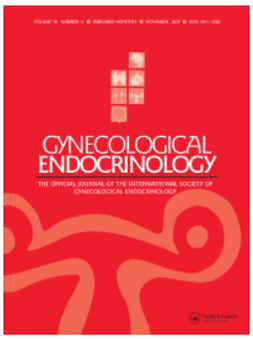

Gynecological Endocrinology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/igye20

Review of menopausal hormone therapy with estradiol and progesterone versus other estrogens and progestins

Shelli Graham, David F. Archer, James A. Simon, Kathleen M. Ohleth & Brian Bernick

To cite this article: Shelli Graham, David F. Archer, James A. Simon, Kathleen M. Ohleth & Brian Bernick (2022) Review of menopausal hormone therapy with estradiol and progesterone versus other estrogens and progestins, Gynecological Endocrinology, 38:11, 891-910, DOI: 10.1080/09513590.2022.2118254

To link to this article: https://doi.org/10.1080/09513590.2022.2118254

GYNECOLOGICAL ENDOCRINOLOGY
2022, VOL. 38, NO. 11, 891–910
https://doi.org/10.1080/09513590.2022.2118254

Taylor & Francis
Taylor & Francis Group

REVIEW
MENOPAUSE

Review of menopausal hormone therapy with estradiol and progesterone versus other estrogens and progestins

Shelli Graham[a], David F. Archer[b], James A. Simon[c], Kathleen M. Ohleth[d] and Brian Bernick[a]

[a]TherapeuticsMD, Boca Raton, FL; [b]Department of Obstetrics and Gynecology, Clinical Research Center, Eastern Virginia Medical School, Norfolk, VA; [c]School of Medicine, George Washington University, Washington, DC; [d]Precise Publications LLC, Far Hills, NJ

ARTICLE HISTORY
Received 21 June 2022
Revised 2 August 2022
Accepted 9 August 2022
Published online 09 September 2022

KEYWORDS
Estradiol; estrogens; menopause; progesterone; progestins

ABSTRACT

Objective: The objective of the present document was to review/summarize reported outcomes compared between menopausal hormone therapy (MHT) containing estradiol (E2) versus other estrogens and MHT with progesterone (P4) versus progestins (defined as synthetic progestogens).

Methods: PubMed and EMBASE were systematically searched through February 2021 for studies comparing oral E2 versus oral conjugated equine estrogens (CEE) or P4 versus progestins for endometrial outcomes, venous thromboembolism (VTE), cardiovascular outcomes, breast outcomes, cognition, and bone outcomes in postmenopausal women.

Results: A total of 74 comparative publications were identified/summarized. Randomized studies suggested that P4 and progestins are likely equally effective in preventing endometrial hyperplasia/cancer when used at adequate doses. E2- versus CEE-based MHT had a similar or possibly better risk profile for VTE and cardiovascular outcomes, and P4- versus progestin-based MHT had a similar or possibly better profile for breast cancer and cardiovascular outcomes. E2 may potentially protect better against age-related cognitive decline and bone fractures versus CEE; P4 was similar or possibly better versus progestins for these outcomes. Limitations are that many studies were observational and some were not adequately powered for the reported outcomes.

Conclusions: Evidence suggests a differential effect of MHT containing E2 or P4 and those containing CEE or progestins, with some evidence trending to a potentially better safety profile with E2 and/or P4.

Introduction

Menopausal hormone therapy (MHT) with estrogen alone or in combination with a progestogen is widely used to prevent or treat menopause-related hot flushes, night sweats, dyspareunia, vaginal dryness, and osteoporosis in postmenopausal women [1]. The most commonly prescribed estrogens are estradiol (E2) and conjugated equine estrogens (CEE), while the common progestogen choices include natural progesterone (P4) and those derived from progesterone or testosterone, such as medroxyprogesterone acetate (MPA) and norethisterone acetate (NETA) (i.e. progestins, defined as synthetic progestogens).

Results from the Women's Health Initiative (WHI) study of CEE plus MPA raised safety concerns of MHT [2, 3]. Many women discontinued MHT, especially oral estrogens or estrogens/progestins, following these publications [4], and use of E2- and P4-containing MHT increased [5].

The objective here was to review and summarize clinical data from studies/publications directly comparing the effects of oral E2 versus CEE and P4 versus progestins on endometrial outcomes, venous thromboembolism (VTE), cardiovascular disease (CVD) outcomes, stroke, breast outcomes, cognition, bone outcomes, vasomotor symptom (VMS), and quality of life (QOL).

Methods

Data sources and searches

The concept of this review stemmed from a request by the US Food and Drug Administration to provide data supporting a therapeutic benefit of low-dose estradiol/progesterone over low-dose estrogen/progestin products. PubMed and EMBASE were systematically searched from inception through February 2021, using keywords: endometrium, endometrial, cardiovascular, coronary, VTE, thrombosis, myocardial infarction (MI), coronary artery bypass graft (CABG), stroke, coagulation, lipids, hypertension, blood pressure (BP), mortality, breast, cognition, bone, hot flush, VMS, QOL, weight, metabolic, and sleep, in conjunction with (E2 and menopause) or (P4 and menopause). Relevant studies were also identified from review articles.

Study selection

English-language clinical studies, including meta-analyses, comparing formulations with different estrogens or different progestogens were included. Only studies on oral E2 and oral CEE were included for estrogen comparisons. Some large observational studies comparing risks for different formulations

CONTACT Shelli Graham sgraham@therapeuticsmd.com TherapeuticsMD, 951 Yamato Road, Suite 220, Boca Raton, 33431, FL, USA

Supplemental data for this article can be accessed online at https://doi.org/10.1080/09513590.2022.2118254

side-by-side were included given the breadth of data. Studies of transdermal estrogens were included only if they compared oral P4 with another progestogen during transdermal estrogen use. Comparisons of P4 versus progestins were limited to oral regimens as transdermal P4 does not provide adequate endometrial protection [6].

Data extraction and summary

Four authors/reviewers independently screened the search results for eligible studies. One author extracted details of study design, patient population, interventions, and targeted outcomes for effects of E2 versus CEE and P4 versus progestins, and a medical writer quality checked the accuracy of data extraction.

Data from the identified studies were not reported/published in a way appropriate to generate a meta-analysis. Results from all identified trials with comparisons were summarized based on study quality by study design with any randomized controlled trials (RCTs) summarized first followed by observational studies, then by study size. Tables of evidence were generated, studies were organized by main outcome, and conclusions were made based on the overall trend of the reported data.

Results

Article review

Twenty-eight articles comparing oral E2 versus CEE [7–34] and 48 articles comparing oral P4 versus progestins were identified (3 studies had both comparisons; Figure 1) with relevant outcomes [21, 28, 34–79]. Among these articles, 32 reported findings from prospective, randomized studies or RCTs [7, 22–25, 51–77]; 19 from prospective, observational/interventional trials [11–18, 26, 33, 36, 43–50]; 18 from retrospective or cross-sectional, observational studies [8, 19–21, 27–32, 34, 35, 37–40, 78, 79]; and 4 from meta-analyses [9, 10, 41, 42]. A recently presented retrospective observational study comparing E2/P4 versus CEE/MPA was also included [80].

Endometrial outcomes

Details of the clinical studies included in this section can be found in Table 1.

Thickness, hyperplasia and cancer

The effect of unopposed estrogens on endometrial thickness was evaluated in one randomized study, which showed that estrogen has a dose-dependent effect on the endometrium, with the 1 mg E2 and 0.625 mg CEE having similar estrogenic effects [7].

Three randomized studies, including the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial [51], showed that the addition of 200 mg P4 to estrogens versus other progestogens (10 mg MPA, 10 mg dydrogesterone [DYD], 5 mg nomegestrol acetate, 10 mg chlormadinone acetate [CMA]) similarly counteracted the effects of the estrogens on endometrial thickness, hyperplasia, and other endometrial biopsy observations [51, 53, 54, 56]. Another randomized study reported a similar proportion of women with increased endometrial thickness ≥5 mm with estradiol valerate plus 100 mg P4 or 4 mg MPA [63].

Endometrial cancer risk was evaluated in two large European (1992–2000) [43] and French (1990–2008) [44] observational studies, which reported increased risks with current or ever use [43, 44] or >5 years use (but not ≤5 years) [44] of estrogens plus P4 versus no hormone use, while estrogens combined with progestins were not associated with an increased risk [43, 44]. However, P4 doses were not reported in either study, a limitation of these observational studies.

Uterine bleeding

One randomized study directly compared unopposed E2 or CEE and reported similar unscheduled vaginal bleeding with 1.0 mg E2 and 0.625 mg CEE, but significantly less with 0.5 mg E2 (versus CEE) [7]. Two randomized studies showed that women using 200 mg P4 cyclically with oral CEE (0.625 mg) had fewer days of bleeding [52, 55], had less blood flow [52, 55], and more were amenorrheic [52] than when using MPA (5 mg). Two other randomized studies showed that when P4 (200 mg, cyclic) was used with transdermal E2 (50 µg), irregular bleeding occurred more frequently than with cyclic MPA (10 mg) [56], nomegestrol acetate (5 mg) [56], DYD (10 mg) [56], or CMA (10 mg) [53]. However, amenorrhea rates were 37.1% with P4 and 11.9% with CMA in one study [53], while the proportions of amenorrhea cycles were similar between all progestogens in the other study [56].

Cardiovascular and thrombotic outcomes

Details of the design and results of the clinical studies included in this section can be found in Table 2.

VTE and coagulation factors

Risk for VTE was similar or lower with oral E2 than with CEE in 4 observational studies (Figure 2A) [12, 27, 31, 32]. In the Million Women Study (MWS), a similar but significant increase in VTE risk was observed with oral E2 (RR 1.45) or CEE alone (RR 1.46) when comparing current vs never users [12]. Similarly, another case-control study ($n = 80{,}396$) showed an increase in VTE risk with E2 (OR 1.27) or CEE (OR 1.49) alone when comparing current users vs non-users [31]. When directly comparing CEE with E2, two case-control studies reported a significantly greater VTE risk with CEE than with E2 [27,31]. However, a recent retrospective cohort study found a similar VTE risk with MHT containing oral E2 or CEE, which did not support a differential effect of E2 compared with CEE on VTE [32].

Surrogate markers of coagulation were reported in some studies. Furthermore, a cross-sectional study ($n = 282$) of coagulation parameters found a more pro-thrombotic profile with CEE versus E2 [13]. This is in contrast to an older and smaller ($n = 35$) randomized study, which showed the opposite with increased plasminogen activity with CEE (0.625 and 1.25 mg) but not E2 (1 and 2 mg), and decreased thrombin time with 1 mg E2 but not with other regimens versus placebo [24].

When evaluating the effects of progestogens on VTE, three large observational studies (Estrogen and Thromboembolism Risk [ESTHER], Etude Epidémiologique de femmes de l'Education Nationale [E3N], and Menopause, Estrogen, and Veins [MEVE]) found increased VTE risk with MHT with norpregnane derivatives but not with P4 or pregnane derivatives (Figure 2B)

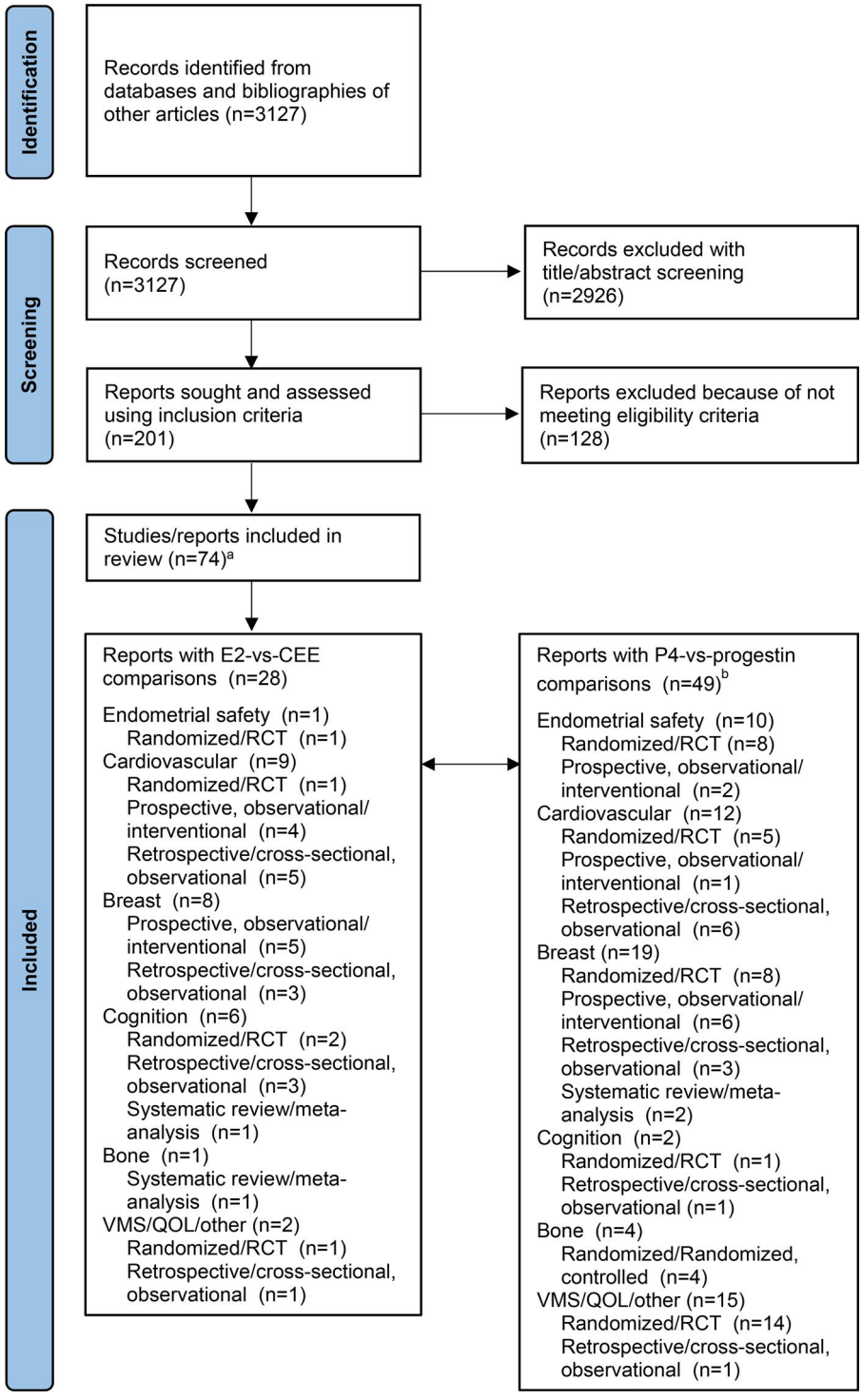

Figure 1. Study selection follow chart. CEE: conjugated equine estrogens; E2: estradiol; P4: progesterone; QOL: quality of life; VMS: vasomotor symptoms. [a]Three articles reported outcomes with both E2 versus CEE and P4 versus progestins. [b]Thirteen articles reported multiple outcomes with P4 versus progestins.

[36, 38, 78]. A recently presented retrospective cohort study found a lower VTE risk in women who initiated E2/P4 versus CEE/MPA (Figure 2B) [80].

Hemostasis data, other surrogate measures, with transdermal estrogens plus different progestogens were consistent with clinical VTE risk data [37, 39]. One French study found that norpregnanes were associated with lower activated protein C (APC) sensitivities and higher prothrombin fragment 1 + 2 concentrations [37], and another that progestins increased thrombin generation [39]; no significant changes on any hemostatic or thrombin generation parameters were seen with P4 in either study [37, 39].

CVD Outcomes

Various CVD risks with CEE or E2 were reported in three observational studies (Figure 2A) [14, 27, 29]. Risks for major coronary heart disease (CHD), stroke, or total CVD with oral E2 formulations were not significantly different from those with

Table 1. Studies comparing endometrial outcomes with E2 versus CEE and P4 versus synthetic progestogens.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
E2 vs CEE				
Ettinger et al. [7]	Prospective randomized study (24 weeks)	87 postmenopausal women aged 45–69 years with a uterus	Unopposed estrogens E2 (0.5 mg; $n = 27$) E2 (1.0 mg; $n = 29$) CEE (0.625 mg; $n = 31$)	Mean weekly endometrial growth 0.5 mg E2: 0.08 ± 0.17 mm/wk ($p < .05$ vs the other two regimens) 1.0 mg E2: 0.19 ± 0.14 mm/wk 0.625 mg CEE: 0.19 ± 0.15 mm/wk Unscheduled vaginal bleeding (% patient) 0.5 mg E2: 15% ($p = .05$ vs CEE) 1.0 mg E2: 32% 0.625 mg CEE: 41% Unscheduled bleeding score ≥20 (% patient) 0.5 mg E2: 7% ($p = .02$ vs CEE) 1.0 mg E2: 14% 0.625 mg CEE: 28%
P4 vs progestin				
Writing group for the PEPI trial [51]	Prospective randomized controlled study (3 years)	596 postmenopausal women aged 45–64 years with a uterus	CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 118$) Continuous MPA (2.5 mg; $n = 120$) Cyclic P4 (200 mg; $n = 120$) CEE alone (0.625 mg; $n = 119$) Placebo ($n = 119$) Cyclic progestogens taken on days 1 to 12 of a 28-day cycle	Occurrence of abnormal endometrial biopsy was similar with any combined MHT vs placebo ($p = .16$), but significantly higher with CEE only vs placebo ($p = .001$); No endometrial adenocarcinoma occurred with any MHT
Ryan and Rosner [52]	Prospective randomized open-label parallel-group study (9 months)	182 postmenopausal, non-hysterectomized women aged 45–65 years who had been amenorrheic for ≥6 months, and had symptoms of estrogen deficiency	CEE (0.625 mg) plus cyclic P4 (200 mg; $n = 89$) MPA (5 mg; $n = 93$) CEE taken on days 1 to 25 of a 30-day cycle, combined with progestogens on days 12 to 25 of the cycle	P4 vs MPA at month 9: Amenorrhea 39% vs 12% ($p = .001$) Days of bleeding 4.3 vs 6.2 ($p = .01$) Blood flow scale 0.9 vs 1.4 ($p < .001$)
Pélissier et al. [53]	Randomized parallel-group study (18 months)	336 postmenopausal amenorrheic women aged ≤57 years with intact uterus	TD E2 (1.5 mg/day) plus cyclic P4 (200 mg; $n = 169$) CMA (10 mg; $n = 167$) E2 taken on days 1 to 24 every month, combined with progestogens on days 11 to 24 of the month	P4 vs CMA at month 18: No significant difference in endometrial biopsy results between groups: No endometrial hyperplasia with both MHT; Atrophic, inactive, secretory endometrium: 86.9% vs 96.3%; Proliferative endometrium: 8.3% vs 3.7%; Amenorrhea rate: 37.1% vs 11.9% Irregular bleeding 15.9% vs 7.4% ($p = .03$)
Jondet et al. [54]	Randomized study (18 months)	336 postmenopausal women	TD E2 (1.5 mg/day) plus cyclic P4 (200 mg; $n = 169$) CMA (10 mg; $n = 167$) E2 taken on days 1 to 24 every month, combined with progestogens on days 11 to 24 of the month	P4 vs CMA at month 18: Atrophic endometrium: 27.1% vs 19.5%; Secretory endometrium: 62.5% vs 76.8%; Proliferative endometrium: 8.3% vs 3.7%; Endometrial polyps: 2.1% vs 0%
Cummings and Brizendine [55]	Prospective randomized study (8 weeks)	23 postmenopausal women aged <59 years with amenorrhea for >1 year	2 cycles of 2-week CEE (0.625 mg) followed by 2-week CEE (0.625 mg) plus P4 (200 mg; $n = 13$) or MPA (5 mg; $n = 10$)	P4 vs MPA: Smaller magnitude and shorter duration of vaginal bleeding
Di Carlo et al. [56]	Prospective randomized study (1 year)	100 postmenopausal women, 12 to 36 months after spontaneous menopause	TD E2 (50 µg) plus oral, cyclic MPA (10 mg; $n = 25$) NOMAC (5 mg; $n = 25$) DYD (10 mg; $n = 25$) P4 (200 mg; $n = 25$) Cyclic progestogens taken on days 14 to 25 of a 28-day cycle	P4 vs MPA, NOMAC, DYD: Endometrial thickness significantly increased versus baseline ($p < .05$), but similar among groups; Amenorrhea episode: 7.5% vs 9.8%, 5.7%, 8.4% (p = NS); Irregular bleeding episode: 12% vs 8.4%, 5.7%, 7.5% ($p < .05$ P4 vs NOMAC)

(*Continued*)

Table 1. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Allen et al. [43]	Prospective cohort study (1992–2000)	115,474 postmenopausal, non-hysterectomized women	Combined MHT containing P4 (9.0%) Progesterone derivatives (35.8%) Testosterone derivatives (54.9%)	HR (95% CI) for endometrial cancer (current vs never use): P4: 2.42 (1.53–3.83) Progesterone derivatives: 1.23 (0.84–1.79) Testosterone derivatives: 1.09 (0.74–1.61) $P_{heterogeneity}$ = .02
Zheng et al. [57]	Prospective randomized study (3 months)	96 early postmenopausal women aged 40–60 years with climacteric symptoms	Oral E2V plus cyclic P4 (n = 32) MPA (n = 32) Cyclic progestogens received on days 19 to 30 of a 30-day cycle	Vaginal bleeding (% patients) P4: 26.7%; MPA: 82.1%
Fournier et al. [44]	Prospective cohort study (1992–2008)	65,630 postmenopausal, non-hysterectomized women aged 40–65 years	In ever users of combined MHT, estrogen plus oral: P4 (40.2%) DYD (28.8%) Progesterone derivative[a] (59%) Norsteroid derivative[b] (13.5)	HR (95% CI) for endometrial cancer: Ever vs never use P4: 1.80 (1.38–2.34) DYD: 1.05 (0.76–1.45) Progesterone derivative: 0.79 (0.60–1.05) Norsteroid derivative: 1.30 (0.85–1.99) Duration ≤5 years vs never use P4: 1.39 (0.99–1.97) DYD: 0.87 (0.57–1.32) Progesterone derivative: 0.81 (0.59–1.13) Norsteroid derivative: 1.32 (0.81–2.15) Duration >5 years vs never use P4: 2.66 (1.87–3.77) DYD: 1.69 (1.06–2.70) Progesterone derivative: 0.94 (0.62–1.44) Norsteroid derivative: 0.98 (0.31–3.07)
Gao et al. [63]	Prospective randomized controlled study (24 months)	96 early postmenopausal women aged 40–60 years with climacteric symptoms	Oral E2V (1 mg) plus cyclic MPA (4 mg, n = 32) P4 (100 mg, n = 32) Cyclic progestogens taken on days 19 to 30 of a 30-day cycle	Compared with baseline at month 24: Endometrial thickness increased significantly with E2V/P4, but not E2V/MPA; Incidence of endometrial thickness ≥5 mm: E2V/P4: 29.6% E2V/MPA: 18.5% p = NS between groups

CEE: conjugated equine estrogens; CI: confidence interval; CMA: chlormadinone acetate; DYD: dydrogesterone; E2: estradiol; E2V: estradiol valerate; HR: hazard radio; MHT: menopausal hormone therapy; MPA: medroxyprogesterone acetate; NOMAC: nomegestrol acetate; P4: progesterone; PEPI: the Postmenopausal Estrogen/Progestin Interventions study; RR; relative risk; TD: transdermal.
Early postmenopausal: amenorrhea >6 months and <5 years.
[a]Progesterone derivative included CMA, cyproterone acetate, demegestone, medrogestone, MPA, NOMAC, or promegestone.
[b]Norsteroid derivative included dienogest, drospirenone, ethynodiol, gestodene, levonorgestrel, norethisterone acetate, or lynestrenol.

Table 2. Studies comparing cardiovascular outcomes with E2 versus CEE and P4 versus synthetic progestogens.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
E2 vs CEE				
Lobo et al. [26]	Prospective cross-over study (1 month)	24 non-obese women aged 54.8 ± 1.2 years, weighed 64 ± 2 kg, postmenopausal ≥2 years, free of VMS, and no recent MHT	CEE (0.3 mg; $n = 6$) CEE (0.625 mg; $n = 6$) ES (0.6 mg; $n = 6$) ES (1.2 mg; $n = 6$) E2 (1 mg; $n = 6$) Each woman took MHT daily for 25 days; six women took 2 different doses with drug-free interval of ≥1 month between doses	No significant changes in mean plasma lipid level except slight decreases in LDL-c from baseline by 0.625 mg CEE and 1 mg E2 ($p < .05$); No significant increase in HDL-c in any groups
Notelovitz et al. [24]	Prospective randomized study (15 months)	35 surgically menopausal women with bilateral oophorectomy and hysterectomy ≥3 months before baseline	Each woman was assigned a randomized sequence of a placebo, E2 (1 mg), E2 (2 mg), CEE (0.625 mg), and CEE (1.25 mg) Each regimen administered 3 of every 4 weeks for a 3-month period	Y: women <40 years; O: women ≥40 years Thrombin time (sec, mean ± SD): Placebo 17.5 ± 1.2 (Y); 17.3 ± 0.9 (O) 1 mg E2 15.3 ± 1.1 (Y); 15.7 ± 0.9 (O) 2 mg E2 18.4 ± 1.0 (Y); 16.7 ± 0.8 (O) 0.625 mg CEE 16.5 ± 0.9 (Y); 18.0 ± 1.1 (O) 1.25 mg CEE 16.0 ± 1.2 (Y); 17.9 ± 1.0 (O) $p < .05$ for 1 mg E2 vs placebo; p = NS for others Fibrinogen activity (mg/dL, mean ± SD): Placebo 387 ± 20 (Y); 375 ± 13 (O) 1 mg E2 413 ± 20 (Y); 403 ± 17 (O) 2 mg E2 362 ± 16 (Y); 386 ± 16 (O) 0.625 mg CEE 390 ± 15 (Y); 371 ± 18 (O) 1.25 mg CEE 393 ± 21 (Y); 367 ± 15 (O) $p < .05$ for 1 mg E2 vs placebo; p = NS for others α_1-antitrypsin antigen (mg/dL, mean ± SD): Placebo 242 ± 7 (Y); 250 ± 19 (O) 1 mg E2 265 ± 10 (Y); 249 ± 12 (O) 2 mg E2 259 ± 14 (Y); 248 ± 11 (O) 0.625 mg CEE 259 ± 10 (Y); 251 ± 19 (O) 1.25 mg CEE 280 ± 13 (Y); 277 ± 15 (O) $p < .02$ for 1.25 mg CEE vs placebo; p = NS for others Plasminogen activity (cyano-trimethyl-androsterone U/mL, mean ± SD): Placebo 3.5 ± 0.2 (Y); 3.7 ± 0.2 (O) 1 mg E2 3.5 ± 0.2 (Y); 3.6 ± 0.2 (O) 2 mg E2 3.5 ± 0.1 (Y); 4.0 ± 0.1 (O) 0.625 mg CEE 3.8 ± 0.2 (Y); 4.0 ± 0.2 (O) 1.25 mg CEE 3.8 ± 0.2 (Y); 4.0 ± 0.1 (O) $p < .002$ for both CEE regimens vs placebo; p = NS for others
Man et al. [11]	Prospective cohort study (unspecified)	145 postmenopausal and premenopausal women aged 30–62 years	MHT user E2 only (2 mg/day; $n = 29$) CEE only (0.625 mg/day; $n = 23$) E2 + NETA (2 mg/1 mg; $n = 23$) Non-user Control A (≤5-year menopause; $n = 22$) Control B (>5-year menopause; $n = 27$) Control C (premenopausal; $n = 21$)	E2 or CEE only users vs nonusers: Significantly lower plasma levels of TC, LDL-c, ApoB, and TC/HDL-c ratio; Significantly higher HDL-c; No significant difference in triglycerides Similar changes with CEE and E2 in TC, LDL-c, HDL-c, triglycerides, ApoAI, and ApoB levels; Plasma homocysteine levels decreased 15% with E2, 13% with CEE, and 15% with E2/NETA.
Sweetland et al. [12]	Population-based prospective cohort study (MWS) (1996–2001)	1,058,259 postmenopausal women aged 50–64 years	In 86,250 current oral estrogen-only users: E2 ($n = 19,818$) CEE ($n = 60,438$) Never users ($n = 476,711$)	RR (95% CI) for VTE (current vs never use) E2: 1.45 (1.06–1.98) CEE: 1.46 (1.23–1.75) p = NS between groups

(*Continued*)

Table 2. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Smith et al. [27]	Retrospective case-control study (2003–2009)	384 postmenopausal women aged 30–79 years using oral MHT (183 cases of women who experienced an incident MI, ischemic stroke, or VTE, and 201 controls of women without a history of VTE, MI, or ischemic stroke)	Controls E2 ($n = 114$) CEE ($n = 87$) VTE cases E2 ($n = 29$) CEE ($n = 39$) MI cases E2 ($n = 29$) CEE ($n = 38$) Stroke cases E2 ($n = 23$) CEE ($n = 25$)	CEE vs E2 (current use) OR (95% CI) for VTE: 2.08 (1.02–4.27) MI: 1.87 (0.91–3.84) Ischemic stroke: 1.13 (0.55–2.31)
Blondon et al. [13]	Cross-sectional study (2003–2010)	282 postmenopausal women randomly selected from the controls of the HVH case-control study	Oral E2 ($n = 93$) Oral CEE ($n = 48$) Nonuser of MHT ($n = 141$)	CEE vs E2 (difference [95% CI]; *P*-value) TG peak (nM): +49.8 (21.0–78.6); 0.001 ETP (nMxMin): +175.0 (54.4–295.7); 0.005 TG lag-time (min): −0.01 (−0.26–0.25); 0.97 TG time to peak (min): −0.2 (−0.5–0.2); 0.27 Factor VII (%): −8.7 (−23.0–5.6); 0.23 Antithrombin (%): −2.7 (−8.4–3.0); 0.35 total protein S (%): −13.4 (−19.8– −6.9); $p < .001$ Differences compared with non-users in TG peak value, ETP, TG lag time, time-to-peak measures, and total protein S concentrations were more pronounced for CEE vs E2 users
Shufelt et al. [14]	Prospective cohort study (WHI-OS) (1994–2009)	41,721 postmenopausal women aged 50–79 years currently using MHT	MHT containing Oral E2 ($n = 3024$) Oral CEE (0.625 mg; $n = 24,399$)	E2 vs CEE HR (95% CI) for: Major CHD: 1.13 (0.79–1.61) Stroke: 0.64 (0.40–1.02) Total CVD: 0.93 (0.71–1.23)
Tsai et al. [29]	Population-based retrospective cohort study (1998–2008)	5489 menopausal women aged >45 years	E2 ($n = 1815$) CEE ($n = 3674$)	CEE vs E2 HR (95% CI) for AF: 1.96 (1.03–3.73) Stroke: 1.30 (1.04–1.62) MACE: 1.26 (1.03–1.54)
Vinogradova et al. [31]	Nested case-control study (1998–2017)	80,396 women aged 40–79 years with VTE, matched by 391,494 women as controls	Case/control Unopposed oral E2 (771/2781) Unopposed oral CEE (1208/4000) Opposed oral E2 (1582/5880) Opposed oral CEE (1354/4277)	OR (95% CI) for VTE (use vs nonuse) Unopposed oral E2: 1.27 (1.16–1.39) Unopposed oral CEE: 1.49 (1.39–1.60) Opposed oral E2: 1.59 (1.49–1.69) Opposed oral CEE: 1.91 (1.79–2.05) E2 vs CEE OR (95% CI) Unopposed: 0.85 (0.76–0.95), $p = .005$ Opposed: 0.83 (0.76–0.91), $p < .001$
Blondon et al. [32]	Retrospective cohort sudy (2003–2011)	51,571 peri- and postmenopausal women who were using MHT at the time of study entry or initiated MHT during the study period and were aged 40–64 years at the time of first MHT use	MHT containing Oral E2 ($n = 6501$; 16.8% with concomitant progestogens) Oral CEE ($n = 38,421$; 28.5% with concomitant progestogens)	Adjusted HR (95% CI) for incident VTE Oral E2 vs CEE (opposed and unopposed) All users: 0.96 (0.64–1.46) Incident users: 0.83 (0.42–1.62) Unopposed oral E2 vs CEE All users: 1.06 (0.69–1.63) Opposed oral E2 vs CEE All users: 0.30 (0.04–2.22)

(*Continued*)

Table 2. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
P4 vs progestin				
Writing group for the PEPI trial [66]	Prospective randomized controlled study (PEPI) (3 years)	875 postmenopausal women aged 45–64 years	CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 174$) Continuous MPA (2.5 mg; $n = 174$) Cyclic P4 (200 mg; $n = 178$) CEE alone (0.625 mg; $n = 175$) Placebo ($n = 174$) Cyclic progestogens taken on days 1 to 12 of a 28-day cycle	Significantly greater increase in HDL-c with CEE/P4 vs both CEE/MPA regimens; Similar decrease in LDL-c and increase in triglyceride with all MHT; TC significantly decreased with CEE/MPA regimens, but not CEE/P4, relative to placebo; No significant difference in effects on SBP or DBP with any MHT vs placebo (p = NS among groups)
Pélissier et al. [53]	Randomized parallel-group study (18 months)	336 postmenopausal amenorrheic women aged ≤57 years with intact uterus	TD E2 (1.5 mg) plus cyclic P4 (200 mg; $n = 169$) CMA (10 mg; $n = 167$) E2 taken on days 1 to 24 every month, combined with progestogens on days 11 to 24 of the month	P4 vs CMA at month 18: Change from baseline in plasma TC and triglycerides were small and similar between the two regimens; SBP and DBP decreased from baseline with E2/P4 and increased with E2/CMA ($p < .05$ between the two regimens)
Matthews et al. [77]	Randomized controlled study (8 weeks)	89 women aged 48–65 years	Estrogen[a] (1.25 mg) plus continuous placebo ($n = 18$) MPA (5 mg; $n = 18$) P4 (100 mg; $n = 17$) Estrogen[a] plus continuous methyl testosterone ($n = 20$) Placebo only ($n = 16$)	After 8-week MHT treatment: SBP reactivity during stress decreased significantly with estrogen/testosterone (p = .007), tended to decrease with estrogen/P4 (p = .095), but did not change with estrogen/MPA; DBP reactivity during stress increased with estrogen/MPA (p = .002), tended to decrease with estrogen/P4 (p = .06), but did not change with testosterone.
Canonico et al. [38]	Case–control study (ESTHER) (1996–2006)	271 consecutive cases with a first-documented idiopathic VTE and 610 controls matched for center, age, and admission date	MHT containing (case/control) P4 (19/63) Pregnane derivatives[b] (39/79) Norpregnane derivatives[c] (40/37)	ORs (95% CI) for VTE (current vs nonuse): P4: 0.7 (0.3–1.9) Pregnane derivatives: 0.9 (0.4–2.3) Norpregnane derivatives: 3.9 (1.5–10.0)
Canonico et al. [37]	Cross-sectional study (2006–2007)	108 postmenopausal women aged 45–70 years	TD E2 (50 µg) plus P4 ($n = 30$) Norpregnanes[c] ($n = 38$) Nonuser ($n = 40$) P4 taken continuously at 100 mg/day or 12 days a month at 200 mg/day; norpregnanes (NOMAC or promegestone) taken continuously at 2.5 mg and 250 µg per day, respectively, or 12 days a month at a mean daily dose of 5 mg and 500 µg, respectively	Thrombin generation parameters: Significant higher APC resistance, peak height$_{+APC}$, and ETP$_{+APC}$ with norpregnanes, vs no MHT use or P4; No significant difference with P4 versus no MHT use Hemostatic parameters: Significantly higher concentration of fragment 1 + 2 with norpregnanes vs no MHT; No significant difference with P4 versus no MHT use
Canonico et al. [36]	Prospective cohort study (E3N) (1990–2005)	80,308 postmenopausal women without personal history of thrombotic events before the start of follow up (549 first-documented incident VTEs [134 PE and 415 DVT]); taking MHT of various formulations and routes of administration	Never use (181 cases, 291,399 PY) MHT containing P4 (47 cases, 87,959 PY) Pregnane derivatives[b] (91 cases, 125,804 PY) Norpregnane derivatives[c] (69 cases, 78,855 PY) NETA (22 cases, 22,911 PY)	HRs (95% CI) for VTE (current vs never use): P4: 0.9 (0.6–1.5) Pregnane derivatives: 1.3 (0.9–2.0) Norpregnane derivatives: 1.8 (1.2–2.7) NETA: 1.4 (0.7–2.4)

(*Continued*)

Table 2. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Olié et al. [78]	Retrospective cohort study (MEVE) (2000–2008)	1023 postmenopausal women aged 45–70 years (893 non-MHT users; 130 MHT users) with a first confirmed VTE	Nonuser (68 cases, 6064 PY) TD estrogen plus P4 (3 cases, 231 PY) Pregnane derivatives[b] (0 cases, 94 PY) Norpregnane derivatives[c] (2 cases, 34 PY)	HRs (95% CI) for recurrent venous event (current vs nonuse) P4: 1.0 (0.3–3.2) Pregnane derivatives: NA Norpregnane derivatives: 4.7 (1.1–20.0) ($P_{heterogeneity}$ = .22 between groups)
Scarabin et al. [39]	Cross-sectional study (unspecified)	115 healthy postmenopausal women, aged 25–65 years	Nonuser (n = 38) Oral estrogen plus P4 (n = 5) Progestins (n = 32) TD estrogen plus P4 (n = 17) Progestins (n = 19)	TD estrogen plus progestins vs P4: Higher ETP (p < .10) and peak (p≤.01) levels; Higher prothrombin levels (p < .05); Other thrombin generation parameters were similar between the two groups
Canonico et al. [35]	Nested case-control study (2009–2011)	Women aged 51–62 years without personal history of cardiovascular disease or gynecological cancers (3144 hospitalized ischemic stroke cases and 12,158 controls)	Nonuser (2950 cases, 11,331 controls) Current users of E2 plus P4 (60 cases, 380 controls) Pregnane derivatives (58 cases, 197 controls) Nortestosterone derivatives (17 cases, 46 controls) Norpregnane derivatives (17 cases, 27 controls)	Adjusted ORs (95% CI) for ischemic stroke (current vs nonuse): P4: 0.78 (0.49–1.26) Pregnane derivatives: 1.00 (0.60–1.66) Nortestosterone derivatives: 1.26 (0.62–2.58) Norpregnane derivatives: 2.25 (1.05–4.81)
Xue et al. [64]	Prospective open-label randomized controlled study (1 year)	123 postmenopausal women with climacteric symptoms	CEE plus cyclic P4 0.3 mg/100 mg (n = 41) 0.625 mg/100 mg (n = 41) CEE plus cyclic DYD: 0.625 mg/10 mg (n = 41) Cyclic progestogens taken on days 17 to 28 of a 28-day cycle	Compared with baseline: Significant increase in triglycerides with CEE/DYD (p = .026); Significant increase in HDL-c and decrease in LDL-c with CEE/P4 (0.625 mg/100 mg; p = .033 and p = .039) and CEE/DYD (p = .006 and p = .029); No significant changes in SBP with any MHT; Significant decrease in DBP with CEE/P4 (0.3 mg/100 mg; p = .007), but not the other two regimens (p = NS)
Gao et al. [63]	Prospective randomized controlled study (24 months)	96 early postmenopausal women aged 40–60 years with climacteric symptoms	Oral E2V (1 mg) plus cyclic MPA (4 mg, n = 32) P4 (100 mg, n = 32) Cyclic progestogens taken on days 19 to 30 of a 30-day cycle	Compared with baseline at month 24: HDL-c significantly decreased with E2V/MPA (p = .019), but remained similar with E2V/P4; Triglycerides did not change significantly with either regimen; SBP and DBP did not change significantly with either regimen
Panay et al. [80]	Retrospective cohort study (2019–2021)	32,536 women aged ≥40 years who were initiated on E2/P4 (1 mg/100 mg) or CEE/MPA and did not have a VTE diagnosis in the 6 months pre-index	E2/P4 (1 mg/100 mg; n = 5288) CEE/MPA (n = 27,248)	HR (95% CI) for VTE (from the IPTW analyses of time to first VTE) E2/P4 vs CEE/MPA 0.59 (0.38–0.90), p < .05

AF: atrial fibrillation; APC: activated protein; ApoAI: apolipoprotein AI; ApoB: apolipoprotein B; CEE: conjugated equine estrogens; CHD: coronary heart disease; CI: confidence interval; CMA: chlormadinone acetate; CVD: cardiovascular disease; DBP: diastolic blood pressure; DYD: dydrogesterone; DVT: deep vein thrombosis; E2: estradiol; E2V: estradiol valerate; E3N: the Etude Epidémiologique de femmes de l'Education Nationale Study; ES: piperazine estrone sulfate; ESTHER: the Estrogen and Thrombo-embolism Risk study; ETP: endogenous thrombin potential; HDL-c: high-density lipoprotein cholesterol; HR: hazard ratio; HVH: Heart and Vascular Health Study; IPTW: inverse probability of treatment weighting; IRR: incidence rate ratio; LDL-c: low-density lipoprotein cholesterol; MACE: major adverse cardiac event; MEVE: the Menopause, Estrogen and Veins study; MHT: menopausal hormone therapy; MI: myocardial infarction; MPA: medroxyprogesterone acetate; NA: not applicable; NETA: norethisterone acetate; NOMAC: nomegestrol acetate; NS: not significant; OR: odds ratio; P4: progesterone; PE: pulmonary embolism; PEPI: the Postmenopausal Estrogen/Progestin Interventions study; PY: person-year; RR: relative risk; SBP: systolic blood pressure; TC: total cholesterol; TD: transdermal; TG: thrombin generation; VMS: vasomotor symptoms; VTE: venous thromboembolism; WHI-OS: the Women's Health Initiate Observational Study; MWS: the Million Women Study.

Early postmenopausal: amenorrhea >6 months and <5 years.

[a]Contains primarily conjugated estrone.

[b]Pregnane derivatives included DYD, medrogestone, CMA, cyproterone acetate, and MPA.

[c]Norpregnane derivatives included NOMAC and promegestone.

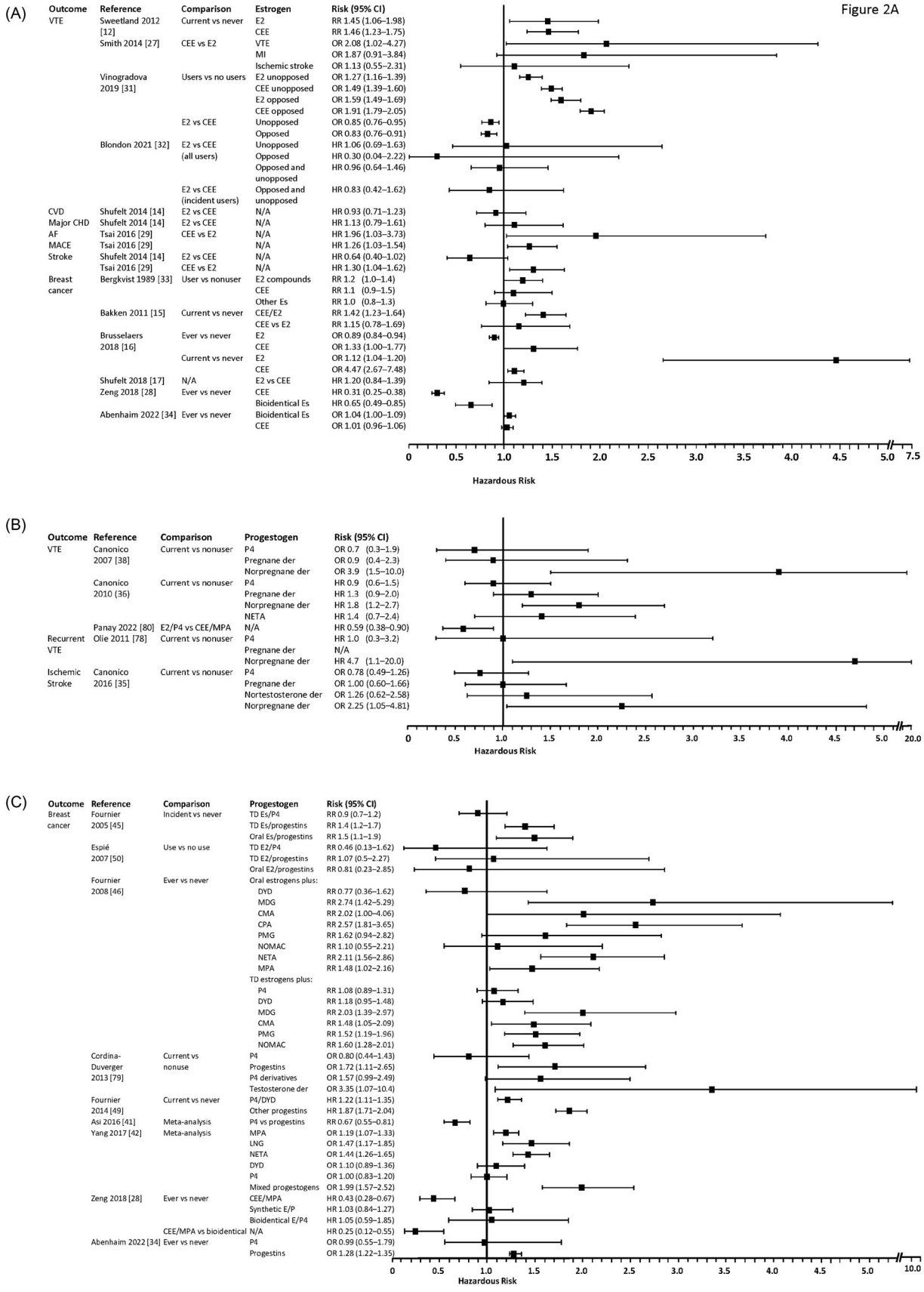

Figure 2. Outcomes with E2 versus CEE and P4 versus synthetic progestogens. (A) Cardiovascular outcome and breast cancer risks with estrogens. (B) Cardiovascular outcome risk with progestogens. (C) Breast cancer risk with progestogens. AF: atrial fibrillation; CEE: conjugated equine estrogens; CHD: coronary heart disease; CI: confidence interval; CMA: chlormadinone acetate; CPA: cyproterone acetate; CVD: cardiovascular disease; der: derivatives; DYD: dydrogesterone; E: estrogen; E2: estradiol; Es: estrogens; HR: hazard radio; LNG: levonorgestrel; MACE: major adverse cardiac event; MDG: medogestone; MPA: medroxyprogesterone acetate; NETA: norethisterone acetate; NOMAC: nomegestrol acetate; OR: odds ratio; P: progestin; P4: progesterone; PMG: promegestone; RR: relative risk; TD: transdermal; VTE: venous thromboembolism.

Table 3. Studies comparing breast outcomes with E2 versus CEE and P4 versus synthetic progestogens.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
E2 vs CEE				
Bergkvist et al. [33]	Prospective cohort study (1977–1980)	23,244 women aged ≥35 years who filled ≥1 estrogen replacement prescription for menopause-related conditions	Estradiol compound (not defined) CEE Other estrogens (mainly estriols) (n for each group unspecified; some women took progestins concurrently)	RR (95% CI) for breast cancer (use vs nonuse): Estradiol compound: 1.2 (1.0–1.4) CEE: 1.1 (0.9–1.5) Other estrogens: 1.0 (0.8–1.3) RR increased with duration of treatment for estradiol compounds (P_{trend} = .001) but not CEE (P_{trend} = .7) and other estrogens (P_{trend} = .7)
Cengiz et al. [30]	Retrospective study (1999–2001)	123 postmenopausal women with normal initial tumor marker levels and no previous use of MHT	Estrogen alone E2 (2 mg; n = 31) CEE (0.625 mg; n = 21) Continuous combined MHT E2/NETA (2 mg/1 mg; n = 37) CEE/MPA (0.625 mg/2.5 mg; n = 34)	Estrogen alone therapy: No effect was observed on serum CA125 II, CA19-9, CEA, and α-FP levels; CA15-3 level significantly decreased with E2 (p < .001), but not with CEE
Bülbül et al. [18]	Prospective cohort study (unspecified)	182 women with VMS, amenorrhea, and FSH >40 mIU/mL	Estrogen alone CEE (0.625 mg; n = 12) E2H (2 mg; n = 34) E2 (3.9 mg; n = 34) Sequential combined MHT CEE/MPA (0.625 mg/5 mg; n = 19) E2/NETA (2 mg/1 mg; n = 15) E2/MAP (2 mg/10 mg; n = 6) Continuous combined MHT CEE/MPA (0.625 mg/2.5 mg; n = 34) E2H/NETA (2 mg/1 mg; n = 8) Tibolone (2.5 mg; n = 18)	Incidence of increased mammographic density was higher with E2 (n = 12, 15%) versus CEE (n = 3, 3.8%)[a], p = NS.
Bakken et al. [15]	Prospective cohort study (EPIC) (1992–2000)	133,744 postmenopausal women without cancer at any site (30.9% women were current MHT users, of which 21.7% used estrogen-only MHT and 65.0% used combined estrogen/progestin MHT)	Current estrogen-only users CEE (21.4%) E2 (61.8%) Low-potency estrogens (11.3%) Other/unknown (5.5%) (MHT included oral and TD preparations)	RR (95% CI) for breast cancer (estrogen-only): Current vs never use: 1.42 (1.23–1.64) CEE vs E2 (current use): 1.15 (0.78–1.69)
Brusselaers et al. [16]	Prospective cohort study (2005–2012)	1,160,351 women aged ≥40 years without a history of malignancy (290,186 ever users with ≥1 MHT prescription and 870,165 never users with no MHT prescription and matched year of birth)	Estrogen only (n = 135,988) E2 (n = 53,339) Estriol (n = 55,653) Tibolone (n = 17,992) CEE (n = 1161) Estrogen/Progestogen (n = 154,198) Never user (n = 870,165) (84.0% of patients used oral MHT)	OR (95% CI) for breast cancer: Ever vs never use E2: 0.89 (0.84–0.94) CEE: 1.33 (1.00–1.77) Current vs never use E2: 1.12 (1.04–1.20) CEE: 4.47 (2.67–7.48)
Shufelt et al. [17]	Prospective cohort study (WHI-OS) (1993–2005)	26,525 postmenopausal women aged 50–79 years with a hysterectomy	Oral estrogen therapy E2 (n = 1226) CEE (<0.625 mg; n = 846) CEE (0.625 mg; n = 9903) CEE (>0.625 mg; n = 2004)	E2 vs CEE (0.625 mg) HR (95% CI) for breast cancer: Total 1.20 (0.84–1.39) <10 yr since menopause 1.46 (0.78–2.73) ≥10 yr since menopause 1.05 (0.67–1.66)
Zeng et al. [28]	Retrospective case-control study (unspecified)	40,046 women aged >50 years (12,404 cases of women who took any MHT after age 50 and 27,642 controls of women who did not take any MHT after age 50)	MHT cases CEE alone (n = 2556) MPA alone (n = 442) Other synthetic estrogen alone (n = 1349) Other synthetic progesterone alone (n = 417) Bioidentical estrogens[b] alone (n = 1441) Bioidentical P4[c] alone (n = 265) CEE/MPA (n = 453) Other synthetic estrogen/ synthetic P4 (n = 2512) Bioidentical estrogens/P4[b,c] (n = 288) Controls (n = 27,642)	HR (95% CI) for breast cancer: Ever vs never use CEE: 0.31 (0.25–0.38) Bioidentical estrogens: 0.65 (0.49–0.85)
Abenhaim et al. [34]	Nested case-control study (1995–2014)	43,183 women aged 50–75 years who had their first diagnosis of invasive breast cancer post-index, matched by 431,830 control women	Estrogen subgroups (cases/controls) No estrogen (36,391/373,019) Bioidentical estrogens[d] (2487/21,579) CEE (3311/28184)	Breast cancer adjusted OR (95% CI) for ever use of any HT vs never use of estrogen: Bioidentical estrogens: 1.04 (1.00–1.09) CEE: 1.01 (0.96–1.06)
P4 vs progestin				

(*Continued*)

Table 3. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Greendale et al. [68]	Randomized controlled study (PEPI) (3 years)	875 postmenopausal women aged 45–64 yearsv	CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 174$) Continuous MPA (2.5 mg; $n = 174$) Cyclic P4 (200 mg; $n = 178$) CEE alone (0.625 mg; $n = 175$) Placebo ($n = 174$) Cyclic progestogens taken days 1 to 12 of each 28-day cycle	Adjusted OR (95% CI) for breast discomfort: MHT vs placebo MPA (cyclic): 2.27 (1.39–3.56) MPA (continuous): 1.92 (1.16–3.09) P4: 2.33 (1.46–3.74) Between MHT regimens MPA (cyclic) vs P4: 0.97 (0.63–1.46) MPA (continuous) vs P4: 0.83 (0.53–1.26)
Greendale et al. [69]	Randomized controlled study (PEPI) (3 years)	307 women from PEPI who had not taken estrogen for ≥5 years before baseline and had baseline and follow-up mammograms	CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 51$) Continuous MPA (2.5 mg; $n = 67$) Cyclic P4 (200 mg; $n = 55$) CEE alone (0.625 mg; $n = 58$) Placebo ($n = 64$) Cyclic progestogens taken days 1 to 12 of each 28-day cycle	Incidence (95% CI) of BI-RADS grade increased at month 12: Cyclic MPA: 23.5% (11.9%–35.1%) Continuous MPA: 19.4% (9.9%–28.9%) Cyclic P4: 16.4% (6.6%–26.2%) p = NS between treatment groups Adjusted OR (95% CI) P4 vs cyclic MPA: 0.5 (0.2–1.8) P4 vs continuous MPA: 0.8 (0.8–2.5)
Cummings and Brizendine [55]	Prospective, randomized study (8 weeks)	23 early postmenopausal women aged <59 years with amenorrhea for >1 year	2 cycles of 2-week CEE (0.625 mg) followed by 2-week CEE (0.625 mg) plus P4 (200 mg; $n = 13$) or MPA (5 mg; $n = 10$)	P4 vs MPA: 31% (4/13) vs 70% (7/10) Fewer self-reported breast tenderness cases, no statistical analysis performed
Greendale et al. [70]	Randomized controlled study (PEPI) (3 years)	571 women from PEPI with baseline and follow-up mammograms	CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 109$) Continuous MPA (2.5 mg; $n = 121$) Cyclic P4 (200 mg; $n = 115$) CEE alone (0.625 mg; $n = 114$) Placebo ($n = 112$) Cyclic progestogens taken days 1 to 12 of each 28-day cycle	Incidence (95% CI) of mammographic density increased at month 12: Placebo: −0.1% (−1.5%–1.4%) Cyclic MPA: 4.8% (3.3%–6.2%) Continuous MPA: 4.6% (3.2%–6.0%) Cyclic P: 3.1% (1.7%–4.5%) p = NS between MHT groups
Fournier et al. [45]	Prospective cohort study (E3N-EPIC) (1990–2000)	29,420 postmenopausal women taking MHT (mostly E2 based, only 1.9% of CEE use) and 25,128 not using MHT	Breast cancer (case/PY) with estrogens/oral progestogens: TD Estrogen/P4 (55/20,685) TD Estrogen/progestins (187/46,242) Oral Estrogen/progestins (80/20,504)	Adjusted RR (95% CI) of breast cancer (incident vs never use) TD estrogen/P4: 0.9 (0.7–1.2) TD estrogen/progestins: 1.4 (1.2–1.7) Oral estrogen/progestins: 1.5 (1.1–1.9) <2 years MHT duration TD estrogen/P4: 0.9 (0.6–1.4) TD estrogen/progestins: 1.6 (1.3–2.0) Oral estrogen/progestins: 1.2 (0.9–1.8) 2–4 years MHT duration TD estrogen/P4: 0.7 (0.4–1.2) TD estrogen/progestins: 1.4 (1.0–1.8) Oral estrogen/progestins: 1.6 (1.1–2.3) ≥4 years MHT duration TD estrogen/P4: 1.2 (0.7–2.0) TD estrogen/progestins: 1.2 (0.8–1.7) Oral estrogen/progestins: 1.9 (1.2–3.2)
Crandall et al. [71]	Prospective, randomized controlled study (PEPI-MDS) (12 months)	533 postmenopausal women (45–64 years) from PEPI without major contraindication to estrogen/progestin therapy (e.g. breast cancer) or breast discomfort at baseline	Breast density CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 99$) Continuous MPA (2.5 mg; $n = 112$) Cyclic P4 (200 mg; $n = 105$) CEE alone (0.625 mg; $n = 105$) Placebo ($n = 103$) Breast discomfort CEE (0.625 mg) plus Cyclic MPA (10 mg; $n = 100$) Continuous MPA (2.5 mg; $n = 112$) Cyclic P4 (200 mg; $n = 109$) CEE alone (0.625 mg; $n = 108$) Placebo ($n = 104$) Cyclic progestogens taken on days 1 to 12 of each 28-day cycle	Incidence of mammographic density increased at month 12 Placebo: −0.4% CEE/cyclical MPA: 4.6% CEE/continuous MPA: 4.4% CEE/cyclical P4: 3.1% Incidence of new-onset breast discomfort at month 12 Placebo: 12.5% CEE/cyclical MPA: 28.0% CEE/continuous MPA: 23.2% CEE/cyclical P4: 27.5% Significantly different from placebo; p = NS between MHT groups

(*Continued*)

Table 3. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Espié [50]	Prospective phase of the MISSION study (2004–2006)	4949 postmenopausal women without breast cancer, exposed or unexposed to MHT	Unexposed ($n = 2256$) Exposed ($n = 2693$) E2 alone E2 plus progestogen E2/P4 (43.7%) E2/Progestins (56.3%; excluding MPA and 19-nortestosterone derivatives) (Route of progestogens unspecified)	Breast cancer incidence: E2/P4: 0.40% E2/progestins: 0.94% p = NS between treatment groups RR (95% CI) for breast cancer (use vs no use): TD E2/P4: 0.46 (0.13–1.62) TD E2/progestins: 1.07 (0.5–2.27) Oral E2/progestins: 0.81 (0.23–2.85)
Fournier et al. [46]	Prospective cohort study (E3N) (1990–2002)	80,377 postmenopausal women without a history of cancer other than a basal cell carcinoma at baseline (23,703 never users and 56,674 ever users of MHT)	Oral estrogens (cases/PY): P4 (<5 cases) MPA (29/7035) NETA (46/7401) DYD (7/3217) Medrogestone (9/1104) CMA (8/1431) CPA (34/4779) Promegestone (13/2814) NOMAC (8/2623) TD estrogens (cases/PY): P4 (121/35,513) MPA (<5 cases) NETA (<5 cases) DYD (90/25,405) Medrogestone (28/4590) CMA (35/7774) CPA (<5 cases) Promegestone (69/14,910) NOMAC (91/18,826)	RR (95%) for invasive breast cancer (ever vs never use) Oral estrogens plus P4: number of cases too low to analyze MPA: 1.48 (1.02–2.16) NETA: 2.11 (1.56–2.86) DYD: 0.77 (0.36–1.62) Medrogestone: 2.74 (1.42–5.29) CMA: 2.02 (1.00–4.06) CPA: 2.57 (1.81–3.65) Promegestone: 1.62 (0.94–2.82) NOMAC: 1.10 (0.55–2.21) TD estrogens plus P4: 1.08 (0.89–1.31) DYD: 1.18 (0.95, 1.48) Medrogestone: 2.03 (1.39–2.97) CMA: 1.48 (1.05–2.09) Promegestone: 1.52 (1.19–1.96) NOMAC: 1.60 (1.28–2.01) MPA, NETA, CPA: number of cases too low to analyze <2 yrs MHT duration P4: 0.71 (0.44–1.14) DYD: 0.84 (0.51–1.38) Other progestogens: 1.36 (1.07–1.72) 2–4 yrs MHT duration P4: 0.95 (0.67–1.36) DYD: 1.16 (0.79–1.71) Other progestogens: 1.59 (1.30–1.94) 4–6 yrs MHT duration P4: 1.26 (0.87–1.82) DYD: 1.28 (0.83–1.99) Other progestogens: 1.79 (1.44–2.23) ≥6 yrs MHT duration P4: 1.22 (0.89–1.67) DYD: 1.32 (0.93–1.86) Other progestogens: 1.95 (1.62–2.35)
Fournier et al. [47]	Prospective cohort study (E3N) (1990–2002)	80,391 postmenopausal women without a history of cancer except cell carcinoma (23,725 never users and 56,666 ever users of MHT)	Ductal cases Estrogen/P4 ($n = 87$) Estrogen/DYD ($n = 70$) Estrogen/other progestogens ($n = 334$) Lobular cases Estrogen/P4 ($n = 24$) Estrogen/DYD ($n = 28$) Estrogen/other progestogens ($n = 113$)	RR (95%) (ever vs never use) Ductal breast cancer P4: 1.0 (0.8–1.3) DYD: 1.1 (0.9–1.4) Other progestogens: 1.6 (1.3–1.8) Lobular breast cancer P4: 1.1 (0.7–1.7) DYD: 1.7 (1.1–2.6) Other progestogens: 2.0 (1.5–2.7)

(*Continued*)

Table 3. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Fournier et al. [48]	Prospective, cohort study (E3N) (1990–2005)	53,310 postmenopausal women without a history of cancer except basal cell carcinoma (21,231 never users and 32,079 ever users of MHT)	Invasive breast cancer cases Estrogen/P4 ($n = 210$) Estrogen/DYD ($n = 150$) Estrogen/other progestogen ($n = 577$)	HR (95% CI) invasive breast cancer (recent vs never use) MHT initiated ≤3 years from menopause ≤2 yrs MHT duration P4: 0.87 (0.57–1.32) DYD: 1.44 (0.99–2.09) Other progestogen: 1.89 (1.53–2.34) 2–5 yrs MHT duration P4: 1.01 (0.72–1.41) DYD: 1.21 (0.85–1.72) Other progestogen: 1.88 (1.56–2.27) 5–10 yrs MHT duration P4: 1.47 (1.11–1.95) DYD: 1.38 (0.98–1.93) Other progestogen: 1.87 (1.54–2.27) >10 yrs MHT duration P4: 1.92 (1.34–2.74) DYD: 1.35 (0.81–2.26) Other progestogen: 2.32 (1.76–3.06) MHT initiated >3 years from menopause ≤2 yrs MHT duration P4: 0.90 (0.45–1.81) DYD: 1.14 (0.51–2.55) Other progestogen: 1.02 (0.59–1.78) 2–5 yrs MHT duration P4: 1.55 (0.96–2.48) DYD: 0.95 (0.42–2.13) Other progestogen: 1.79 (1.22–2.63) 5–10 yrs MHT duration P4: 0.89 (0.50–1.59) DYD: 1.77 (1.02–3.09) Other progestogen: 2.21 (1.56–3.14) >10 yrs MHT duration P4: 0.97 (0.36–2.62) DYD: 1.83 (0.68–4.93) Other progestogen: 1.07 (0.40–2.87)
Cordina-Duverger et al. [79]	Population-based, case-control study (2005–2007)	1555 menopausal women aged 25–75 (739 incident cases of *in situ* or invasive breast cancer and 816 controls without prior history of breast cancer)	Breast cancer (case/control) Estrogen plus P4 (25/34) Progestins (67/48) P4 derivatives (55/43) Testosterone derivatives (11/5) Never use (311/357)	ORs (95% CI) for breast cancer (current vs nonuse) P4: 0.80 (0.44–1.43) Progestins: 1.72 (1.11–2.65) P4 derivatives: 1.57 (0.99–2.49) Testosterone derivatives: 3.35 (1.07–10.4) <4 yrs MHT duration P4: 0.69 (0.29–1.68) Progestins: 1.17 (0.48–2.86) P4 derivatives: 1.02 (0.40–2.58) Testosterone derivatives: 1.64 (0.38–7.15) ($n < 5$) ≥4 yrs MHT duration P4: 0.79 (0.37–1.71) Progestins: 2.07 (1.26–3.39) P4 derivatives: 1.92 (1.13–3.27) Testosterone derivatives: 9.47 (1.09–82.6) ($n < 5$)
Zheng et al. [57]	Prospective, randomized study (3 months)	96 early postmenopausal women aged 40–60 years with climacteric symptoms	Oral E2V plus oral, cyclic P4 ($n = 32$) MPA ($n = 32$) Cyclic progestogens taken on days 19 to 30 of a 30-day cycle	Breast tenderness incidence in 3 months P4: 36.7% MPA: 14.3%

(*Continued*)

Table 3. Continued.

Reference	Study design (duration)	Population	Treatment (dose; number of subjects)	Reported outcomes
Fournier et al. [49]	Prospective, cohort study (E3N) (1990–2008)	78,353 postmenopausal women without a history of cancer except basal cell carcinoma (31,223 never users, 21,601 past users, and 17,986 current users of MHT)	Invasive breast cancer cases Never use ($n=890$) Current use of estrogen plus P4/DYD ($n=638$) Other progestogens[e] ($n=931$) Past use of estrogen plus P4/DYD ($n=552$) Other progestogens[e] ($n=708$)	HR (95% CI) for invasive breast cancer Current vs never use P4/DYD: 1.22 (1.11–1.35) Other progestogens 1.87 (1.71–2.04) Past vs never use P4/DYD: 0.96 (0.87–1.06) Other progestogens 1.12 (1.02–1.23)
Asi et al. [41]	Meta-analysis	3 comparative/controlled studies of women aged 45–59 years, <10 years from menopause, followed up for ≥6 months (2 studies compared progesterone with progestins)	Estrogens plus P4 Progestins	RR (95% CI) for breast cancer: P4 vs progestins 0.67 (0.55–0.81)
Yang et al. [42]	Meta-analysis	9 observational comparison studies with combined MHT containing opposed or unopposed E2 or E2V; peri/postmenopausal women who received MHT (including hysterectomized with ovaries)	E2/E2V plus MPA (2 studies) LNG (2 studies) NETA (4 studies) DYD (3 studies) P4 (2 studies) Mixed progestogens (6 studies) (route of progestogens unspecified)	Pooled ORs (95% CI) for breast cancer MPA: 1.19 (1.07–1.33) LNG: 1.47 (1.17–1.85) NETA: 1.44 (1.26–1.65) DYD: 1.10 (0.89–1.36) P4: 1.00 (0.83–1.20) Mixed progestogens: 1.99 (1.57–2.52)
Zeng et al. [28]	Retrospective case-control study (unspecified)	40,046 women aged >50 years (12,404 cases: women who took any MHT after age 50; 27,642 controls: women who did not take any MHT after age 50	MHT cases CEE/MPA ($n=453$) Synthetic estrogen/ synthetic progestins ($n=2512$) Bioidentical estrogens/P4[b,c] ($n=288$)	HR (95% CI) for breast cancer (ever vs never use) CEE/MPA: 0.43 (0.28–0.67) Synthetic estrogens/synthetic progestins: 1.03 (0.84–1.27) Bioidentical estrogens/P4: 1.05 (0.59–1.85) CEE/MPA vs bioidentical estrogens/P4[b,c]: 0.25 (0.12–0.55)
Gao et al. [65]	Prospective, randomized, controlled study	96 early postmenopausal women aged 40–60 years	Oral E2V (1mg) plus cyclic MPA (4 mg; $n=32$) P4 (100 mg; $n=32$) Cyclic progestogens taken on days 19 to 30 of a 30-day cycle	Breast tenderness incidence in 12 months: MPA: 80.8% P4: 72.0% (p = NS between groups)
Wang et al. [58]	Prospective, randomized study	96 early postmenopausal women aged 40–60 years	Oral E2V (1 mg) plus cyclic P4 (4 mg; $n=32$) MPA (100 mg; $n=32$) Cyclic progestogens taken on days 19 to 30 of a 30-day cycle	Breast pain incidence in 6 months: MPA: 71.4% P4: 62.1% (p = NS between groups) No significant differences in duration of breast pain; Pain intensity was similar
Abenhaim et al. [34]	Nested case-control study (1995–2014)	43,183 women aged 50–75 years who had the first diagnosis of invasive breast cancer post-index, matched by 431,830 women as controls	Progestogen subgroups (cases/controls) No progestogen (40,352/410,256) P4 (12/125) Progestins[f] (2817/21,434) Both progestogen formulations (2/15)	Breast cancer adjusted OR (95% CI) for ever use of any HT vs never use of progestogen: P4: 0.99 (0.55–1.79) Progestins: 1.28 (1.22–1.35)

BI-RADS: Breast Imaging Reporting and Data System; CEE: conjugated equine estrogens; CI: confidence interval; CMA: chlormadinone acetate; CPA: cyproterone acetate; DYD: dydrogesterone; E2: estradiol; E2H: estradiol hemihydrate; E2V: estradiol valerate; E3N: the Etude Epidémiologique de femmes de l'Education Nationale Study; EPIC: the European Prospective Investigation into Cancer and Nutrition study; FSH: follicle-stimulating hormone; HR: hazard ratio; LNG: levonorgestrel; MHT: menopausal hormone therapy; MISSION: the Menopause: Risk of Breast Cancer, Morbidity and Prevalence study; MPA: medroxyprogesterone acetate; NETA: norethisterone acetate; NOMAC: nomegestrol acetate; NS: not significant; OR: odds ratio; P4: progesterone; PEPI: the Postmenopausal Estrogen/Progestin Interventions study; PEPI-MDS: the PEPI Mammographic Density Study; RR: relative risk; TD: transdermal; VMS: vasomotor symptoms; WHI-OS: the Women's Health Initiate Observational Study.

Early postmenopausal: amenorrhea >6 months and <5 years.

[a]Calculation of percentages not consistent with n in each group, not clear in paper how it was calculated.

[b]Bioidentical estrogens included: estradiol oral, Estrace oral, 17β-estradiol, micronized estrogen, estradiol acetate oral, estradiol hemihydrate oral, Gynodiol oral, Femtrace, Innofem, estradiol acetate oral, Delestrogen, estradiol valerate, estradiol cypionate, Depo-Estradiol, estradiol transdermal, Alora, Climara, Esclim, Estraderm, Vivelle, Vivelle-Dot, Dot, Estrogel, Estrasorb, Estradiol Transdermal, Transdermal Estradiol, Fem-Patch, Menostar, Elestrin, Divigel, Evamist, Estrasorb, Minivelle (as reported).

[c]Bioidentical progesterone included: micronized progesterone, Prometrium, Prochieve, Crinone (as reported).

[d]Bioidentical estrogens included: estradiol (Estraderm, Evorel, Oestrogel, FemSeven, Elleste Solo, Sandrena, Progynova, Fematrix, Zumenon, Estradot, Menorest, Dermestril, Bedol, Nuvelle TS Phase 1, Adgyn, Indivina), estriol (Ovestin), estrone (piperazine estrone sulfate, Improvera), and a tri-estrogen formulation containing estriol, estradiol, and estrone (Hormonin).

[e]Other progestogens included: CMA, CPA, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, LNG, lynestrenol, medrogestone, MPA, nomegestrol acetate, NOMAC, NETA, and promegestone.

[f]Progestins included: predominantly MPA (Depo-provera, Provera, Sayana Press, Climanor, Premique, Indivina), norgestrel, and levonorgestrel (FemSeven).

CEE (0.625 mg) in the WHI observational study (WHI-OS) [14]. Similarly, no differences in risk for MI and ischemic stroke were observed between CEE or E2 in a case-control study [27]. Finally, a population-based, cohort study found women had higher risk of new-onset atrial fibrillation (AF), stroke, and major adverse cardiac events when using CEE than E2 [29].

One case-control comparative study examining CVD risk among progestogens showed that current users of E2 plus norpregnane derivatives had an increased risk for ischemic stroke, but this was not observed with E2 plus P4, pregnane derivatives, or nortestosterone derivatives (Figure 2B) [35].

Lipids

Two prospective studies investigated plasma lipids, a surrogate marker for CVD risk, with different oral estrogens. The first study found an improved lipid profile and decreased homocysteine level in women using E2 or CEE alone versus no use [11]. The other study was small ($n = 6$ per group) and found no significant lipid changes with any estrogen, except for significant decreases in low-density lipoprotein cholesterol (LDL-c) from baseline with CEE (0.625 mg) and E2 (1 mg) [26].

Four randomized trials showed that the use of P4 had no adverse lipid effects in postmenopausal women. In the PEPI trial, women using CEE plus cyclic P4 had similar high-density lipoprotein cholesterol (HDL-c) levels to those using CEE-alone but significantly higher levels than with CEE plus cyclic or continuous MPA; all regimens decreased LDL-c and increased triglycerides compared with placebo [66]. Similarly, another study reported significant increases in HDL-c and decreases in LDL-c with CEE (0.625 mg) when combined with P4 (100 mg) or DYD (10 mg); while triglycerides only significantly increased with DYD [64]. In another study using E2V, HDL-c levels remained unchanged with P4, but significantly decreased with MPA, while triglycerides did not change with either regimen [63]. Finally, a study of transdermal E2 plus P4 or CMA revealed little impact of either on total cholesterol and triglycerides [53].

Blood pressure

No studies comparing oral E2 with CEE on the effects on BP were identified. Five randomized studies showed similar or better effects of MHT containing P4 versus other progestogens. The PEPI trial [66] as well as two other randomized trials [63, 64] found no changes from baseline in systolic BP (SBP) and diastolic BP (DBP) with oral CEE or E2V when combined with P4 or MPA [63, 66], or DYD [64], except for a significant decrease in DBP for CEE/P4 (0.3 mg/100 mg) [64]. Further, one randomized study showed that SBP and DBP decreased from baseline with E2/P4, but increased with E2/CMA [53]. Finally, a RCT found that SBP and DBP reactivity during stress tended to decrease after 8 weeks of estrogen/P4, while estrogen/MPA maintained SBP reactivity and significantly increased DBP reactivity [77].

Breast

Details of the clinical studies included in this section can be found in Table 3.

Breast cancer

Effects of MHT containing E2 or CEE on the breast were compared in six observational studies (Figure 2A) [15–17, 28, 33, 34]. The European Prospective Investigation into Cancer and Nutrition (EPIC) trial [15], the WHI-OS trial [17], and one prospective study [33] showed that breast cancer risk increased in estrogen-only users but with no significant difference between CEE and E2 users. The prospective study also showed that breast cancer risk significantly increased with longer duration of E2 products, but not CEE [33]. Increased breast cancer risk with E2 or CEE in current users was also observed in a Swedish retrospective study, with CEE having a higher risk than E2 [16]. However, the same Swedish study found that the risk of breast cancer remained similar in ever users of CEE and decreased in ever users of E2 [16]. Finally, a retrospective analysis showed a decreased breast cancer risk with either bioidentical estrogens or CEE alone [28], while a more recent retrospective study found no association of MHT containing bioidentical estrogens or CEE with breast cancer [34].

Various analyses of the E3N observational study, including the E3N-EPIC study, and two case-controlled studies found increased breast cancer risk with MHT containing progestins but not progesterone (Figure 2C). The French E3N study ($n = 80{,}377$) showed elevated breast cancer risk with transdermal estrogens plus progestins (medogestone [MDG]/CMA/promegestone [PMG]/norethisterone acetate [NETA]) but not with P4 or DYD for overall risk and by 2-year increments of MHT duration [46]. Similar results were also reported in the E3N-EPIC ($n = 54{,}548$) [45] and two case-control studies ($n = 1555$ and 475,013, respectively) [34, 79]. When the E3N data were analyzed by years from menopause, breast cancer risk did not increase with P4 with ≤5 years of use or when initiation was >3 years after menopause, but it did increase with >5 years of duration or when MHT was initiated ≤3 years from menopause; other progestogens, except DYD, increased breast cancer risk when used for 2 to 10 years [48]. When analyzed by current versus never use, breast cancer risk was found elevated in both P4/DYD and other progestin groups, while past versus never use, showed an increased risk with past use of estrogen/progestins, but not with estrogen plus P4/DYD [49]. Finally, the neutral effect of estrogen plus P4 was also consistent by breast cancer subtype (ductal or lobular), while increased risk was associated with estrogen/DYD for the lobular subtype and with estrogen/other progestins for all subtypes studied [47]. Two meta-analyses had results consistent with the observational studies, with P4 associated with lower breast cancer risk versus progestins [41, 42].

Only two studies showed no difference between P4 and other progestins for breast cancer risk. One prospective French cohort study showed no increase in breast cancer risk with E2 with P4 nor progestins [50], while the other showed no increase in breast cancer for synthetic estrogens/progestins or bioidentical estrogens/P4 and a significantly lower risk with CEE/MPA from baseline and when compared with bioidentical estrogens/P4 [28].

Breast density and breast tenderness

One prospective study evaluated the effects of E2 vs CEE on mammographic breast density (MBD), which showed no significant difference between the two groups [18].

Studies focusing on breast tissue changes revealed similar or better effects for P4- versus progestin-containing MHT on MBD

[68–71] and breast tenderness [55, 58, 65]. In the PEPI trial, MBD analyses found that women taking CEE with MPA or P4 had significant increases in breast density compared with placebo at month 12, but with no difference between groups [69–71]. Similarly, women using CEE with MPA or P4 also had higher odds of breast discomfort compared with placebo, with no difference between MPA versus P4 [68,71]. A randomized study comparing E2V with P4 or MPA found more breast tenderness with P4 than with MPA (36.7% vs 14.3%) at 3 months [57], but not at 6 and 12 months [58, 65]. While one small prospective study ($n = 23$) showed more breast tenderness cases with CEE/MPA than CEE/P4, no statistical analysis was performed, and neither P4 or MPA alone were associated with breast tenderness [55].

Cognition

Observational studies and a meta-analysis comparing different estrogens on cognitive outcomes reported mostly better outcomes with E2 than CEE (Supplementary Table 1). The meta-analysis of 36 RCTs showed that cognition tended ($p = .1$) to be slightly worse with CEE versus E2 alone [9]. A small retrospective study showed a better neural response in women using opposed CEE or opposed E2 versus MHT-naïve women; however, verbal learning and recall performance was worse in CEE than E2 users [19]. Postmenopausal women at risk for dementia or Alzheimer's disease (AD) taking MHT for ≥1 year had better cognitive outcomes with E2 versus CEE [20–22], including E2 users performing significantly better in verbal memory [20, 21] and with a significantly higher brain metabolism level versus CEE users [20]. Two years after either continuing or discontinuing MHT, women who had used E2-based MHT had better verbal memory ($p = .01$) than those who had used CEE-based MHT [23], while continued CEE use and discontinuation of E2 use significantly decreased cerebral metabolism [22].

Two small studies provided head-to-head comparisons of MHT containing P4 versus progestins for their influence on cognition (Supplementary Table 1). A 12-week RCT of women using CEE plus cyclic P4 or MPA found significantly improved working memory and significantly decreased delayed verbal memory with CEE/P4; while no changes with CEE/MPA were observed [72]. Verbal memory, visual memory, executive function, or attention/working memory/processing speed did not differ with ≥1-year use of MHT containing P4 versus MPA in a cross-sectional study of women with increased AD risk [21].

Bone

A systematic review and meta-analysis of 28 RCTs found that MHT containing either E2 or CEE reduced bone fracture risk versus placebo with a significantly greater reduction with E2 than with CEE (Supplementary Table 1) [10].

Head-to-head comparisons of MHT containing P4 or other progestins on bone mineral density (BMD) did not show significant differences (Supplementary Table 1). In the PEPI trial, CEE with P4 or MPA significantly increased spinal and hip BMD from baseline to 3 years, in contrast to the decrease with placebo; CEE with continuous MPA was significantly better than CEE with cyclic MPA/P4 for spinal BMD [67]. Three other randomized, open-label studies also found improved BMD and bone metabolism from baseline with no differences between groups for transdermal E2 with continuous P4 or MPA [59], or oral CEE with cyclic P4 or DYD [73, 74].

Menopausal symptoms and QOL

Study details for this section can be found in the Supplemental Materials and Supplemental Table 1. For the most part, outcomes were similar between formulations for vasomotor symptoms and body weight and composition. Limited evidence suggests that P4 may provide better QoL and sleep than other progestogens.

Discussion

This comprehensive literature review of clinical studies comparing the safety and effectiveness of MHT containing E2 versus CEE and of P4 versus progestins found some differential effects between these different formulations, suggesting a mostly similar or better safety profile with E2 and/or P4. Most of the studies revealed similar or lower risk for breast cancer, VTE, cardiovascular outcomes, and cognitive parameters for E2- or P4-based MHT compared with CEE- or progestin-based MHT, respectively. Data suggest that E2- or P4-containing formulations are as effective as other estrogens or progestogens for relieving menopausal symptoms and maintaining bone health, but with potentially better tolerability.

Concomitant progestogen use with estrogen therapy is indicated in postmenopausal women with a uterus for endometrial protection [1]. Although a systematic review reported an increased risk of endometrial cancer with P4-containing MHT [81] mainly based on results from the two observational studies described [43, 44], randomized-controlled studies showed that P4 prevents endometrial hyperplasia, offering similar endometrial protection, compared with progestins when used at an adequate dose [51, 53]. The most recent, phase 3, randomized, placebo-controlled trial, REPLENISH, demonstrated adequate endometrial protection with P4 when given with E2 for menopausal symptom control [82, 83].

Initial publication of increased risk of CHD, VTE, and breast cancer with CEE/MPA in the WHI raised concerns of cardiovascular diseases and breast cancer with MHT use [2, 3]. Our review of large, observational studies of MHT, including MWS, WHI-OS, EPIC, ESTHER, and E3N, showed that E2 has similar or lower risk compared with CEE on the breast and cardiovascular outcomes including VTE [12, 14–17, 29, 31, 32, 34], and similarly, P4 had a risk profile similar to or better compared with progestins for these outcomes [34–36, 38, 45–48, 50, 78, 79]. In addition, the randomized, placebo-controlled PEPI trial showed no negative impact of CEE/P4 on lipids [66] and comparable effects on breast density or breast discomfort with CEE/P4 and CEE/MPA [68–71]. A lower risk for VTE with E2/P4 versus CEE/MPA was also observed in a retrospective study [80].

Whether MHT could protect against cognitive aging and dementia in postmenopausal women has been inconclusive [84]. Outcomes in cognition tests from a limited number of smaller studies suggest that E2 could provide better protection against age-related cognitive decline versus CEE [20–23], whereas effects of P4 were similar to or better than MPA [21, 72]. However, additional studies are necessary to conclude whether P4 influences cognitive function differently from other progestogens.

Data from prospective, randomized trials, including PEPI, revealed similar improvements in bone health with P4-based MHT versus MPA- or DYD-based MHT [59, 67, 73, 74], while a meta-analysis reported a greater reduction in total fractures with MHT containing E2 versus CEE [10]. Moreover, comparative studies showed that the influence on VMS reduction and body weight or composition was similar for MHT containing

E2 versus CEE [8, 25] or P4 versus progestins [53, 55, 60, 62, 66, 68, 75, 76], while QOL and sleep disorders appeared to be similarly or better improved with P4-based versus progestin-based MHT [40, 52, 57, 60, 61, 63, 76, 77].

Our review has limitations. Studies included are of diverse designs and few RCTs directly compared E2 versus CEE or P4 versus progestins. Many studies were observational, and therefore, could not exclude selection bias. Details of hormone use, such as specific products or exact doses, are often unknown in observational studies. For example, in patients receiving P4-based MHT, different estrogen types or products could have been used, which can influence the results. Sample sizes of the studies also varied largely, and some studies may not have been adequately powered for the reported outcomes. In addition, we also acknowledge that when individualizing MHT for women, there may be certain advantages to utilizing transdermal E2 over oral estrogens because transdermal E2 bypasses the first-pass hepatic effect, especially on VTE risk [85]. However, given the breadth of that literature and the aim of our review, we considered that topic beyond the scope of this article and did not include studies comparing transdermal and oral estrogens as part of our study inclusion criteria. While we also believe performing a meta-analysis of the results from the identified studies would help quantify the differences in hormones reviewed, given the inconsistencies in data reporting between studies and within outcomes, a meta-analysis was not feasible. Another limitation of the review process was having access only to PubMed and EMBASE databases for searching. Nevertheless, this is a comprehensive and systematic review of the available literature on the differential effects of E2 versus CEE and P4 versus progestins, which could provide insights in the benefit/risk profile of MHT containing E2 and P4 that could be considered when prescribing women MHT and developing related guidelines.

Conclusion

Current evidence supports that MHT containing E2 and/or P4 is a safe and effective MHT option, and provides a similar and possibly better safety profile for some endpoints compared with CEE-based or progestin-based MHT.

Disclosure statement

Medical writing assistance provided by Hui Zhang, PhD and Dominique Verlaan, PhD was supported by TherapeuticsMD. DFA has received research support from AbbVie, Mithra, Myovant, and ObsEva; has consulted for Agile Therapeutics, Evestra, Exeltis, Lupin, Mithra, ObsEva, and TherapeuticsMD; and has stock holdings with Agile Therapeutics and InnovaGyn, Inc. JAS has received grant/research support from AbbVie, Bayer Healthcare, Endoceutics, GTx Inc, Ipsen, Myovant Sciences, ObsEva SA, TherapeuticsMD, and Viveve Medical; has consulted or advised for AbbVie, AMAG Pharmaceuticals, Bayer HealthCare, CEEK Enterprises, Covance, DEKA M.E.L.A S.r.l, Daré Bioscience, Duchesnay USA, Hologic, KaNDy/NeRRe Therapeutics Ltd, Madorra Pty Ltd, Mitsubishi Tanabe Pharma Development America, Sebela Pharmaceuticals, Shionogi Inc, Sprout Inc., and TherapeuticsMD; serves on the speaker's bureaus of AbbVie, AMAG Pharmaceuticals, Duchesnay USA, and TherapeuticsMD; and is a stockholder (direct purchase) in Sermonix Pharmaceuticals. KMO is the owner of Precise Publications, which received fees from TherapeuticsMD for the research and medical writing services for this manuscript and other publications/presentations. SG and BB are employees of TherapeuticsMD with stock/stock options.

Funding

The medical writing assistance provided by Hui Zhang, PhD, and Dominique Verlaan, PhD of Precise Publications, LLC, was supported by TherapeuticsMD.

References

[1] The NAMS Hormone Therapy Position Statement Advisory Panel. The 2022 hormone therapy position statement of the North American menopause society. Menopause. 2022;29(7):767–794.
[2] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA. 2002;288(3):321–333.
[3] Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. JAMA. 2004;292(13):1573–1580.
[4] Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004;291(1):47–53.
[5] American College of Obstetricians and Gynecologists. Committee opinion no. 532: compounded bioidentical menopausal hormone therapy. Obstet Gynecol. 2012;120(2 Pt 1):411–415.
[6] Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. Climacteric. 2016;19(4):316–328.
[7] Ettinger B, Bainton L, Upmalis DH, et al. Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women. Am J Obstet Gynecol. 1997;176(1):112–117.
[8] Dittmar M. Comparison of soft tissue body composition in postmenopausal women with or without hormone replacement therapy considering the influence of reproductive history and lifestyle. Ann Hum Biol. 2001;28(2):207–221.
[9] Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. Maturitas. 2010;66(1):56–71.
[10] Zhu L, Jiang X, Sun Y, et al. Effect of hormone therapy on the risk of bone fractures: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2016;23(4):461–470.
[11] Man RY, Ting LK, Fan S, et al. Effect of postmenopausal hormone replacement therapy on lipoprotein and homocysteine levels in Chinese women. Mol Cell Biochem. 2001;225(1):129–134.
[12] Sweetland S, Beral V, Balkwill A, et al. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012;10(11):2277–2286.
[13] Blondon M, van HV, Wiggins KL, et al. Differential associations of oral estradiol and conjugated equine estrogen with hemostatic biomarkers. J Thromb Haemost. 2014;12(6):879–886.
[14] Shufelt CL, Merz CN, Prentice RL, et al. Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the women's health initiative observational study. Menopause. 2014;21(3):260–266.
[15] Bakken K, Fournier A, Lund E, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European prospective investigation into cancer and nutrition. Int J Cancer. 2011;128(1):144–156.
[16] Brusselaers N, Tamimi RM, Konings P, et al. Different menopausal hormone regimens and risk of breast cancer. Ann Oncol. 2018;29(8):1771–1776.
[17] Shufelt C, Bairey Merz CN, Pettinger MB, et al. Estrogen-alone therapy and invasive breast cancer incidence by dose, formulation, and route of delivery: findings from the WHI observational study. Menopause. 2018;25(9):985–991.
[18] Bulbul NH, Ozden S, Dayicioglu V. Effects of hormone replacement therapy on mammographic findings. Arch Gynecol Obstet. 2003;268(1):5–8.
[19] Gleason CE, Schmitz TW, Hess T, et al. Hormone effects on fMRI and cognitive measures of encoding: importance of hormone preparation. Neurology. 2006;67(11):2039–2041.

[20] Silverman DH, Geist CL, Kenna HA, et al. Differences in regional brain metabolism associated with specific formulations of hormone therapy in postmenopausal women at risk for AD. Psychoneuroendocrinology. 2011;36(4):502–513.
[21] Wroolie TE, Kenna HA, Williams KE, et al. Differences in verbal memory performance in postmenopausal women receiving hormone therapy: 17beta-estradiol versus conjugated equine estrogens. Am J Geriatr Psychiatry. 2011;19(9):792–802.
[22] Rasgon NL, Geist CL, Kenna HA, et al. Prospective randomized trial to assess effects of continuing hormone therapy on cerebral function in postmenopausal women at risk for dementia. PLoS One. 2014;9(3):e89095.
[23] Wroolie TE, Kenna HA, Williams KE, et al. Cognitive effects of hormone therapy continuation or discontinuation in a sample of women at risk for Alzheimer disease. Am J Geriatr Psychiatry. 2015;23(11):1117–1126.
[24] Notelovitz M, Kitchens CS, Ware MD. Coagulation and fibrinolysis in estrogen-treated surgically menopausal women. Obstet Gynecol. 1984;63(5):621–625.
[25] Utian WH, Speroff L, Ellman H, et al. Comparative controlled trial of a novel oral estrogen therapy, estradiol acetate, for relief of menopause symptoms. Menopause. 2005;12(6):708–715.
[26] Lobo RA, Brenner P, Mishell DR. Jr. Metabolic parameters and steroid levels in postmenopausal women receiving lower doses of natural estrogen replacement. Obstet Gynecol. 1983;62(1):94–98.
[27] Smith NL, Blondon M, Wiggins KL, et al. Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. JAMA Intern Med. 2014;174(1):25–31.
[28] Zeng Z, Jiang X, Li X, et al. Conjugated equine estrogen and medroxyprogesterone acetate are associated with decreased risk of breast cancer relative to bioidentical hormone therapy and controls. PLoS One. 2018;13(5):e0197064.
[29] Tsai WC, Haung YB, Kuo HF, et al. Hormone replacement therapy and risk of atrial fibrillation in taiwanese menopause women: a nationwide cohort study. Sci Rep. 2016;6:24132.
[30] Cengiz B, Atabekoglu C, Cetinkaya E, et al. Effect of hormone replacement therapy on serum levels of tumor markers in healthy postmenopausal women. Maturitas. 2003;46(4):301–306.
[31] Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019;364:k4810.
[32] Blondon M, Timmons AK, Baraff AJ, et al. Comparative venous thromboembolic safety of oral and transdermal postmenopausal hormone therapies among women veterans. Menopause. 2021;28(10):1125–1129.
[33] Bergkvist L, Adami HO, Persson I, et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med. 1989;321(5):293–297.
[34] Abenhaim HA, Suissa S, Azoulay L, et al. Menopausal hormone therapy formulation and breast cancer risk. Obstet Gynecol. 2022;139(6):1103–1110.
[35] Canonico M, Carcaillon L, Plu-Bureau G, et al. Postmenopausal hormone therapy and risk of stroke: impact of the route of estrogen administration and type of progestogen. Stroke. 2016;47(7):1734–1741.
[36] Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. Arterioscler Thromb Vasc Biol. 2010;30(2):340–345.
[37] Canonico M, Alhenc-Gelas M, Plu-Bureau G, et al. Activated protein C resistance among postmenopausal women using transdermal estrogens: importance of progestogen. Menopause. 2010;17(6):1122–1127.
[38] Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840–845.
[39] Scarabin PY, Hemker HC, Clement C, et al. Increased thrombin generation among postmenopausal women using hormone therapy: importance of the route of estrogen administration and progestogens. Menopause. 2011;18(8):873–879.
[40] Fitzpatrick LA, Pace C, Wiita B. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. J Womens Health Gend Based Med. 2000;9(4):381–387.
[41] Asi N, Mohammed K, Haydour Q, et al. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev. 2016;5(1):121.
[42] Yang Z, Hu Y, Zhang J, et al. Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: a systematic review and meta-analysis. Gynecol Endocrinol. 2017;33(2):87–92.
[43] Allen NE, Tsilidis KK, Key TJ, et al. Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European prospective investigation into cancer and nutrition. Am J Epidemiol. 2010;172(12):1394–1403.
[44] Fournier A, Dossus L, Mesrine S, et al. Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008. Am J Epidemiol. 2014;180(5):508–517.
[45] Fournier A, Berrino F, Riboli E, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer. 2005;114(3):448–454.
[46] Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008;107(1):103–111.
[47] Fournier A, Fabre A, Mesrine S, et al. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. J Clin Oncol. 2008;26(8):1260–1268.
[48] Fournier A, Mesrine S, Boutron-Ruault MC, et al. Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J Clin Oncol. 2009;27(31):5138–5143.
[49] Fournier A, Mesrine S, Dossus L, et al. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. Breast Cancer Res Treat. 2014;145(2):535–543.
[50] Espie M, Daures JP, Chevallier T, et al. Breast cancer incidence and hormone replacement therapy: results from the MISSION study, prospective phase. Gynecol Endocrinol. 2007;23(7):391–397.
[51] Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA. 1996;275(5):370–375.
[52] Ryan N, Rosner A. Quality of life and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for nonhysterectomized, postmenopausal women. Clin Ther. 2001;23(7):1099–1115.
[53] Pelissier C, Maroni M, Yaneva H, et al. Chlormadinone acetate versus micronized progesterone in the sequential combined hormone replacement therapy of the menopause. Maturitas. 2001;40(1):85–94.
[54] Jondet M, Maroni M, Yaneva H, et al. Comparative endometrial histology in postmenopausal women with sequential hormone replacement therapy of estradiol and, either chlormadinone acetate or micronized progesterone. Maturitas. 2002;41(2):115–121.
[55] Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. Menopause. 2002;9(4):253–263.
[56] Di Carlo C, Sammartino A, Di Spiezio SA, et al. Bleeding patterns during continuous estradiol with different sequential progestogens therapy. Menopause. 2005;12(5):520–525.
[57] Zheng TP, Sun AJ, Xue W, et al. Efficacy and safety of cimicifuga foetida extract on menopausal syndrome in Chinese women. Chin Med J (Engl). 2013;126(11):2034–2038.
[58] Wang YP, Ma D, Cheng XT, et al. Comparison of *Cimicifuga foetida* extract and different hormone therapies regarding in causing breast pain in early postmenopausal women. Gynecol Endocrinol. 2019;35(2):160–164.
[59] Sun A, Lin S, Yu W, et al. Percutaneous estrogen in prevention of early postmenopausal bone loss in Chinese women. Chin Med J (Engl). 2002;115(12):1790–1795.

[60] Montplaisir J, Lorrain J, Denesle R, et al. Sleep in menopause: differential effects of two forms of hormone replacement therapy. Menopause. 2001;8(1):10–16.
[61] Leeangkoonsathian E, Pantasri T, Chaovisitseree S, et al. The effect of different progestogens on sleep in postmenopausal women: a randomized trial. Gynecol Endocrinol. 2017;33(12):933–936.
[62] Deng Y, Xue W, Wang Y, et al. Effects of different menopausal hormone replacement regimens on body composition in Chinese women. Climacteric. 2018;21(6):607–612.
[63] Gao L, Zheng T, Xue W, et al. Efficacy and safety evaluation of *Cimicifuga foetida* extract in menopausal women. Climacteric. 2018;21(1):69–74.
[64] Xue W, Deng Y, Wang YF, et al. Effect of half-dose and standard-dose conjugated equine estrogens combined with natural progesterone or dydrogesterone on components of metabolic syndrome in healthy postmenopausal women: a randomized controlled trial. Chin Med J (Engl). 2016;129(23):2773–2779.
[65] Gao L, Zuo H, Zheng T, et al. Influence of hormone therapy or *C. foetida* extract on breast tenderness in postmenopausal women. Climacteric. 2018;21(3):292–297.
[66] Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA. 1995;273(3):199–208.
[67] Writing Group for the Pepi Trial. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA. 1996;276(17):1389–1396.
[68] Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the postmenopausal estrogen/progestin interventions trial. Obstet Gynecol. 1998;92(6):982–988.
[69] Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal estrogen/progestin interventions (PEPI) investigators. Ann Intern Med. 1999;130(4 Pt 1):262–269.
[70] Greendale GA, Reboussin BA, Slone S, et al. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst. 2003;95(1):30–37.
[71] Crandall CJ, Karlamangla A, Huang MH, et al. Association of new-onset breast discomfort with an increase in mammographic density during hormone therapy. Arch Intern Med. 2006;166(15):1578–1584.
[72] Sherwin BB, Grigorova M. Differential effects of estrogen and micronized progesterone or medroxyprogesterone acetate on cognition in postmenopausal women. Fertil Steril. 2011;96(2):399–403.
[73] Zhu SY, Deng Y, Wang YF, et al. Bone protection for early menopausal women in China: standard or half-dose estrogen with progestin? A one-year prospective randomized trail. Gynecol Endocrinol. 2019;35(2):165–169.
[74] Zuo H, Sun A, Gao L, et al. Effect of menopausal hormone therapy on bone mineral density in Chinese women: a 2-year, prospective, open-label, randomized-controlled trial. Med Sci Monit. 2019;25:819–826.
[75] Espeland MA, Stefanick ML, Kritz-Silverstein D, et al. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. Postmenopausal Estrogen-Progestin interventions study investigators. J Clin Endocrinol Metab. 1997;82(5):1549–1556.
[76] Gambacciani M, Ciaponi M, Cappagli B, et al. Effects of low-dose, continuous combined hormone replacement therapy on sleep in symptomatic postmenopausal women. Maturitas. 2005;50(2):91–97.
[77] Matthews KA, Owens JF, Salomon K, et al. Influence of hormone therapy on the cardiovascular responses to stress of postmenopausal women. Biol Psychol. 2005;69(1):39–56.
[78] Olie V, Plu-Bureau G, Conard J, et al. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause. 2011;18(5):488–493.
[79] Cordina-Duverger E, Truong T, Anger A, et al. Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. PLoS One. 2013;8(11):e78016.
[80] Panay N, Nappi RE, Boolell M, et al. Venous thromboembolism risk in menopausal women treated with oral estradiol/micronised progesterone versus conjugated estrogens/medroxyprogesterone: a claims data analysis in the United States. The 20th World Congress – International Society of Gynecological Endocrinology; 2022; Florence, Italy.
[81] Tempfer CB, Hilal Z, Kern P, et al. Menopausal hormone therapy and risk of endometrial cancer: a systematic review. Cancers (Basel). 2020;12(8):2195.
[82] Lobo RA, Archer DF, Kagan R, et al. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. Obstet Gynecol. 2018;132(1):161–170.
[83] Mirkin S, Goldstein SR, Archer DF, et al. Endometrial safety and bleeding profile of a 17β-estradiol/progesterone oral softgel capsule (TX-001HR). Menopause. 2020;27(4):410–417.
[84] Henderson VW. Gonadal hormones and cognitive aging: a midlife perspective. Womens Health (Lond). 2011;7(1):81–93.
[85] Rovinski D, Ramos RB, Fighera TM, et al. Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: a systematic review and meta-analysis. Thromb Res. 2018;168:83–95.