CLIMACTERIC
https://doi.org/10.1080/13697137.2025.2503874

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REVIEW ARTICLE



# Safety of menopause hormone therapy in postmenopausal women at higher risk of venous thromboembolism: a systematic review

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**ABSTRACT**

**Objective:** Studies have shown that oral estrogen with or without progestogen increases the risk of venous thromboembolism (VTE). Recent data suggest that transdermal estrogen confers little to no increased risk of VTE. There is no systematic review that examines menopause hormone therapy (MHT) use in women with risk factors for VTE. This systematic review therefore aims to summarize the evidence in this population.

**Method:** The OVID Medline, Embase, PubMed and CENTRAL online databases were searched. A total of 762 studies were screened and 10 were included in the study.

**Results:** Six studies were case–control studies, two were randomized controlled trials (RCTs), one was an RCT that contained a nested case–control study and one was a cohort study. Studies were heterogeneous in their definition of menopause, dose, form and route of administration of MHT, and the underlying VTE risk factor being assessed. In women with risk factors for VTE, transdermal estrogen conferred no increased risk of VTE. Oral estrogen alone has the next safest profile, and oral estrogen plus a progestogen conferred the highest increased risk of VTE.

**Conclusion:** Transdermal MHT appears safe in women with risk factors for VTE. Oral MHT, notably oral estrogen plus a synthetic progestogen, does increase relative risk. More contemporary data are required to confirm these findings.

**ARTICLE HISTORY**
Received 3 November 2024
Revised 30 March 2025
Accepted 27 April 2025

**KEYWORDS**
Menopause hormone therapy; hormone replacement therapy; venous thromboembolism; deep vein thrombosis; pulmonary embolism; thrombophilia; systematic review

## Introduction

Menopause hormone therapy (MHT) is prescribed to many postmenopausal women with the aim to alleviate symptoms and improve quality of life. Despite consistently proven benefits and guidelines for the safe prescribing and management of MHT, there is still considerable discrepancy between the number of women experiencing symptoms and those currently taking MHT [1]. Benefits of MHT include control of vasomotor symptoms and urogenital symptoms, and improved sleep, psychological well-being and sexual health [2]. MHT has also been shown to reduce the risk of diabetes and colon cancer if used in a combined preparation [2,3].

Historically, risks associated with use of MHT significantly affected prescribing practices, particularly after the publication of the Women's Health Initiative (WHI) trial. These risks include breast cancer (with combined therapy, with the risk level dependent on the progestogen type), myocardial infarction, stroke and venous thromboembolic events such as pulmonary embolism (PE) and deep vein thrombosis (DVT) [4]. Therefore, prescribing MHT for women with known risk factors for venous thromboembolism (VTE) was heavily cautioned [5]. More recent studies have shown that the risks of MHT are related to whether estrogen is combined with a progestogen and the route of administration.

VTE is a complex condition with a host of risk factors including age, thrombophilia, overweight or obesity, older age, smoking, recent surgery or immobilization, malignancy, prior history of VTE, acute myocardial infarction, congestive heart failure, pregnancy and hormone replacement therapy [6]. It is well established that the use of oral estrogens with or without a synthetic progestogen can significantly increase the risk of VTE, particularly in those with known risk factors [7,8]. These studies often examine use of oral estrogens alone or group all forms of MHT together in their analyses, without delineating between routes of administration. Recent narrative analysis of literature suggests that the risks of MHT with respect to VTE are different when considering timing of commencement, preparation, route of administration and duration of use [9]. Furthermore, it is emerging that transdermal estrogen use is associated with no increased risk of VTE in the postmenopausal population and may confer no additional risk in women with risk factors for VTE [2,10–12]. Despite narrative reviews of the literature, to date there are no systematic reviews that have assessed the data addressing the safety of MHT in women at risk of VTE.

The aim of this systematic review is to summarize the current body of evidence regarding the use of MHT in women with identified risk factors for VTE.

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Supplemental data for this article is available online at https://doi.org/10.1080/13697137.2025.2503874

## Method

This systematic review was registered with PROSPERO (ID: CRD42024582546) on 18 March 2024. The PubMed, OVID Embase, OVID Medline and CENTRAL online databases were searched. A rigorous search strategy was developed to identify relevant clinical literature that addressed MHT in postmenopausal women and VTE (Supplementary Material 1). Searches were dated from the origin of the databases to the date of the search (20 March 2024). The search was updated in January 2025. A validated search limiter was used for searches in OVID Embase and OVID Medline to limit the search to clinical research [13]. In PubMed, the search was limited to all clinical trials using the search filter. No restrictions were placed on language or publication period in the initial search strategy.

Studies from the search were screened against strict inclusion and exclusion criteria. Studies were included if they included postmenopausal women only and studied a group of postmenopausal women with risk factors for VTE. Included studies must have assessed use of oral or transdermal estrogen, with or without progestogens. They must have had a control group of women without known risk factors for VTE or who were not taking MHT. VTE must have been diagnosed by imaging (either ultrasound Doppler, ventilation-perfusion lung scan or computed tomography pulmonary angiogram). All interventional and observational trials were included (randomized controlled trials [RCTs], cohort studies and case–control studies). Exclusion criteria were that studies included premenopausal or perimenopausal women, and examined intranasal, subcutaneous and vaginal administration of MHT or oral contraceptives. They were also excluded if there was no appropriate control group or VTE was diagnosed clinically or biochemically with markers of coagulation. Reviews, abstracts, case reports, consensus statements and expert opinions, and full texts that were unable to be sourced in English were excluded.

Initially, the authors hoped to include RCTs only; however, on test search runs, it was evident that this would return limited results. Therefore, the inclusion criteria were expanded to also include observational studies. Clinically suspected VTE and biochemical markers of VTE were excluded to reduce diagnostic bias. If clinicians were unblinded to MHT status, they may be more likely to clinically suspect VTE or prescribe anticoagulation based on that information. Perimenopause was excluded in attempt to reduce heterogeneity of data and because of the difficulty in providing a precise definition [14].

In this review, women were defined as high risk for VTE if they were overweight (body mass index [BMI] 25–30 kg/m$^2$) or obese (BMI >30 kg/m$^2$), current smokers, had a personal history of VTE or family history of VTE, had type 2 diabetes, recent surgery (<3 months), personal history of or current underlying cancer, or had known inherited or acquired thrombophilia (e.g. antiphospholipid syndrome, factor V Leiden [FVL], prothrombin gene mutation). The authors acknowledge that increasing age is a risk factor for VTE, but no age criteria were applied to the search in an attempt to avoid narrowing the search results. These risk factors have been established from interrogation of multiple registries [15] and used consistently in the literature addressing VTE risk in the context of MHT [16].

Title and abstract screening and full text review were performed using the Covidence platform. Reporting of the review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The authors planned to extract data using the Extraction 2 template; however, due to the heterogeneity of study designs and data, a blank data extraction sheet was created to include the study design, methodology, funding resources, participant details, population description, inclusion criteria, exclusion criteria, method of recruitment, total number of participants, and baseline population characteristics including age, BMI, smoking status, personal history of VTE, family history of VTE, diabetes, recent surgery (<3 months), personal history of cancer and known thrombophilia. Intervention data extracted included the definition of cases, definition of controls, definition of postmenopause, definition of VTE, number of participants in the intervention/exposure group and the dose, route, frequency and form of MHT. Outcome data extracted included image-diagnosed DVT or PE, the Odds Ratio (OR), hazard ratio (HR) or relative risk (RR) of VTE events amongst the exposure/intervention groups compared with controls.

The quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS) risk of bias tool [18] and the Cochrane risk-of-bias tool (RoB2) for the randomized trials [19]. The NOS is a validated tool for assessing risk of bias in non-randomized studies. This tool was chosen given that most papers included in the review were case–control studies. The RoB2 tool was chosen to address risk of bias in the three randomized trials. Both tools were used to address the study which contained a nested case–control within an RCT. Two reviewers performed screening, full text review, data extraction and risk of bias, and conflicts were resolved with a third reviewer.

## Results

A total of 1271 studies were obtained from the search strategy: 509 were duplicates, and 762 were screened. A total of 730 studies were excluded due to the title and abstracts not being relevant to the review (wrong study design or the study not addressing VTE risk in the postmenopausal cohort). Thirty-two studies were reviewed in full, and 10 studies were included in the systematic review. The reasons for exclusion of 22 studies are outlined in the PRISMA diagram (Figure 1). The updated search in January 2025 identified a further 49 studies, but none fulfilled our inclusion criteria and therefore no further studies were included for analysis. Risk of bias scores according to the NOS were 8–9 for all studies with overall low risk in the RoB tool (see Supplementary Material 2).

Six studies were case–control studies, two were randomized double-blinded, placebo-controlled trials (RCTs), one contained a nested case–control study within a double-blinded RCT and one study was a retrospective cohort study. Seven of the 10 studies included used data from an index study. Interestingly, all studies collected data as early as 1993 and

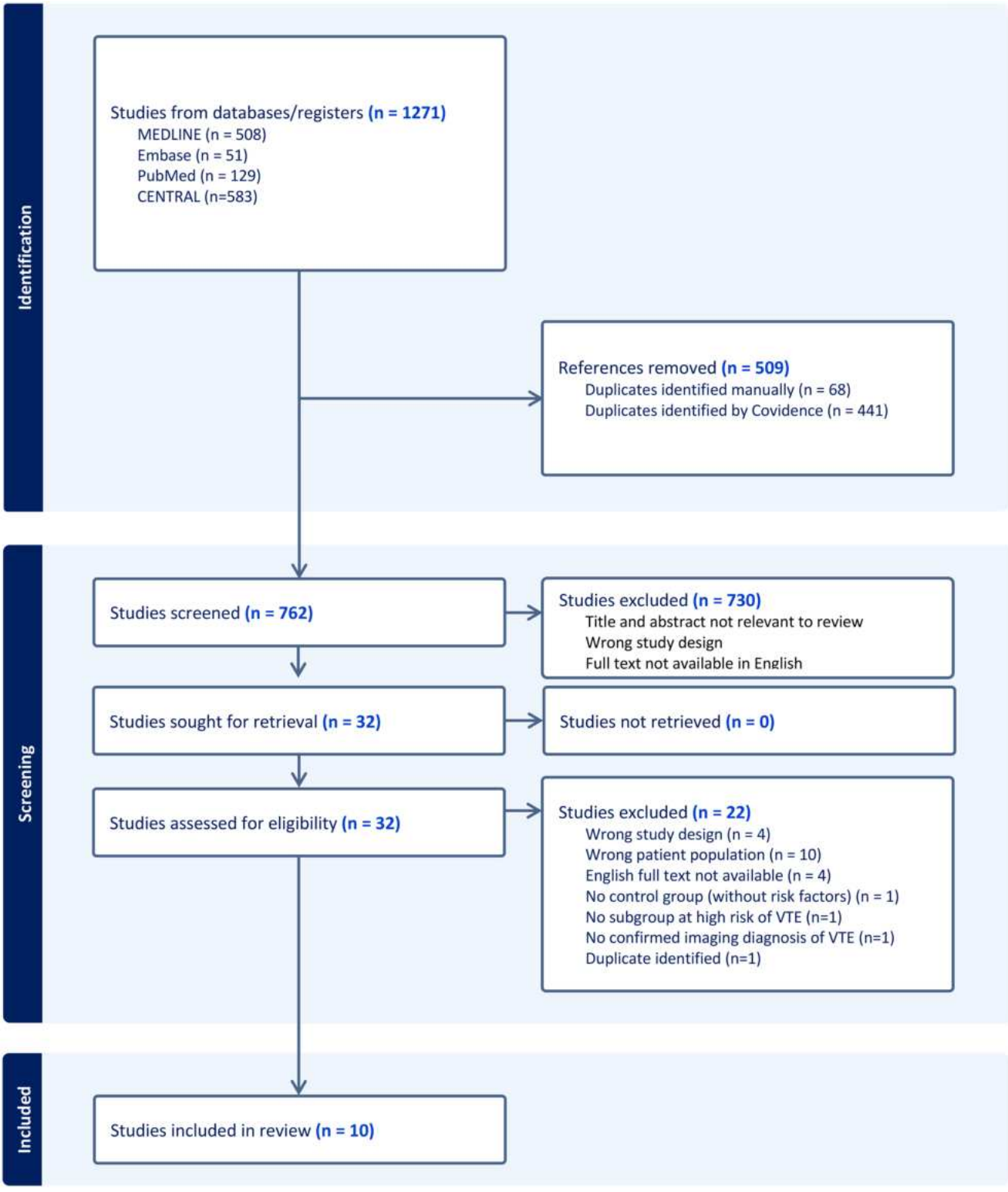


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. VTE, venous thromboembolism.

as late as 2008 and were predominantly performed in the USA, Canada, France and the Netherlands. No studies found in our search presented data collected after 2008 despite the search being conducted from the database origin to the current date (4 February 2025). All studies were conducted in the Caucasian population and therefore results from these are only applicable to western women. Appendix Table A1 outlines the study characteristics, design, inclusion and exclusion criteria, primary outcome measure, duration of follow-up and exposure data that were either reported in the studies or sought from index studies cited.

The average age range of participants included in studies was 55–74 years. Nine out of 10 studies reported patient characteristics such as age, BMI, current smoking status, personal history of VTE and family history of VTE. Three studies provided information relating to known thrombophilia

(Appendix Table A1). All studies provided clear definition of postmenopause and venous thrombosis. The increased risk of VTE in all case–control studies was reported as ORs with reference groups being women not on MHT and with or without the studied risk factor. The RCT data were reported as either the HR or RR and the cohort study data were reported as the HR (Supplementary Material 3).

When extracting exposure data, there was very clear heterogeneity in the type of MHT used between studies, and often unclear delineation of the number of participants using estrogen in combination with progestogen and the type of progestogen used (Appendix Table A1). Oral estrogen types included conjugated equine estrogen (CEE), esterified estrogens or 17β-estradiol. Progestogens included either medroxyprogesterone, norethisterone or micronized progesterone. Some studies did not define the MHT type further than simply stating 'oral estrogen' or 'oral estrogen plus progestogen'. Furthermore, when reporting outcome data, many studies did not report VTE data according to the specific MHT type and route of administration but grouped all MHT use together (Appendix Table A1 and Supplementary Material 3). Appendix Table A2 presents the increased risk of VTE found in individual studies according to the underlying risk factors for VTE and type of MHT studied.

Two studies included patients using anticoagulants [20,21]. Four studies did not specify and five studies excluded those using anticoagulants. Grady et al.'s randomized, double-blinded controlled trial included patients on aspirin and warfarin, but there was no statistical difference in the proportion of users between treatment and placebo groups [20]. Hurbanek et al.'s study included patients receiving pharmacological antithrombotic prophylaxis and found that cases were less likely than controls to receive prophylaxis, potentially contributing to higher rates of DVT and/or PE within 45 days of surgery in cases [21].

### *Overweight/obesity*

Two studies examined the increased risk of VTE in overweight (BMI 25–30 kg/m$^2$) and obese (BMI >30 kg/m$^2$) women taking MHT [22,23]. Canonico et al. referenced the ESTHER study, which studied women taking mainly oral 17β-estradiol 1.5 mg daily (two participants used CEE) or 50 µg transdermally with or without a progestogen (15% participants used estrogen alone) [23]. Cushman et al. examined only women using oral CEE (0.625 mg/day) plus medroxyprogesterone acetate (MPA) (2.5 mg/day) [22]. Using non-users of same BMI group as the reference group, women with a BMI of 25–30 kg/m$^2$ taking oral estradiol alone had an OR for VTE of 3.70 (confidence interval [CI] 1.30–11.00) and that for transdermal estradiol was 1.10 (CI 0.50–2.10) [23]. The HR for those taking CEE + MPA was 3.80 (CI 2.08–6.94) [22]. In women with BMI > 30 kg/m$^2$, the OR for VTE in women taking oral estradiol alone was 5.1 (CI 1.20–22.00) and for transdermal estrogen was 1.40 (CI 0.50–3.50) [23]. The HR for women taking oral CEE + MPA was 5.61 (CI 3.12–10.11) [22]. Given these results, transdermal estrogen confers no additional VTE risk in women with BMI > 25.

### *Smoking*

Only one study examined the increased risk of VTE in smokers using either CEE 0.625 mg/day or esterified estrogen [24]. In this study, 9.9% of participants used a progestogen, almost exclusively MPA. Using current smokers not on MHT as the reference group, Blondon et al. reported a non-significant OR of 1.60 (CI 1.00–2.62) for current smokers on any MHT [24]. Using never smokers not on MHT as a reference group, women on oral estrogen only had an OR for VTE of 1.73 (CI 1.03–2.91). This study concluded that there was no suggestion of additive interaction between smoking and MHT.

### *Genetic thrombophilia*

Five studies examined the risk of VTE in women with underlying thrombophilia (any), FVL or prothrombin gene mutation (Prothrombin 20210) [22,25–28]. All studies assessed oral estrogen or oral estrogen + progesterone, but only one study examined the effects of transdermal estrogen [25].

### *Any thrombophilia*

In the analysis of EVTET data, an RCT that was terminated early due to increased VTE recurrence in women receiving oral 2 mg estradiol + 1 mg norethisterone, it was found that of eight women who suffered recurrent VTE, five tested positive for thrombophilia. Two women were FVL heterozygous, one FVL homozygous and two had anticardiolipin antibodies. It was reported for women with any thrombophilia and a history of VTE that the RR of VTE recurrence on MHT (oral estradiol + norethisterone) was 2.60 (CI 1.30–5.04) compared with women not on MHT with no thrombophilia. Women were excluded from the study if they were currently taking anticoagulants or had been within the last 3 months [26].

### *Factor V Leiden (genotype not specified)*

Douketis et al. examined the outcome of DVT alone (not PE) and classified MHT users as either oral estrogen–progestin, oral estrogen only or transdermal users. Unfortunately, the authors did not report the types of estrogen/progestogens used [27]. For women with FVL (genotype not specified), the OR for DVT without MHT was 5.30 (CI 1.90–15.40) [27]. For women on oral estrogen + progesterone with FVL, the OR for DVT was 17.10 (CI 3.70–78.00) compared to MHT non-users without the mutation [27]. Curb et al. reported that women on CEE with FVL (homozygous and heterozygous) had an OR of 4.00 (CI 1.07–14.97) for VTE [28].

Straczek et al. studied women using either CEE or oral 17β-estradiol or transdermal estrogen alone [25]. Compared to non-users with FVL, the OR for VTE was 6.30 (CI 1.40–27.60) for oral estrogen use (CEE or 17β-estradiol). However, those using transdermal estrogen alone had no significant increased risk of VTE (OR 1.80, CI 0.50–6.30) [25].

### *Factor V Leiden (heterozygous)*

For women with FVL (heterozygous), the OR for VTE was 4.00 (CI 1.07–14.97) for oral CEE use (compared with women on

placebo with FVL) [28] and 2.60 (CI 1.30–5.20) for oral CEE + MPA (compared with women on placebo with FVL) [22]. In an analysis of EVTET data, the RR of VTE for women with previous VTE on estradiol + norethisterone and FVL (heterozygous) was 1.40 (CI 0.40–5.30), which was a non-significant excess risk recurrence as compared with no thrombophilia [26].

### *Factor V Leiden (homozygous)*

Only one study separated data for women with FVL (homozygous) and found an OR of 7.50 (CI 0.60–87.80) for women taking CEE + MPA when compared with women on placebo with FVL (homozygous) [22].

### *Prothrombin gene mutation*

Three studies examined women with prothrombin gene mutation. In women with the mutation (homozygous + heterozygous), taking CEE alone led to an OR for VTE of 2.61 (CI 0.42–16.11) when compared with women with the mutation taking placebo [28]. Among those taking CEE + MPA, the OR for VTE was 2.43 (CI 1.59–3.70) compared to placebo in those with the mutation [22]. When compared with non-users who had the mutation, transdermal estrogen use had no significant increased risk (OR 0.50, CI 0.10–2.20) [25].

### *Previous VTE*

Two studies examined the risk of VTE in women with a prior history of VTE [26,29]. In an RCT that was terminated early, the incidence rate per 100 patient years in women taking oral estradiol plus norethisterone was 8.50 (CI 2.60–14.40) compared with 1.1 (CI 0.00–3.20) in women taking placebo [26]. This study reported an identified overall rate of thrombophilia amongst women with recurrent VTE as 25%, with the majority (16.5%) of women having heterozygous FVL. In the retrospective cohort study, the HR of VTE in women taking oral estrogen was 6.40 (CI 1.50–27.30), and transdermal estrogen and transdermal estrogen plus micronized progesterone had no significant difference (HR 1.10, CI 0.20–8.10 and HR 1.00, CI 0.30–3.20, respectively). Transdermal estrogen plus norpregnane derivatives had an HR of 4.70 (CI 1.10–20.00) [29], suggesting that norpregnane derivatives play a role in VTE risk.

### *Recent surgery*

Recent surgery (<3 months) was addressed in two studies. One of these poorly defined the postmenopausal status and did not report any significant increased risk of VTE in women on oral estrogen, oral estrogen + progesterone or transdermal estrogen (OR 0.77, 0.64 and 0.60 respectively) [21]. Although this study met the inclusion criteria for the review, the study scored poorly in the risk of bias assessment (Appendix Table A2) making the conclusions drawn difficult to interpret. A higher quality RCT reported an HR of 4.90 (CI 2.00–9.80) in women on CEE + MPA who underwent inpatient surgery in the previous 3 months. This study also reported an HR of 5.60 (CI 0.70–43.80) for those with recent hip fracture and an HR of 18.10 (CI 5.40–60.40) for other lower extremity fractures in women on CEE + MPA [20]. These data suggest that women on oral estrogen + progesterone MHT should consider withholding MHT in the context of recent hip fracture or lower extremity fracture unless adequate anticoagulant is instituted.

## Discussion

This systematic review is the first of its study design in the literature to review the available evidence surrounding the risk of VTE in women with background risk factors for VTE and taking MHT. What is clear from the results of this review is that there is heterogeneity among studies and a lack of studies providing data after 2008. There was significant heterogeneity in the study design, definition of menopause, type of MHT studied and the underlying risk factor for VTE that was studied. Even where studies examined the same risk factor (i.e. thrombophilia, FVL, prothrombin gene mutation), the form, dose and route of administration varied between studies. Due to large clinical and methodological heterogeneity, we opted not to conduct a meta-analysis and test for heterogeneity as it would be difficult to derive reliable pooled estimates. Instead, we provided a comprehensive narrative synthesis in an attempt to discuss the findings and implications of the individual studies.

Drawing from the data synthesized in this review, caution and adequate counseling should be undertaken when considering oral estrogen with or without progesterone in women with BMI 25–30 kg/m$^2$ and avoided in women with BMI >35 kg/m$^2$.

Although smoking was found to have no interaction with MHT, it increases the risk of arterial cardiovascular disease and oral estrogens can increase the incidence of stroke and coronary heart disease, so caution is advised in prescribing oral MHT to this population. In women with FVL, oral estrogen with or without progestogens should not be prescribed. Transdermal estrogen use confers no additional risk (compared to their already elevated background risk of VTE). In women with previous VTE, transdermal estrogen plus micronized progesterone appears to be safe.

In women without risk factors for VTE, MHT increases the background risk of VTE with combined oral preparations conferring the highest risk. Amongst oral estrogens, CEE is highest risk with estradiol preparations being lower risk. Transdermal MHT is not associated with any increased VTE risk amongst women without risk factors for VTE [30]. The data presented from this systematic review followed a similar pattern to this literature. Despite the underlying risk factors assessed, combined oral preparations and oral estrogen-only preparations conferred the higher increased risks of VTE, with transdermal estrogen adding no additional significant risk for VTE among women with defined risk factors (except when combined with norpregnane derivatives).

Despite searching up to the current date, all studies that qualified for inclusion in this systematic review were conducted or used data collected between 1993 and 2008. Prescribing practices at this time were primarily oral

estrogens or oral estrogen + progestogen as reflected in the data. Where oral estrogen was studied, CEE, estradiol or esterified estrogens were prescribed in mean doses of 0.625 mg/day, 2 mg/day and 1.5 mg/day, respectively [20,22–26,28]. Prescribing practices have changed considerably since 2010. Overall, there is an increase in first-users of MHT and a particularly sharp increase in those using transdermal preparations [31]. This highlights the need for more contemporary studies that reflect current prescribing practices, particularly in women with risk factors for VTE.

Overall, the results from this review suggest that in women who have undergone recent surgery, with BMI of 25–30 kg/m$^2$ or >30 kg/m$^2$, with prothrombin gene mutation or with a personal history of VTE or FVL, the use of transdermal estrogen with or without micronized progesterone confers no significant increased risk of VTE.

When considering prescribing oral preparations, combined preparations are higher risk and use should be avoided in women with FVL (homozygous) (17-fold increased risk of VTE) and heavily cautioned in women with BMI >25 kg/m$^2$, FVL (heterozygous) and prothrombin gene mutation as this significantly increases the risk of VTE (2.5-fold to 5-fold). If oral estrogens are prescribed, esterified estrogens seem be to be safer than 17β-estradiol, with CEE conferring greatest risk with respect to VTE. It is important to note that most studies in this review stated use of anticoagulants (or recent use) in their exclusion criteria and therefore the safety of these preparations in the context of anticoagulation is likely to be improved.

The strengths of this study include a rigorous and comprehensive protocol following PRISMA guidelines that ensured most clinical studies were captured and relevant papers included/excluded by two independent reviewers, with a third to resolve conflicts. The inclusion criteria of postmenopausal women with a clear definition of image-diagnosed VTE ensured that results bias was minimized and studies containing data that were potentially overestimating risk were not included.

The authors chose to exclude studies not published in English or lacking full text. This is acknowledged as a limitation of the study, and although attempts were made through affiliations to obtain these, there were only four papers excluded for this reason at the stage of title and abstract screening. Two risk of bias tools were selected for this review. The NOS is validated for case–control and cohort studies, but is not the most appropriate tool to assess quality for the RCTs included in the review. Therefore, RoB2 was used for these. Finally, there was variation in the study design, forms and preparations of MHT used between studies. This made it difficult to provide any meaningful subgroup analyses and is a limitation of this review. This highlights the authors' position that there is a need for contemporary, robust studies that clearly define the population, underlying risk factors for VTE, and form, dose and route of administration of MHT, with particular attention paid to transdermal administration of estrogen.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## Funding

Nil.

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## Appendix 1

Table A1. Summary of data.

| *Studies 1–5* | *Blondon et al. (2013)*[24] | *Canonico et al. (2006)*[23] | *Curb et al. (2006)*[28] | *Cushman et al. (2004)*[22] | *Douketis et al. (2011)*[16] |
|---|---|---|---|---|---|
| Type of study | Case–control | Case–control | Nested case–control | Double-blinded RCT + nested case–control | Prospective nested case–control |
| Index study (if applicable) | Heart and Vascular Health Study | ESTHER | WHI | WHI | |
| Year | 1995–2009 | 1999–2005 | 1993–2001 | 1993–2002 | 1998–2001 |
| Country | USA | France | USA/ Netherlands | USA | Canada |
| Funding | None | Foundation de France, Foundation pour la Recherche Medicale, Institut National de la sante de la recherche medicale, Aventis, Besins International, Sanofi, Sevier Institute | The Netherlands Heart Foundation (funding for genetic analyses) | The WHI was funded by the National Heart, Lung and Blood Institute. Wyeth-Ayerst Research provided the study medications (active and placebo). Additional funding was provided by grant 2001.029 from the Netherlands Heart Foundation | Canadian Institute of Health Research |
| Definition of postmenopause | Cessation of ovarian function that occurred naturally or through bilateral oophorectomy (if unclear, age >55 years) | Amenorrhea for 12 months, bilateral ovariectomy or hysterectomy and age older than 52 years | Not defined | Not defined | Spontaneous menopause, with no menses for at least 6 months<br>Surgical menopause due to bilateral oophorectomy or presence of menopausal symptoms such as VMS for at least 6 months |
| Definition of VTE | Diagnosed by imaging modality or by physician judgment in the presence of symptoms or according to treatment strategies<br>DVT: doppler or duplex ultrasound<br>PE: computed tomography, pulmonary angiography or ventilation-perfusion scan | Diagnosed by imaging modality<br>DVT: compression ultrasonography<br>PE: Helical-computed tomography showing at least one intraluminal defect in one segmental pulmonary artery, high-probability ventilation-perfusion scan | Diagnosed by imaging modality<br>DVT: positive results at Doppler or duplex ultrasonography, venography, plethysmography or isotope scanning<br>PE: positive results at ventilation-perfusion lung scanning, pulmonary angiography or computed tomography, or documented signs and symptoms suggestive of PE in setting of documented DVT | Diagnosed by physician + confirmed on imaging<br>DVT: positive findings on Doppler or duplex ultrasound, venogram, plethysmography or isotope scan<br>PE: signs and symptoms in the presence of documented DVT | Diagnosed by imaging modality<br>DVT confirmed by non-compressible vein on ultrasound or constant intraluminal filling defect on venography |
| Inclusion criteria | Postmenopausal women<br>Age 30–89 years | Postmenopause<br>Age 45–70 years<br>First documented episode of idiopathic VTE | Postmenopausal women without a uterus<br>Age 50–79 years | Postmenopausal women without a uterus<br>Age 50–79 years | Postmenopausal<br>Suspected lower-limb DVT |
| Exclusion criteria | Perimenopause, smoked pipes/cigars, missing smoking data, users of oral contraceptives during menopause, users of estrogen patches or oral progesterone without estrogens | Personal history of VTE, contraindication for MHT, predisposing factor for VTE (history within previous months of surgical intervention, trauma with immobilization, illness necessitating bed rest, known cancer, systemic inflammatory disease) | Medical conditions predictive of a survival time <3 years, alcoholism, drug dependency, mental illness, dementia, active participant in another RCT, breast cancer, osteoporosis, previous VTE | Medical conditions predictive of a survival time <3 years, alcoholism, drug dependency, mental illness, dementia, active participant in another RCT, breast cancer, osteoporosis, previous VTE | Antecedent risk factors for VTE (other than HRT use), suspected PE, amenorrhea due to primary or secondary ovarian failure, cognitive impairment or language barrier |
| Outcome | First deep venous thrombosis and/or PE | Idiopathic VTE (DVT and/or PE) | Diagnosis of DVT/PE | Centrally validated DVT and PE | Unprovoked (idiopathic DVT) |
| Duration of follow-Up | 7 years | 6 years | 7.1 years | 5.6 years | 6 years |
| Number of participants | 6992 | 850 | 10,739 | 16,608 | 340 |

(*Continued*)

Table A1. Continued.

| Studies 1–5 | Blondon et al. (2013)[24] | | Canonico et al. (2006)[23] | | Curb et al. (2006)[28] | | Cushman et al. (2004)[22] | | Douketis et al. (2011)[16] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Current anticoagulant use | Not specified | | Not specified | | Excluded | | Excluded | | Not specified | |
| Characteristics of MHT | Oral CEE or esterified estrogen with progesterone (almost exclusively medroxyprogesterone acetate) | | Majority oral estrogen therapy received 17β-estradiol. Two participants oral CEE. Most users used E + P and only 15% E alone | | Oral CEE | | Oral CEE + MPA | | Not defined further than:<br>Oral E + P<br>Oral E only<br>TDE | |
| Dose | 0.625 mg/day CEE or equivalent | | 17β-estradiol: 1.5 mg/day<br>TDE: 50 mcg/day | | 0.625 mg/day | | 0.625 mg/day +2.5 mg/day | | Not stated | |
| | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Definition | Postmenopausal women with first DVT or PE | No history of VTE, matched on age, treated hypertension status and calendar year identification to cases of myocardial infarction (MI) | First documented episode of idiopathic VTE | Admitted to the hospital with a diagnosis a priori of the eye, ear, skin, respiratory and alimentary tracts, bones and joints, kidneys, infectious diseases and diabetes<br>Community controls matched by age and area of residence | Postmenopausal women without a uterus who had a diagnosed VTE in the study period (who were randomly assigned to either combined oral CEE or placebo) | Postmenopausal women without a uterus who did not have a diagnosed VTE in the study period (who were randomly assigned to either combined oral conjugated equine estrogen or placebo) | Validated case of VTE | No VTE, matched on age, randomization date, presence of baseline vascular disease specific to the case and follow-up time | Patients with unprovoked (idiopathic) DVT, in whom DVT occurred without the presence of risk factors: recent (within 1 month) surgery, immobility or trauma, thrombophilia, previous venous thromboembolism, active cancer (treated within 6 months) | Patients in whom DVT was excluded and who did not have risk factors |
| Number of participants according to type of MHT | No MHT ($n = 767$)<br>Any MHT ($n = 222$) | No MHT ($n = 2062$)<br>Any MHT ($n = 709$) | No MHT ($n = 136$)<br>Oral E ($n = 0$)<br>TDE ($n = 13$)<br>TDE + P ($n = 104$) | No MHT ($n = 372$)<br>Oral E (no = 2)<br>TDE ($n = 40$)<br>TDE + P ($n = 185$) | TBC | TBC | E + P ($n = 8506$) | Placebo ($n = 8102$) | No MHT ($n = 43$)<br>Any MHT ($n = 14$)<br>Oral E ($n = 3$)<br>Oral E + P ($n = 11$)<br>TDE ($n = 1$) | No MHT ($n = 190$)<br>Any MHT ($n = 93$)<br>Oral E ($n = 70$)<br>Oral E + P ($n = 23$)<br>TDE ($n = 12$) |
| Age (years) | – | – | 61.6 | 61.4 | 63.6 | 65.6 | 66.4 | 63.2 | 71.5 | 67 |
| BMI | – | – | 26.8 | 24.5 | 32.4 | 30 | 30.7 | 28.4 | 28.9 | 29.1 |
| Current smoker | – | – | – | – | 10.30% | 10.50% | 5.40% | 10.50% | 18% | 17% |
| Smoker, >10 pack year history | – | – | – | – | – | – | – | – | – | – |
| Personal history of VTE | – | – | – | – | 3% | 1.60% | 3.30% | 0.80% | – | – |
| Family history of VTE | – | – | 30.80% | 20.70% | – | – | – | – | – | – |
| Cancer | – | – | – | – | – | – | – | – | – | – |
| At least one risk factor for VTE | – | – | 31.80% | 25% | – | – | – | – | – | – |
| Diabetes | – | – | – | – | – | – | 5.80% | 4.40% | – | – |
| Factor V Leiden (overall) | – | – | – | – | – | – | – | – | – | – |
| Factor V Leiden (heterozygous) | – | – | – | – | – | – | – | – | 9% | 9% |

(*Continued*)

Table A1. Continued.

| *Studies 1–5* | *Blondon et al. (2013)*[24] | | *Canonico et al. (2006)*[23] | | *Curb et al. (2006)*[28] | | *Cushman et al. (2004)*[22] | | *Douketis et al. (2011)*[16] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Factor V Leiden (homozygous) | – | – | – | – | – | – | – | – | 0 | 2% |
| Prothrombin gene mutation | – | – | – | – | – | – | – | – | 4% | 2% |
| Antiphospholipid antibody | – | – | – | – | – | – | – | – | 6% | 29% |

| *Studies 6–10* | *Grady et al. (2000)*[20] | *Hoibraaten et al. (2000)*[26] | *Hurbanek et al. (2004)*[21] | *Olie et al. (2011)*[29] | *Straczek et al. (2005)*[25] |
|---|---|---|---|---|---|
| Type of study | Randomized, double-blinded, placebo-controlled | Randomized, double-blinded, placebo-controlled | Case–control | Retrospective cohort study | Case–control |
| Index study (if applicable) | HERS (The Heart and Estrogen/progestin Replacement Study) | EVTET | | MEVE | ESTHER ESTHER |
| Year | 1993–1994 | 1996–1998 | 1997–2002 | 200–2008 | 1994–2004 |
| Country | USA | Norway | USA | France | France |
| Funding | Grant Support by Wyeth-Ayerst Laboratories Novo-NordiskPharma, Research Forum, Ulleval Unviversity Hospital, Oslo | None disclosed | This study partially supported by a grant from Pierre Fabre Santé | Fondation de France, the Fondation pour la Recherche Médicale, and Institut National de la Santé et de la Recherche Médicale (INSERM) and by grants from Aventis, Besins International, Sanofi, and Servier Institute | Fondation de France, the Fondation pour la Recherche Médicale, and Institut National de la Santé et de la Recherche Médicale (INSERM) and by grants from Aventis, Besins International, Sanofi, and Servier Institute |
| Definition of postmenopause | Age >55 years and no natural menses for at least 5 years. No natural menses for at least 1 year and serum FSH >40. Documented bilateral oophorectomy. Reported bilateral oophorectomy, FSH >40 and estradiol <25 | No natural menstruation for at least 1 year | Age >50 years | 12 consecutive months without menstrual periods (unless due to hysterectomy) or had undergone bilateral oophorectomy or had ever used HRT | Amenorrhea for 12 months, bilateral ovariectomy or hysterectomy and age older than 52 years |
| Definition of VTE | Diagnosed by imaging modality<br>DVT: thrombosis of the popliteal or more proximal veins of the legs by venography, impedance plethysmography or sonography<br>PE: documentation by a nuclear lung scan that suggested high probability of a PE or by pulmonary angiography that revealed a constant intraluminal filling defect on multiple films | Diagnosed by imaging modality<br>DVT: venography or ultrasound<br>PE: lung scan, helical computed tomography or angiography<br>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 | Diagnosed by imaging modality and their thrombi were considered acute (not chronic) by the physicians involved in the patients' care<br>DVT: duplex ultrasound<br>PE: angiography, helical computed tomography of the chest, or radionucleotide lung scan | Diagnosed by imaging modality<br>DVT: compression ultrasonography or venography<br>PE: positive pulmonary angiogram or a high-probability VQ scan. | Diagnosed by imaging modality.<br>DVT: compression ultrasonography<br>PE: helical-computed tomography showing at least one intraluminal defect in one segmental pulmonary artery, high probability ventilation/perfusion scan |
| Inclusion criteria | Postmenopause with uterus<br>Age <80 years<br>Coronary disease (MI, coronary artery bypass surgery, percutaneous coronary revascularization, or angiographic evidence of at least 50% narrowing of one or more major coronary arteries) | Postmenopause<br>Age <70 years<br>Previous VTE verified by objective means or typical history and subsequent treatment | Age >50 years<br>Total, partial and revision arthroplasty, bilateral total knee arthoplasty, secondary or primary diagnosis of deep vein thrombosis or pulmonary embolism during the initial hospitalization or within 45 days of surgery | Postmenopause<br>Age 45–70 years<br>First episode VTE | Postmenopause<br>Age 45–70 years<br>First documented episode of idiopathic VTE, admitted with a priori diagnosis unrelated to hormone therapy (diseases of eye, ear, skin, respiratory and alimentary tracts, bone and joints, kidneys, infectious diseases and diabetes) |

(*Continued*)

Table A1. Continued.

| *Studies 6–10* | *Grady et al. (2000)*[20] | | *Hoibraaten et al. (2000)*[26] | | *Hurbanek et al. (2004)*[21] | | *Olie et al. (2011)*[29] | | *Straczek et al. (2005)*[25] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exclusion criteria | Coronary event within 6 months of randomization, use of hormone therapy within 3 months of randomization, history or baseline findings suggestive of venous thromboembolism, breast cancer or endometrial cancer, uncontrolled HTN, diabetes or other life-threatening illness | | Current use or use of anticoagulants in the last 3 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 2 years; or women who had taken part in other clinical trials within 12 weeks before study entry | | Degenerative joint diseases and gout, incomplete documentation of hormone replacement or other important clinical factors | | Superficial vein thrombosis, upper extremity VTE, central retinal vein obstruction | | Previous VTE, contraindication for HRT, or predisposing factor for VTE (history within previous month of surgical intervention, trauma with immobilization for >8 days, illness necessitating bed rest for >8 days, known cancer, systemic inflammatory disease), referred to clinical centers for estrogen advice or known prothrombotic mutations | |
| Outcome | Documented DVT or PE | | DVT and/or PE | | DVT and/or PE within 45 days of surgery | | Recurrent VTE event | | Idiopathic VTE | |
| Duration of follow-up | 4.1 years | | 2 years | | 45 days | | 8 years | | 5 years | |
| Number of participants | 2763 | | 140 | | 318 | | 1023 | | 789 | |
| Current anticoagulant use | Included (aspirin and warfarin) – no difference in proportion of users between groups | | Excluded | | Included – cases less likely than controls to receive pharmacological antithrombotic prophylaxis | | Excluded (follow-up commenced when anticoagulation ceased) | | Not specified | |
| Characteristics of MHT | Oral CEE + MPA | | Oral estradiol plus norethisterone | | Not defined further than: Oral E<br>Oral E + P<br>TDE | | Not defined further than:<br>Oral E<br>TDE alone<br>TDE + micronized progesterone<br>TDE + pregnane derivatives<br>TDE + norpregnane derivatives | | Oral 17β-Estradiol<br>CEE<br>TDE alone | |
| Dose | 0.625 mg/day + 2.5 mg/day | | 2mg estradiol +1 mg norethisterone | | Not stated | | Not stated | | 17β-estradiol = 1.5 mg/day (mean dose)<br>CEE: not stated<br>TDE: most <50 µg/day, 10% >100 µg/day | |
| | Treatment | Placebo | Treatment | Placebo | Cases | Controls | Non-Users of HRT | Users of HRT | Cases | Controls |
| Definition | CEE | Placebo, identical in appearance | Estradiol plus norethisterone | Equal looking placebo tablets | Underwent joint arthoplasty + concurrent diagnosis of VTE within 45 days of surgery | Aged matched | Non-user of hormone therapy but history of VTE | User of any hormone therapy + history of VTE | First documented idiopathic VTE (DVT or PE) | Age-matched and area of residence matched hospital and community controls, and matched risk factors (high blood pressure, obesity or diabetes) |

(*Continued*)

Table A1. Continued.

| *Studies 6–10* | *Grady et al. (2000)*[20] | | *Hoibraaten et al. (2000)*[26] | | *Hurbanek et al. (2004)*[21] | | *Olie et al. (2011)*[29] | | *Straczek et al. (2005)*[25] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of participants according to type of MHT | $n=1380$ | $n=1383$ | $n=71$ | $n=69$ | Any MHT ($n=18$)<br>Oral E ($n=9$)<br>Oral E+P ($n=6$)<br>TDE ($n=1$) | Any MHT ($n=49$)<br>Oral E ($n=25$)<br>Oral E+P ($n=14$)<br>TDE ($n=3$) | Non-users ($n=893$) | Users ($n=130$) | No MHT ($n=124$)<br>17β-Estradiol ($n=49$)<br>CEE ($n=2$)<br>TDE ($n=60$) | No MHT ($n=341$)<br>17β-Estradiol ($n=44$)<br>CEE ($n=0$)<br>TDE ($n=169$) |
| Age | 67 | 67 | 55.7 | 55.8 | 74 | 73 | 58.3 | 55.4 | 61.8 | 61.3 |
| BMI | | | 27.4 | 26.8 | 30 | 29 | 25.2 | 23.7 | 26.7 | 24.6 |
| >27 kg/m$^2$ | 57% | 55% | 21% | 29% | – | – | – | – | – | – |
| Overweight (25–30 kg/m$^2$) | – | – | – | – | – | – | 30.90% | 23.40% | – | – |
| Obese (>30 kg/m$^2$) | – | – | – | – | – | – | 13.20% | 8.60% | 21% | 12.50% |
| Current Smoker | 13% | 13% | – | – | – | – | – | – | 10.70% | 12.70% |
| Smoker >10 pack year history | – | – | – | – | 26.40% | 25.70% | – | – | – | – |
| Personal history of VTE | – | – | – | – | 18.50% | 9.10% | – | – | – | – |
| DVT | – | – | 52% | 49% | – | – | – | – | – | – |
| PE | – | – | 28% | 29% | – | – | – | – | – | – |
| >1 VTE | – | – | 6% | 6% | – | – | – | – | – | – |
| Family history of VTE | – | – | 25% | 18% | – | – | 48.20% | 40.30% | – | – |
| Cancer | – | – | – | – | 8.30% | 4.30% | – | – | – | – |
| At least one risk factor for VTE | – | – | – | – | – | – | – | – | 30% | 25% |
| Diabetes | 19% | 18% | – | – | 8.30% | 11.40% | – | – | – | – |
| Thrombophilia | – | – | 28% | 22% | – | – | 27.60% | 15.40% | – | – |
| Factor V Leiden (overall) | – | – | | | – | – | 14.80% | 11.60% | – | – |
| Factor V Leiden (heterozygous) | – | – | 3.70% | 0 | – | – | – | – | – | – |
| Factor V Leiden (homozygous) | – | – | – | – | – | – | – | – | – | – |
| Prothrombin gene mutation | – | – | – | – | – | – | 9.00% | 3.20% | – | – |

CEE, conjugated equine estrogen; DVT, deep vein thrombosis; E, estrogen; FSH, follicle stimulating hormone; HRT, hormone replacement therapy; HTN, hypertension; MHT, menopause hormone therapy; MPA, medroxyprogesterone acetate; P, progesterone; PE, pulmonary emboli; RCT, randomized controlled trial; TDE, transdermal estrogen; VMS, vasomotor symptoms; VTE, venous thromboembolism; WHI, Women's Health Initiative.

Table A2. Risk of VTE according to underlying risk factor and prescribed MHT.

| | *Smoking* | *Recent surgery* | *BMI 25–30 kg/m²* | *BMI >30 kg/m²* | *FVL (genotype not specified)* | *FVL (heterozygous)* | *FVL (homozygous)* | *Prothrombin gene mutation* | *Thrombophilia + history of VTE* | *History of VTE* |
|---|---|---|---|---|---|---|---|---|---|---|
| Any MHT | NS | – | – | – | – | – | – | – | – | – |
| Oral estrogen (type not defined) | OR 1.73 | NS | – | – | – | – | – | – | – | OR 6.40 |
| Oral estrogen + progestogen (not defined) | – | NS | – | – | OR 17.10 | – | – | – | – | – |
| CEE + MPA | – | HR 4.90 | HR 3.80 | HR 5.61 | – | OR 2.60 | OR 7.50 | OR 2.43 | – | – |
| Oral Estradiol + Norethisterone | – | – | – | – | – | NS | – | – | RR 2.60 | – |
| CEE alone | – | – | – | – | OR 4.00 / 6.30 | OR 4.00 | – | OR 2.61 | – | – |
| Oral estradiol alone | – | – | OR 3.70 | OR 5.10 | OR 6.30 | – | – | – | – | – |
| TDE alone | – | – | NS | NS | NS | – | – | NS | – | NS |
| TDE + micronized progesterone | – | NS | – | – | – | – | – | – | – | NS |
| TDE + norpregnane derivative | – | – | – | – | – | – | – | – | – | HR 4.70 |

Note: Further outcome data can be viewed in Supplementary Material 3. BMI, body mass index; CEE, conjugated equine estrogen; FVL, factor V Leiden; HR, hazard ratio; MHT, menopause hormone therapy; NS, non-significant result; OR, odds ratio; RR, relative risk; TDE, transdermal estrogen; VTE, venous thromboembolism.