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ORIGINAL STUDY

Does hormone therapy exacerbate other venous thromboembolism risk factors?

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Abstract

Objective: Postmenopausal symptoms in women at higher risk for venous thromboembolism (VTE) due to comorbidities are often undertreated because of concerns that hormone therapy (HT) may increase VTE risk; however, it is unclear how much HT impacts risk of VTE when compared with other risk factors.

Methods: This is a case-control study in a commercial claims database from 2007 to 2019. Women aged 50 to 64 years (n = 223,949) were classified as cases if they had an *International Classification of Diseases* code indicating an acute VTE plus a filled prescription for an anticoagulant, placement of intravascular vena cava filter, or death within 30 days of diagnosis. Controls were matched 10:1 to each case by index date and age. Risk factors and comorbidities present within the year before index were examined. Exposure was defined as a HT prescription within 60 days before index.

Results: There were 20,359 VTE cases and 203,590 matched controls. A conditional logistic regression indicated that the greatest risks for VTE were from metastatic cancer (odds ratio [OR], 13.66; 95% CI, 12.64-14.75), hospitalization/surgery (OR, 8.51; 95% CI, 8.09-8.96), trauma (OR, 3.52; 95% CI, 3.32-3.73), comorbidity burden (OR, 3.51; 95% CI, 3.34-3.69), history of hypercoagulable condition (OR, 3.10; 95% CI, 2.87-3.36), and varicose veins (OR, 2.87; 95% CI, 2.56-3.22). Regarding hormone exposure, we observed ORs of 1.51 (95% CI, 1.43-1.60) for any recent hormone exposure; 1.13 (95% CI, 1.04-1.23; number needed to harm, 4,274) for unopposed estrogen menopausal HT; 1.23 (95% CI, 1.10-1.38; number needed to harm, 2,440) for combined menopausal HT; and 5.22 (95% CI, 4.67-5.84) for combined hormonal contraceptives compared with no recent HT exposure.

Conclusions: Hormone therapy exposure did not appear to adversely influence other risk factors, and exposure generally played a minor role in VTE risk. Contraceptives, however, were a strong risk factor.

Key Words: Case-control studies – Contraceptive agents – Estrogens – Females – Hormone therapy – Postmenopausal – Risk factors – Venous thromboembolism.

Menopausal symptoms are very common in the perimenopausal period[1,2] and can have a marked effect on the quality of life,[3-5] perceived health status,[3,5] mood,[3-5] cognition,[6-8] energy,[3] sleep,[7,9,10] sexual function,[3,11] and social relationships[12] of women. Hormone therapy (HT) is highly effective in alleviating menopausal symptoms and improving many of the areas of life affected by these symptoms.[3,10,13] As recently as the 1990s, HT was considered the standard of care and used by over half of women in their 50s.[14-16] However, a dramatic decrease occurred[17-21] after the Women's Health Initiative (WHI) trials showing HT's increased risk for cardiovascular events and venous thromboembolism (VTE).[17-20,22-26] There has been growing

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concern that WHI findings were generalized to populations and settings that were insufficiently studied,[22,27-37] meaning that many women who might benefit from HT will not receive it.

Recent studies suggest that the conjugated equine estrogen and medroxyprogesterone acetate used in the WHI trials confer a higher cardiovascular risk compared with other HT therapies and that the route of HT administration also affects risk, with transdermal formulations not being associated with increased risk.[33,38-51] Nonetheless, in the past two decades, clinical use of HT has been markedly constrained, with many women around the world failing to receive therapy for severe symptoms.[14,52,53] However, even as safer menopausal HT options have been underused in recent decades,[19,21] overuse of contraceptive HT in higher-risk populations may be a problem as well. Some clinical guidelines encourage the use of low-dose combined hormonal contraceptives (CHCs) as a safe option for treatment of menopausal symptoms in women up to 55 years who lack risk factors such as smoking, obesity, or cardiovascular disease.[48,54] Guidelines and product labels currently only discourage HT in the presence of extreme risk factors, such as vaginal bleeding of unknown etiology, breast cancer, a history of VTE, active stroke or myocardial infarction, liver disease, thrombophilic disorders, or pregnancy.[55,56] Interactions have previously been identified between oral contraceptive use and air travel[57] but not for menopausal HT and genetic susceptibility to VTE.[58] It is unclear if other risk factors might interact with HT to increase thrombosis risk.[55,56]

Although current guidelines for menopausal HT increasingly emphasize an individualized shared decision-making approach in prescribing HT,[59] clinicians may be insufficiently prepared to counsel individual risk profiles without further evidence. Risk factors for VTE include older age, trauma, surgery, malignancy, smoking, comorbidities, hospitalization, and immobilization.[60-64] However, it is unclear whether these risk factors interact with HT to increase risk of VTE.

Our previous research explored the correlation between type, formulation, and route of administration of hormone exposures with risk of VTE.[49] This case-control study updates estimates of the relative association of VTE risk factors with VTE and the subcomponents, pulmonary embolism (PE) and deep vein thrombosis (DVT), in a large contemporary US cohort and addresses a clinically important question of whether hormone exposure might adversely affect other risk factors.

METHODS

Data source

An age- and date-matched nested case-control design was used to compare relative risk between VTE cases and controls. A base cohort of all women 50 to 64 years of age with a minimal enrollment of 1 year were selected from a national US health insurance database from January 1, 2007, through December 31, 2019. This study is part of a larger study on VTE in women 50 to 64 years of age, and details on the cohort selection and definitions including *International Classification of Diseases* codes appear elsewhere.[49] Optum's deidentified Clinformatics Data Mart Database contains individual-level, longitudinal billing data and is one of the largest commercial insurance populations in the United States. The longitudinal data source contains up to 12 years of data for over 50 million unique members across all regions of the United States. It includes administrative data, medical claims, pharmacy claims, and laboratory results.

Cases

Incident cases occurring after a 12-month lookback period were selected with a diagnostic code for acute VTE accompanied by a filled prescription for an anticoagulant (excluding heparin flushes), intravascular vena cava filter, or death within 30 days after the VTE diagnosis. Anyone with a prior VTE (acute or chronic) or an intravascular vena cava filter in the previous year or with an anticoagulant exposure within 14 days before the index date was excluded.

Controls

Controls were selected by matching women (10:1) to each case on the case index date (month and year) and age (±2 years). The same exclusions applied to both controls and cases. A minimal matching strategy was used so that controls might better represent the population and with a large matching ratio to estimate associations with low frequency categories.

Risk factors

Known risk factors (age; hospitalization/surgery or trauma within 30 d; and any malignancy, hypercoagulable condition, varicose veins, documented smoking within the past year) as well as coronary artery disease (CAD) and stroke were recorded for each woman. Recent hormone exposure was defined as any estrogen or progestogen prescription that resulted in hormone exposure within 60 days of the index date (excluding low-dose vaginal exposures). A 60-day window was used because previous research found that risk diminished after 60 days.[49] To control for possible differences in underlying health status between cases and controls, comorbidities were recorded using the Elixhauser comorbidity index.[65,66] The Elixhauser index includes 31 conditions such as hypertension, diabetes, obesity, and liver disease and is predictive of mortality.[65,66] Cancers and hypercoagulable conditions were removed from the index and retained as separate VTE risk factors.

Analysis

Conditional logistic regression[67] was used to estimate the association of all risk factors on incident VTE while controlling for region of residence. The odds ratio (OR) was used to estimate relative risk. Separate models estimated relative risk for VTE, DVT (without PE), and PE (with or without DVT). The Elixhauser comorbidity index was coded into terciles (0, 1 or 2, and 3 or more), and age was categorized into 5-year subcategories. Two-way interactions ($P < 0.05$) between recent hormone exposure and the other risk factors tested whether hormone exposure might exacerbate VTE risks. Number needed to harm (NNH)[68] was estimated assuming a population VTE incidence of 180/100,000 for women in this age range[69] and the adjusted OR from conditional logistic regression models.

RESULTS

Sample

From a total sample of 223,949 women, all cases were matched, resulting in 20,359 acute VTE cases and 203,590

TABLE 1. *VTE risk factors*

Variable	VTE cases (n = 20,359)	Controls (n = 203,590)	Total (n = 223,949)	Crude OR (95% CI)	Multivariable adj. OR[a] (95% CI)
Age					
50-55 y (ref)	33.35% (6,789)	34.84% (70,927)	34.70% (77,716)	1	1
56-60 y	34.80% (7,084)	33.52% (68,237)	33.63% (75,321)	1.09 (1.05-1.12)	1.31 (1.20-1.42)
61-64 y	31.86% (6,486)	31.64% (64,426)	31.66% (70,912)	1.05 (1.02-1.09)	1.31 (1.17-1.46)
EH comorbid					
None (ref)	13.81% (2,812)	37.32% (75,981)	35.18% (78,793)	1	1
1 or 2	30.25% (6,158)	40.23% (81,909)	39.32% (88,068)	2.03 (1.94-2.13)	1.61 (1.53-1.69)
3+	55.94% (11,389)	22.45% (45,700)	25.49% (57,089)	6.73 (6.45-7.03)	3.51 (3.34-3.69)
Cancer					
None (ref)	74.00% (15,065)	94.42% (192,220)	92.56% (207,285)	1	1
Nonmetastatic	11.11% (2,262)	4.80% (9,764)	5.37% (12,026)	2.96 (2.82-3.10)	2.06 (1.95-2.19)
Metastatic	14.89% (3,032)	0.79% (1,606)	2.07% (4,638)	24.09 (22.62-25.65)	13.66 (12.64-14.75)
Hospital/surg	30.22% (6,152)	2.29% (4,672)	4.83% (10,824)	18.44 (17.68-19.22)	8.51 (8.09-8.96)
Trauma	15.03% (3,060)	2.96% (6,030)	4.06% (9,090)	5.80 (5.53-6.07)	3.52 (3.32-3.73)
Varicose veins	2.73% (556)	0.88% (1,790)	1.05% (2,346)	3.17 (2.87-3.49)	2.87 (2.56-3.22)
Any hypercoag	10.99% (2,237)	1.25% (2,551)	2.14% (4,788)	9.73 (9.17-10.32)	3.10 (2.87-3.36)
CAD	13.47% (2,743)	4.80% (9,775)	5.59% (12,518)	3.09 (2.95-3.23)	1.23 (1.16-1.31)
Stroke	7.34% (1,495)	2.40% (4,886)	2.85% (6,381)	3.22 (3.04-3.42)	1.17 (1.08-1.27)
Smoking	23.13% (4,710)	9.46% (19,263)	10.70% (23,973)	2.88 (2.78-2.99)	1.29 (1.23-1.35)
Recent hormone	10.46% (2,130)	8.56% (17,428)	8.73% (19,558)	1.25 (1.19-1.31)	1.51 (1.43-1.60)

Adj, adjusted; Any hypercoag, any hypercoagulable condition; CAD, coronary artery disease; EH comorbid, Elixhauser comorbidity; Hospital/surg, hospitalization or surgery; OR, odds ratio; ref, reference; VTE, venous thromboembolism.
[a]Adjusted for all risk factors and region of residence.

controls that met the inclusion criteria (Table 1). Participants were distributed equally across 5-year age categories, but the 2-year matching interval resulted in slightly more controls than cases who were younger. We additionally controlled for age statistically in analyses to minimize residual age confounding,[70] although model estimates were unaffected by the adjustment. Approximately one third of the sample did not have any Elixhauser comorbidities.

VTE risk factors

Smoking was the most prevalent risk factor (10.70% of participants), followed by recent hormone exposure (8.73%), CAD (5.59%), nonmetastatic cancer (5.37%), hospitalization or surgery (4.83%), and trauma (4.06%). Other risk factors in the overall population included stroke (2.85%), any hypercoagulable condition (2.14%), metastatic cancer (2.07%), and varicose veins (1.05%). When all VTE risks were considered together, all were significantly associated with the occurrence of VTE (Table 1). The ORs were highest for metastatic cancer (OR, 13.66; 95% CI, 12.64-14.75) and hospitalization or surgery (OR, 8.51; 95% CI, 8.09-8.96), followed by trauma (OR, 3.52; 95% CI, 3.32-3.73), higher comorbidity burden (three or more comorbidities; OR, 3.51; 95% CI, 3.34-3.69), a

TABLE 2. *VTE risk factors stratified by PE cases and DVT cases*

Variable	DVT cases (n = 9,364)	DVT controls (n = 93,640)	DVT multivariable adj. OR[a] (95% CI)	PE cases (n = 10,995)	PE controls (n = 109,950)	PE multivariable adj. OR[a] (95% CI)
Age (terciles)						
50-55 y (ref)	34.68% (3,247)	36.07% (33,779)	1	32.21% (3,542)	33.79% (37,148)	1
56-60 y	35.59% (3,333)	34.03% (31,867)	1.31 (1.16-1.47)	34.12% (3,751)	33.08% (36,370)	1.32 (1.18-1.48)
61-64 y	29.73% (2,784)	29.90% (27,994)	1.18 (1.00-1.39)	33.67% (3,702)	33.14% (36,432)	1.42 (1.23-1.66)
EH comorbid						
0 (ref)	15.27% (1,430)	37.54% (35,149)	1	12.57% (1,382)	37.14% (40,832)	1
1 or 2	31.75% (2,973)	40.14% (37,583)	1.51 (1.41-1.62)	28.97% (3,185)	40.31% (44,326)	1.71 (1.60-1.84)
3+	52.98% (4,961)	22.33% (20,908)	2.79 (2.59-3.00)	58.46% (6,428)	22.55% (24,792)	4.27 (3.99-4.58)
Cancer						
None (ref)	76.19% (7,134)	94.46% (88,454)	1	72.13% (7,931)	94.38% (103,766)	1
Nonmetastatic	10.55% (988)	4.79% (4,482)	1.88 (1.72-2.06)	11.59% (1,274)	4.80% (5,282)	2.23 (2.07-2.41)
Metastatic	13.26% (1,242)	0.75% (704)	12.77 (11.33-14.40)	16.28% (1,790)	0.82% (902)	14.48 (13.09-16.02)
Hosp/surgery	33.17% (3,106)	2.22% (2,079)	10.15 (9.40-10.95)	27.70% (3,046)	2.36% (2,593)	7.37 (6.88-7.90)
Trauma	18.25% (1,709)	2.88% (2,697)	4.86 (4.47-5.29)	12.29% (1,351)	3.03% (3,333)	2.58 (2.37-2.80)
Varicose veins	3.61% (338)	0.86% (807)	4.13 (3.54-4.83)	1.98% (218)	0.89% (983)	1.93 (1.62-2.30)
Any hypercoag	13.61% (1,274)	1.26% (1,183)	4.08 (3.65-4.57)	8.76% (963)	1.24% (1,368)	2.35 (2.10-2.63)
CAD	12.86% (1,204)	4.64% (4,345)	1.25 (1.14-1.37)	14.00% (1,539)	4.94% (5,430)	1.21 (1.12-1.31)
Stroke	7.53% (705)	2.34% (2,193)	1.23 (1.09-1.39)	7.19% (790)	2.45% (2,693)	1.13 (1.02-1.26)
Smoking	22.20% (2,079)	9.45% (8,851)	1.22 (1.13-1.31)	23.93% (2,631)	9.47% (10,412)	1.34 (1.26-1.42)
Recent hormone exp	10.55% (988)	8.60% (8,057)	1.52 (1.40-1.65)	10.39% (1,142)	8.52% (9,371)	1.50 (1.39-1.61)

Adj, adjusted; Any hypercoag, any hypercoagulable condition; CAD, coronary artery disease; DVT, deep vein thrombosis; EH comorbid, Elixhauser comorbidity; Exp, exposure; Hosp/surg, hospitalization or surgery; OR, odds ratio; PE, pulmonary embolism; ref, reference; VTE, venous thromboembolism.
[a]Adjusted for all risk factors and region of residence.

TABLE 3. *ORs for types of hormone exposures for VTE, DVT, and PE outcomes controlling for all other risk factors*[a]

Hormone	VTE Case n (%)	VTE Control n (%)	VTE OR (95% CI)[a]	DVT Case n (%)	DVT Control n (%)	DVT OR (95% CI)[a]	PE Case n (%)	PE Control n (%)	PE OR (95% CI)[a]
No hormone exposure in the past (0-365 d)	17,730	181,167	1.00 (ref)	8,126	83,199	1.00 (ref)	9,604	97,968	1.00 (ref)
Recent hormone exposures (0-60 d)									
Menopausal ET exposure	915	8,735	1.13 (1.04-1.23)	422	4,030	1.14 (1.01-1.29)	493	4,705	1.13 (1.01-1.26)
Menopausal EPT exposure	433	4,727	1.23 (1.10-1.38)	190	2,189	1.17 (0.98-1.39)	243	2,538	1.28 (1.10-1.49)
Contraceptive EPT exposure	561	1,915	5.22 (4.67-5.84)	274	885	5.45 (4.62-6.43)	287	1,030	5.00 (4.29-5.82)
Past hormone exposure (61-365 d)	499	4,995	0.94 (0.84-1.05)	250	2,384	0.95 (0.80-1.11)	249	2,611	0.92 (0.79-1.08)

DVT, deep vein thrombosis; ET, estrogen therapy; EPT, estrogen-progestogen therapy; OR, odds ratio; PE, pulmonary embolism; ref, reference; VTE, venous thromboembolism.
[a]Controlling for all risk factors, including region. Estrogen-testosterone combinations and progestogen-only exposures were also included in the model.

history of any hypercoagulable condition (OR, 3.10; 95% CI, 2.87-3.36), and varicose veins (OR, 2.87; 95% CI, 2.56-3.22). The OR for recent exposure to any exogenous hormone was 1.51 compared with those without recent hormone exposure (OR, 1.51; 95% CI, 1.43-1.60).

Risk factor profiles varied somewhat between PE and DVT cases. Of 20,359 VTE cases, over half were cases of PE with or without a concurrent diagnosis of DVT (n = 10,995), and the remainder of cases had a diagnosis of DVT without PE (n = 9,364) (Table 2). The OR for HT was not meaningfully different for PE and DVT outcomes.

Although the ORs for any HT exposure were similar for DVT, PE, and VTE, risk varied by type of HT exposures. Specifically, menopausal HT exposures were lower risk, and CHCs were higher risk (Table 3). OR for VTE with unopposed estrogen menopausal HT was 1.13 (95% CI, 1.04-1.23), and for combined estrogen and progestogen menopausal HT, it was 1.23 (95% CI, 1.10-1.38) compared with those without any HT exposure. In contrast, the OR for VTE with combined estrogen and progestogen contraceptive HT was 5.22 (95% CI, 4.67-5.84) compared with those without any HT exposure. The ORs for all other variables remained as in Table 1. To understand the risk posed by these hormone exposures, we estimated the NNH. For each 4,274 women exposed to menopausal therapy with unopposed estrogen or each 2,440 women exposed to menopausal combined therapy (estrogen-progestogen), one additional woman would be expected to experience a VTE. In contrast, there was a substantially greater risk with CHCs. For each 132 women exposed to CHCs, 1 additional woman would be expected to experience a VTE.

Statistical interactions

To test whether the thrombotic effect of hormones might exacerbate other risk factors, interaction terms tested for homogeneity in ORs between risk factors and VTE across those with and without recent HT exposure. Hormone exposure did not interact with or exacerbate the presence of varicose veins, prior stroke, smoking, a hypercoagulable condition, trauma, hospitalization/surgery, or cancer. However, HT did have significant interactions with comorbidity burden ($P < 0.01$), CAD ($P = 0.03$), and age ($P < 0.01$). Interactions indicated that the ORs between these risk factors and the occurrence of VTE were not homogeneous across women with and without recent HT exposures.

However, risk was lower for CAD, the Elixhauser comorbidity burden, and age for women with recent HT exposure. The direction of the associations in the interactions can be seen by examining the ORs in women with and without recent HT exposure (Table 4). CAD appeared to elevate risk for VTE overall by 23% compared with women without CAD. However, risk was elevated 24% for women without recent HT with CAD exposure compared with those without recent HT exposure and without CAD (OR, 1.24; 95% CI, 1.17-1.32), but risk was not elevated for women with recent hormone exposure with CAD (OR, 0.95; 95% CI, 0.75-1.20) compared with women with recent hormone exposure without CAD. Presence of comorbidities

TABLE 4. *ORs for age, comorbidity burden, and CAD with and without recent hormone exposure*

Interaction Variable	*P*	Recent HT exposure Cases (n = 2,130)	Recent HT exposure Controls (n = 17,428)	Recent HT exposure ORs (95% CI)[a]	No recent HT exposure Cases (n = 18,229)	No recent HT exposure Controls (n = 186,162)	No recent HT exposure ORs (95% CI)[a]	Total sample Cases (n = 20,359)	Total sample Controls (n = 203,590)	Total sample ORs (95% CI)[a]
CAD[a]	0.03	155	614	0.95 (0.75-1.20)	2,588	9,161	1.24 (1.17-1.32)	2,743	9,775	1.23 (1.16-1.31)
Elixhauser score: 1 or 2 vs 0	0.17	802	8,057	1.27 (1.11-1.45)	5,356	73,852	1.67 (1.59-1.76)	6,158	81,909	1.61 (1.53-1.69)
Elixhauser score: 3+ vs 0	<0.001	894	3,500	2.48 (2.15-2.85)	10,495	42,200	3.68 (3.49-3.89)	11,389	45,700	3.51 (3.34-3.69)
Age: 56-60 y vs 50-55 y	0.28	622	5,519	0.94 (0.82-1.08)	6,462	62,718	1.37 (1.26-1.49)	7,084	68,237	1.31 (1.20-1.42)
Age: 61-64 y vs 50-55 y	<0.001	405	4,568	0.76 (0.64-0.90)	6,081	59,858	1.40 (1.25-1.56)	6,486	64,426	1.31 (1.17-1.46)

CAD, coronary artery disease; HT, hormone therapy; OR, odds ratio.
[a]Adjusted for all risk factors and region of residence.

elevated the OR for VTE (OR, 1.61, with 1 or 2 comorbidities; OR, 3.51, with 3 or more comorbidities) compared with women without comorbidities, but without recent HT exposure, ORs were larger (OR, 1.67, with 1 or 2 comorbidities; OR, 3.68, with 3 or more comorbidities) compared with unexposed women without comorbidities than ORs for women with HT exposure (OR, 1.27, with 1 or 2 comorbidities; OR, 2.48, with 3 or more comorbidities) compared with exposed women without comorbidities. Similarly, older age increased risk for women without recent HT exposures compared with younger women without recent HT exposure but did not appear to elevate risk among women with recent hormone exposures.

These somewhat paradoxical findings may be due to the lower risk profile of women exposed to hormones. A comparison of risk factors by exposure indicated that unexposed women were older (53.25% of unexposed and 44.06% of exposed were 58 years or older; OR, 0.69 [95% CI, 0.67-0.71]), more likely to have CAD (5.75% vs 3.93%; OR, 0.67 [95% CI, 0.62-0.72]) and nonmetastatic or metastatic cancer (7.80% vs 3.71%; OR, 0.46 [95% CI, 0.42-0.49]), more likely to smoke (10.95% vs 8.13%; OR, 0.72 [95% CI, 0.68-0.76]), and slightly more likely to have two or more Elixhauser comorbidities (42.05% vs 40.56%; OR, 0.94 [95% CI, 0.91-0.97]).

DISCUSSION

To our knowledge, this is the first study to test interactions between HT and the most common risk factors for VTE in women 50 to 64 years of age. HT did not appear to worsen or exacerbate VTE risk factors. Metastatic cancer, hospitalization/surgery, and CHCs were major risk factors for VTE, with the OR of VTE 5 to 13 times higher than for those without those risk factors. Additional risk factors that doubled or tripled the risk of VTE included trauma, a history of a hypercoagulable condition, three or more comorbidities, and varicose veins. Risk factors with lower impacts on risk included CAD, stroke, smoking, and menopausal HT. VTE risk conferred by hormone exposure was a function of the type of hormone exposure. Menopausal HT was among the lower risks for VTE (NNH, 4,274 for estrogen only; 2,440 for estrogen-progestogen), whereas contraceptives were a major risk factor for VTE in women 50 to 64 years of age (NNH, 132). Women taking CHCs were much more likely to have a VTE. More investigation is needed to understand why these women were taking CHCs and if the benefits outweigh these significant risks.

A comparison of those with and without recent HT exposure suggested that risk for multiple comorbidities, CAD, and older age was not higher among those with recent HT exposure. However, women exposed to hormones tended to be younger and somewhat healthier.

One of the greatest challenges in the clinical care of perimenopausal and postmenopausal women is the treatment of women with severe symptoms and VTE risk factors or multiple comorbidities whose symptoms have not responded to nonhormone therapies. Little evidence has been available to guide clinicians in joint decision making about HT for these higher risk women. Our study found that, in commercially insured women aged 50 to 64 years, menopausal HT played a minor role in VTE risk compared with other risk factors and contraceptives. In contrast, CHCs were much more strongly associated with VTE risk, and their prevalence in the sample highlights the need for further study on the risks of continuing contraceptive-grade HT into perimenopausal years.

Strengths and weaknesses

A strength of this study is that the large claims database allows for exploration of the relatively rare events of VTE and cancer, whereas prospective designs are unlikely to feasibly follow a sample size large enough to draw conclusions.[69] In addition, the early termination of the WHI studies because of increased risk of VTE and other serious adverse events raises ethical concerns for conducting RCTs with HT. Observational studies now show little to no risk for specific hormones (eg, estradiol) and formulations (eg, transdermal) and suggest that new prospective trials may be warranted on these lower-risk therapies. This study may help identify women who are at increased risk for VTE and perhaps should be excluded from interventional trials.

A limitation of claims-based studies such as this is the lack of detailed information about participants, including factors such as socioeconomic status, race/ethnicity, medication adherence, the indication for HT prescriptions, duration of hormone use, a participant's age of menopause onset, and other factors. HT exposure in this study was estimated from filled prescriptions without information on actual adherence. Claims-based data also are likely to underestimate risk factors such as smoking because of limited sensitivity.[71] Optum's deidentified Clinformatics Data Mart Database includes only commercially insured members and may not be representative of publicly insured or uninsured populations. In addition, observational studies are susceptible to bias because of lack of randomization.[72] In particular, indication (and contraindication) bias can impact results, with the women exposed to HT in this study tending to be younger and healthier. Although it would be impossible to randomize women to unmodifiable risk factors (eg, hospitalization/surgery, trauma, etc), estimation of risks due to drug exposures should be considered preliminary, with more prospective studies needed to confirm results. To minimize bias, we statistically controlled for health status of cases and controls with the Elixhauser comorbidity index and included additional risk factors (CAD, stroke, smoking) to control for factors that might affect prescribing. Nevertheless, without random assignment to exposures, some residual confounding may remain between groups.

The design of this study ensured that no one had a VTE in the prior year and that risk factors occurred in the 12-month period before the VTE diagnosis. Exposures may be overestimated because of lack of adherence data. Women whose filled HT prescription overlapped the 60-day interval before the index date but who subsequently discontinued would still be considered exposed in this study. Also, because the design used an inexact match on age, associations with age may be underestimated. Matching minimized selection bias from the population cohort but precluded precise measurement of the association between age and the outcome.

Implications for future research

Observational studies, including a recent study conducted by the authors in the United States,[49] increasingly suggest that certain formulations and delivery methods of HT, such as estradiol and transdermal therapies, are safer than the formulations that led to early termination of the WHI studies. [48,49] This study showed that the risk for VTE with HT (except contraceptives) was minimal compared with other risk factors. Future research will need to explore risk by type of hormone exposure and age, as little data exist on the use of menopausal HT or CHCs in women 45 to 55 years of age. Our study highlights that CHCs have a very different risk profile from menopausal HT and yet may be prescribed for perimenopausal women who are at higher risk of thrombosis than younger women. Because prevention of pregnancy remains an important concern for many perimenopausal women, it is urgent for additional research into markers of fertility that can guide step-down from CHCs given the high risk for VTE.

CONCLUSIONS

Menopausal HT appears to add a minimal contribution to VTE risk in women older than 50 years, whereas CHCs are a major risk factor. Because of potential for confounding in this study by indication bias, additional studies are needed to explore the safety of HT in women who have higher risk for VTE. Risk factors such as hospitalization/surgery and trauma may be unavoidable, but risk factors in the medical record (cancer, hypercoagulable conditions, varicose veins, and age) should be carefully reviewed when considering HT for women older than 50 years.

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