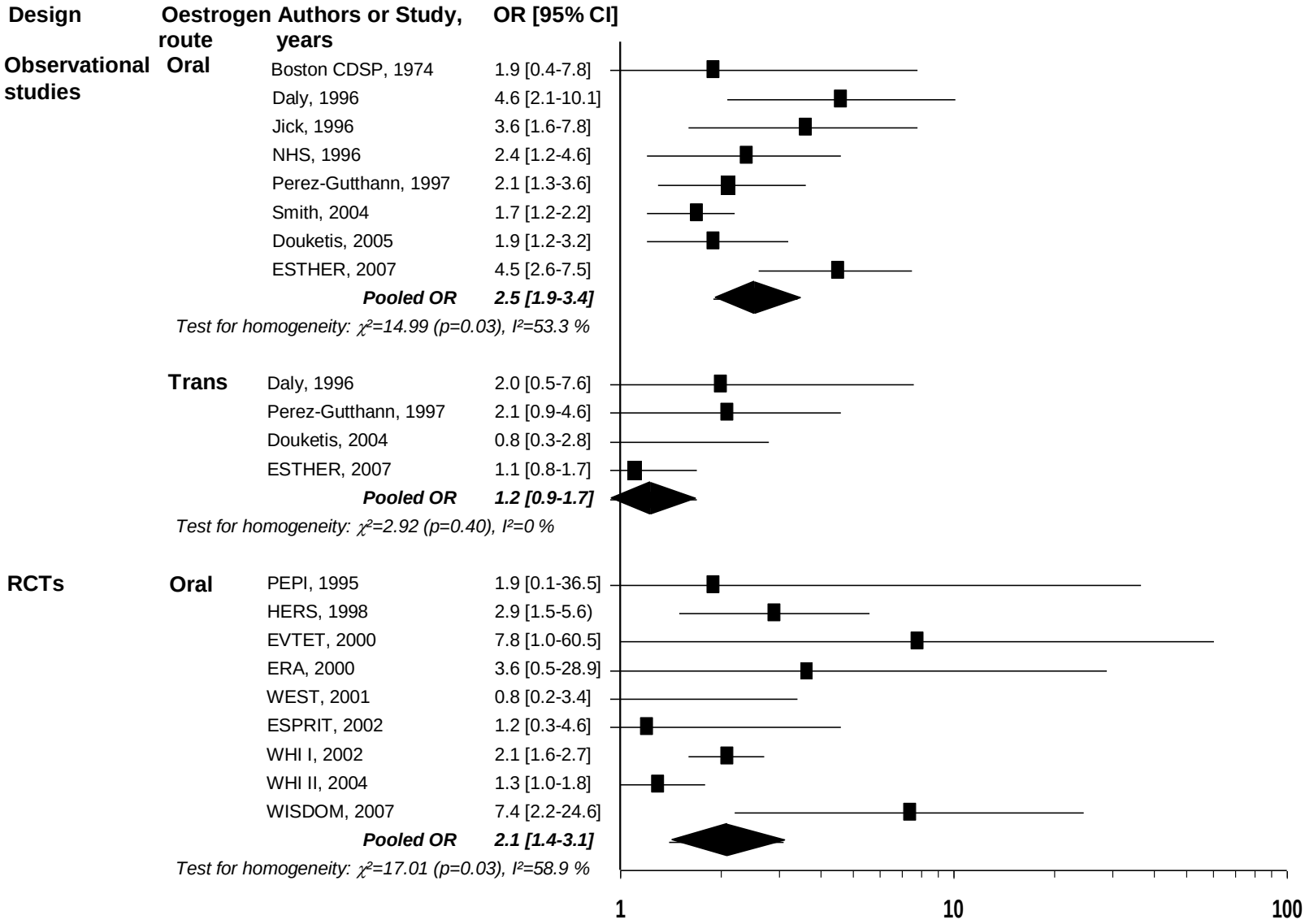
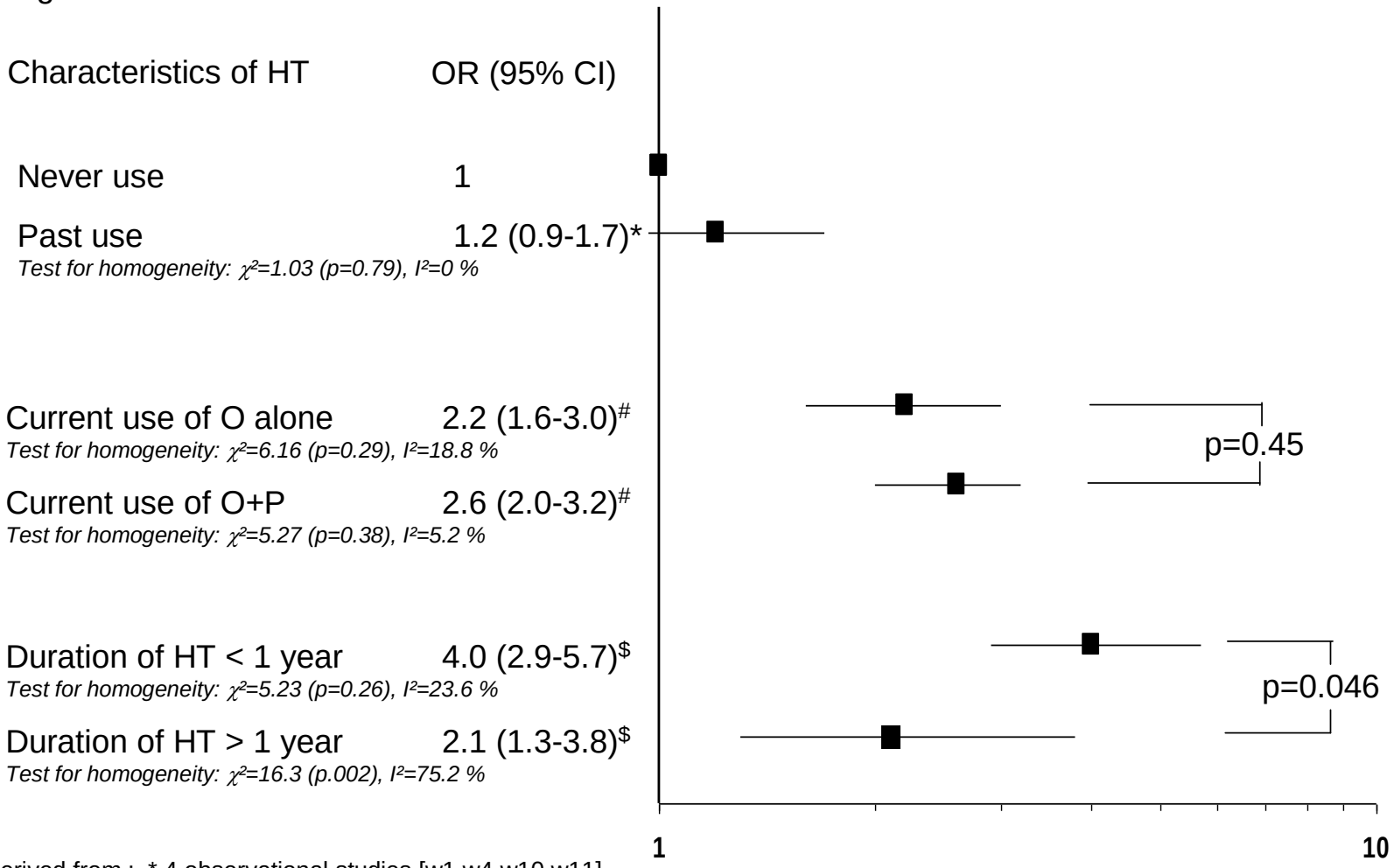

Design
Oestrogen route
Authors or Study, years
OR [95% CI]
Observational studies
Oral
Boston CDSP, 1974 1.9 [0.4-7.8]
Daly, 1996 4.6 [2.1-10.1]
Jick, 1996 3.6 [1.6-7.8]
NHS, 1996 2.4 [1.2-4.6]
Perez-Gutthann, 1997 2.1 [1.3-3.6]
Smith, 2004 1.7 [1.2-2.2]
Douketis, 2005 1.9 [1.2-3.2]
ESTHER, 2007 4.5 [2.6-7.5]
Pooled OR 2.5 [1.9-3.4]
Test for homogeneity: χ²=14.99 (p=0.03), I²=53.3 %
Trans
Daly, 1996 2.0 [0.5-7.6]
Perez-Gutthann, 1997 2.1 [0.9-4.6]
Douketis, 2004 0.8 [0.3-2.8]
ESTHER, 2007 1.1 [0.8-1.7]
Pooled OR 1.2 [0.9-1.7]
Test for homogeneity: χ²=2.92 (p=0.40), I²=0 %
RCTs
Oral
PEPI, 1995 1.9 [0.1-36.5]
HERS, 1998 2.9 [1.5-5.6)
EVTET, 2000 7.8 [1.0-60.5]
ERA, 2000 3.6 [0.5-28.9]
WEST, 2001 0.8 [0.2-3.4]
ESPRIT, 2002 1.2 [0.3-4.6]
WHI I, 2002 2.1 [1.6-2.7]
WHI II, 2004 1.3 [1.0-1.8]
WISDOM, 2007 7.4 [2.2-24.6]
Pooled OR 2.1 [1.4-3.1]
Test for homogeneity: χ²=17.01 (p=0.03), I²=58.9 %
1
10
100

Figure 3



Derived from : * 4 observational studies [w1 w4 w10 w11]

6 observational studies [w1 w3 w5 w9-w11]

$ 5 observational studies [w1 w3 w5 w10 w11]

Figure 4

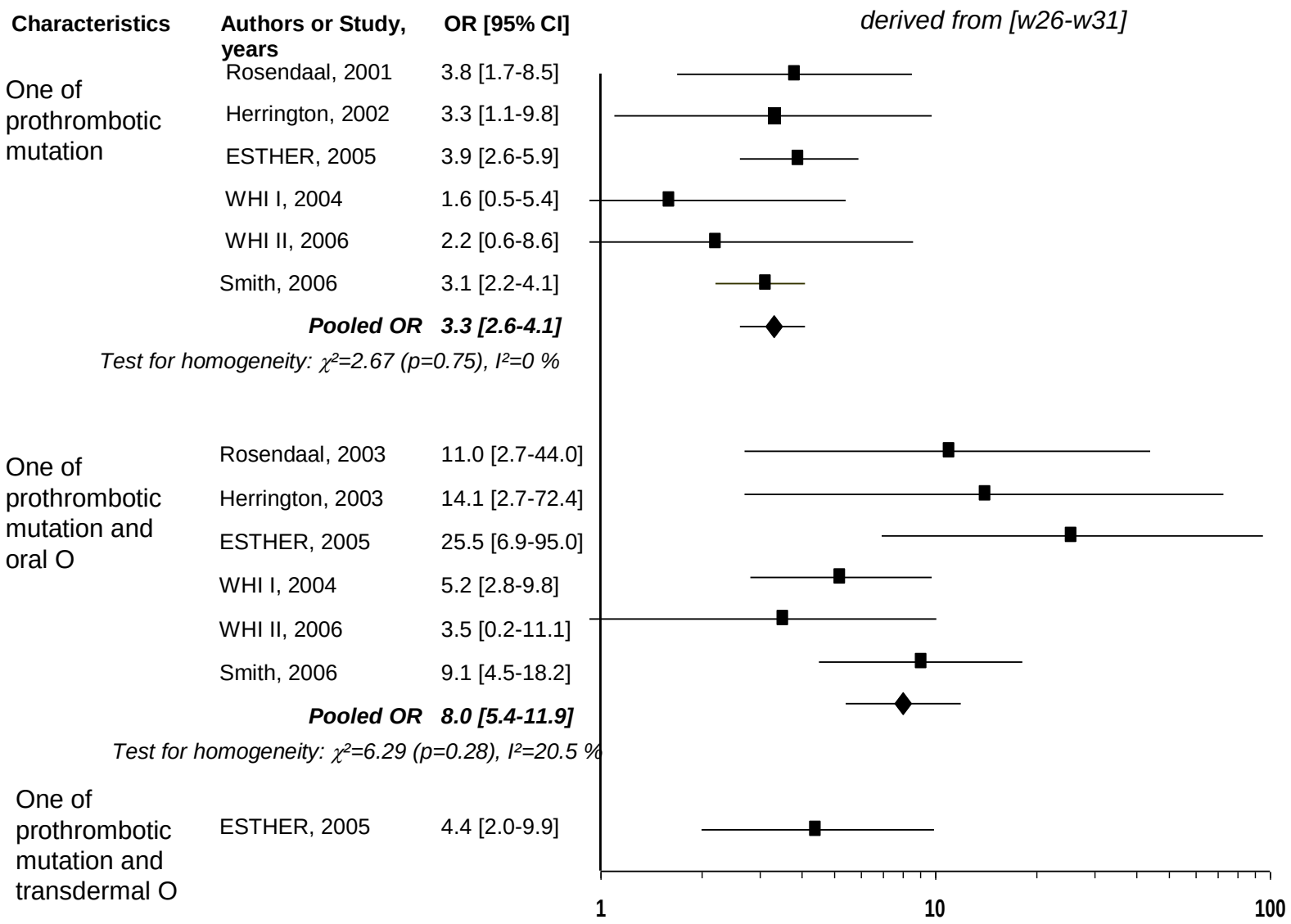
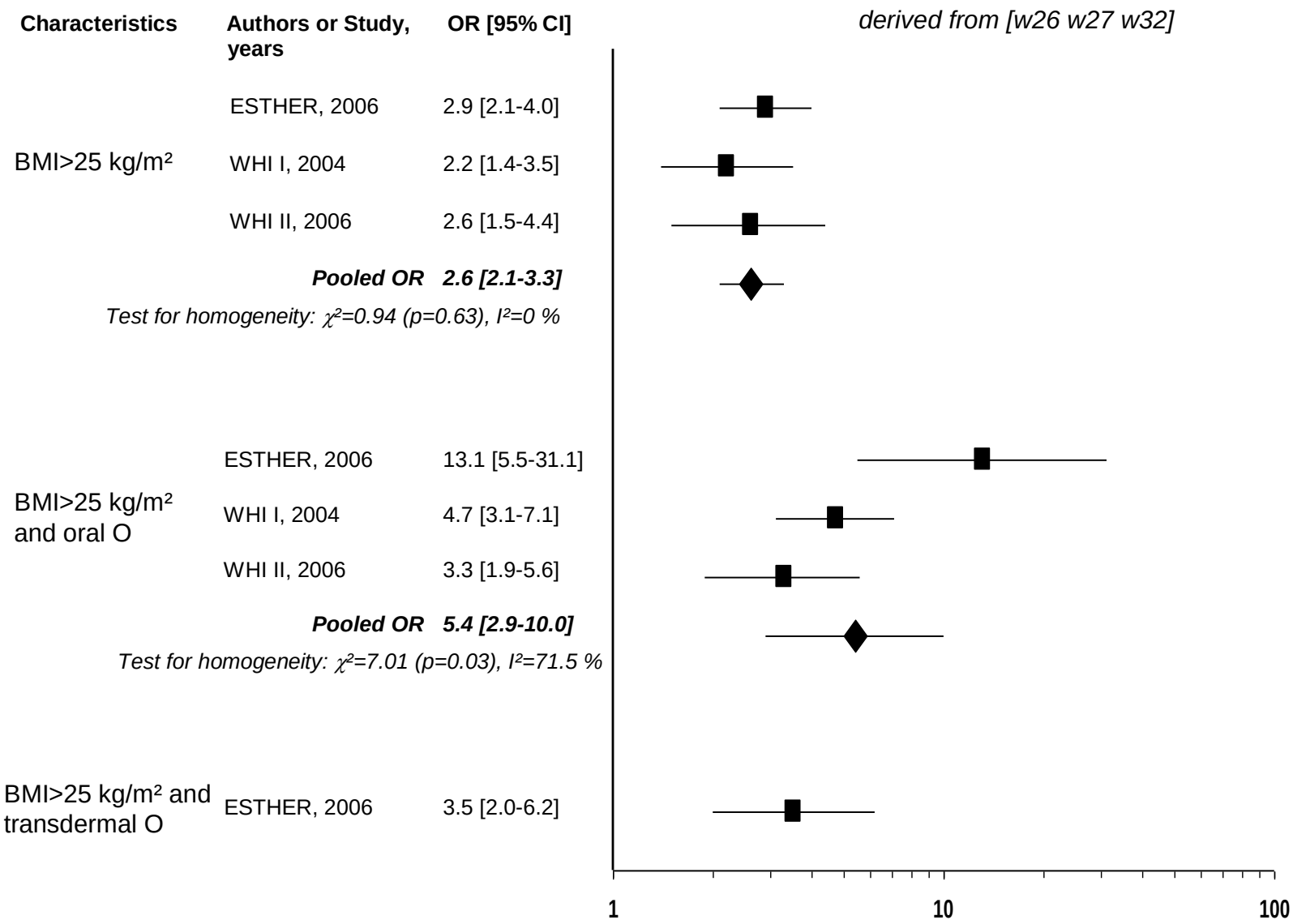

derived from [w26-w31]
Characteristics
Authors or Study, years
OR [95% CI]
One of prothrombotic mutation
Rosendaal, 2001 3.8 [1.7-8.5]
Herrington, 2002 3.3 [1.1-9.8]
ESTHER, 2005 3.9 [2.6-5.9]
WHI I, 2004 1.6 [0.5-5.4]
WHI II, 2006 2.2 [0.6-8.6]
Smith, 2006 3.1 [2.2-4.1]
Pooled OR 3.3 [2.6-4.1]
Test for homogeneity: χ²=2.67 (p=0.75), I²=0 %
One of prothrombotic mutation and oral O
Rosendaal, 2003 11.0 [2.7-44.0]
Herrington, 2003 14.1 [2.7-72.4]
ESTHER, 2005 25.5 [6.9-95.0]
WHI I, 2004 5.2 [2.8-9.8]
WHI II, 2006 3.5 [0.2-11.1]
Smith, 2006 9.1 [4.5-18.2]
Pooled OR 8.0 [5.4-11.9]
Test for homogeneity: χ²=6.29 (p=0.28), I²=20.5 %
One of prothrombotic mutation and transdermal O
ESTHER, 2005 4.4 [2.0-9.9]
1
10
100

Figure 5


derived from [w26 w27 w32]
Characteristics
Authors or Study, years
OR [95% CI]
BMI>25 kg/m²
ESTHER, 2006 2.9 [2.1-4.0]
WHI I, 2004 2.2 [1.4-3.5]
WHI II, 2006 2.6 [1.5-4.4]
Pooled OR 2.6 [2.1-3.3]
Test for homogeneity: χ²=0.94 (p=0.63), I²=0 %
BMI>25 kg/m² and oral O
ESTHER, 2006 13.1 [5.5-31.1]
WHI I, 2004 4.7 [3.1-7.1]
WHI II, 2006 3.3 [1.9-5.6]
Pooled OR 5.4 [2.9-10.0]
Test for homogeneity: χ²=7.01 (p=0.03), I²=71.5 %
BMI>25 kg/m² and transdermal O
ESTHER, 2006 3.5 [2.0-6.2]
1
10
100