Factor V Leiden, Hormone Replacement Therapy, and Risk of Venous Thromboembolic Events in Women With Coronary Disease

David M. Herrington, Eric Vittinghoff, Timothy D. Howard, David A. Major, John Owen, David M. Reboussin, Donald Bowden, Vera Bittner, Joel A. Simon, Deborah Grady, Stephen B. Hulley

Abstract—Oral contraceptive use in women with factor V Leiden is associated with increased rates of venous thromboembolic events (VTEs). However, the effects of hormone replacement therapy (HRT) in postmenopausal women with factor V Leiden are not known. A nested case-control study was conducted among women with established coronary disease enrolled in 2 randomized clinical trials of HRT, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trial. The Leiden mutation was present in 8 (16.7%) of 48 cases with VTE compared with only 7 (6.3%) of 112 controls (odds ratio [OR] Leiden 3.3, 95% CI 1.1 to 9.8; \( P = 0.03 \)). In women without the factor V Leiden mutation, risk associated with HRT use was significantly increased (OR HRT 3.7, 95% CI 1.4 to 9.4; \( P < 0.01 \)). On the other hand, in women with the factor V Leiden mutation, the estimated risk associated with HRT was increased nearly 6-fold, although the CIs were wide and included unity (OR HRT 5.7, 95% CI 0.6 to 53.9; \( P = 0.13 \)). The OR for women with the Leiden mutation who were also assigned to HRT compared with wild-type women assigned to placebo was 14.1 (95% CI 2.7 to 72.4, \( P = 0.0015 \)). In women with the factor V Leiden mutation who were treated with HRT, the estimated absolute incidence of VTE was 15.4 of 1000 per year compared with 2.0 of 1000 per year in women without the mutation who were taking a placebo (\( P = 0.0015 \)). On the basis of these data, in women with coronary disease, the estimated number needed to screen for factor V Leiden to avoid an HRT-associated VTE during 5 years of treatment is 376. If factor V Leiden genotyping becomes less expensive, it could be cost effective to screen for the presence of the mutation before instituting HRT in women with coronary disease. (Arterioscler Thromb Vasc Biol. 2002;22:1012-1017.)

Key Words: cardiology ■ risk factors for stroke ■ genetics ■ thrombosis risk factors

In 1994, Bertina et al 1 described a single point mutation in the gene coding for factor V. This mutation, referred to as the factor V Leiden mutation, renders factor Va relatively resistant to degradation by the natural anticoagulant, activated protein C (APC).2–3 The presence of this mutation or its functional consequence, APC resistance, is associated with an increased risk of venous thromboembolic events (VTEs).1–4–6 Risk for VTE appears to be even higher in women with APC resistance or the factor V Leiden mutation who are also pregnant7–11 or who use oral contraceptives.7,12–15 The effect of hormone replacement therapy (HRT) on the risk of VTE in women with APC resistance is not well established. One observational study found a multiplicative relationship between the effects of HRT and APC resistance on VTE risk,16 whereas a small randomized clinical trial of oral HRT in women with previously verified VTE failed to confirm such a relationship.17 Determining the relative and absolute impact of HRT and factor V Leiden on VTE risk is especially important for older women or for women with coronary disease, whose baseline risk of VTE is considerably higher than that of healthy premenopausal women.18,19

See page 879

To evaluate the association between factor V Leiden and VTE in women with coronary disease and its impact on the relationship between HRT and VTE in this population, we conducted a nested case-control study among participants of 2 multicenter randomized clinical trials of HRT in women with established coronary disease, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trial.

Methods

Study Populations

The details of the HERS20 and ERA21 trial designs and primary results22,23 have been previously reported. Participants were post-

Received February 19, 2002; revision accepted April 2, 2002.

From the Department of Internal Medicine, Sections on Cardiology (D.M.H., D.A.M.), Medical Genetics (T.D.H.), and Hematology and Oncology (J.O.), and the Departments of Public Health Sciences (D.M.R.) and Biochemistry (D.B.), Wake Forest University School of Medicine, Winston-Salem, NC; the Department of Epidemiology and Biostatistics (E.V., J.A.S., D.G., S.B.H.), University of California, San Francisco; and the Department of Medicine (V.B.), University of Alabama at Birmingham.

Reprint requests to David M. Herrington, MD, MHS, Department of Internal Medicine/Cardiology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1040. E-mail dherring@wfubmc.edu

© 2002 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

DOI: 10.1161/01.ATV.000018301.91721.94

1012
menopausal women aged <80 years with documented coronary artery disease. The participating clinical centers included 22 academic or community hospitals scattered throughout the continental United States. The exclusion criteria for both trials included a history of deep vein thrombosis (DVT) or pulmonary embolism (PE). In HERS, participants were randomly assigned to receive oral conjugated equine estrogen (0.625 mg daily) plus medroxyprogesterone acetate (2.5 mg daily) or placebo and were followed for an average of 4.1 years. In ERA, women were randomized to receive oral conjugated equine estrogen (0.625 mg daily), estrogen plus medroxyprogesterone acetate (2.5 mg daily), or placebo and were followed for 3.25 years.

Data Collection
At 4- to 6-month follow-up visits, women were queried about blood clots in the legs or lungs or any hospitalizations. A positive reply prompted retrieval of all pertinent medical records to verify the occurrence of a VTE. A diagnosis of DVT required confirmation by venography, impedance plethysmography, or ultrasound. A diagnosis of PE required confirmation by a segmental or larger ventilation/perfusion mismatch on a nuclear lung scan or an intraluminal filling defect by pulmonary angiography. VTEs were classified as idiopathic if they occurred in women without a preexisting diagnosis of cancer or the occurrence of an inpatient hospitalization or lower extremity or hip fracture within 3 months before the VTE. Events were adjudicated by individuals who were unaware of treatment assignment or factor V genotype.

In HERS, 47 (1.7%) of the women had a VTE (32 DTVs and 15 PEs). At the final follow-up visit, cases and 2 age- and clinic-matched controls were asked to provide an additional specimen of whole blood for factor V genotyping. For women who could not return for the final visit or who had died, consent was sought from them or their next of kin to use a previously collected Pap smear for extraction of DNA and genotyping. Consent was obtained, and factor V genotype was ascertained in 40 of 47 cases and 80 matched controls. Three of the remaining 7 cases declined participation, 3 did not have blood or a Pap smear available for analysis, and 1 matched control had a Pap smear that did not yield enough DNA for genotyping.

Genotyping for the presence of the Leiden mutation (G1691A) in the factor V gene was performed on DNA extracted from anonymously labeled peripheral blood leukocytes or cells retrieved from Pap smears (Pap smear slides yielded ∼200 ng DNA per slide). The general region containing the mutational site was amplified by polymerase chain reaction, and the presence of the Leiden mutation was inferred from the observed cleavage pattern with the restriction enzyme Mnl-I.1

Statistical Analyses
Baseline and on-study characteristics of the cases and controls were compared within each study and in the combined data; random effects models25 were used for continuous variables, and conditional logistic regression23 was used for binary variables, to take account of the matched case-control design. The association between factor V genotype and risk of VTE was examined by using conditional logistic regression models, again to take account of the matching and to adjust for treatment assignment. Odds ratios (ORs) generated by these models, accompanied by 95% CIs and nominal 2-tailed probability values, were used to approximate relative risks. In exploratory analyses, results from the 2 study cohorts were similar; therefore, the data from the 2 cohorts were combined. Similarly, preliminary analysis within the ERA cohort found no significant difference between the effects of unopposed estrogen and estrogen plus medroxyprogesterone acetate; thus, data from these 2 active treatment arms were combined. Additional models were also examined with adjustment for potential risk factors for VTE, including a previous diagnosis of cancer (excluding nonmelanoma skin cancer) or myocardial infarction (MI), inpatient hospitalization, or lower extremity or hip fracture within 90 days of the VTE, or use of aspirin or statins documented during the most recent clinic visit before the VTE. In these models, as well as in the initial comparison with cases, on-trial risk factors for controls were evaluated at the time in days since the randomization of VTE onset for the matched case. Tests for additive and multiplicative interaction were performed by using previously described methods.26

Results
Characteristics of the VTE cases and controls from each clinical trial cohort are summarized in Table 1. In the pooled data, prior MI, cancer (other than nonmelanoma skin cancer), or hospitalization within 90 days were significantly associated with occurrence of VTE, and there was a nonsignificant trend toward increased risk among women with elevated triglycerides or a recent lower extremity or hip fracture and in women who did not use aspirin. In multivariate analyses, only hospitalization within 90 days and a history of MI remained significantly associated with VTE.

The Leiden mutation was present in 8 (16.7%) of the 48 cases of VTE compared with only 7 (6.3%) of the 112 controls (Table 2). On the basis of these numbers, the estimated prevalence of factor V Leiden in the entire study population was 6.4%. After the age- and clinic-matched case-control design was taken into account and adjustments were made for treatment assignment, the risk of VTE was 3- to 5-fold greater in women with factor V Leiden compared with women without the mutation (ORLeiden 3.3, 95% CI 1.1 to 9.8; P=0.03). Similarly, the ORLeiden for a DVT was 3.2 (95% CI 1.0 to 10.3, P=0.05), and for a PE, it was 3.5 (95% CI 0.2 to 69.6, P=0.41). After additional adjustment for recent hospitalization and prior MI, the ORLeiden for VTE increased to 6.8 (95% CI 1.1 to 42.8, P=0.05). The number of cases was too small to support fully adjusted models with stable estimates for DVT or PE separately. Factor V Leiden was present in 5 (16%) of the 31 women with idiopathic VTE and 3 (18%) of the 17 women with nonidiopathic VTE.

HRT use was associated with a 3- to 5-fold increase in the risk of VTE (OR 3.4, 95% CI 1.4 to 8.1; P=0.06). Adjustment for factor V Leiden status resulted in a slightly higher estimate of risk (ORHRT 3.9, 95% CI 1.6 to 9.6; P=0.004). After additional adjustment for recent hospitalization and prior MI, the risk associated with HRT use remained significant (ORHRT 4.8, 95% CI 1.3 to 17.5; P=0.02). Among women without factor V Leiden, the ORHRT was 4.5 (95% CI 1.2 to 16.9, P=0.02; Table 3). In contrast, among the fewer women with factor V Leiden, the OR for HRT suggested a >10-fold increase in risk compared with placebo; however, the CIs were wide and included unity (ORHRT 10.2, 95% CI 0.3 to 344; P=0.20). Compared with women without factor V Leiden taking placebo, women with factor V Leiden taking HRT had a 14-fold greater risk of VTE (ORHRT 14.1, 95% CI 2.7 to 72.4; P=0.002). Despite the suggestion of excess risk of VTE in women with factor V Leiden, formal tests for additive or multiplicative interaction were negative.

Overall, 1.56% of the combined study cohort (n=3072) suffered a VTE. If it is assumed that the prevalence of factor V Leiden in the sample of controls was representa-
tive of all noncases, 2.08% of women with factor V Leiden had a VTE versus 1.49% of the women without factor V Leiden. If the variable length of follow-up among women in the 2 studies is taken into account, the overall incidence of VTE was 7.1 per 1000 women per year. In women without factor V Leiden who were assigned to placebo, the incidence of VTE was 2.0 (95% CI 0.8 to 3.2) events per 1000 women per year (Table 4). Treatment with HRT increased the estimated incidence to 5.8 events per 1000 women per year (95% CI 4.5 to 7.1). In factor V Leiden women treated with HRT, the incidence was further increased to 15.4 (95% CI 3.5 to 27.3) events per 1000 women per year. On the basis of these estimates, if women with coronary disease were screened for factor V Leiden

### Table 1. Characteristics of the Case-Control Samples from HERS and ERA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HERS Cases (n=40)</th>
<th>HERS Controls (n=80)</th>
<th>P</th>
<th>ERA Cases (n=8)</th>
<th>ERA Controls (n=32)</th>
<th>P</th>
<th>Overall Cases vs Controls P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67.7±1.00</td>
<td>67.8±0.7</td>
<td>0.36</td>
<td>64.3±2.1</td>
<td>63.9±1.0</td>
<td>0.15</td>
<td>0.87</td>
</tr>
<tr>
<td>Minority, N (%)</td>
<td>2 (5.0)</td>
<td>4 (5.0)</td>
<td>1.00</td>
<td>3 (37.5)</td>
<td>4 (12.5)</td>
<td>0.11</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension, N (%)*</td>
<td>28 (70.0)</td>
<td>49 (62.8)</td>
<td>0.41</td>
<td>4 (50.0)</td>
<td>20 (62.5)</td>
<td>0.53</td>
<td>0.66</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)*</td>
<td>10 (25.0)</td>
<td>20 (25.0)</td>
<td>1.00</td>
<td>1 (12.5)</td>
<td>11 (34.4)</td>
<td>0.28</td>
<td>0.54</td>
</tr>
<tr>
<td>Current smokers, N (%)</td>
<td>3 (7.5)</td>
<td>3 (7.5)</td>
<td>1.00</td>
<td>2 (25.0)</td>
<td>12 (37.5)</td>
<td>0.45</td>
<td>0.64</td>
</tr>
<tr>
<td>Sedentary lifestyle, N (%)†</td>
<td>30 (75.0)</td>
<td>59 (73.8)</td>
<td>0.87</td>
<td>1 (12.5)</td>
<td>7 (21.9)</td>
<td>0.55</td>
<td>0.68</td>
</tr>
<tr>
<td>Previous MI, N (%)</td>
<td>24 (60.0)</td>
<td>35 (43.8)</td>
<td>0.09</td>
<td>4 (50.0)</td>
<td>8 (25.0)</td>
<td>0.21</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>235.1±6.4</td>
<td>222.4±3.9</td>
<td>0.10</td>
<td>212.5±16.8</td>
<td>219.6±7.9</td>
<td>0.65</td>
<td>0.15</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>151.6±5.8</td>
<td>138.8±3.7</td>
<td>0.07</td>
<td>131.9±18.0</td>
<td>139.9±7.2</td>
<td>0.60</td>
<td>0.14</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>46.1±1.6</td>
<td>48.8±1.5</td>
<td>0.25</td>
<td>44.3±3.2</td>
<td>46.3±2.4</td>
<td>0.67</td>
<td>0.27</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>187.6±9.4</td>
<td>174.0±6.8</td>
<td>0.31</td>
<td>221.1±33.8</td>
<td>167.6±16.1</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>On-trial VTE risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer, N (%)‡</td>
<td>6 (15.0)</td>
<td>3 (3.8)</td>
<td>0.04</td>
<td>1 (12.5)</td>
<td>0</td>
<td>N/A</td>
<td>0.02</td>
</tr>
<tr>
<td>Fracture§</td>
<td>4 (10.0)</td>
<td>1 (1.3)</td>
<td>0.06</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td>24 (60.0)</td>
<td>7 (8.8)</td>
<td>&lt;0.0001</td>
<td>2 (25.0)</td>
<td>2 (6.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Recent statin use, N (%)¶</td>
<td>11 (27.5)</td>
<td>32 (40.0)</td>
<td>0.17</td>
<td>2 (25.0)</td>
<td>8 (25.0)</td>
<td>1.00</td>
<td>0.22</td>
</tr>
<tr>
<td>Recent aspirin use, N (%)¶</td>
<td>24 (60.0)</td>
<td>63 (78.8)</td>
<td>0.04</td>
<td>4 (50.0)</td>
<td>15 (47.0)</td>
<td>0.87</td>
<td>0.07</td>
</tr>
<tr>
<td>Recent coumadin use, N (%)</td>
<td>2 (5.0)</td>
<td>5 (2.5)</td>
<td>0.49</td>
<td>0</td>
<td>1 (3.0)</td>
<td>1.00</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Continuous variables presented as mean± standard error.
*Hypertension classification based on response to the question, “Have you ever been told by a physician that you have hypertension or high blood pressure?”; diabetes classification based on response to the question, “Have you ever been told by a physician that you have diabetes, sugar diabetes, or high blood sugar?”
†Based on self-report of walking “seldom” or “none” (HERS) or “much less” or “somewhat less active than other women your age” (ERA).
‡Any diagnosis of cancer (except non-melanoma skin cancer) before VTE.
§Lower extremity or hip fracture ≤90 days before time of VTE diagnosis in the index case (measured as days since randomization).
¶Documented at most recent clinic visit before time of VTE diagnosis in the index case (measured as days since randomization).

### Table 2. Distribution of Factor V Leiden Genotype by Study and Case-Control Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Genotype</th>
<th>Cases (n=48)</th>
<th>Controls (n=112)</th>
<th>OR* 95% CI</th>
<th>P</th>
<th>Adjusted OR† 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>Wild-type</td>
<td>25 (52)</td>
<td>55 (23)</td>
<td>1.0</td>
<td></td>
<td>1.0 to 10.3</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Leiden</td>
<td>5 (2)</td>
<td>1 (5)</td>
<td>3.2</td>
<td></td>
<td>0.2 to 69.6</td>
<td>0.41</td>
</tr>
<tr>
<td>PE‡</td>
<td>Wild-type</td>
<td>11 (23)</td>
<td>23 (8)</td>
<td>1.0</td>
<td></td>
<td>1.0 to 6.6</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Leiden</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>3.5</td>
<td></td>
<td>0.2 to 69.6</td>
<td>0.41</td>
</tr>
<tr>
<td>VTE (DVT+PE)</td>
<td>Wild-type</td>
<td>34 (61)</td>
<td>24 (31)</td>
<td>1.0</td>
<td></td>
<td>1.0 to 6.6</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Leiden</td>
<td>6 (2)</td>
<td>6 (1)</td>
<td>3.3</td>
<td></td>
<td>1.1 to 9.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Based on conditional logistic regression taking into account age- and clinic-matched case-control design and adjusting for treatment assignment (HRT versus placebo).
†Also adjusted for a history of previous MI and hospitalization.
‡Two women had a DVT and a PE.
before initiating HRT and if HRT was withheld from carriers of the mutation, the estimated number needed to screen to prevent 1 VTE during 5 years of therapy would be 376.

**Discussion**

These data reveal significant increases in the risk of VTE in women with coronary disease who are carriers of the factor V Leiden mutation. The 6.4% prevalence of the mutation in this study population and the 3- to 6-fold relative increase in the risk of VTE in women with the mutation are consistent with earlier reports from studies of largely healthy normal subjects. However, because of the substantially higher baseline risk of VTE in this group of women with coronary disease, the absolute increase in risk associated with factor V Leiden (≈0.5% per year) was much higher than that in healthier cohorts. Use of HRT in factor V Leiden–positive women further increased the risk to >1.5% per year. On the basis of these data, in women with coronary disease, 1 DVT might be prevented during a planned 5 years of treatment by withholding HRT from the expected 24 Leiden-positive women among 376 screened. For women who would use HRT for 10 years, the number needed to screen would be 188.

The results of the present study are consistent with the results of previous studies demonstrating a multiplicative relationship between factor V Leiden or APC resistance and exogenous estrogen use and the risk of VTE. In a case-control study of idiopathic VTEs, Lowe et al observed a 13-fold increased risk in HRT users with APC resistance compared with women without APC resistance or HRT use; this risk was very similar to the 15-fold excess risk observed in the doubly exposed women in the present study.

**TABLE 3. Effects of HRT on Risk for VTE by Factor V Leiden Genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Cases (n=48)</th>
<th>Controls (n=112)</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>OR†</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>Placebo</td>
<td>8</td>
<td>45</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
<td>32</td>
<td>60</td>
<td>3.7</td>
<td>1.4–9.4</td>
<td>&lt;0.01</td>
<td>4.5</td>
<td>1.2–16.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Leiden</td>
<td>Placebo</td>
<td>2</td>
<td>4</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
<td>6</td>
<td>3</td>
<td>5.7</td>
<td>0.6–53.9</td>
<td>0.13</td>
<td>10.2</td>
<td>0.3–344</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Based on conditional logistic regression taking into account age- and clinic-matched case-control design and adjusting for treatment assignment (HRT versus placebo).
† Also adjusted for a history of MI and recent hospitalization.

The precise mechanism for the association between estrogen exposure and risk for VTE remains uncertain. Some, but not all, studies indicate that oral contraceptive use or pregnancy may result in an acquired form of APC resistance, similar to the functional defect associated with the factor V Leiden mutation. However, Douketis et al failed to find evidence of an effect of oral HRT on APC resistance. Currently available data are also inconsistent regarding the effects of HRT on thrombin generation or fibrinolytic potential.

There are several limitations of the present study. The number of cases is small, thereby limiting precision in the estimates of the effects of factor V Leiden and the complexity of the models that could be used to adjust for other covariates. No information is available about concurrent thrombophilic states in the study participants. Some evidence suggests that factor V Leiden may be most important as a VTE risk factor in the presence of other thrombophilic conditions. Protein C deficiency, protein S deficiency, hyperhomocysteinemia, and the prothrombin G20210A genotype have all been reported to further increase the risk of VTE associated with factor V Leiden. The effects of HRT on the risk of VTE in women with or without heart disease who also have such thrombophilic conditions are not yet established. The estimates of the risk of VTE in the clinical trial participants reported in the present study may underestimate the risks in the general population, because women with a prior history of VTE or women with hypertriglyceridemia or advanced heart failure were excluded from participation. In addition, after it became clear that HRT was associated with an increased VTE risk in HERS, the protocol was changed so that HRT was withheld during acute hospitalizations, which may have further minimized the overall risk in this study population.

Finally, the results of the present study may not apply to women of other ethnic backgrounds. The prevalence of the Leiden mutation is highest in northern Europeans and is almost nonexistent in most Asian populations.

It is also important to emphasize that the observations in the present study are limited to women with established coronary disease. The joint effects of HRT and factor V Leiden in healthy women are not yet determined. In younger women with factor V Leiden, oral contraceptives increase risk by ≈0.2 per 1000 women per year. In the present study, in women with coronary disease and factor V Leiden, the increase in absolute risk associated with HRT use was ≈40-fold greater (8.3 per 1000 women per year). It is difficult

**TABLE 4. Absolute Risk of VTE by Factor V Leiden Genotype and Treatment Assignment**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Treatment</th>
<th>Estimated Rate (1000/yr)*</th>
<th>95% CI</th>
<th>Excess Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>Placebo</td>
<td>2.0</td>
<td>0.8–3.2</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
<td>5.8</td>
<td>4.5–7.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Leiden</td>
<td>Placebo</td>
<td>7.1</td>
<td>0.0–17.5</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
<td>15.4</td>
<td>3.5–27.3</td>
<td>13.4</td>
</tr>
</tbody>
</table>

*Estimated events per 1000 women per year. For both HRT and placebo, event rates are estimated by treatment assignment from observed genotype prevalence in cases and controls and VTE event rates in the combined HERS/ERA cohorts. By virtue of randomization, genotype is assumed to be unrelated to treatment assignment in the entire study population.
to imagine many clinical settings in which the benefits of postmenopausal HRT would outweigh this increase in risk in women with existing coronary heart disease (CHD). This is especially true in light of the evidence that HRT is ineffective at slowing clinical or anatomic manifestations of atherosclerosis and may even be associated with an early increase in CHD events. Unfortunately, despite the higher absolute risk of VTE in women with CHD, the prevailing costs of $150 to $600 for a single clinical factor V Leiden determination makes screening impractical. Even if the low end of this range of cost is assumed, ~$50 000 would be spent on screening to prevent 1 VTE hospitalization. If clinical genotyping for factor V Leiden becomes less expensive, screening could become a cost-effective strategy in women with heart disease.

In summary, in women with coronary disease, factor V Leiden and HRT use are independently associated with an increase in VTE risk. In women who have both risk factors, the absolute risk is ~1.5% per year. If less expensive methods for factor V genotyping become more widely available, screening for factor V Leiden before initiating HRT might become a cost-effective strategy in women with coronary disease. However, even in women with coronary disease without factor V Leiden, the HRT-associated VTE risk must be carefully considered when HRT is used for approved noncoronary indications.

Acknowledgments

This study was supported by grants U01 HL-45488 (Principal Investigator, D.M. Herrington) and M01 RR-07122 (General Clinical Research Center, Wake Forest University Baptist Medical Center) from the National Institutes of Health, Bethesda, Md, and a contract from Wyeth-Ayerst Research, Radnor, Pa. The authors thank Georgia Saylor for database construction and analyses, Karen Craver and Bridget Fitzgerald for the factor V Leiden genotyping, J.T. Tolentino for research assistance, and Karen Potvin Klein, MA, ELS, for her invaluable editorial assistance.

References


Factor V Leiden, Hormone Replacement Therapy, and Risk of Venous Thromboembolic Events in Women With Coronary Disease

David M. Herrington, Eric Vittinghoff, Timothy D. Howard, David A. Major, John Owen, David M. Reboussin, Donald Bowden, Vera Bittner, Joel A. Simon, Deborah Grady and Stephen B. Hulley

Arterioscler Thromb Vasc Biol. 2002;22:1012-1017; originally published online April 11, 2002; doi: 10.1161/01.ATV.0000018301.91721.94

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/22/6/1012

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/