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REVIEW

The impact of micronized progesterone on cardiovascular events – a systematic review

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ABSTRACT

Biologically identical menopausal hormone therapy (MHT) including micronized progesterone (MP) has gained much attention. We aimed to assess the impact of MP in combined MHT on venous and arterial thromboembolism (VTE/ATE) (e.g. deep venous thrombosis/pulmonary embolism, myocardial infarction [MI] and ischemic stroke). Articles were eligible if they provided endpoints regarding cardiovascular events and use of exogenous MP. Literature searches were designed and executed for the databases Medline, Embase, CINAHL, the Cochrane Library, ClinicalTrials.gov and interdisciplinary database Web of Science. Twelve studies consisting of randomized controlled trials (RCTs), case–control studies and prospective or retrospective cohort studies were included, and risk of bias was assessed. Only a minority assessed thromboembolic events as a primary endpoint, showing that in contrast to norpregnane derivatives, primary and recurrent VTE risk was not altered by combining estrogens with MP, which was also true for ischemic stroke risk. Similarly, in placebo-controlled RCTs assessing VTE/ATE as adverse events there were no significant intergroup differences. Studies on MI as a primary endpoint are missing. In conclusion, while available data suggest that MP as a component in combined MHT may have a neutral effect on the vascular system, more RCTs investigating the impact of MP alone or in combined MHT on vascular primary endpoints are needed.

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Introduction

Many menopausal women have been seeking menopausal hormone therapy (MHT) for climacteric symptom relief. However, since the publication of the results of the Women's Health Initiative (WHI) trial [1] there have been concerns about the safety of MHT with respect to cardiovascular risk. The WHI showed an increased risk for coronary heart disease, venous thromboembolism (VTE) and ischemic stroke in women taking conjugated equine estrogens (CEE), 0.625 mg/day, plus medroxyprogesterone acetate (MPA), 2.5 mg/day [1]. Subsequent analyses and studies have already shown that the route of estrogen application has a decisive role. Oral estrogen application is associated with a significantly increased risk of VTE in comparison to transdermal estrogen application [2–4].

In symptomatic menopausal women with an intact uterus, current international guidelines recommend combined estrogen–progestogen therapy to ensure endometrial safety [5–7]. Therefore, the question arises of whether the type of progestogen also has an impact on vascular events. Progestogens can be either synthetic (progestins) or biologically identical (micronized progesterone [MP]). MP is available either, for example, as a US Food and Drug Administration (FDA)/European Medicines Agency (EMA)-approved drug or as a customized treatment by compounding pharmacies. Internationally, MP is available at different dosages and routes of application. Also, indication and approval by regulatory authorities may differ from country to country. In Europe, systemic MP is available as a capsule (100 mg, 200 mg) for vaginal or oral application, or as a vaginal gel (8% corresponding to 90 mg MP).

The aim of this systematic review was to assess the impact of exogenous MP on vascular events like VTE, coronary heart disease and stroke.

Materials and methods

Information sources and search strategy

To identify all potentially relevant documents on the topic, systematic literature searches were designed and executed according to the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 [8] and PRISMA-Search [9]. An initial search strategy in Medline was drafted by H.J. and tested against a list of core references to see whether they were included in the search results. After refinement and consultation, search strategies were set up for each information source based on database-specific controlled vocabulary (thesaurus terms/subject headings) and

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Supplemental data for this article can be accessed here.

text words. No limits have been applied in any database considering study types, languages, publication years or any other formal criteria. Beside the medical bibliographic databases Medline, Embase, CINAHL and the Cochrane Library, one international trials registry (ClinicalTrials.gov) and the interdisciplinary database Web of Science have been searched. The searches were run on 4 February 2021. The search topics selected were 'hormone replacement therapy', 'micronized progesterone' and endpoints like cardiovascular events, thromboembolism, stroke and cardiac infarction. In addition to electronic database searching, reference lists and bibliographies from relevant publications were checked for relevant studies. The final detailed search strategies are presented in Supplementary files.

Study selection process

All identified citations were imported into EndNote and duplicates were removed. The screening of titles and abstracts was performed by two independent reviewers (L.M.K., A.S.) and tested against the inclusion and exclusion criteria. All randomized controlled trials (RCTs), cohort studies, cross-sectional studies and case–control studies with postmenopausal female participants were considered. Moreover, systematic reviews and meta-analysis have been screened for relevant studies. Included studies had to provide endpoints regarding cardiovascular events in postmenopausal women and the use of exogenous MP in comparison to non-use or estrogen-only use. Conference abstracts, editorials or letters were not considered due to low evidence. Studies assessing transgender women or patients with Turner syndrome have been excluded because this review was designed to focus on MHT and not other hormone therapies. The full texts of all studies included after screening by title and abstract were read, analyzed and reviewed for inclusion and exclusion criteria (Figure 1).

Data extraction

Information from the included studies has been collected for data extraction according to a predefined protocol prepared by two reviewers (L.M.K., P.S.). For all studies, details about the study design, sample size, mean age and body mass index (BMI) of the participants, location, study duration, and MHT dosage and application regimen were sought. The individual endpoints of cardiovascular events were included and, for studies assessing cardiovascular events as adverse events, primary endpoints were also recorded. Results were either reported by odds ratio (OR), hazard ratio (HR) or case numbers and *p* values for significance of intergroup difference.

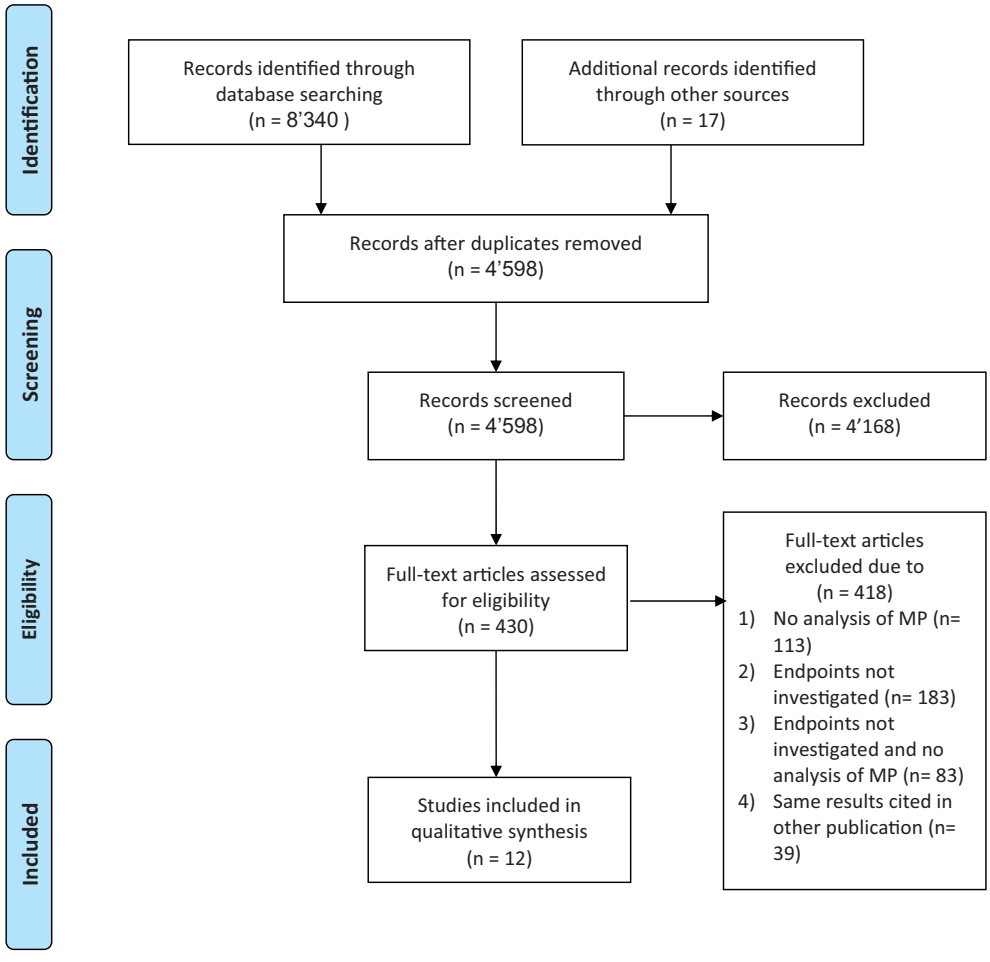

Figure 1. The PRISMA flowchart of study inclusion. MP, micronized progesterone; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

There was no meta-analysis performed due to a small number of included studies for each outcome. Moreover, study designs varied, as did the applied drug dose, formulation and route of administration or details were not given at all for some MHT regimens. In conclusion, meta-analysis was precluded due to incomparability and insufficient data.

Data analysis and risk-of-bias assessment

The risk of bias has been assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [10] for all included RCTs and the Newcastle–Ottawa scale [11] was used to assess the risk of bias for included non-randomized studies. The assessment by the first author (L.M.K.) was verified by a second reviewer (A.S.).

Results

Characteristics of selected articles

The described search strategies yielded a total of 8340 articles published between 1968 and 2021, out of which 4598 unique articles were identified after exclusion of duplicates.

Overall, 12 articles were included in this systematic review [12–23] (Tables 1 and 2). Study designs were either RCTs [12–14,16,22,23], case–control studies [15,21] and prospective [17,19,20] or retrospective [18] cohort studies, respectively. Study size ranged from 107 [13] to 1845 [12] in RCTs, from 871 [21] to 15,302 [15] in case–control studies and from 189 [19] to 80,308 [20] participants in cohort studies. Study duration ranged from 1 year [12,13] to 5 years [14] in RCTs, from 3 years [15] to 6 years [21] in case–control studies and from 1 year [19] to 10 years [20] in cohort studies. The mean age ranged between 49 years [18] and 64 years [14]. Mean BMI was either normal [13,20,21], obese [12,14,16–18,21,22,24] or not reported [15,19]. MHT regimens contained either CEE [13,16,21–23], estradiol (E2) [12,14–16,18–21] or estriol [19], respectively, with either oral [12–17,20–23], sublingual [19] or transdermal [15–18,20,21] route of application. Estrogen dosages ranged from low dose [12,13,16] to standard dose [12–14,16,18,19,22,23]. The progestogen component was either MP or a progestin (pregnane derivatives [15,17,20,21] – in particular MPA [22,23] or dydrogesterone (DYD) [13] – norpregnane derivatives [15,17,20,21], nortestosterone derivatives [15,20]). MP was applied either orally [12,13,16,18,22,23], sublingually [19] or vaginally [14] in a sequentially [13,14,16,18,22,23] or continuously combined [12,18] regimen at dosages ranging from 45 mg/day [14] to 200 mg/day [16,18,22,23], respectively. Four studies did not clearly specify the MHT regimen and dosage [15,17,20,21]. There was no study investigating the impact of MP alone without application of estrogen. Different cardiovascular events have been assessed (see Tables 1 and 2); however, no study has been conducted with myocardial infarction (MI) as a primary endpoint.

Micronized progesterone and cardiovascular events (primary endpoint)

Our search revealed four studies [15,17,20,21] on the impact of MHT containing MP on cardiovascular events assessed as primary endpoints. These studies focused on primary [20,21] or recurrent [17] VTE, respectively. Only one study [15] assessed the impact of MHT containing MP on ischemic stroke risk.

With regard to primary VTE, the prospective cohort study Etude Epidémiologique de femmes de la Mutuelle Générale de l'Education Nationale (E3N) [20] and the multicenter case–control study Estrogen and Thromboembolism Risk (ESTHER) [21] showed similar results in women with no personal history or predisposing factors for VTE. Oral but not transdermal estrogen therapy was associated with a higher risk for VTE (oral estrogen: OR 4.2, 95% confidence interval [CI] 1.5–11.6 [ESTHER] and HR 1.7, 95% CI 1.1–2.8 [E3N] vs. transdermal estrogen: OR 0.9, 95% CI 0.4–2.1 [ESTHER] and HR 1.1, 95% CI 0.8–1.8 [E3N]; Table 1) [20,21]. There were no significant associations of VTE risk with MP and pregnane derivatives (MP: OR 0.7, 95% CI 0.3–1.9 [ESTHER] and HR 0.9, 95% CI 0.6–1.5 [E3N]) [20,21].

The prospective cohort study Menopause, Estrogen, and Veins Study (MEVE) assessed the impact of MHT containing various progestogens on VTE relapse [17]. It supports the E3N and ESTHER findings, showing an increased risk for recurrent VTE in oral but not transdermal estrogen user (oral estrogen: HR 6.4, 95% CI 1.5–27.3 vs. transdermal estrogen: HR 1.1, 95% CI 0.2–8.1; Table 1). In combined MHT users, MP was not associated with an increased risk of VTE relapse (HR 1.0, 95% CI 0.3–3.2).

The nested case–control 'French National Health Insurance System Study' assessed the impact of MHT containing MP on ischemic stroke risk [15]. Again, oral but not transdermal estrogens were associated with an increased ischemic stroke risk in a dose-dependent manner. Similar to observations related to VTE, concomitant MP again did not alter the ischemic stroke risk.

Micronized progesterone and cardiovascular events (adverse events)

Our search revealed eight studies [12–14,16,18,19,22,23] on the impact of MHT containing MP on cardiovascular events assessed as adverse events (Table 2). In the RCT Postmenopausal Estrogen/Progestin Interventions (PEPI), postmenopausal women were randomized to either oral estrogen only (CEE), continuously combined MHT (CEE + MPA), sequentially combined MHT (CEE + MPA, CEE + MP) or placebo, respectively [23]. During 3 years of treatment, in 875 women 10 cases of VTE were diagnosed, of which two occurred in the CEE + MP group and none in the placebo group. In addition, one case of cardiac arrest, one case of cerebral vascular accident, one case of transient ischemic attack and two cases of MI were diagnosed as cardiovascular events. Again, none of these events were seen in the placebo group, whereas three occurred in the CEE + MP

Table 1. Overview of studies investigating the impact of micronized progesterone (MP) on cardiovascular events as the primary endpoint.

Author (year)	*Study design*	*Sample size, mean age (years) and BMI (kg/m²) of participants*	*Country*	*Study duration*	*MHT dosage and application regimen*	*Endpoints*	*Results*
Canonico (2007)	Multicenter case–control study (ESTHER study)	Cases with first documented idiopathic VTE ($n = 271$): age 61.6 ± 6.7, BMI 27.0 ± 5.7 Controls ($n = 610$): age 61.5 ± 6.6, BMI 24.5 ± 4.8	France	6 years	MHT regimen and dosage not specified; tE (26.0% of cases, 29.9% of controls), oE (17.4% of cases, 6.5% of controls), E alone (5.4% of cases, 6.7% of controls), EPT users: MP (7.4% of cases, 10.4% of controls), pregnane derivatives (DYD, medrogestone, CMA, CPA, MPA) (15.1% of cases,13.1% of controls), norpregnane derivatives (NOMAC, promegestone) (15.5% of cases, 6.1% of controls)	OR for idiopathic VTE (PE, DVT)	Adjusted[a] OR (95% CI): oE 4.2 (1.5–11.6), tE 0.9 (0.4–2.1), MP 0.7; (0.3–1.9)
Canonico (2010)	Prospective cohort study (E3N cohort)	$N = 80,308$ women, age 54.0 ± 4.3, BMI 22.6 ± 3.2	France	10.1 ± 4.6 years	MHT regimen and dosage not specified, I: never MHT use (reference group), II: past MHT use, III: current use of oE (mostly E2), IV: current use of tE (mostly E2), V: no P use, VI: current use of E + MP, VII: current use of E + pregnane derivatives (DYD, medrogestone, CMA, CPA, MPA), VIII: current use of E + norpregnane derivatives (NOMAC, promegestone), IX: current use of E + nortestosterone derivatives (NETA), X: current other treatment, XI: unknown	HRs for idiopathic VTE (PE, DVT) by Cox's proportional hazards models with age as the basic time scale	Adjusted[b] HR (95% CI): oE 1.7 (1.1–2.8), tE 1.1 (0.8–1.8), E + MP 0.9 (0.6–1.5)
Olie (2011)	Prospective cohort study (MEVE cohort study)	$N = 1023$ women with confirmed first VTE, age at inclusion 57.9 ± 6.2, age at recurrence 62.0 ± 6.6, BMI 25.0 ± 4.5	France	Mean follow-up: 79 months after discontinuation of anticoagulation therapy	MHT regimen and dosage not specified, I: non-users (reference group), II: oE, III: tE ± P, IV: tE alone, V: tE + MP, VI: tE + pregnane derivatives, VII: tE + norpregnane derivatives	HRs for recurrent VTE (PE, DVT) by Cox's proportional hazards models with age as the basic time scale	Adjusted[c] HR (95% CI): oE 6.4 (1.5–27.3), tE ± P 1.0 (0.4–2.4), IV: tE alone 1.1 (0.2–8.1), V: tE + MP 1.0 (0.3–3.2)
Canonico (2016)	Case–control study	$N = 15,302$ women, age 56.7 ± 2.8 (cases), 56.6 ± 2.7 (controls), BMI not reported	France	3 years	MHT regimen and dosage not specified, I: non-users (reference group), II: oE2, III: tE2, IV: E2 + MP, V: E2 + pregnane derivatives, VI: E2 + norpregnane derivatives, VII: E2 + nortestosterone derivatives	OR for ischemic stroke	Adjusted[d] OR (95% CI): oE2 1.58 (1.01–2.49), tE2 0.83 (0.56–1.24), E2 + MP 0.78 (0.49–1.26)

BMI, body mass index; CI, confidence interval; CMA, chlormadinone acetate; CPA, cyproterone acetate; DVT, deep vein thrombosis; DYD, dydrogesterone; E, estrogen; E2, estradiol; E3N, Etude Epidémiologique de femmes de la Mutuelle Générale de l'Education Nationale; EPT, estrogen–progestogen therapy; ESTHER, Estrogen and Thromboembolism Risk; HR, hazard ratio; MEVE, Menopause, Estrogen, and Veins Study; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; NOMAC, nomegestrol acetate; o, oral; OR, odds ratio; P, progestogen; PE, pulmonary embolism; t, transdermal; VTE, venous thromboembolic event(s).

[a]Adjusted for obesity status, familial history of VTE, history of varicose veins, education, age at menopause, hysterectomy and cigarette smoking.

[b]Adjusted for BMI, parity, education level, and time period (before or after 2003 to take into account the changes in hormone therapy use after the publication of the Women's Health Initiative [WHI] trial results).

[c]Adjusted for age, overweight, obesity and characteristics of the first event (idiopathic or secondary).

[d]Adjusted for antidiabetic medication, antihypertensive medication, antidyslipidemia medication and long-term chronic disease.

Table 2. Overview of studies investigating the impact of micronized progesterone (MP) on cardiovascular events as adverse events.

Author (year)	Study design	Sample size, mean age (years) and BMI (kg/m^2) of participants	Country	Study duration	Treatment arms: dosage and application regimen	Endpoints	Results
Miller (1995)	PC-RCT (PEPI trial)	$N = 875$ women, age 56.1 ± 4.3, BMI 26.0 ± 4.5 [24]	USA	3 years	I: placebo, II: oCEE 0.625 mg/day, III: oCEE 0.625 mg/day + seq. oMPA 10 mg/day, IV: oCEE 0.625 mg/day + cont. oMPA 2.5 mg/day, V: oCEE 0.625 mg/day + seq. oMP 200 mg/day	Primary endpoints: serum HDL-cholesterol, insulin, fibrinogen, systolic blood pressure, cardiovascular events (cardiac arrest, CVA, TIA, MI) and VTE (PE, DVT, SP) as adverse events	Cardiovascular events $n = 5$ (I: placebo 0, II: CEE 1, III: CEE + seq. MPA 1, IV: CEE + cont. MPA 0, V: CEE + seq. MP 3; $p = 0.29$) VTE $n = 10$ (I: placebo 0, II: CEE 4, III: CEE + seq. MPA 2, IV: CEE + cont. MPA 2, V: CEE + seq. MP 2; $p = 0.42$)
Whiteman (1999)	PC-RCT (PEPI sub-analysis)	$N = 875$ women, age 56.1 ± 4.3, BMI 26.0 ± 4.5	USA	3 years	I: placebo, II: oCEE 0.625 mg/day, III: oCEE 0.625 mg/day + seq. oMPA 10 mg/day, IV: oCEE 0.625 mg/day + cont. oMPA 2.5 mg/day, V: oCEE 0.625 mg/day + seq. oMP 200 mg/day	Correlation of predisposing factors for women using MHT to VTE (PE, DVT, SP)	10 women with VTE: PE $n = 2$, DVT $n = 2$, SP $n = 6$ Risk of VTE did not vary by progestogen used, participants assigned to MHT at almost two-fold increased risk of DVT and PE compared to general population, women with VTE had a significantly lower mean fibrinogen level (249.0 mg/dl) than those without (280.8 mg/dl) ($p < 0.03$)
Harman (2014)	PC-RCT (KEEPS)	$N = 727$ randomized, age 52.7 ± 2.6 years, BMI 26.2 ± 4.3	USA	34.6–37.6 months	I: placebo, II: oCEE 0.45 mg/day + seq. oMP 200 mg/day, III: tE2 50 μg/day + seq. oMP 200 mg/day	Primary endpoint: annual change in CIMT, cardiovascular events (MI, venous thrombotic disease, stroke) as adverse events	MI: placebo $n = 0$, oCEE + MP $n = 0$, tE2 + MP $n = 1$ Venous thrombotic disease: placebo $n = 1$, oCEE + MP $n = 0$, tE2 + MP $n = 1$ Stroke: placebo $n = 0$, oCEE + MP $n = 0$, tE2 + MP $n = 0$
Hodis (2016)	PC-RCT (ELITE)	$N = 643$ women: early PM $n = 271$, late PM $n = 372$, age: early PM 55.4, late PM 63.6, BMI: early PM 26.0 (placebo), 26.2 (oE2 + MP), late PM 26.4 (placebo), 27.2 (oE2 + MP)	USA	Median 4.8 years (range 0.5–6.7 years)	I: placebo, II: oE2 1 mg/day + seq. vMP 45 mg/day	Primary endpoint: rate of change in CIMT, cardiovascular events (MI, TIA, DVT, PE, unstable angina) as adverse events	Early PM ($p = 0.62$): MI, placebo $n = 1$, oE2 + MP $n = 0$; TIA, placebo $n = 1$, oE2 + MP $n = 0$ Late PM ($p = 0.58$): MI, placebo $n = 2$, oE2 + MP $n = 1$; TIA, placebo $n = 1$, oE2 + MP $n = 1$; DVT, placebo $n = 2$, oE2 + MP $n = 1$; PE, placebo $n = 0$, oE2 + MP $n = 2$; unstable angina. placebo $n = 0$, oE2 + MP $n = 2$
Lobo (2019)	PC-RCT (REPLENISH trial)	$N = 1845$ women, age 54.6, BMI 26.7	USA	1 year	I: placebo, II: oE2 1 mg + cont. oMP 100 mg, III: oE2 0.5 mg + cont. oMP 100 mg, IV: oE2 0.5 mg + cont. oMP 50 mg, V: oE2 0.25 mg + cont. oMP 50 mg	Primary endpoints: lipid, coagulation and glucose parameters, cardiovascular events (CHD, DVT, stroke) as adverse events	CHD: 3 events in 2 women (not considered treatment related): unstable angina ($n = 1$ E2/MP 0.5/50), angina and coronary artery disease ($n = 1$ E2/MP 1/100) [25], DVT (possibly related to treatment): $n = 1$ E2/MP 0.5/50, stroke $n = 0$

(*continued*)

Table 2. Continued.

Author (year)	Study design	Sample size, mean age (years) and BMI (kg/m^2) of participants	Country	Study duration	Treatment arms: dosage and application regimen	Endpoints	Results
Xue (2016)	Head-to-head RCT	$N = 107$ women, age: I 53.7 ± 4.2, II 53.1 ± 3.1, III 53.4 ± 4.5; BMI: I 23.6 ± 3.1, II 22.8 ± 3.0, III 23.6 ± 2.3	China	1 year	I: oCEE 0.3 mg/day + seq. oMP 100 mg/day, II: oCEE 0.625 mg/day + seq. oMP 100 mg/day, III: oCEE 0.625 mg/day + seq. oDYD 10 mg/day	Primary endpoints: lipid and carbohydrate parameters, body composition, blood pressure, cardiovascular and VTE as adverse events	No cardiovascular and VTE occurred
Mahmud (2010)	Prospective cohort study	$N = 189$ women, age 53.7 ± 6.9, BMI not provided	USA	At least 12 months of MHT and average follow-up of 30 months	All: t (or sublingual) Biest cream (E2 1 mg + E3 4 mg/g) 2 × 0.5 g/day initially, adjusted according to symptoms, achieved blood level: 50 pg/ml + sublingual MP (50–100 mg), achieved blood level: 4 ng/ml, additionally: in 125 women testosterone perivaginal, (achieved blood level: 25 ng/dl) and/or in 146 women DHEA (usual dose 25 mg/day, achieved blood level: 120 µg/dl)	Primary endpoints: symptom control, cardiovascular events (MI, thromboembolism, stroke) as adverse events	No cardiovascular event occurred
Perez-Lopez (2010)	Retrospective cohort study	$N = 273$ women, age at baseline 49.0 ± 6.2, BMI at baseline: I 28.18 ± 4.18.II 28.54 ± 4.48, III 27.61 ± 5.03, IV 26.91 ± 5.03	Spain	Retrospective (10 years of MHT)	I: control (no MHT), II: tE2 50 µg/day, III: tE2 50 µg/day + seq. oMP 200 mg/day, IV: tE2 50 µg/day + cont. oMP 100 mg/day	Primary endpoints: Systemic Coronary Risk Evaluation (SCORE) values, cardiovascular events (MI, stroke) as adverse events	Stroke: control $n = 0$, E2 $n = 0$, E2 + seq. MP $n = 0$, E2 + cont. MP $n = 1$; MI: control $n = 0$, E2 $n = 1$, E2 + seq. MP $n = 0$, E2 + cont. MP $n = 0$

BMI, body mass index; CEE, conjugated equine estrogens; cont., continuously combined; CHD, coronary heart disease; CIMT, carotid artery intima-media thickness; CVA, cerebral vascular accident; DHEA, dehydroepiandrosterone; DVT, deep vein thrombosis; DYD, dydrogesterone; E2, estradiol; E3, estriol; ELITE, Early versus Late Intervention Trial with Estradiol; HDL, high-density lipoprotein; KEEPS, Kronos Early Estrogen Prevention Study; MHT, menopausal hormone therapy; MI, myocardial infarction; MPA, medroxyprogesterone acetate; o, oral; PC-RCT, placebo-controlled randomized clinal trial; PE, pulmonary embolism; PEPI, Postmenopausal Estrogen/Progestin Interventions; PM, postmenopause; seq., sequentially combined; SP, superficial phlebitis; t, transdermal; TIA, transient ischemic attack; v, vaginal; VTE, venous thromboembolic event(s).

group. However, overall, no significant intergroup differences for venous and arterial thromboembolic events were found ($p = 0.29$ and $p = 0.42$, respectively). Whiteman et al. conducted a sub-study of the PEPI trial assessing the association between predisposing factors in MHT users on VTE risk [22]. Their analyses revealed a two-fold increased risk of DVT and PE in oral MHT users (oral CEE combined with oral MPA or oral MP) compared to the general population, with the progestogen type displaying no significant impact (Table 2).

In the RCT Kronos Early Estrogen Prevention Study (KEEPS), postmenopausal women were randomized to either oral combined MHT (CEE + oral MP), transdermal combined MHT (E2 + oral MP) or placebo, respectively [16]. During 4 years of treatment, in 727 women there were one MI (transdermal MHT) and two VTE cases (transdermal MHT, placebo group) but no stroke. Overall, no significant intergroup differences for venous and arterial thromboembolic events were found. Two further RCTs, Early versus Late Intervention Trial with Estradiol (ELITE) [14] and REPLENISH [12], assessed the impact of oral E2 combined with either vaginal MP [14] or oral MP [12] for either 5 years [14] or 1 year [12], respectively. In the ELITE trial, in 643 women there was one case of MI in the early postmenopausal group ($n = 1$ placebo, $n = 0$ MHT) and three cases in the late postmenopausal group ($n = 2$ placebo, $n = 1$ MHT), one case of transient ischemic attack in the early postmenopausal group ($n = 1$ placebo, $n = 0$ MHT) and two cases in the late postmenopausal group ($n = 1$ placebo, $n = 1$ MHT), and five cases of VTE in the late postmenopausal group ($n = 2$ placebo, $n = 3$ in MHT), respectively. Overall, no significant intergroup differences for venous and arterial thromboembolic adverse events were found ($p = 0.62$ in early postmenopausal group, $p = 0.58$ in late postmenopausal group). In the REPLENISH trial, in 1845 women there were three events of coronary heart disease in two women in the MHT treatment arms that were not considered treatment related, no cases of stroke in any group and one case of DVT possibly related to treatment in the MHT treatment arm. Again, overall, no significant intergroup differences for venous and arterial thromboembolic adverse events were found. One further head-to-head RCT [13] compared the impact of oral CEE combined with either oral MP or oral DYD, respectively. During 1 year of treatment, in 107 women there were no cases of venous and arterial thromboembolic adverse events. In one prospective cohort study [19], 189 women received transdermal estrogen-only therapy combined with sublingual MP. Some women also received vaginal dehydroepiandrosterone and/or perivaginally applied testosterone in varying, serum level-adapted dosages. Again, during at least 1 year of treatment and an average follow-up of 30 months, there were no venous and arterial thromboembolic adverse events. Finally, in one retrospective cohort study [18], women using either transdermal E2 alone or combined with oral MP (sequential or continuous regimen) were compared to controls. After 10 years of treatment, in 273 women one case of stroke (combined MHT) and one case of MI (transdermal estrogen-only therapy) were diagnosed.

Risk of bias

All included RCTs [12–14,16,22,23] showed a low risk of bias in the domain of the randomization process and with respect to bias due to missing outcome data (Supplemental Figure S1). However, most studies did not provide enough information to assess bias due to deviations from intended intervention and partly to assess bias in selection of the reported result. Two studies [12,22] showed a high risk of bias in measurement of the outcome of interest (cardiovascular events), since there was no statistical analysis performed and information about how adverse events have been assessed was not provided.

Both of the included case–control studies [15,21] overall showed low risk of bias in all domains (selection, comparability and exposure), with some limitation due to missing information about ascertainment of exposure and non-response rate in the ESTHER study (Supplemental Table S1).

A difference in risk of bias could be seen between cohort studies assessing cardiovascular events as the primary endpoint [17,20] and those registering the outcomes as an adverse event [18,19] (Supplemental Table S2). While the studies conducted by Canonico et al. [20] and Olie et al. [17] in total showed low risk of bias in the selection, comparability and outcome domain, there were some concerns and a high risk of bias in the cohort study conducted by Perez-Lopez et al. [18] in the selection and comparability domains. The study by Mahmud [19] showed high risk of bias or concerns in all three domains, especially due to low representativeness of the cohort and short length of the follow-up.

Discussion

In particular since 2002, there has been considerable debate about the role of MHT in cardiovascular disease. Initially, the safety concern was high as both WHI studies revealed an increased risk of venous and arterial thromboembolism (VTE/ATE) [1,26]. A subsequent WHI sub-analysis found that age and years since menopause had a significant impact [27]. Later, at least in younger hysterectomized women, estrogen-only therapy was found to have a sustainably protective effect on the heart [28] which made others consider MHT for prevention of cardiovascular disease [29]. As in the USA, oral CEE and oral CEE + MPA have been the dominant MHT formulations, the question arose of whether other application routes and MHT types display a different risk profile. Thus, our systematic review aimed to assess the role of biologically identical MP in combined MHT on VTE/ATE.

We found that, overall, only few studies focused on the impact of MP in combined MHT on VTE/ATE, with only a minority assessing thromboembolic events as a primary endpoint. However, there was the homogeneous observation of neutral effects on primary and recurrent VTE risk when MP was used as a component in combined MHT in VTE (E3N, ESTHER, MEVE), which was also true for ischemic stroke risk (French nested case–control study). Similarly, in placebo-controlled RCTs assessing VTE/ATE as adverse events (PEPI, KEEPS, ELITE, RELENISH) there were no significant intergroup

differences for VTE, MI and stroke, which was supported by some smaller head-to-head RCTs and prospective and retrospective trials, respectively. However, comparability of the latter is limited due to different study designs, MHT regimens and dosages and very low case numbers of reported adverse events.

Generally, the four large studies assessing cardiovascular events as primary endpoints showed homogeneous results [15,17,20,21]. This might also be contributed to similar study populations, since all studies were conducted in France, and similar study designs of observational studies. However, risk of bias was low for all four studies. Results slightly differed in studies assessing cardiovascular events as adverse events. While most studies did not show any intergroup differences [12,14,16,18,23], some did not observe any cardiovascular events at all [13,19]. These differences can be explained by the short study duration and small study population of both studies. While Whiteman et al. [22] also showed no risk alteration using different progestin types, an almost two-fold increased risk of DVT and PE in women assigned to MHT compared to the general population was calculated. These results might be biased, because of the low total numbers of cardiovascular events observed and the combination of the progestins with an orally applied estrogen. Both cohort studies assessing cardiovascular events as adverse events [18,19] showed high risk of bias in comparability since no adjustments between the exposed and non-exposed cohort have been made. Therefore, interpretation is limited, also due to short follow-up and selection bias. The study design was not optimal to answer our review question.

Although there was no statistical analysis and direct comparison between the different progestin groups and therefore comparisons and interpretation should be regarded carefully, one remarkable difference in progestin groups should be noticed. All three larger studies assessing primary and recurrent VTE and stroke risk observed a significantly higher risk in women receiving MHT containing norpregnane derivatives, while it was not altered by combining estrogens with MP (risk for primary VTE: MP, OR 0.7, 95% CI 0.3–1.9 [ESTHER] and HR 0.9, 95% CI 0.6–1.5 [E3N] vs. norpregnane derivatives, OR 3.9, 95% CI 1.5–10.0 [ESTHER] and HR 1.8, 95% CI 1.2–2.7 [E3N] [20,21]; risk for recurrent VTE: MP, HR 1.0, 95% CI 0.3–3.2 vs. norpregnane derivatives, HR 4.7, 95% CI 1.1–20.0 [17]; risk for stroke: MP, OR 0.78, 95% CI 0.49–1.26 vs. norpregnane derivatives, OR 2.25, 95% CI 1.05–4.81 [15]). Even though the comparability is very limited, these findings might suggest that the risk varies depending on the progestin and, in this context, MP might have a more favorable profile than norpregnane derivatives.

These reported neutral effects of MP in combined MHT on vascular events has been supported by studies addressing vascular surrogate markers. For example, some of the included studies also assessed such parameters showing neutral effects of combined MHT containing MP on body weight, blood pressure (KEEPS [16], ELITE [14], PEPI [23]), and a significantly lowering effect on fasting serum glucose compared to placebo [16,23]. The latter finding has been supported by a systematic review [30]. In respect to serum lipids, PEPI reported the most favorable effect on high-density lipoprotein-cholesterol for combined MHT containing MP [23]. Even if other clinical studies failed to demonstrate a significantly more favorable effect of MP compared to other progestogens, predominantly neutral effects on lipid metabolism have been observed [31]. Within the coagulation system, mainly the association of oral estrogens versus non-oral estrogens in relation to procoagulant markers has been well reported [32]. So far, in clinical studies, clear differences between pharmacologic classes of concomitant progestogens have not yet been described [33]. Only one clinical study demonstrated an increased activated protein C resistance in women using MHT containing norpregnane derivatives compared to those using MP [34], supporting the clinical observations in ESTHER and E3N

However, the identified clinical trials also have specific limitations. While the French studies ESTHER [21], E3N [20] and MEVE [17] included women using both or either oral or transdermal E2, the US-American PEPI [22,23] trial only randomized subjects to oral estrogens. Thus, ESTHER, E3N and MEVE were able to compare the VTE risk in oral and transdermal estrogen users, with the VTE risk being significantly higher in oral estrogen users [17,20,21]. When assessing the impact of progestogen type in combined MHT, data were adjusted for several but varying confounding factors. For example, in ESTHER, information on VTE risk factors such as varicose veins, prothrombotic mutations and family VTE history was available [21]. In contrast, in E3N, prothrombotic mutations or family VTE history were not assessed [20]. In MEVE, data were adjusted for age, BMI and characteristics of the first VTE event (idiopathic or secondary) [17]. Furthermore, oral and transdermal estrogen users were combined for statistical analysis in ESTHER, E3N and MEVE, thus weakening the informative value [17,20,21]. Nevertheless, the authors of all three studies indicated that there was no statistical interaction between the route of estrogen administration in combined MHT on VTE risk. Further limitations of identified prospective and retrospective trials (ESTHER, E3N, MEVE) were heterogeneous MHT regimens with different hormone types, application modes, dosages and treatment durations, thus providing insufficient sample sizes for further subanalyses. Only one case–control study assessed the impact of progestogen type in combined MHT on ischemic stroke risk [15]. Although the absolute numbers of ischemic stroke cases ($n = 3144$) and controls ($n = 12{,}158$) were high, the prevalence of MHT use within 3 months prior to the event was quite low (cases 6.2%, controls 6.8%), making further subanalyses difficult. Still, data were adjusted for some ischemic stroke risk factors based on drug reimbursement data (e.g. diabetes mellitus, hypertension, dyslipidemia) while other ischemic stroke risk factors such as BMI and smoking status could not be ascertained. Surprisingly, there was no study assessing the impact of progestogen type in combined MHT on MI risk as a primary endpoint. In studies assessing VTE/ATE as adverse events, the absolute numbers of such events were low and thus statistical power was insufficient to draw valid conclusions [12–14,16,18,19,23]. Another potential bias is age at MHT initiation. The RCT ELITE was designed to test

the so-called timing hypothesis [35]. Accordingly, in women in the early and late menopause randomized to either MHT or placebo, respectively, carotid intima-media thickness was examined prospectively. As expected, in the group of early menopausal women there were less vascular adverse events than in the group of late menopausal women. However, the number of vascular adverse events did not significantly differ between treatment groups in either stratum.

The impact of progestogen type in combined MHT on vascular risk has only been addressed by the European Menopause and Andropause Society (EMAS) so far [36], recommending the use of transdermal estrogens combined with MP or DYD in women at increased VTE risk. For clinical practice further investigations, especially RCTs are needed in order to improve guidelines with respect to the concomitant progestin in MHT and to verify the neutral effect of MP on the cardiovascular system, which would make it a good choice in combined MHT.

Limitations

Although our systematic review provides some strengths, such as a broad systematic literature research including multiple medical bibliographic databases as well as an international trials registry and an interdisciplinary database, screening of titles and abstracts by two independent reviewers and data extraction according to a predefined protocol, there have also been some limitations. No quantitative synthesis and statistical analysis have been performed due to incomparability in study designs and insufficient data. No graphical or statistical tests to investigate publication bias could be performed, because there were not enough studies for each outcome of interest. This review has not been registered beforehand.

Comparability and interpretation of the observations was limited due to different study designs and few observed events in RCTs.

Conclusion

Menopausal women with an intact uterus using estrogen therapy should receive a progestogen for endometrial protection. While transdermal estrogens are considered to be safe with respect to vascular health, our systematic review supports the use of MP as a concomitant progestogen in combined MHT as it displays a neutral effect on the vascular system. Clearly, more RCTs investigating the impact of MP alone or in combined MHT on vascular primary endpoints are needed to generate more evidence to broaden the clinical use of MP.

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