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Original article

Oral estradiol/micronized progesterone may be associated with lower risk of venous thromboembolism compared with conjugated equine estrogens/ medroxyprogesterone acetate in real-world practice

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ABSTRACT

Objectives: The Women's Health Initiative study reported an increased risk of venous thromboembolism among menopausal women treated with conjugated equine estrogens/medroxyprogesterone acetate (CEE/MPA) versus placebo. Newer hormone therapies may have a lower venous thromboembolism risk. The study compared the risk of venous thromboembolism between women treated with the combined oral product 17β-estradiol/ micronized progesterone (E2/P4) and those treated with oral CEE/MPA regimens.

Study design: In a retrospective longitudinal study using real-world claims data from April 2019 to June 2021, women aged 40 years or more treated with oral E2/P4 or oral CEE/MPA who did not have a venous thromboembolism diagnosis before first dispensing claim of CEE/MPA or E2/P4 identified on or after May 1st 2019 (index date) were observed for 6 months or more after the index date. Oral E2/P4 and oral CEE/MPA had been prescribed by the treating physician in real-world practice and were observed through pharmacy dispensing records.

Main outcome measures: Venous thromboembolism risk was compared between women receiving oral E2/P4 versus oral CEE/MPA.

Results: The study included 36,061 women treated with oral E2/P4 or oral CEE/MPA. In the analyses weighted by the inverse probability of treatment for control of potential confounding factors, the incidence of venous thromboembolism was significantly lower for oral E2/P4 compared with oral CEE/MPA (37/10,000 women-years for oral E2/P4 vs 53/10,000 women-years for oral CEE/MPA; incidence rate ratio 0.70, 95 % confidence interval: 0.53–0.92).

Conclusions: Real-world evidence suggests that the risk of venous thromboembolism is significantly lower among women treated with oral E2/P4 compared with oral CEE/MPA.

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1. Introduction

Menopause, a natural phase in the life cycle of women that usually occurs between ages 40 and 58 years, is often associated with bothersome vasomotor, urogenital, and sleep disturbances [1]. Hot flashes and night sweats affect up to 80 % of women [2] and can significantly impair the women's quality of life. Hot flashes represent the most common menopause-related reason for which women seek medical care in the perimenopausal and menopausal period [3,4].

Hormone therapy (HT) is the mainstay treatment to control for moderate to severe vasomotor symptoms [5,6]. In women with an intact uterus (i.e., the majority of women) the recommended HT includes various combinations of estrogens (e.g., 17b-estradiol [E2], conjugated equine estrogens [CEEs], estradiol valerate, ethinyl estradiol) and progestogens (e.g., drospirenone, dydrogesterone, levonorgestrel, medroxyprogesterone acetate [MPA], micronized progesterone [P4], norethindrone acetate, norgestimate) [7]. In North America, oral continuous-combined estrogen-progestogen therapies are the most used HTs [7], including older products such as CEE/MPA (Prempro®, approved by the Food and Drug Administration [FDA] in June 2003) and newer products such as E2/P4 (Bijuva®, 1 mg E2 and 100 mg P4 combined in a single capsule, approved by the FDA in October 2018).

Safety concerns associated with CEE/MPA and other HT types include increased risk of venous thromboembolism (VTE), coronary heart disease, stroke, and breast cancer [8,9]. Given these safety concerns led to a substantial decline in the use of HT worldwide [10,11], it is important to reassess the safety of HT in the light of the new treatment options. Indirect evidence from the REPLENISH trial [12,13] and real-world studies [14] suggest progestogens that are chemically and biologically identical to natural progesterone such as P4 may have lower risk of VTE than synthetic progestogens such as MPA. However, oral CEE/MPA and oral E2/P4 have never been compared head-to-head with respect to VTE.

Using a large claims database from the United States (US), we compared the risk of VTE between women treated with oral E2/P4 and oral CEE/MPA regimens in real-world practice.

2. Methods

2.1. Data source

We used the Symphony Health Integrated Dataverse® ("Symphony") database, a large US claims database that includes pharmacy claims for >93 % of prescriptions dispensed in the US as well as medical claims from 1.9 million practitioners in the US [15]. Symphony links longitudinal US patient-level data on pharmacy and medical services from clearing house transactions, pharmacy point-of-service, and additional direct prescription, medical, and hospital claims data feeds. All payers (e.g., Medicaid/Medicare, commercial, cash payers) are represented. Given Symphony includes data on >317 million active patients in the US and has a short data lag, it was particularly well suited for the current study that investigates VTE, a rare outcome, among patients treated with E2/P4, a recently approved HT. Data are de-identified and comply with the Health Insurance Portability and Accountability Act requirements. Ethics approval and consent to participate were not applicable.

2.2. Study design and patient selection

This retrospective longitudinal study used Symphony data from April 1st 2019 to June 30, 2021. Eligible women aged ≥40 years had ≥1 prescription fill for oral E2/P4 or oral CEE/MPA as prescribed by the treating physician in the real-world practice and observed through pharmacy dispensing records (all oral E2/P4 or CEE/MPA regimens observed in real-world practice were included). The first dispensing claim for oral E2/P4 or oral CEE/MPA, which was required to be on or after May 1st 2019, was used to identify the ***index date*** and to identify the mutually exclusive ***E2/P4 and CEE/MPA cohorts*** (Fig. 1).

Women's characteristics at the index date were measured based on information available in the data from the first medical or pharmacy claim to the index date, inclusive (***baseline period***). Given Symphony is a provider-based database that does not have information of the patient healthcare plan enrollment, we required evidence of medical and pharmacy clinical activity in the baseline period to ensure the women were active in the database during the baseline period when patient characteristics were measured. Thus, by design, all women in the study sample had ≥1 medical claims and ≥1 pharmacy claims during the baseline period. The length of the baseline period, which was allowed to vary across study subjects to maximize the sample size, was controlled for in the analyses (Section 2.4).

The VTE outcome, described in Section 2.3, were measured from the index date to the earliest of the end of medical and pharmacy clinical activity, the day before the first prescription fill for oral CEE/MPA for women in the E2/P4 cohort or of the first prescription fill for oral E2/P4 for women in the CEE/MPA cohort, or the data cut-off date on June 30, 2021. By design, all women in the study sample were required to have ≥6 months of observation after the index date and no VTE diagnosis before the index date. As above, medical and pharmacy clinical activity was required after the index date to ensure the women were active in the database over the period when VTE and treatment discontinuation events were measured. Specifically, women were assumed to have continuous clinical activity from the index date until the last day before the first gap of ≥12 months between either two consecutive prescription fills or two consecutive medical claims, if any such gap was observed. Since the risk of VTE is highest in the first year of HRT use [16], a sensitivity analysis was performed among women with a baseline period of ≥6 months and no HT use in the 6-month period before the index date.

2.3. Outcome and measurements

The study outcome was the first VTE event post-index, identified based on ICD-10 diagnosis codes (Supplemental Table S1).

Characteristics of women in the study sample, measured in the baseline period, included demographics and risk factors for VTE. Given patients may refill prescriptions for stable chronic conditions without having a medical visit, comorbidities were identified, whenever possible, based on both ICD-10 diagnosis codes recorded on medical claims and dispensing of comorbidity specific medications. Classes of medications that were frequently used by women in the study sample were also reported.

2.4. Statistical analysis

When comparing the study cohorts, confounding control was achieved via inverse probability of treatment (IPT) weighting, a methodology that is commonly used to analyze rare outcomes [17]. IPT weights were calculated based on a propensity score model conditional on baseline covariates. The IPT weights were normalized to reduce the influence of large weights. Standardized differences were used to compare covariates pre-IPT weighting (actual distribution of covariates among women receiving oral E2/P4 and oral CEE/MPA) post-IPT weighting (covariate distribution in the re-weighted cohorts to assess whether the IPT-weighting methodology has achieved covariate balance). To align with the literature, a standardized difference threshold of $>|0.15|$ was used to identify imbalanced covariates [18].

The time to first VTE event post-index was compared between the E2/P4 and CEE/MPA cohorts using IPT-weighted Kaplan-Meier plots and IPT-weighted Cox proportional hazard regression models.

An IPT-weighted Poisson regression model (or, when overdispersion was detected, negative binomial regression model) was also used to compare E2/P4 and CEE/MPA with respect to the VTE incidence defined as VTE events per 10,000 women-years post-index. Because diagnosis

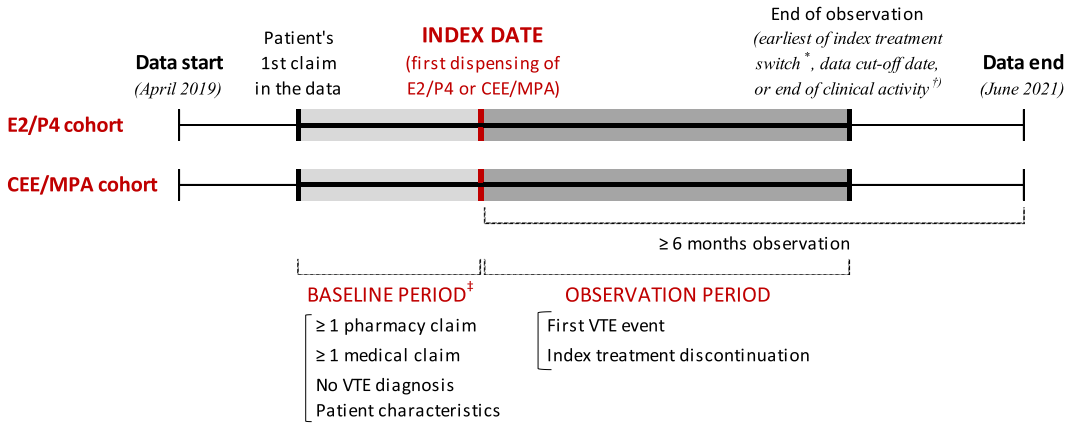

Fig. 1. Study design.
HT, hormone therapy.
*Switch from oral E2/P4 to oral CEE/MPA, or from oral CEE/MPA to oral E2/P4.
†Pharmacy-based activity was defined as no gap ≥12 months between two prescriptions claims (for hormone therapy or any other prescription drugs); medical-based activity was defined as no gap ≥12 months between two medical claims.
‡Range <1 month to 21 months (length of baseline period was controlled for in the analysis).

codes in claims data cannot distinguish between new VTE events and follow-up visits after the first VTE event, only the first observed VTE event post-index was counted in the VTE incidence numerator.

All data analyses for this paper were performed using WPS Analytics software version 4.0 (SAS programming language).

3. Results

3.1. Patient characteristics

Overall, 36,061 women satisfied the sample selection criteria (Fig. 2), most of which were aged 50–59 years (57 %). The E2/P4 and CEE/MPA cohorts included 6526 and 29535 women, observed on average for 1.2 and 1.4 years post-index, respectively.

Before IPT weighting, women receiving oral E2/P4 were younger than those receiving oral CEE/MPA (mean age: 54 vs 56 years), had less cardiovascular disease (34 % vs 44 %), less hypercholesterolemia (24 % vs 31 %), and higher prior use of oral HT (estrogen/estradiol-based oral HT for menopause other than oral E2/P4 or oral CEE/MPA: 20 % vs 12 %; oral contraceptives: 9 % vs 5 %; progesterone/progestogen only: 18 % vs 5 %) (standardized differences >|0.15| indicating covariate imbalance; Table 2). Other clinical characteristics, although common, were not different between the E2/P4 and CEE/MPA cohorts (e.g., diabetes 8 % vs 12 %; use of analgesics/relaxants medications: 36 % vs 41 %; antiarthritic medications: 29 % vs 31 %; medications for anxiety/depression/sleep disturbances: 58 % vs 62 %; corticosteroids: 28 % vs 26 %; proton pump inhibitors: 17 % vs 23 %, respectively; standardized differences ≤|0.15|; Table 2).

After IPT weighting, all baseline characteristics became well balanced between the two study cohorts (standardized differences < |0.15|; Table 2).

3.2. Risk of VTE in IPT-weighted cohorts

Before IPT weighting, 25/6526 (0.38 %) women receiving oral E2/P4 experienced a VTE event and 225/29,535 (0.76 %) women receiving oral CEE/MPA experienced a VTE event (over a total of 7925 and 40,650 women-years after the index date, respectively). The VTE incidence post-index was significantly lower for women receiving oral E2/P4 than women receiving oral CEE/MPA (number of patients with ≥1 VTE event in IPT-weighted cohorts: 82.6 vs 132.4, respectively; incidence rate in IPT-weighted cohorts: 37 vs 53 VTE events per 10,000 women-years, respectively; IPT-weighted incidence rate ratio [IRR] 0.70, 95 % CI 0.53–0.92). Similar trends were observed in time to event analyses (Fig. 3; IPT-weighted hazard ratio [HR] 0.70, 95 % CI 0.53–0.92; Kaplan-Meier curves started to diverge ~5 months post-index date).

The sensitivity analysis among women with a baseline period of ≥6 months and no HT use in the 6-month period before the index date found similar results (IPT-weighted IRR 0.60, 95 % CI 0.38–0.97).

4. Discussion

This large retrospective longitudinal real-world study found that women aged ≥40 years receiving oral E2/P4 had an estimated VTE risk that was significantly lower than that estimated for women receiving oral CEE/MPA regimens in the two years following the index date when data were analyzed independently of potential confounding factors (30 % risk reduction, $p < 0.05$). The separation of risk between the two treatment cohorts started six months post-index date. These study findings are particularly relevant to clinicians given concerns about VTE risk associated with CEE/MPA highlighted in the Women Health Initiative (WHI) trial that led to a drastic reduction in the use of HT, even in women for whom HT was recommended [10,11].

The current study is the first head-to-head study comparing VTE risk between women treated with oral CEE/MPA and oral E2/P4. While our IRR and HR estimates could not be directly compared to the literature, the VTE rate observed in the current study for women treated with oral CEE/MPA (53 per 10,000 women-years over 1.4 years follow-up on average) was comparable to that reported in the WHI trial over a similar follow-up period (58 per 10,000 women-years in the year following treatment initiation [8]). Given the WHI trial was conducted approximately 20 years ago, it is possible differences in patient cohorts explain the slightly higher rate in the WHI trial compared to the current study (e.g., mean age: 63 years [8] vs 54 years, respectively). Furthermore, WHI was a controlled trial, while CEE/MPA dosage regimens may vary in real-world settings.

The real-world evidence of the current study supports the hypothesis that P4, which is chemically and biologically identical to natural progesterone, has a better safety profile with respect to VTE than MPA, a synthetic progestogen. While there are no head-to-head studies of P4 versus MPA in combination with estrogens, two 2022 systematic literature reviews concluded that current evidence is consistent with a neutral effect of P4 on VTE [19,20]. For example, some studies found higher risk of primary and recurrent VTE and stroke in women receiving HT containing norpregnane derivatives, without similar risk elevation for women who received combined estrogens with P4 [19,21–23]. Other

Table 1
Characteristics of women receiving oral E2/P4 and oral CEE/MPA.

	Pre-IPT weighting (study cohorts as observed in the data)		
	E2/P4 cohort n = 6526	CEE/MPA cohort n = 29535	STDIFF[a]
Age at index date			
Mean age ± SD [median]	53.9 ± 5.6 [53.0]	56.3 ± 7.8 [55.0]	0.351*
Age category, n (%)			
40–44 years	270 (4.1 %)	1092 (3.7 %)	0.023
45–49 years	956 (14.6 %)	3861 (13.1 %)	0.046
50–54 years	2563 (39.3 %)	8973 (30.4 %)	0.187*
55–59 years	1818 (27.9 %)	7302 (24.7 %)	0.071
60–64 years	624 (9.6 %)	4021 (13.6 %)	0.127
65–69 years	224 (3.4 %)	2018 (6.8 %)	0.155*
70–74 years	56 (0.9 %)	1260 (4.3 %)	0.217*
75+ years	15 (0.2 %)	1008 (3.4 %)	0.240*
Census region, n (%)			
Midwest	1202 (18.4 %)	7057 (23.9 %)	0.134
Northeast	841 (12.9 %)	5944 (20.1 %)	0.196*
South	3660 (56.1 %)	12,250 (41.5 %)	0.295*
West	809 (12.4 %)	4200 (14.2 %)	0.054
Unknown	14 (0.2 %)	84 (0.3 %)	0.014
Insurance plan type on the index date, n (%)			
Commercial	5857 (89.7 %)	21,643 (73.3 %)	0.434*
Governmental (e.g., Medicaid, Medicare)	629 (9.6 %)	7776 (26.3 %)	0.445*
Other (cash)	40 (0.6 %)	116 (0.4 %)	0.031
Select comorbidities in the baseline period, n (%) (identified based on diagnosis codes, unless otherwise specified)			
Anxiety	965 (14.8 %)	4979 (16.9 %)	0.057
Autoimmune diseases[b]	336 (5.1 %)	1544 (5.2 %)	0.004
Blood coagulation defect	15 (0.2 %)	74 (0.3 %)	0.004
Antithrombin deficiency/ thrombophilia	8 (0.1 %)	32 (0.1 %)	0.004
Coagulopathy/hemophilia/Von Willebrand's disease	7 (0.1 %)	44 (0.1 %)	0.012
Cancer[c]	189 (2.9 %)	888 (3.0 %)	0.007
Cardiovascular disease[d]	2237 (34.3 %)	12,939 (43.8 %)	0.196*
Depression	671 (10.3 %)	3800 (12.9 %)	0.081
Diabetes[e]	534 (8.2 %)	3499 (11.8 %)	0.122
Hypercholesterolemia[e]	1553 (23.8 %)	9107 (30.8 %)	0.158*
Lower extremity paralysis	4 (0.1 %)	34 (0.1 %)	0.018
Obesity[e]	639 (9.8 %)	2896 (9.8 %)	0.000
Osteoporosis[f]	234 (3.6 %)	1164 (3.9 %)	0.019
Sleep disorders[g]	769 (11.8 %)	3552 (12.0 %)	0.007
Urinary tract infection	317 (4.9 %)	1479 (5.0 %)	0.007
Elixhauser Comorbidity Index score[h]			
Mean score ± SD [median]	0.2 ± 0.7 [0.0]	0.3 ± 0.9 [0.0]	0.120
Score ≤0	5503 (84.3 %)	22,842 (77.3 %)	0.178*
Score 1–2	958 (14.7 %)	5971 (20.2 %)	0.146
Score ≥3	65 (1.0 %)	722 (2.4 %)	0.112
Medications dispensed in the baseline period, n (%)			
Analgesics/relaxants	2376 (36.4 %)	12,229 (41.4 %)	0.103
Antiarthritics	1913 (29.3 %)	9253 (31.3 %)	0.044
Anticoagulants	49 (0.8 %)	348 (1.2 %)	0.044
Anxiety/depression/sleep disorders	3761 (57.6 %)	18,153 (61.5 %)	0.078
Aspirin	81 (1.2 %)	605 (2.0 %)	0.063
Hormonal drugs			
Androgens	30 (0.5 %)	19 (0.1 %)	0.077
Corticosteroids	1814 (27.8 %)	7566 (25.6 %)	0.049
Estrogen/estradiol-based oral HT for menopause (excl. oral E2/P4 and oral CEE/MPA)	1289 (19.8 %)	3395 (11.5 %)	0.229*
Oral contraceptives	561 (8.6 %)	1377 (4.7 %)	0.159*
Oral progesterone/progestin alone	1147 (17.6 %)	1540 (5.2 %)	0.397*
Thyroid hormone	1436 (22.0 %)	5983 (20.3 %)	0.043
Proton pump inhibitors	1114 (17.1 %)	6863 (23.2 %)	0.154
Smoking cessation treatments	57 (0.9 %)	661 (2.2 %)	0.110
Hip or pelvic fracture in the baseline period, n (%)	3 (0.0 %)	40 (0.1 %)	0.030
Hip fracture	2 (0.0 %)	27 (0.1 %)	0.025
Pelvic fracture	1 (0.0 %)	14 (0.0 %)	0.018
Surgery in an inpatient setting in the baseline period, n (%)	58 (0.9 %)	418 (1.4 %)	0.049
Year of the index date, n (%)			
2019	2292 (35.1 %)	14,779 (50.0 %)	0.305*
2020	4234 (64.9 %)	14,756 (50.0 %)	0.305*
Duration of the baseline period (years), mean ± SD [median]	0.9 ± 0.5 [0.9]	0.7 ± 0.5 [0.6]	0.403*
<30 days	71 (1.1 %)	1258 (4.3 %)	0.198*
≥30 and <90 days	336 (5.1 %)	6528 (22.1 %)	0.510*
≥90 days and <180 days	1148 (17.6 %)	4882 (16.5 %)	0.028
≥180 days	4971 (76.2 %)	16,867 (57.1 %)	0.413*

HT, hormone therapy; SD, standard deviation; STDIFF, standardized differences.

[a] The symbol * is used to indicates imbalanced covariates (i.e., STDIFF > |0.15|).

[b] Diagnoses included autoimmune urticaria, Crohn's disease, systemic lupus erythematosus (≤0.5 % in both cohorts), atopic dermatitis, psoriasis, rheumatoid arthritis (≤1.1 % in both cohorts), and irritable bowel disease (2.3 % and 2.0 % in the E2/P4 and CEE/MPA cohorts) (all STDIFF <0.03).

[c] Diagnoses included breast, endometrial, and ovarian cancer (each <0.3 % in both cohorts), and other cancers (<3 % in both cohorts; all STDIFF <0.02).

[d] Identified using both diagnosis codes and disease-specific medication dispensing in the baseline period. Diagnoses included hypertension (13.5 % in the E2/P4 cohort and 20.6 % women in the CEE/MPA cohort; STDIFF = 0.192) and angina pectoris, cardiomyopathy, congestive heart failure, ischemic stroke, myocardial infarction, other coronary disease (<2 % in both cohorts; all STDIFF <0.08). Drug classes used to identify cardiovascular diseases included ACE inhibitors, adenosine receptor antagonists, angiotensin II antagonists, antiarrhythmia agents, antihypertensives, beta-blockers, calcium channel blockers, digoxin, direct renin inhibitors, diuretics, IF channel inhibitors, and nitrites.

[e] Identified using both diagnosis codes and disease-specific medication.

[f] Identified using both diagnosis code for osteoporosis or bisphosphonates dispensing in the baseline period.

[g] Diagnoses included circadian rhythm sleep disorders, hypersomnia, insomnia, narcolepsy, restless legs syndrome and sleep apnea (all STDIFF <0.04).

[h] The Elixhauser Comorbidity Index assigns integer values to 20 comorbidities identified on the basis of diagnosis codes. Lower scores indicate lesser disease burden while higher scores indicate greater disease burden [30].

literature reviews also concluded the VTE risk depends on the type of progestogen used, with P4 likely having lower risk than synthetic progestogens [7,14]. Furthermore, evidence from observational studies suggest that non-oral routes of administration, such as transdermal and vaginal, may mitigate the risk of VTE by bypassing the first-pass hepatic effect [24,25].

Indirect evidence from the literature suggests coagulation and vascular effects may mediate the impact of progestogens on VTE. The REPLENISH trial showed no significant changes on coagulation parameters between women treated with E2/P4 versus placebo [12,13], while other studies showed protein C resistance activation in women using norpregnane derived progestogens but not in women using P4 [22]. Further, the vasoconstrictive effect of synthetic MPA appears to have an attenuating effect on the vasodilatory benefits of estrogen, whereas natural progesterone does not attenuate this benefit [26]. Finally, synthetic progestogens may also interact with aldosterone and androgen receptors resulting in fluid retention and other androgenic adverse events [27].

In addition to the type of progestogen, the type of estrogen may also have an independent effect on the VTE risk. Indeed, the WHI trial found that women with hysterectomy treated with CEE alone had higher risk of VTE than women treated with placebo [28], while other studies suggested oral CE is more pro-thrombotic than oral estradiol [29]. Furthermore, a 2022 literature review concluded E2- versus CEE-based HT had a similar or possibly better risk profile for VTE and other cardiovascular outcomes [20].

While the plausibility and evidence to date on different types of progestogens/estrogens suggesting a reduced VTE risk with E2/P4 compared to CEE/MPA is compelling, it is important to confirm our findings in other head-to-head studies conducted in similar/other population bases and using different data, study designs, and methodologies. Furthermore, in the absence of a comparison group of non-HT users, the current study cannot inform on whether the use of oral E2/P4 is associated with an increased or unmodified risk of VTE compared with no HT use.

This study is subject to some limitations. First, claims databases may contain occasional coding errors or omissions. Second, because Symphony data is provider-based, the period when women were captured in the data was inferred from their clinical activity including medical visits and prescription fills. Thus, women who do not incur clinical services on regular basis may not have been included in the study, may have been censored early, or may have had certain comorbidities underestimated. Third, given this study focuses on a rare outcome, the baseline period was allowed to vary across subjects to maximize the sample size. To mitigate the impact of having a varying baseline period across subjects, the duration of the baseline period was accounted for in the IPT weights and was balanced post-weighting. Fourth, residual confounding may

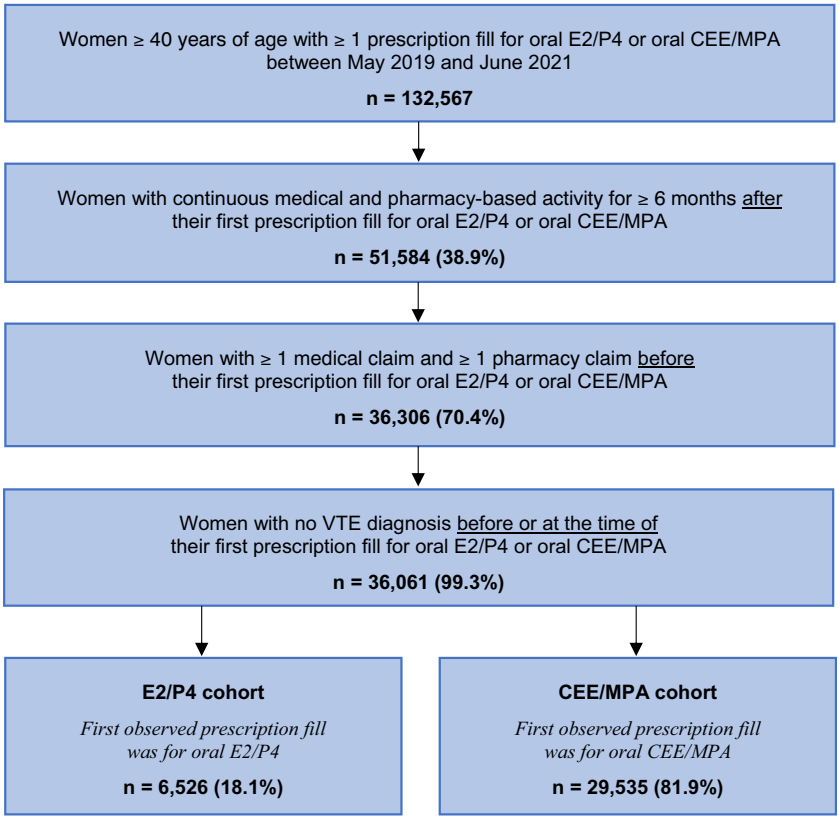

Fig. 2. Sample selection flowchart.
VTE, venous thromboembolism.

Table 2
Covariate balance post-IPT weighting.

Covariates[a]	Post-IPT weighting[b] (pseudo cohorts that were re-weighted to ensure covariate balance)		
	E2/P4 cohort n = 17,388	CEE/MPA cohort n = 18,673	STDIFF[c]
Age at index date			
Mean age ± SD [median]	54.9 ± 11.2 [54.0]	55.9 ± 6.0 [55.0]	0.105
Age category, n (%)			
40–44 years	749 (4.3 %)	707 (3.8 %)	0.027
45–49 years	2529 (14.5 %)	2499 (13.4 %)	0.034
50–54 years	5998 (34.5 %)	5986 (32.1 %)	0.052
55–59 years	4371 (25.1 %)	4720 (25.3 %)	0.003
60–64 years	2130 (12.2 %)	2396 (12.8 %)	0.018
65–69 years	930 (5.3 %)	1156 (6.2 %)	0.036
70–74 years	388 (2.2 %)	680 (3.6 %)	0.083
75+ years	293 (1.7 %)	529 (2.8 %)	0.077
Census region, n (%)			
Midwest	3908 (22.5 %)	4267 (22.9 %)	0.009
Northeast	3190 (18.3 %)	3509 (18.8 %)	0.011
South	7946 (45.7 %)	8251 (44.2 %)	0.030
West	2299 (13.2 %)	2593 (13.9 %)	0.019
Unknown	45 (0.3 %)	53 (0.3 %)	0.006
Insurance plan type on the index date, n (%)			
Commercial	14,045 (80.8 %)	14,253 (76.3 %)	0.108
Governmental (e.g., Medicaid, Medicare)	3264 (18.8 %)	4338 (23.2 %)	0.110
Other (cash)	79 (0.5 %)	82 (0.4 %)	0.002
Select comorbidities in the baseline period, n (%) (identified based on diagnosis codes, unless otherwise specified)			
Anxiety	2835 (16.3 %)	3073 (16.5 %)	0.004
Autoimmune diseases[d]	892 (5.1 %)	973 (5.2 %)	0.004
Blood coagulation defect	39 (0.2 %)	46 (0.2 %)	0.005
Antithrombin deficiency/ thrombophilia	15 (0.1 %)	21 (0.1 %)	0.008
Coagulopathy/hemophilia/Von Willebrand's disease	24 (0.1 %)	27 (0.1 %)	0.001
Cancer[d]	587 (3.4 %)	558 (3.0 %)	0.022
Cardiovascular disease[d]	7110 (40.9 %)	7856 (42.1 %)	0.024
Depression	2122 (12.2 %)	2312 (12.4 %)	0.005
Diabetes[d]	1965 (11.3 %)	2091 (11.2 %)	0.003
Hypercholesterolemia[d]	4983 (28.7 %)	5519 (29.6 %)	0.020
Lower extremity paralysis	16 (0.1 %)	20 (0.1 %)	0.005
Obesity[d]	1906 (11.0 %)	1833 (9.8 %)	0.038
Osteoporosis[d]	613 (3.5 %)	723 (3.9 %)	0.018
Sleep disorders[d]	2114 (12.2 %)	2240 (12.0 %)	0.005
Urinary tract infection	892 (5.1 %)	931 (5.0 %)	0.007
Elixhauser Comorbidity Index score[d]			
Mean score ± SD [median]	0.2 ± 1.3 [0.0]	0.2 ± 0.7 [0.0]	0.003
Score category, n (%)			
≤0	13,835 (79.6 %)	14,683 (78.6 %)	0.023
1–2	3195 (18.4 %)	3583 (19.2 %)	0.021
≥3	357 (2.1 %)	407 (2.2 %)	0.009
Medications dispensed in the baseline period, n (%)			
Analgesics/relaxants	6778 (39.0 %)	7556 (40.5 %)	0.030
Antiarthritics	5491 (31.6 %)	5792 (31.0 %)	0.012
Anticoagulants	144 (0.8 %)	204 (1.1 %)	0.027
Anxiety/depression/sleep disorders	10,656 (61.3 %)	11,350 (60.8 %)	0.010
Aspirin	295 (1.7 %)	355 (1.9 %)	0.015
Hormonal drugs			
Androgens	27 (0.2 %)	29 (0.2 %)	0.001
Corticosteroids	4825 (27.7 %)	4875 (26.1 %)	0.037
Estrogen/estradiol-based oral HT for menopause (excl. oral E2/P4 and oral CEE/MPA)	2886 (16.6 %)	2485 (13.3 %)	0.092
Oral contraceptives	1048 (6.0 %)	1018 (5.5 %)	0.025
Oral progesterone/progestin alone	1513 (8.7 %)	1420 (7.6 %)	0.040
Thyroid hormone	3602 (20.7 %)	3849 (20.6 %)	0.003
Proton pump inhibitors	3826 (22.0 %)	4131 (22.1 %)	0.003
Smoking cessation treatments	356 (2.0 %)	372 (2.0 %)	0.004
Hip or pelvic fracture in the baseline period, n (%)	7 (0.0 %)	22 (0.1 %)	0.028
Hip fracture	5 (0.0 %)	15 (0.1 %)	0.022
Pelvic fracture	2 (0.0 %)	8 (0.0 %)	0.019
Surgery in an inpatient setting in the baseline period, n (%)	205 (1.2 %)	246 (1.3 %)	0.012
Year of the index date, n (%)			
2019	7176 (41.3 %)	8788 (47.1 %)	0.117
May	1334 (7.7 %)	1912 (10.2 %)	0.090
June	1166 (6.7 %)	1597 (8.6 %)	0.070
July	859 (4.9 %)	977 (5.2 %)	0.013
August	852 (4.9 %)	1040 (5.6 %)	0.030
September	745 (4.3 %)	882 (4.7 %)	0.021
October	838 (4.8 %)	941 (5.0 %)	0.010
November	759 (4.4 %)	774 (4.1 %)	0.011
December	623 (3.6 %)	665 (3.6 %)	0.001
2020	10,212 (58.7 %)	9885 (52.9 %)	0.117
January	720 (4.1 %)	746 (4.0 %)	0.007

(continued on next page)

Table 2 (*continued*)

Covariates[a]	Post-IPT weighting[b] (pseudo cohorts that were re-weighted to ensure covariate balance)		
	E2/P4 cohort n = 17,388	CEE/MPA cohort n = 18,673	STDIFF[c]
February	801 (4.6 %)	724 (3.9 %)	0.036
March	824 (4.7 %)	700 (3.7 %)	0.049
April	516 (3.0 %)	507 (2.7 %)	0.015
May	552 (3.2 %)	600 (3.2 %)	0.002
June	835 (4.8 %)	848 (4.5 %)	0.012
July	1055 (6.1 %)	1057 (5.7 %)	0.017
August	1158 (6.7 %)	1080 (5.8 %)	0.036
September	1080 (6.2 %)	1079 (5.8 %)	0.018
October	1034 (5.9 %)	1011 (5.4 %)	0.023
November	869 (5.0 %)	817 (4.4 %)	0.029
December	769 (4.4 %)	715 (3.8 %)	0.030
Duration of the baseline period (years), mean ± SD [median]	0.8 ± 0.8 [0.8]	0.8 ± 0.4 [0.7]	0.109
<30 days	522 (3.0 %)	687 (3.7 %)	0.038
≥30 and <90 days	2602 (15.0 %)	3545 (19.0 %)	0.107
≥90 days and <180 days	2659 (15.3 %)	3090 (16.5 %)	0.034
≥180 days	11,605 (66.7 %)	11,351 (60.8 %)	0.124

IPT, inverse probability of treatment; HT, hormone therapy; SD, standard deviation; STDIFF, standardized differences.

[a] For the full list of covariates please see Supplemental Table S2.

[b] IPT-weights were calculated based on the propensity score estimated from a logistic regression model with the treatment group as independent variable and the following dependent variables: age category, region, healthcare insurance type, Elixhauser comorbidity burden category, hip fracture, pelvic fracture, hospitalization for surgery, comorbidities that impact the risk of VTE, dispensing of medications that impact the risk of VTE, dispensing of medications in frequently used drug classes, the number of distinct non-topical medications dispensed during the baseline period, the month/year of the index date, and the duration of the baseline period. All comorbidities and medications listed in Table 1 were included in the propensity score.

[c] The symbol * is used to indicates imbalanced covariates (i.e., STDIFF > |0.15|).

[d] Please see Table 1 footnotes for details.

have occurred from VTE risk factors that were not available in claims data (e.g., body mass index, alcohol consumption, genetics, physical inactivity, dose of estrogen in the CEE MPA combinations) or that may have been underestimated in claims data (e.g., obesity and smoking, which were only captured for severe cases who received treatments). Fifth, due to difficulties in separating new VTE events from subsequent follow-up visits in the claims data, only the first VTE event after the index date was reported and counted in the analyses. Rates of VTE events may thus be underestimated. Sixth, to reflect real-world practices, we included all women treated with oral E2/P4 and oral CEE/MPA, regardless of the regimen (i.e., strength and dosage) used. Thus, the findings of the study cannot be attributed to specific dosages for E2/P4 and CEE/MPA. Seventh, we required an observation period of ≥6 months after the index date to ensure we have sufficient time to capture VTE events. However, given date of death is not available in the Symphony data, this resulted in the exclusion from the study sample of women who died in the first 6 months after the index date, including those who died due to a fatal VTE event. Thus, the VTE rates reported in the current study may be underestimated. To the extent to which the effect of oral E2/P4 versus oral CEE/MPA is not different for early fatal VTE events and other VTE events, the exclusion of patients who died within 6 months of the index date is not expected to impact the main study findings. Finally, while the Symphony database covers a large share of medical and pharmacy claims in the US, it is possible some medical services were not captured.

5. Conclusion

After controlling for many potential confounders, the current study found that women treated with oral E2/P4 had a significantly lower risk of VTE than women treated with oral CEE/MPA. Since VTEs are relatively rare events, further studies with different data sources are needed to confirm the findings of these exploratory analyses.

Contributors

Nick Panay contributed to the study concept and study design, and participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

Rossella E. Nappi participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

Petra Stute participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

Santiago Palacios participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

Tomasz Paszkowski participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

Risa Kagan participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

David F. Archer participated in the interpretation of data and the editing and review of the manuscript for important intellectual content.

Julie Héroux contributed to the study design and statistical analyses, and participated in the interpretation of data and review of the manuscript for important intellectual content.

Mitra Boolell contributed to the study concept, study design, and acquisition of data, and participated in the interpretation of data and review of the manuscript for important intellectual content.

All authors approved the final version.

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Ethical approval

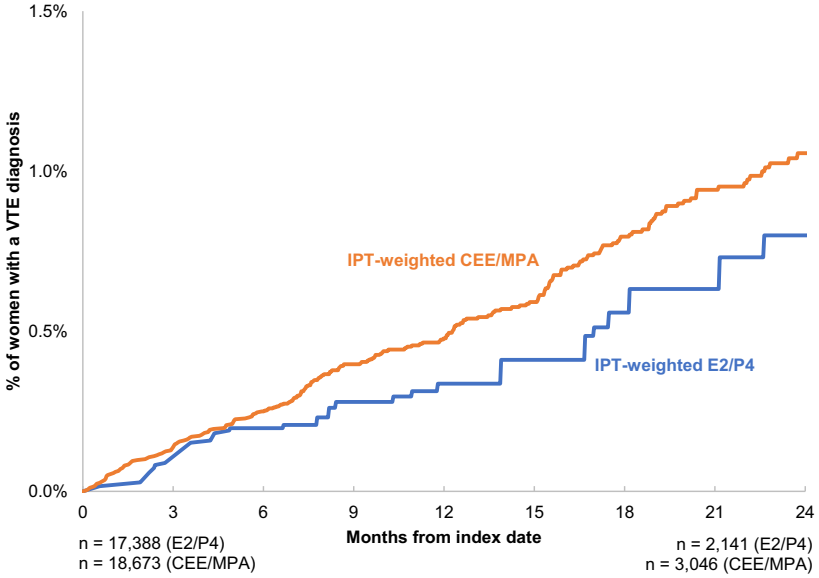
Approval from an institutional review board/independent ethics committee is not required for this study as only de-identified secondary data from administrative claims that comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 were used.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The data that support the findings of this study are available from Source Healthcare



Time post-index date	Time to first VTE in IPT-Weighted Cohorts		
	VTE rates (95% CI)		HR (95% CI)
	E2/P4 Cohort	CEE/MPA Cohort	E2/P4 vs. CEE/MPA
3 months	0.09% (0.03-0.30)	0.13% (0.10-0.18)	0.70 (0.53 – 0.92)*
6 months	0.20% (0.09-0.44)	0.25% (0.20-0.31)	
1 year	0.34% (0.17-0.65)	0.48% (0.40-0.57)	
2 years	0.80% (0.37-1.73)	1.06% (0.91-1.23)	

Fig. 3. Time to first VTE event.
CI: confidence interval; HR, hazard ratio, VTE, venous thromboembolism.
*Statistically significant at $p < 0.05$.

Analytics, LLC, but restrictions apply to the availability of these data, which were used under a license agreement for the current study and, accordingly, are not publicly available. Access to the Symphony Health Integrated Dataverse® can be requested by contacting Source Healthcare Analytics, LLC.

Declaration of competing interest

N. Panay has lectured and acted in an advisory capacity for a number of pharma companies, including Theramex. R.E. Nappi has lectured and acted in an advisory/consultant capacity for a number of pharma companies, including Theramex. P. Stute has been a consultant with honorarium for Theramex. S. Palacios has been a consultant with honorarium for Theramex and has lectured and acted in and advisory/consultant capacity for other pharma companies. T. Paszkowski has been a consultant with honorarium for Theramex and received honoraria as consultant/member of advisory boards/lecturer from a number of pharma companies, including Theramex. R. Kagan has been an Advisor/Consultant with honorarium and has lectured for a number of pharma companies, including TherapeuticsMD. D. F. Archer has been a consultant with honorarium for a number of pharma companies, including TherapeuticsMD. J. Heroux is an employee and the owner of Heroux Consulting, which received research funding for the conduct of the current study. M. Boolell is an employee of and stockholder in Theramex.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2023.04.004.

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