Conjugated Equine Estrogen, Esterified Estrogen, Prothrombotic Variants, and the Risk of Venous Thrombosis in Postmenopausal Women

Nicholas L. Smith, Susan R. Heckbert, Rozenn N. Lemaitre, Alexander P. Reiner, Thomas Lumley, Frits R. Rosendaal, Bruce M. Psaty

Background—Joint exposure to oral conjugated equine estrogen (CEE) and prothrombotic genetic variants factor II G20210A or factor V G1601A (Leiden) increase venous thrombotic risk 6- to 16-fold in postmenopausal women. Esterified estrogen (EE), an alternative estrogenic compound, appears not to be associated with increased risk and nothing is known about the joint risk with prothrombotic genetic variants.

Methods and Results—We conducted a population-based, case-control study among postmenopausal women within a health maintenance organization. Subjects included 328 cases who sustained a first venous thrombosis and 1591 controls. Current hormone use was defined using electronic pharmacy records and variants FII G20210A and FV Leiden were genotyped using blood samples. FII and FV Leiden variants were associated with 2.1-fold and 3.7-fold increases in venous thrombotic risk, respectively. Overall, CEE use was associated with a 2.5-fold increase in risk compared with no hormone use, whereas EE use was not associated with a statistically increased risk. Compared with no hormone use and no variant, joint exposure to CEE and either prothrombotic variant was associated with an odds ratio (OR) of 9.1 (95% CI: 4.5 to 18.2), whereas joint exposure to EE and either variant was associated with an OR of 2.1 (0.6 to 6.8). When analyses were restricted to hormone users with either variant, CEE use was associated with an OR of 5.3 (1.3 to 21.7) compared with EE use.

Conclusions—These findings need replication and suggest EE use is associated with less risk than CEE use especially among 5% to 10% of women who are carriers of a prothrombotic variant. (Arterioscler Thromb Vasc Biol. 2006;26:2807-2812.)

Key Words: epidemiology ■ genetics ■ hormones ■ venous thrombosis ■ women

The use of oral estrogen therapy with or without concomitant progestin in postmenopausal women increases the risk of venous thrombosis 2- to 4-fold in experimental and observational studies that primarily investigated conjugated equine estrogen (CEE).1-7 Carriers of the prothrombotic genetic variant factor II (prothrombin) G20210A or factor V G1601A (Leiden) have a 2 to 8-fold increased risk of venous thrombosis compared with noncarriers.8-12 Women who are carriers of a prothrombotic genotype and are using oral hormone therapy experience a 6- to 16-fold increase in risk compared with women not using oral hormones who are not carriers of either variant.13-15

In our population-based, case-control study of venous thrombosis, esterified estrogen (EE), a synthetic plant-based estrogen, was not associated with an increased risk of venous thrombosis compared with nonuse of estrogens. By contrast, CEE use was associated with a 65% to 80% increase in risk compared with nonuse of estrogens or to EE use, respective-ly.16 The extent to which venous thrombotic risk is affected by the presence of EE and the factor II (FII) and V (FV) prothrombotic variants is not known. Using data from our population-based, case-control study of venous thrombosis in postmenopausal women, we extend previous analyses and estimate the association of hormone type, CEE versus EE, with venous thrombotic risk among carriers and noncarriers of the FII 20210A and FV Leiden variants.

Methods

Setting and Design

The setting for this observational study was Group Health Cooperative (GHC), a large health-maintenance organization in western Washington state. These analyses were part of a large ongoing, population-based, case-control study of myocardial infarction, stroke, atrial fibrillation, and venous thrombosis.17,18 This study was approved by the GHC Human Subjects Review Committee.
Study Population
Subjects were perimenopausal and postmenopausal female GHC members 30 to 89 years of age. Case subjects were GHC members who had an incident deep venous thrombosis (DVT) or pulmonary embolism (PE) between January 1, 1995 and December 31, 2002, and who were alive at the time of study recruitment. The date of venous thrombosis served as an index date. Control subjects were a random sample of GHC members that comprised a pool of control subjects shared by several case-control studies conducted at GHC.12-16 The control group was frequency matched by age (within decade), sex, treated hypertension status, and calendar-year of identification to myocardial infarction cases, the largest case group. Subjects were not matched on prevalent myocardial infarction or other cardiovascular diseases. This selection process created a pool of controls with the same characteristics in terms of prevalent comorbidities as GHC members within the matching strata. All control subjects for this analysis met the same inclusion criteria as venous thrombosis cases and had no history of DVT or PE. For control subjects, the index date was a randomly chosen date within the calendar year from which they were selected as a control.

Our previously published work on estrogen therapy and venous thrombotic risk included all cases of venous thrombosis from years 1995 to 2001.12 These analyses include an additional year of data collection (2002) but restrict subjects to those who were alive and consented to phlebotomy.

Women with venous thrombosis were identified from inpatient and outpatient care settings. In the inpatient setting, ICD-9 codes were obtained from GHC hospitalization records, which included hospital stays at GHC and non-GHC facilities. In the outpatient setting, GHC pharmacy records were used to identify women who were dispensed a prescription for a low-molecular-weight heparin as initial DVT treatment. Additionally, women were identified from the 3 GHC clinics where a pharmacy-based outpatient treatment protocol for DVT was implemented in 1997. Trained medical record abstractors reviewed the medical records of all potential cases to verify the diagnosis of venous thrombosis and to determine how the diagnosis was made. Ninety-five percent of eligible cases (n = 313) had a diagnosis that was confirmed with a diagnostic imaging test, 3% (n = 10) had tests that were considered equivocal or intermediate probability, and 2% (n = 5) had no diagnostic imaging test and only the diagnosis of the physician.

Measures
Hormones
Use of hormones was determined using the GHC computerized pharmacy database that contains records of all prescriptions filled through GHC since 1977. More than 95% of GHC members in this age group fill all or almost all their prescriptions through GHC pharmacies.19 Pharmacy data contain detailed information that includes drug name, prescription fill date, quantity of medication prescribed, and dosing instructions or the day’s supply of medication. Oral estrogens were classified into 3 subgroups: (1) CEE, such as Premarin; (2) EE, such as Estratab and Menest; and (3) other estrogens, primarily micronized estradiol, which accounted for <1% of all estrogen prescriptions during the 8 years of the study. The type of estrogen received was dictated primarily by changes over time in the GHC formulary; women treated before October 1999 primarily received EE, whereas women treated after this date received CEE. Formulary switches such as these occur in health maintenance organization settings when medications are thought to be therapeutically interchangeable.20-22 The progesterin prescribed was almost exclusively medroxyprogesterone acetate and was dispensed as a separate pill from estrogen in virtually all subjects. A woman was considered a current user of a hormone if she had received enough medication with her last prescription to last until her index date, based on an assumption of 80% compliance. We excluded women for whom there was no record of a GHC pharmacy prescription fill in the 5 years before the index date (n = 53), women using progesterin without estrogen at the index date (n = 46), and women who were current users of hormone creams or patches and who were not using estrogen pills (n = 65).

Prothrombotic Variants
Carriers of the FII 20210 A or FV Leiden variants were identified using DNA from a blood sample that was collected from consenting subjects who were alive at the time of recruitment to the study. All DNA was genotyped for the variants using the Illumina platform (Illumina Inc, San Diego, Calif). Laboratory personnel were blinded to case-control and hormone status. Agreement between Illumina results and results from a subset of subjects who also had restricted fragment length genotyping (n = 1472) was excellent for FV Leiden (kappa = 0.99) and perfect for FII 20210 A (kappa = 1.0).

Demographic and Clinical Information
Demographic and health status information was obtained by review of the entire GHC ambulatory medical record up to the index date by trained medical record abstractors. Medical records include notes from primary care and specialty physician visits, emergency department visit notes, discharge summaries, and laboratory and diagnostic test reports. Data were abstracted on information such as treated hypertension, hysterectomy, and menopause status, and outpatient surgical or major diagnostic procedures. Menopause was defined by the cessation of ovarian function that occurred naturally or through a bilateral oophorectomy. If menopausal status was not explicitly stated in the record, women 55 years of age and older were considered postmenopausal. Information was collected on most recent weight and height, birth date, and race.

We supplemented data collection from the ambulatory medical record with information from several GHC databases. In particular, cancer history information was collected from a GHC cancer registry file based on the Surveillance Epidemiology and End Results (SEER) registry, which included all diagnosed cancers except nonmelanoma skin cancers. Information on hospitalizations and bone fractures before the index date were collected from GHC administrative files that included diagnoses from inpatient and outpatient care delivered at GHC and non-GHC facilities.

Missing values for demographic and clinical characteristics collected from the medical record or telephone interview were imputed using IVWare software.23 Missing data were uncommon.

Statistical Analyses
Unconditional multivariate logistic regression was used to model the risk of venous thrombosis associated with prothrombotic variants and with the 2 estrogen types. The joint exposure of variants and estrogen type was modeled in 2 ways. The first approach included all women and used nonusers of hormones as the reference group. To avoid confounding by indication, the second approach included only women using hormones and used PE users as the reference group. Relative risks were estimated by odds ratios (ORs) with 95% confidence intervals (CIs). All multivariate models were adjusted for matching variables that included age, index year, and treated hypertension status. Potential confounders for the hormone–venous thrombosis relationship included body mass index (weight [kg]/height [m^2]), hysterectomy status, recent cancer history (cancer diagnosed within 5 years of index), hospitalizations that lasted at least 2 nights, major bone fractures, or surgical or major diagnostic procedures in the 30 days before the index date, and current use of concomitant proton pump therapy.

Three sensitivity analyses were conducted that: (1) assumed 100% compliance with prescribed hormone use rather than 80% compliance; (2) restricted subject inclusion to whites; and (3) restricted subject inclusion to those free of a major venous thrombosis risk factor (cancer, hospitalizations, fractures, and outpatient procedures).

Results
We identified 328 postmenopausal women who had an incident venous thrombosis (193 with DVT alone, 52 with DVT and PE, and 83 with PE alone) and who provided a blood sample. From among the 502 case subjects who were
alive at the time of study recruitment, blood samples could not be obtained from 74 (15%) who were too ill or who were assessed not to be able to give informed consent, and from 76 (15%) who refused study participation. Another 24 (5%) were excluded because blood could not be drawn or genotyping on the sample failed or was pending at the time of the analyses. Controls consisted of 1591 postmenopausal women who also provided a blood sample that was successfully genotyped for both prothrombotic variants. Excluded subjects were more likely to be older and non-white, and to have a lower body mass index, a history of cancer, and a recent hospitalization or fracture.

Characteristics of the cases and controls are presented in Table 1. Risk factors for venous thrombosis such as cancer and recent hospitalization and fractures were more common in case than control subjects. Table 2 presents the association of the prothrombotic variants and the association of estrogen type with venous thrombotic risk. Among controls, the prevalence of the FII 20210A variant was 3% and the prevalence of FV Leiden was 5%. Two subjects (0.1%) carried both variants, 1 subject (a case) was homozygous for FII 20210A, and 4 subjects (3 cases and 1 control) were homozygous for the FV Leiden variant. Carriership of the FII variant was associated with a 2.1-fold increase in incident venous thrombosis risk and carriership of the FV variant was associated with a 3.7-fold increase in risk. After adjusting for confounding factors of age, hypertension status, index year, race, hysterectomy status, body mass index, and the presence of a known risk factor that included recent cancer, hospitalization, fracture, or outpatient procedure, current CEE use was associated with a 2.5-fold increase in risk, whereas EE use was associated with a nonsignificant 1.5-fold increase in risk compared with nonuse of hormones. Among hormone users, current CEE use was associated with a 2-fold increase in risk compared with EE use.

Fully adjusted estimates of venous thrombotic risk for the joint exposure of hormones and either prothrombotic variant are presented at the top of Table 3. Compared with no hormone use and no variant, use of either CEE or EE among women with no variant was associated with a 2-fold higher risk (OR, 2.4; 95% CI, 1.7 to 3.6; and OR, 1.8; 95% CI, 1.2 to 2.8; respectively); presence of either variant and use of CEE was associated with a 9-fold higher risk (OR, 9.1; 95% CI, 4.5 to 18.2), whereas presence of either variant and use of

### TABLE 1. Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case n=328</th>
<th>Control n=1591</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>66.5* (10.7)</td>
<td>68.0 (9.4)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>305 (97*)</td>
<td>1433 (94)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m² (SD)</td>
<td>31.1* (7.8)</td>
<td>28.4 (6.4)</td>
</tr>
<tr>
<td>History of cancer within 5 years of index date, n (%)</td>
<td>42 (13*)</td>
<td>83 (5)</td>
</tr>
<tr>
<td>Hospitalization within 30 days before index date, n (%)</td>
<td>82 (25*)</td>
<td>7 (&lt;1)</td>
</tr>
<tr>
<td>Outpatient diagnostic or surgical procedure within 30 days before index date, n (%)</td>
<td>15 (5*)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Major fracture within 30 days before index date, n (%)</td>
<td>5 (2*)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Perimenopausal, n (%)</td>
<td>11 (3)</td>
<td>43 (3)</td>
</tr>
<tr>
<td>Hysterectomy, n (%)</td>
<td>113 (35*)</td>
<td>657 (41)</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

*P<0.05 for case-control characteristic comparison of means or proportions.

### TABLE 2. Main Associations of Polymorphic Factor II and V Genotypes and Hormone Type on Risk of Incident Venous Thrombosis

<table>
<thead>
<tr>
<th>Main Associations</th>
<th>Cases n=328</th>
<th>Controls n=1591</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FII 20210 GG</td>
<td>310</td>
<td>1545</td>
<td>1.0 (reference)*</td>
<td>NA</td>
</tr>
<tr>
<td>FII 20210 AG or AA</td>
<td>18</td>
<td>47</td>
<td>2.1 (1.2–3.8)</td>
<td>NA</td>
</tr>
<tr>
<td>FV 1691 GG</td>
<td>282</td>
<td>1517</td>
<td>1.0 (reference)*</td>
<td>NA</td>
</tr>
<tr>
<td>FV 1691 AG or AA</td>
<td>49</td>
<td>75</td>
<td>3.7 (2.5–5.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Current nonuse</td>
<td>183</td>
<td>982</td>
<td>1.0 (reference)†</td>
<td>NA</td>
</tr>
<tr>
<td>Current EE</td>
<td>48</td>
<td>316</td>
<td>1.5 (0.9–2.3)</td>
<td>1.0 (reference)‡</td>
</tr>
<tr>
<td>Current CEE</td>
<td>97</td>
<td>293</td>
<td>2.5 (1.7–3.5)</td>
<td>2.0 (1.1–3.7)</td>
</tr>
</tbody>
</table>

*Adjusted for matching factors (age, hypertension status, index year).
†Adjusted for matching factors (age, hypertension status, index year), race, hysterectomy status, body mass index, and presence of known risk factor (recent cancer, hospitalization, fracture, or outpatient surgical or diagnostic procedure within 30 days of index).
‡Adjusted for matching factors (age, hypertension status, index year), race, progestin use, and presence of known risk factor (recent cancer, hospitalization, fracture, or outpatient surgical or diagnostic procedure within 30 days of index).

NA indicates adjustments not applicable.
EE was associated with a nonsignificant 2-fold risk (OR, 2.1; 95% CI, 0.6 to 6.8). On the bottom of Table 3, we present the joint exposure of hormones and individual prothrombotic variants with venous thrombotic risk. When compared with non-users of hormones with neither variant, CEE use and the FV Leiden variant was associated with a nearly 15-fold increase in risk (OR, 14.8; 95% CI, 6.7 to 32.8), whereas EE use and the FV Leiden variant was not associated with risk (OR, 2.4; 95% CI, 0.6 to 10.0). Use of CEE or EE and the FII 20210A variant was not associated with increased risk (OR, 2.4; 95% CI, 0.6 to 9.3; and OR, 1.3; 95% CI, 0.2 to 10.2; respectively), although there were few subjects with this joint exposure.

Table 3 also presents fully adjusted analyses restricted to hormone users. Compared with CEE use and neither variant, EE use and either prothrombotic variant was not associated with an increase in risk (OR, 1.1; 95% CI, 0.3 to 3.8), whereas EE use and the FII 20210A variant was not associated with risk (OR, 2.4; 95% CI, 0.6 to 10.0). Use of CEE or EE and the presence of FII 20210A variant was not associated with increased risk (OR, 2.4; 95% CI, 0.6 to 9.3; and OR, 1.3; 95% CI, 0.2 to 10.2; respectively), although there were few subjects with this joint exposure.

Table 3 also presents fully adjusted analyses restricted to hormone users. Compared with EE use and neither variant, EE use with either prothrombotic variant was not associated with an increase in risk (OR, 1.1; 95% CI, 0.3 to 3.8), whereas CEE use with either variant was associated with a 6-fold increase in risk (OR, 6.1; 95% CI, 2.5 to 14.7). To highlight the comparison of risk by hormone type among those carrying either prothrombotic variant, we changed the reference group to EE use with either variant and found that CEE use with either variant was associated with a significant 5-fold increase in risk (OR, 5.3; 95% CI, 1.3 to 21.7).

In sensitivity analyses in which 100% hormone medication compliance was assumed, and in which subjects were restricted either to whites or to those without major venous thrombotic risk factors, the associations of hormones and variants with venous thrombotic risk were altered only slightly. This held true for models with non-users of hormones and EE users as reference groups.

**Discussion**

Among post-menopausal women in this population-based, case-control study, the joint exposure of CEE use and either the FII 20210A or FV Leiden variant was associated with a 9-fold increase in the risk of venous thrombosis when compared with nonusers of hormones who were not carriers of a prothrombotic variant. The use of EE, however, was not associated with an increased risk of venous thrombosis among carriers of either prothrombotic variant. Among hormone users carrying either variant, CEE use was associated with a 5-fold increase in risk compared with EE use. These findings suggest the presence of gene–drug interaction for CEE but not for EE. Importantly, EE and CEE were associated with increased risk among those without either prothrombotic variant.

**TABLE 3. Estrogen Type, Factor II and V Variants, and Risk of Incident Venous Thrombosis**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Estrogen Use and Type</th>
<th>Cases n</th>
<th>Controls n</th>
<th>Nonuse of Hormone as Reference* OR (95% CI)</th>
<th>EE Use as Reference† OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FII 20210 or FV Leiden</td>
<td>Wild-type</td>
<td>Not current</td>
<td>145</td>
<td>916</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>Wild-type</td>
<td>Current EE</td>
<td>44</td>
<td>289</td>
<td>1.8 (1.2–2.9)</td>
</tr>
<tr>
<td></td>
<td>Wild-type</td>
<td>Current CEE</td>
<td>77</td>
<td>266</td>
<td>2.4 (1.7–3.6)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Not current</td>
<td>38</td>
<td>66</td>
<td>4.4 (2.6–7.4)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Current EE</td>
<td>4</td>
<td>27</td>
<td>2.1 (0.6–6.8)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Current CEE</td>
<td>20</td>
<td>27</td>
<td>9.1 (4.5–18.2)</td>
</tr>
<tr>
<td>FII 20210</td>
<td>Wild-type</td>
<td>Not current</td>
<td>170</td>
<td>959</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td>Wild-type</td>
<td>Current EE</td>
<td>47</td>
<td>304</td>
<td>1.6 (1.0–2.5)</td>
</tr>
<tr>
<td></td>
<td>Wild-type</td>
<td>Current CEE</td>
<td>93</td>
<td>282</td>
<td>2.6 (1.8–3.7)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Not current</td>
<td>13</td>
<td>23</td>
<td>4.0 (1.7–9.7)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Current EE</td>
<td>1</td>
<td>12</td>
<td>1.3 (0.2–10.2)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Current CEE</td>
<td>4</td>
<td>11</td>
<td>2.4 (0.6–9.3)</td>
</tr>
<tr>
<td>FV Leiden</td>
<td>Wild-type</td>
<td>Not current</td>
<td>157</td>
<td>939</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>Wild-type</td>
<td>Current EE</td>
<td>45</td>
<td>301</td>
<td>1.7 (1.1–2.6)</td>
</tr>
<tr>
<td></td>
<td>Wild-type</td>
<td>Current CEE</td>
<td>80</td>
<td>277</td>
<td>2.3 (1.6–3.3)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Not current</td>
<td>26</td>
<td>43</td>
<td>4.3 (2.3–7.9)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Current EE</td>
<td>3</td>
<td>15</td>
<td>2.4 (0.6–10.0)</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Current CEE</td>
<td>17</td>
<td>16</td>
<td>14.8 (6.7–32.8)</td>
</tr>
</tbody>
</table>

*Adjusted for matching factors (age, hypertension status, index year), race, hysterectomy status, body mass index, and presence of known risk factor (recent cancer, hospitalization, fracture, or outpatient surgical or diagnostic procedure within 30 days of index)
†Adjusted for matching factors (age, hypertension status, index year), race, progestin use, and presence of known risk factor (recent cancer, hospitalization, fracture, or outpatient surgical or diagnostic procedure within 30 days of index).
Our findings on venous thrombotic risk for women exposed to prothrombotic variants and CEE are similar in magnitude to previously published work and suggest that the inherited FV Leiden variant and the acquired risk factor of CEE use independently increase thrombotic risk.\textsuperscript{13–15} The EE findings presented here, however, are novel and expand analyses previously published that investigated the main associations of estrogen type with venous thrombotic risk. Current findings suggest that the lower risk profile of EE compared with CEE may in part be attributable to a weak risk of venous thrombosis among EE users who are carriers of a prothrombotic variant and a robust risk among CEE users who are carriers. Findings should not be interpreted as EE conveying risk protection from either prothrombotic variant. Importantly, the results of this study address the cause of venous thrombosis in postmenopausal women and do not serve as clinical recommendations for decision making regarding the use of hormone treatment in women who are carriers of either prothrombotic variant. We have not addressed the complex issues about the appropriateness of screening and screening policy and these issues clearly deserve increased attention as new risks are identified and quantified.

Because of the low prevalences of the FV and especially the FII mutations, confidence intervals around risk estimates were wide and we had limited ability to explore other analyses, including associations with concomitant progestin therapy. Other study limitations include retrospective case identification that did not allow us to include fatal PE cases or case subjects who died after the incident event and before study recruitment. Many of these women had cancer at the time of the venous thrombotic diagnosis. The similarity in risk estimates between our CEE findings and prospective studies suggest that the impact of any case fatality bias in our study recruitment. Many of these women had cancer at the time of the venous thrombotic diagnosis. The similarity in risk estimates between our CEE findings and prospective studies suggest that the impact of any case fatality bias in our findings is small.\textsuperscript{13,15} The use of hormone therapy was not randomly assigned but the type of estrogen received was dictated primarily by changes over time in the GHC formulation. Use of hormone therapy was prospectively collected in the GHC pharmacy database and not subject to recall or information bias. Other methodologic strengths of this study include a population-based study design where hospitalized and nonhospitalized case subjects were included.

Conjugated equine estrogens are derived from the urine of pregnant mares and contain 10 known biologically active estrogen compounds as well as others that have yet to be described.\textsuperscript{24,25} Esterified estrogens are synthetic and fabricated from soybean and yam. Comparative pharmacological data for CEE and EE are limited and differences in compounds are not well-documented.\textsuperscript{26} A cross-sectional study by our group has examined the association of estrogen type on resistance to activated protein C (APC) in healthy subjects and found that CEE users, compared with EE users, were significantly more resistant to the anti-coagulation effects of APC.\textsuperscript{26} The observation of a differential risk of clotting associated with various hormone products is not unique. Data from the oral contraceptive literature suggest that different progestin compounds in second- and third-generation pills are associated with a differential risk of venous thrombosis.\textsuperscript{27–31} Experimental data on hormone replacement therapy indicate that transdermal delivery of hormones is less thrombotic than oral delivery.\textsuperscript{32,33} Findings from a recent publication of the ESTHER case-control study that compared oral and transdermal estrogen therapy in women who were carriers and noncarriers of the 2 prothrombotic mutations suggest that transdermal hormone use, unlike oral hormones, does not confer additional venous thrombotic risk in the presence of FII 20210 and FV Leiden variants.\textsuperscript{34}

Venous thrombotic risk may be the most serious side-effect of short-term hormone therapy to treat vasomotor symptoms of menopause. Unfortunately, data on the safety of oral and transdermal estrogen products are limited and hinder women and their physicians from making evidence-based decisions when choosing a hormone therapy to treat symptoms.

Findings from our observational study suggest the use of CEE among women carrying either the FII 20210 or FV Leiden prothrombotic variants conferred additional risk of venous thrombosis beyond the risks associated with either exposure alone. By contrast, EE use among those carrying a prothrombotic variant was not associated with additional risk. These findings need replication and suggest that EE is associated with less risk of venous thrombosis than CEE, especially among the 5% to 10% of women who are carriers of FII 20210A or FV Leiden.

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**Disclosures**

None.

**References**


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